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BRAIN AND BONE METASTASES IN LUNG CANCER: IMPACT OF CLINICO-PATHOLOGICAL FACTORS

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ABSTRACT – *Objective:* Lung cancer is a leading cause of cancer-related mortality, primarily due to its high metastatic potential, particularly to the brain and bones. Brain metastases significantly challenge clinical management, impacting treatment efficacy and patient survival, while bone metastases cause severe complications such as pathological fractures and hypercalcemia. Understanding the clinico-pathological factors influencing these metastases is essential for improving patient outcomes.

Materials and Methods: This study examined a cohort of 158 patients with primary lung cancer treated at the Cheikh Zaid International University Hospital in Rabat, Morocco. Clinical data, including demographic information, smoking status, and histological and molecular characteristics, were collected. The incidences of bone and brain metastases were analyzed. Statistical analysis was performed using Excel and Jamovi software, with qualitative variables expressed as frequencies and quantitative variables as central tendencies. Associations between variables were evaluated using Chi-square and Fisher's exact tests, with a significance threshold set at $p < 0.05$.

Results: Bone metastases were identified in 31 patients (19.6%) via bone scintigraphy, while brain metastases were confirmed in 29 patients (18.4%) through cerebral MRI. No significant differences were observed between males and females or among different age groups. However, smoking was significantly associated with bone metastases ($p = 0.034$), with smokers exhibiting a higher incidence. A significant association was found between brain metastases and the adenocarcinoma histological subtype ($p = 0.001$), indicating that specific tumor characteristics influence metastatic patterns. No significant correlation was observed between molecular status and the occurrence of metastases.

Conclusions: This study underscores the importance of clinico-pathological factors in lung cancer metastasis. Smoking is significantly correlated with bone metastases, while adenocarcinoma is closely linked with brain metastases. These findings highlight the need for personalized management strategies and improved data documentation to enhance clinical care.

KEYWORDS: Lung cancer, Brain metastasis, Bone metastasis, Metastatic sites, Clinico-pathological factors.

INTRODUCTION

Lung cancer remains one of the leading causes of cancer-related mortality worldwide. Despite significant advancements in diagnosis and treatment, the prognosis of this disease remains poor due to its high propensity for metastasis. Among common metastatic sites, brain metastases pose a major clinical challenge due to the complexities associated with the central nervous system. This metastatic involvement complicates treatment, impairs quality of life, and reduces patient survival[1]. Additionally, bone metastases, responsible for pathological fractures, severe pain, and hypercalcemia, further deteriorate patients' quality of life and survival prospects[1].

Despite substantial advances in elucidating the biological mechanisms underlying metastasis, the epidemiological characterization of metastatic dissemination remains insufficiently defined. Existing data on site-specific metastatic patterns are often heterogeneous, fragmented, and lacking standardization[1]. This limitation largely reflects the design of population-based cancer registries, which predominantly capture information on primary tumors, while metastatic events are inconsistently recorded. Although the Tumor, Nodes, Metastasis (TNM) classification provides information on the presence of distant metastases at diagnosis, it does not systematically capture their anatomical distribution or temporal evolution. Consequently, a more comprehensive, standardized, and population-level documentation of metastatic patterns is essential to refine prognostic stratification and optimize the clinical management of lung cancer patients[2].

The epidemiology of lung cancer in Morocco presents a complex picture that requires a nuanced approach. According to IARC official site data[2], in 2020, there were 7,353 new cases of lung cancer in Morocco, with a marked male predominance (6,502 men and 851 women). Similarly, the mortality rate due to lung cancer in Morocco in 2020 was 6,551 deaths, distributed between 5,802 men and 749 women. However, it is essential to note that these figures, although provided by the IARC, may not fully reflect the current situation. In Morocco, lung cancer statistics primarily come from two registers located in Casablanca and Rabat. These registers may have limitations due to the age of the data, such as the Greater Casablanca Cancer Registry (GCCR) from 2013 to 2017 and the Rabat Cancer Registry (RCR) from 2009 to 2012, and their limited coverage focusing on specific geographical areas. Furthermore, studies conducted by researchers, oncologists, and epidemiologists in various medical oncology departments across the country may also have limitations due to the small size of the cohorts studied or the number of cases analyzed.

In this study, we aim to elucidate the incidence and correlation of brain and bone metastases with various clinico-pathological characteristics among Moroccan patients diagnosed with primary lung cancer. By examining a cohort of patients treated at the Oncology Center of the Cheikh Zaid International University Hospital in Rabat, Morocco, we seek to identify significant associations that could inform clinical practice and improve patient outcomes.

PATIENTS AND METHODS

Data Collection

This study was conducted on a cohort of 158 patients with primary lung cancer who were treated at the Oncology Center of Cheikh Zaid International University Hospital. Clinical data were extracted from the patients' medical records. The inclusion criteria were rigorously defined to ensure the quality and relevance of the data. Patients had to have a complete medical record, including all necessary information for clinical and epidemiological analysis. Both sexes were included to ensure sample representativeness and to explore potential sex-related differences in metastatic spread. All age groups were considered, allowing evaluation of the impact of age on the distribution and characteristics of metastases. Patients needed to have a confirmed diagnosis of primary lung cancer, established by reliable histological or cytological examinations. All histological types of lung cancer were included (such as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, etc.) as well as various stages of the disease (from early to advanced stages) to cover a broad spectrum of clinical presentations and better understand the factors influencing metastatic spread. The exclusion criteria were also strict to maintain the study's rigor. Incomplete medical records, which did not provide sufficient data for thorough analysis, were excluded. Additionally, only Moroccan patients were included in the study to focus on a homogeneous population and avoid variations related to genetic and environmental differences that might exist between different nationalities. Particular attention was paid to evaluating metastatic spread, specifically focusing on the detection of bone and brain metastases. The data were analyzed considering epidemiological criteria and clinico-pathological characteristics to assess the correlation between the presence of metastases and these various parameters.

