

# Different distant metastasis pattern based on tumor size could be found in extensive-stage small cell lung cancer patients: a large population-based study

Jia Li <sup>Equal first author, 1</sup>, Feng Liu <sup>Equal first author, 1</sup>, Zhenxiang Li <sup>2</sup>, Haiyong Wang <sup>Corresp. 3</sup>

<sup>1</sup> Department of Oncology, Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine(TCM), ShangHai, China

<sup>2</sup> Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong Cancer Hospital affiliated to Shandong University, Shandong Academy of Medical Sciences, Jinan, China

<sup>3</sup> Department of internal Medicine-Oncology, Shandong Cancer Hospital and Institute, Shandong Cancer Hospital affiliated to Shandong University, Shandong Academy of Medical Sciences, Jinan, China

Corresponding Author: Haiyong Wang  
Email address: wanghaiyong6688@126.com

**BACKGROUND:** Fewer studies were explored the association between tumor size and the sites of distant metastasis in Extensive-Stage Small cell lung cancer (ES-SCLC).

**PATIENTS AND METHODS:** We used Surveillance, Epidemiology, and End Results (SEER) population-based data to identify 11058 SCLC patients with distant metastatic between 2010 and 2013. Univariate and multivariate Logistic regression analysis were used to demonstrate the association between tumor size and distant metastasis patterns including bone, liver, brain, and lung.

**RESULTS:** Subtle differences could be found in patients with different metastasis pattern based on different tumor size. Interestingly, we found that the tumor size 3-7 was more prone to bone metastasis ( $p = 0.003$ ); tumor size  $\leq 3$  had a significantly greater possibility to develop brain metastasis ( $p < 0.001$ ) and liver metastasis ( $p < 0.001$ ); However, tumor size  $\geq 7$  more likely to develop lung metastasis ( $p = 0.011$ ).

**CONCLUSION:** The difference could be found between tumor size and distant metastasis pattern in ES-SCLC.

**Title:** Different distant metastasis pattern based on tumor size could be found in Extensive-Stage Small Cell Lung Cancer patients: a large population-based study

**Author order:** Jia Li<sup>1#</sup>, Feng Liu<sup>1#</sup>, Zhenxiang Li<sup>2</sup>, Haiyong Wang<sup>3\*</sup>.

**Author affiliations:**

<sup>1</sup>Department of Oncology, Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine(TCM), Shanghai 200032, China.

<sup>2</sup> Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong Cancer Hospital affiliated to Shandong University, Shandong Academy of Medical Sciences, Jinan 250117, China.

<sup>3</sup>Department of internal Medicine-Oncology, Shandong Cancer Hospital and Institute, Shandong Cancer Hospital affiliated to Shandong University, Shandong Academy of Medical Sciences, Jinan 250117, China.

**#Authors contributed equally to this work. Jia Li and Feng Liu are first authors and contributed equally to this work.**

**\*Corresponding authors:**

Haiyong Wang

Department of internal Medicine-Oncology, Shandong Cancer Hospital and Institute, Shandong Cancer Hospital affiliated to Shandong University, Shandong Academy of Medical Sciences, Jinan 250117, China.

Tel: 860531-67626332; Fax: 86531-67626332;

E-mail: [wanghaiyong6688@126.com](mailto:wanghaiyong6688@126.com)

Running title: the relationship between tumor size and distant metastasis pattern

**Conflicts of interest:** All the authors have no conflicts of interest to declare.

**Acknowledgments:** We would like to thank the staff members of the National Cancer Institute and their

colleagues across the United States and at Information Management Services, Inc., who have been involved with the Surveillance, Epidemiology and End Results (SEER) Program.

# **ABSTRACT:**

**BACKGROUND:** Fewer studies were explored the association between tumor size and the sites of distant metastasis in Extensive-Stage Small cell lung cancer (ES-SCLC).

**PATIENTS AND METHODS:** We used Surveillance, Epidemiology, and End Results (SEER) population-based data to identify 11058 SCLC patients with distant metastatic between 2010 and 2013. Univariate and multivariate Logistic regression analysis were used to demonstrate the association between tumor size and distant metastasis patterns including bone, liver, brain, and lung.

