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Original Article

Extracapsular extension is a powerful prognostic factor in stage IIA-IIIA non-small cell lung cancer patients with completely resection

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Abstract: The purpose of this study is to evaluate the relationship between extracapsular extension (ECE) and clinicopathology, and its influence on the prognosis in non-small cell lung cancer (NSCLC) patients. Clinical data from 388 stage IIA-IIIA NSCLC patients who underwent curative resection and confirmed ECE positive were reviewed. The Fisher's exact or Chi-square test was used to analyze the associations between ECE and the clinical pathology. The log-rank test and Cox regression model were used to evaluate the factors influencing disease-free survival (DFS) and overall survival (OS). ECE was detected in 85 (21.9%) patients, and it had a significant correlation with advanced T stage, pathological stage and histologic type of adenocarcinoma. For the whole population, the median OS was 39.0 months, and the 5-year OS rate was 33.9%. In multivariate analysis, both ECE status and postoperative chemotherapy were significant factors for OS. The median DFS for all patients was 26.0 months, and the 5-year DFS rate was 21.7%. In multivariate analysis, pathologic stage, ECE, and postoperative chemotherapy were the independent predictor factors for DFS. Further analysis found that the locoregional recurrence-free survival and the distant recurrence-free survival rates in ECE negative group were also significantly higher than in the ECE positive group. For NSCLC patients with lymph node metastasis, the presence of ECE occurs more frequently in advanced stage and histologic type of adenocarcinoma and it may be a powerful prognostic factor which reflects the aggressive biological behavior.

Keywords: Non-small cell lung cancer, extracapsular extension, surgery, prognosis

Introduction

In recent years, lung cancer has become the most commonly diagnosed carcinoma and the most frequent cause of cancer-relative death in China and other countries [1, 2]. Approximately 75% to 85% of all lung cancer patients are diagnosed with non-small cell lung cancer (NSCLC) [3], and according to the NCCN guidelines [4], surgery remains a mainstay of treatment for NSCLC patients with stage IA-IIIA if the tumor is resectable. As we all known, the status of mediastinal lymph node metastasis is a critical factor that impacts the prognosis of NSCLC treated with surgical resections and lymph node dissections [5]. According to the mediastinal lymph nodal staging which is proposed by the International Association for the Study of Lung Cancer (IASLC), intrapulmonary, mediastinal, or contralateral mediastinal metastasis have a different prognosis [6]. What's more, in clinical practice, for patients with the same character of lymph node involvement, the prognosis is quite heterogeneous. Till now, several reports [7-9] have shown that the prognosis of patients with lymph nodal metastasis was associated with many subclassifications, for example, the number and the ratio of positive mediastinal lymph nodes, and single-station or multiple-station involvement.

As we know, in a number of other cancers, including head and neck cancer [10] and esophageal cancers [11], nodal extracapsular extension (ECE) is an adverse risk factor for the prognosis and is usually associated with a risk of recurrence. In daily practice, oncologists tend to extrapolate the findings to lung cancer patients with mediastinal disease and consider ECE as an additional indicator of greater local

