Clinical Imaging 47 (2018) 52–56

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

A retrospective clinicopathological study of lung adenocarcinoma: Total tumor size can predict subtypes and lymph node involvement☆

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ARTICLE INFO

Keywords:
Adenocarcinoma in situ
Invasive adenocarcinoma
Lymph node involvement
Minimally invasive adenocarcinoma
Total tumor size

ABSTRACT

Purpose: To analyze the predictive ability of total tumor size in lung adenocarcinoma subtype and lymph node involvement.
Materials and methods: 1018 patients, ≤ 3 cm tumor, were enrolled. The maximum diameter and other variables of each tumor were measured.
Results: The optimal cut-off value for total tumor size in differentiating AIS and MIA from IAC was < 1.15 cm, in distinguishing lymph node involvement, it was 1.65 cm.
Conclusions: Total tumor size could be a reliable predictor of lung adenocarcinoma subtype and lymph node involvement irrespective of ground glass, part solid and solid characteristics.

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Of these, non-small cell lung cancer (NSCLC) accounts for approximately 85% and encompasses several subtypes; adenocarcinoma is the most common histological subtype [2]. With the increase in the utilization of computed tomography (CT), the detected numbers of the small-sized lung adenocarcinoma are remarkably increasing.

Tumor size is one of the main prognostic determinants for lung cancer, the larger tumor size, the poorer prognosis [3,4]. In lung adenocarcinoma, the CT findings of ground glass opacities tend to correlate with the histologic lepidic growth pattern while the solid components tend to correlate with the invasive adenocarcinoma pattern [5–7]. Some studies have shown that the solid component size can differentiate adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) from invasive adenocarcinoma (IAC) [8,9]. However, this correlation between the solid component and invasive adenocarcinoma pattern is not absolute, and the solid component could represent a benign scar or collapse of the alveolar wall [10,11]. MIA or IAC can also solely be a ground glass nodule (GGN) [8,12,13]. As a result of these controversial hypotheses, a general consensus with respect to the approach for size measurements of pulmonary nodules on CT, especially small-sized, part-solid nodules, in predicting adenocarcinoma subtype is lacking. The extent of the impact of the total tumor size on adenocarcinoma subtype differentiation was not well established.

Lymph node involvement is another important prognostic factor in lung cancer patients. The frequency of lymph node metastasis has been known to increase with the increase in tumor size [14]. Nevertheless, even the small size lung adenocarcinoma can present with lymph node metastasis [15]. On the other hand, a previous study had demonstrated that there were no cases with lymph node involvement in AIS or MIA, irrespective of the tumor size [16]. Thus identifying a critical range within which no lymph node involvement was found, would be beneficial for the prediction of prognosis and selection of the surgical procedure.

In the present study, we analyzed and validated the predictive impact of the total tumor size on adenocarcinoma subtype and lymph node involvement in lung adenocarcinoma patients with a size of ≤ 30 mm on preoperative CT, irrespective of ground glass, part solid and solid characteristics.

☆ The authors declare no conflict of interest.
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http://dx.doi.org/10.1016/j.clinimag.2017.08.009
Received 18 April 2017; Received in revised form 10 August 2017; Accepted 22 August 2017
0899-7071/

2. Materials and methods

2.1. Patient population

We retrospectively reviewed the prospective database of patients who underwent surgical resection at the Department of Thoracic Surgery, Zhoushan Hospital from 2007 to 2015. The routine preoperative tests included contrast-enhanced chest CT and high-resolution CT scans, cardiopulmonary tests, brain magnetic resonance imaging or brain CT, bone scanning, and abdominal CT or abdominal ultrasonography. The inclusion criteria were: (1) Peripheral non-small cell lung cancer with tumor size ≤ 3 cm in diameter. (2) Histological type was determined as adenocarcinoma according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Classification of Lung Adenocarcinoma. Atypical adenomatous hyperplasia (AAH) was not included in this study. (3) Lobectomy or sublobectomy combined with systemic lymph node dissection was performed as the standard surgical procedure. The least dissection number of the lymph node was 6. The exclusion criteria were as follows: (1) Clinical diagnosis with lymph node metastasis or distant metastasis. (2) Received preoperative chemotherapy or radiotherapy. (3) History of malignant tumors. This study was approved by the Institutional Review Board of Zhoushan Hospital.

2.2. Image analyses

Chest CT was performed with 64 row Multidetector Computed Tomography scanners (Aquilion 64, Toshiba, Japan). The scans were acquired from the supraclavicular region through the adrenal glands following deep inspiration. CT images were reconstructed using the high-frequency algorithm with a section thickness of 1.25 mm or 1 mm. The largest transverse cross-sectional diameter of the whole nodule in the lung window image was measured by two experienced thoracic radiologists. The measurements were performed using a window setting of 1500 HU and − 700 HU.

