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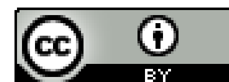

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ABSTRACT

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SMOKING AS A PREDICTOR OF IMMUNE CHECKPOINT INHIBITOR EFFICACY IN METASTATIC NON-SMALL CELL LUNG CANCER PATIENTS

Immunotherapy is currently the most promising treatment approach for metastatic non-small cell lung cancer (mNSCLC). Despite significant improvements clinical outcomes, prognostic criteria for responses to immune checkpoint inhibitors (ICIs) remain evasive. Smoking is one of the most common causes of lung cancer. However, several studies have confirmed the positive prognostic value of smoking in patients treated with ICI.

The aim of the study was to evaluate the prognostic significance of smoking status in mNSCLC patients treated with ICIs and to compare clinical outcomes by type of medication therapy and smoking history.

Materials and methods. This retrospective cohort study included 205 patients with mNSCLC treated at Sumy Regional Clinical Oncology Center (2016–2024). Among them, 105 patients received ICI therapy (atezolizumab or pembrolizumab), and 100 received platinum-based chemotherapy. Patients were stratified into never-smokers, light smokers (<28 pack-years), and heavy smokers (≥28 pack-years). Clinical outcomes – progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) – were analyzed using Kaplan–Meier and Cox regression models.

Results. In the immunotherapy group, heavy smokers exhibited significantly better PFS (15.3 vs. 8.5 and 8.1 months; p=0.0001), OS (23.3 vs. 12.6 and 9.7 months; p=0.0013), and ORR (75.6% vs. 41.9% and 23.8%) compared to light smokers and never-smokers. Conversely, in the chemotherapy group, non-smokers had superior outcomes. PD-L1 overexpression and heavy smoking were identified as independent predictors of improved survival in ICI-treated patients (p<0.05).

Conclusion. Heavy smokers receiving ICI therapy experienced more prolonged survival and better objective response rates than light smokers and never-smokers. In contrast, smokers treated with chemotherapy or

chemoradiotherapy had worse survival and objective response rates than never-smokers.

Keywords: heavy smokers, pack-years, non-small cell lung cancer, immune checkpoint inhibitor, efficacy.

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ПАЛІННЯ ЯК ПРЕДИКТОР ЕФЕКТИВНОСТІ ІНГІБІТОРІВ ІМУННИХ КОНТРОЛЬНИХ ТОЧОК У ХВОРИХ НА МЕТАСТАТИЧНИЙ НЕДРІБНОКЛІТИННИЙ РАК ЛЕГЕНЬ

Імунотерапія в даний час є найбільш перспективним підходом до лікування метастатичного недрібноклітинного раку легень (мНДКРЛ). Незважаючи на значне покращення клінічних результатів, прогностичні критерії відповіді на інгібітори імунних контрольних точок (ІІКТ) залишаються невловимими. Паління є однією з найпоширеніших причин раку легень. Проте кілька досліджень підтвердили позитивну прогностичну цінність паління у пацієнтів, які отримували лікування ІІКТ.

Метою дослідження було оцінити прогностичне значення статусу паління у пацієнтів з мНДКРЛ, які отримували лікування ІІКТ, і порівняти клінічні результати за типом медикаментозної терапії та історією куріння.

Матеріали та методи. Це ретроспективне когортне дослідження включало 205 пацієнтів з мНМРЛ, які проходили лікування в Сумському обласному клінічному онкологічному центрі (2016–2024 рр.). Серед них 105 пацієнтів отримували ІІКТ (атезолізумаб або пембролізумаб), а 100 отримували хіміотерапію на основі платини або хіміопроменеву терапію. Пацієнти були розділені на тих, хто ніколи не курив, тих, хто палив помірно (<28 пачко-років) і завзятих курців (≥28 пачко-років). Клінічні результати – виживаність без прогресування, загальна виживаність і об'єктивна відповідь на лікування – були проаналізовані за допомогою методу Каплана–Майєра та регресійної моделі Кокса.

Результати. У групі імунотерапії у завзятих курців спостерігали значно кращу виживаність без прогресування (15,3 проти 8,5 і 8,1 місяців; p=0,0001), загальну виживаність (23,3 проти 12,6 і 9,7 місяців; p=0,0013) та об'єктивну відповідь на лікування (75,6% проти 41,9% і 23,8%) порівняно з помірними курцями та пацієнтами, які ніколи не палили. Навпаки, у групі хіміотерапії некурці мали кращі результати. Гіперекспресія PD-L1 і інтенсивне паління були визначені як незалежні предиктори покращення виживання пацієнтів, які отримували ІІКТ (p<0,05).