**RESULTS:** Subtle differences could be found in patients with different metastasis pattern based on different tumor size. Interestingly, we found that the tumor size 3-7 was more prone to bone metastasis ( $p = 0.003$ ); tumor size  $\leq 3$  had a significantly greater possibility to develop brain metastasis ( $p < 0.001$ ) and liver metastasis ( $p < 0.001$ ); However, tumor size  $\geq 7$  more likely to develop lung metastasis ( $p = 0.011$ ).

**CONCLUSION:** The difference could be found between tumor size and distant metastasis pattern in ES-SCLC.

**KEYWORDS:** small cell lung cancer; tumor size; metastatic sites.

# **Introduction**

Small-cell lung cancer (SCLC) is one of the most aggressive malignancies, making up 14% of lung cancer overall, with approximately 31,000 patients diagnosed annually in the United states [1]. Small cell lung cancer has many metastatic sites, of which bone, brain, liver and lung metastases are the most common[2-3]. There are also many factors affecting the metastasis of small cell lung cancer, such as tumor size, lymph node

involvement, functional status and gender[4].However, our understanding of the relationship between clinically relevant factors and patterns of distant metastasis is indeed limited.Even fewer studies were explored about the association between tumor size and the sites of distant metastasis.Progress in the treatment of SCLC has been lagged significantly behind Non-small cell lung cancer(NSCLC) and other cancers in the development of molecular profiling and targeted therapy[5].Increasing the understanding of metastatic sites by assessing clinically relevant factors, such as tumor size, has implications for the treatment of cancer patients. In this study, using a database of Surveillance, Epidemiology, and End Results (SEER)-registered, we evaluated the effects of several clinical features on the metastasis distribution in ES-SCLC.Importantly, we mainly analyzed the relationships between the tumor size and the exact distant metastasis patterns.

## Methods

### Patient selection

The current study data were obtained from the SEER registry of the US National Cancer Institute [6].The SEER database covers approximately one-quarter of cancer patients in the United States and is constantly revising the data.The SEER\*Stat software (SEER\*Stat 8.3.5) was used to identify and screen the appropriate patients.Through this software, we selected ES-SCLC patients between 2010 and 2013.The pathological diagnosis is strict and there is only one primary tumor. They should have specific metastatic sites, including at least the lung, liver, brain and bone. Patients lacking information about variables, including age, race, gender, tumor size, AJCC staging N, and metastatic patterns were excluded.

### Ethics statement

This study was in line with the Helsinki Declaration and approved by the Ethics Committee of the Shandong Cancer Hospital. This study was based on the SEER database and did not involve personal privacy information,

so no informed consent is required.

## Statistical analysis

The following variables (age, race, gender, tumor size, N-stage and metastatic site) were included in univariate and multivariate logistic regression analysis to analyze the association between clinically relevant factors and specific metastatic patterns. Univariate and multivariate logistic regression models were used to assess the comparative risk of metastasis. SPSS 22.0 (SPSS, IL, Chicago) was used for data analysis. All statistical tests were bilateral and  $P < 0.05$  was considered statistically significant.

## Result

### Patient demographics

From 2010 to 2013, 11058 ES-SCLC patients were reported in the SEER database, and their clinical characteristics are presented in Table 1. Only 41% of patients are younger than 65 years old. Most patients were white (86.4%), more than half of whom were male. Moreover, the composition of patients with tumor size  $\leq 3$ , 3-7 and  $\geq 7$  accounted for 23.8%, 47.6% and 28.6%, respectively. According to the AJCC guidelines for tumor nodule metastasis (TNM) staging, patients with N2 (57.3%) had the highest proportion, while patients with N1 had the lowest proportion, which was only 6.3% of the entire cohort, and N3 patients (24.0 %) was in the middle.

