Occult Nodal Metastasis Defined by PET-CT Identifies a Unique Clinical Subtype of Lung Cancer: A Retrospective Multicenter Study

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Research Article

Keywords: Non-small cell lung cancer, Lymph node metastasis, PET-CT, Prognosis

Posted Date: September 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-932003/v1

Abstract

Purpose

To investigate the surgical prognosis and efficacy of adjuvant therapy in non-small cell lung cancer (NSCLC) with occult lymph node metastasis (ONM) defined by positron emission tomography-computed tomography (PET-CT).

Methods

A total of 3537 NSCLC patients receiving surgical resection were included in this study. The prognosis between patients with ONM and evident nodal metastasis, ONM patients with and without adjuvant therapy were compared, respectively.

Results

ONM was associated with significantly better prognosis than evident nodal metastasis whether for patients with N1 (5-year OS: 56.8% versus 52.3%, adjusted p value=0.267; 5-year RFS: 44.7% versus 33.2%, adjusted p value=0.031) or N2 metastasis (5-year OS: 42.8% versus 32.3%, adjusted p value=0.010; 5-year RFS: 31.3% versus 21.6%, adjusted p value=0.025). In ONM population, patients receiving adjuvant therapy yielded better prognosis comparing to those without adjuvant therapy (5-year OS: 50.1% versus 33.5%, adjusted p value<0.001; 5-year RFS: 38.4% versus 22.1%, adjusted p value<0.001).

Conclusions

ONM defined by PET-CT identifies a unique clinical subtype of lung cancer, ONM is a favorable prognostic factor whether for pathological N1 or N2 NSCLC and adjuvant therapy could provide additional survival benefits for ONM patients.

Introduction

Lymph node staging is a critical determinant for the therapeutic strategy in patients with non-small cell lung cancer (NSCLC). The occurrence of lymph node metastasis generally heralds a more guarded prognosis [1] and therefore calls for a more aggressive treatment [2]. For NSCLC with lymph node involvement, surgery alone cannot provide adequate oncological efficacy, adjuvant therapy have been proved to confer additional survival benefits [3-8].

In the clinical practice of lymph node staging, there is a highly specialized population of occult lymph node metastasis (ONM), in whom lymph nodal metastasis is ignored by preoperative staging modalities but unexpectedly recognized during surgery. ONM presents specific clinicopathologic characteristics and may represent a distinct invasive extent from clinically evident nodal metastasis [9, 10], which implies the prognostic and therapeutic uniqueness of ONM.

However, the prognosis and treatment strategy of ONM have not been clarified. For one thing, the controversy continues on the oncological results of ONM. Previous publications tended to favor ONM, demonstrating that ONM yielded better prognosis than clinically evident nodal metastasis [11, 12]. Conversely, there were also several studies drawing a negative conclusion, revealing ONM was not a significant prognostic factor in NSCLC with lymph node involvement [13, 14]. And the existing evidences only limited in the N2 subgroup, the significance of ONM in N1 population remains ambiguous. For another, the therapeutic strategy of ONM has not been fully investigated yet. The most common option for ONM is probably to proceed with surgery and administer adjuvant therapy. However, the benefits of adjuvant therapy remain an issue of contention [12-15].

In addition, ONM in prior studies were mainly defined according to the computed tomography modality. Positron emission tomography-computed tomography (PET-CT), which simultaneously provides the functional and anatomical information of tumors, has emerged as a more effective staging modality [16]. In the era of PET-CT, whether ONM defined by PET-CT represents a unique clinical subtype of NSCLC requires further investigation.

In such instances, this study aims to reveal the heterogeneity of prognosis between ONM and clinically evident nodal metastasis and tentatively explore the efficacy of adjuvant therapy in NSCLC with ONM.

Materials And Methods

Patients

We retrospectively reviewed 6737 consecutive patients with NSCLC who received surgical resection with hilar and mediastinal lymphadenectomy at Shanghai Pulmonary Hospital, Ningbo No. 2 Hospital, The First Hospital of Lanzhou University and Affiliated Hospital of Zunyi Medical College from January 2016 to September 2016. The approval of Institutional Review Board and waiver of written informed consent were obtained for this research.

Patients were excluded when meeting the following criteria: history of malignancy, sublobar resection, non-R0 resection, insufficient lymphadenectomy (numbers of resected lymph nodes < 6 or resected mediastinal stations < 3), carcinoma in situ or minimally invasive carcinoma, pathological N3 involvement, distant metastasis, pathological lymph node metastasis but without preoperative Positron emission tomography-computed tomography (PET-CT) and conduction of neoadjuvant therapy. Finally, a total of 3537 NSCLC patients were included ***(Figure 1)***.