Ethics Committee

To comply with the ethical requirements of the scientific community, the protocols and methodologies employed in this project were submitted to the Ethics Committee for evaluation under file number PR_KC-BRPL_2021. The study was assessed for compliance with international ethical regulations and received a favorable opinion from the Ethics Committee of the Cheikh Zaid Foundation (CEFCZ/AB/28/06/2021), attesting to its alignment with fundamental ethical research principles. The study was conducted by collecting data from the medical records of patients. Although this study required authorization from the hospital administration and the Ethics Committee, it did not require informed consent from patients, as the data were collected without regard to patient identity, focusing solely on clinical parameters.

Statistical Analysis

The data were processed using Excel 2016 for efficient organization. Statistical analysis was performed with Jamovi (The Jamovi Project, Sydney, Australia; https://www.jamovi.org/), suitable for complex analyses. The qualitative variables included sex (male/female), tobacco consumption (yes/no), alcohol consumption (yes/no), tumor localization (right lung/left lung), and histological type [adenocarcinoma (ADC), squamous cell carcinoma (SCC), large cell carcinoma (LCC), small cell lung cancer (SCLC)]. The quantitative variables included age (in years) and molecular statuses [epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), programmed death-ligand 1 (PD-L1)]. Qualitative variables were expressed as absolute and relative frequencies, and quantitative variables were presented with their central tendencies and dispersions. Chi-square and Fisher's exact tests were used to explore the associations between qualitative variables. A significance threshold of p-value < 0.05 was set to indicate a statistically significant association between variables.

RESULTS

Among the 158 patients studied, bone metastases were detected by bone scintigraphy in 31 (19.6%). Brain metastases were observed and confirmed by cerebral MRI in 29 patients, accounting for 18.4% of the cases (Table 1).

Regarding sex, no significant difference was observed between males and females for bone metastases (p = 0.53) and brain metastases (p = 0.53). Age also did not appear to be a significant factor for bone metastases (p = 0.72), although patients aged 50 to 59 years showed a slightly increased risk of brain metastases (p = 0.12).

Data analysis revealed a significant correlation between the presence of bone metastases and certain clinico-pathological factors. Specifically, tobacco consumption was significantly associated with the occurrence of bone metastases (p = 0.034). Among the 31 patients with bone metastases, 24 were tobacco users, representing 77.4%. In contrast, alcohol consumption was not significantly associated (p = 0.39). Regarding brain metastases, although the link with tobacco use was not statistically significant (p = 0.13), there was a noticeable trend indicating a potential association. The location of the tumor (p = 0.94 for bone metastases, p = 0.74 for brain metastases) and molecular status (p = 0.36 for bone metastases, not applicable for brain metastases due to their low incidence) did not present significant differences in the occurrence of metastases, either at the bone or brain level. The analysis highlighted a significant correlation between the presence of brain metastases and the histological type of adenocarcinoma, with a p-value of 0.001. This underscores the crucial importance of considering the tumor's histological type in evaluating the metastatic risk in patients with lung cancer.

The study revealed a notable prevalence of bone and brain metastases in patients with lung cancer, with significant associations with tobacco consumption and the adenocarcinoma histological subtype. This highlights the need for rigorous monitoring and tailored management strategies. Clinico-pathological factors, such as histological type and cancer stage, play a crucial role in predicting metastatic sites.

DISCUSSION

Several studies have confirmed a high incidence of brain metastases originating from the lungs, reaching up to 88%, making it the primary site for distant metastases[4-6]. Bone metastases rank second, followed by the liver and mediastinal lymph nodes.

Table 1. Analysis of clinical and molecular factors in bone and brain metastases.

		Bone metastases (N=31)		Brain metastases (N=29)	
		N (%)	*p*-value	N (%)	*p*-value
Gender	**Male**	29 (93.5%)	0.53	27 (93.1%)	0.53
	Female	2 (6.5%)		2 (6.9%)	
Age	**< 50 years**	2 (6.5%)	0.72	1 (3.4%)	0.12
	50 - 59 years	7 (22.6%)		12 (41.4%)	
	60 - 69 years	15 (48.4%)		10 (34.5%)	
	≥ 70 years	7 (22.6%)		6 (20.7%)	
Toxic Substances	**Tobacco**	24 (77.4%)	**0.034**	14 (48.3%)	0.13
	Alcohol	8 (25.8%)	0.39	3 (10.3%)	0.14
Localization	**Right lung**	13 (54.2%)	0.94	13 (56.5%)	0.74
	B	11 (45.8%)		10 (43.5%)	
Molecular aspect	**EGFR +**	4 (12.9%)	0.36	2 (6%)	
	ALK+	1		1	
	PD-L1 +	1		1	
Histology aspect	**ADC**	22 (70.9%)	0.31	24 (85.7%)	**0.001**
	SCC	3 (9.6%)		0	
	LCC	0		1 (3.6%)	
	SCLC	3 (9.6%)		3 (10.7%)	

EGFR: Epidermal Growth Factor Receptor; ALK: Anaplastic Lymphoma Kinase positive; PD-L1: Programmed Death-Ligand 1; ADC: Adenocarcinoma; SCC: Squamous Cell Carcinoma; LCC: Large Cell Carcinoma; SCLC: Small Cell Carcinoma.