At last, the table shows that a total of 3871(35.0%), 2851(25.8%), 4956(44.8%) and 2275 (20.6%) patients were diagnosed with bone, brain, liver and lung metastases, respectively. And bone metastases were the most common (44.8%), and lung metastases were the least common (20.6%). The detailed information was presented on table 1.

### Metastasis pattern based on different tumor size

The metastatic sites were summarized as follows: bone metastasis, brain metastasis, liver metastasis, and lung metastasis. In addition, patients were divided into the following subgroups according to tumor size:  $\leq 3$ , 3-7, and  $\geq 7$ . As shown in Figure 1A, the liver was the most common site of metastases, and the lung was the least common site of metastasis in all ES-SCLCs. The proportion of patients with tumor size  $\leq 3$ , bone, brain, liver, and lung metastasis was 33.3%, 27.2%, 46.8%, and 19.0%, respectively; in 3-7 patients, the ratio was 36.9%, 26.5%, 46.8%, 20.6%; the proportion of patients with tumor size  $\geq 7$  cm was 33.4%, 23.5%, 39.8%, 21.9%.

As shown in Figure 1B, patients with tumor sizes of 3-7 were most likely to metastasize, and patients with tumor size  $\leq 3$  were unlikely to metastasize regardless of metastatic pattern. Among the patients with bone metastases, most of them were 3-7, accounting for 50.2%, and only 22.6% of patients with tumor size  $\leq 3$ ; the proportion of patients with brain metastasis were tumor size  $\leq 3$  (25.1%), tumor size 3-7 (48.9%), tumor size  $\geq 7$  (26.0%); the proportion of patients with liver metastasis were tumor size  $\leq 3$  (24.9%), tumor size 3-7 (49.8%), tumor size  $\geq 7$  (25.4%). In patients with lung metastasis, the proportion of patients were tumor size  $\leq 3$  (22.0%), tumor size 3-7 (47.6%), tumor size  $\geq 7$  (30.4%) (Figure 1).

#### **The association between tumor size and the sites of distant metastasis**

We used univariate and multivariate logistic regression analysis to analyze the association between metastatic patterns and clinically relevant factors. For bone metastasis, we analyzed the risk factors for bone metastasis from ES-SCLC patients. Age, race, sex, tumor size and N stage were selected in the logistic regression model. Age, race, sex, tumor size and N stage were all independent risk factors in the multivariable analysis. The results showed that the incidence of patients with tumors 3-7 was significantly higher than patients with tumor size  $\leq 3$  (OR 1.165, 95% CI 1.055-1.287,  $P=0.003$ ). Moreover, there was no significant difference in bone metastasis between patients with tumor size  $\geq 7$  and tumor size  $\leq 3$  (OR 0.965, 95% CI 0.863-1.079,  $P=0.531$ ).

For brain metastasis, age, race, sex, tumor size and N stage were all independent risk factors in the multivariable analysis. The results showed that patients with tumor size  $\geq 7$  were significantly less likely than patients with tumor size  $\leq 3$  (OR 0.799, 95% CI 0.709-0.901,  $P < 0.001$ ). Moreover, there was no significant difference in brain metastases between the patients with tumor size 3-7 and tumor size  $\leq 3$  (OR 0.968, 95% CI 0.871-1.077,  $P = 0.553$ ). For liver metastasis, race, sex, tumor size and N stage were all independent risk factors in the multivariable analysis. The results showed that patients with tumor size  $\geq 7$  were significantly less likely than patients with tumor size  $\leq 3$  (OR 0.747, 95% CI 0.672-0.830,  $P < 0.001$ ). Moreover, there was no significant difference in liver metastases between the patients with tumor size 3-7 and tumor size  $\leq 3$  (OR 0.994, 95% CI 0.904-1.092,  $P = 0.894$ ). For lung metastasis, age, tumor size and N stage were all independent risk factors in the multivariable analysis. The results showed that patients with tumor size  $\geq 7$  were significantly more likely than patients with tumor size  $\leq 3$  (OR 1.183, 95% CI 1.039-1.347,  $P = 0.011$ ). In addition, there was no significant difference in lung metastasis between the patients with tumor size 3-7 and tumor size  $\leq 3$  (OR 1.097, 95% CI 0.975-1.235,  $P = 0.125$ ) (Table 2).