Preoperative evaluation and surgical treatment

Routine evaluation before surgery included chest X-ray and computed tomography (CT) scan, abdominal ultrasound, pulmonary function test, flexible bronchoscopy, assessment of cardiac function. Magnetic resonance imaging (MRI) of cerebrum and bone scintigraphy and were applied to rule out the distant metastasis. Considering PET-CT was not a routine administration in our institutions, we excluded patients

with pathological lymph node metastasis but without preoperative PET-CT to confirm the reliability of the clinical staging in lymph node involved patients. Lymph nodes with short-axis diameter > 1cm on CT or maximum standardized uptake value ≥ 2.5 on PET were defined as suspected lymph node metastasis [10]. The tumor stages were re-assessed according to eighth edition of the TNM staging system [1].

Adjuvant therapy and follow-up

Adjuvant chemotherapy was conducted for stage IB diseases with high-risk factors and stage IIA-IIIB tumors after surgery. Platinum-based doublet regimens were given for 4-6 cycles (3 weeks per cycle) after surgery. Adjuvant radiotherapy was administrated for stage III-N2 diseases. A radiotherapy dose of 50-60 Gy in 1.8-2.0 Gy per fraction was delivered for 5-6 weeks.

Follow-up was conducted at 3, 6, 12 months within the first postoperative year and then at one-year interval. Chest CT scan and abdominal ultrasound were routinely implemented. MRI scan for cerebrum and bone were adopted to excluded the distant metastasis. The PET-CT scan or/and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) were recommended when recurrence was suspected. Survival data were acquired from the outpatient visit and telephone follow-up. The overall survival (OS) was estimated as the duration since the day of surgery until the day of death or last follow-up visit. Recurrence-free survival (RFS) was defined as the time elapsed between the date of surgery and the date of progress or death or last follow-up visit. All patients completed follow-up survey up to September 2021.

Statistical analysis

Categorical data were presented as frequency (percentage) and compared by Pearson $\chi 2$ test or Fisher exact test. Normally distributed continuous parameters were exhibited as mean ± standard deviation and analyzed using Student t-test, and continuous variables in skewed distribution were described as median (interquartile range [IQR]) and assessed by Mann-Whitney U test. The Kaplan-Meier method and Log-rank test were used to estimate the survival outcomes. Cox proportional hazards regression model was performed to identify the risk factors for the prognosis. All statistical analyses were conducted via SPSS 23.0 (IBM Corporation, Armonk, NY).

Results

Study population

The baseline characteristics were summarized in ***Table 1***. The entire cohort of 3537 patients included 2220 (62.8%) men and 1317 (37.2%) women. There were 2110 (59.7%) adenocarcinomas and 999 (28.2%) squamous cell carcinomas. Most tumors (n=3145, 88.9%) were treated with lobectomy. The median resected lymph node numbers and stations were 13 (range, 10-17) and 6 (range, 5-7), respectively. Postoperative adjuvant therapy was administered to 2132 (60.3%) patients. With respect to

nodal status, most patients (n=2762, 78%) were diagnosed as pathological N0 diseases, N1 and N2 metastasis were identified in 259 (7.23%) and 516 (14.63%) patients, respectively.

According to the preoperative staging outcome, 118 (3.36%) patients were categorized as occult N1 disease and 234 (6.62%) as occult N2 disease. No matter for N1 or N2 disease, ONM was significantly associated with less male (occult N1 versus evident N1: 60.2% versus 82.3%, p<0.001; occult N2 versus evident N2: 53.8% versus 70.6%, p<0.001), higher frequency of lobectomy (occult N1 versus evident N1: 83.05% versus 73.76%, p=0.032; occult N2 versus evident N2: 86.32% versus 74.47%, p=0.003), less resected lymph node numbers (occult N1 versus evident N1: 14 versus 15, p=0.008; occult N2 versus evident N2: 13 versus 14, p=0.002), more adenocarcinomas (occult N1 versus evident N1: 65.25% versus 34.04%, p<0.001; occult N2 versus evident N2: 68.4% versus 56.4%, p=0.020). In addition, as summarized in ***Table 2*** station 11 (occult N1: 68.6%; evident N1: 64.5%) and station 4 (occult N2: 44%%; evident N2: 51.4%) were most frequently involved N1 station and N2 station, respectively.

Surgical prognosis of ONM

As displayed in ***Figure 2 & Table 3***, ONM was associated with significantly better prognosis than clinically evident lymph node metastasis whether for patients with N1 (5-year OS: 56.8% [47.8%-67.6%] versus 52.3% [44.0%-62.2%], adjusted p value=0.267; 5-year RFS: 44.7% [35.8%-55.8%] versus 33.2% [25.5%-43.3%], adjusted p value=0.031) or N2 metastasis (5-year OS: 42.8% [36.7%-49.9%] versus 32.3% [27.0%-38.5%], adjusted p value=0.010; 5-year RFS: 31.3% [25.7%-38.1%] versus 21.6% [17.1%-27.4%], adjusted p value=0.025).

