Article published online: 2022-07-14

Original Article

Trends, and Tumor Characteristics of Lung Cancer and Malignant Pleural Mesothelioma in the East of Libya

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Abstract

Background: Lung cancer is the most common cancer worldwide and the leading cancer killer. Lung cancer is classified histologically into two types; small-cell lung cancer and nonsmall-cell lung cancer (NSCLC) (squamous cell carcinoma, adenocarcinoma (AC), large cell carcinoma [LCC]). Malignant pleural mesothelioma is a rare thoracic tumor. We aimed to provide comprehensive epidemiological data about lung cancer in the eastern part of Libya. **Patients and Methods:** A retrospective medical records review of lung cancer patients attending the oncology department of Benghazi Medical Center from January 1, 2006 to December 31, 2015. **Results:** There were 684 lung cancer cases out of 7725 total registered cancer cases (8.85%), 627 were male (91.7%, median age 63.5), and 57 females (8.3%, median age 64). NSCLC was the dominant histology 78.5%, SCLC 11%, and malignant mesothelioma 2.5%. NSCLC subtypes were AC (35.1%), squamous carcinoma (25.7%), LCC (4.6%), and not otherwise specified (12.6%). Only 30.6% of cases were diagnosed in Libya, the most commonly used diagnostic modalities were bronchoscopic biopsy 46.6%, and computed tomography guided biopsy 17.4%. Only 18 cases were tested for epidermal growth factor receptor sensitizing mutations and anaplastic lymphoma kinase rearrangement fusion. Stage IV was the most common initial stage for NSCLC 60%, malignant mesothelioma 47.1%, and 74.7% of SCLC presented with extensive disease. Only 42.9% of males and 5.3% of female lung cancer patients were smokers. **Conclusions:** Lung cancer is a major health burden in Libya, and it is increasing in incidence; this epidemiological study tries to put this problem into public health and clinical perspective.

Keywords: Adenocarcinoma, asbestos, large cell carcinoma, lung cancer, malignant pleural mesothelioma, nonsmall-cell lung cancer, small-cell lung cancer, smoking, squamous cell carcinoma

Introduction

Lung cancer is the most common type of cancer worldwide. It represents 11.6% of cancer cases and leading cancer to kill.[1]. It was estimated that

Access this article online

Quick Response Code:

Website: www.ijmbs.org

DOI: 10.4103/ijmbs.ijmbs_79_20

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Submitted: 22-Jun-2020 **Revised:** 31-Aug-2020
Accepted: 13-Sep-2020 **Published:** 04-Nov-2020

How to cite this article: Eldukali WA, Omran KE, Azzuz R. Trends, and tumor characteristics of lung cancer and malignant pleural mesothelioma in the East of Libya. Ibnosina J Med Biomed Sci 2020;12:272-9.

234,030 new lung cancer cases were diagnosed in the USA, and 83,550 estimated deaths in 2018.[2] In Africa, lung cancer incidence was 7.3%, and the mortality rate was 5.8% of total cancer cases for both sexes. The world age-standardized ratio among men and women in northern Africa was 16.9 and 3.4/100,000, respectively, in 2018.[1] There are no detailed data on lung cancers from Libya.

Lung cancer includes small-cell lung cancer (SCLC) and nonsmall cell lung cancer (NSCLC). NSCLC has four main histological types; squamous cell carcinoma (SQC), adenocarcinoma (AC), and large cell carcinoma (LCC).[3] Malignant mesothelioma is a rare tumor from the mesothelial lining of pleural space, peritoneum, pericardium, and tunica vaginalis. The most common of which is the malignant pleural mesothelioma (MPM) representing 80%–90%.[4,5] It is associated with asbestos exposure in 60%–70% as a causative agent.[6] Smoking is implicated in >30% of all cancer deaths,[7] and >80% of lung cancers in the Western world are associated with smoking.[1] Smoking is linked to the histological subtype, where SCLC and SQC are thought to be caused mainly by smoking maybe they tend to develop in a main or segmental bronchus (central types) with the highest exposure where this relation is weaker in AC and LC (the peripheral type),[8-10] preventing smoking and encourage smoking cessation decreases lung cancer burden.[8] NSCLC is clinically staged to Stage I, II, III (Loco-regional), and IV (distant metastasis). SCLC is classified as either a limited or extensive disease.[11]