## Discussion

Small-cell lung cancer (SCLC) is characterized by a rapid doubling time and early, widespread metastases. The incidence of distant metastasis at the time of the initial diagnosis of SCLC was more than 60%, and the most common metastatic sites were the liver, bone, brain, lung and adrenal glands[3]. Because of small diagnostic biopsies and the rare use of surgical resection in standard treatment, We lack sufficient tumor tissue for translational research and can't understand the underlying mechanisms of disease progression and metastasis in SCLC[7-8]. Knowledge on the risks factors of different metastatic sites would help in properly classifying patients with advanced disease and may serve as a reference for personalized treatment strategies.

The aim of the study was to better understand the impact of different clinically relevant factors on distant metastasis, particularly the association between tumor size and the exact pattern of distant metastasis. Tumor size is one of the major prognostic factors in the staging system for non-small cell lung cancer (NSCLC)[9]. The prognostic value of tumor size has been demonstrated in pathologically early-and late-stage NSCLC[10]. However, the effect of tumor size on distant metastasis and prognosis of SCLC has not been reported.

Lung cancer is a malignant tumor with high metastatic ability. Metastatic sites and survival in metastatic lung cancer is influenced by sex, histological subtype and age at diagnosis which varies with the site of metastasis[11]. Bone is the common site of distant metastasis of lung cancer. A recent study has shown that patients' age (OR = 1.024,  $p < 0.001$ ), concentrations of neuron-specific enolase (OR = 1.212,  $p = 0.004$ ), and histopathological types (OR = 0.995,  $p = 0.001$ ) were the independent risk factors for bone metastases in patients with lung cancer [12-13]. The other study also showed that clinical stages, histology and the clinicopathological characteristics were related with a higher risk of bone metastasis in patients with completely resected non-small-cell lung cancer (NSCLC) [14-15]. The risk factors for bone metastasis in SCLC were less reported, and we found that in addition to age, race, gender, and N stage, the tumor size was also risk factor for bone metastasis. More interestingly, it was not that the larger the tumor was, the higher the risk of bone metastasis, and we found that the tumor size 3-7 was more prone to bone metastasis (odds ratio = 1.165,  $p = 0.003$ ), but not the tumor size  $\geq 7$  (odds ratio = 0.965,  $p = 0.531$ ). The reason that lung cancer is more prone to bone metastases may be related to the bone microenvironment affecting by the bone matrix, the immune system cells, and the same cancer cells. Many aspects of the cross-talk among lung tumor cells, the immune system, and bone cells are not clear [16].

At the time of the initial diagnosis, approximately 20% of the patients with SCLC have detectable brain



metastases[17], which is roughly in line with our findings. A study showed that High T stage, high neutrophil-to-lymphocyte ratio, early thoracic radiotherapy and fewer chemotherapy cycles were the risk factors of brain metastases[18]. Others have reported cumulative pack years smoking is associated with a greater brain metastasis velocity [19]. According to the most recent Eighth Edition of the Tumor, Node, and Metastasis (TNM) Classification of Lung Cancer, tumors  $\leq 1$  cm, 1–2 cm, 2–3 cm, 3–4 cm, 4–5 cm, 5–7 cm, and  $> 7$  cm are staged as T1a, T1b, T1c, T2a, T2b, T3, and T4, respectively[20]. So the larger the tumor, the higher the T stage. Inconsistent with the studies, our results showed that the patients with tumor size  $\geq 7$  (odds ratio = 0.799,  $p < 0.001$ ) had a significantly lower probability than those with tumor size  $\leq 3$  to develop brain metastasis.