Cancer databases and registries are often incomplete, leading to an underestimation of the incidence of metastases. This incidence has significantly increased since the reporting of metastases in cancer registries became mandatory. Several factors contribute to this situation. Firstly, underreporting and the absence of systematic monitoring have led to an underestimation of the true incidence of metastases. Furthermore, before the improvement and accessibility of imaging techniques such as magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT), and scintigraphy, metastatic assessments were more difficult to perform, especially in asymptomatic patients. The focus on primary cancer, at the expense of monitoring and documenting metastatic spread, also contributed to this low reported incidence. Finally, the limited resources allocated to cancer registries and data collection have restricted the ability to obtain comprehensive information on metastases[3,4,7].

Brain Metastases

Brain metastases, unlike metastases to other distal organs, must cross the blood-brain barrier (BBB), which separates the blood from the cerebrospinal fluid in the central nervous system (CNS). The BBB is composed of endothelial cells connected by tight junctions, the basement membrane, pericytes, astrocytic end-feet, and various protein transport mechanisms (Figure 1). The BBB limits the diffusion of microorganisms, pathogens, and toxins by preventing the entry of particles larger than 500 Daltons[8]. In most cases of brain metastases, the BBB is disrupted by several mechanisms. Cancer cells release metalloproteinases (MMPs) that degrade the basement membrane and the tight junctions of endothelial cells, facilitating their passage. Additionally, the presence of tumor cells triggers a local inflammatory response, with cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) increasing BBB permeability. Finally, oxidative stress, due to increased production of free radicals, damages endothelial cells, further increasing BBB permeability[9,10]. The degree of BBB disruption influences the penetration

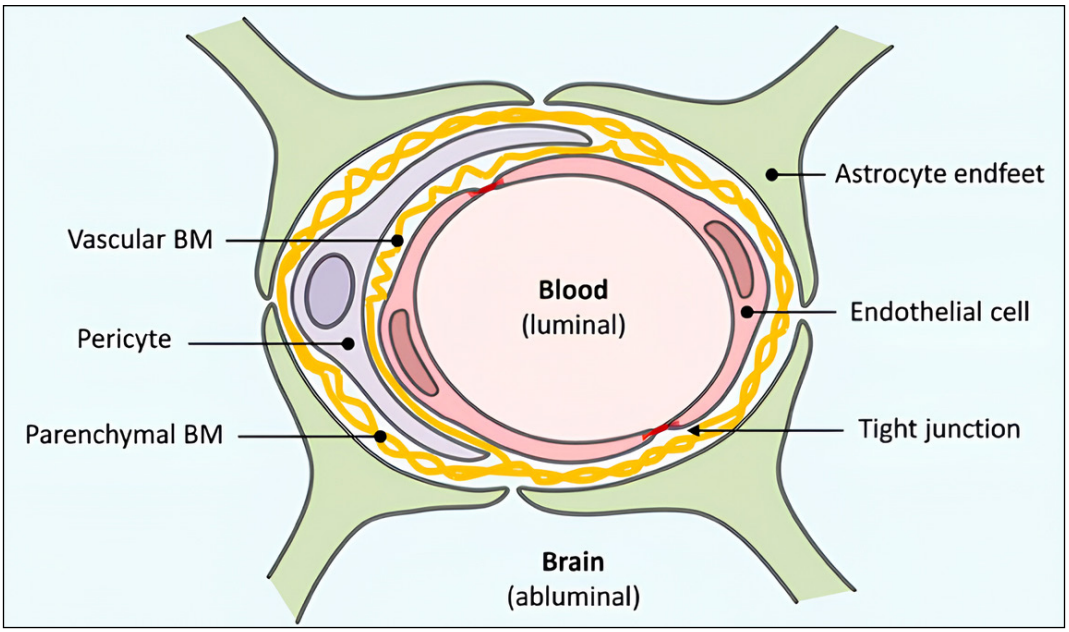

Figure 1. Anatomical structure of the blood–brain barrier (BBB).

of therapeutic agents into the central nervous system (CNS). A highly altered BBB allows these agents to cross more easily, enhancing their effectiveness against tumor cells in the brain. Conversely, an intact BBB can prevent drug access, limiting their therapeutic impact on brain metastases.

Lung cancer frequently metastasizes to the brain due to several specific pathophysiological mechanisms. Firstly, lung tumor cells can directly invade the pulmonary veins (Figure 2), facilitating their access