Treatment of lung cancer requires a multidisciplinary team, including medical oncology, radiotherapy oncology, histopathologist, chest physician, thoracic surgery, radiologist, and others. Patients with lung cancer stage I, II, or III and localized MPM are generally treated with curative intent using surgery, chemotherapy, radiation therapy, or a combined modality approach.[12] The management goals for patients with stage IV lung cancer and advanced MPM are to increase survival and maintain the quality of life for as long as possible while minimizing the side effects due to treatment.[13]

The development of newer agents that target specific molecular pathways in malignant cells has resulted from a better understanding of the molecular pathways that drive malignancy in NSCLC. Therapy could be individualized based on the specific abnormality, if any, present in a given patient. These developments included the discovery of the genomic alterations of epidermal growth factor receptor (EGFR) gene mutation and anaplastic lymphoma kinase (ALK) gene fusion.[14,15]

Despite the notable advances in cancer diagnosis and treatment modalities, the overall 5-year survival for lung cancer remains poor compared to other types of cancer.[16] Patients with MPM most commonly present at an advanced stage and the overall median survival in untreated patients is less than a year.[17,18]

This study aims to provide an epidemiological survey about lung cancer in the east of Libya and study the population's specific characteristics and the different disease patterns to effectively implement and direct the medical resources to improve patient care.

Patients and Methods

Design and settings

This is a retrospective medical records review of patients with lung cancer and MPM who were diagnosed between January 1, 2006, and December 31, 2015 and treated at the oncology department of Benghazi Medical Center (BMC). BMC is a tertiary medical center serving the eastern part of Libya inhabited by about two million people. The medical records were searched, and the study's records were retrieved. The collected data were de-identified for subsequent analysis. We included all patients who attended the oncology department older than 18 years with the complete medical records that identified them as lung cancer or mesothelioma from January 1, 2006 to December 31, 2015.

Staging

Lung cancer codes and definition: were made using the International Classification of Diseases, 10th revision, lung cancer code (C33-34) and mesothelioma C45, and the staging of lung cancer was according to the American Joint Committee on Cancer tumor node metastasis (TNM) system 8th edition.[9,19]

Statistical analysis

Statistical software SPSS package Version 22.0 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA) was used for descriptive analysis. The odds ratio with confidence intervals was calculated using multinomial logistic regression with a specified reference category using SPSS. Chi-square test of independence with Cramer's V (V) as a measure of effect size and the likelihood ratio was performed to examine the association among the categorical variables such as sex, smoking status, and the histopathology subtype.

Results

Lung cancer rates

In the period between 2006 and 2015, there were 7725 cancer cases, males were 3491 (45.2%) and females were 4234 (54.8%), of which there were 684 lung cancer cases. Lung cancer represented 8.9% of the total number of cancer cases, with an annual rate of 8.8%. There were 627 male cases out of 684 lung cancer cases (91.7%) and 57 female cases (8.3%), where the male to female ratio is about 9:1. The annual rate of lung cancer in men was17.9% of total male cancer cases, and for women was 1.3% of total female cancer cases. The demographic characteristics of patients and the annual trend of lung cancer rates are presented in Table 1 and Figure 1. The median age of both sexes was 63.5 years, for men was 64, and for females, 60 years.

Diagnostic modalities

Tunisia was the commonest place of diagnosis (46.6%) followed by Libya (30.6%). The most commonly used diagnostic modality, overall, was bronchoscopic biopsy (46.6%) followed by CT-guided biopsy (17.4%). The most frequently used diagnostic modalities in Libya were bronchoscopic biopsy (48.3%) and radiological diagnosis only (15.3%). The most common diagnostic modalities for MPM were pleural biopsy CT-guided biopsy and open biopsy [Table 1].