For liver metastasis, liver was the most prevalent site (61.9%) and liver metastasis was the most common site of hematogenous metastasis in ES-SCLC[21]. The predictive value is also controversial. Some studies have demonstrated that liver metastasis might not necessarily be associated with advancement of TNM staging[22]. We analyzed the risk factors for liver metastasis from ES-SCLC patients. Race, sex, tumor size, N stage were all independent risk factors in the multivariable analysis. Also interestingly, the risk of liver metastasis was lower when the tumor size  $\geq 7$  (odds ratio = 0.747,  $p < 0.001$ ). More in-depth research is warranted to identify why patients of tumor size  $\geq 7$  are not prone to develop distant metastasis, especially to liver. For lung metastasis, we found that age, tumor size and N stage were independent risk factors, and the larger the tumor size ( $\geq 7$ , odds ratio = 1.183,  $p = 0.011$ ) and the higher N stage (N3, odds ratio = 1.501,  $p < 0.001$ ) were, the more likely the lung metastasis would occur. This may be that larger tumor size is associated with higher probability of lymph node metastasis and local disease extension (eg, mainstem bronchus involvement, visceral pleura invasion, chest wall invasion) [23]. Finally, we found that in addition to age, race, and gender

as independent risk factors for the metastasis of certain parts, N stage is an independent risk factor for all metastatic sites and the higher N stage (N2 and N3,  $P < 0.001$ ) were, the more likely the metastasis (except lung metastasis, N2, odds ratio = 1.134,  $p = 0.104$ ) would occur. This is consistent with current reports that the volume and number of metastatic lymph nodes are closely related to the site of metastasis [24].

There are also some limitations in this study. First, because there is no information on chemotherapy or radiation therapy in the SEER database, it is not possible to assess its impact on metastasis as early as possible. Some study shows that prophylactic cranial irradiation (PCI), thoracic radiotherapy and fewer chemotherapy cycles were the risk factors of brain metastases [25-26]. Second, this study is a non-randomized study. Although our sample size is large, there are inherent defects in any retrospective study. Third, in this study, we only analyzed the following metastatic sites (bone, lung, liver, and brain). Although the common sites of SCLC metastasis are bone, liver, lung and brain. Metastasis and combined metastasis of the adrenal gland or other metastatic sites may occur in ES-SCLC patients.

In summary, our study further analyzed the relationship between tumor size and distant metastasis patterns. And we were the first to analyze risk factors for different distant metastatic patterns based on tumor size in ES-SCLC patients.

## Reference

1. Tarver T. American Cancer Society Cancer Facts & Figures 2014. J. Consumer Health Internet 16(3), 366–367 (2012).
2. Nakazawa K, Kurishima K, Tamura T, et al. Specific organ metastases and survival in small cell lung cancer[J]. Oncol Lett, 2012, 4(4):617-620.
3. Cai H, Wang H, Li Z, et al. The prognostic analysis of different metastatic patterns in extensive-stage

small-cell lung cancer patients: a large population-based study [J]. *Future Oncology*,2018,14(14):1397-1407.

4. Tas F, Aydiner A, Topuz E, et al. Factors influencing the distribution of metastases and survival in extensive disease small cell lung cancer [J]. *Acta Oncol*, 1999, 38 (8):1011-1015.

5. Byers L A, Rudin C M. Small cell lung cancer: where do we go from here? [J]. *Cancer*, 2015,121 (5):664-672.

6. Surveillance: Epidemiology: and End Results (SEER) Program. SEER\*Stat Database: Incidence - SEER 18 Regs Research Data +Hurricane Katrina Impacted Louisiana Cases: Nov 2016 Sub (1973–2014 varying) - Linked To County Attributes - Total U.S.:1969–2015 Counties: National Cancer Institute: DCCPS: Surveillance Research Program: released April 2017: based on the November 2016 submission. [www.seer.cancer.gov](http://www.seer.cancer.gov).

7. Qin A, Kalemkerian G P. Treatment Options for Relapsed Small-Cell Lung Cancer: What Progress Have We Made?[J]. *J Oncol Pract*,2018,14(6):369-370.

8. Oberndorfer F, Mullauer L. Molecular pathology of lung cancer: current status and perspectives[J]. *Curr Opin Oncol*,2018,30(2):69-76.

