Preoperative risk factors of lymph node metastasis in clinical N0 lung adenocarcinoma of 3 cm or less in diameter

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Abstract
Background: Lung adenocarcinoma is the most common subtype of non-small cell lung cancer. The surgical strategy of lymph node dissection is controversial because many more patients are diagnosed at an early stage in clinical practice.

Methods: We retrospectively reviewed 622 clinical N0 lung adenocarcinoma patients with 3 cm or less in tumor size who underwent lobectomy or segmentectomy combined with lymph node dissection in our hospital from January 2017 to December 2019. We performed univariate and multivariate analyses to identify preoperative risk factors of lymph node metastasis.

Results: Lymph node metastasis was found in 60 out of 622 patients. On univariate analysis, lymph node metastasis was linked to smoking history, preoperative CEA level, tumor size, tumor location (peripheral or central), consolidation/tumor ratio, pleural invasion, and pathologic type. However, only the preoperative CEA level, tumor size, and consolidation/tumor ratio were independent risk factors in multivariate analysis. The ROC curve showed that the cutoff value of tumor size was 1.7 cm. There was no lymph node metastasis in patients without risk factors.

Conclusions: The preoperative CEA level, tumor size, and consolidation/tumor ratio were independent risk factors of lymph node metastasis in clinical N0 lung adenocarcinoma with tumor size ≤3 cm. The lymph node metastasis rate was extremely low in clinical N0 lung adenocarcinoma patients without risk factors and lymph node dissection should be avoided in these patients to reduce surgical trauma.

Keywords: Lung adenocarcinoma, Risk factor, Lymph node metastasis, Lymph node dissection
lungenkrebs mit reinem Grundgrasopaz (GGO) trat nicht mit Lymphknotenmetastasen auf, und die Inzidenz der Lymphknotenmetastasen war niedriger im GGO-dominanten Lungenkrebs [2, 3]. Systematische Lymphknotenresektion ist tatsächlich unnötig und erhöht nur die chirurgische Traumatisierung bei Patienten mit Frühzuständen des Lungenkrebses. Es ist schwierig, den korrekten Stadiumstatus der Lymphknoten vor der Operation festzulegen. Liberman et al. berichteten über eine Sensitivität und Spezifität von 12.8% und 99.6%, respektive, für die Diagnose von Lymphknotenmetastasen auf einem Plain-CT, während die Sensitivität und Spezifität 39.7% und 80.3%, respektive, für die Diagnose von Lymphknotenmetastasen auf einem PET/CT in der Diagnose von Lymphknotenmetastasen [4].

Aus der Literatur wurden mehrere Risikofaktoren in Verbindung mit der Lymphknotenmetastasierung wie Alter [5], Tumordurchmesser [6, 7], Karzinomembryonales Antigen (CEA) [8], Konsolidierung/tumor ratio (CTR) [9], Tumorlokation [10], Differenzierung [11], Pleurainvasion [12], lymphatische Invasion [13], mikropapilläre Komponente [14], und Tumorausbreitung in Luftwegen [15]. Jedoch, die Charakteristika wie die mikropapilläre Komponente, lymphatische Invasion, Differenzierung, und Tumorausbreitung in Luftwegen waren oft nicht bestätigt bis mindestens eine Woche nach der Operation in paraffin-gekoppelter Pathologie-Spezimen. Chirurgen können nur die Ergebnisse der präoperativen Untersuchungen, intraoperativen Exploration, und fast frozen Pathologie während der Operation vor Lymphknotenresektion. Fast frozen Pathologie während der Operation in unserem Krankenhaus können nur die Typologie des Lungenkrebses (z.B. Schleimzellkarzinom oder Adenokarzinom) und auch die invasive Grade des Tumors (Adenokarzinom in situ, mikroinvasive und invasive Adenokarzinom). Lepidic-dominierendes Adenokarzinom kann auch durch fast frozen Pathologie während der Operation in unserem Krankenhaus diagnostiziert werden.

Derzeit, die Notwendigkeit der Lymphknotenresektion bei Frühstadium des Lungenkrebses bleibt kontrovers und fehlt eine Konsensus in der klinischen Praxis [16, 17]. Wir analysierten die präoperative Charakteristika des Adenokarzinoms kombiniert mit der invasiven Grade, die mit fast frozen Pathologie während der Operation, und versuchten, die Risikofaktoren der Lymphknotenmetastasierung von Adenokarzinomen die Referenzdaten für klinische Praxis zu geben.

