J Surg Med. 2020;4(11):965-969.
DOI: 10.28982/josam.804514

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

The effect of bone metastases on survival in lung cancer

Akciğer kanserinde kemik metastazlarının sağkalıma etkisi

Suphi Aydın [1], Aydın Balcı [2]

[1] Afyonkarahisar Health Sciences University, Department of Thoracic Surgery, Afyonkarahisar, Turkey
[2] Afyonkarahisar Health Sciences University, Department of pulmonology, Afyonkarahisar, Turkey

ORCID ID of the author(s)

SA: 0000 0003 2102 0484
AB: 0000 0002 6723 2418

Corresponding author / Sorumlu yazar:
Suphi Aydın
Address / Adres: Afyonkarahisar Sağlık Bilimleri Üniversitesi Göğüs Cerrahisi Kliniği, Afyonkarahisar, Türkiye
E-mail: dr_suphi@hotmail.com

Ethics Committee Approval: Ethics committee approval was obtained from Afyonkarahisar Health Sciences University on 7/3/2020 with the number 2020/303. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Afyonkarahisar Sağlık Bilimleri Üniversitesi 03.07.2020 tarih ve 2020/303 tarihli kararı ile etik kurul onayı alınmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

Abstract

Aim: The most common sites of distant metastasis in lung cancers are bones. In our study, we aimed to investigate the incidence of bone metastasis in lung cancers, and the effects of single and multiple bone metastases on survival. We conducted such a study to contribute to the literature due to the small number of studies on this subject.

Methods: Lung cancer patients diagnosed with bone metastases in our hospital between January 2012-December 2018 were identified. A total of 103 (60.59%) patients with single bone metastasis, and 67 (39.41%) patients with multiple bone metastases were included in the study. Patients' demographic characteristics, symptoms, radiological findings, diagnostic methods, histological subtypes, survival, biochemistry values, tumor markers were analyzed retrospectively according to single and multiple bone metastases. A cohort study was conducted, and the results were presented as mean and standard deviation for continuous variables, and percentage for categorical variables.

Results: Among the 170 patients included in the study, 147 (86.5%) were male, and 23 (13.5%) were female. The overall mean age of the patients was 64.32 (9.965) years. The most common symptom was dyspnea, reported by 58 (34.1%) patients. Bronchoscopic biopsy was most used for diagnosis, in 116 (68.2%) patients. Among patients with adenocarcinoma, squamous cell carcinoma, and small cell lung carcinoma, the number of those with single and multiple bone metastases were 44 (55%) and 36 (45%), 37 (75.5%) and 12 (24.5%), and 22 (53.7%) and 19 (46.3%), respectively. Vertebrae were the most common site of metastasis in single bone metastases. The mean survival times of adenocarcinoma, squamous cell carcinoma, and small cell lung carcinoma patients with single and multiple bone metastases were 14.93 (11.8) and 13.03 (9.32), 15.55 (9.41) and 9.42 (5.744), and 10.55 (8.32) and 8.79 (4.171) months, respectively.

Conclusion: No significant differences were detected in terms of survival between adenocarcinoma and small cell lung cancer patients with single and multiple bone metastases. However, multiple bone metastases were observed to significantly decrease survival in squamous cell carcinoma.

Keywords: Lung cancer, Histological subtypes, Metastasis, Survival

Öz

Amaç: Akciğer kanserlerinde en sık uzak metastaz yerleri kemiklerdir. Çalışmamızda akciğer kanserlerinin kemik metastazı insidansını, tek ve multıpl kemik metastazlarının sağkalıma etkisini araştırmayı amaçladık. Bu konudaki çalışmaların az olması nedeniyle literatüre katkı sağlamak amacıyla böyle bir çalışma yaptık.

Yöntem: Ocak 2012-Aralık 2018 yılları arasında kemik metastazı yapmış akciğer kanseri hastaları tespit edildi. Tek kemik metastazı tespit edilen 103(%60.59), multipl kemik metastazı tespit edilen 67(%39,41) hasta çalışmaya alındı. Hastaların demografik özellikleri, semptomları, radyolojik bulguları, tanı yöntemleri, histolojik alt tipleri, tek ve multıpl kemik metastazlarına göre sağkalım, biyokimya değerleri, tümör markırları retrospektif incelendi. Kohort çalışması yapıldı, sürekli değişkenler için ortalama, standart sapmaya, kategorik değişkenler için yüzdeye göre analizi yapıldı.