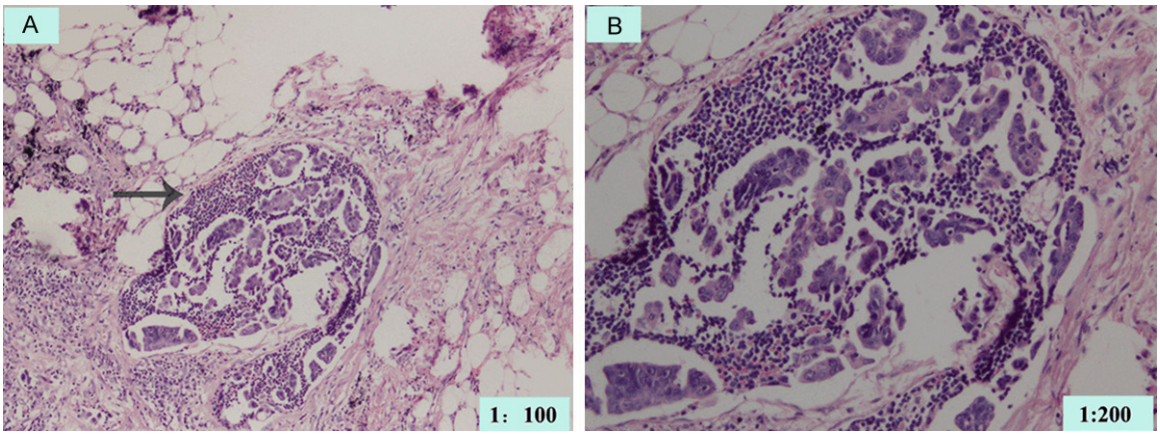

Figure 1. Hematoxylin-eosin (H&E) staining shows extracapsular extensionsis (ECE) in NSCLC patients with completely resection. Tumor cells are scattered into the adipose connective tissue distinct from the metastatic lymph node, arrow indicates the ECE. A: Original ×100. B: Original ×200.

risk. However, the evidence about the relationship between ECE and clinical pathology, and the influence on prognosis in NSCLC patients has not been sufficiently established yet [12]. Therefore, this study retrospectively analyzed the clinicopathological data in pT1a-T3, N1-2, M0 NSCLC patients with complete resection and aims to find the relationship between ECE and clinical pathology, and its influence on locoregional recurrence (LRR), distant recurrence (DR) and overall survival (OS).

Patients and methods

Patients

This clinical study was approved by our institutional review board. From January 2008 to December 2009, the clinicopathological characteristics and the prognosis of consecutive NSCLC patients who received surgical resection at our hospital were retrospectively reviewed. The inclusion criteria were as follows: patients had pathologically proven NSCLC, patients received a complete resection and systematic lymph node dissection, and had a pathologic stage T1a-T3, N1-2, M0. We excluded patients who received preoperative chemotherapy or radiotherapy. Pathologic staging was performed according to the current American Joint Committee on Cancer (AJCC) criteria for NSCLC [6].

In total, three hundreds and eighty-eight patients were included in this study. All patients had chest radiographs, an abdominal color Doppler ultrasound (CDUS), or a computed tomography (CT) scan preoperatively. After resection, patients with positive mediastinal lymph nodes or T3, T4 stage were advised to receive postoperative chemotherapy [4]. The chemotherapy regime was platinum based doublets, with the most commonly used combination being a platinum-based drug combined with either vinorelbine, or paclitaxel or gemcitabine. The 13 patients who did not receive postoperative chemotherapy, mainly due to their poor performance status (6 patients), severe complications (4 patients), or who refused chemotherapy (3 patients), were also included in the study. According to the results of our previous study [13], patients who had advanced stage or other risk factors (T>3 cm and ratio of positive mediastinal lymph nodes >1/3) were recommended to receive radiotherapy. The radiation volume covered the bronchial stump, ipsilateral hilum and the mediastinal lymph nodes which featured confirmed metastasis by preoperative CT scan and/or postoperative pathological evaluation.

Tumor specimen

The pathological examination of the surgical specimens was conducted following a standardized pathological procedure. All resected specimens including tumors and lymph nodes which contained some amounts of surrounding fat tissues were fixed in 10% formalin, embedded in paraffin, and sectioned for microscopic examination after stained with hematoxylin-eosin (H&E). Histological diagnosis and patho-

Table 1. The correlation between extracapsular extensionsis (ECE) and clinicopathological characteristics in non-small cell lung cancer (NSCLC) patients who underwent curative resection

