Original paper

Correlation of programmed death cell ligand-1 expression in non-small cell lung cancer between small biopsy and surgical specimens

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Immunotherapy with programmed death cell ligand-1 (PD-L1) antibodies is an essential treatment for non-small cell lung cancer (NSCLC), and immunohistochemical assessment of PD-L1 expression is required for therapeutic stratification. This study analyzed PD-L1 expression in paired small biopsy and surgical specimens from patients with NSCLC, including adenocarcinoma and squamous cell carcinoma. Associations with the histological type, pathological stage, and clinicopathological parameters were evaluated, and concordance between biopsies and corresponding resections was assessed. A five-year retrospective-prospective study included 102 patients. Programmed death cell ligand-1 expression was determined by immunohistochemistry using monoclonal antibody clone 28-8.

Membranous staining in more than 1% of tumour cells was considered positive. No statistically significant difference in PD-L1 expression was found between small biopsy and surgical specimens ($p = 0.790$). Expression showed no significant association with patient age or gender. A significant association was observed between PD-L1 expression and smoking status in both specimen types ($p = 0.012$ and $p = 0.019$). Programmed death cell ligand-1 expression was not significantly related to the T descriptor ($p = 0.548$) or N descriptor ($p = 0.617$).

A statistically significant correlation was identified between PD-L1 positivity and disease stage ($p = 0.012$). The high concordance of PD-L1 expression between biopsy and surgical material supports use of biopsies for immunotherapy planning in ineligible patients and confirms reliability of resection specimens for adjuvant treatment decisions.

Key words: adenocarcinoma, squamous cell carcinoma, pulmonary neoplasms, immunotherapy, PD-L1.

Introduction

Lung cancer has remained the leading cause of cancer-related mortality and morbidity worldwide for several decades [1]. Despite the development of novel therapeutic models for non-small cell lung cancer (NSCLC), overall survival rates remain low [2].

Immunotherapy with immune checkpoint inhibitors, particularly programmed death cell ligand-1 (PD-L1) antibodies has become a standard treatment for NSCLC in patients whose tumours demonstrate PD-L1 expression by immunohistochemistry [3–6]. These agents have shown significant clinical benefits in both metastatic and locally advanced diseases [7].

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In the years, immune checkpoint inhibitors have also been increasingly used in adjuvant and neoadjuvant settings, either as monotherapy or in combination with chemotherapy [8].

Each PD-L1 antibody is associated with a specific companion or complementary diagnostics assay. Currently, four different antibodies and corresponding platforms are approved for use and each is related with a different immunotherapy agent [9].

One of the major challenges in immunohistochemical assessment of PD-L1 expression, particularly in small biopsy specimens, is intratumoural heterogeneity [6, 9, 10]. Small biopsies may sample only a limited portion of the tumour, raising concerns regarding their representativeness and the accuracy of PD-L1 evaluation when the entire tumour mass is not available or taken for analysis [8, 11].

The aims of this study were:

- to evaluate PD-L1 expression in small biopsy and surgical specimens from patients with NSCLC (adenocarcinoma and squamous cell lung carcinoma),
- to assess differences in PD-L1 expression between adenocarcinoma and squamous cell carcinoma,
- to investigate the association of PD-L1 expression and the pathological stage of the disease,
- and to examine the concordance of PD-L1 expression between small biopsy and corresponding surgical specimens.

Material and methods

A five-year retrospective-prospective study was conducted including 102 patients with NSCLC, comprising 51 adenocarcinomas and 51 squamous cell lung cancers. All cases were initially diagnosed in small biopsy specimens and subsequently confirmed in surgical specimens obtained after complete tumour resection. Small biopsy material was collected during diagnostic bronchoscopy and included transbronchial biopsy and transbronchial needle aspiration specimens. Surgical specimens consisted of lobectomy, segmentectomy, pneumonectomy, and wedge resection samples. All specimens were immediately fixed in 10% buffered formalin.

Inclusion criteria for patients were the presence of at least 100 viable tumour cells in small biopsy specimens and ≤ 20% tumour necrosis in surgical specimens. Exclusion criteria included specimens with > 20% necrosis, fewer than 100 of viable tumour cells, discordant histological diagnosis between biopsy and surgical specimens, multiple primary tumours, a history of malignancy at any site, or treatment with radiotherapy, chemotherapy or immunotherapy in the past.

Demographic data (gender and age) and smoking habits data were obtained from the institutional medical records.

Histological evaluation was performed using an *Olympus* BX 43 (Japan) microscope equipped with digital camera Olympus SC 50 (Japan) and CellSens entry digital image analysis software. According to current recommendations, one representative small biopsy specimen containing at least 100 tumour cells and one surgical specimen with ≤ 20% necrosis were selected based on hematoxylin and eosin-stained microscopical slides [12]. Tumour regions were randomly selected for analysis, excluding tissue edges and necrotic areas.