Bulgular: Çalışmaya 147 (%86,5)'si erkek, 23 (%13,5)'ü kadın 170 hasta dahil edildi. Yaş ortalaması 64,32(9,965) idi. En sık semptom 58 (%34,1) hastada izlenen dispneydi. Tanıda 116 (%68,2) hasta ile en sık bronkoskopik biyopsi kullanılmıştı. 80 hastada adenokarsinoma (44 (%55) hastada tek kemikte, 36 (%45) hastada multıpl kemikte metastaz), 49 hastada skuamöz hücreli karsinoma (37 (%75,51) hastada tek kemikte, 12 (%24,49) hastada multıpl kemikte metastaz), 41 hastada küçük hücreli akciğer karsinomu (22 (%53,65) hastada tek kemikte, 19 (%46,35) hastada multıpl kemikte metastaz) izlendi. Tek kemik metastazlarında en sık metastaz yeri vertebralardı. Adenokarsinomada tek kemik metastazlarında sağkalım (ay) 14,93 (11,795), multıpl kemik metastazlarında sağkalım (ay) 13,03 (9,321), squamöz hücreli karsinomada tek kemik metastazlarında sağkalım (ay) 15,55 (9,414), multıpl kemik metastazlarında sağkalım (ay) 9,42 (5,744), küçük hücreli akciğer karsinomunda tek kemik metastazlarında sağkalım (ay) 10,55 (8,319), multıpl kemik metastazlarında sağkalım (ay) 8,79 (4,171) idi.

Sonuç: Adenokarsinom ve küçük hücreli akciğer kanserlerinde tek kemik metastazı ile multıpl kemik metastazı arasında sağkalım açısından fark izlenmezken, skuamöz hücreli karsinomada multıpl kemik metastazlarının sağkalımı anlamlı derecede azalttığı izlendi.

Anahtar kelimeler: Akciğer kanseri, Histolojik alt tip, Metastaz, Sağkalım

How to cite/Atıf için: Aydın S, Balcı A. The effect of bone metastases on survival in lung cancer. J Surg Med. 2020;4(11):965-969.

Introduction

Lung cancer is the most diagnosed cancer among males. It is the leading cause of cancer-related deaths in developed and less developed countries. Non-small cell lung cancer (NSCLC) is the most common type, accounting for 80% [1].

Bones are the third most common place of metastasis in all cancer types [2]. Bone metastasis is one of the late-stage common complications of malignant tumors. It can be seen in all types of cancer, especially breast, prostate, and lung cancers [3].

In lung cancers, bones are the most common and earliest metastatic sites. Bone metastasis develops in 30-40% of lung cancer patients [4]. Lung cancer is responsible for 30-70% of bone metastases. Bone metastasis is present in 20-30% of patients with lung cancer at the time of diagnosis [5].

There are many factors affecting bone metastasis in lung cancer, including age, gender, number of primary lesions, histological subtypes, serum markers, and treatment regimens [5].

Bone metastases are often painful and cause serious morbidity [6]. Pain is caused by the release of cytokines and chemical mediators that stimulate the periosteum and bone, and the mechanical stress of the tumor tissue in osteolytic lesions [5]. It may cause pathological fractures in bones, skeletal system problems, spinal cord compression, and hypocalcemia [7].

Currently, studies on the relationship between primary lung cancers and bone metastases and the effect of bone metastases on survival are rare. Median survival has been reported to vary between 12 and 33 months in patients with prostate, breast, and kidney cancers with bone metastasis [8], while the 1-year survival rate in lung cancers is between 9.5% and 12% [9]. As the time between the time of diagnosis and the time of metastasis development increases, the survival time increases [10].