Variable	All patients	ECE		χ^2	*P* value
		Positive, no. (%)	Negative, no. (%)		
All	388	85 (21.9)	303 (78.1)	-	-
Gender					
Male	228	48 (21.1)	180 (78.9)	0.235	0.628
Female	160	37 (23.1)	123 (76.9)		
Age					
<60	213	53 (24.9)	160 (75.1)	2.073	0.150
≥60	175	32 (18.3)	123 (76.9)		
Smoking status					
Never	163	38 (23.3)	125 (76.7)	0.325	0.569
Ever	225	47 (20.9)	178 (79.1)		
T stage					
T1	132	13 (9.8)	119 (90.2)	74.754	<0.001
T2	187	28 (15.0)	15.9 (85.0)		
T3	69	44 (63.8)	25 (36.2)		
N stage					
N1	152	29 (19.1)	123 (80.9)	0.912	0.339
N2	236	56 (23.7)	180 (76.3)		
Pathologic stage					
IIA	84	10 (11.9)	74 (88.1)	7.462	0.024
IIB	64	15 (23.4)	47 (73.4)		
IIA	240	60 (25.0)	180 (75.0)		
Histologic type					
Squamous cell carcinoma	129	20 (15.5)	109 (84.5)	7.071	0.029
Adenocarcinoma	230	61 (26.5)	169 (73.3)		
Others	29	4 (13.8)	25 (86.2)		
Tumor differentiation					
Well-differentiated	40	10 (25.0)	30 (75.0)	0.262	0.877
Moderately differentiated	280	60 (21.4)	22.0 (78.6)		
Poorly differentiated	68	15 (22.1)	53 (77.9)		
Surgical procedure					
Lobectomy	370	80 (21.6)	290 (78.4)	0.380	0.537
Pneumoectomy	18	5 (27.8)	13 (72.2)		

logical features were obtained, including tumor cell type, grade of tumor differentiation, regional lymph nodes metastasis, and the presence or absence of ECE seen microscopically. ECE was defined as the presence of tumor cells in soft tissue that was discontinuous with the primary lesion or the locoregional lymph nodes. Soft tissue with confirmed metastasis without a recognizable lymph node was also considered as ECE, unless this metastasis was associated with peripheral and/or vessel involvement (**Figure 1**). Three senior pathologists investigated all the sections of the primary tumors based on the seventh edition of the AJCC TNM classification system for NSCLC [6]. Moreover, the clinicopathological findings were determined based on the criteria provided by the Chinese Guidelines on the Diagnosis and Treatment of Primary Lung Cancer (2011 Version) [14].

Survival and recurrence

The OS, locoregional recurrence-free survival (LRFS), distant recurrence-free survival (DRFS), and disease-free survival (DFS) were calculated