**Methoden**

**Patientenselektion**

Wir retrospektiv analysierten die klinischen Daten der Patienten, die für Lungenkrebs in unserer Klinik vom Januar 2017 bis Dezember 2019 operiert wurden. Wir beinhalteten (1) Alle Patienten, die konventionelle präoperative Untersuchungen erhalten hatten; (2) Die Pathologie wurde als Adenokarzinom bestätigt; (3) Der klinische N-Score sollte N0 sein, und der maximale Durchmesser des Tumors sollte in CT-Bild sollte ≤ 3 cm sein; und (4) Lobektomie oder Segmentektomie kombiniert mit Lymphknotenresektion wurde durchgeführt. Der Anteil der Patienten, die Segmentektomie war in den letzten Jahren in unserer Klinik ansteigend. In unserer Klinik bestand die Tendenz, Stelobale Resektionen anstelle von Lobektomien durchzuführen.
**Statistical analysis**
Continuous variables were expressed as mean ± SD, and compared by Student’s t test. Categorical variables were compared by Chi-squared test or Fisher exact test. Multivariate analysis by logistic regression was done using variables with statistical significance in univariate analysis. The cutoff value of tumor size was determined by the receiver operating characteristic (ROC) curve. P values less than 0.05 were considered statistically significant. Statistical analysis was performed by the SPSS software (version 19, IBM, USA). This research was permitted by the ethical committee of the first affiliated hospital of Zhejiang University (Hangzhou, China).

**Results**
In the study, we included 221 men and 401 women. The median age was 61 years (range from 26 to 85 years), 74 patients benefitted from segmentectomy while 548 patients from lobectomy. Most patients had tumors located at the right upper lobe (202 patients) while 33 patients had tumors located at the right middle lobe, which was the least. Sixty patients presented with lymph node metastasis (28 patients at N1 stage and 32 patients at N2 stage). No lymph node metastasis was found in the pure GGO group. In the GGO-predominant group, 1 patient had N1 lymph node metastasis. The general characteristics of the patients were listed in Table 1.

Univariate analysis showed that the smoking history, preoperative CEA level, tumor size, tumor location (peripheral or central), consolidation/tumor ratio, pleural invasion and pathologic type were related to lymph node metastasis. Gender, age, and lobe distribution of the tumor did not correlate with lymph node metastasis (Table 2). Preoperative CEA level, tumor size, and consolidation/tumor ratio were found to be independent risk factors in multivariate analysis (Table 3). ROC curve was used to determine the cutoff value of tumor size to predict lymph node metastasis (Fig. 1). The result showed that the cutoff value of tumor size was 1.7 cm and the area under curve (AUC) were 0.74 (p < 0.001, 95% CI 0.68–0.80).

According to the result of multivariate analysis, patients were divided into risk factors positive (R+) and risk factors negative (R−) groups. The R− group was patients with preoperative CEA levels ≤ 5 ng/ml, CTR ≤ 0.5, and tumor size less than 1.7 cm. We included 185 patients in the R− group, and no lymph node metastasis was found. We classified 427 patients into the R+ group and 10 patients were excluded due to lack of CEA level. We found 60 patients with lymph node metastasis in

| Table 1 The general characteristics of the patients |
|-----------------|-----------------|-----------------|
| Variables       | Number          | Percentage (%)  |
| Gender          |                 |                 |
| Male            | 221             | 35.5            |
| Female          | 401             | 64.5            |
| Age             |                 |                 |
| < 60            | 273             | 43.9            |
| ≥ 60            | 349             | 56.1            |
| Smoking history |                 |                 |
| Yes             | 132             | 21.2            |
| No              | 487             | 78.3            |
| Missing         | 3               | 0.5             |
| CEA level (ng/ml)|                |                 |
| ≤ 5             | 533             | 85.7            |
| > 5             | 79              | 12.7            |
| Missing         | 10              | 1.6             |
| Tumor Size (cm) |                 |                 |
| ≤ 1             | 120             | 19.3            |
| > 1 and ≤ 2     | 310             | 49.8            |
| > 2 and ≤ 3     | 192             | 30.9            |
| Lobe distribution|                |                 |
| Right upper lobe| 202             | 32.5            |
| Right middle lobe| 33              | 5.3             |
| Right lower lobe| 81              | 13.0            |
| Left upper Lobe  | 177             | 28.5            |
| Left lower lobe  | 129             | 20.7            |
| Operation type  |                 |                 |
| Segmentectomy   | 74              | 11.9            |
| Lobectomy       | 548             | 88.1            |
| Tumor location  |                 |                 |
| Central         | 20              | 3.2             |
| Peripheral      | 602             | 96.8            |
| Consolidation tumor ratio | | |
| Pure GGO        | 146             | 23.5            |
| GGO-predominant | 163             | 26.2            |
| Solid-predominant| 62              | 9.9             |
| Solid           | 251             | 40.4            |
| Pleural invasion|                 |                 |
| Yes             | 62              | 10.0            |
| No              | 560             | 90.0            |
| Pathologic type |                 |                 |
| MIA             | 34              | 5.5             |
| LPA             | 89              | 14.3            |
| IA              | 499             | 80.2            |

