

## Research Article

# Laterality of Adrenal Gland Metastasis in Lung Cancer: Results of a Comparative Study

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### Abstract

**Objectives:** The adrenal gland is one of the most common metastatic sites in lung cancer. The anatomical localization and symmetrical nature of the glands provided the concepts of laterality and resectability of adrenal gland metastasis (AGM) in lung cancer. In this trial, we aimed to investigate the clinical features and prognosis specific to ipsilateral AGM and compare them with contralateral AGM in lung cancer patients from a single tertiary center.

**Methods:** Data of 135 lung cancer patients with AGM were retrospectively collected. The patients were divided into two groups as ipsilateral AGM and contralateral AGM. Clinicopathological features and survival outcomes were compared.

**Results:** 57 lung cancer patients (42.2%) had ipsilateral AGM. Isolated AGM was significantly more prevalent in patients with ipsilateral AGM than those with contralateral AGM (29.4% vs. 14.1%;  $p=0.026$ ). Patients with ipsilateral AGM have a survival advantage compared to contralateral AGM (The median OS: 11.6 months vs. 7.8 months;  $p=0.008$ ). In multivariate analysis, ipsilateral AGM had a favorable independent prognostic factor (Hazard Ratio=0.61; %95Confidential interval: 0.40-0.92;  $p=0.018$ ).

**Conclusion:** In patients with lung cancer, ipsilateral AGM is more likely to be isolated and is associated with a better prognosis compared to contralateral AGM.

**Keywords:** Adrenal, laterality, lung cancer, survival, adrenalectomy

**Cite This Article:** Ferhatoglu F, Cagatay T, Okumus G, Aydiner A, Paksoy N, Ak N, et al. Laterality of Adrenal Gland Metastasis in Lung Cancer: Results of a Comparative Study. EJMI 2023;7(2):101–106.

Although lung cancer mortality is decreased due to advances in treatment, it remains the primary cause of cancer-related death.<sup>[1,2]</sup> In 2020, the incidence of lung cancer and cancer-related deaths were 2.2 million and 1.7 million, respectively.<sup>[3]</sup> Lung cancer has three main subgroups: non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and other rare tumors. The five-year survival rate is about 5% in metastatic disease, and 40% of patients are diagnosed with stage IV disease.<sup>[4,5]</sup> The most common distant metastatic sites are the liver (34.3%), adrenal glands

(32.6%), and bones (14.9%).<sup>[6]</sup>

Because adrenal glands are bilateral and potentially resectable, adrenal gland metastasis (AGM) can be evaluated in clinical practice as ipsilateral, contralateral, bilateral, and solitary metastasis. In particular, many studies showed that curative treatments such as radiotherapy to the adrenal gland or adrenalectomy combined with systemic therapy provide better survival when compared with systemic therapy alone in solitary AGM. The overall survival (OS) was 6-9 months in patients who received systemic chemotherapy

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**Submitted Date:** February 02, 2023 **Accepted Date:** March 10, 2023 **Available Online Date:** March 21, 2023

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alone and 9-40 months received curative treatment.<sup>[7-9]</sup> However, these studies have limitations due to the retrospective design, small sample size, and selection bias.

The primary tumor can colonize in specific organs after acquiring the ability of metastasis in a particular stage of their development. Hypothetically, the "seed and soil theory" proposed by Steven Paget in 1889 is one of the most important phenomena explaining cancer cells' preference for a specific tissue.<sup>[10]</sup> According to the theory, the metastatic cell is located in a tissue with an appropriate micro-environment for survival. In recent studies, this process is systematically explained by intravasation (passage into the vessel from the primary organ), extravasation (entry to target tissue of metastasis from vessels), pre-metastatic niche, and macro-metastasis.<sup>[11]</sup> If the lung cancer cells spread to adrenal glands according to "seed and soil theory," it means that ipsilateral and contralateral AGM have the same biological behavior and survival. However, indirect evidence supports that ipsilateral AGM may occur via the lymphatic route, unlike contralateral AGM. In a postmortem study on coal miners, direct passage to the retroperitoneal region from the pulmonary parenchyma via the lymphatic route was demonstrated by the presence of coal dust deposition in the retroperitoneal lymph nodes in 87% of cases.<sup>[12]</sup> In an autopsy study on cadavers of 3827 untreated cancer patients, Disibo G. et al. evaluated the metastasis patterns of primary tumors. The authors showed that distinct primary tumors have specific patterns regarding metastasis region and frequency.<sup>[13]</sup> Based on the study, the mathematical models produced for metastatic lung cancer showed that AGM had a shorter passage time and high passage probability, similar to lymph node metastasis.<sup>[14,15]</sup>

In addition, a limited number of studies showed that ipsilateral AGM occurred more commonly than contralateral AGM at early phases of tumor progression, with fewer distant metastases in other regions.<sup>[7,16,17]</sup> We reviewed the clinicopathological findings of lung cancer cases with AGM in the shed of available literature.