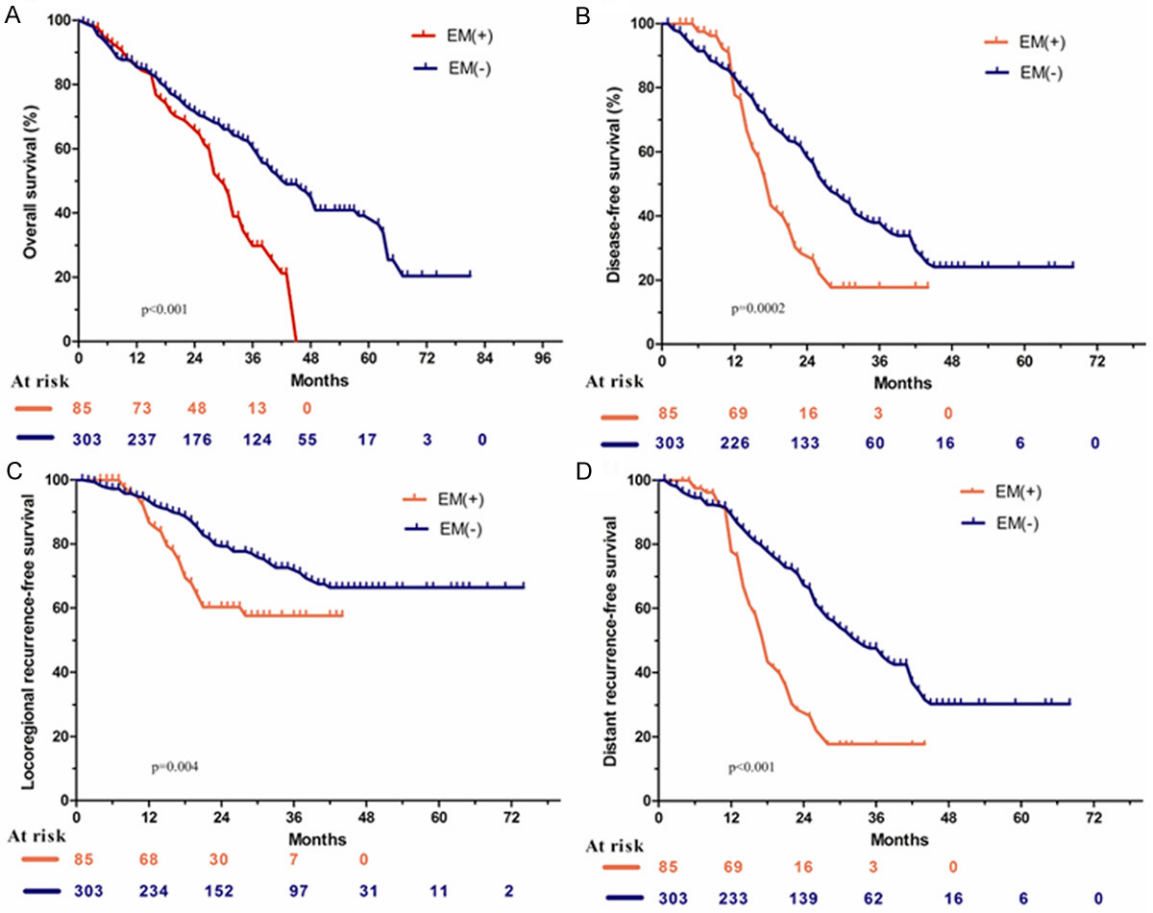

Figure 2. Comparison of the survival curves by Kaplan-Meier method in NSCLC patients with completely resection according to the status of extracapsular extensionsis (ECE). A: The median overall survival (OS) in the ECE positive group was 30.0 months versus 43.0 months in the ECE negative group (hazard ratio =2.17, P<0.001). B: And the corresponding median disease-free survival (DFS) was 18.0 months versus 27.0 months, respectively (hazard ratio =2.08, P=0.0002). C: The 3-year locoregional recurrence-free survival (LRFS) rate were 71.8% and 57.6% in the ECE negative group and in the ECE positive group, respectively (hazard ratio =2.21, P=0.004). D: And the corresponding 5-year distant recurrence-free survival (DRFS) rate were 47.6% and 47.6%, respectively (hazard ratio =3.42, P<0.001).

using the clinical diagnosis date as the starting point. The endpoint for OS was the date of death or the date of the last follow-up; the endpoint for LRFS was the date of LRR or the last follow-up date; and the endpoint for DRFS was the date of DR or the date of last follow-up; and the endpoint for DFS was the date of LRR or DR or death from any cause or the date of last follow-up. LRR was defined as recurrence occurring at the surgical site, in the ipsilateral hilum, mediastinum or in the supraclavicular area. Recurrence beyond those areas was considered to be DR. LRR and DR were diagnosed using either imaging (CT or positron emission tomography/CT) or biopsy.

Follow-up

The follow-up schedule started from the time of surgery, and the patients were followed-up every three months for the first year, and every six months thereafter. The content of each follow-up included chest X-ray or CT scan, and abdomen CDUS. Cranial CT/magnetic resonance imaging was utilized if necessary. Regardless of the follow-up stage, development of symptoms resulted in an immediate examination.

