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Research article

Biological and clinical characteristics of non-small cell lung cancer non-specific subtype

Xiaohong Xie [a,1], Chen Zeng [a,1], Fei Wang [a], Guihuan Qiu [a], Ziyao Chen [a], Ting Liu [a], Xinqing Lin [a], Zhanhong Xie [a], Yinyin Qin [a], Yansheng Wang [a], Xiaodong Ma [b], Ming Liu [a,**], Chengzhi Zhou [a,*]

[a] *The First Affiliated Hospital of Guangzhou Medical University, National Center for Respiratory Medicine,National Clinical Research Center for Respiratory Disease,State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Health, Guangzhou, 510000, China*
[b] *Institute for Brain Research and Rehabilitation, Guangdong Key Laboratory of Mental Health and Cognitive Science, Center for Studies of Psychological Application, South China Normal University, Guangzhou, China*

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ABSTRACT

Background: Non-small cell lung cancer-not otherwise specified (NSCLC-NOS) is a rare subtype of NSCLC that cannot be classified specifically based on morphology and/or special staining. This study aimed to explore the clinical features, biological and pathological characteristics, treatment, and prognosis of NSCLC-NOS.

Methods: This retrospective study included NSCLC-NOS patients diagnosed and treated between 2010 and 2022. Clinical features, gene expression, first-line treatment, and prognosis were analyzed. Kaplan-Meier methods were calculated and log-rank tests and univariable and multivariable Cox regression analyses were performed to determine the relationship between prognostic factors and survival.

Results: Of 105 NSCLC-NOS patients, most were male (92.4 %), smokers (78.1 %), with a median age of 64 years, and advanced stage (IIIc-IV, 72.4 %). Immunohistochemical analysis showed minimal expression of p40, NapsinA, and TTF-1, whereas cytokeratin (CK) was expressed in 100 % of cases. 20.5 % of 39 patients who underwent genetic testing had driver gene mutations, including EGFR, KRAS, and ROS1. Among 69 patients with complete treatment information, 58 received platinum-based chemotherapy, with paclitaxel being the most commonly used combination chemotherapy drug (n = 25), followed by pemetrexed (n = 21). The objective response rate (ORR) of paclitaxel was found to be higher compared to pemetrexed (83.3 % vs. 54.5 %, P = 0.296). Furthermore, the combination of paclitaxel with immunotherapy demonstrated superior benefits in comparison to pemetrexed (76.9 % vs. 50.0 %, P = 0.367). The median progression-free survival (PFS) for patients treated with monotherapy paclitaxel, the paclitaxel-immunotherapy combination, and the pemetrexed-immunotherapy combination were 6.6 months (95 % CI: 1.508–11.692; P = 0.017), 15.7 months (95 % CI: 14.071–17.329; P = 0.017), and 11.8 months (95 % CI: 10.279–13.321; P = 0.324), respectively. The median overall survival

* Corresponding author. Guangzhou Institute of Respiratory Health, State Key Laboratory of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang Road, Guangzhou 510120, China.
** Corresponding author. Guangzhou Institute of Respiratory Health, State Key Laboratory of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang Road, Guangzhou 510120, China.
E-mail addresses: mingliu128@hotmail.com (M. Liu), zhouchengzhi@gird.cn (C. Zhou).
[1] These authors contributed equally to this article.

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(OS) was 13.6 months. Anatomic location (P = 0.026) and immunotherapy use (P = 0.003) were associated with OS. Multivariate analysis confirmed that anatomical location and immunotherapy use were factors influencing the prognosis.
Conclusion: NSCLC-NOS is common in male smokers and often diagnosed at an advanced stage with low mutation rate. Paclitaxel with immunotherapy may have better benefits as a first-line treatment. Anatomic location and immunotherapy use are prognostic factors.