Materials and methods

Patients diagnosed with lung cancer in our hospital between 1 January 2012-31 December 2018 were retrospectively analyzed. Patients with multiorgan and non-bone tissue metastases, along with those without metastases were excluded, and patients with single or multiple bone metastases were included in the study.

Clinical and demographic data were extracted from physical and electronic medical records. The patients' ages, genders, symptoms, diagnostic methods used, pathology results (histological types), radiological findings and reports, metastasis locations, smoking statuses, other accompanying lung diseases and whether there was a family history of cancer were noted. Active smokers were classified as "smokers" (currently smoking), those who smoked but quit were "ex-smokers" and those who never smoked were "nonsmokers."

Among laboratory values, erythrocyte sedimentation rate, C-reactive protein (CRP), albumin, total protein, Alkaline Phosphatase (ALP), Calcium (ca), and Lactate Dehydrogenase (LDH) levels were recorded.

Cancer markers of the patients were examined. The levels of carcinoembryonic antigen (CEA), CA 19-9 and CA 125 were noted.

Information on imaging methods such as chest radiography, thoracic computed tomography (CT), brain CT, abdominal CT, abdominal ultrasonography (USG), positron emission tomography (PET-CT) and bone scintigraphy were evaluated. Staging was performed with TNM classification according to The World Health Organization (WHO) staging criteria. Histological subtypes were classified according to the International Classification of Diseases for Oncology, 3rd Edition.

The treatment group was classified into chemotherapy, radiotherapy, and combined therapy (chemotherapy + radiotherapy).

The performances of the patients were determined according to the criteria of the Eastern Cooperative Oncology Group (ECOG), as follows: 0: Carries on with normal activities, 1: Has symptoms of the disease, but can walk and perform daily activities, 2: Is out of bed more than 50% of their time, sometimes needs help. 3: In bed more than 50% of the time, needs someone's care, 4: Fully bedridden; hospitalization may be required.

The most frequent site of metastasis, the histological subtypes, and mean survival times were compared between patients with single and multiple bone metastases.

Statistical analysis

Kaplan-Meier method was used to evaluate the monthly survival outcomes in lung cancers with bone metastases. SPSS v20 program was used for statistical analysis to evaluate the data obtained in this study. Data were presented as mean, standard deviation, number of persons and percentages. Compliance of quantitative data to normal distribution were evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson's chi-square and Fisher's exact tests were used to compare qualitative data. $P<0.05$ was considered statistically significant.

Results

A total of 170 patients who were diagnosed with lung cancer in our clinic between January 2012 and December 2018 and found to have bone metastases were included in the study. The mean age of the patients was 64.32 (9.965) years. There were 147 (86.5%) males and 23 (13.5%) females. Among them, 65 (38.2%) were active smokers, 78 (45.9%) were ex-smokers, 26 (15.3%) were non-smokers. The average pack-year rate was 43.21 (16.248). Lung cancer was accompanied by other lung diseases such as asthma and chronic obstructive pulmonary disease in 105 (61.8%) of the patients. There was a family history of cancer in 64 (38.8%) patients. In terms of performance scores, thirty-six patients (21.2%) were ECOG 0, 58 (34.1%) patients were ECOG 1, 52 (30.6%) patients, ECOG 2, 16 (9.4%) patients, ECOG 3, and 8 (4.6%) patients were identified as ECOG 4 (Table 1).

The most common symptom was dyspnea, seen in 58 (34.1%) patients. Other symptoms included cough in 45 (26.6%) patients, chest pain in 36 (21.1%) patients, musculoskeletal pain in 18 (10.6%) patients, and hoarseness in 7 (4.1%) patients. Hemoptysis was observed in 6 (3.5%) (Figure 1).

In radiological examinations and reports, the most common finding was a primary cancer mass and nodule appearance in 106 (62.4) patients. This was followed by hilar

fullness in 21 (12.4%) patients, effusion in 20 (11.8%), consolidation in 14 (8.2%), atelectasis in 5 (2.9%), and cavity in 4 (2.4%).