Statistical analysis

Statistical analysis was performed with SPSS 17.0 software. The correlation between ECE

and other clinicopathological variables was identified using Fisher's exact, or Chi-square test. The OS, LRFS, DRFS and DFS rate curves were obtained by the Kaplan-Meier method. Log-rank test was used to compare different impact factors of OS and DFS. Factors deemed as potentially important (P<0.05) in univariate analyses were included in the multivariate analyses for OS and DFS using a Cox proportional hazards model with a stepwise variable selection procedure. All tests were two-sided, and statistical significance level was set at P=0.05.

Results

To the date of last follow-up in December 2014, one hundred and ninety-one patients died and the median follow-up duration for the entire cohort was 28.0 months (range: 2-81 months).

Patients

Altogether, 228 (58.8%) of the 388 patients were male. The median age of patients was 59 years (range: 27-79 years). One hundred and sixty-three (42.0%) patients had never smoked cigarettes. Overall, 370 (95.4%) patients underwent a lobectomy, 18 (4.6%) patients underwent a pneumonectomy. The diagnosis of squamous cell carcinoma was found in 129 (33.2%) patients, 230 (59.3%) patients were diagnosed as adenocarcinoma, and only 29 (7.5%) patients were diagnosed as other histologic type. A total of 84 (21.6%) patients were diagnosed with pathological stage IIA (T1a-T2aN1M0, T2bN0M0) disease, 64 (16.5%) patients were diagnosed with pathological stage IIB (T2bN1M0, T3N0M0) disease and 240 (61.9%) patients were diagnosed with pathological stage IIIA (T1a-T3N2M0, T3N1M0) disease. Two hundred and eighteen (56.2%) patients received postoperative chemotherapy and 50 (12.9%) patients received postoperative radiotherapy. The postoperative chemotherapy was given with a median of three cycles (range: 1-7) (**Table 1**).

Correlation between ECE and clinicopathological characteristics

Among the entire population, ECE was detected in 85 (21.9%) patients and was absent in 303 (78.1%). Correlations of ECE with the clinicopathological characteristics are shown in **Table 1**. The incidence of ECE was significantly greater in advanced T stage (P<0.001), pathological stage (P=0.024) and adenocarcinoma histologic type (P=0.029). However, other clinicopathological factors including gender, age, smoking status, N stage, tumor differentiation and surgical procedure were not linked with the incidence of ECE (all P value >0.05).

Influence of ECE on prognosis

The median follow-up duration for ECE negative patients and ECE positive patients were 30.0 months (range: 2-81 months) and 26.0 months (range: 4-45 months), respectively. The median OS for all patients was 39.0 months and the 1-, 3- and 5-year OS rates were 85.5%, 54.0% and 33.9%, respectively. Subsequent analysis found that ECE status had a significant impact on OS, with a median OS of 43.0 months in the ECE negative group, versus 30.0 months in the ECE positive group, and the 1-, 3-, 5-year OS rates were 85.4%, 60.4%, and 39.1% in the ECE negative group, versus 85.7%, 29.8%, and not assessable in the ECE positive group, respectively (P<0.001) (**Figure 2A**).

During the follow-up period, recurrence of the disease occurred in 216 (55.7%) of the 388 patients, including 34 (15.7%) patients who developed LLR and 123 (57.0%) patients developed DR and 59 (27.3%) concurrent LRR and DR. The first DR site was the brain 64 (35.2%), followed by bone 45 (24.7%), lung 30 (16.5%), liver 24 (13.2%), and others 19 (10.4%). The median DFS for all patients was 26.0 months, and the 1-, 3- and 5-year DFS rates were 82.0%, 33.6% and 21.7%, respectively. DFS rates in the ECE negative group were significantly higher than in the ECE positive group (P=0.0002, **Figure 2B**). For the whole population, the 1-, 3-, 5-year LRFS rates were 91.8%, 68.4% and 63.4%, respectively, and the corresponding DRFS rates were 86.6%, 41.0% and 26.5%, respectively. Further analysis also found that ECE status significantly affected the LRFS and DRFS. In ECE negative group, the 1-, 3-, 5-year LRFS rates were 93.3%, 71.8%, and 66.4% versus 86.7%, 57.6% and not assessed in the ECE positive group, respectively (P=0.004, **Figure 2C**). The corresponding DRFS rates were 89.2%, 47.6%, and 30.3% versus 77.8%, 17.7% and not assessed, respectively (P<0.001, **Figure 2D**).