Висновок. Завзяті курці, які отримували терапію ІІКТ, мали довшу виживаність і кращу об'єктивну відповідь на лікування, ніж помірні курці та ті, хто ніколи не палив. Навпаки, курці, які отримували хіміотерапію або хіміопроменеву терапію, мали гірші показники виживаності та об'єктивної відповіді на лікування, ніж ті, хто ніколи не палив.

Ключові слова: завзяті курці, пачко-роки, недрібноклітинний рак легень, інгібітор імунної контрольної точки, ефективність.

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INTRODUCTION

Immunotherapy is currently the most promising treatment approach for metastatic non-small cell lung cancer (mNSCLC). Despite significant improvements in patient survival, prognostic criteria for responses to immune checkpoint inhibitors (ICIs) remain evasive. The effectiveness of immunotherapy potentially depends on numerous factors, and therefore, the search for accessible and reliable prognostic biomarkers remains one of the pressing challenges in modern clinical oncology [1].

Smoking is one of the most common causes of lung cancer. Tobacco smoke contains over 79 carcinogens and approximately 9,500 harmful chemical compounds, including benzo[a]pyrene and nitrosoaminoketones [2]. Exposure to tobacco carcinogens leads to a substantial number of somatic mutations, resulting in a high tumor mutational burden [3] and a specific mutational signature (the smoking signature), which is characterized by C>A transversions. The pattern of somatic mutations in NSCLC patients varies significantly and largely depends on smoking history [4].

Smoking negatively affects not only DNA stability. Upregulation of the programmed death-ligand 1 (PD-L1) receptor impairs antitumor immune responses [5]. In healthy individuals, the PD-1/PD-L1 signaling pathway protects against autoimmune reactions. During carcinogenesis, tumor cells actively exploit this mechanism to evade immune response. As a result, smoking is strongly associated with PD-L1 overexpression. The longer a patient smokes, the higher the risk of dysregulation of receptor expression. The underlying mechanism is linked to the negative influence of benzo[a]pyrene on aryl hydrocarbon receptors (AhR). Expression levels of both PD-L1 and AhR are higher in tumor tissue of smokers compared to non-smokers [6].

Thus, smoking induces a high tumor mutational burden and PD-L1 overexpression. Interestingly, both biomarkers and microsatellite instability are key predictive factors of ICI therapy efficacy, as approved by the U.S. Food and Drug Administration (FDA) [7]. Understanding the interaction between smoking and the immune system has led to extensive investigation of the impact of this harmful habit on ICI effectiveness. Several studies have confirmed the positive prognostic value of smoking [8–10]. However, not all authors agree with this conclusion [11].

The present study aimed to evaluate the prognostic significance of smoking in patients with mNSCLC treated with ICIs and to analyze patient survival and treatment response according to the type of medication therapy and smoking status.

MATERIALS AND METHODS

Patient selection and data collection. A total of 205 patients with mNSCLC were enrolled in the study, including 105 patients who received immune ICI therapy (either in combination with chemotherapy or ICI monotherapy) and 100 patients treated only with platinum-based chemotherapy or chemoradiotherapy. The study was conducted at the Sumy Regional Clinical Oncology Center between 2016 and 2024.

To be included in the immunotherapy group, patients had to meet the following criteria: confirmed diagnosis of NSCLC, metastatic stage of the disease, administration of ICI therapy (atezolizumab or pembrolizumab), age 18 years or older, and available data on PD-L1 expression. Inclusion criteria for the chemotherapy group were age 18 years or older, platinum-based chemotherapy or chemoradiotherapy administration, and metastatic stage of NSCLC.

Clinical and pathological characteristics of the patients, including sex, age, smoking status, and type of medical treatment, were assessed prospectively. According to smoking status, patients were categorized as smokers or non-smokers. Non-smokers were defined as those who had smoked fewer than 100 cigarettes in their lifetime. Smokers included both former smokers who had quit more than one year prior and current smokers who had either quit less than one year ago or were still actively smoking. The number of pack-years was calculated using the formula: number of cigarette packs smoked per day × number of years smoked. The cut-off value for stratification based on pack-years was determined using the mean value method. Smokers with a smoking history of <28 pack-years were considered light smokers, and those with ≥ 28 pack-years were considered heavy smokers. The study was approved by the Bioethics Committee of the Medical Institute of Sumy State University (Protocol No. 3/12 dated December 17, 2024). All patients provided written informed consent.

