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Original Article

Lung adenocarcinoma size as a predictor of distant metastasis: A CT scan-based measurement

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Abstract

Previous studies have associated tumor size with metastasis and prognosis in lung carcinoma; however, a precise cut-off for predicting distant metastasis in lung adenocarcinoma remains unclear. The aim of this study was to determine the cut-off point for predicting distant metastasis in lung adenocarcinoma. A cross-sectional study was conducted at Dr. Moewardi Hospital, Surakarta, Indonesia, from January 2022 to September 2023. Total sampling was employed, involving patients over 18 years old with a confirmed diagnosis of lung adenocarcinoma based on lung computed tomography (CT) scan findings, who had not yet received chemotherapy and had confirmed metastasis outside the lung. The study's dependent variable was the incidence of distant metastasis, while the independent variable was lung adenocarcinoma size. Two experienced thoracic radiologists measured lung adenocarcinoma size by assessing the longest axis using chest multi-slice computed tomography (MSCT) in the lung window setting. Receiver operating characteristic (ROC) curve analysis determined the optimal tumor size cut-off for predicting distant metastasis. Of 956 thoracic cancer patients, 108 were diagnosed with lung adenocarcinoma. After applying the inclusion and exclusion criteria, 89 patients were eligible. In the present study, tumor size predicted 68.1% of distant metastasis cases, with a cut-off point of 7.25 cm, yielding a sensitivity of 61.9% and a specificity of 61.5%. Tumors >7.25 cm had a 2.60-fold higher risk of distant metastasis compared to smaller tumors, with larger tumors more likely to spread to various sites. In conclusion, lung adenocarcinomas larger than 7.25 cm have a 2.60-fold increased risk of distant metastasis, making tumor size a crucial predictive factor. The study provides valuable insights for radiologists and can improve diagnosis accuracy and treatment planning by emphasizing tumor size as a key factor in managing lung adenocarcinoma.

Keywords: Lung cancer, metastasis, prognosis, predictor, CT scan

Introduction

Lung carcinoma is the leading cause of cancer-related mortality, responsible for over 8 million deaths globally each year [1]. In Indonesia, it accounts for 26,095 deaths annually—the highest in Southeast Asia [2]. Lung adenocarcinoma, a subtype of non-small cell lung cancer (NSCLC), is the most common form of lung carcinoma [3]. Unlike small cell lung cancer (SCLC), it grows and spreads more slowly [4]. Adenocarcinoma, typically located in the lung's peripheral regions, presents unique challenges due to its often delayed symptom onset and subsequent detection [5]. Early diagnosis is crucial for improving prognosis, with treatment options including surgery, radiotherapy, and chemotherapy [6,7].

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NSCLC, particularly adenocarcinoma, has a high propensity for metastasis, spreading to various sites such as liver, brain, bone, and lungs [8-11]. Originating from glandular cells of the bronchial mucosa, adenocarcinoma is a dominant NSCLC subtype with a poor prognosis due to its rapid growth [12]. Previous studies have identified tumor size as a prognostic factor in NSCLC, with larger tumors typically associated with poorer outcomes due to increased angiogenesis [13-15]. However, the association between tumor size and distant metastasis remains inadequately studied.

While radiographic tumor morphology is routinely assessed to differentiate benign from malignant lung tumors, it is not commonly used to predict lung cancer metastasis [16,17]. Metastasis prediction relies on the TNM staging system (tumor size, lymph nodes, and metastasis) and tumor-related factors (histopathological, anatomical, and biochemical features) [16]. However, the role of TNM staging in relation to lung cancer size as a metastasis predictor requires further elaboration. Moreover, although chest computed tomography (CT) scans are regularly employed in lung cancer management for diagnosis, therapy planning, and treatment evaluation [18-20], the potential of CT-assessed tumor morphology as a predictor of metastasis remains unexplored [21].

Distant metastasis is a major cause of cancer-related mortality, with cancers often showing specific metastatic patterns [11,22,23]. Lung carcinomas are frequently detected at a metastatic stage, where the primary tumor spreads to distant sites through processes such as angiogenesis, hypoxia, and circulation [22]. Previous studies have explored the association between tumor size and metastasis or prognosis in lung carcinoma [11,23,24]. Li *et al*. found that tumor size is associated with the pattern of distant metastasis, potentially indicating metastatic sites [11]. Cimen *et al*. showed that tumor diameter is associated with cancer survival and serves as a prognostic marker [23]. Yanagawa *et al*. demonstrated that high-resolution CT scans can predict lung adenocarcinoma invasiveness, with tumor size being a significant factor [24]. However, a precise cut-off for predicting distant metastasis in lung adenocarcinoma remains unclear. The aim of this study was to determine the cut-off point for predicting distant metastasis in lung adenocarcinoma.