Adjuvant therapy benefits of ONM

In the ONM population (n=352), adjuvant therapy was administrated to 292 (83%) patients, of them, 264 (75%) cases received adjuvant chemotherapy and 89 (25.3%) cases underwent adjuvant radiotherapy. The baseline between patients with and without adjuvant therapy did not differ significantly (***Table 4)***. As illustrated in ***Figure 3 & Table 5***, patients receiving adjuvant therapy were associated with improved prognosis comparing to those without adjuvant therapy (5-year OS: 50.1% [44.4%-56.6%] versus 33.5% [23.0%-48.9%], adjusted p value<0.001; 5-year RFS: 38.4% [32.9%-44.8%] versus 22.1% [13.3%-36.7%], adjusted p value<0.001.

Discussion

ONM is a highly specialized group of lung cancer, in whom nodal metastasis evaded from the preoperative monitoring and only discovered during surgery. The current study raises several questions: should ONM defined by PET-CT be considered as a different category from evident nodal metastasis? If such is the case, how is the prognosis of ONM population? Could the adjuvant therapy confer additional benefits for ONM?

It is presumed that compared to evident nodal metastasis, ONM may be associated with lower extent of nodal involvement and tumor metastasis burden. In early studies, favorable prognostic impacts have been initially observed in ONM based on chest x-ray and bronchoscopy [11]. Thereafter, Andre et al. [12] claimed that occult N2 disease defined by CT and mediastinoscopy yielded better OS than evident N2 disease (evident N2 disease versus occult N2 disease: HR=1.8, p<0.001). In the era of modern staging modality, a recent study [13] revealed that N2 metastasis negative on PET-CT achieved excellent surgical prognosis with 5-year OS of 48%, despite better than N2 disease positive on PET-CT, the results did not differ significantly (p=0.457). The current study included larger sample size of occult N2 disease and concurrently investigated the prognosis of occult N1 metastasis, revealing that ONM was associated with significantly better prognosis than evident lymph node metastasis whether for patients with N1 (5-year OS: 56.8% versus 52.3%, adjusted p value=0.267; 5-year RFS: 44.7% versus 33.2%, adjusted p value=0.031) or N2 metastasis (5-year OS: 42.8% versus 32.3%, adjusted p value=0.010; 5-year RFS: 31.3% versus 21.6%, adjusted p value=0.025). These results proved that ONM and evident nodal metastasis were basically two distinct groups of NSCLC.

Lymph node staging determined the optimal therapeutic strategy of NSCLC [2]. The occurrence of lymph node metastasis would significantly reduce the oncological efficacy of surgery alone, postoperative adjuvant therapy was proved to confer additional survival benefits [4, 5]. However, controversy continues on the role of postoperative adjuvant therapy in the ONM. In the study of Andre et al. [12] and Kim et al. [13], adjuvant therapy was not a significant prognostic predictor for the survival outcomes of occult N2 disease. In contrast, Kim et al. [15] analyzed 115 pathological N2 disease negative on PET-CT, concluding that patients receiving adjuvant therapy were associated with better 5-year OS rate, but the difference did not reach statistical significance. Our results revealed that adjuvant chemotherapy did provide significant survival improvements whether for the occult N1 or N2 population, we speculated that it was attributable to the large sample size of our study, which enhanced the statistical efficacy of the results.

There are several limitations of our study. Firstly, due to the retrospective nature, this study suffered from its inherent selection bias. Another limitation was represented by the heterogeneity in therapeutic regimens. The current study included the fact that not all patients received adjuvant therapy, and different drugs protocols and irradiation courses were administrated. Thirdly, in handing the lymph nodes in the N1 region, station 12-14 nodes were not routinely dissected, which potentially resulted in the underestimation of N1 metastasis. In such instances, the generalization and robustness of our conclusion await validated by a randomized controlled trial.

In conclusion, our study demonstrated that ONM defined by PET-CT was a distinct group of NSCLC, which correlated to significantly better prognosis than clinically evident nodal metastasis. In treatment, adjuvant therapy could significantly improve the prognosis of ONM patients.

Declarations

Acknowledgment: None

Funding: This work was supported by the Shanghai Pulmonary Hospital Innovation Team (fkcx1906) and Clinical Research Foundation of Shanghai Pulmonary Hospital (FK1938).