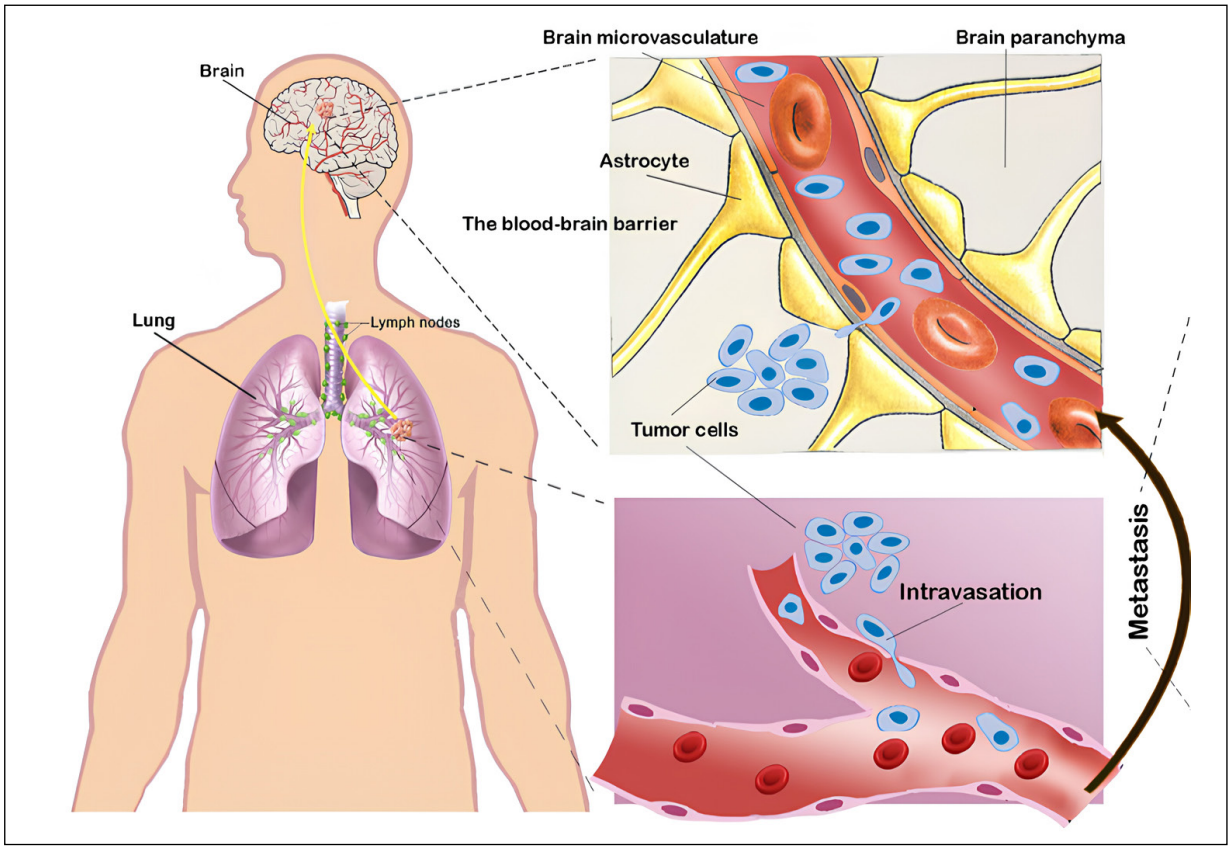

Figure 2. Schematic of the mechanisms of brain metastasis formation in lung cancer.

to the arterial circulation *via* the left atrium and ventricle of the heart. This direct pathway allows cancer cells to rapidly distribute throughout the body, including the brain. Additionally, lung cancer cells are often relatively small, allowing them to traverse the BBB more easily. According to Paget's 1889 'Seed-and-Soil' hypothesis[11], the brain provides a favorable environment (soil) for lung cancer cells (seeds) due to factors such as specific nutrients and a unique immunological environment that promotes tumor growth. Lung tumors can create an inflammatory environment that facilitates the release of cytokines and other inflammatory mediators, which can alter the BBB and increase the permeability of cerebral blood vessels, thus facilitating the invasion of tumor cells into the brain[12]. Finally, certain lung cancer cells exhibit distinct biological and molecular characteristics, including the expression of specific receptors and adhesion molecules, which facilitate their migration and implantation in the brain. For example, specific genetic alterations can confer increased aggressiveness and an enhanced ability to survive and proliferate in the unique microenvironment of brain tissue[13].

A multitude of studies have attempted to identify high-risk individuals and delineate prognostic factors for brain metastases in lung cancer patients. It has been found that sex cannot be used as a marker to predict the development of brain metastases[14]. However, in patients with early-stage, completely resected non-small cell lung cancer (NSCLC), women may have predictive value for the incidence of brain metastases[15].

Many studies[16-20] have reported that being under the age of 69 is a risk factor for brain metastases in lung cancer. The predictive value of age has been analyzed, and it has been found that patients under the age of 69 are associated with a higher risk of brain metastases[16-20], which is consistent with our results. The reason why these patients are at higher risk of brain metastases remains unknown. It is, therefore, imperative that further studies explore the variation in the expression of biomarkers such as vascular endothelial growth factor (VEGF), Ki-67, and caspase-3 between younger and older patients, as these differences could shed light on the increased risk of brain metastases in younger patients[21]. Moreover, improved clinical performance and prolonged survival observed in younger patients could also contribute to their increased susceptibility to brain metastases.

Regarding smoking, our results do not show an association with the occurrence of brain metastases, unlike bone metastases. The results of a meta-analysis conducted by Sun et al[14] confirmed that no statistical significance was noted in all studies that analyzed smoking status as a risk factor for the occurrence of brain metastases, although some tended to show that it was a protective factor.

The study by Jain et al[22] highlighted that patients with both a history of smoking and brain metastases have the worst outcomes in terms of survival and quality of life, but without being a risk factor. This can be explained by the chronic inflammation and vascular damage that smoking can cause, which could disrupt the BBB.

Knowing that adenocarcinoma is the most common histological type in metastatic lung cancers, our results do not present any statistical significance of association between adenocarcinoma (ADK) and the occurrence of brain metastases. Our results are consistent with those of Dimitropoulos et al[23] and Ceresoli et al[24], who found no correlation between histological type and the occurrence of brain metastases. Nevertheless, the study by Wang et al[25] of a cohort of 159,241 lung cancer patients with extrathoracic metastases, primarily to the brain and bone, demonstrated that an incidence of 47.2% of the histological subtypes were ADK.

Studies have shown that mutations in the *EGFR* gene in lung cancer are associated with brain metastases. Studies conducted by Matsumoto et al[26], Gow et al[27], and Li et al[28] demonstrated an incidence of mutated *EGFR* in 63%, 44%, and 64% of lung cancer patients, respectively. These percentages are significantly higher compared to those without brain metastases. Furthermore, Eichler et al[29] demonstrated that patients with NSCLC with *EGFR* mutations had more brain metastases compared to those with wild-type *EGFR*. Exon 19 deletions and the L858R mutation are most associated with brain metastases. *EGFR* mutations are also more frequent in Asian patients, with a prevalence of up to 63% for brain metastases in some studies[21]. This frequency is much lower in Caucasian populations[21].