2.3. Pathology

The tumor specimens were fixed in 10% neutral buffered formalin and embedded in paraffin, followed by hematoxylin and eosin staining. The final pathologic diagnoses were determined by a retrospective pathological review of all the specimens, according to the new adenocarcinoma classification. The tumors were classified as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (IAC). Also, visceral pleural invasion, vascular invasion, and bronchus invasion were examined in all the cases.

2.4. Statistical analysis

The statistical analysis was performed using SPSS, version 16.0 software. Date was expressed as mean ± SD. The differences between the means of analyzed variables were calculated by independent samples *t*-test or bivariate correlation analysis. The differences between the tumor subgroups (location and subtype) in the total tumor size were analyzed using one-way analysis of variance (ANOVA) followed by LSD for multiple mean comparisons. Pearson's chi-squared test or independent samples *t*-test were used to assess the correlations between lymph node involvement and clinicopathological variables. To identify the variables that could be utilized in differentiating lymph node involvement, logistic regression analysis was conducted. Characteristics with a P value < 0.05 in univariate analysis were used as the input variables for multiple logistic regression analysis. The optimal cut-off values of the total tumor size in differentiating adenocarcinoma subtype and lymph node involvement were estimated by receiver operating characteristic (ROC) curve analysis. The optimal cut-off values were further determined as the point closest to the upper left corner of the ROC curve. P < 0.05 was considered statistically significant.

Table 1
Correlation between clinicopathologic characteristics and total tumor size.

Variable	N	Size (cm)		P
Age (years)				
57.8 ± 10.56	1018	1.32 ± 0.67	R = 0.370	< 0.001[a]
Gender				
Female	671	1.26 ± 0.67		
Male	347	1.43 ± 0.66	T = 3.799	< 0.001[c]
Tumor location				
RUL	366	1.304 ± 0.66		
RML	94	1.267 ± 0.71		
RLL	176	1.32 ± 0.68		
LUL	261	1.36 ± 0.68		
LLL	121	1.32 ± 0.67	0.443	0.778[b]
Adenocarcinoma subtype				
AIS	275	0.79 ± 0.27		
MIA	268	1.01 ± 0.42		
IAC	475	1.80 ± 0.62	F = 429.348	< 0.001[b]
Lymph node involvement				
Positive	64	2.20 ± 0.51		
Negative	954	1.26 ± 0.64	T′ = 13.864	< 0.001[c]
Visceral pleural invasion				
Positive	77	2.15 ± 0.58		
Negative	941	1.25 ± 0.63	T = 11.939	< 0.001[c]
Lymphovascular invasion				
Positive	7	2.36 ± 0.23		
Negative	1011	1.31 ± 0.02	T = 4.121	< 0.001[c]
Bronchus invasion				
Positive	3	2.20 ± 0.54		
Negative	1015	1.31 ± 0.02	T = 2.271	= 0.023[c]

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.
[a] Bivariate correlation analysis.
[b] One way ANOVA test.
[c] Independent samples *t*-test.

3. Results

3.1. Clinicopathological characteristics

A cohort of 1018 patients fulfilling the above-mentioned inclusion criteria were enrolled from January 2007 to December 2015 (Table 1). The cohort consisted of 347 males and 671 females, with a mean age of 57.8 ± 10.56 years. The mean total tumor size was 1.32 ± 0.67 cm. The tumors were located in the upper right lobe in 366 patients, middle right lobe in 94 patients, lower right lobe in 176 patients, upper left lobe in 261 patients, and lower left lobe in 121 patients. The histological subtypes were: 275 AIS, 268 MIA, 475 IAC, lymph node involvement (pN1 + pN2) was found in 64 patients, visceral pleural invasion in 77 patients, vascular invasion in 7 patients, and bronchus invasion in 3 patients. A lymph node involvement was not found in patients with a total tumor size ≤ 1 cm. No lymph node involvement, visceral pleural invasion, vascular invasion, and bronchus invasion was found in patients with AIS or MIA. Gender, age, adenocarcinoma subtype, lymph node involvement, visceral pleural invasion, vessel invasion, and bronchus invasion were significantly correlated with the total tumor size (P < 0.05).

3.2. Total tumor size in predicting AIS, MIA, and IAC

To identify the total tumor size in predicting AIS or MIA, we compared the total tumor size of the AIS, MIA, and IAC subgroups, One-way ANOVA test showed significant differences between the adenocarcinoma subtype (F = 429.348, P < 0.001) (Table 1). According to the LSD test, a statistically significant difference between each of the two groups was observed (P < 0.05).

The predictability of the adenocarcinoma subtype was evaluated by