Analysis of independent prognosis factors

The univariate analysis of factors that affect OS revealed that N stage (P=0.016), pathological

Table 2. Result of univariate analyses to identity factors associated with disease-free survival (DFS) and overall survival (OS) in NSCLC patients who underwent curative resection

	DFS							OS						
	Median (mon)	95% CI	1 y (%)	3 y (%)	5 y (%)	χ^2	*P* value	Median (mon)	95% CI	1 y (%)	3 y (%)	5 y (%)	χ^2	*P* value
All	26.0	23.680-28.351	86.7	33.6	21.7	-	-	39.0	35.504-42.496	85.5	54.0	33.9	-	-
Gender														
Male	26.0	23.252-28.748	81.5	32.9	19.6	0.253	0.615	40.0	33.999-46.001	87.2	56.4	37.3	0.826	0.364
Female	26.0	22.034-29.966	82.8	34.6	24.8			37.0	32.313-41.687	83.0	50.8	28.3		
Age														
<60	24.0	20.904-27.096	78.9	29.6	21.0	2.432	0.119	38.0	32.864-43.136	83.3	52.7	37.1	0.077	0.782
≥60	27.0	23.431-30.569	85.8	38.4	22.9			39.0	34.211-43.789	88.1	55.6	30.9		
Smoking status														
Never	25.0	20.209-29.791	81.6	33.6	24.0	0.113	0.736	42.0	34.349-49.651	86.0	55.8	37.8	1.020	0.313
Ever	26.0	34.469-28.531	86.9	33.6	20.3			38.0	33.398-42.602	85.1	52.6	30.4		
T stage														
T1	28.0	22.179-33.281	84.8	39.5	25.9	4.266	0.118	43.0	38.212-47.788	85.6	63.1	32.9	2.161	0.338
T2	26.0	24.016-27.984	80.4	32.2	20.7			38.0	31.219-44.781	83.2	51.0	38.0		
T3	18.0	14.522-21.478	81.6	27.2	-			32.0	28.304-35.696	91.2	45.4	-		
N stage														
N1	26.0	24.048-27.952	84.4	38.3	27.9	5.848	0.017	46.0	41.464-50.536	89.9	63.2	39.0	5.836	0.016
N2	22.0	18.164-25.836	80.3	29.6	14.1			36.0	31.478-40.522	82.5	47.1	31.5		
Pathologic stage														
IIA	28.0	22.734-33.266	85.4	40.2	33.8	8.439	0.015	49.0	44.076-53.924	89.1	70.2	40.5	6.485	0.039
IIB	26.0	23.388-28.612	87.0	37.0	19.2			38.0	30.713-45.287	92.0	53.7	38.7		
IIIA	22.0	18.123-25.877	79.2	29.7	13.0			36.0	31.467-40.533	82.3	-	-		
Extracapsular extensionsis														
Yes	18.0	16.396-19.604	77.8	17.7	-	14.137	<0.001	30.0	27.235-32.765	85.7	29.8	-	15.210	<0.001
No	27.0	23.196-30.084	83.3	37.9	24.1			43.0	37.131-48.869	85.4	60.4	39.1		
Histologic type														
Squamous cell carcinoma	30.0	24.065-35.092	85.5	43.2	25.9	5.056	0.08	41.0	34.300-47.700	86.5	57.9	39.4	1.763	0.414
Adenocarcinoma	24.0	20.749-27.251	81.4	27.7	22.3			40.0	35.458-44.542	84.7	51.9	30.3		
Others	24.0	12.431-35.569	81.8	31.0	-			38.0	21.204-54.792	86.2	50.6	25.3		
Tumor differentiation														
Well-differentiated	25.0	22.497-27.503	78.3	31.8	-	3.801	0.150	40.0	36.617-43.383	85.7	54.5	30.6	2.421	0.298
Moderately differentiated	33.0	23.426-42.574	83.0	31.0	24.1			43.0	35.563-50.437	88.1	55.0	48.7		
Poorly differentiated	18.0	7.741-28.259	85.0	44.2	24.4			31.0	12.934-49.066	79.3	47.0	26.8		
Surgical procedure														
Lobectomy	16.0	23.866-28.134	82.8	34.1	22.6	2.644	0.103	40.0	36.415-43.585	86.2	54.8	33.6	1.274	0.259
Pneumoectomy	18.0	12.010-23.990	66.7	24.2	-			32.0	17.139-46.861	70.6	38.1	38.1		