Clinical outcomes. In the chemotherapy group, treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). In contrast, in the immunotherapy group, the response was assessed using immune-related response criteria (iRECIST). The objective response rate (ORR) was defined as the percentage of patients achieving complete or partial response to treatment. Progression-free

survival (PFS) was defined as the time from the first ICI or chemotherapy infusion to disease progression. Overall survival (OS) was defined as the time from treatment initiation to death.

Statistical analysis. Clinical and pathological patient data were presented as absolute numbers and percentages. Associations between smoking status, age, sex, PD-L1 expression, and type of medical treatment were evaluated using Fisher's exact test. Kaplan–Meier method was used to estimate median survival in the immunotherapy and chemotherapy groups and survival outcomes were visualized using Kaplan–Meier curves. The prognostic value of smoking was assessed using Cox proportional hazards regression modeling. Statistical analysis and graph generation were performed using Stata software version 18.0. A p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics. In the immunotherapy group, 21 (20.0%) patients were non-smokers, and 84 (80.0%) were smokers, including 43 (51.2%) light smokers and 41 (48.8%) heavy smokers. The study cohort included 16 (15.2%) women and 89 (84.8%) men, with a mean age of 60.9 years (range 34–78). A higher frequency of PD-L1 overexpression was observed among heavy smokers receiving ICI therapy (χ^2=33.8401, p=0.0001). Additionally, this subgroup included more patients aged ≥65 years compared to non-smokers and light smokers (χ^2=22.7028, p=0.0001; Table 1).

Table 1. Patients with mNSCLC in the immunotherapy group, stratified by smoking status

Clinicopathological characteristics	Immunotherapy group, n=105			χ2 (p)
	Light smokers, n=43	Heavy smokers, n=41	Never-smokers, n=21	
Age, n (%):				
Medium	60,8	60,9	61,0	**22,7028**
Range	36–78	34–78	49–74	**(0,0001)**
< 65	40 (93,0)	19 (46,3)	16 (76,2)	
≥ 65	3 (7,0)	22 (53,7)	5 (23,8)	
Sex, n (%):				
Female	7 (16,3)	6 (14,6)	3 (14,3)	0,0624
Male	36 (83,7)	35 (85,4)	18 (85,7)	(1,000)
PD-L1 expression, n (%):				
1–49%	42 (97,7)	20 (48,7)	20 (95,2)	**33,8401**
≥50%	1 (2,3)	21 (51,2)	1 (4,8)	**(0,0001)**
Type of medication therapy, n (%):				
ICI monotherapy	19 (44,2)	11 (26,8)	8 (38,1)	2,7792
ICI+chemotherapy	24 (55,8)	30 (73,2)	13 (61,9)	(0,261)

In the chemotherapy group, 17 (17.0%) patients were non-smokers, and 83 (83.0%) were smokers, including 43 (51.8%) light smokers and 40 (48.2%) heavy smokers. The cohort included 32 (32.0%) women and 68 (68.0%) men, with a mean age of 60.5 years (range 40–76). Female patients predominated among non-smokers receiving chemotherapy (χ^2=24.2545, p=0.0001). Furthermore, most heavy smokers were aged ≥65 years (χ^2=35.7655, p=0.0001; Table 2).

Table 2. Patients with mNSCLC in the chemotherapy group, stratified by smoking status

Clinicopathological characteristics	Chemotherapy group, n=100			χ2 (p)
	Light smokers, n=43	Heavy smokers, n=40	Never-smokers, n=17	
Age, n (%):				
Medium	60,4	60,6	60,5	**35,7655**
Range	40–76	41–74	45–70	**(0,0001)**
< 65	41 (95,3)	13 (35,3)	10 (64,7)	
≥ 65	2 (4,7)	27 (64,7)	7 (35,3)	
Sex, n (%):				
Female	8 (18,6)	10 (25,0)	14 (82,4)	**24,2545**
Male	35 (81,4)	30 (75,0)	3 (17,6)	**(0,0001)**
Type of medication therapy, n (%):				
Chemotherapy	38 (88,4)	37 (92,5)	15 (88,2)	0,4632
Chemoradiation therapy	5 (11,6)	3 (7,5)	2 (11,8)	(0,745)

Progression-free survival in the immunotherapy and chemotherapy groups. Disease progression was documented in 96/105 (91.4%) patients in the immunotherapy group and 83/100 (83.0%) in the chemotherapy group. In the immunotherapy group, the best PFS was observed in heavy smokers. Median PFS was 8.1 months, 8.5 months, and 15.3 months for non-smokers, light, and heavy smokers, respectively (Log-rank p=0.0001).