Conflicts of interest: Not applicable

Availability of data and material: Not applicable

Code availability: Not applicable

Authors' contributions: Yifan Zhong, Jiajun Deng, Yunlang She and Chang Chen contributed to the concept and design of the study. Minglei Yang, Minjie Ma and Yongxiang Song were responsible for acquiring the data. Tingting Wang performed data analysis and statistical analysis. Yifan Zhong and Jiajun Deng drafted the manuscript. Yunlang She and Chang Chen critically reviewed and approved the manuscript.

Ethics approval: Institutional Review Board of Shanghai Pulmonary Hospital, Ningbo No. 2 Hospital, The First Hospital of Lanzhou University and Affiliated Hospital of Zunyi Medical College approved this research.

Consent to participate: Waiver of written informed consent was obtained for this retrospective research.

Consent for publication: All authors agreed publication

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Tables

Table 1 Baseline characteristics of the entire cohort

Characteristics	Entire cohort	Occult N1	Evident N1	Occult N2	Evident N2	p1 value	p2 value
	n=3537	n=118	n=141	n=234	n=282		
Age (years)						0.860	0.669
≤65, n (%)	2607 (73.70)	89 (75.40)	105 (74.50)	178 (76.10)	219 (77.70)		
>65, n (%)	930 (26.30)	29 (24.60)	36 (25.50)	56 (23.90)	63 (22.30)		
Sex, n (%)						<0.001	<0.001
Male	2220 (62.80)	71 (60.20)	116 (82.30)	126 (53.80)	199 (70.60)		
Female	1317 (37.20)	47 (39.80)	25 (17.70)	108 (46.20)	83 (29.40)		
Smoking, n (%)						0.818	0.676
Never	1869 (52.84)	46 (39.00)	53 (37.60)	93 (39.70)	107 (37.90)		
Ever	1668 (47.16)	72 (61.00)	88 (62.40)	141 (60.30)	175 (62.10)		
Surgery procedure, n (%)						0.032	0.003
Lobectomy	3145 (88.90)	98 (83.05)	104 (73.76)	202 (86.32)	210 (74.47)		
Bilobectomy	202 (5.70)	12 (10.17)	15 (10.64)	12 (5.13)	31 (10.99)		
Pneumonectomy	190 (5.40)	8 (6.78)	22 (15.60)	20 (8.55)	41 (14.54)		
Location, n (%)						0.108	0.359
Right	2135 (60.36)	72 (61.00)	72 (51.10)	141 (60.30)	181 (64.20)		
Left	1402 (39.64)	46 (39.00)	69 (48.90)	93 (39.70)	101 (35.80)		
Resected lymph node numbers, median (IQR)	13 (10-17)	14 (10-18)	15 (12-19)	13 (10-17)	14 (11-18)	0.008	0.002
Resected lymph node Stations, median (IQR)	6 (5-7)	6 (5-7)	6 (5-7)	6 (5-7)	6 (5-7)	0.428	0.063
Pathological type, n (%)						<0.001	0.020
Adenocarcinoma	2110 (59.70)	77 (65.25)	48 (34.04)	160 (68.40)	159 (56.40)		

Squamous cell carcinoma	999 (28.20)	21 (17.80)	60 (42.55)	36 (15.40)	73 (25.90)		
Adenosquamous carcinoma	136 (3.80)	7 (5.93)	11 (7.80)	18 (7.70)	23 (8.20)		
Others	292 (8.30)	13 (11.02)	22 (15.60)	20 (8.50)	27 (9.60)		
Visceral pleural invasion, n (%)						0.389	0.143
Absent	2364 (66.84)	70 (59.30)	91 (64.50)	132 (56.41)	177 (62.77)		
Present	1173 (33.16)	48 (40.70)	50 (35.50)	102 (43.59)	105 (37.23)		
Pathological T stage, n (%)						0.001	0.164
T1	1487 (42.00)	44 (37.30)	39 (27.70)	70 (29.90)	76 (27.00)		
T2	1651 (46.70)	63 (53.40)	62 (44.00)	138 (59.00)	155 (55.00)		
T3	285 (8.10)	7 (5.90)	31 (22.00)	15 (6.41)	32 (11.35)		
T4	114 (3.20)	4 (3.40)	9 (6.40)	11 (4.70)	19 (6.74)		
Pathological N stage, n (%)						1.000	1.000
N0	2762 (78.09)	0	0	0	0		
N1	259 (7.32)	118 (100)	141 (100)	0	0		
N2	516 (14.59)	0	0	234 (100)	282 (100)		
Pathological TNM stage, n (%)						<0.001	1.000
1	2266 (64.10)	0	0	0	0		
2	633 (17.90)	107 (90.70)	101 (71.60)	0	0		
3	638 (18.00)	11 (9.30)	40 (28.40)	234 (100)	282 (100)		
Adjuvant therapy, n (%)	2132 (60.3)	94 (79.66)	112 (79.43)	198 (84.62)	242 (85.82)	0.964	0.702