1. Introduction

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 85 % of cases [1]. Different pathological subtypes have different molecular characteristics, treatment options, and prognoses. With the development of targeted therapy and immunotherapy, more precise pathological classification of lung cancer is required [2,3], including squamous cell carcinoma (SCC), adenocarcinoma (ADC), large cell carcinoma (LCC), and not otherwise specified (NOS). NOS refers to situations where there is not enough tissue to further classify or the further classification steps are unclear [4,5]. In 2015, the WHO stated that if routine pathology and immunohistochemistry (IHC) do not support the diagnosis of ADC and SCC [6,7], the term " NSCLC-NOS" can be used at the discretion of the pathologist. In 2021, the WHO stated that NSCLC-NOS is the morphological and/or special staining feature of NSCLC that cannot be further classified [8], and it is applicable in cases where IHC testing information is ambiguous or unclear. However, in most cases, the amount of tumor tissue obtained from the primary or metastatic site is limited, usually obtained through fine-needle aspiration cytology or small bronchoscopic biopsy, which can be used for pathological examination. In this situation, the morphological diagnostic criteria may fail, especially in cancers that lack special differentiation, making accurate histological typing difficult. The American Thoracic Society (ATS)/European Respiratory Society (ERS)/International Association for the Study of Lung Cancer (IASLC) guidelines recommend using IHC to distinguish subtypes in biopsy samples when accurate subtyping cannot be achieved based on morphology, including surgical specimens [9–11], cytology [12], or biopsy samples [13–16]. Studies have shown that using four markers (TTF-1, p63, Desmocollin-3, and Napsin-A) helps in lung cancer classification and can reduce the diagnostic category of NSCLC-NOS from 36 % to 14 % 17]. In addition, the study of lung cancer molecular pathology is rapidly developing, and targeted therapy and immunotherapy have become one of the main treatment methods, bringing new hope for these patients [17]. Due to the limited number of reports on NSCLC-NOS, this study aimed to analyze its clinicopathological and biological characteristics, treatment, and prognosis in order to improve the understanding of the diagnosis and treatment of this disease.

2. Patients and methods

2.1. Patients

The study included NSCLC-NOS patients treated at the First Affiliated Hospital of Guangzhou Medical University from January 2010 to December 2022. All diagnoses were confirmed by histopathology, and staging evaluations were conducted using the 8th edition of the AJCC TNM staging system, which included physical examination, chest computed tomography (CT), positron emission tomography-CT (PET-CT), magnetic resonance imaging (MRI), and bone scan [18]. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (approval number: 2022-194).

2.2. Diagnosis

Except for one patient who was diagnosed through pathological examination after surgery, all other patients were diagnosed through biopsy. Among them, 74 cases underwent fiberoptic bronchoscopy biopsy, and 30 cases underwent lung puncture biopsy.

2.3. Clinicopathological factors and observation endpoints

The study collected clinical and pathological factors, including age, gender, smoking history, performance status (PS) score, tumor location, baseline tumor size, TNM staging, presence of distant metastasis, and use of immunotherapy were collected. Non-smoking was defined as the consumption of fewer than 100 cigarettes throughout one's entire lifetime (Sun S, 2007). Overall survival (OS) was defined as the time from the start of the first treatment to death or last follow-up. Progression-free survival (PFS) was defined as the time from the first treatment to the first disease progression, death for any reason, or last follow-up.

2.4. Immunohistochemistry staining

Immunohistochemistry stains were performed using an automated immunostainer machine (LEICA, BOND-MAX, M495539, Germany). The following antibodies were utilized: cytokeratin (CK) (clone 830F6E7), CK7 (clone 435D4D6), p40 (clone 513M2A7), p63 (clone 281B6A9), NapsinA (clone 810B1C8), and thyroid transcription factor-1 (TTF1) (clone 847G1A6), in accordance with the manufacturer's instructions. Negative and positive controls were included in each batch to ensure accuracy.