The tumors were in the right upper lobe in 41 (24.1%) patients, the left upper lobe in 41 (24.1%) patients, the right lower lobe in 36 (21.8%) patients, the right middle lobe in 16 (9.4%) patients, and the left lower lobe in 18 (10.6%). Primary site could not be determined in 18 (10.6%) patients (Figure 2).

Table 1: Demographic characteristics of the patients

	n	%
Total Patients	170	100
Gender		
Male	147	86.5
Female	23	13.5
Smoking		
Active Smoker	65	38.2
Exmoker	78	45.9
Nonsmoker	26	15.3
Other Lung Diseases		
Yes	105	61.8
No	65	38.2
Cancer History in The Family		
Yes	64	38.8
No	106	61.2
ECOG		
0	36	21.2
1	58	34.1
2	52	30.6
3	16	9.4
4	8	4.6

ECOG Score: Eastern Cooperative Oncology Group Performance Score

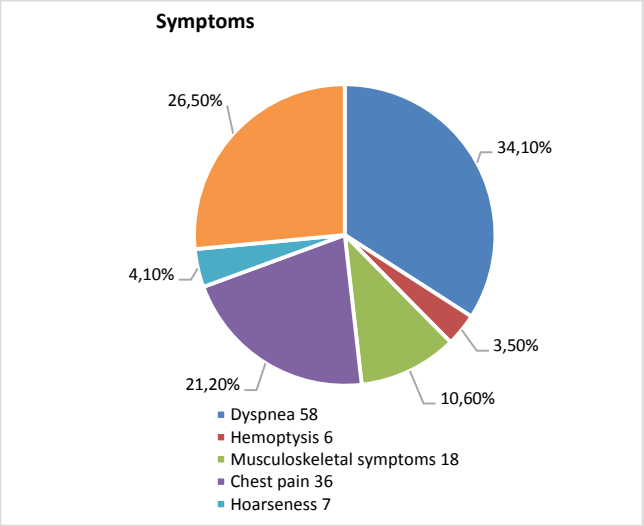

Figure 1: Patients' symptoms

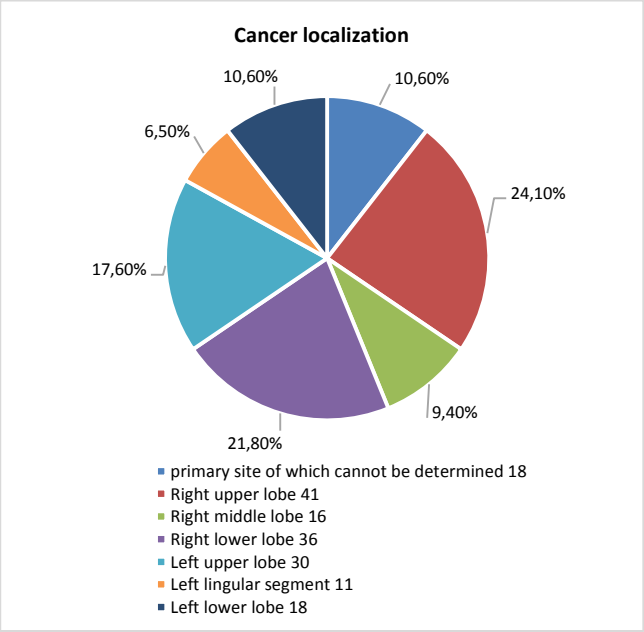

Figure 2: Cancer localizations

In 116 (68.2%) of the patients, biopsy was obtained with bronchoscopy, in 31 (18.2%), with transthoracic fine needle aspiration biopsy (TTIAB), and in 17 (10%), with other methods (cytology, mediastinoscopy-guided biopsy, Video Assisted Thoracic Surgery (VATS), biopsies taken from peripheral lymph nodes and metastatic lesions). Six (3.5%) were diagnosed with closed pleural biopsy.

When the laboratory data of the patients were examined, it was found that calcium levels of patients with squamous cell carcinoma were higher than those with adenocarcinoma and small cell lung carcinoma (P<0.001), and CEA levels were higher in those with adenocarcinoma (P=0.013). There were no significant differences between the groups in terms of LDH, ALP, total protein, sedimentation rate, CRP, albumin, Ca 19-9, Ca 125 levels (Table 2).