Chemotherapy, n (%)	2063 (58.30)	90 (76.30)	107 (75.90)	174 (74.36)	206 (73.05)
Radiotherapy, n (%)	208 (5.90)	5 (4.24)	7 (4.96)	84 (35.90)	112 (39.70)

p1 value for comparing the occult N1 group with the evident N1 group; p2 value for comparing the occult N2 group with the evident N2 group. IQR, interquartile range

Table 2 Distribution of positive lymph node stations for the entire cohort

Characteristics	Occult N1	Evident N1	Occult N2	Evident N2	p1 value	p2 value
	n=118	n=141	n=234	n=282		
Positive N2 station, n (%)						
2	0	0	56 (23.90)	84 (29.80)	1	0.136
3	0	0	29 (12.40)	63 (22.30)	1	0.003
4	0	0	103 (44.00)	145 (51.40)	1	0.094
5	0	0	46 (19.70)	54 (19.10)	1	0.884
6	0	0	23 (9.80)	30 (10.60)	1	0.763
7	0	0	90 (38.50)	123 (43.60)	1	0.236
8	0	0	16 (6.80)	32 (11.30)	1	0.079
9	0	0	19 (8.10)	24 (8.50)	1	0.873
Positive N1 station, n (%)						
10	51 (43.20)	74 (52.50)	58 (24.80)	84 (29.80)	0.137	0.205
11	81 (68.60)	91 (64.50)	79 (33.80)	116 (41.10)	0.486	0.085
12	10 (8.47)	13 (9.22)	19 (8.12)	22 (7.80)	0.834	0.894
13	8 (6.78)	10 (7.09)	13 (5.56)	15 (5.32)	0.922	0.906
14	7 (5.90)	8 (5.70)	10 (4.30)	14 (5.00)	0.929	0.711

p1 value for comparing the occult N1 group with the evident N1 group; p2 value for comparing the occult N2 group with the evident N2 group.

Table 3 Multivariate Cox analysis of overall survival and recurrence-free survival for in the entire cohort

Variables	Overall survival		Recurrence-free survival	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (>65)	1.381 (1.213-1.573)	<0.001	1.226 (1.085-1.385)	0.001
Sex (Male)	1.356 (1.171-1.570)	<0.001	1.310 (1.159-1.481)	<0.001
Pathological type (Adenocarcinoma)	0.759 (0.663-0.869)	<0.001	0.732 (0.654-0.818)	<0.001
Pathological T stage				
T1	Reference		Reference	
T2	1.575 (1.365-1.817)	<0.001	1.572 (1.382-1.788)	<0.001
T3	2.512 (2.046-3.083)	<0.001	2.494 (2.062-3.017)	<0.001
T4	3.423 (2.625-4.463)	<0.001	3.398 (2.648-4.361)	<0.001
N classification				
N0	Reference		Reference	
Occult N1	2.584 (1.941-3.440)	<0.001	2.591 (1.995-3.366)	<0.001
Evident N1	3.178 (2.464-4.099)	<0.001	3.721 (2.970-4.661)	<0.001
Occult N2	4.154 (3.465-4.980)	<0.001	4.133 (3.488-4.896)	<0.001
Evident N2	5.490 (4.675-6.447)	<0.001	5.201 (4.469-6.055)	<0.001
Adjuvant therapy (Yes)	0.640 (0.562-0.730)	<0.001	0.716 (0.635-0.809)	<0.001

HR, Hazard Ratio; CI, confidence interval

Table 4 Baseline characteristics between patients with and without adjuvant therapy in patients with occult nodal metastasis

`Characteristics	Without adjuvant therapy	Without adjuvant therapy	p value
	n=60	n=292	
Age (years)			0.135
≤65, n (%)	41 (68.30)	226 (77.40)	
>65, n (%)	19 (31.70)	66 (22.60)	
Sex, n (%)			0.329
Male	37 (61.67)	160 (54.79)	
Female	23 (38.33)	132 (45.21)	
Smoking, n (%)			0.284
Never	20 (33.30)	119 (40.80)	
Ever	40 (66.70)	173 (59.20)	
Surgery procedure, n (%)			0.501
Lobectomy	53 (88.30)	247 (84.60)	
Bilobectomy	2 (3.30)	22 (7.50)	
Pneumonectomy	5 (8.30)	23 (7.90)	
Location, n (%)			0.623
Right	38 (63.33)	175 (59.93)	
Left	22 (36.67)	117 (40.07)	
Resected lymph node numbers, median (IQR)	13 (10-16)	13 (10-17)	0.855
Resected lymph node Stations, median (IQR)	6 (5-6)	6 (5-7)	0.086
Pathological type, n (%)			0.847
Adenocarcinoma	39 (65.00)	198 (67.80)	
Squamous cell carcinoma	12 (20.00)	45 (15.40)	
Adenosquamous carcinoma	4 (6.70)	21 (7.20)	
Others	5 (8.30)	28 (9.60)	
Visceral pleural invasion, n (%)			0.306
Absent	38 (63.30)	164 (56.20)	
Present	22 (36.70)	128 (43.80)	