2.5. DNA isolation, next generation sequencing (NGS) and fluorescent PCR

Formalin-fixed and paraffin-embedded (FFPE) sample DNA extraction was performed using the QIAamp DNA FFPE tissue kit (QIAGEN, Valencia, CA), followed by DNA concentration measurement using Qubitds (Thermo Fisher Scientific, Waltham, MA, USA). Subsequently, PCR amplification was carried out using magnetic bead enrichment of 200-400bp fragments and library construction was completed. After DNA library construction, the Burning Rock Biotech (Guangzhou, People's Republic of China) 1.67M 520-gene panel was used to capture human genome regions, followed by target region sequencing.

Fluorescent PCR was performed using the SuperARMS® technology from Amoy Diagnostics Co., Ltd. (AmoyDx), with the human EGFR mutation gene detection kit (multiplex fluorescent PCR, product number: January 8, 0147) and the human EGFR/ALK/ROS1 gene mutation combined detection kit (fluorescent PCR, product number: 8.0125501W008A).

2.6. Clinical assessment

Regular tumor assessments for all patients were carried out by CT-scan. Response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

2.7. Statistical analysis

The ORR comparisons among subgroups were conducted using the chi-square test. The Kaplan-Meier method was used to calculate survival rates, and the log-rank test was used to conduct univariate prognostic analysis using SPSS 25.0 software. The Cox proportional hazards regression model was used to analyze the factors affecting OS. A difference with a p-value less than 0.05 was considered statistically significant.

Table 1
Clinical data of 105 patients with NSCLC-NOS.

	n	Percent
Age (years)		
<65	54	51.4 %
≥65	51	48.6 %
Sex		
Male	97	92.4 %
Female	8	7.6 %
Smoking history		
Yes	82	78.1 %
No	23	21.9 %
ECOG PS		
<2	54	51.4 %
≥2	51	48.6 %
Baseline tumor size (cm)		
>3	89	84.8 %
≤3	16	15.2 %
Anatomical location		
Central type	43	41.0 %
Peripheral type	62	59.0 %
Tumor location		
Right lung	67	63.8 %
Left lung	34	32.4 %
other	4	3.8 %
Pathological diagnostic methods		
Postoperative pathology	1	1.0 %
Fiberoptic bronchoscopy biopsy	74	70.5 %
Percutaneous puncture biopsy	30	28.5 %
AJCC TNM staging		
I-IIIa	16	15.2 %
IIIb	13	12.4 %
IIIc-IV	76	72.4 %
Distant metastasis		
Yes	65	61.9 %
No	40	38.1 %
Use of immunotherapy[a]		
Yes[b]	33	47.8 %
No	36	52.2 %

[a] 69 patients had complete treatment data (chemotherapy, immunotherapy, targeted therapy).
[b] Among the 33 patients undergoing immunotherapy, 8 received it alone, while 25 received it alongside chemotherapy.

3. Results

3.1. Clinical, histological and biological features of NSCLC-NOS patients

A total of 105 patients were included in the study, with a median follow-up of 23.5 months (range: 6.6–47.7 months) and a median age of 64 years (range: 36–87 years). Most were male (n = 97, 92.4 %), smokers (n = 82, 78.1 %), and had a PS score of less than 2 points (n = 54, 51.4 %). Most tumors were located in the right lung (n = 67, 63.8 %) and in the peripheral area (n = 62, 59.0 %). The baseline tumor size was frequently greater than 3 cm (n = 89, 84.8 %). Stage IIIc-IV accounted for 72.4 % (n = 76), and distant metastasis was present in 61.9 % of patients (n = 65), with the most frequent sites being bone and adrenal glands (n = 48) (Table 1). Fig. 1A and B exhibit clear adenocarcinoma (ADC) or squamous cell carcinoma (SQCC) morphology. If there is no clear ADC or SQCC morphology, the tumor is pathologically diagnosed as NSCLC-NOS (Fig. 1C). IHC analysis showed that all patients had CK expression (92/92, 100 %), and 27 cases showed CK7 expression (27/31, 87.1 %). Regarding CK7, p40, p63, NapsinA, and TTF-1, 95.1 % (78/82), 78.9 % (60/76), 97.4 % (76/78), and 94.6 % (88/93) of individuals did not express these proteins, respectively. Gene testing was performed on 39 patients (Fig. 2), and 8 had driver gene mutations, with EGFR mutations being the most common (n = 4). One case had both TP53 and EGFR mutations, 3 cases had KRAS mutations, and 1 case had ROS1 mutation.