**N stage**
- N0: 562 (90.4)
- N1: 28 (4.5)
- N2: 32 (5.1)

GGO ground grass opacity; MIA micro invasive adenocarcinoma; LPA lepidic-predominant adenocarcinoma; IA invasive adenocarcinoma
R+ group, 28 patients were staged as N1 while 32 patients were staged as N2. The lymph node metastasis rate was 14% in the R+ group (Fig. 2).

### Table 2  Risk factors of lymph node metastasis by univariate analysis

| Variables                  | N0     | N1 + N2 | P value |
|----------------------------|--------|---------|---------|
| Gender                     |        |         | 0.296   |
| Male                       | 196    | 25      |         |
| Female                     | 366    | 35      |         |
| Age                        |        |         | 0.715   |
| < 60                       | 248    | 25      |         |
| ≥ 60                       | 314    | 35      |         |
| Smoking history            |        |         | 0.017   |
| Yes                        | 112    | 20      |         |
| No                         | 447    | 40      |         |
| CEA level (ng/ml)          |        | <0.001  |
| ≤ 5                        | 499    | 34      |         |
| > 5                        | 53     | 26      |         |
| Tumor size (cm)            | 1.64±0.62 | 2.17±0.56 | <0.001 |
| Lobe distribution          |        | 0.748   |         |
| Right upper lobe           | 186    | 16      |         |
| Right middle lobe          | 30     | 3       |         |
| Right lower lobe           | 74     | 7       |         |
| Left upper lobe            | 159    | 18      |         |
| Left lower lobe            | 113    | 16      |         |
| Tumor location             |        | 0.008   |         |
| Central                    | 14     | 6       |         |
| Peripheral                 | 548    | 54      |         |
| CTR                        |        | <0.001  |         |
| ≤ 0.5                      | 308    | 1       |         |
| > 0.5                      | 254    | 59      |         |
| Pleural invasion           |        | <0.001  |         |
| Yes                        | 46     | 16      |         |
| No                         | 516    | 44      |         |
| Pathologic type            |        | <0.001  |         |
| MIA                        | 34     | 0       |         |
| LPA                        | 89     | 0       |         |
| IA                         | 439    | 60      |         |

CTR consolidation/tumor ratio; MIA micro invasive adenocarcinoma; LPA lepidic-predominant adenocarcinoma; IA invasive adenocarcinoma

### Table 3  Independent risk factors of lymph node metastasis by multivariate analysis

| Variables                  | Odds ratio | 95% CI      | p value |
|----------------------------|------------|-------------|---------|
| CEA level                  | 4.23       | 2.21–8.12   | <0.001  |
| Tumor size                 | 2.27       | 1.37–3.75   | 0.001   |
| CTR                        | 49.92      | 6.81–366.27 | <0.001  |

CI confidence interval; CTR consolidation/tumor ratio

Discussion

Our research showed that the preoperative CEA level, tumor size, and consolidation/tumor ratio were independent risk factors of lymph node metastasis in lung adenocarcinoma at clinical N0 stage with tumor size ≤ 3 cm, which was in accordance with previous reports. Koike et al. reviewed 894 patients with peripheral clinical stage IA non-small cell lung cancer and reported that the preoperative serum CEA level, tumor size and consolidation/tumor ratio were risk factors. They found patients with preoperative CEA level more than 5 ng/ml had higher rate of lymph node metastasis. The cutoff point of preoperative serum CEA level was 3.5 ng/ml [5]. Simon et al. performed a meta-analysis which included 12 studies with 4666 patients who were clinical stage I involved. They found that higher preoperative CEA level was associated with
higher rate of occult lymph node metastasis [8]. Chen et al. retrospectively reviewed 10,885 non-small cell lung cancer patients staged as clinical T1. They divided patients into three groups according to the tumor size (＞0 and ≤1 cm; >1 and ≤2 cm; >2 and ≤3 cm). They found that with the increase of tumor size, the rate of lymph node metastasis also increased [19]. In our research, we found that the best cutoff value of tumor size was 1.7 cm. The preoperative CEA level was classified into normal group (≤5 ng/ml) or abnormal group (＞5 ng/ml). Consolidation/tumor ratio was also divided into two groups according to the proportion of GGO component (CTR ≤0.5 and CTR >0.5). Preoperative CEA > 5 ng/ml, CTR > 0.5, and tumor size ≥1.7 cm were independent risk factors of lymph node metastasis according to the result of multivariate analysis.