Pathological T stage, n (%)			
T1	22 (36.67)	92 (31.51)	0.826
T2	31 (51.67)	170 (58.22)	
T3	4 (6.70)	18 (6.20)	
T4	3 (5.00)	12 (4.10)	
Pathological N stage, n (%)			0.642
N1	24 (40.00)	94 (32.19)	
N2	36 (60.00)	198 (67.81)	
Pathological TNM stage, n (%)			0.395
2	21 (35.00)	86 (29.45)	
3	39 (65.00)	206 (70.55)	

IQR, interquartile range

Table 5 Multivariate Cox analysis of overall survival and recurrence-free survival for patients with occult nodal metastasis

Variables	Overall survival		Recurrence-free survival	
	HR (95% CI)	p value	HR (95% CI)	p value
Pathological T stage				
T1	Reference		Reference	
T2	1.044 (0.760-1.434)	0.792	0.535 (0.387-0.740)	<0.001
T3	1.793 (0.996-3.228)	0.051	1.964 (1.132-3.409)	0.016
T4	1.979 (1.037-3.776)	0.039	2.202 (1.187-4.083)	0.012
N classification				
N1	Reference		Reference	
N2	1.630 (1.181-2.252)	0.003	1.605 (1.190-2.163)	0.002
Adjuvant therapy (Yes)	0.587 (0.416-0.827)	0.002	0.535 (0.387-0.740)	<0.001