Methods

Study design and setting

A cross-sectional study was conducted at Dr. Moewardi Hospital, Surakarta, Indonesia, from January 2022 to September 2023. Ethical clearance was granted by the Ethical Committee of Health Research, Dr. Moewardi Hospital, Surakarta, Indonesia (Approval number: 2.066/XI/HREC/2023). Total sampling was utilized, involving patients over 18 years old with a confirmed lung adenocarcinoma diagnosis from CT scan findings, who had not undergone chemotherapy and had confirmed metastasis outside the lung, as determined by CT scan results. The study's dependent variable was the incidence of distant metastasis, while the independent variable was lung adenocarcinoma size. Receiver operating characteristic (ROC) curve analysis determined the optimal tumor size cut-off for predicting distant metastasis.

Sampling strategy and criteria

Total sampling was employed. The study included patients with a confirmed diagnosis of lung adenocarcinoma based on lung CT scan findings. Both male and female patients who were diagnosed with lung cancer for the first time, aged over 18 years, who had not undergone chemotherapy and had confirmed metastasis outside the lung, as determined by CT scan or magnetic resonance imaging (MRI) results, were eligible. Exclusion criteria included the presence of comorbidities such as tuberculosis, diabetes mellitus, or chronic heart failure, as well as incomplete medical records.

Study procedures and variables

The study's dependent variable was the incidence of distant metastasis, while the independent variable was lung adenocarcinoma size. Lung adenocarcinoma size was measured by two thoracic radiologists with over 10 years of experience. Tumor size was determined by assessing the longest

axis of the adenocarcinoma using chest multi-slice computed tomography (MSCT) in the lung window setting. This measurement included both the lung nodules and their associated spread. Distant metastasis in the present study refers to cancer that has spread from the lung to distant organs or distant lymph nodes outside of the lung [25]. The incidence of distant metastasis was assessed using lung and abdominal CT scans to evaluate the lungs, liver, and kidneys. Lung CT scans detected nodules or masses, while abdominal CT scans identified liver and kidney metastases. Bone metastasis was initially assessed with X-rays, guided by clinical symptoms such as pain or fractures. MRI was used for more detailed evaluation, particularly when X-ray findings were inconclusive.

Patients' data, including age, sex, and lung cancer stage, were documented from medical records. Age was categorized as less than 40, between 40 and 60, and more than 60. Lung cancer staging was based on the Eighth Edition of TNM Staging System for Lung Cancer, which classifies lung cancer by tumor size and extent (T), lymph node involvement (N), and distant metastasis (M). The "T" category ranges from T1 (small, localized tumors) to T4 (larger tumors or those invading nearby structures). The "N" category ranges from N0 (no lymph node involvement) to N3 (spread to lymph nodes on the opposite side of the chest or near the collarbone). The "M" category is either M0 (no distant metastasis) or M1 (presence of distant metastasis). These components are combined to assign an overall stage, from Stage I (localized) to Stage IV (advanced with distant metastasis), as outlined in the guidelines [16].

Statistical analysis

SPSS version 25.0 software (IBM SPSS, Chicago, Illinois, USA) was used for data analysis, with $p<0.05$ considered statistically significant. Continuous data were presented as mean and standard deviation for normally distributed data or median (minimum-maximum) for non-normally distributed data; categorical data were presented as frequency and percentages. Shapiro-Wilk test was utilized to assess data normality. A Chi-square test assessed the association between tumor size and distant metastasis. An independent Student's T-test compared the mean tumor sizes between patients with and without distant metastasis. ROC curve analysis determined the optimal tumor size cut-off for predicting distant metastasis, with the area under the ROC curve (AUC), sensitivity, and specificity reported. Inter-observer reliability was assessed using intraclass correlation coefficient (ICC) analysis. Levels of agreement were interpreted as follows: <0.5 indicated poor reliability, 0.5–0.75 indicated moderate reliability, 0.75–0.9 indicated good reliability, and >0.9 indicated excellent reliability.

Results

Characteristics of the patients

Of 956 thoracic cancer patients, 108 were diagnosed with lung adenocarcinoma. After applying the inclusion and exclusion criteria, 89 patients were eligible, of whom 69.7% had distant metastasis and 30.3% had non-distant metastasis. The age distribution showed that 48.3% of patients were aged 40–60, and 47.2% were over 60. Among the patients with metastasis, 36% were aged 40–60, and 31.5% were over 60. Regarding sex distribution, 59.6% of the patients were male, with 42.7% having metastasis, while only 28.1% of the female patients had metastasis. Lung cancer staging data indicated that 42.7% of patients were in stage IVA, with 20.2% of these having metastasis, while 51.6% were in stage IVB, with 47.2% having metastasis. The predominant sites of metastasis were the lungs, either as isolated metastasis (27%) or in combination with other organs. Specifically, concurrent lung and bone metastasis were present in 22.5% of cases, while concurrent lung and liver metastasis were observed in 20.2% of cases. Additionally, 12.4% of patients had metastasis in the lung, bone, and liver simultaneously (**Table 1**).