Conversely, in the chemotherapy group, the best PFS was recorded in non-smokers. Median PFS was 9.8 months, 7.0 months, and 6.6 months for non-smokers, light, and heavy smokers, respectively (Log-rank p=0.0002; Figure 1).

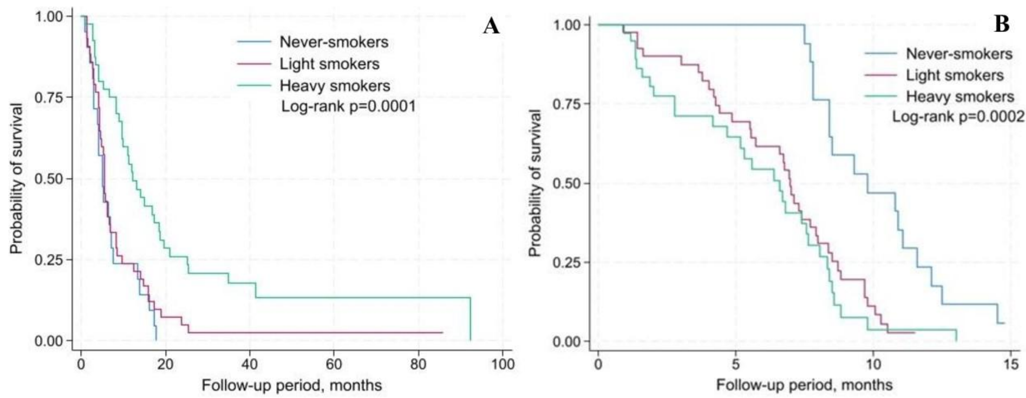

Figure 1. Progression-free survival in patients of the immunotherapy group (A) and chemotherapy group (B) depending on smoking status

Overall survival in the immunotherapy and chemotherapy groups

Death due to mNSCLC progression or other causes occurred in 100/105 (95.2%) patients in the immunotherapy group and 92/100 (92.0%) in the chemotherapy group. The OS pattern mirrored that observed for PFS. In the immunotherapy group, the best OS was recorded in heavy smokers. Median OS was 9.7 months, 12.6 months, and 23.3 months for non-smokers, light, and heavy smokers, respectively (Log-rank p=0.0013).

In contrast, in the chemotherapy group, the best OS was observed in non-smokers. Median OS was 16.8 months, 12.4 months, and 6.9 months for non-smokers, light, and heavy smokers, respectively (Log-rank p=0.0001; Figure 2).

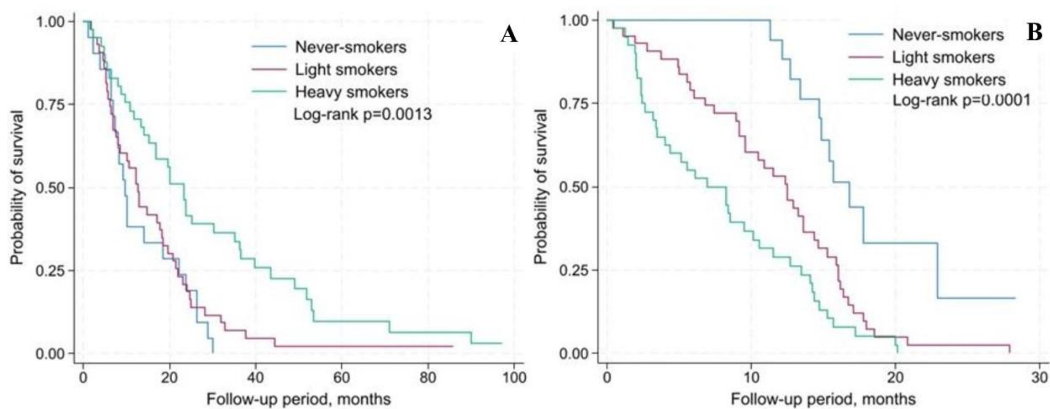

Figure 2. Overall survival in patients of the immunotherapy group (A) and chemotherapy group (B) depending on smoking status

Treatment response evaluation. In the immunotherapy group, ORR was achieved in 5/21 (23.8%) non-smokers, 18/43 (41.9%) light smokers, and 31/41 (75.6%) heavy smokers. In the chemotherapy group, ORR was achieved in 11/17 (64.7%) non-smokers, 15/43 (34.9%) light smokers, and 11/40 (27.5%) heavy smokers. A statistically significant difference in ORR was observed between heavy smokers in the immunotherapy and chemotherapy groups (75.6% vs. 27.5%, p=0.0045; Figure 3).