Table 2: Laboratory findings

	Squamous cell carcinoma	Adenocarcinoma	Small cell lung carcinoma	Total	*P*-value
LDH(U/L)	343(62-6161)	440(46-5104)	460(38-2603)	416(38-6161)	0.054
ALP(U/L)	102(51-733)	113(0-1319)	94(0-931)	100(0-1319)	0.585
*Ca(mg/dL)	9.35 (1.85)	8.29 (19.4)	8.15 (18.8)	8.57 (1.43)	<0.001
Total protein(g/dL)	6.29(0.57-61.60)	5.83(2.98-75.40)	6.06(3.57-76.10)	6.1(0.57-76.1)	0.800
*Sedimentation rate (mm/h)	65.97 (31.18)	58.77 (37.57)	54.26 (35.6)	59.79 (35.41)	0.341
CRP (mg/L)	9.89(0.23-46.20)	8.19(0.13-46.50)	7.13(0.03-35.90)	8.1(0.13-46.50)	0.113
CEA (ng/dL)	4.26(0.5-1000)	9.37(1.38-2393)	3.71(0,62-645)	4.81(0.5-2393)	0.013
Ca 19-9(U/mL)	17.13(0.6-832)	12.76(0-8425)	18.23(1.58-1969)	15.41(0-8425)	0.467
Ca 125(U/mL)	21.17(7.57-1154)	50.54(5.37-765.7)	21.44(15.91-28.72)	28.72(5.37-1154)	0.442
*Albumin (g/dL)	2.92 (0.67)	2.86 (0.68)	3.02 (0.82)	2.81 (1.17)	0.528

LDH: Lactate dehydrogenase, ALP: Alkaline phosphatase, ca: calcium, CRP: C-Reactive Protein, CEA: Carcinoembryonic Antigen, * mean (standard deviation)

Among those with bone metastases, the most common histological subtype was adenocarcinoma with 80 patients (47.06%), followed by squamous cell carcinoma (n=49, 28.82%), and small cell lung carcinoma (n=41, 24.12%). The most common type causing multiple bone metastases was adenocarcinoma with 36 (53.73%) patients, followed by small cell lung carcinoma with 19 (28.36%) patients and squamous cell carcinoma with 12 (17.91%) patients.

In all lung cancer types which cause bone metastasis, the most common site of metastasis was the vertebrae with 52 (30.58%) patients. The most common cancer type causing single bone metastasis was adenocarcinoma with 24 (30%) patients. This was followed by squamous cell carcinoma with 17 (34.69%) patients and small cell lung carcinoma with 11 (26.82%) patients. Multiple bone metastases were observed in 36 (45%) patients with adenocarcinoma, 19 (46.34%) patients with small cell lung carcinoma with and 12 (24.48%) patients with squamous cell carcinoma (Table 3).

In terms of treatment, 70 patients received chemotherapy, 3 received radiotherapy, 97 received combined therapy (chemotherapy and radiotherapy) and 24 received bisphosphonates.

The mean survival times of adenocarcinoma, squamous cell carcinoma, and small cell lung carcinoma patients with single and multiple bone metastases were 14.93 (11.8) and 13.03 (9.32), 15.55 (9.41) and 9.42 (5.744), and 10.55 (8.32) and 8.79 (4.171) months, respectively (Figures 3, 4). Single and multiple bone metastases were observed to significantly affect survival in squamous cell carcinoma (P=0.013). The overall survival of patients with adenocarcinoma, squamous cell carcinoma, and

small cell lung carcinoma were 14.07 (10.71), 13.91 (8.96), and 9.73 (6.70) months, respectively (Table 4).