HR, Hazard Ratio; CI, confidence interval

Figures

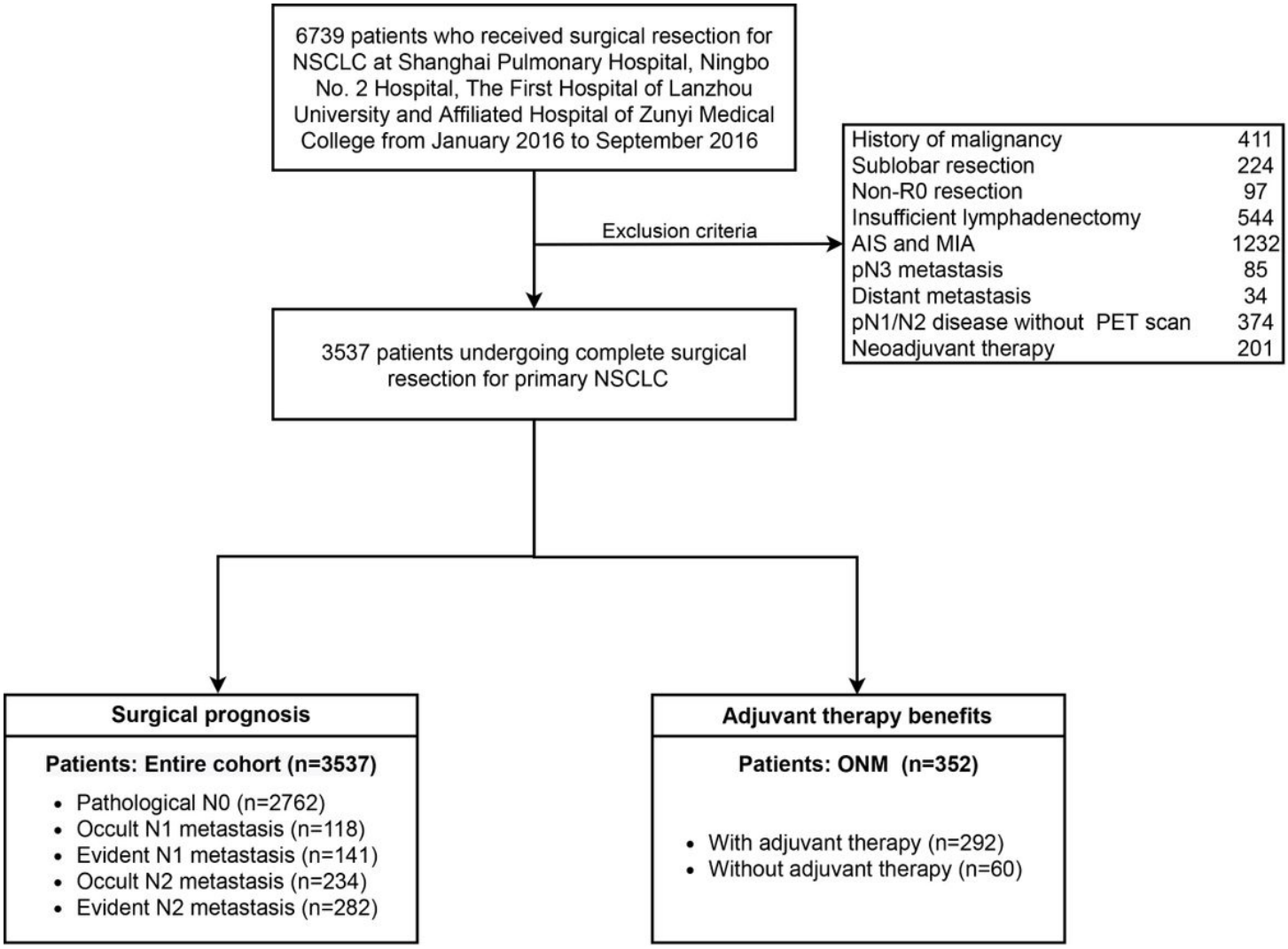
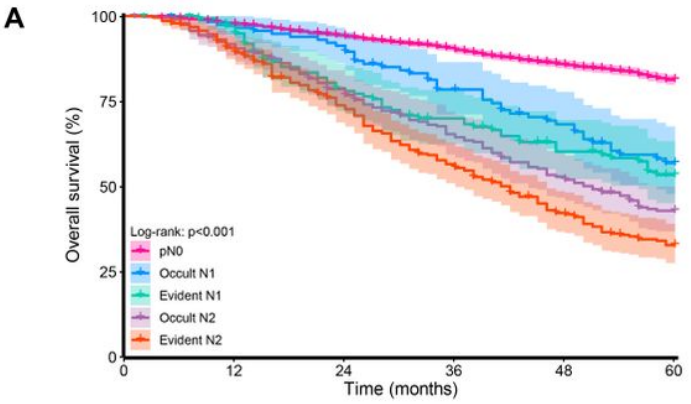
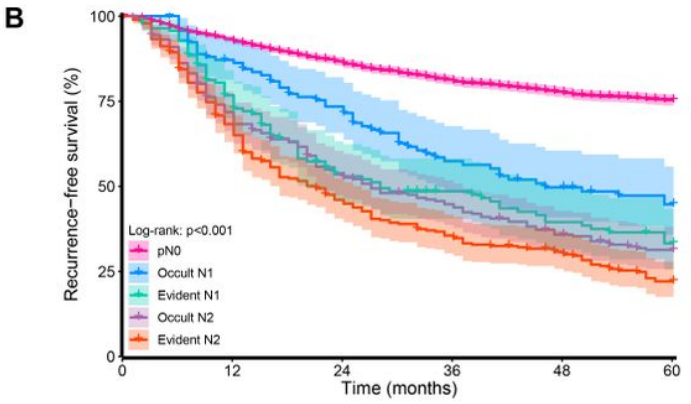


Figure 1

Flow chart of study design NSCLC, non-small cell lung cancer; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; ONM, occult lymph node metastasis





Number at risk

pN0	2762	2689	2556	2408	2231	2032
Occult N1	118	112	104	79	63	45
Evident N1	141	132	99	82	65	51
Occult N2	234	211	175	142	114	85
Evident N2	282	251	197	150	106	76

Number at risk

pN0	2762	2554	2340	2148	2001	1859
Occult N1	118	98	78	53	43	35
Evident N1	141	100	61	50	39	31
Occult N2	234	163	118	96	75	60
Evident N2	282	189	123	94	74	48

Multivariable Cox analysis of OS (Ajusted for Age, Sex, Histology, pT stage and Adjuvant therapy)