3.2. Treatments and outcomes

Sixty-nine patients had complete treatment information. Among them, 84 % of patients (n = 58) received platinum-based chemotherapy, with paclitaxel being the most used combination chemotherapy drug (n = 25, 43.1 %), followed by pemetrexed (n = 21, 36.2 %), docetaxel (n = 6, 10.3 %), and gemcitabine (n = 6, 10.3 %). The group of patients who received chemotherapy included those who were treated with chemotherapy alone (n = 33, 56.9 %) and those who received chemotherapy in combination with immunotherapy (n = 25, 43.1 %), including 13 with paclitaxel, 10 with pemetrexed, 1 with docetaxel, and 1 with gemcitabine. Among the 33 patients undergoing immunotherapy (PD-1 inhibitors), 8 received it alone, while 25 received it alongside chemotherapy. PD-1 inhibitors comprised sintilimab (n = 13), pembrolizumab (n = 8), camrelizumab (n = 6), tislelizumab (n = 3), and other (n = 3). Subsequent analysis of treatment efficacy revealed that the objective response rates (ORRs) for patients treated with paclitaxel and pemetrexed were 83.3 % and 54.5 %, respectively (P = 0.296) (Table 2). When combined with immunotherapy, paclitaxel exhibited a higher ORR than pemetrexed (76.9 % vs 50.0 %, P = 0.367), albeit without reaching statistical significance (Table 2).

3.3. Prognostic analysis

Univariate analysis indicated that (central type cancer) (P = 0.026, HR: 2.188) and immunotherapy treatment (P = 0.003, HR: 0.305) were prognostic factors for OS, while sex, age, smoking history, TNM stage, PS score, tumor baseline size, tumor location, and distant metastasis did not exhibit a significant association with prognosis (Table 3). Moreover, Cox regression analysis confirmed that anatomical location (P = 0.005, HR: 3.009) and immunotherapy use (P < 0.01, HR: 0.201) were significant factors affecting prognosis (Table 4). The median PFS for patients treated with monotherapy paclitaxel, paclitaxel-immunotherapy combination, and pemetrexed-immunotherapy combination were calculated using the Kaplan-Meier method with log-rank tests. It was found to be 6.6 months (95 % CI: 1.508–11.692; P = 0.017) (Fig. 3A), 15.7 months (95 % CI: 14.071–17.329; P = 0.017) (Figs. 3B), and 11.8 months (95 % CI: 10.279–13.321; P = 0.324) (Fig. 3C), respectively. The median OS of all patients was 13.6 months. Kaplan-Meier analysis indicated that the addition of immunotherapy to chemotherapy resulted in a more favorable OS compared to chemotherapy alone (P < 0.001), with the combination of paclitaxel and immunotherapy yielding better benefits (P = 0.010) (Fig. 4A, B and 4C). These findings suggest that the combination of chemotherapy and immunotherapy significantly enhances PFS and OS compared to chemotherapy alone. Particularly, the combination of paclitaxel and immunotherapy demonstrates notably superior benefits (Figs. 3C and 4C).

4. Discussion

NSCLC-NOS is an undifferentiated type of lung cancer that primarily affects male smokers [19]. We found that NSCLC-NOS was typically located in the right lung, predominantly presenting as a peripheral type, and had a lower mutation rate. This disease was

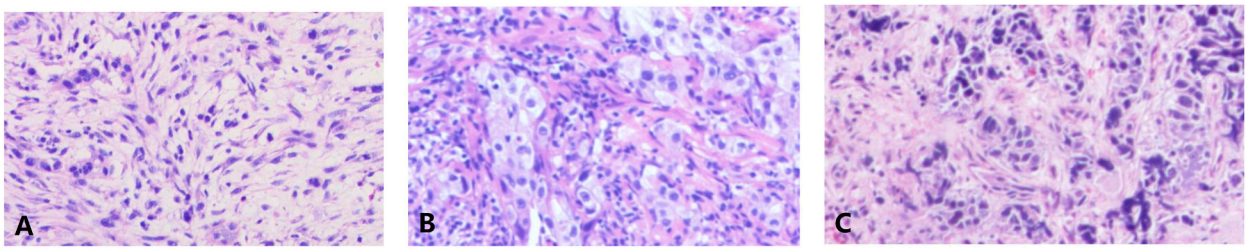

Fig. 1. Pathological findings (H.E. staining, × 100) revealed (A) a combination of squamous and glandular components, indicating the post-operative diagnosis of adenosquamous carcinoma, (B) keratinized cells, indicative of squamous cell carcinoma, and (C) NSCLC-NOS.

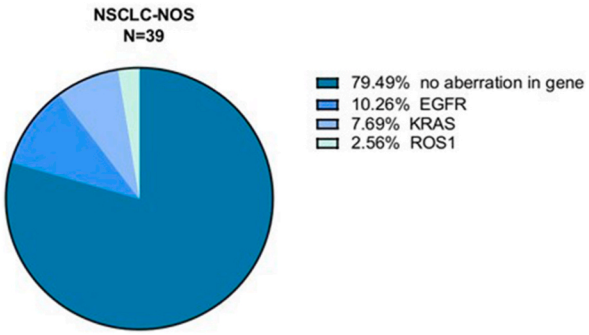

Fig. 2. The mutation status of driver genes in 39 patients with NSCLC-NOS.

Table 2
The Efficacy of paclitaxel or pemetrexed with or without immunotherapy.

Regimen	PR	PD or SD	ORR (%)	P
Paclitaxel	10	2	83.3	0.296
Pemetrexed	6	5	54.5	
Paclitaxel + immunotherapy	10	3	76.9	0.367
Pemetrexed + immunotherapy	5	5	50.0	

PR, partial response; PD, progressive disease; SD, stable disease; ORR, objective response rate.

Table 3
Univariate prognosis analysis for OS of patients with NSCLC-NOS.

Factors	B	df	P	Exp (B)	95 % CI for Exp (B)	
					lower limit	upper limit
Age (<65 vs ≥ 65years)	−0.289	1	0.407	0.749	0.378	1.483
Sex (Male vs Female)	−1.209	1	0.102	0.298	0.07	1.27
Smoking history (Yes vs No)	0.383	1	0.313	1.466	0.697	3.082
ECOG PS(<2 vs ≥ 2)	−0.096	1	0.783	0.909	0.459	1.8
Baseline tumor size (>3 vs ≤ 3 cm)	0.367	1	0.45	1.444	0.557	3.743
Anatomical location (Central vs Peripheral type)	0.783	1	0.026	2.188	1.099	4.357
Tumor location (Right vs Left lung vs Other)	0.345	1	0.736	1.412	0.189	10.539
AJCC TNM staging (I-IIIa vs IIIb vs IIIc-IV)	−0.569	1	0.351	0.566	0.171	1.872
Distant metastasis[a]						
Liver	−0.462	1	0.341	0.63	0.243	1.632
Brain	−0.569	1	0.183	0.566	0.245	1.308
Bone	−0.096	1	0.821	0.908	0.394	2.093
Adrenal gland	0.033	1	0.935	1.034	0.466	2.293
Other	−0.46	1	0.197	0.631	0.314	1.27
Use of immunotherapy (Yes vs No)	−1.186	1	0.003	0.305	0.142	0.659

[a] Some patients have multiple-site metastases.

Table 4
Multivariate analysis for OS using Cox model.

Factors	B	df	P	Exp (B)	95 % CI for Exp (B)	
					lower limit	upper limit
Age	−0.873	1	0.022	0.417	0.197	0.884
Anatomical location	1.102	1	0.005	3.009	1.384	6.541
Baseline tumor size	−0.057	1	0.913	0.944	0.336	2.653
Distant metastasis	−0.573	1	0.154	0.564	0.257	1.240
Use of immunotherapy	−1.605	1	<0.001	0.201	0.086	0.468

commonly detected in stages IIIc-IV, with a majority of patients presenting with distant metastases at the time of diagnosis. Single metastasis was more frequent, while multiple metastases were less common, with bones and adrenal glands being the most common sites of metastasis. Previous research has demonstrated that NSCLC-NOS exhibits the highest incidence of bone metastasis [20], which

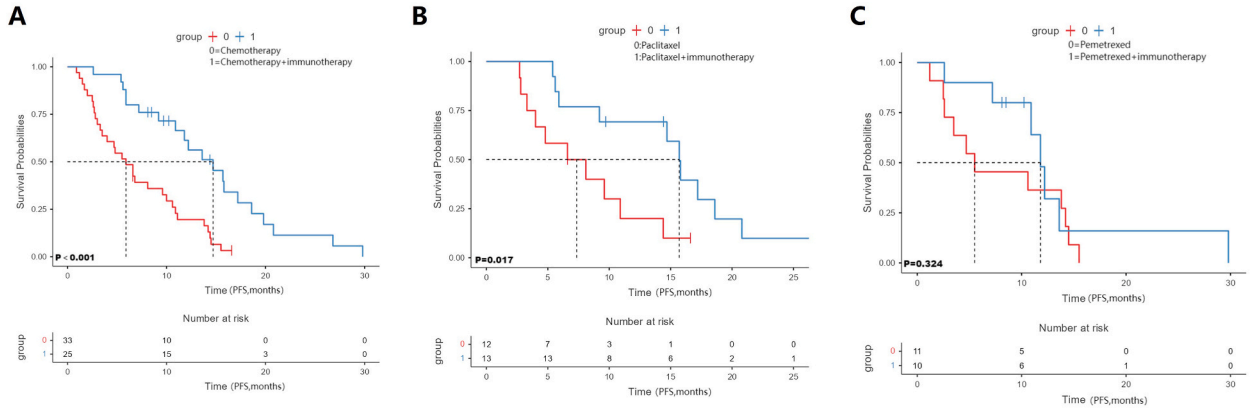

Fig. 3. Kaplan–Meier curve of PFS. (A) Chemotherapy vs. chemotherapy combined with immunotherapy; (B) Paclitaxel vs. paclitaxel combined with immunotherapy. (C) Pemetrexed vs. pemetrexed combined with immunotherapy.

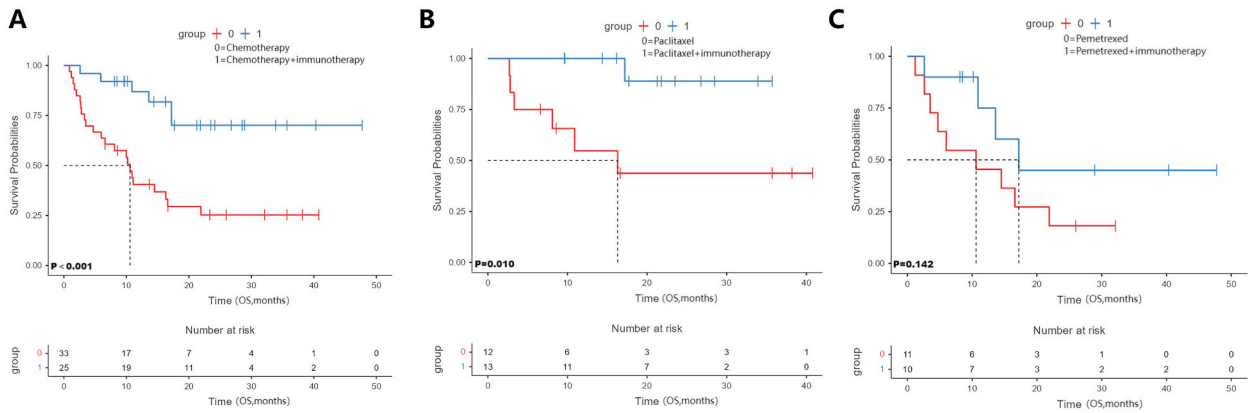

Fig. 4. Kaplan–Meier curve of OS. (A) Chemotherapy vs. chemotherapy combined with immunotherapy; (B) Paclitaxel vs. paclitaxel combined with immunotherapy. (C) Pemetrexed vs. pemetrexed combined with immunotherapy.

is consistent with the findings of our study. Additionally, NSCLC-NOS is generally diagnosed using cytology or biopsy specimens, rather than surgical resection specimens [21]. In our study involving 105 patients, only one patient was pathologically confirmed after surgery. The remaining 104 patients were diagnosed via biopsy, with 74 patients undergoing fiberoptic bronchoscopy biopsy and 30 patients undergoing lung puncture biopsy, consistent with prior reports.

In recent years, the detection rate of NSCLC-NOS has gradually declined with the continuous improvement of diagnostic techniques. Initially, studies indicated that NSCLC-NOS accounted for approximately 20 % [22]. However, other studies have reported that it accounts for about 10 % [23], and recent studies suggest that the detection rate has further decreased to 5 % 20]. These changes may be attributed to the improvement in histological classification in current research. In many cases, histological diagnosis is based on small tissue samples, which poses challenges in accurately subtyping the histology. In 2021, the World Health Organization (WHO) [8] provided a clear definition for NSCLC-NOS, which refers to cases where it is difficult to differentiate between ADC, SCC, or neuroendocrine tumors in small biopsy samples. Accurate histological diagnosis is crucial for the treatment of NSCLC. In 2015, WHO [24] recommended that if glandular or squamous differentiation is clearly visible on microscopy, then the tumor should be diagnosed as ADC or SCC, respectively. If there is uncertainty, it should be described as "poorly differentiated non-small cell carcinoma, favoring ADC or SCC". If the diagnosis of ADC and SCC cannot be supported by routine pathology and immunohistochemistry, the term " NSCLC-NOS" can be used appropriately. WHO [8] emphasizes that the principle is still based on morphology, supported by IHC, and finally, molecular testing. Ota et al. [25] conducted a study on 152 patients previously diagnosed with NSCLC-NOS based on morphology alone and performed IHC analysis for TTF-1, SP-A, p40, and CK5/6. The results indicated that 50 % of patients were classified as favoring ADC, 31 % were classified as favoring SCC, and 19 % were classified as NSCLC-NOS. Therefore, adding IHC to morphology improves the refinement of NSCLC histological classification compared to morphology alone. Other studies have suggested [24] that TTF-1 and p40 are the optimal markers for distinguishing between ADC and SCC histological subtypes. The use of these specific IHC markers can enhance diagnostic precision and prevent the diagnosis of NSCLC-NOS in up to 90 % of cases [26,27,28]. However, reports suggest that both lineage-specific markers are negative in approximately 15–20 % of cases [29,30]. Consistent with previous studies, immunohistochemical analysis in our study showed 100 % CK expression, 95.1 % p40 non-expression, 97.4 %

NapsinA non-expression, and 94.6 % TTF-1 non-expression.

In summary, the combined approach of morphology and IHC markers has made a significant improvement in the accurate subtyping of all undifferentiated lung cancers. Moreover, in this study, 8 cases (20.5 %) had driver gene mutations. There is a report indicating that in 920 cases of NSCLC-NOS, 42.5 % of patients had gene mutations (KRAS 27.7 %, EGFR 7.1 %, BRAF 2.6 %, MET 1.8 %, ALK 1.6 %, RET 1.0 %, and ROS1 and ERBB2 were both 0.3 %) [31]. This study differs from our study, possibly due to variations in patient populations. Furthermore, our study is a single-center retrospective analysis with a limited number of cases, which may introduce selection bias.

There are few literatures on the treatment of NSCLC-NOS, and its treatment principles mainly follow the treatment model of NSCLC, emphasizing comprehensive treatment. A study reported [32] a 74-year-old male patient diagnosed with primary NSCLC-NOS, clinically staged as IVb. Blood tests showed leukocytosis and abnormal expression of granulocyte colony-stimulating factor (G-CSF). TTF-1, Napsin A, p40, CgA, Syn, and CD56 immunostaining were negative. EGFR mutations and ALK rearrangements were not expressed. As PD-L1 is highly expressed in the patient's tumor cells, pembrolizumab monotherapy was chosen as initial treatment. The results of the study showed that pembrolizumab monotherapy may be an effective treatment for patients with advanced NSCLC-NOS who produce G-CSF, and white blood cell count monitoring may be a useful biomarker for predicting the efficacy of pembrolizumab monotherapy. Our study showed that chemotherapy combined with immunotherapy can improve PFS more than chemotherapy alone, and further exploration revealed that paclitaxel combined with immunotherapy had better benefits. There are few reports on the impact on prognosis, with studies indicating [33] that there is no difference in prognosis between the morphological ADC and NSCLC-tending ADC groups in advanced NSCLC patients receiving pemetrexed, while NSCLC-NOS has a significantly poorer prognosis in terms of PFS or OS. Our study analyzed the general clinical characteristics and the impact of treatment regimens on prognosis, and the results showed that anatomical location (central type) and the use of immunotherapy were prognostic factors for OS.

5. Limitations

There are some limitations of this study. Firstly, our study is a retrospective analysis in a single center, which inherently brings certain limitations, notably the small sample size. The small sample size limits the statistical power of the study and should be considered when interpreting the results. Future research could benefit from a prospective approach with a larger cohort to validate and expand upon our findings. Secondly, the variability in chemotherapy regimens among the patients may introduce variability in the therapeutic responses and survival outcomes. Future investigations should aim to implement standardized protocols to ensure that results are attributable to the studied variables and not to differences in treatment regimens. Lastly, radiation therapy, as one of the major treatment methods for tumor treatment, was not covered in this study. We intend to include radiation therapy to provide a more comprehensive understanding of all potential treatment options for NSCLC-NOS.

6. Conclusions

In conclusion, anatomical location and the use of immunotherapy were identified as prognostic factors. Paclitaxel combined with immunotherapy was found to be more beneficial in first-line treatment regimens. Therefore, combining paclitaxel with immunotherapy in first-line treatment could enhance patient outcomes. However, challenges such as retrospective analysis, single-center data, small sample size, and variable chemotherapy protocols need consideration. Integrating these recommendations into practice requires standardized protocols, larger studies for validation, and interdisciplinary collaboration among healthcare providers.

CRediT authorship contribution statement

Xiaohong Xie: Project administration, Investigation, Formal analysis, Conceptualization. **Chen Zeng:** Project administration, Methodology, Investigation, Formal analysis. **Fei Wang:** Software, Resources, Project administration, Methodology. **Guihuan Qiu:** Visualization, Validation, Supervision, Data curation, Conceptualization. **Ziyao Chen:** Formal analysis, Data curation, Conceptualization. **Ting Liu:** Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Xinqing Lin:** Project administration, Methodology, Investigation, Funding acquisition. **Zhanhong Xie:** Project administration, Methodology, Investigation, Data curation, Conceptualization. **Yinyin Qin:** Project administration, Methodology, Investigation. **Yansheng Wang:** Software, Resources, Project administration, Methodology, Data curation, Conceptualization. **Xiaodong Ma:** Project administration, Methodology, Investigation. **Ming Liu:** Visualization, Validation, Supervision. **Chengzhi Zhou:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethics statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (approval number: 2022-194). Written informed consent was obtained from all patients. All patients whose data or images are included in this article have provided explicit consent for the publication of all images, clinical data, and other relevant information. No identification of the participant's identity is present neither in the manuscript nor in the images or tables.

Data availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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