Table 3: Bone metastasis locations in lung cancers according to histological subtypes

	Single bone metastasis					Multiple bone metastasis	Total
Histological subtype	Spine	Skull	Bones of limbs	Thoracic wall	Pelvis		
Squamous cell carcinoma n (%)	17(34.6)	2(4.08)	6(12.24)	10(20.40)	2(4.08)	12(24.49)	49(100)
Adenocarcinoma n (%)	24(30)	2(2.5)	4(5)	9(11.25)	5(6.2)	36(45)	80(100)
Small cell lung carcinoma n (%)	11(26.8)	1(2.43)	3(7.31)	5(12.19)	2(4.87)	19(46,34)	41(100)
Total n (%)	52(30.5)	5(2.9)	13(7.6)	24(14.11)	9(5.29)	67(39.4)	170(100)

Table 4: Survival by histological subtype and bone metastasis status

Histological subtype	Survival (month)	Single bone metastasis survival (month)	Multiple bone metastasis survival (months)	*P*-value*
Squamous cell carcinoma n (%)	13.91(8.957)	15.55(9.414)	9.42(5.744)	0.013
Adenocarcinoma n (%)	14.07(10.717)	14.93(11.795)	13.03(9.321)	0.365
Small cell lung carcinoma n (%)	9.73(6.705)	10.55(8.319)	8.79(4.171)	0.564

*Kaplan-Meier

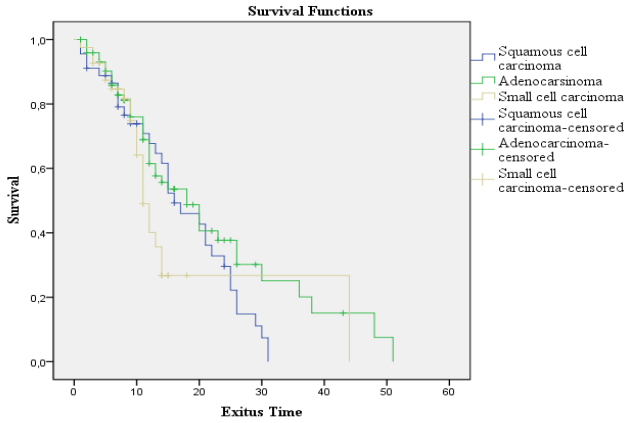

Figure 3: Single bone metastasis survival (month) curve

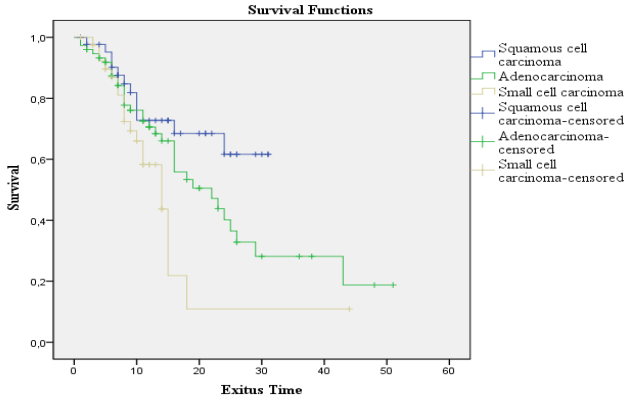

Figure 4: Multiple bone metastasis survival (month) curve

Discussion

Lung cancer is most common in the 40-70 years-age range. Its incidence increases in the 6th and 7th decades. In studies on lung cancers, it was observed that 90% of the cases were male [11].

In our study, the age range was 33-85 years, with an overall mean age of 64.32(9.965) years. A total of 147 (86.5%) patients were male and 23 (13.5%) were female, which were coherent with data reported in the literature.

ECOG performance scores are a measure of general well-being and activities of daily living for cancer patients. Although the ECOG score is used to evaluate the overall survival in cancer patients, it has been found that patients with high ECOG scores show less tolerance to chemotherapy and radiotherapy [12]. ECOG score has been accepted as a prognostic factor for bone metastases in lung cancer [5]. In our study, in terms of performance scores, 36 patients (21.2%) were ECOG 0, 58 (34.1%) patients were ECOG 1, 52 (30.6%) patients, ECOG 2, 16 (9.4%) patients, ECOG 3, and 8 (4.6%) patients were identified as ECOG 4. In the literature, the most common symptoms in lung cancers were dyspnea (3-60%) and cough (8-75%) [13]. In our study, the most common complaints of our patients were dyspnea in 58 (34.1%) patients and cough in 45 (26.5%) patients. These symptoms were followed by chest pain in 36 (21.1%), musculoskeletal pain in 18 (10.6%), hoarseness in 7 (4.1%) and hemoptysis in 6 (3.5%).