Patients with anaplastic lymphoma kinase (ALK) mutations have a high rate of brain metastases. One study[30] revealed that nearly 24% of patients with ALK-positive NSCLC had brain metastases at the initial diagnosis, and this rate increases significantly over time. These data suggest that ALK mutations are associated with an increased risk of brain metastases[30].

BONE METASTASES

Bone metastases are a common complication of cancer, with an incidence reaching 64% in lung cancer[31]. The process of bone metastasis in lung cancer can be divided into three main stages: tumor invasion, migration of tumor cells, and invasion of bone tissue (Figure 3). During the first stage of tumor invasion, mesenchymal stem cells from the bone marrow (BMSC) prepare favorable areas for metastasis for-

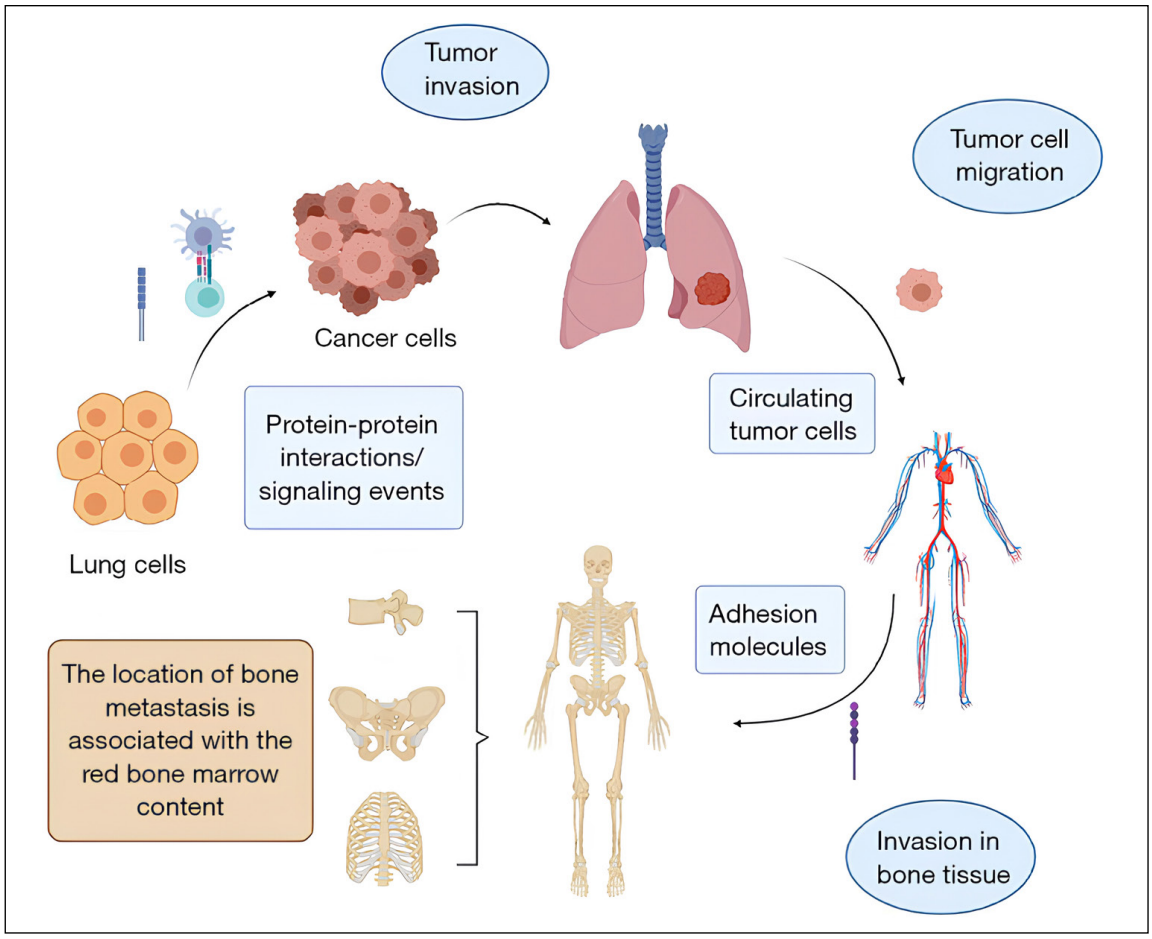

Figure 3. The process of bone metastasis in lung cancer.

mation, known as pre-metastatic niches[32]. During this stage, cancer cells undergo morphological and functional changes, losing their epithelial characteristics, such as E-cadherin and cytokeratins, as well as their polarity and intercellular junctions. They then acquire mesenchymal characteristics, including N-cadherin, fibronectin, and vimentin. They acquire traits that make them more mobile and invasive, including the ability to move and infiltrate other tissues and an increase in enzymes such as matrix metalloproteinases (MMPs), which degrade surrounding tissues. This process, known as the "epithelial-mesenchymal transition," enhances the ability of cancer cells to migrate and invade other tissues, thereby facilitating the formation of metastases[33].

Next, during the stage of tumor cell migration, lung cancer cells enter the bloodstream, becoming circulating tumor cells (CTCs). They target areas of red bone marrow, such as the spine, pelvis, and ribs, where they can settle. Upon reaching the bones, cancer cells attach to the bone surface through the overexpression of chemokine receptors on their surface, such as the CXCR-4 receptor, which binds to its ligand CXCL-12, secreted by stromal cells, including mesenchymal stem cells from the bone marrow (BMSC). Other chemokine axes, including CXCR-6/CXCL-16 and CXCR-3/CXCL-10, also play a role in this process[34]. Additionally, the migration of cancer cells to calcium-rich bone sites is facilitated by the engagement of calcium-sensitive receptors[35].

Studies[36,37] have attempted to identify high-risk populations and define prognostic factors for bone metastases in patients with lung cancer. Research conducted by Ryan et al[36] and Huang et al[37] both established a correlation between bone metastases of pulmonary origin and demographic factors such as sex and age. Ryan et al[36] demonstrated that bone metastases are more common in adult male patients over the age of 25. This observation was corroborated by Huang et al[37], who reported a high incidence of these metastases in men aged 61 to 80 years.

Regarding smoking status, our study highlights a significant link between smoking and the occurrence of bone metastases of pulmonary origin (p-value = 0.034). Da Silva et al[38] also suggested that patients with lung cancer who are smokers have a significantly higher risk of developing bone metasta-

ses. Indeed, among smoking patients, 30% developed bone metastases, compared to only 15% among non-smokers. Moreover, the prognosis for smokers is less favorable, with a 6-month survival rate of 40% *vs.* 60% for non-smokers. This could be explained by the presence of toxic substances in cigarettes that stimulate angiogenesis, facilitating the dissemination of tumor cells into the bloodstream. Additionally, smoking weakens the immune system, reducing the body's ability to destroy circulating cancer cells, and alters the bone microenvironment, making bones more vulnerable to tumor invasion. Finally, it induces chronic systemic inflammation and stimulates the production of pro-metastatic factors that promote the migration and implantation of cancer cells in the bones. However, studies by Chambard et al[39] and Landi et al[40] noted that no significant difference in terms of smoking status and bone metastases was observed among lung cancer patients.

Our study showed no association between the appearance of bone metastases and histological type or molecular status. This is consistent with the study by Shan et al[41], which also found no significant difference regarding the occurrence of bone metastases based on the histological type of lung cancer. In contrast, the study conducted by Oliveira et al[42] examined the relationship between lung cancer histology and the clinico-pathological characteristics of bone metastases. It found that among patients with bone metastases, 50% had adenocarcinoma, 30% had squamous cell carcinoma, and 20% had large cell cancer. The study also revealed that 60% of bone metastases related to adenocarcinoma were located in the spine, while 45% of metastases associated with squamous cell carcinoma were located in the bones of the limbs.

Regarding mutational status, studies have proven a significant statistical association between the presence of bone metastases of pulmonary origin and mutations in the *EGFR* gene. This was described in the study conducted by Na et al[43], which, in addition to mutated *EGFR*, showed that patients with rearrangements in the *ALK* gene are more likely to develop bone metastases, indicating that these mutations could influence metastatic progression to the bones.

STUDY'S STRENGTHS AND LIMITATIONS

The study presents several strengths; firstly, it provides valuable insights into the epidemiology and clinico-pathological factors associated with lung cancer metastasis in a Moroccan population, which is underrepresented in the existing literature. Secondly, the study utilizes a well-defined cohort from a reputable oncology center, ensuring the reliability of the clinical data. Thirdly, the focus on both bone and brain metastases offers a comprehensive understanding of the metastatic patterns in lung cancer patients. Additionally, the rigorous inclusion criteria and thorough data extraction methods enhance the accuracy and consistency of the findings. Lastly, the use of advanced statistical analysis with tools like Jamovi ensures robust and reliable results, contributing to the scientific understanding of lung cancer metastasis. However, this study also has several important limitations. First, the lack of information in the medical records led to the exclusion of a significant number of patients, which limited the sample size. This potentially reduced the representativeness and statistical significance of the results. Second, the retrospective data extracted from the medical records may contain inaccuracies or omissions, introducing biases into the analysis. Third, the absence of long-term follow-up of the patients restricts the understanding of long-term outcomes, particularly regarding disease progression, survival, and patient mortality. Fourth, we worked exclusively with patients from Cheikh Zaid Hospital. The patients treated there mostly come from Rabat or surrounding areas, meaning the study does not consider the genetic diversity and environmental factors that may influence metastatic spread in patients from different regions of Morocco.

CONCLUSIONS

This study reveals a significant incidence of bone and brain metastases, highlighting the importance of understanding their correlations with clinico-pathological characteristics in patients with lung cancer. The data underscore a significant association between tobacco consumption and the occurrence of bone metastases, indicating that smoking could play a crucial role in the progression and dissemination of tumor cells to the bone. Additionally, a marked correlation has been established between the histological type of adenocarcinoma and the occurrence of brain metastases, suggesting that certain biological and molecular characteristics of tumors may influence their propensity to invade the central nervous system. These findings emphasize the importance of rigorous clinical monitoring and personalized management of lung cancer patients, particularly those with specific risk factors such as smoking and the adenocarcinoma histological subtype. Such an approach could not only improve therapeutic

strategies but also potentially increase overall survival and quality of life for patients. Furthermore, the study highlights existing gaps in the documentation of metastases in cancer registries, calling for an improvement in data collection practices for a more comprehensive understanding of the epidemiology of metastases and better clinical management of lung cancer cases.

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Authors' Contributions:
O. Morjani: Conceptualization, Methodology, Data Curation, Formal Analysis, Investigation, Writing-Original Draft Preparation. S. Benlhachemi: Data Curation, Formal Analysis, Writing - Review & Editing. S.K. Mai Abdou: Investigation, Data Curation, Resources. H. Errihani: Supervision, Resources, Writing - Review & Editing. E.M. Elfahime: Conceptualization, Supervision, Validation, Writing - Review & Editing. H. Lakhiari: Conceptualization, Supervision, Project Administration, Validation, Writing - Review & Editing.

Availability of Data and Materials:
All data generated and analyzed during this study are included in this published article. All data were extracted from the medical records of patients treated at Cheikh Zaid International University Hospital (Rabat, Morocco). Due to ethical considerations and patient confidentiality, the medical records cannot be publicly shared. Access to data is restricted and managed according to ethical and institutional guidelines to protect patient privacy.