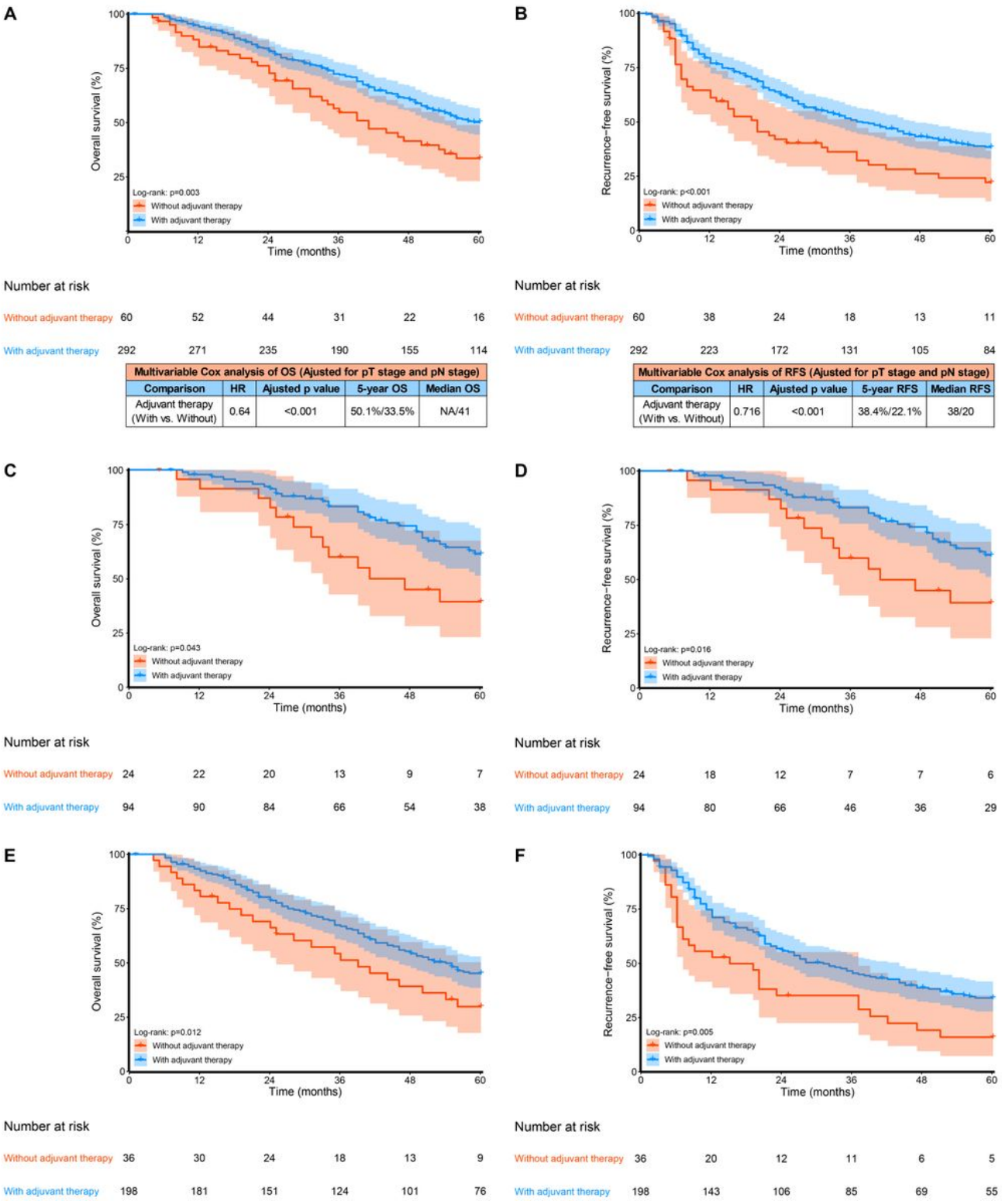
Comparison	HR	Ajusted p value	5-year OS	Median OS
Occult N1 vs. pN0	2.584	<0.001	56.8%/80.5%	NA/NA
Evident N1 vs. Occult N1	1.230	0.267	52.3%/56.8%	NA/NA
Occult N2 vs. Evident N1	1.307	0.071	42.8%/52.3%	51/NA
Evident N2 vs. Occult N2	1.321	0.010	32.3%/42.8%	42/51

Multivariable Cox analysis of RFS (Ajusted for Age, Sex, Histology, pT stage and Adjuvant therapy)

Comparison	HR	Ajusted p value	5-year RFS	Median RFS
Occult N1 vs. pN0	2.591	<0.001	44.7%/75.1%	46/NA
Evident N1 vs. Occult N1	1.436	0.031	33.2%/44.7%	28/46
Occult N2 vs. Evident N1	1.111	0.432	31.3%/33.2%	27/28
Evident N2 vs. Occult N2	1.259	0.025	21.6%/31.3%	21/27

Figure 2

Overall survival (A) and recurrence-free survival (B) curves of N classifications for the entire cohort HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival



Multivariable Cox analysis of OS (Ajusted for pT stage and pN stage)

Comparison	HR	Ajusted p value	5-year OS	Median OS
Adjuvant therapy (With vs. Without)	0.64	<0.001	50.1%/33.5%	NA/41

Multivariable Cox analysis of RFS (Ajusted for pT stage and pN stage)

Comparison	HR	Ajusted p value	5-year RFS	Median RFS
Adjuvant therapy (With vs. Without)	0.716	<0.001	38.4%/22.1%	38/20

Figure 3

Overall survival and recurrence-free survival curves of patients with and without adjuvant therapy for the ONM population (A & B), occult N1 population (C & D) and occult N2 population (E & F) ONM, occult lymph node metastasis; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival