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Original Article / Özgün Makale

Analysis of predictors of lymph node metastasis in clinical $T_1aN_0M_0$ pulmonary adenocarcinoma

Klinik $T_1aN_0M_0$ akciğer adenokarsinomunda lenf nodu metastazının öngördürücülerinin analizi

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ABSTRACT

Background: This study aims to identify the predictors of lymph node metastasis in patients with $T_1aN_0M_0$ adenocarcinoma of the lung.

Methods: In this retrospective study, a total of 364 patients (170 males, 194 females; mean age 60.8±8.4 years; range: 33 to 82 years) with clinical stage $T_1aN_0M_0$ pulmonary adenocarcinoma who were treated between January 2011 and October 2015 were included. Medical records were analyzed and relevant clinical data and pathological results were recorded. Univariate and multivariate analyses were performed to identify the predictors of lymph node metastasis.

Results: Multivariate analysis demonstrated that ground-glass opacity, high serum carcinoembryonic antigen concentrations (>5 ng/mL), and pathogenic type were the predictors of lymph node metastasis in T_1a pulmonary adenocarcinoma. For solid nodules, tumor diameter, air bronchogram, and high serum carcinoembryonic antigen concentrations were the predictors of lymph node metastasis.

Conclusion: Lymph node metastasis cannot be found in patients with clinical stage $T_1aN_0M_0$ pulmonary adenocarcinoma presenting as a pure ground-glass opacity or mixed tumor with solid component of diameter <5 mm. However, systematic lymphadenectomy is indicated in all patients with pure solid nodules and those with mixed nodules with solid component ≥5 mm diameter, particularly those with serum carcinoembryonic antigen concentrations higher than 5 ng/mL.

Keywords: Cancer; clinical stage; lymph node; non-small cell lung cancer; pulmonary adenocarcinoma.

ÖZ

Amaç: Bu çalışmada $T_1aN_0M_0$ akciğer adenokarsinomlu hastalarda lenf nodu metastazının öngördürücüleri belirlendi.

Çalışma planı: Bu retrospektif çalışmaya Ocak 2011 - Ekim 2015 tarihleri arasında tedavi edilen $T_1aN_0M_0$ klinik evre akciğer adenokarsinomlu toplam 364 hasta (170 erkek, 194 kadın; ort. yaş 60.8±8.4 yıl; dağılım 33-82 yıl) alındı. Tıbbi kayıtlar incelendi ve ilgili klinik veriler ve patoloji sonuçları kaydedildi. Lenf nodu metastazının öngördürücülerini belirlemek için tek değişkenli ve çok değişkenli analizler yapıldı.

Bulgular: Çok değişkenli analizde buzlu cam opasitesi, yüksek serum karsinoembriyonik antijen konsantrasyonları (>5 ng/mL) ve patojenik tip T_1a akciğer adenokarsinomunda lenf nodu metastazının öngördürücüleri olarak bulundu. Solid nodüllerde ise; tümör çapı, hava bronkogramı ve yüksek serum karsinoembriyonik antijen konsantrasyonları lenf nodu metastazının öngördürücüleri idi.

Sonuç: Lenf nodu metastazı, yalnızca buzlu cam opasitesi veya <5 çaplı solid içerikli karma tip tümör ile birliktelik gösteren, klinik evresi $T_1aN_0M_0$ akciğer adenokarsinomlu hastalarda bulunmayabilir. Ancak sistematik lenfadenektomi, yalnızca solid nodülleri olan hastalarda ve ≥5 milimetre çaplı solid içerikli karma tip nodülleri olanlarda, özellikle serum karsinoembriyonik antijen konsantrasyonu 5 ng/mL'den yüksek olanlarda endikedir.

Anahtar sözcükler: Kanser; klinik evre; lenf nodu; küçük hücreli dışı akciğer kanseri; pulmoner adenokarsinoma.

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High-resolution thin-layer computed tomography (CT) can detect early stage pulmonary adenocarcinomas, which improves the survival rate.[1] A randomized-controlled study carried out in 1995 found that the optimal surgical procedure for clinical stage IA non-small cell lung cancer is pulmonary lobectomy plus systematic lymphadenectomy.[2] More recently, some researchers have reported that pulmonary adenocarcinomas presenting as pure ground-glass opacity (GGO) has a better prognosis than tumors with a solid component.[1,3,4] Tumors presenting as pure GGOs are weakly invasive, whereas mixed GGOs or pure solid nodules are associated with a higher incidence of lymph node metastasis (LNM).[5] Therefore, whether systematic lymphadenectomy is indicated for clinical stage $T_1aN_0M_0$ pulmonary adenocarcinomas remains controversial; no consensus has yet been reached.[6] Determination of the invasiveness of clinical stage $T_1aN_0M_0$ pulmonary adenocarcinomas would be useful for identifying the patients most likely to benefit from lymphadenectomy.