Histopathology

NSCLC was the most common diagnosis of lung cancer cases (78.5%), followed by SCLC (11.0%). In NSCLC, AC was the most common type, followed by SQC in both sexes ($P = 0.075$). There were 17 cases of MLP with a mean of age 67.8 years (standard deviation 7.7), representing 2.5% of total lung cancer cases, 15 were males (88%), and 2 were females (12%). The rest of the lung cancer type by sex are presented in Table 2.

Table 1: Demographic data, type of lung cancer, place of diagnosis, and diagnostic modality

Parameters	Details	*n* (%)
Demographics		
Sex	Male/female	627 (91.7)/57 (8.3)
Ethnicity	Libyan/expatriates	672 (98.3%)/12 (1.7)
Place of residence	Benghazi/Outside Benghazi	402 (58.8)/282 (41.2)
Smoking status	Current	272 (39.8)
	Former	71 (10.4)
	Never	50 (7.3)
	Unknown	287 (42
Place of diagnosis	Tunisia	319 (46.6)
	Libya	209 (30.6)
	Egypt	108 (15.8)
	Jordan	35 (5.1)
	Ohter	13 (1.9)
Type of lung cancer	NSCLC	537 (78.5%)
	SCLC	75 (11.0)
	Malignant pleural mesothelioma	17 (2.5)
	Lung cancer (not determined)	55 (8.0)
Diagnostic modality	Bronchoscopic biopsy	319 (46.6)
	CT-guided bipsy	119 (17.4)
	Open biopsy	54 (7.9)
	Radiological	41 (6.0)
	Pleaural biopsy	18 (2.6)
	Lymph node biopsy	17 (2.5)
	Bone biopsy	16 (2.3)
	Mediastinoscopy	15 (2.2)
	Broncheoalveolar lavage	12 (1.8)
	Pleural fluid aspiration cytology	7 (1.0)
	Other or not recorded	66 (9.6)

CT: Computed tomography, SCLC: Small cell lung cancer

Genomic and molecular tests

Three hundred and fifteen out of 537 NSCLC patients presented with locally advanced or metastatic disease of NSCLC and were eligible for genomic and molecular testing. Only 18 cases had molecular testing; the majority were AC (14/18) and one each of LCC, SCLC, not otherwise specified (NOS). Overall, the actual molecular test results were mainly EGFR sensitizing mutation (8) followed by EGFR wild type (7) and one each of EGFR resistant mutation, ALK rearrangement, and combined EGFR and ALK mutation.

Staging and pattern of metastatic disease

Most of the staging was clinical (92.4%), and pathological staging was performed for only 7.6% of total cases. The most common initial stage for NSCLC cases was stage IV (60.33%), and for SCLC was extensive disease (74.66%). Table 3 summarizes the initial stages of each cancer type. The majority of lung cancer cases were diagnosed late. Almost one fifth of all cases presented with multiple sites of metastasis at different sites, the bone came second as the most common single metastatic site. The spectrum of initial metastatic sites for the different histology types is presented in Table 4.

Smoking status

Three hundred and ninety three out of 684 patients were with known smoking status (57.4%), 269 men and 57 women were current smokers. There was a significant relationship between sex and smoking habits ($P < 0.00$) and strong with Cramer's V effect size (0.54), where the smoking habit was dependent on the gender of the patient. The highest rate of smoking among the different histopathological types was noted in LCC, followed by SCLC, NOS, SQC, and the least was seen in AC class [Table 5].

Table 2: Lung cancer type according to gender

Histopathological subclass	All (%)	Males (%)	Females (%)
AC	35.1	33.3	54.4
SQC	25.7	26.5	17.5
LCC	4.6	4.6	5.3
Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements	1.2	1	3.5
Carcinoid tumor	0.1	0.2	0
SCLC	10.8	11.5	3.5
NOS	12.6	12.6	8.8
MPM	7.3	2.4	3.5
Unknown	2.5	7.7	3.5

SCLC: Small cell lung cancer, MPM: Malignant pleural mesothelioma, NOS: Not otherwise specified, AC: Adenocarcinoma, SQC: Squamous cell carcinoma, LCC: Large cell carcinoma