## Methods

We retrospectively reviewed the clinical data of 1461 Turkish-Caucasian patients diagnosed with lung cancer in our oncology department between 13.01.2014 and 03.08.2019. Of the 534 patients (aged  $\geq 18$  years) with a diagnosis of metastatic lung cancer, 135 patients (25.2%) had AGM.

Age, gender, smoking status, and treatment characteristics were extracted from the patients' medical records. The pathological classifications of primary lung tumors were performed in accordance with the 2015 World Health Organization Classification.<sup>[18]</sup> TNM status and primary localiza-

tion (left or right lung) of the tumor were recorded based on pretreatment images. Clinical staging was performed according to the 8<sup>th</sup> edition AJCC/UICC stage classification for the lung cancer system.<sup>[19]</sup> The radiological progression was evaluated with the Response Evaluation Criteria in Solid Tumor 1.1.<sup>[20]</sup>

The AGM was subgrouped based on laterality (ipsilateral or contralateral according to the primary tumor side), solitary or multiple organ involvement, and the timing of metastasis (synchronous or metachronous). *Synchronous metastasis* was defined as the presence of AGM at the time of diagnosis. In contrast, *metachronous metastasis* was defined as a lack of metastasis at the time of diagnosis with AGM development at least six months after diagnosis.<sup>[21]</sup> OS was primarily targeted in the survival analysis. OS was considered the time from the first adrenal metastasis detection to death.

## Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (SPSS Inc, Chicago, Ill). For descriptive statistics, categorical variables are presented as count and percent. Numerical variables are presented as mean, standard deviation, and minimum and maximum values. Proportions in independent groups were analyzed using the Chi-square test. Comparisons of numerical variables in two independent groups were made using the Mann-Whitney U test or Student's t-test. Survival rates were calculated using the Kaplan-Meier analysis. Risk factors were analyzed using Cox regression analysis. The statistical significance level of alpha was accepted as  $p < 0.05$ .

## Results

### Demographic and Clinicopathological Characteristics

One hundred thirty-five lung cancer patients with adrenal metastasis were enrolled in the study. The median age was 59 years (33-87 years), and there was a male preponderance (118 men, 87.4%). The median smoking duration was 44 pack years. In the primary tumors, the most common pathological type was adenocarcinoma (52; 38.5%), followed by unclassified and rare types (34, 25.2%), squamous cell carcinoma (26, 19.3%), and small cell carcinoma (23, 17.0%).

The EGFR, ALK, and ROS-1 mutations were assessed in 42 patients, and it was found that there was EGFR mutation in 3 patients and ROS-1 mutation in one patient. There were 57 patients with ipsilateral AGM (42.2%) and 78 with contralateral AGM (57.8%). The isolated AGM was detected in only 28 patients (20.7%). In patients with multiple organ metastasis, the most common organ accompanied by AGM

was bone (66, 48.9%), followed by the brain (50, 37.6%). The majority of patients had synchronous metastasis (117, 86.5%). There was no significant correlation between AGM laterality and age, gender, smoking, primary tumor pathology, the timing, or other metastatic sites ( $p>0.05$ ). However, ipsilateral AGM was more common than contralateral AGM in cases with isolated AGM (29.4% vs. 14.1%, respectively;  $p=0.026$ ). Table 1 presents the clinicopathological characteristics and distribution of the patients according to AGM laterality.

The majority of patients received platinum-based systemic chemotherapy (67.4%). In addition, 31 patients (23.0%) received palliative treatment alone due to low-performance scores and declination of treatment. Table 2 presents systemic and local therapies. Adrenalectomy plus primary tumor resection was performed on a 57-years-old woman with isolated and ipsilateral AGM. The patient received an adjuvant four cycle of cisplatin/gemcitabine regimen and lived 110 months. Another long-term survival (110 months) was achieved in a patient with SCLC after right pulmonary lobectomy and nephrectomy to the ipsilateral AGM (Table 3).