According to Bircan et al. [14], the most common locations of primary lung cancers were the right upper lobe (25.3%), left upper lobe (24.1%), right middle lobe (9.2%), right lower lobe (18.4%), left lower lobe (20.7%) and non-localized in 2.3%. In our study, the tumors of 41 (24.1%) patients were in the right upper lobe, 41 (24.1%) patients, in the left upper lobe, 36 (21.8%) patients, in the right lower lobe, 16 (9.4%) patients, in the right middle lobe, and 18 (10.6%) patients, in the left lower lobe. Primary site could not be determined in 18 (10.6%) patients.

Cavitation can be observed in chest radiographs, especially in squamous cell carcinoma, adenocarcinoma, and large cell cancers. It is reported that 16% of lung cancers show cavitation [15]. When the radiological studies and reports of our patients were examined, the most common finding was the appearance of primary cancer mass and nodule in 106 (62.4) patients, followed by hilar fullness in 21 (12.4%) patients, effusion in 20 (11.8%) patients, consolidation in 14 (8.2%) patients, atelectasis in 5 (2.9%) patients, and cavity in 4 (2.4%) patients.

In their study on 168 lung cancer patients, Li Zhang et al. [5] found the overall median survival as 13 months, the rates of 1 and 2-year survivals as 54.3% and 12.9%, respectively, and stated that bone metastases negatively affect survival and prognosis in lung cancer patients.

In our study, the mean survival times in squamous cell carcinoma, adenocarcinoma and small cell lung carcinoma with bone metastases were 13.91 (8.96), 14.07 (10.72) and 9.73 (6.71) months, respectively. We found a statistically significant difference in survival times between squamous cell carcinoma patients with single and multiple bone metastases.

There are publications claiming that the prognosis of adenocarcinoma with multiple bone metastases is worse than those of small cell and squamous cell carcinomas, and that bone metastases are independent prognostic factors in adenocarcinoma [16].

Wang et al. [17] found that adenocarcinomas have a higher incidence of bone metastasis and that the vertebrae are the most common sites of involvement.

In our study, the most common metastasis site in all lung cancer types was the vertebrae and the most common histologic subtype which metastasized to the vertebrae was squamous cell carcinoma, with a rate of 34.69%. This was followed by adenocarcinoma (30%) and small cell lung carcinoma (26.82%). The subtype with the most common multiple bone metastasis was small cell lung carcinoma with a rate of 46.34%, which was followed by adenocarcinoma (45%) and squamous cell carcinoma (24.48%).

In their study, Lee et al. [18] showed that increased serum CEA levels may be an indicator of increased bone metastasis potential in stage IV lung cancers.

Our univariate analysis revealed that the mean calcium level of squamous cell carcinoma patients with bone metastases was 9.35 (1.85) mg/dL and the CEA value of adenocarcinoma patients with bone metastases was 9.37 (1.38-2393) ng/dL, both of which were significantly different compared to the other groups. LDH, ALP, total protein, sedimentation rate, CRP, CA 19-9, CA 125, and albumin values were similar between all groups.

Univariate and multivariate analyses revealed that histological type, clinical stage, ECOG scores, serum ALP levels, and the number of bone metastases were important prognostic factors. Histological subtype in lung cancers is a crucial factor in bone metastases [5].

Limitations

The date of diagnosis was considered as the date the patients were diagnosed with various tests performed in our hospital. Previous symptoms and their durations were unknown. While searching the database, some deficiencies were detected in the proportion of patients with bone metastasis. Most of the lung cancer cases with distant organ metastases had multi-organ metastases and only the cases with bone metastases were included in our study. This caused a decrease in the number of included patients.

Conclusions

Histological subtype and stage of lung cancer are principal factors in bone metastases. Among all histological subtypes, the most common site of metastasis was the vertebrae. In our study, squamous cell carcinoma was the most common subtype with single bone metastases, while adenocarcinoma was most detected in those with multiple bone metastases. The survival times of squamous cell carcinoma patients with single and multiple bone metastases were significantly different. Further studies are required to elucidate the effects of bone metastases on survival in lung cancer patients, as well as its relationship with histological subtypes.