Discussion

The eastern part of Libya covers the half surface area of Libya, and it is inhabited by 1.6 million people, who representing 28.3% of the population.[20] The present study is a hospital registry-based analysis for lung cancer in BMC, which was the only cancer center in the eastern of Libya during the study period. We found that the annual burden of lung cancer cases was 8.9% of total cancer cases, with an annual rate of lung cancer for men was 17.9% and for women was 1.3%. In comparison

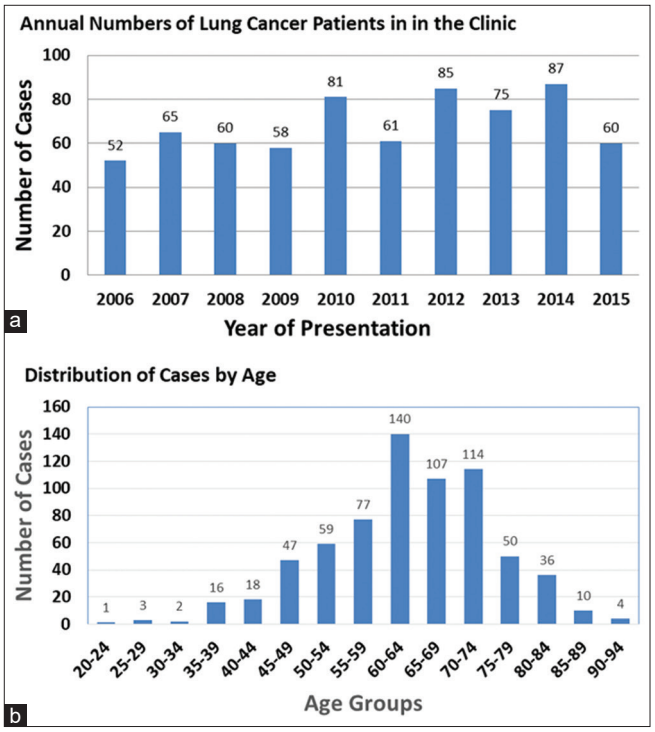

Figure 1: The annual trend for newly presenting patients to the clinic (2004–2015) and the distribution of ages of patients attending the clinic. (a) Annual Numbers of Lung Cancer Patients in in the Clinic. (b) Distribution of cases by age

Table 3: The initial stage of each lung cancer type on presentation

Lung cancer type	Initial stage on presentation (%)						
	I	II	III	IV	Limited	Extensive	Unknown
SCLC	-	-	-	-	22.7	74.7	2.7
NSCLC	0.6	3.7	25.9	60.3	-	-	9.5
Malignant mesothelioma	0	0	23.5	47.1	-	-	29.4
Lung cancer undetermined	0	0	0	72.7	-	-	27.3

SCLC is staged as limited or extensive; other types staged according to the AJCC TNM system (AJCC 8th edition) AJCC: American Joint Committee on Cancer, SCLC: Small cell lung cancer, NSCLC: Nonsmall cell lung cancer, TNM: Tumor node metastasis

with the national cancer registry of Eastern Libya NCREL (2003 and 2007), which was a population-based registry[21,22] the total rate of lung cancer of NCREL was higher at about 19%, and the rate in men was similar 18.9% and higher in women 8%. This difference may be explained by the fact that NCREL was made by 3 years of data, whereas our study spanned over 10 years. In Libya, lung cancer is the most common cancer in men, and in women, it is not in the top ten.[20]. Our data showed that the male to female ratio was 9:1; however, NCREL was higher 14:1.[21,22] If we compare that with lung cancer incidence in the neighboring countries such as Egypt, the lung cancer incidence rate for both sexes was 4.2% and for males 5.7% and for females 2.7%,[23] whereas the total new lung cancer cases rates for Tunisia and Algeria were 13.3% and 8.0%, respectively, which were more or less comparable with our results.[1,24] Globally, lung cancer is first in incidence (14.5%) and mortality among males and the third in incidence (8.4%) and second in mortality among females.[1] this lower rate of lung cancer among Libyan females could be attributed to the lower rate of smoking.