In the present study, we aimed to identify predictors of LNM in patients with clinical stage $T_1aN_0M_0$ pulmonary adenocarcinoma.

PATIENTS AND METHODS

In this retrospective study, relevant data from medical records of patients who underwent resection of non-small cell lung cancer between January 2011 and October 2015 in our institution were extracted. The study protocol was approved by the Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria were as follows: (i) clinical stage $T_1aN_0M_0$ pulmonary adenocarcinoma without other pulmonary nodules; *(ii)* previous systematic lymphadenectomy; and *(iii)* previous pulmonary segments or pulmonary lobe excision.

Exclusion criteria were as follows: (i) CT scanning showing one or more lymph node larger than 1 cm in diameter which indicated metastasis; *(ii)* N_0 adenocarcinomas as assessed by mediastinoscopy; *(iii)* recent auxiliary chemotherapy or radiotherapy; and *(iv)* history of other malignant diseases.

All study patients underwent enhanced CT chest scanning and most patients with nodules <2 cm in diameter also underwent 2 mm high-resolution thin-layer CT scanning. Other routine preoperative investigations included the assessment of heart and lung function, brain CT or magnetic resonance imaging, bone scan, and abdominal CT or ultrasound. Based on the results of thin-layer CT examinations, the patients were assessed as having pure GGO lesions, mixed GGO lesions or solid nodules. The mixed GGO lesions were further subdivided as GGOs with a minimal solid content (solid content less than 5 mm diameter on imaging studies) and those with a marked solid content (solid content ≥5 mm diameter on imaging studies). In addition, GGO was defined as a slight uniform increase in density which was insufficient to obscure the pulmonary blood vessels. Pure solid nodules were defined as having totally solid content with a ground-glass component. Based on their CT scan findings, 364 patients (170 males, 194 females; mean age 60.8±8.4 years; range 33 to 82 years) were classified as having stage $T_1aN_0M_0$. Lymph nodes with short axis larger than 1 cm were considered to denote presence of LNM.

All patients underwent lobectomy or segmentectomy, and the procedure depending on the surgeon's preference, as there is still no consensus on which of these procedures is optimal. In general, segmentectomy was preferred for pure GGO lesions and lobectomy for mixed GGO and pure solid lesions.

Variables including age, gender, smoking history, relevant symptoms (i.e., cough, bloody phlegm, fever, chest pain or discomfort), tumor diameter, GGO status (GGO, mixed GGO and solid nodule), pleural involvement, air bronchogram, and serum carcinoembryonic antigen (CEA) concentrations were analyzed. The relationship between these variables and postoperative LNM status was assessed.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 2.0 software (IBM Corp., Armonk, NY, USA). The Student's t-test and Fisher's exact test were used to assess the results of univariate and multivariate analysis. Logistic regression analysis was used to carry out multivariate analysis. A p value of <0.05 was considered statistically significant.

RESULTS

All patients underwent high-resolution CT, which resulted in the following subgroups: 136 patients (37.4%) with pure GGO tumors, 154 (42.3%) with GGO with tumors with minimal solid content (diameter of solid content <5 mm), 18 (4.9%) with tumors with GGO and marked solid content (≥5 mm diameter), and 56 (15.4%) with pure solid tumors.

In the pathological examination, of 364 patients, 15 (4.1%) and nine (2.5%) were found to have Stage N_1 and N_2 disease, respectively. Eight of nine patients with Stage N_2 disease had also metastases in Stage

N_1 lymph nodes, while the remaining patients (11.1%) had saltatory LNM. Univariate analysis revealed a relationship between the LNM, and appearance of nodule on CT scans, serum CEA concentrations, and pathological type (Table 1).

All tumors classified as pure GGO or GGO lesions with a minimal solid content (<5 mm diameter) were found to have Stage N_0 disease. Pathological examination revealed that 22 of 56 patients (39.3%) with pure solid nodules had LNM (14 Stage N_1 and eight N_2); however, only three of the 172 patients (1.7%) with nodules with solid content diameter ≥5 mm were found to have LNM (two Stage N_1 and one N_2). The relationships between the GGO status, surgical procedure, LNM, and pathological tumor type are shown in Table 2. Standard pulmonary lobectomy was performed in 237 patients (65.1%) and 10 of whom

Table 1. Univariate analysis of associations between variables and lymph node metastasis in patients with clinical stage $T_1aN_0M_0$ pulmonary adenocarcinoma

Variables	Patient number	Clinical Stages			χ^2 value	*p*
		pN_0 (n=340)	pN_1 (n=15)	pN_2 (n=9)		
Age (year)					0.145	0.703
≤59	162	150	8	4		
>59	202	190	7	5		
Gender					0.0288	0.865
Female	194	182	7	5		
Male	170	158	8	4		
Smoking history					0.0289	0.865
None	205	192	8	5		
Yes	159	148	7	4		
Symptoms					3.387	0.0657
None	271	258	7	6		
Yes	93	82	8	3		
Tumor diameter					0.375	0.54
<1.0 cm	98	93	3	2		
1.0-2.0 cm	266	247	12	7		
Imaging manifestations of nodule					88.382	<0.001
Pure GGO	136	136	0	0		
GGO with solid content (diameter <5 mm)	154	154	0	0		
GGO with solid content (diameter no <5 mm)						
GGO as the main body	6	6	0	0		
Solid as the main body	12	9	2	1		
Pure solid	56	35	13	8		
Pleural indentation					1.728	0.189
None	224	115	7	2		
Yes	140	125	8	7		
Air bronchogram					0.529	0.467
None	204	190	7	7		
Yes	160	150	8	2		
Carcinoembryonic antigen					19.43	<0.001
≤5 ng/mL	260	233	5	2		
>5 ng/mL	104	87	10	7		
Pathological types					98.469	<0.001
Atypical adenomatoid hyperplasia	38	38	0	0		
Adenocarcinoma *in situ*	90	90	0	0		
Microinvasive adenocarcinoma	168	168	0	0		
Invasive adenocarcinoma	68	44	15	9		

GGO: Ground glass opacity.

Table 2. Ground glass opacity status and surgical procedure, lymph node metastasis, and pathological type in patients with pulmonary adenocarcinoma undergoing computed tomography

Surgical pathological features	Pure GGO group (n=136)	Mixed GGO group (n=172)	Pure solid group (n=56)	χ^2 value	*p*
Surgical method				5.729	0.0167
Lung segmentectomy	58	54	15		
Pulmonary lobectomy	78	118	41		
Lymph node metastasis				56.975	<0.001
N_0	136	169	35		
N_1	0	2	13		
N_2	0	1	8		
Pathological types				319.5	<0.001
Atypical adenomatoid hyperplasia	38	0	0		
Adenocarcinoma *in situ*	90	0	0		
Minimally invasive adenocarcinoma	8	158	2		
Invasive adenocarcinoma	0	14	54		

GGO: Ground-glass opacity.

were found to have stage N_1 and four N_2 diseases. Segmentectomy was performed in 127 patients (34.8%), six of whom had Stage N_1 and four N_2 diseases. A total of 38 (11.2%) patients without LNM had atypical adenomatous hyperplasia (AAH), 100 patients (29.5%) had an adenocarcinoma *in situ* (AIS), and 168 patients (49.6%) had a minimally invasive adenocarcinoma (MIA).

Pathological examination of the resected specimens of 136 patients with pure GGO tumors revealed that 90 (66.2%) were AIS, 38 (28.0%) were AAH, and eight (5.8%) were MIA. Of 172 patients with mixed GGO tumors, 158 (91.9%) were MIA, while the remaining 14 (8.1%) were IA. Of 56 patients with pure solid tumors, 54 (96.4%) had an invasive adenocarcinoma (IA), while remaining two had a mucinous adenocarcinoma.

Multivariate analysis showed that the GGO status, pathological type, and serum CEA concentrations were statistically significant predictors of LNM ($p<0.05$, Table 3).

In addition, multivariate analysis revealed that air bronchogram, tumor diameter, and high serum CEA concentrations were significant predictors of LNM ($p<0.05$, Table 4).

DISCUSSION

Although 2009 Guidelines of the International Association of Lung Cancer state that clinical stage IA pulmonary adenocarcinomas are generally weakly invasive, such tumors vary in invasiveness.[7] In 2011, a new typing of pulmonary adenocarcinomas based on multidisciplinary diagnostic methods combining multiple clinical, molecular, imaging, and surgical factors was proposed,[8,9] supporting the concept that T_1a lung adenocarcinomas are heterogeneous and contain identifiable subgroups.

The ability to confidently predict LNM can result in safe avoidance of systematic lymphadenectomy in some patients. Several studies have already shown that systematic mediastinal lymphadenectomy is not essential.[3,6] However, there are two important differences between the aforementioned studies and the present study: first, our sample size was the largest thus far reported for this category of lung cancer; and second, our study incorporated the new pathological subtypes and new pulmonary adenocarcinoma staging of 2011.[8,9]

Table 3. Multivariate analysis of factors associated with lymph node metastasis in patients with clinical stage of $T_1aN_0M_0$ pulmonary adenocarcinoma

Variables	Odds ratio	HR (95% CI)	*p*
Ground-glass opacity status	42.100	8.012-244.48	0.000
Carcinoembryonic antigen	7.664	1.523-40.422	0.011
Pathological types	7.201	1.224-36.65	0.025

HR: Hazard ratio: CI: Confidence interval.

Table 4. Multivariate analysis of predictors of lymph node metastasis in patients with clinical stage T_1a pulmonary adenocarcinoma

Variables	Odds ratio	HR (95% CI)	*p*
Tumor diameter (cm)	2.02	1.000-4.402	0.031
Air bronchogram	4.64	2.120-6.232	0.027
Carcinoembryonic antigen	4.802	3.624-8.825	0.012

HR: Hazard ratio: CI: Confidence interval.

Previous studies also showed that clinical stage T1a lung cancer was not accompanied by mediastinal LNM.[4] However, in the current study, we identified LNM in 24 patients (6.6%) with clinical stage T_1a pulmonary adenocarcinomas. Therefore, we believe that these patients require systematic lymph dissection.

In the present study, we also identified predictors of LNM in patients with clinical stage T1a lung adenocarcinomas that have not previously been reported. Hattori et al.[10] reported that tumor diameter, pure solid CT appearance, pleural involvement, air bronchogram, high CEA concentrations (>5 ng/mL), and positron emission tomography (PET) with maximum standard intake value (SUV_{max} value >5) were the main risk factors for LNM.

In our study, univariate and multivariate analysis revealed that the GGO status, high serum CEA concentrations (>5 ng/mL), and pathological type were the main predictors of LNM. As the GGO status can predict LNM more accurately than the tumor diameter,[11] we believe decisions on whether to perform mediastinal lymphadenectomy should not be based purely on the tumor size.

In addition, we also found that, of 136 patients with GGO tumors, 90 with AIS and eight with MIA had no LNM. Among 172 patients with mixed GGO tumors (158 with MIA and 14 with IA), two had LNM. Of 56 patients with pure solid nodules, 54 (96.5%) were IA and two (3.5%) were MIA, while 21 of these patients (37.5%) had LNM.

We, therefore, believe that all patients with nodules with a solid content of >5 mm in diameter or pure solid nodules should undergo systematic lymphadenectomy. Consistent with the current findings, Hattori et al.[10] also reported that solid nodules had a high-risk of lymph node involvement. In addition, Russell et al.[9] showed a relationship between Stage I-III lung adenocarcinoma subtypes and clinical characteristics and found that none of the patients with AIS, MIA, lepidic-predominant adenocarcinomas, or invasive mucinous adenocarcinomas had LNM, which is consistent with our findings. Additionally, we found that none of the patients with AAH, AIS or MIA had LNM, indicating that histological classification of clinical stage IA pulmonary adenocarcinomas can enable avoidance of systematic lymphadenectomy in a large proportion of patients. In the current study, Stage T_1a pulmonary adenocarcinomas presenting as pure solid nodules on thin-layer CT had a high incidence of LNM. Multivariate analysis also showed that tumor diameter, high serum CEA concentrations, and pathological type were the main predictors of LNM. Based on these findings, we believe that patients with pure solid nodules must undergo systematic lymphadenectomy.

Limitations of the current study include its retrospective nature and lack of uniform PET scanning. Therefore, the relationship between the GGO status and lung adenocarcinoma subtypes requires further verification. We, hence, plan to perform a prospective, randomized-controlled study to confirm the present findings.

In conclusion, patients with clinical stage $T_1aN_0M_0$ lung adenocarcinoma which has a solid content of <5 mm in diameter or pure ground-glass opacity on imaging studies do not require lymphadenectomy. However, systematic lymphadenectomy is indicated in patients with pure solid nodules or a solid content of ≥5 mm in diameter, particularly those whose serum carcinoembryonic antigen concentration is higher than 5 ng/mL.

Declaration of conflicting interests

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