**Table 2.** Characteristics of local and systemic treatment

Treatment Characteristics	Number of patients	%
Local treatment		
RT to adrenal gland	2	(1.5)
Adrenalectomy	1	(0.7)
Nephrectomy	1	(0.7)
Systemic treatment		
Cisplatin/Gemcitabine	33	(24.4)
Palliative care	31	(23.0)
Paclitaxel/Carboplatin	23	(17.0)
Cisplatin/Etoposide	16	(11.9)
Cisplatin/Pemetrexed	10	(7.4)
Carboplatin/Pemetrexed	4	(3.0)
Carboplatin/Etoposide	3	(2.2)
Erlotinib	3	(2.2)
Gemcitabine/Carboplatin	2	(1.5)
Pemetrexed	2	(1.5)
Crizotinib	1	(7.0)
Gemcitabine	1	(0.7)
Paclitaxel	1	(0.7)
Docetaxel	1	(0.7)

**Table 1.** Comparisons for Patients Depending on Parameters Related to Clinic and pathologic features

	Ipsilateral adrenal gland metastasis		Contralateral adrenal gland metastasis		Total number of patients		p
	N	%	N	%	N	%	
Age	61±1	40-87	58±1	33-84	59±1	33-87	0.777 <sup>a</sup>
Gender							
Male	50	(87,7)	68	(87,2)	118	(87,4)	0.926
Female	7	(12,3)	10	(12,8)	17	(12,6)	
Smoking (Pack-year)	41±3	0±90	46±3	10-100	44±2	0-100	0,459 <sup>a</sup>
Primary tumor pathology							
Adenocarcinoma	24	(42,1)	28	(35,9)	52	(38,5)	0.617
Squamous cell carcinoma	8	(14,0)	18	(23,1)	26	(19,3)	
Unclassified and rare types of NSCLC	15	(26,3)	19	(24,4)	34	(25,2)	
SCLC	10	(17,5)	13	(16,7)	23	(17,0)	
Isolated or multiple metastasis							
Isolated adrenal gland metastases	17	(29,8)	11	(14,1)	28	(20,7)	0.026 <sup>β</sup>
Other distance metastases	40	(70,2)	67	(85,9)	107	(79,3)	
Timing of adrenal gland metastasis							
Synchronous	41	(78,8)	76	(91,6)	117	(86,5)	0.164
Metachronous	11	(21,2)	7	(8,4)	18	(13,5)	
Metastatic Sites							
Contralateral lung	4	(7,0)	12	(15,6)	16	(11,9)	0.137
Bone	23	(40,4)	42	(54,5)	66	(48,9)	0.090
Liver	10	(17,5)	16	(21,1)	26	(19,4)	0.640
Brain	20	(35,7)	30	(39,5)	50	(37,6)	0.703
Other distant metastasis	13	(22,8)	28	(36,4)	42	(31,1)	0,075

NSCLC: Non-small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; <sup>a</sup> analyzed by Student's t-Test; <sup>β</sup> indicates a significant difference.

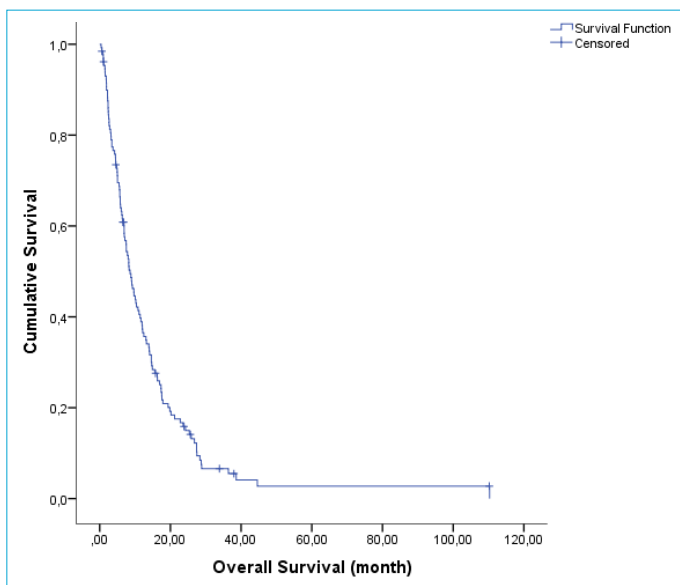
**Table 3.** Clinical characteristics of patients who underwent adrenalectomy and nephrectomy

Gender	Age	Primary tumor pathology	Stage (8 <sup>th</sup> )	Laterality of adrenal metastasis	Timing of adrenal metastasis	Local treatment	Systemic treatments (Cycles)	Survival (mo)
Female	57	Adenocarcinoma	T3N0M0	Ipsilateral	Synchronous	Adrenalectomy	Cisplatin/Gemcitabine (4)	110.3
Male	55	Small cell Lung Cancer	T3N0M1	Ipsilateral	Synchronous	Nephrectomy	Cisplatin/Etoposide (6)	110.2