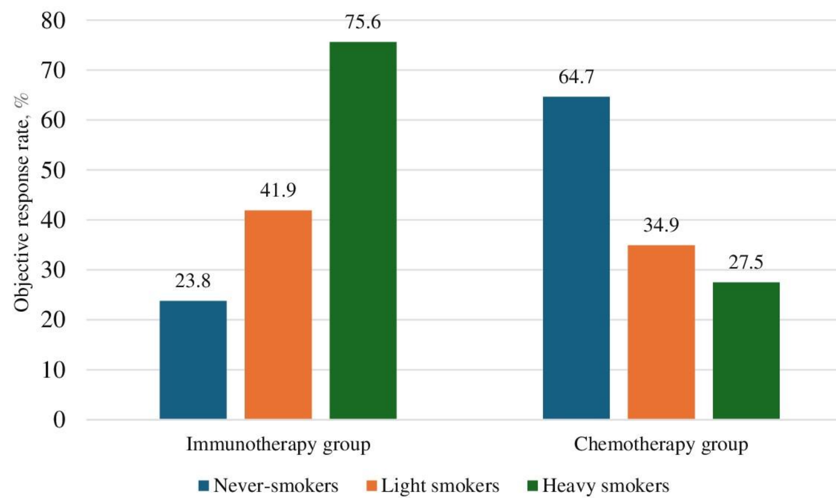

Figure 3. Objective response to treatment in the immunotherapy and chemotherapy groups depending on the smoking status of patients with mNSCLC

Independent predictors of survival in ICI-treated patients. PD-L1 expression and smoking status were found to have significant prognostic value. Patients with PD-L1 overexpression demonstrated improved PFS (HR=0.41, 95% CI 0.23–0.74, p=0.003) and OS (HR=0.40, 95% CI 0.22–0.73, p=0.003). A history of heavy smoking was also associated with a favorable prognosis. Heavy smokers treated with ICIs showed improved PFS (HR=0.88, 95% CI 0.62–1.30, p=0.026) and OS (HR=0.63, 95% CI 0.36–0.89, p=0.013; Table 3).

Table 3. Identification of independent predictors of survival in patients with mNSCLC treated with ICI (n=105)

Clinicopathological characteristics	Progression-free survival			Overall survival		
	HR	95% CI	p	HR	95% CI	p
Age (<65 versus ≥65)	0,99	0,61–1,62	0,992	0,98	0,61–1,58	0,946
Sex (male versus female)	1,22	0,71–2,11	0,460	1,17	0,67–2,04	0,569
PD-L1 expression (1–49% versus ≥50%)	0,41	0,23–0,74	0,003	0,40	0,22–0,73	0,003
Type of medication therapy (ICI monotherapy versus ICI+chemotherapy)	0,90	0,59–1,38	0,652	1,11	0,73–1,68	0,615
Smoking status:						
Never-smokers versus light smokers	0,74	0,51–1,00	0,056	0,79	0,56–1,09	0,162
Never-smokers versus heavy smokers	0,88	0,62–1,30	0,026	0,63	0,36–0,89	0,013

DISCUSSION

In the present study, we examined the association between clinical outcomes and the quantitative impact of smoking in patients with mNSCLC, stratified by the type of medication therapy. Notably, heavy smokers treated with ICIs demonstrated improved PFS and OS compared to non-smokers and light smokers. In contrast, smoking negatively impacted survival among patients receiving chemotherapy for treatment mNSCLC. Heavy smokers in our cohort were more likely to be aged ≥65 and had PD-L1 expression ≥50%. These findings suggest that, beyond PD-L1 expression, smoking pack-years may serve as an additional prognostic factor for ICI efficacy.

The impact of smoking on clinical outcomes in mNSCLC has been of considerable interest in the scientific community. Most studies categorize patients as never, former, or current smokers. Several studies have focused specifically on the influence of smoking on survival outcomes in patients undergoing ICI monotherapy. Reck et al. [12] reported that patients with high PD-L1 expression who received pembrolizumab had improved five-year survival compared to those treated with platinum-based chemotherapy or chemoradiation therapy (median OS: 26.3 months vs. 13.4 months). Former smokers derived greater benefit from ICI therapy, whereas never and current smokers experienced less favorable outcomes [13].

Similar observations were made in studies assessing the efficacy of atezolizumab monotherapy compared to chemotherapy in treatment-naïve mNSCLC patients. Greater clinical benefit from ICI therapy was reported

among current and former smokers than among never-smokers [14, 15]. However, in contrast to studies involving pembrolizumab and atezolizumab, the phase III MYSTIC trial did not demonstrate a statistically significant OS advantage for durvalumab, regardless of smoking status [16].

For patients with PD-L1 expression ranging from 1–49%, ICIs are commonly administered in combination with platinum-based chemotherapy. In the phase III KEYNOTE-189 trial, patients receiving pembrolizumab, pemetrexed, and cisplatin experienced superior OS compared to those receiving placebo with the same chemotherapy regimen (median OS: 22.0 months vs. 10.6 months). Although current and former smokers appeared to benefit more from the treatment, the difference was not statistically significant [17].

Atezolizumab has also improved clinical outcomes in patients with mNSCLC. The combination of carboplatin, nab-paclitaxel (or paclitaxel), and atezolizumab showed improved PFS compared to chemotherapy alone. Interestingly, never-smokers demonstrated better treatment outcomes, although the difference was minimal [18].

In the IMpower150 trial, current and former smokers had a better treatment response than never-smokers. The study randomized 1202 patients with mNSCLC into three groups: atezolizumab + chemotherapy, atezolizumab + bevacizumab + chemotherapy, and bevacizumab + chemotherapy. The highest OS was observed in the group receiving atezolizumab + bevacizumab + chemotherapy. Among smokers, median OS was 19.0 months in the atezolizumab + chemotherapy group, compared to 14.1 months in the bevacizumab + chemotherapy group [19].

Combining cemiplimab with platinum-based chemotherapy also improved survival compared to placebo + chemotherapy. Smoking-stratified analysis revealed that never-smokers derived no additional benefit from ICI therapy, whereas smokers achieved more favorable clinical outcomes [20].

Similar to our findings, some authors have explored the dose-dependent effects of smoking. The CarmeL-Sq trial enrolled 389 mNSCLC patients and demonstrated that combining camrelizumab with chemotherapy significantly outperformed the placebo-chemotherapy regimen. Heavy smokers treated with camrelizumab had significantly better survival than light or never-smokers [21]. Wang et al. [22] also reported a strong association between prolonged, intensive smoking and improved survival in patients receiving ICI monotherapy for mNSCLC, concluding that smoking pack-years may serve as a predictive marker of ICI efficacy.

Taken together, these findings suggest that smokers may derive greater benefits from ICI therapy. We hypothesize that the strong association between smoking and PD-L1 expression primarily drives this effect. In our study, the majority of patients with high PD-L1 expression had a smoking history of ≥28 pack-years. PD-L1 expression is a reliable predictor of ICI efficacy. Consequently, we observe a paradoxical phenomenon wherein intensive smoking correlates with improved clinical outcomes in patients receiving immunotherapy. Conversely, in the chemotherapy group, smoking was associated with worse outcomes. This may be attributable to impaired PD-L1 regulation in smokers and the absence of ICI therapy.

Our study has several limitations. PD-L1 expression was not assessed in the chemotherapy group. Additionally, molecular genetic testing and TMB analysis were not performed in either treatment group. The rationale for using 28 pack-years as a cut-off is based on mean value method, but a more standardized threshhold may improve generalizability.

CONCLUSIONS

Heavy smokers receiving ICI therapy experienced more prolonged survival and better objective response rates than light smokers and never-smokers. In contrast, smokers treated with chemotherapy or chemoradiotherapy had worse survival and objective response rates than never-smokers.

AUTHOR CONTRIBUTIONS

Conceptualization Y.M.; methodology Y.M., V.B., and A.B.; investigation Y.M. and V.B.; resources Y.M.; data curation Y.M.; writing – original draft preparation V.B., A.B. and Y.M.; writing—review and editing Y.M.; visualization Y.M.; supervision Y.M.; project administration Y.M.; funding acquisition Y.M. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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