



Lung cancer with PET/CT-defined occult nodal metastasis yields favourable prognosis and benefits from adjuvant therapy: a multicentre study

Jiajun Deng¹ · Yifan Zhong¹ · Tingting Wang² · Minglei Yang^{3,4} · Minjie Ma^{5,6} · Yongxiang Song⁷ · Yunlang She¹ · Chang Chen^{1,5,6} · the Multiomics classifier for pulmonary Nodules (MISSION) Collaborative Group

Received: 22 September 2021 / Accepted: 12 January 2022 / Published online: 20 January 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

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 was 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.

Keywords Non-small cell lung cancer · Lymph node metastasis · PET/CT · Prognosis

This article is part of the Topical Collection on Oncology - Chest

J Deng and Y Zhong contributed equally to this work; Y She and C Chen are co-corresponding authors.

✉ Yunlang She
langthoracic@tongji.edu.cn

✉ Chang Chen
changchenc@tongji.edu.cn

¹ Department of Thoracic Surgery, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai 200443, China

² Department of Radiology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

³ Department of Thoracic Surgery, Hwa Mei Hospital, Chinese Academy of Sciences, Zhejiang, China

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

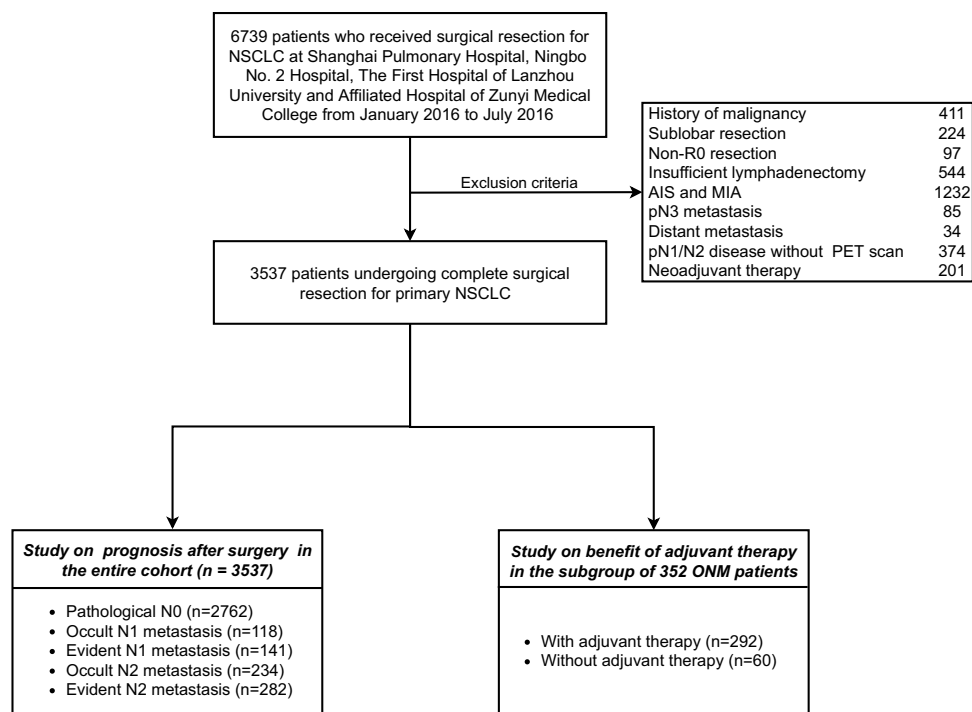
⁴ Ningbo Institute of Life and Health Industry, University of Chinese Academy of Sciences, Ningbo City, Zhejiang, China

⁵ Department of Thoracic Surgery, The First Hospital of Lanzhou University, Gansu, China

⁶ The International Science and Technology Cooperation Base for Development and Application of Key Technologies in Thoracic Surgery, Lanzhou, Gansu Province, China

⁷ Department of Thoracic Surgery, Affiliated Hospital of Zunyi Medical College, Zunyi Medical College, Guizhou, China

Fig. 1 Flowchart of study design. NSCLC, non-small cell lung cancer; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; ONM, occult 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 has 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 favour 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 tumours, 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.