**Survival and Risk Factors**

The cohort's median OS was 8.5 months (6.9-10.2 months). The 1-, 2- and 5-years survival rates were 38.1%, 15.9%, and 2.7%, respectively (Fig. 1). In survival analysis, primary tumor pathology was a significant factor for OS (p=0.04). The most prolonged median OS was observed in patients with squamous cell carcinoma (13.9 months), followed by SCLC (13.1 months), adenocarcinoma (8.2 months), unclassified and rare types of NSCLC ( 6.2 months).

The median OS was significantly more favorable in patients with ipsilateral AGM than those with contralateral AGM (11.6 months vs. 7.8 months, respectively; p=0.008; Fig. 2). The timing of AGM had no effects on survival (Median OS: 14.6 months vs. 8.2 months in patients with metachronous AGM and synchronous AGM, respectively; p=0.142). Also, no survival advantages were observed in isolated AGM patients (p=0.668). Bone metastasis was determined as another significant parameter for OS. Median OS was 6.2 months in patients with bone metastasis and 11.6 months without bone metastasis (p<0.001). Compared to systemic treatment, palliative treatment had associated with a lower median OS (2.5 months vs. 11.1 months; p<0.001).

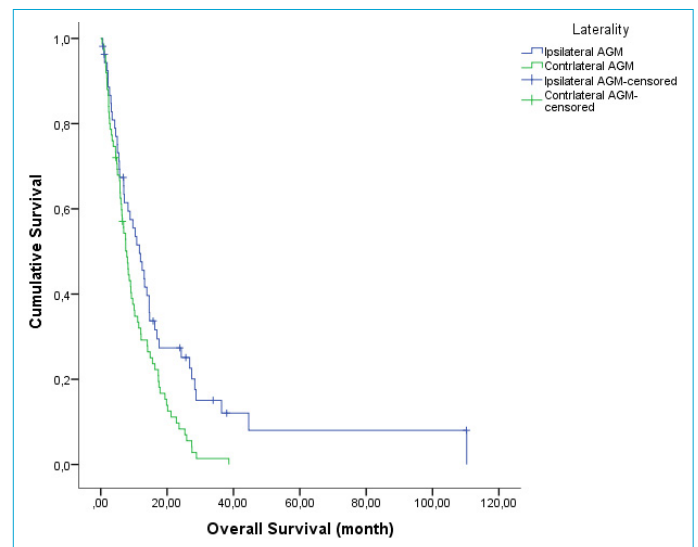


**Figure 1.** The median overall survival was 8.5 months. The 1-, 2- and 5-year survival rates were 38.1%, 15.9%, and 2.7% in the whole study population, respectively.

In multivariate analysis, ipsilateral metastasis and palliative treatment were independent prognostic risk factors. Ipsilateral AGM had favorable effect on OS (Hazard rate [HR]. 0.61; 95% Confidence Interval [CI]: 0.40-0.92; p=0.018) while palliative treatment had negative impact on OS (HR: 3.76; 95% CI: 2.29-6.16; p<0.01) (Table 4).

**Discussion**

We compared demographic, clinicopathological characteristics, and survival rates of ipsilateral and contralateral AGM in 135 lung cancer patients. There was no significant correlation between AGM laterality, age, gender, and smoking. Also, no significant relation was determined between AGM laterality and primary tumor pathology, the timing of AGM, or extra-adrenal metastatic sites. We did not observe a survival difference between patients with synchronous or metachronous AGM (8.2 months vs. 10.6 months; p>0.05). Previous studies addressing the efficacy of adrenalectomy in lung cancer patients with isolated AGM investigated the effects of synchronous and metachronous AGM on survival. In these studies, the number of patients ranged from 37 to 94, and survival was comparable between the



**Figure 2.** Ipsilateral adrenal gland metastasis (AGM) showed better median overall survival compared to contralateral AGM (11.6 months vs. 7.8 months, respectively; P=0.008). The 1-, 2- and 5-year survival rates were 47.6% vs. 32.0%, 27.4% vs. 8.3% and 8.0% vs. 0%.