Postoperative chemotherapy														
Yes	27.0	24.548-28.316	88.2	36.9	23.9	9.343	0.002	49.0	38.579-59.421	92.4	74.9	47.3	91.055	<0.001
No	21.0	15.740-26.260	73.1	28.2	-			25.0	22.909-27.091	76.1	9.6	-		
Adjuvant radiotherapy														
Yes	26.0	23.818-28.182	81.8	33.4	20.1	0.023	0.987	46.0	36.028-55.972	87.1	64.6	42.3	1.600	0.206
No	23.0	15.312-30.688	83.5	34.3	-			38.0	34.037-41.963	85.2	52.5	32.8		

Table 3. Result of multivariate analyses to identity factors associated with disease-free survival (DFS) and overall survival (OS) in NSCLC patients who underwent curative resection

	DFS				OS			
	HR	Wald χ^2	*P* value	95% CI	HR	Wald χ^2	*P* value	95% CI
N stage	0.970	0.009	0.925	0.513-1.834	1.284	2.685	0.101	0.952-1.731
Pathologic stage	1.290	14.230	0.003	1.090-1.527	0.975	0.068	0.794	0.064-1.470
Extracapsular extensionsis	1.856	12.242	<0.001	1.346-2.559	1.233	1.288	0.025	1.014-1.770

stage (*P*=0.039), ECE (*P*<0.001) and postoperative chemotherapy (*P*<0.001) were all significant factors that correlated with survival (**Table 2**). However, gender, age, smoking status, T stage, histologic type, tumor differentiation, surgical procedure, and postoperative radiotherapy were not associated with OS (all *P* value >0.05). Multivariate analysis showed that ECE (*P*=0.025) and postoperative chemotherapy (*P*<0.001) were still significant factors for survival (**Table 3**).

Univariate analysis revealed that N stage (*P*=0.017), pathologic stage (*P*=0.017), ECE (*P*<0.001), and postoperative chemotherapy (*P*=0.002) were independent predictors for DFS. Gender, age, smoking status, histologic type, tumor differentiation, surgical procedure, and postoperative radiotherapy were not associated with DFS (**Table 2**). In multivariate analysis, pathologic stage (*P*=0.003), ECE (*P*<0.001), postoperative chemotherapy (*P*=0.003) were the independent predictor factors for DFS (**Table 3**).

Discussion

Though several studies have confirmed that pathological evidence of regional nodal metastases is associated with a marked decrease in overall and disease-specific survival in resected NSCLC patients, limited research has reported the prognostic value of ECE [12, 15]. Our study identified that ECE was related to tumor aggressive behavior and could be a powerful prognostic factor in predicting LRR, DR and OS in NSCLC patients with lymph node disease.