9. Giroux D J, Van Schil P, Asamura H, et al. The IASLC Lung Cancer Staging Project: A Renewed Call to Participation [J]. *J Thorac Oncol*, 2018, 13 (6):801-809.

10. Zhang J, Gold K A, Lin H Y, et al. Relationship between tumor size and survival in non-small-cell lung cancer (NSCLC): an analysis of the surveillance, epidemiology, and end results (SEER) registry [J]. *J Thorac Oncol*,2015,10 (4):682-690.

11. Riihimaki M, Hemminki A, Fallah M, et al. Metastatic sites and survival in lung cancer [J]. *Lung Cancer*,2014,86(1):78-84.

12. Zhou Y, Chen W Z, Peng A F, et al. Neuron-specific enolase, histopathological types, and age as risk factors for bone metastases in lung cancer [J]. *Tumour Biol*,2017,39(7):1393375470.

13. Niu Y J, Wen Y T, Shen W W, et al. Risk factors for bone metastasis in patients with primary lung cancer: study protocol for a systematic review [J]. *BMJ Open*,2014,4(7):e5202.

14. Wang H, Zhang Y, Zhu H, et al. Risk factors for bone metastasis in completely resected non-small-cell lung cancer [J]. *Future Oncol*, 2017,13(8):695-704.

15. Shabani M, Binesh F, Behniafard N, et al. Clinicopathologic characteristics and survival of patients with bone metastasis in Yazd, Iran: a cross-sectional retrospective study [J]. *Medicine (Baltimore)*,2014,93(28):e317.
16. Roato I. Bone metastases: When and how lung cancer interacts with bone [J]. *World J Clin Oncol*,2014,5(2):149-155.
17. Eze C, Roengvoraphoj O, Niyazi M, et al. Treatment Response and Prophylactic Cranial Irradiation Are Prognostic Factors in a Real-life Limited-disease Small-cell Lung Cancer Patient Cohort Comprehensively Staged With Cranial Magnetic Resonance Imaging [J]. *Clin Lung Cancer*,2017,18(4):e243-e249.
18. Zheng Y, Wang L, Zhao W, et al. Risk factors for brain metastasis in patients with small cell lung cancer without prophylactic cranial irradiation [J]. *Strahlenther Onkol*,2018.
19. Shenker R F, Mctyre E R, Ruiz J, et al. The Effects of smoking status and smoking history on patients with brain metastases from lung cancer [J]. *Cancer Med*,2017,6(5):944-952.
20. Rami-Porta R, Asamura H, Travis W D, et al. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual [J]. *CA Cancer J Clin*,2017,67(2):138-155.
21. Ren Y, Dai C, Zheng H, et al. Prognostic effect of liver metastasis in lung cancer patients with distant metastasis [J]. *Oncotarget*, 2016,7(33):53245-53253.
22. Kagohashi K, Satoh H, Ishikawa H, et al. Liver metastasis at the time of initial diagnosis of lung cancer[J]. *Medical oncology* (Northwood, London, England), 2003, 20 (1):25-28.
23. Chen C, Chen Z, Cao H, et al. A retrospective clinicopathological study of lung adenocarcinoma: Total tumor size can predict subtypes and lymph node involvement [J]. *Clin Imaging*, 2018 ,47:52-56. Zhang Y, Sun Y, Chen H.
24. Zhang Y, Sun Y, Chen H. Effect of tumor size on prognosis of node-negative lung cancer with sufficient lymph node examination and no disease extension [J]. *Onco Targets Ther*,2016, 9:649-653.
25. Bernhardt D, Adeberg S, Bozorgmehr F, et al. Outcome and prognostic factors in single brain metastases from small-cell lung cancer [J]. *Strahlenther Onkol*,2018 ,194 (2):98-106.
26. Franchino F, Ruda R, Soffietti R. Mechanisms and Therapy for Cancer Metastasis to the Brain[J]. *Front Oncol*,2018, 8:161.