Material 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),

Table 1 Baseline characteristics of the entire cohort

Characteristics	Entire cohort <i>n</i> = 3537	Occult N1 <i>n</i> = 118	Evident N1 <i>n</i> = 141	Occult N2 <i>n</i> = 234	Evident N2 <i>n</i> = 282	p1 value	p2 value
Age (years)						0.860	0.669
≤ 65, <i>n</i> (%)	2607 (73.70)	89 (75.40)	105 (74.50)	178 (76.10)	219 (77.70)		
> 65, <i>n</i> (%)	930 (26.30)	29 (24.60)	36 (25.50)	56 (23.90)	63 (22.30)		
Sex, <i>n</i> (%)						<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, <i>n</i> (%)						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, <i>n</i> (%)						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, <i>n</i> (%)						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, <i>n</i> (%)						<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, <i>n</i> (%)						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, <i>n</i> (%)						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, <i>n</i> (%)						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)		
Multi-station invasion, <i>n</i> (%)	0	17 (14.41)	27 (19.15)	103 (44.00)	154 (54.60)	0.311	0.017
Pathological TNM stage, <i>n</i> (%)						<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, <i>n</i> (%)	2132 (60.3)	94 (79.66)	112 (79.43)	198 (84.62)	242 (85.82)	0.964	0.702
Chemotherapy, <i>n</i> (%)	2063 (58.30)	90 (76.30)	107 (75.90)	174 (74.36)	206 (73.05)		
Radiotherapy, <i>n</i> (%)	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 n = 118	Evident N1 n = 141	Occult N2 n = 234	Evident N2 n = 282	p1 value	p2 value
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

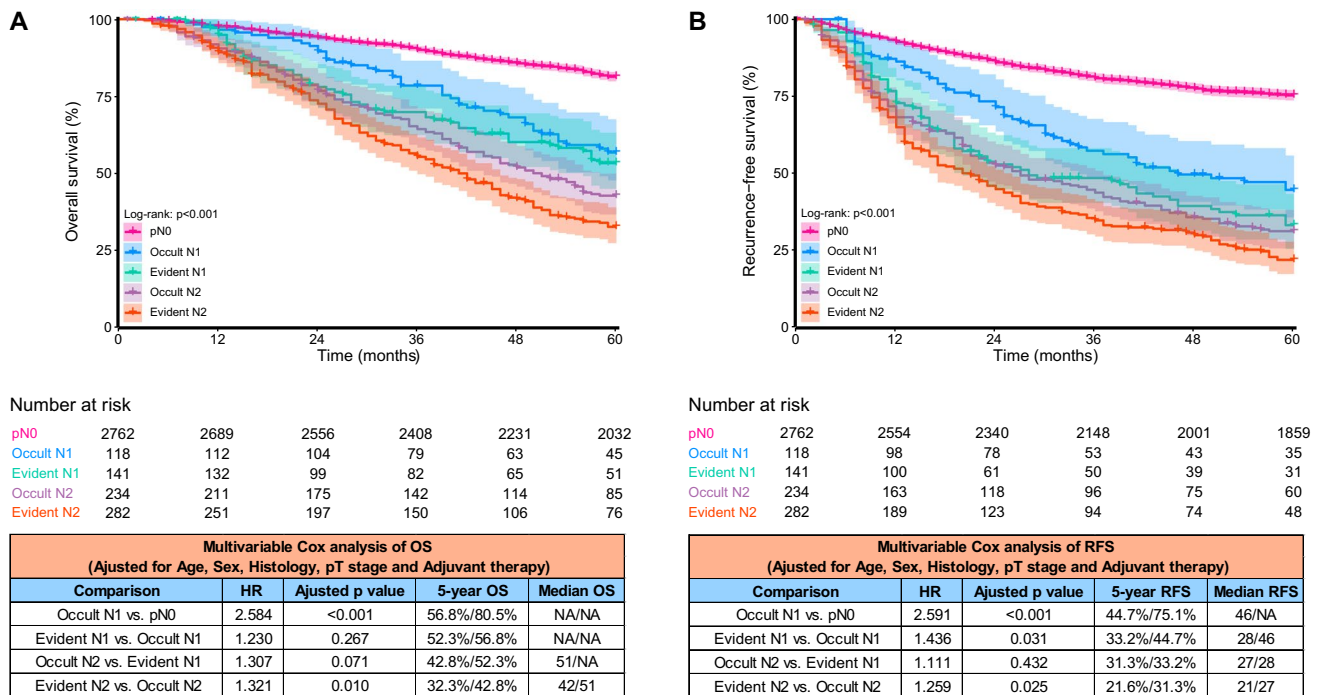


Fig. 2 Overall survival **A** and recurrence-free survival **B** curves of N classifications for the entire cohort. HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival

carcinoma in situ or minimally invasive carcinoma, pathological N3 involvement, distant metastasis, pathological lymph node metastasis but without PET/CT and conduction of neoadjuvant therapy. Finally, a total of 3537 NSCLC patients were included (Fig. 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