ECE is well known as an important pathological factor contributing to the poor prognosis in several types of cancers. For breast carcinoma, ECE was determined to be a prognostic factor of DFS [16] and had been considered as the separate pN1biii subcategory in the last edition of the TNM classification for malignant tumors [6]. However, this parameter was omitted in the recent edition of the aforementioned classification scheme. A study by Zhang et al. [17] also found that ECE was a powerful prognostic factor reflecting a particularly aggressive biological behavior in adenocarcinoma of the esophagogastric junction patients. Additionally, in cervical cancer and bladder carcinoma, ECE was associated with a high rate of local failure and reduced RFS and OS [18, 19]. Conventional reports of ECE in these tumors could be used to improve patient counseling and to change follow-up plans and treatment strategies regarding adjuvant therapies. However, research on the effect of ECE on patients with NCSCLC was scarce [20]. In a prospective study [12], with 199 lymph nodal involvement NSCLC patients, it was found that the presence of ECE was a significant prognostic factor and patients with ECE had a worse survival. Unfortunately, that study did not provide any details concerning the pattern of recurrence and provided no information on local control versus distant failure based on ECE status. Further more, it should be noted that all patients included in that study were not receiving any adjuvant therapy especially postoperative chemotherapy. Another study [15] which investigated the prognostic significance of different clinicopathologic features in patients with resected NSCLC with pN2 status also found that ECE status was significantly associated with higher LRFS and DFS rates but not OS or DRFS rates. However, in the subgroup analysis, the results suggest that postoperative radiotherapy paradoxically leads to longer OS times for patients with resected pN2 NSCLC with a negative ECE status but not with a positive ECE status and the authors speculate that a positive ECE status may be an indicator for a higher risk for clinically occult distant metastatic disease in NSCLC. This present study, which only contains a consecutive series of node-positive patients in order to lessen the confounding effect since most ECE patients were found in node-positive cases, and lymph node status had an important effect

on prognosis, showed that ECE negative patients have lower LRR, DR and higher OS compared with ECE positive patients. In order to get a comprehensive understanding of the clinical significance of ECE, we also compared the prognosis of ECE status by stratification according to the pathological stage. The results found that in stage IIIA patients, ECE negative group had a significantly better of OS and DFS than that of the ECE positive group. However, in stage IIA and IIB patients, though ECE negative group showed a trend towards a higher OS and DFS than that of ECE positive group, this did not reach a significant difference (detailed data are not shown). These results suggest that a tumor with ECE has high LRR rates and DR potential, and adjuvant therapy after surgery may be helpful to improve patient's prognosis. Unfortunately, both our study and Lee's study [12] have no data about the effect of adjuvant therapy on the prognosis according to the status of ECE. So, further studies need to evaluate the prognosis of postoperative chemotherapy in ECE positive and negative patients.

Our study also showed that ECE is more frequent in advanced T stage, pathological stage and the histologic type of adenocarcinoma, which is correlated with the findings of several previous studies [12, 15, 17]. Recent studies [21, 22] have shown that poor differentiation and advanced nodal disease may be significantly associated with higher ECE. However, our study found that the tumor differentiation have no correlation with the frequency of ECE, but in subgroup analysis we also found that the worse tumor differentiation the higher frequency of ECE in adenocarcinoma. N stage had no significant association with ECE in our study. We could not find the reason to explain these inconsistent results, and future studies should be addressing these issues. What's more gender did not have an association with ECE in our study, the lower percent (63%) of female patients who had adenocarcinoma maybe the reason. In Lee's study, 76.1% of female patients had adenocarcinoma.

We aware of numerous limitations of this study: First, the present study is a retrospective study and has included a relatively small sample population. Second, there was a lack of standardized postoperative chemotherapy regimens and the cycles of chemotherapy varied. What's more, postoperative radiotherapy more applied in N2 patients. Despite of these limitations, our data shows that ECE can be an important and adverse prognostic factor that affects DFS and OS, and further prospective studies should determine the prognostic value of ECE in resected NSCLC patients with lymph nodal metastasis.

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Disclosure of conflict of interest

None.

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