**Table 4.** Risks features in determining overall survival, multivariate Cox Regression Analysis

	P	HR	95% CI	
Ipsilateral adrenal metastasis	0.018	0.613	0.409	0.920
Palliative treatment	<0.01	3.760	2.291	6.169

CI: Confidential interval; HR: Hazard ratio.

two groups.<sup>[7,17,21]</sup> Despite differences in the design of the studies (including our study), the lack of survival difference between patients with synchronous or metachronous AGM indicates that the timing of AGM does not affect survival.

Isolated AGM was significantly more common in patients with ipsilateral metastasis in our cohort. In a study on cadavers of 405 lung cancer patients with isolated AGM, Karoly P. et al. showed that ipsilateral AGM was significantly more common in the early phases of tumor progression. However, such correlation disappeared with the increasing number of metastasis.<sup>[16]</sup> In another study on the effects of adrenalectomy in NSCLC patients with isolated AGM, the number of patients with ipsilateral AGM was significantly higher than those with contralateral AGM (31 vs. 12;  $p < 0.01$ ).<sup>[17]</sup> These results are consistent with our study, supporting the theory that lung cancer involves the ipsilateral adrenal glands via the lymphatic route in the early phases of tumor progression. These results may support curative therapy options in lung cancer patients with isolated and ipsilateral AGM. Long-term survival benefits can be expected in lung cancer patients with isolated and ipsilateral AGM with curative therapy options.

In our study, it was found that ipsilateral AGM tended to be isolated; in addition, it was an independent prognostic risk factor with a positive effect on survival when compared to contralateral AGM. Thus, the mortality rate was lower among patients with ipsilateral AGM. Among patients with ipsilateral AGM, 1-, 2- and 5-years survival rates were 47.6%, 27.4%, and 8.0%, respectively (Fig. 2). As expected, palliative treatment is an unfavorable prognostic risk factor. Although primary tumor pathology and bone metastasis were prognostic factors in univariate analysis, we found them insignificant in multivariate analysis. In a study on 37 lung cancer patients with isolated AGM, Raj DJ. et al. evaluated the effects of adrenalectomy and systemic treatment on survival. In the study, patients with ipsilateral AGM comprised 35% of both groups. Authors reported that the 5-years survival rate was 34% in patients who underwent surgery while 0% in patients treated with systemic therapy ( $p = 0.002$ ). In the adrenalectomy group, the 5-years survival rates were 83% and 0% in patients with ipsilateral and contralateral AGM, respectively

( $p = 0.003$ ).<sup>[7]</sup> In another study conducted by Porte H. et al., 43 lung cancer patients with isolated AGM underwent adrenalectomy. The authors reported that the median OS was 11 months in the whole cohort and that neither laterality nor the timing of metastasis had an effect on survival.<sup>[17]</sup> Together with available studies, we concluded that systemic therapy alone is insufficient in lung cancer with isolated AGM and that adrenalectomy potentially provides long-term survival. Our study found ipsilateral metastasis as a favorable independent prognostic factor. We observed better OS rates in patients with ipsilateral AGM even when we excluded two patients with ipsilateral AGM who achieved 110 months of survival by adrenalectomy (10.8 months vs. 7.8 months,  $p = 0.034$ ). The lower risk for mortality in ipsilateral AGM may be due to higher rates of isolated AGM, less aggressive biological behavior, and higher chemotherapy susceptibility.

## Conclusion

In our study, the finding that ipsilateral AGM was more frequently seen as an isolated metastasis and a prognostic factor for survival supports the idea that ipsilateral involvement is more common in early tumor progression and has less aggressive potential. Regardless of being synchronous or metachronous, curative methods such as adrenal gland resection or RT may have positive effects on survival. In addition, it should be considered that the positive effect may be higher in tumors with ipsilateral AGM. This study has some limitations, including retrospective design and heterogeneity regarding primary tumor pathology and treatment characteristics. In addition, the limited number of studies on AGM laterality makes it difficult to interpret our results. We must confirm our results in multicenter studies with homogeneous patient groups.

## Disclosures

**Ethics Committee Approval:** Retrospective analyses of clinical data were approved by the Academic Committee of Istanbul University (File no: 2021/1956). The committee had agreed to the retrospective analysis of routinely collected clinical data without prior informed consent of patients.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Funding:** This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

**Authorship Contributions:** Concept – G.O., T.C., N.P.; Design – F.F., G.O., T.C., A.A., P.S.; Supervision – P.S., A.A; Materials – F.F., G.O., T.C., A.A., P.S.; Supervision – P.S., A.A; Data collection & processing – F.F., N.P.; Analysis and interpretation – F.F., N.A., E.A.; Literature search – F.F., N.A., E.A.; Writing – F.F., G.O., T.C.; Critical review – T.C., A.A.

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