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)	<i>p</i> value	HR (95% CI)	<i>p</i> 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 (Adeno-carcinoma)	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

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 pre-operative PET/CT to confirm the reliability of the clinical staging in lymph node involved patients. ONM patients were defined as patients in whom there was no suspicion of lymph node involvement neither on CT (short-axis diameter < 1 cm), nor on PET (standardized uptake value < 2.5) [10]. The Parameters of The CT and PET Scanners were detailed in the supplementary material. The tumour stages were re-assessed according to eighth edition of the TNM staging system [1].

Adjuvant therapy and follow-up

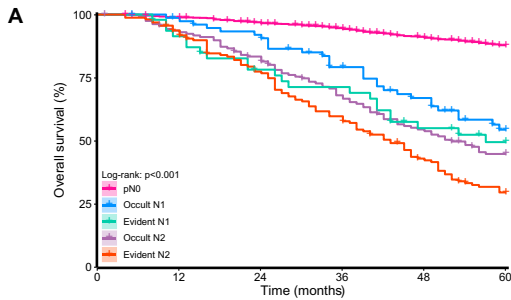
Adjuvant chemotherapy was conducted for stage IB diseases with high-risk factors and stage IIA-IIIB tumours after surgery. Platinum-based doublet regimens were given for 4–6 cycles (3 weeks per cycle) after surgery. Adjuvant radiotherapy was administrated for stage III-N2 diseases. A radiotherapy dose 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, and 12 months within the first postoperative year and then at 1-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. Patients alive would be censored at the last follow-up. 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. Patients alive or without recurrence would be censored at the last follow-up. All patients completed follow-up survey up to September 2021.

Statistical analysis

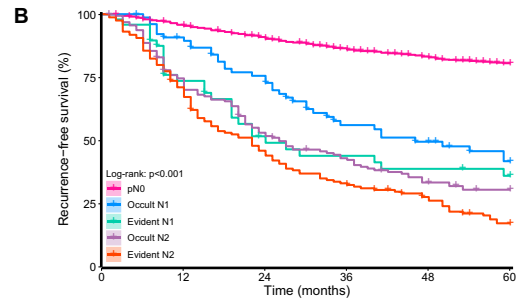
Categorical data were presented as frequency (percentage) and compared by Pearson χ^2 test or Fisher exact test. Normally distributed continuous parameters were exhibited as mean \pm standard deviation and analysed using Student *t*-test, and continuous variables in skewed distribution were described 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).



Number at risk

pN0	1666	1645	1603	1543	1467	1372
Occult N1	77	74	68	53	41	26
Evident N1	48	42	34	31	22	17
Occult N2	160	146	127	101	80	63
Evident N2	159	146	118	91	62	40

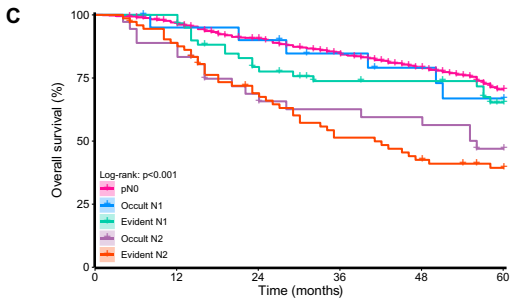
Multivariable Cox analysis of OS (Adjusted for Age, Sex, pT stage and Adjuvant therapy)				
Comparison	HR	Adjusted p value	5-year OS	Median OS
Occult N1 vs. pN0	4.439	<0.001	54.4%/87.8%	NA/NA
Evident N1 vs. Occult N1	1.302	0.343	49.4%/54.4%	57/NA
Occult N2 vs. Evident N1	1.085	0.732	44.8%/49.4%	52/57
Evident N2 vs. Occult N2	1.454	0.011	29.5%/44.8%	43/52