# Figure legends

**Figure 1.** The percentage of distant metastasis sites. A. The percentage of distant metastasis sites based on different tumor size. B. The percentage of tumor size based on different distant metastasis sites

**Table 1: Characteristics of extensive-stage small cell lung cancer from SEER Database from 2010-2013**

Variables	Number	%
<b>Age</b>		
< 65	4536	41.0
≥ 65	6522	59.0
<b>Race</b>		
White	9555	86.4
Black	1057	9.6
Others	446	4.0
<b>Sex</b>		
Female	5288	47.8
Male	5770	52.2
<b>Tumor size</b>		
≤ 3	2630	23.8
3-7	5269	47.6
≥ 7	3159	28.6
<b>N stage</b>		
N0	1375	12.4
N1	693	6.3
N2	6341	57.3
N3	2649	24.0
<b>Bone metastasis</b>		
Yes	3871	35.0
No	7187	65.0
<b>Brain metastasis</b>		
Yes	2851	25.8

No	8207	74.2
<b>Liver metastasis</b>		
Yes	4956	44.8
No	6102	55.2
<b>Lung metastasis</b>		
Yes	2275	20.6
No	8783	79.4

**Table 2: Univariate and multivariate logistic regression analysis was used to evaluate the relationship between tumor size and distant metastasis sites**

Variables	Bone metastasis		Brain metastasis		Liver metastasis		Lung metastasis	
	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>
<b>Age</b>		0.010		< 0.001		0.851		< 0.001
< 65	Reference		Reference		Reference		Reference	
≥ 65	0.899 (0.830-0.975)	0.010	0.703 (0.644-0.767)	< 0.001	0.993 (0.919-1.072)	0.851	1.209 (1.099-1.330)	< 0.001
<b>Race</b>		< 0.001		0.005		< 0.001		0.337
White	Reference		Reference		Reference		Reference	
Black	0.737 (0.641-0.848)	< 0.001	1.233 (1.071-1.419)	0.004	0.713 (0.625-0.813)	< 0.001	1.119 (0.959-1.306)	0.152
Others	0.711 (0.576-0.878)	0.002	1.196 (0.966-1.481)	0.100	0.690 (0.566-0.841)	< 0.001	1.055 (0.837-1.329)	0.651
<b>Sex</b>		< 0.001		0.001		0.001		0.118
Female	Reference		Reference		Reference		Reference	
Male	1.282 (1.184-1.388)	< 0.001	1.152 (1.057-1.256)	< 0.001	1.152 (1.068-1.243)	0.001	1.077 (0.981-1.182)	0.118
<b>Tumor Size</b>		< 0.001		< 0.001		< 0.001		0.040
≤ 3	Reference		Reference		Reference		Reference	
3-7	1.165 (1.055-1.287)	0.003	0.968 (0.871-1.077)	0.553	0.994 (0.904-1.092)	0.894	1.097 (0.975-1.235)	0.125
≥ 7	0.965 (0.863-1.079)	0.531	0.799 (0.709-0.901)	< 0.001	0.747 (0.672-0.830)	< 0.001	1.183 (1.039-1.347)	0.011
<b>N stage</b>		< 0.001		< 0.001		< 0.001		< 0.001
N0	Reference		Reference		Reference		Reference	
N1	1.379 (1.128-1.687)	0.002	1.022 (0.839-1.245)	0.829	1.346 (1.117-1.621)	0.002	1.155 (0.916-1.458)	0.223
N2	1.570 (1.375-1.793)	< 0.001	0.729 (0.642-0.829)	< 0.001	1.500 (1.330-1.692)	< 0.001	1.134 (0.975-1.320)	0.104
N3	2.060 (1.782-2.382)	< 0.001	0.671 (0.580-0.777)	< 0.001	1.280 (1.119-1.465)	< 0.001	1.501 (1.273-1.770)	< 0.001

# Figure 1

The percentage of distant metastasis sites. A. The percentage of distant metastasis sites based on different tumor size. B. The percentage of tumor size based on different distant metastasis sites