The tumor invasive degree was an important pathologic characteristic and is related with the stage of lung cancer. Wang et al. retrospectively analyzed the clinical data of 327 patients with clinical stage IA peripheral lung cancer and the pathologic type was divided as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (IA). Patients in the AIS and MIA group had no lymph node metastasis, and 26 (10.6%) patients had positive lymph nodes in IA group. Tumor invasive degree was found to be an independent risk factor of lymph node metastasis [20]. In our study, we excluded patients with adenocarcinoma in situ because it was impossible for patients in this group to have lymph node metastasis. Lepidic-predominant adenocarcinoma (LPA) was reported to have lower tumor metastasis and better survival rate than other types of invasive adenocarcinoma, such as acinar predominant adenocarcinoma (APA), papillary predominant adenocarcinoma (PPA), micropapillary predominant adenocarcinoma (MPA) and solid predominant adenocarcinoma (SPA) [21]. We divided patients with invasive adenocarcinoma into LPA group and other types of invasive adenocarcinoma. In our study, patients in the MIA and LPA group had no lymph node metastasis and the lymph node metastasis rate was significantly lower than for other types of invasive adenocarcinomas. However, the tumor invasive degree was not an independent risk factor in multivariate analysis when analyzed together with the consolidation/tumor ratio.

Occult lymph node metastasis is not rare in clinical N0 lung cancer [14, 22]. The preoperative radiologic examinations were not reliable in predicting lymph node metastasis according to the research reported by Liberman et al. [4]. However, most patients with clinical N0 stage do have no lymph node metastasis. Wang et al. reported that 7.95% of the clinical stage IA patients had lymph node metastasis [20]. In our study, only 60 of 622 patients had lymph node metastasis and the lymph node metastasis rate was 9.6% in patients with clinical N0 stage. Lymph node dissection was unessential in many patients with clinical early stage for the low lymph node metastasis rate. According to the result of multivariate analysis, we further divided patients into risk factors positive (R+) group and risk factors negative (R−) group. Patients with preoperative CEA level ≤5 ng/ml, CTR ≤0.5, and tumor size less than 1.7 cm were classified into R− group. There were 185 patients in the R− group and no lymph node metastasis was found. 60 out of 427 (14.1%) patients were found to have lymph node metastasis in R+ group. According to the results, we considered that the lymph node metastasis rate was extremely low in clinical N0 lung adenocarcinoma patients with preoperative CEA level ≤5 ng/ml, CTR ≤0.5 and tumor size less than 1.7 cm. Lymph node dissection was unessential for these patients and should be avoided to reduce surgical trauma because lymph node dissection prolonged operative time, increased blood loss and might lead to postoperative complications such as lymphatic leakage.

This study had some limitations. First, it was a retrospective study and conducted in a single center. Second, PET-CT was performed in only a small number of patients for its high cost. If further multicenter randomized trial including routine PET-CT examination can be conducted, the results will be more convinced.

**Conclusions**

Our study demonstrated that preoperative CEA level, tumor size and consolidation/tumor ratio were independent risk factors of lymph node metastasis in clinical N0 lung adenocarcinoma with tumor size ≤3 cm. Lymph node metastasis rate was extremely low in clinical N0 lung adenocarcinoma patients without risk factors and lymph node dissection should be avoided in these patients to reduce surgical trauma.

**Abbreviations**

CT: Computer tomography; PET/CT: Positron emission tomography/computed tomography; GGO: Ground grass opacity; CEA: Carcinoembryonic antigen; CTR: Consolidation/tumor ratio; MIA: Micro invasive adenocarcinoma; LPA: Lepidic-predominant adenocarcinoma; IA: Invasive adenocarcinoma; ROC: Receiver operating characteristic; AUC: Area under curve.
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Author contributions

CF collected the clinical data. CF and YX performed statistical analysis. CF conducted a literature search and drafted this manuscript; WH revised the manuscript. All authors read and approved of the final manuscript.

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Availability of data and materials

The clinical data can be achieved in the electronic medical record system in the first affiliated hospital of Zhejiang university.

Declarations

Ethics approval and consent to participate

The study followed the ethical standards of the World Medical Association Declaration of Helsinki and all methods were performed in accordance with relevant guidelines and regulations. This was a retrospective study, informed consent was waived (approved by Clinical Research Ethics Committee of the First Affiliated Hospital of Zhejiang University).

Consent for publication

Not applicable.

Competing interests

We declare that there are no competing interests.

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