Number at risk

pN0	1666	1588	1499	1405	1332	1253
Occult N1	77	67	54	34	29	21
Evident N1	48	31	20	17	15	13
Occult N2	160	115	80	63	48	41
Evident N2	159	111	71	51	38	22

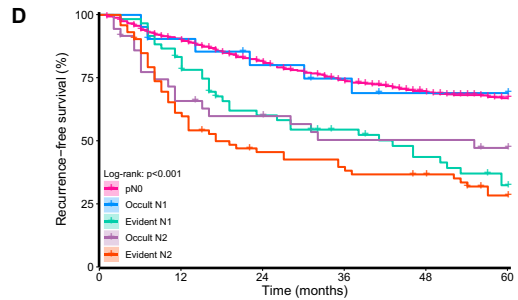
Multivariable Cox analysis of RFS (Adjusted for Age, Sex, pT stage and Adjuvant therapy)				
Comparison	HR	Adjusted p value	5-year RFS	Median RFS
Occult N1 vs. pN0	3.678	<0.001	41.7%/80.6%	46/NA
Evident N1 vs. Occult N1	1.406	0.049	35.9%/41.7%	24/46
Occult N2 vs. Evident N1	1.109	0.633	30.4%/35.9%	26/24
Evident N2 vs. Occult N2	1.354	0.021	17.1%/30.4%	22/26



Number at risk

pN0	809	773	700	633	558	469
Occult N1	21	19	18	15	13	11
Evident N1	60	60	44	37	36	28
Occult N2	36	32	23	20	19	14
Evident N2	73	64	47	35	29	24

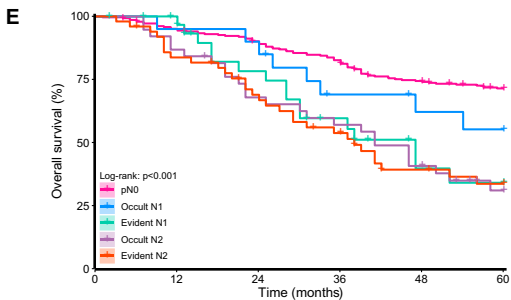
Multivariable Cox analysis of OS (Adjusted for Age, Sex, pT stage and Adjuvant therapy)				
Comparison	HR	Adjusted p value	5-year OS	Median OS
Occult N1 vs. pN0	1.139	0.753	66.9%/70.5%	NA/NA
Evident N1 vs. Occult N1	1.148	0.768	65.3%/66.9%	NA/NA
Occult N2 vs. Evident N1	1.847	0.062	47.0%/65.3%	56/NA
Evident N2 vs. Occult N2	1.225	0.471	39.4%/47.0%	41/56



Number at risk

pN0	809	721	628	546	484	430
Occult N1	21	18	15	13	11	11
Evident N1	60	49	32	26	20	14
Occult N2	36	23	20	16	16	14
Evident N2	73	44	31	27	24	16

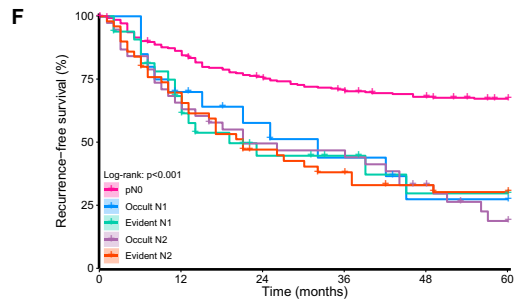
Multivariable Cox analysis of RFS (Adjusted for Age, Sex, pT stage and Adjuvant therapy)				
Comparison	HR	Adjusted p value	5-year RFS	Median RFS
Occult N1 vs. pN0	0.959	0.919	69.0%/67.0%	NA/NA
Evident N1 vs. Occult N1	2.258	0.035	32.5%/69.0%	43/NA
Occult N2 vs. Evident N1	0.878	0.652	47.3%/32.5%	55/43
Evident N2 vs. Occult N2	1.526	0.047	28.4%/47.3%	17/55



Number at risk

pN0	287	271	253	232	206	191
Occult N1	20	19	18	11	9	8
Evident N1	33	30	21	14	7	6
Occult N2	38	33	25	21	15	8
Evident N2	50	41	32	24	15	12