Conflict of Interest:
The authors declare no conflict of interest. The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval:
To comply with the ethical requirements mandated by the scientific community, the protocols and methodologies employed in this project were submitted to the Ethics Committee for evaluation under the file number PR_KCBRPL_2021. The study was assessed for its compliance with international ethical regulations and received a favorable opinion granted by the Ethics Committee of the Cheikh Zaid Foundation, referenced CEFCZ/AB/28/06/2021. This approval attests to the alignment of the study with fundamental ethical research principles.

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The study was conducted by collecting data from the medical records of patients. Although this study required authorization from the hospital administration and the ethics committee, it did not require informed consent from patients, as the data were collected without regard to patient identity, focusing solely on clinical parameters.

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REFERENCES

1. D'Antonio C, Passaro A, Gori B, Del Signore E, Migliorino MR, Ricciardi S, Fulvi A, de Marinis F. Bone and brain metastasis in lung cancer: recent advances in therapeutic strategies. Ther Adv Med Oncol 2014; 6: 101-114.
2. IARC (WHO). Data visualization tools for exploring the global cancer burden in 2022. Available at: https://gco.iarc.who.int/today/.

3. Langley RR, Fidler IJ. Tumor cell-organ microenvironment interactions in the pathogenesis of cancer metastasis. Endocr Rev 2007; 28: 297-321.
4. Riihimäki M, Hemminki A, Fallah M, Thomsen H, Sundquist K, Sundquist J, Hemminki K. Metastatic sites and survival in lung cancer. Lung Cancer 2014; 86: 78-84.
5. Villano JL, Durbin EB, Normandeau C, Thakkar JP, Moirangthem V, Davis FG. Incidence of brain metastasis at initial presentation of lung cancer. Neuro Oncol 2015; 17: 122-128.
6. Wu S, Pan Y, Mao Y, Chen Y, He Y. Current progress and mechanisms of bone metastasis in lung cancer: a narrative review. Transl Lung Cancer Res 2021; 10: 439.
7. Kuchuk M, Kuchuk I, Sabri E, Hutton B, Clemons M, Wheatley-Price P. The incidence and clinical impact of bone metastases in non-small cell lung cancer. Lung Cancer 2015; 89: 197-202.
8. Waqar SN, Samson PP, Robinson CG, Bradley J, Devarakonda S, Du L, Govindan R, Gao F. Non-small-cell lung cancer with brain metastasis at presentation. Clin Lung Cancer 2018; 19: e373-e379.
9. Serlin Y, Shelef I, Knyazer B, Friedman A. Anatomy and physiology of the blood-brain barrier. Semin Cell Dev Biol 2015; 38: 2-6.
10. Neumaier F, Zlatopolskiy BD, Neumaier B. Drug penetration into the central nervous system: pharmacokinetic concepts and in vitro model systems. Pharmaceutics 2021; 13: 1542.
11. Gaudino S, Martucci V, D'Amico A, Visconti E, Russo R, Ragozzino A, Bianchi M, Colosimo C. Magnetic resonance imaging of solitary brain metastases: main findings of nonmorphological sequences. Radiol Med 2012; 117: 1225-1241.
12. Yousefi M, Bahrami T, Salmaninejad A, Nosrati R, Ghaffari P, Ghaffari SH. Lung cancer-associated brain metastasis: molecular mechanisms and therapeutic options. Cell Oncol (Dordr) 2017; 40: 419-441.
13. Wang Y, Jiang T, Xu X, Zhou Q, Wang Z, Jingbo W, Su C, Ren S, Chen X, Zhou C. Tumor immune microenvironment and immunotherapy in brain metastasis from non-small cell lung cancer. Front Immunol 2022; 13: 829451.
14. Remon J, Besse B. Brain metastases in oncogene-addicted non-small cell lung cancer patients: incidence and treatment. Front Oncol 2018; 8: 88.
15. Sun DS, Liu XE, Zhang YH, Wang HJ, Qin QY, Wang J, Yu H, Zhou JY. A systematic review of risk factors for brain metastases and value of prophylactic cranial irradiation in non-small cell lung cancer. Asian Pac J Cancer Prev 2014; 15: 1233-1239.
16. Ding X, Dai H, Hui Z, Ji W, Liang J, Jiang S, Wang L, Zhou Z. Risk factors of brain metastases in completely resected pathological stage IIIA-N2 non-small cell lung cancer. Radiat Oncol 2012; 7: 119.
17. Robnett TJ, Machtay M, Stevenson JP, Algazy KM, Hahn SM. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. J Clin Oncol 2001; 19: 1344-1349.
18. Ceresoli GL, Reni M, Chiesa G, Carretta A, Schipani S, Passoni P, Bonfanti G, De Vincenzo F, Villa E. Brain metastases in locally advanced nonsmall cell lung carcinoma after multimodality treatment: risk factors analysis. Cancer 2002; 95: 605-612.
19. Schouten LJ, Rutten J, Huveneers HAM, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer 2002; 94: 2698-2705.
20. Carolan H, Sun AY, Bezjak A, Yi QL, Payne D, Kane G, Lauchlan D, Laperriere N. Does the incidence and outcome of brain metastases in locally advanced non-small cell lung cancer justify prophylactic cranial irradiation or early detection? Lung Cancer 2005; 49: 109-115.
21. Ji Z, Bi N, Wang J, Hui Z, Xiao Z, Feng Q, Shi X, Wang L, Wang R, Liang J. Risk factors for brain metastases in locally advanced non-small cell lung cancer with definitive chest radiation. Int J Radiat Oncol Biol Phys 2014; 89: 330-337.
22. An N, Chen P, Wei X, Guo W, Li C, Xie C, Mao D, Jiang B. Risk factors for brain metastases in patients with non-small-cell lung cancer. Cancer Med 2018; 7: 6357.
23. Jain A, Liu D, Chan J, Bitting RL, Wolfe K, Tagawa ST, Zeidan AM, Borgia J, Scher HI, Fossella F, Pao W, Hoang T, Lynch TJ, Halmos B, Kris MG, Miller VA. Impact of smoking and brain metastasis on outcomes of advanced EGFR mutation lung adenocarcinoma patients treated with first line epidermal growth factor receptor tyrosine kinase inhibitors. PLoS One 2015; 10: e0123587.
24. Dimitropoulos C, Hillas G, Trigonis I, Nikoloutsou A, Tsirigoti L, Rasidakis A, Mazarakis N. Prophylactic cranial irradiation in non-small cell lung cancer patients: who might be the candidates? Cancer Manag Res 2011; 3: 287-294.
25. Ceresoli GL, Reni M, Chiesa G, Carretta A, Schipani S, Passoni P, Bonfanti G, De Vincenzo F, Villa E. Brain metastases in locally advanced nonsmall cell lung carcinoma after multimodality treatment: risk factors analysis. Cancer 2002; 95: 605-612.
26. Wang X, Zhao J, Liu T, Qu X, Liu F, Zhang Y. Patterns of extrathoracic metastases in different histological types of lung cancer. Front Oncol 2020; 10: 715.
27. Matsumoto S, Takahashi K, Iwakawa R, Matsuno Y, Nakanishi Y, Kohno T, Yokota J, Hioki K, Mizuno H, Kondo H. Frequent EGFR mutations in brain metastases of lung adenocarcinoma. Int J Cancer 2006; 119: 1491-1494.
28. Gow CH, Chang YL, Hsu YC, Tsai MF, Wu CT, Yu CJ, Shih JY, Yang CH, Chang YC, Chen KC, Shih JY, Yang PC. Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naive non-small-cell lung cancer. Ann Oncol 2009; 20: 696-702.
29. Li Z, Lu J, Zhao Y, Guo H. The retrospective analysis of the frequency of EGFR mutations and the efficacy of gefitinib in NSCLC patients with brain metastasis. J Clin Oncol 2011; 29: e18065.
30. Eichler AF, Kahle KT, Wang DL, Joshi VA, Willers H, Engelman JA, Sequist LV, Loefler JS, Jain RK. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. Neuro Oncol 2010; 12: 1193-1199.
31. Hanibuchi M, Kim SJ, Fidler IJ, Nishioka Y. The molecular biology of lung cancer brain metastasis: an overview of current comprehensions and future perspectives. J Med Invest 2014; 61: 241-253.
32. Sousa S, Clézardin P. Bone-targeted therapies in cancer-induced bone disease. Calcif Tissue Int 2018; 102: 227-250.
33. Sceneay J, Smyth MJ, Möller A. The pre-metastatic niche: finding common ground. Cancer Metastasis Rev 2013; 32: 449-464.
34. Meng F, Wu G. The rejuvenated scenario of epithelial-mesenchymal transition (EMT) and cancer metastasis. Cancer Metastasis Rev 2012; 31: 455-467.
35. Lee JH, Kim D, Oh SH, Kwak C, Jung C, Oh YT, Chang SG, Kim IH, Cho CJ, Park S. CXCL10 promotes osteolytic bone metastasis by enhancing cancer outgrowth and osteoclastogenesis. Cancer Res 2012; 72: 3175-3186.
36. Saidak Z, Mentaverri R, Brown EM. Extracellular calcium promotes the migration of breast cancer cells through the activation of the calcium sensing receptor. Exp Cell Res 2009; 315: 2072-2080.
37. Ryan C, McNicholas D, McCabe A, Cousins G, Ryan C. Epidemiology of bone metastases. Bone 2022; 158: 115783.

38. Huang JF, Shen J, Li X, Rengan R, Morris J, Beasley GM, Salama AKS, Hwang ES, Moschos SJ, Yin DT, Anders CK, Carey LA, Dees EC, Ewend MG, Graham DW. Incidence of patients with bone metastases at diagnosis of solid tumors in adults: a large population-based study. Ann Transl Med 2020; 8: 482.
39. Da Silva LM, Da Silva GT, Bergmann A, Costa GJ, Zamboni MM, Santos Thuler LC. Impact of different patterns of metastasis in non-small-cell lung cancer patients. Future Oncol 2021; 17: 775-782.
40. Chambard L, Girard N, Ollier E, Rousseau C, Fervers B, Pérol D. Bone, muscle, and metabolic parameters predict survival in patients with synchronous bone metastases from lung cancers. Bone 2018; 108: 202-209.
41. Landi L, Cappuzzo F, Raphael J, Banna G, Massari F, Ferrara R, Capelletto E, De Toma A, Caglevic C, Di Costanzo G, Horn L, Gridelli C, Novello S. Bone metastases and immunotherapy in patients with advanced non-small-cell lung cancer. J Immunother Cancer 2019; 7: 79.
42. Shan Q, Li X, Zhang Q, Yan L, Zheng W, Zhao J, Dai X, Zhang H, Deng Q. Tumor primary location may affect metastasis pattern for patients with stage IV NSCLC: a population-based study. J Oncol 2020; 2020: 4784701.
43. Oliveira MB, de Q. Mello FC, Paschoal MEM. The relationship between lung cancer histology and the clinicopathological characteristics of bone metastases. Lung Cancer 2016; 96: 19-24.
44. Na II, Park JH, Choe DH, Lee JK, Koh JS. Association of epidermal growth factor receptor mutations with metastatic presentations in non-small cell lung cancer. ISRN Oncol 2011; 2011: 756265.