Association between tumor size and distant metastasis

Inter-observer reliability of tumor size measurement was confirmed with a Kappa value of 0.84, indicating good reliability. Tumor size was significantly larger in patients with distant metastasis (8.93±3.88 cm) compared to those without (6.55±2.26 cm), with a mean difference of 2.38 cm (95%CI: 1.07–3.69, $p=0.001$), as described in **Table 2**.

Table 1. Patients' characteristics (n=89)

Characteristics	Lung adenocarcinoma n (%)	Metastasis n (%)	Non-metastasis n (%)
Age			
<40 years	4 (4.5)	3 (3.4)	1 (1.1)
40–60 years	43 (48.3)	32 (36.0)	11 (12.3)
>60 years	42 (47.2)	28 (31.5)	14 (15.7)
Sex			
Male	53 (59.6)	38 (42.7)	15 (16.9)
Female	36 (40.4)	25 (28.1)	11 (12.3)
Stage			
IIB	1 (1.1)	0 (0)	1 (1.1)
IIIB	2 (2.2)	1 (1.1)	1 (1.1)
IIIC	2 (2.2)	0 (0)	2 (2.2)
IVA	38 (42.7)	18 (20.2)	20 (22.5)
IVB	46 (51.6)	42 (47.2)	4 (4.4)
Metastasis			
Distant	62 (69.7)	-	-
Non-distant	27 (30.3)	-	-
Site of metastasis			
None	3 (3.4)	-	-
One site			
Bone	4 (4.5)	-	-
Liver	2 (2.2)	-	-
Lung	24 (27.0)	-	-
Kidney	1 (1.1)	-	-
Two sites			
Liver and bone	6 (6.7)	-	-
Lung and bone	20 (22.5)	-	-
Lung and liver	18 (20.2)	-	-
Three sites			
Lung, bone, and liver	11 (12.4)	-	-

ROC analysis and tumor size cut-off for predicting distant metastasis

ROC curve analysis identified a tumor size cut-off point of 7.25 cm, with an AUC of 0.681, indicating a 68.1% probability of predicting distant metastasis based on tumor size (**Figure 1**). This cut-off point has a sensitivity of 61.9% for predicting distant metastasis (tumor size >7.25 cm) and a specificity of 61.5% for excluding non-distant metastasis (tumor size <7.25 cm). The 2×2 cross-tabulation showed a significant association between tumor size and distant metastasis (OR: 2.60; 95%CI: 1.02–6.65, p=0.043), with tumors >7.25 cm having a 2.60-fold higher risk of distant metastasis compared to those <7.25 cm (**Table 2**).

Table 2. Tumor size and its predictive value for distant metastasis in lung adenocarcinoma

Variables	Distant metastasis, n (%)	Non-distant metastasis, n (%)	p-value
Tumor size, mean±SD	8.93±3.88	6.55±2.26	0.001
≥7.25 cm	39 (61.9)	10 (38.5)	0.043
<7.25 cm	24 (38.1)	16 (61.5)	

Table 2. Tumor size and its predictive value for distant metastasis in lung adenocarcinoma (continued)

Variables	Mean difference (95%CI)	Cut-off	AUC (95%CI)	Sensitivity	Specificity	Odds ratio (95%CI)
Tumor size	2.38 (1.07–3.69)	>7.25 cm	0.681 (0.568–0.795)	0.619	0.615	-
≥7.25 cm	-	-	-	-	-	2.60 (1.02–6.65)
<7.25 cm	-	-	-	-	-	

AUC: area under the receiver operating characteristic curve

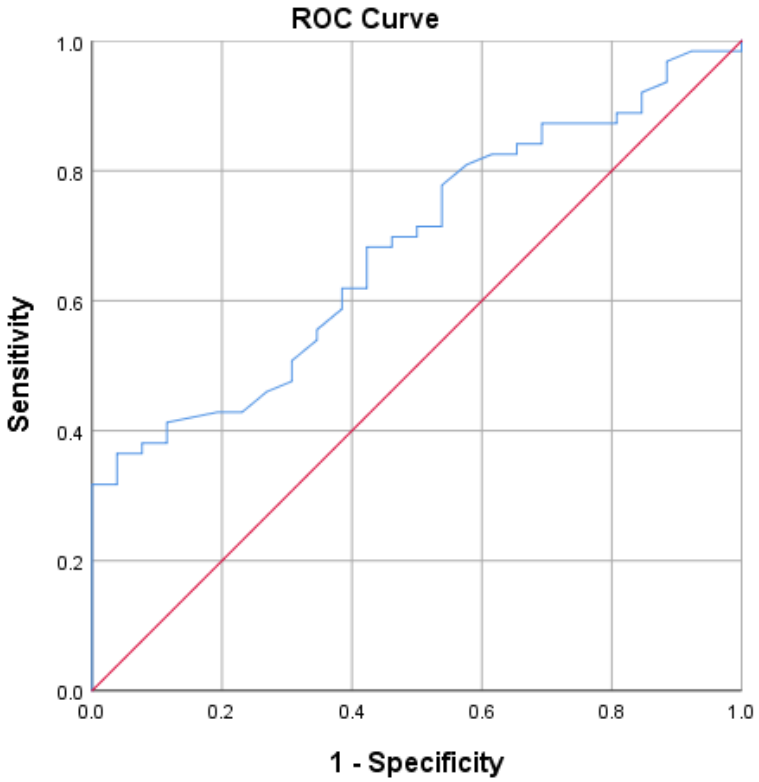

Figure 1. Receiving operating characteristic (ROC) curve of tumor size for predicting distant metastasis.

Discussion

In the present study, tumor size predicted 68.1% of distant metastasis cases, with a cut-off point of 7.25 cm, yielding a sensitivity of 61.9% and a specificity of 61.5%. Tumors larger than 7.25 cm had a 2.60-fold higher risk of distant metastasis compared to smaller tumors, with larger tumors more likely to spread to various sites. This finding highlights the importance of considering tumor size in evaluating and planning treatment for lung adenocarcinoma, as it may indicate a higher risk of metastasis.

Several studies have investigated the association between tumor size and metastasis to organs such as brain and bones [9,10,22,26-30]. Shan *et al.* found that in stage IV NSCLC, tumors ≥7 cm increase the risk of bone metastases, while tumors 3–7 cm are more prone to liver metastases [22]. Zhang *et al.* reported that tumor size significantly affects postoperative survival in NSCLC patients [26]. Feng *et al.* identified common lung cancer metastasis sites as the contralateral lung, brain, bone, and liver [10]. Okauchi *et al.* found a specific metastasis pattern in 84.8% of lung cancer patients with pancreatic metastasis [9]. In epidermal growth factor receptor (EGFR)-mutated NSCLC, liver and brain metastases were shown to be independent predictors of poor overall survival [28-30]. Lashari *et al.*, studying SCLC with bone metastases, indicated the liver as the most frequent site for further metastasis, followed by the lung [27]. These findings underscore the importance of understanding metastatic patterns in lung cancer to improve early detection and treatment.

Lung cancer commonly metastasizes to the contralateral lung, brain, bone, and liver [31]. Once tumor cells invade the stroma, a vascular supply for growth must be established, primarily by promoting angiogenesis through the release of factors such as vascular endothelial growth factor (VEGF) or by interacting with macrophages [32]. In adenocarcinomas, angiogenesis depends on macrophages, which differentiate into M1 or M2 types [4]. M1 macrophages inhibit tumor invasion via interleukin 12 (IL-12) secretion, while M2 macrophages, driven by low Notch activity, promote tumor progression through interleukin 10 (IL-10) [4].

As the primary tumor grows, insufficient blood vessel formation leads to hypoxia, which triggers further angiogenesis [33]. Angiogenesis drives lung cancer progression by promoting

tumor growth, invasion, metastasis, and altering immune responses in the tumor microenvironment [34]. Protein expressions, such as nestin, correlate with tumor size and enhance proliferation, migration, invasion, and sphere formation in adenocarcinoma cells [35]. To metastasize, tumor cells adapt by migrating either as single cells or small clusters, typical in small-cell carcinoma and undifferentiated NSCLC, or as larger clusters, common in acinar adenocarcinoma and some squamous cell carcinomas [32].

The present study suggests that a tumor size cut-off point for lung adenocarcinoma with distant metastasis could guide oncologists in more vigilant metastasis monitoring, leading to quicker treatment decisions and improved patient prognosis. However, the present study has several limitations. Firstly, it is restricted to a single hospital, which may limit the generalizability of the findings to other settings. Additionally, the present study did not account for potential confounding variables, such as patient comorbidities or variations in treatment protocols, which could influence the outcomes. Future research should involve multicenter studies with larger, more diverse populations and consider comorbidities as risk factors. Prospective studies integrating volumetric tumor assessments, genetic profiling, or multimodal imaging are recommended.

Conclusion

Lung adenocarcinomas larger than 7.25 cm have a 2.60-fold increased risk of distant metastasis, making tumor size a crucial predictive factor. This study provides valuable insights for radiologists and can improve diagnostic accuracy and treatment planning by emphasizing tumor size as a key factor in managing lung adenocarcinoma.

Ethics approval

Ethical clearance was granted by the Ethical Committee of Health Research, Dr. Moewardi Hospital, Surakarta, Indonesia (Approval number: 2.066/XI/HREC/2023).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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