Multivariable Cox analysis of OS (Adjusted for Age, Sex, pT stage and Adjuvant therapy)				
Comparison	HR	Adjusted p value	5-year OS	Median OS
Occult N1 vs. pN0	1.677	0.164	55.2%/71.5%	NA/NA
Evident N1 vs. Occult N1	1.664	0.240	34.1%/55.2%	47/NA
Occult N2 vs. Evident N1	1.140	0.683	31.0%/34.1%	41/47
Evident N2 vs. Occult N2	1.002	0.936	33.7%/31.0%	38/41



Number at risk

pN0	287	245	213	197	185	176
Occult N1	20	13	9	6	3	3
Evident N1	33	20	9	7	4	4
Occult N2	38	25	18	17	11	5
Evident N2	50	34	21	16	12	10

Multivariable Cox analysis of RFS (Adjusted for Age, Sex, pT stage and Adjuvant therapy)				
Comparison	HR	Adjusted p value	5-year RFS	Median RFS
Occult N1 vs. pN0	2.589	0.002	27.5%/67.3%	32/NA
Evident N1 vs. Occult N1	1.079	0.839	29.8%/27.5%	19/32
Occult N2 vs. Evident N1	1.141	0.660	18.9%/29.8%	21/19
Evident N2 vs. Occult N2	0.913	0.772	30.3%/18.9%	21/21

Fig. 3 Overall survival and recurrence-free survival curves of N classifications for patient with adenocarcinoma (A & B), squamous cell carcinoma (C & D) and other histologies (E & F). HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival

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 tumours ($n=3145$, 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 Fig. 2 and 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). Subgroup analyses based on histology were illustrated in Fig. 3, for adenocarcinoma, ONM patients

yielded significantly favourable prognosis than those with evident nodal metastasis no matter in N1 (5-year OS: 54.5% [43.3–68.3%] versus 49.4% [36.4–67.1%], adjusted p value = 0.342; 5-year RFS: 41.7% [31.1–56.0%] versus 35.9% [23.8–54.3%], adjusted p value = 0.049) or N2 disease (5-year OS: 44.8% [37.4–53.5%] versus 29.5% [23.0–37.9%], adjusted p value = 0.011; 5-year RFS: 30.4% [23.9–38.8%] versus 17.1% [12.0–24.6%], adjusted p value = 0.021). Similarly, for patients with squamous cell carcinoma, the occurrence of ONM was relevant to significantly improved prognosis compared with evident nodal metastasis in both N1 (5-year OS: 66.9% [48.2–92.9%] versus 65.3% [53.6–89.4%], adjusted p value = 0.768; 5-year RFS: 69.0% [51.1–93.3%] versus 32.5% [21.7–48.7%], adjusted p value = 0.035) and N2 involvement (5-year OS: 47.0% [32.7–67.4%] versus 39.4% [29.3–52.9%], adjusted p value = 0.471; 5-year RFS: 47.3% [33.1–67.6%] versus 28.4% [19.4–41.7%], adjusted p value = 0.047). However, in other histologies, ONM did not predict improved prognosis whether in N1 (5-year OS: 55.2% [35.9–85.0%] versus 34.1% [18.8–61.9%], adjusted p value = 0.240; 5-year RFS: 27.5% [11.6–65.3%] versus 29.8% [14.7–60.5%], adjusted p value = 0.839) or N2 disease (5-year OS: 31.0% [18.8–51.2%] versus 33.7% [22.0–51.5%], adjusted p value = 0.936; 5-year RFS: 18.9% [9.1–39.0%] versus 30.3% [19.4–47.4%], adjusted p value = 0.772).

Adjuvant therapy benefits of ONM

In the ONM population ($n=352$), adjuvant therapy was administered 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 Fig. 4 & 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 two questions: does ONM defined by PET/CT yield better prognosis than evident nodal metastasis? If such is the case, should ONM population be considered as patients without histological nodal invasion, or as genuine positive nodal invasion?

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

Characteristics	Without adjuvant therapy <i>n</i> = 60	Without adjuvant therapy <i>n</i> = 292	p value
Age (years)			0.135
≤ 65, <i>n</i> (%)	41 (68.30)	226 (77.40)	
> 65, <i>n</i> (%)	19 (31.70)	66 (22.60)	
Sex, <i>n</i> (%)			0.329
Male	37 (61.67)	160 (54.79)	
Female	23 (38.33)	132 (45.21)	
Smoking, <i>n</i> (%)			0.284
Never	20 (33.30)	119 (40.80)	
Ever	40 (66.70)	173 (59.20)	
Surgery procedure, <i>n</i> (%)			0.501
Lobectomy	53 (88.30)	247 (84.60)	
Bilobectomy	2 (3.30)	22 (7.50)	
Pneumonectomy	5 (8.30)	23 (7.90)	
Location, <i>n</i> (%)			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, <i>n</i> (%)			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, <i>n</i> (%)			0.306
Absent	38 (63.30)	164 (56.20)	
Present	22 (36.70)	128 (43.80)	
Pathological T stage, <i>n</i> (%)			0.826
T1	22 (36.67)	92 (31.51)	
T2	31 (51.67)	170 (58.22)	
T3	4 (6.70)	18 (6.20)	
T4	3 (5.00)	12 (4.10)	
Pathological N stage, <i>n</i> (%)			0.642
N1	24 (40.00)	94 (32.19)	
N2	36 (60.00)	198 (67.81)	
Pathological TNM stage, <i>n</i> (%)			0.395
2	21 (35.00)	86 (29.45)	
3	39 (65.00)	206 (70.55)	

IQR, interquartile range

Regarding the first question, it is presumed that compared to evident nodal metastasis, ONM may represent a lower extent of nodal involvement and tumour metastasis burden, which could be proved by results of this study that ONM patients tended to have a lower frequency of visceral pleural metastasis (42.6% versus 48.9%) and multi-station involvement (34.1% versus 42.8%). In addition, the occurrence of ONM may imply less aggressiveness and proliferation of the primary tumour, which was also indicated by

the earlier T stage of ONM population in the current study (T3 and T4 stage: 10.5% versus 21.5%). Therefore, lower metastasis burden and less tumour aggressiveness of ONM jointly supported our hypothesis that ONM may be associated with better prognosis than evident nodal metastasis in patients with NSCLC.

In early studies, favourable prognostic impacts have been initially observed in ONM based on chest x-ray and bronchoscopy [11]. Thereafter, Andre et al. [12] claimed

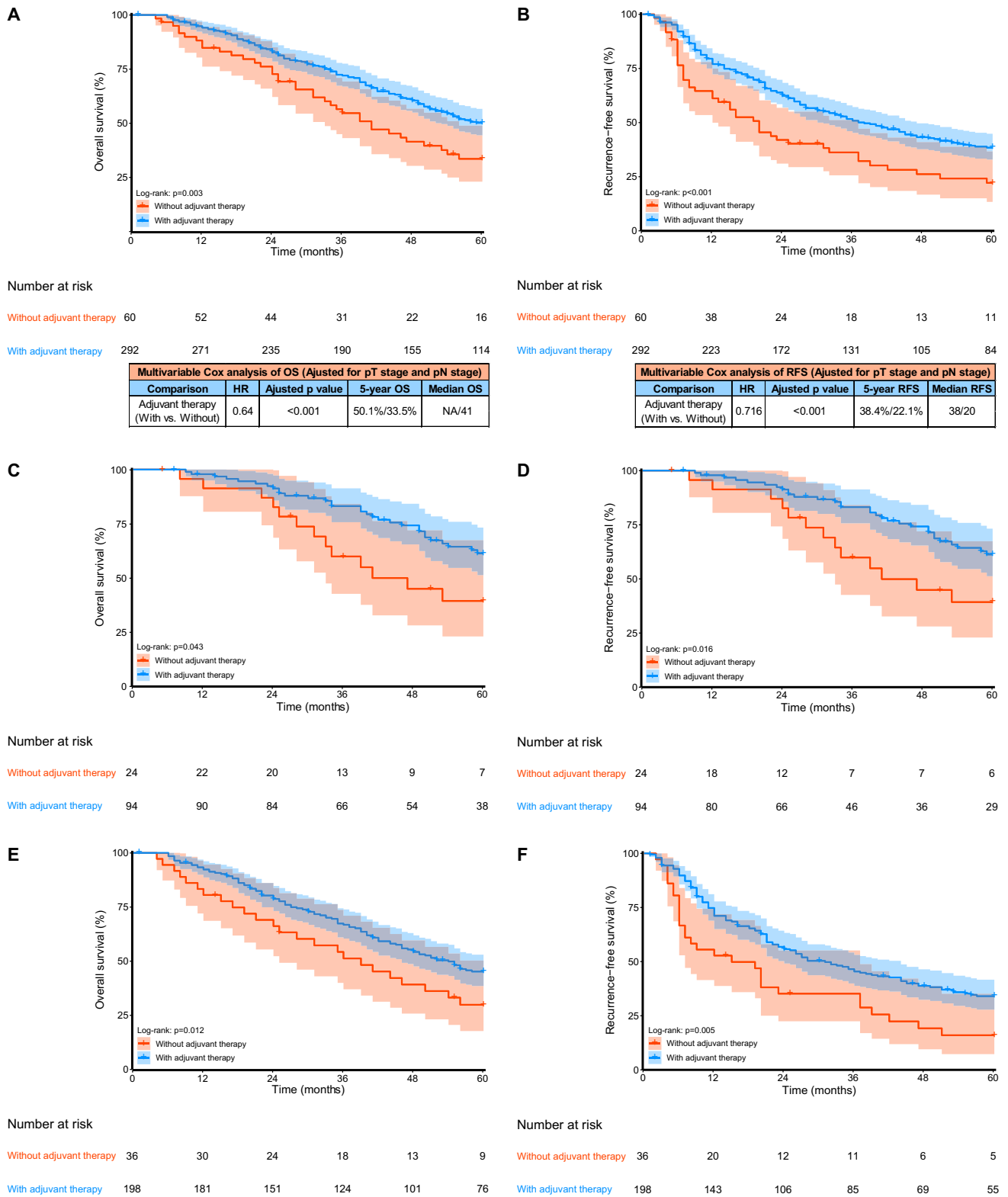


Fig. 4 Overall survival and recurrence-free survival curves of patients with and without adjuvant therapy for the ONM population (A & B), occult N1 population (C & D) and occult N2 population

(E & F). ONM, occult lymph node metastasis; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival

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)	<i>p</i> value	HR (95% CI)	<i>p</i> 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

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, Cerfolio RJ, et al. [17] reported the first large PET/CT cohort in 2008. This study, however, did not directly compare the prognosis of occult N2 and evident N2, they found the 5-year survival of patients with occult N2 was 35%, better than the 5-year survival rate reported in previous publications. As such, they did not provide direct evidence regarding the difference between the prognosis of occult and evident N2 disease. A recent study conducted in 2018 [13] revealed that N2 metastasis negative on PET/CT achieved excellent surgical prognosis with 5-year OS of 48%, but 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 or N2 metastasis. These results proved that ONM and evident nodal metastasis were basically two distinct groups of NSCLC.

Answers of the second question would determine the optimal therapeutic strategy of NSCLC with ONM. If ONM population could be considered as patients without histological nodal invasion, postoperative monitoring is sufficient for those without high-risk components. According to our results, ONM was associated with significantly adverse prognosis compared to pathological N0 disease. Therefore,

it would be more appropriate to classify ONM as genuine positive nodal invasion. In such instances, whether adjuvant therapy could confer additional survival benefits for ONM population becomes a crucial point. 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] analysed 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. Therefore, adjuvant therapy should be administrated as a routine procedure for ONM population.

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 handling the lymph nodes in the N1 region, station 12–14 nodes were not routinely dissected, which potentially resulted in the underestimation of N1 metastasis. Finally, all included patients underwent PET/CT scans in four hospitals, the discrepancies in nuclear medicine physicians reporting, patient management and scan protocols, such as different resolution the equipment employed, different administration of a carbohydrate free diet before scanning and different time for uptake, were inevitable, which might result in heterogeneous results. 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.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00259-022-05690-3>.

Author contribution 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. The authors are on behalf of the Multiomics classifier for pulmonary Nodules (MISSION) Collaborative Group.

Funding Supported by the National Natural Science Foundation of China (91959126, 8210071009), Science and Technology Commission of Shanghai Municipality (20XD1403000, 21YF1438200), Shanghai Municipal Health Commission (201940018), Shanghai Hospital Development Center (SHDC2020CR3047B), and Clinical Research Foundation of Shanghai Pulmonary Hospital (FK1943, FK1937).

Data availability Not applicable.

Code availability Not applicable.

Declarations

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.

Conflict of interest The authors declare no competing interests.

References

- Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol.* 2016;11:39–51. <https://doi.org/10.1016/j.jtho.2015.09.009>.
- National Comprehensive Cancer Network. (NCCN) Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer, Version 7. 2021. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 29 Oct 2021.
- Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet (London, England).* 2014;383:1561–71. [https://doi.org/10.1016/s0140-6736\(13\)62159-5](https://doi.org/10.1016/s0140-6736(13)62159-5).
- Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med.* 2004;350:351–60. <https://doi.org/10.1056/NEJMoa031644>.
- Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol.* 2008;26:3552–9. <https://doi.org/10.1200/jco.2007.13.9030>.
- Scagliotti GV, Pastorino U, Vansteenkiste JF, Spaggiari L, Facciolo F, Orlovski TM, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. *J Clin Oncol.* 2012;30:172–8. <https://doi.org/10.1200/jco.2010.33.7089>.
- Song WA, Zhou NK, Wang W, Chu XY, Liang CY, Tian XD, et al. Survival benefit of neoadjuvant chemotherapy in non-small cell lung cancer: an updated meta-analysis of 13 randomized control trials. *J Thorac Oncol.* 2010;5:510–6. <https://doi.org/10.1097/JTO.0b013e3181cd3345>.
- Uy KL, Darling G, Xu W, Yi QL, De Perrot M, Pierre AF, et al. Improved results of induction chemoradiation before surgical intervention for selected patients with stage IIIA-N2 non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2007;134:188–93. <https://doi.org/10.1016/j.jtcvs.2007.01.078>.
- Chen Z, Xiong S, Li J, Ou L, Li C, Tao J, et al. DNA methylation markers that correlate with occult lymph node metastases of non-small cell lung cancer and a preliminary prediction model. *Transl Lung Cancer Res.* 2020;9:280–7. <https://doi.org/10.21037/tlcr.2020.03.13>.
- Vaghjiani RG, Takahashi Y, Eguchi T, Lu S, Kameda K, Tano Z, et al. Tumor Spread Through Air Spaces Is a Predictor of Occult Lymph Node Metastasis in Clinical Stage IA Lung Adenocarcinoma. *J Thorac Oncol.* 2020;15:792–802. <https://doi.org/10.1016/j.jtho.2020.01.008>.
- Martini N, Flehinger BJ, Zaman MB, Beattie EJ Jr. Results of resection in non-oat cell carcinoma of the lung with mediastinal lymph node metastases. *Ann Surg.* 1983;198:386–97. <https://doi.org/10.1097/00000658-198309000-00015>.
- Andre F, Grunenwald D, Pignon JP, Dujon A, Pujol JL, Brichon PY, et al. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. *J Clin Oncol.* 2000;18:2981–9. <https://doi.org/10.1200/jco.2000.18.16.2981>.
- Kim MP, Correa AM, Hofstetter WL, Mehran RJ, Rice DC, Roth JA, et al. Occult stage IIIA-N2 patients have excellent overall survival with initial surgery. *J Thorac Dis.* 2018;10:6670–6. <https://doi.org/10.21037/jtd.2018.10.94>.
- Yang CF, Kumar A, Gulack BC, Mulvihill MS, Hartwig MG, Wang X, et al. Long-term outcomes after lobectomy for non-small cell lung cancer when unsuspected pN2 disease is found: A National Cancer Data Base analysis. *J Thorac Cardiovasc Surg.* 2016;151:1380–8. <https://doi.org/10.1016/j.jtcvs.2015.12.028>.
- Kim HK, Choi YS, Kim K, Shim YM, Park K, Ahn YC, et al. Outcomes of mediastinoscopy and surgery with or without neoadjuvant therapy in patients with non-small cell lung cancer who are N2 negative on positron emission tomography and computed tomography. *J Thorac Oncol.* 2011;6:336–42. <https://doi.org/10.1097/JTO.0b013e318201212e>.
- Whitson BA, Groth SS, Maddaus MA. Recommendations for optimal use of imaging studies to clinically stage mediastinal lymph nodes in non-small-cell lung cancer patients. *Lung cancer (Amsterdam, Netherlands).* 2008;61:177–85. <https://doi.org/10.1016/j.lungcan.2007.12.019>.
- Cerfolio RJ, Bryant AS. Survival of patients with unsuspected N2 (stage IIIA) nonsmall-cell lung cancer. *Ann Thorac Surg.* 2008;86:362–6; discussion 6–7. <https://doi.org/10.1016/j.athoracsur.2008.04.042>.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.