References

1. Niu Y, Lin Y, Pang H, Shen W, Liu L, Zhang H. Risk factors for bone metastasis in patients with primary lung cancer A systematic review. Medicine. 2019;98:3. doi: 10.1097/MD.0000000000014084
2. Ibrahim T, Mercatali L, Amadori D. Bone and cancer: the osteoncology. Clin Cases Miner Bone Metab. 2013;10:121–3.
3. Brodowicz T, O'Byrne K, Manegold C. Bone matters in lung cancer. Ann Oncol. 2012;23:2215-22.
4. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev. 2001;27:165–76.
5. Zhang L, Gong Z. Clinical Characteristics and Prognostic Factors in Bone Metastases from Lung Cancer. Med Sci Monit, 2017;23:4087-94. doi: 10.12659/MSM.902971
6. Svensson E, Christiansen CF, Ulrichsen SP, Rørth MR, Sørensen HT. Survival after bone metastasis by primary cancer type: a Danish population-based cohort study. BMJ Open. 2017;7:e016022. doi:10.1136/bmjopen-2017-016022
7. Husaini H, Wheatley-Price P, Clemons M, Shephered FA. Prevention and management of bone metastases in lung cancer: a review. J Thorac Oncol. 2009;4:251–9.
8. Santoni M, Conti A, Procopio G, Porta C, Ibrahim T, Barni S, et al. Bone metastases in patients with metastatic renal cell carcinoma: are they always associated with poor prognosis? J Exp Clin Cancer Res. 2015;34:10.
9. Santini D, Barni S, Intagliata S, Falcona A, Ferrau F, Galetta D, et al. Natural history of non-small-cell lung cancer with bone metastases. Sci Rep. 2015;5:18670.
10. Cetin K, Christiansen CF, Sværke C, Jacobsen JB, Sørensen HT. Survival in patients with breast cancer with bone metastasis: a Danish population-based cohort study on the prognostic impact of initial stage of disease at breast cancer diagnosis and length of the bone metastasis-free interval. BMJ Open. 2015;5:e007702.
11. Goksel T, Akkoclu A. Patern of lung cancer in Turkey, 1994-1998. Respiration. 2002;69:207-10.
12. De Kock I, Mirhosseini M, Lau F, Thai V, Downing M, Quan H, et al. Conversion of Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Performance Status (ECOG) to Palliative Performance Scale (PPS) and the interchangeability of PPS and KPS in prognostic tools. J Palliat Care. 2013;29:163–9.
13. Beckles MA, Spiro SG, Colice GL, Rudd RM. Initial Evaluation of the patient with lung cancer. Symptoms, signs, laboratory tests, and paraneoplastic syndromes. Chest. 2003;123:97-104.
14. Bircan AH, Öztürk Ö, Şahin Ü, Özaydın N, Akkaya A. Akciğer kanseri tanısı alan olgularımızın Retrospektif değerlendirilmesi. SDÜ Tıp Fak Derg. 2005;2(3):1-6.
15. Balcı P, Altay C. Akciğer Kanserinde Radyolojik Bulgular. turkradyolojiseminerleri.org doi: 10.5152/trs.2014.025
16. Kadota K, Sima CS, Arcila ME, Hedvat C. KRAS Mutation Is a Significant Prognostic Factor in Early-stage Lung Adenocarcinoma. Am J Surg Pathol. 2016;40:1579–90.
17. Wang Z, Ning L, Li H, Yang YM. Clinical observation of percutaneous osteoplasty in the treatment of 92 lung cancer patients with extraspinal bone metastases. Tumor. 2014;34(5):443–9.
18. Lee DS, Kim SJ, Kang JH, Hong SH, Jeon EK, Kim YK, et al. Serum carcinoembryonic antigen levels and the risk of whole-body metastatic potential in advanced non-small cell lung cancer. J Cancer. 2014;5:663–9.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.