Table 4: Pattern of metastatic disease by cancer type

Metastatic status	SCLC (%)	NSCLC (%)	MPM (%)
M0	19	161	3
M1 - Brain	61 (10.8)	40 (10.0)	0
M1 - Lymph nodes	1 (1.8)	3 (0.75)	0
M1 - Respiratory	11 (19.8)	64 (16.0)	3 (21.4)
M1 - Liver	6 (10.8)	24 (6.0)	2 (14.3)
M1 - Bone	4 (7.2)	75 (18.8)	0
M1 - Skin	0	2 (0.5)	0)
M1 - Adrenals	1 (1.8)	22 (5.5)	0
M1 - Multiple sites	17 (86.6)	88 (22.0)	1 (7.1)
M1- Unknown	10 (18.0)	58 (14.5)	8 (57.1)

M0: Nonmetastatic disease, M1: Metastatic disease, SCLC: Small cell lung cancer, NSCLC: Nonsmall cell lung cancer, MPM: Malignant pleural mesothelioma

In this study, NSCLC was the most common type of lung cancer, 78.5%, followed by SCLC 11.0%. However, data from the United States (2013–2017), NSCLC was the dominant subtype (84.3%) followed by SCLC (12.5%) of total lung cancer cases.[25,26] In the present study, AC was the most common subtype for both sexes but relatively higher in women than other histopathological subtypes, similar to other international figures in the USA, Canada, and Japan.[27] We also noticed that SQC and SCLC were higher in males than in females, which could be attributed to high smoking exposure rates in males.[28] Moreover, the NOS subtype of NSCLC represented 12.6% of reported pathology in our study, which was relatively high in comparison to SEERS data, in which NOS represented 2.9% of NSCLC subtypes.[29] It is crucial to identify the subtype of NSCLC histopathology as it predicts the prognosis and directs the type of therapy for each subtype. For example, anti-EGFR tyrosine kinase Inhibitors and anti-ALK therapy are working with AC, and anti-angiogenesis therapy is associated with bleeding in squamous pathology.[30,31] Moreover, NOS subtype is associated with poor prognosis and aggressive behavior.[30] Mesothelioma was more common in men aged >60 years (88%). Worldwide, the age-adjusted incidence ratio of MPM in 2011 was 4.9/million, the mean age at death was 70 years, and male to female was ratio 3.6:1.[31] There was no data about asbestos exposure in the participants' file records.

Although smoking history was not recorded for all participants, from the available data, the rate of smoking in men was 42.9% and for women was 5.2%. These rates were similar to the latest WHO report on the global tobacco epidemic in 2019 showed that the prevalence of tobacco smoking in Libyan males (ages 25–64) is 49.6% and 0.7%

Table 5: Relation between histology subtype and smoking exposure

Smoking status	Histopathological type of lung cancer (*n*)			
	SQC (112)	LCC (21)	NOS (41)	SCLC (41)
Current	77; 2.14 (1-4.6)	16; 2.4 (0.5-11.3)	30; 9.2 (1.19-70.6)	31; 3.17 (0.8-11.2)
Former	24; 2.8 (1.12-6.9)	3; 1.92 (0.29-12.6)	10; 12.8 (0.5-108.5)	7; 3 (0.6-13)
Never	11	2	1	3

Results are expressed as *n*; OR (95% CI). OR: Odds ratio, CI: Confidence interval, SQC: Squamous cell carcinoma, LCC: Large cell carcinoma, NOS: Not otherwise specified, SCLC: Small cell lung cancer

in females. The Global Youth Tobacco Survey, 2010 reported that current tobacco product use among Libyan students aged between 13 and 15 was 12.4%.[32] The prevalence of tobacco use in neighboring countries such as Egypt was in males 46.4% and 0.2% in females, and in Tunisia was 48.4% in males and 8.2% in females.[23] The most common associated histopathological subtype with smoking was NOS, followed by SCLC, LCC, and SQC. These results are similar to the data from Italy.[33]

Majority of the of lung cancer cases reported here (69.4%) were diagnosed abroad, reflecting the low accessibility and utilization of medical facilities and resources. For simple diagnostic procedures such as bronchoscopy, patients need to travel abroad to be diagnosed. Furthermore, we noticed the high rate of radiological diagnosis (15%) among those diagnosed in Libya compared to patients diagnosed abroad. Furthermore, we had a higher rate of unknown histology, and NOS histopathology (17.2% and 16.7% respectively) who were diagnosed in Libya, in comparison with Libyan patients diagnosed in Tunisia were (2.2% and 9.1%) and in Egypt (5.6% and 13.9%), respectively. This high NOS histology rate could be attributed to the lack of immunohistochemical staining and molecular markers locally.

Only a minority of our patients (18 cases; 5.7%) were subjected to molecular testing for EGFR gene mutation and ALK rearrangement gene fusion. This low rate of testing was due to the unavailability of testing locally. The need for the second biopsy, the patients' low-performance status, and the high cost of testing abroad, the targeted tyrosine kinases inhibitors to treat those patients with positive mutations were unavailable and expensive to afford. Therefore, the testing was impractical in that period of our study. This low rate of testing was also reported across academic and national cancer centers in the USA. In 2012, a survey of National Cancer Institute-designated cancer centers regarding biologic molecular testing for NSCLC; only 34% used upfront testing for the newly diagnosed patients, and 22% used a sequential protocol after the progression of lung cancer.[34]

The majority of lung cancer cases are asymptomatic or presented with nonspecific symptoms at the earlier stages; hence the majority of lung cancer patients presented with locally advanced or metastatic disease, where the role of curable therapeutic interventions are only applicable to lung cancer patients presented at an early stage.[10,11] The majority (86.2%) of NSCLC were diagnosed at late Stages (III and IV). Similarly, for SCLC patients, nearly three quarters were diagnosed as an extensive disease. About 70.6% of cases were diagnosed with late stages for MPM, and 10.7% for all lung cancer cases were unstaged/unknown. In the USA between the calendar year 2010–2016, 54% of all NSCLC lung cancer cases were with distant metastasis when diagnosed, 24% were regional, 20% were localized, and only 2% were unstaged/unknown[26,27] for SCLC 4% were localized, 20% were regional, 75% were distant, and 2% were unstaged/unknown.[27]

In the present study, the most common metastatic sites for NSCLC were bone and brain. For SCLC, the lung was the most common metastasis, followed by the brain. These are widely different from larger previous reports.[35,36] A previous population-based study involving 21,169 patients, the most frequent metastatic sites were the nervous system, bone, liver, respiratory, and adrenal gland.[35]Furthermore, another large study of 1994 patients, the most frequent metastatic sites were lung, bone, brain, liver, and adrenals.[36]

The quality of medical records and the absence of national central electronic medical records are apparent limitations of the present study. Many patients diagnosed elsewhere have not provided adequate information about the diagnostic workup, staging, and pathology reports. Besides, insufficiency and shortage of local diagnostic investigations such as immunohistochemistry and molecular testing hindered further classifications and patients' management. These limitations had made some gaps in this study's results

Conclusions

Lung cancer in Libya represents a significant health issue in primary prevention, screening, diagnosis, and therapy costs. A central national cancer registry

center is essential and must be done promptly to enable researchers to study and assess the current burden of cancer in Libya for future planning and directing the best strategies to tackle this significant health problem. Any primary prevention intervention should include tobacco control initiative at the governmental level. This type of epidemiological study helps put this problem into perspective for better use of already limited resources to provide the best care for cancer patients. Future studies about epidemiology, therapy, and survival of cancer are much needed in this area of the world.

Acknowledgments

The authors would like to thank all doctors, nurses, and clerks of the oncology department of BMC, Benghazi, Libya, for their support in data collection during the study.

Authors' contribution

The authors jointly conceived and conducted the study jointly. Wail A. Eldukali analyzed the data and drafted the manuscript. Other authors reviewed the manuscript for intellectual content, and all authors approved its final version.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

The Research Ethics Board of Benghazi Medical Center approved the study (Ref 2017-22-44-1). All patients attending the institution sign a general consent form allowing their de-identified data for quality assurance and research. All data were analyzed and reported anonymously.

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