Immunohistochemical evaluation was performed on formalin-fixed paraffin-embedded tissue samples, following deparaffinization and rehydration. Programmed death cell ligand-1 expression was assessed using the monoclonal antibody clone 28-8 (Rabbit monoclonal 28-8; ab205921; Abcam, Cambridge, United Kingdom) and Dako Autostainer Link 48 according to the manufacturer's protocol. Programmed death cell ligand-1 positivity in NSCLC was partial or complete membrane expression of tumour cells, regardless of intensity. Cases with PD-L1 expression in > 1% of tumour cells were considered positive. Cytoplasmic or granular staining, staining of tumour associated immune cells, cellular debris, tissue edges and necrotic areas, were not included in the evaluation.

For surgical specimens, PD-L1 expression was assessed using tumour proportion score, calculated as the mean percentage of PD-L1 positive cells across multiple tumour areas. In small biopsy specimens, PD-L1 expression was assessed as the percentage of PD-L1 positive viable tumour cells among 100 evaluated tumour cells. Each staining run included an external positive control (placenta sample) and internal controls (alveolar macrophages and lymphocytes) [6, 12].

Statistical analysis was performed using IBM SPSS 24.0 statistical software. Descriptive statistics were expressed as mean value ±standard deviation or as frequencies and percentages, as appropriate. Group comparisons were performed using the non-parametrical χ^2 test and Mann-Whitney *U* test. Correlations were analyzed using Spearman's rank correlation coefficient. A p value < 0.05 was considered statisticallysignificant.

Results

There were 88.4% (80/102) male and 21.6% (22/102) female patients, with ages ranging 46–97, and an average of 63.43 ±7.67. The majority were current smokers 46.1% (47/102), followed by non-smokers 29.4% (30/102) and former smokers 24.5% (25/102). Slightly more patients had squamous cell lung cancer 52.9% (54/102) than adenocarcinoma 47.1% (48/102).

Analysis of the baseline characteristics demonstrated a statistically significant difference between smoking status and histological subtype. The pro-

Table I. Baseline characteristics of patients with non-small cell lung cancer

Parameters	Number of patients (p)	Age (p)	Smoking habits (p)	Histology (p)
Age	0.987	0.831		
Gender	0.001*	0.473	0.00001*	0.0001*
Smoking habits	0.020*	0.275	0.041	
Histology	0.621	0.143		

*$p < 0.05$

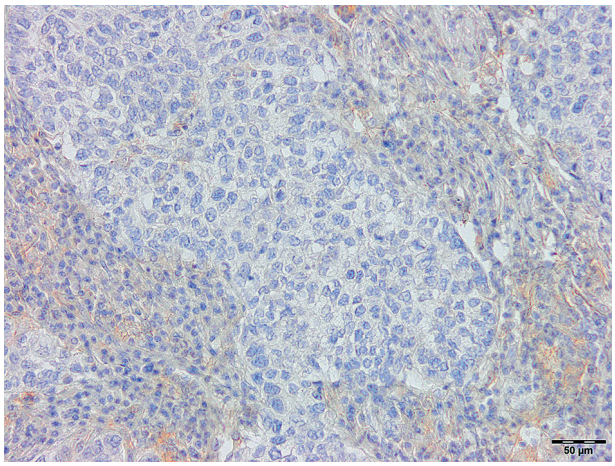

Figure 1. No programmed death cell ligand-1 expression in tumour cells

portion of current smokers was significantly higher among patients with squamous cell lung cancer compared with non-smokers, former smokers, and patients with lung adenocarcinoma (Table I).

Following the PD-L1 immunostaining of small biopsy and surgical samples, patients were stratified into five categories:

1. no PD-L1 expression in tumour cells (Figure 1),
2. PD-L1 expression in < 1% of tumour cells (Figure 2A),
3. PD-L1 expression in 1–5% of tumour cells (Figure 2B),
4. PD-L1 expression in 5–10% of tumour cells (Figure 2C),
5. PD-L1 expression in > 10% of tumour cells (Figure 2D).

The proportion of patients without PD-L1 expression was significantly higher in both small biopsy ($p < 0.0001$, χ^2 test) and surgical specimens ($p < 0.0001$, χ^2 test) (Figure 3). No statistically significant differences in PD-L1 expression were observed between small biopsy and surgical specimens with respect to demographic characteristics, smoking habits, and tumour histology ($p = 0.790$) (Table II).

Patients with positive PD-L1 expression were more frequently diagnosed with adenocarcinoma than with squamous cell lung cancer (Table III). However, there was no statistically significant difference in PD-L1 expression between adenocarcinoma and squamous cell lung cancer ($p = 0.383$, χ^2 test).

Among patients with adenocarcinoma and positive PD-L1 expression, the acinar subtype was the most frequent, followed by the solid type. All the cases with lepidic-type adenocarcinoma were negative for PD-L1 expression (Table IV). A statistically significant association was observed between PD-L1 expression and the histological type of adenocarcinoma ($p = 0.004$, χ^2 test).

Slightly more patients with squamous cell lung cancer had the non-keratinizing subtype (Table V). No statistically significant differences in PD-L1 expression were observed according to the histological type of squamous cell lung cancer.

Most of the patients, regardless of PD-L1 status, had tumours classified as T3, while the fewest patients had tumours with T1a descriptor (Table VI). No statistically significant association was observed between T descriptors and PD-L1 expression ($p = 0.548$, χ^2 test).

The N0 descriptor was the most frequent, and N2 the least frequent, among patients, regardless of PD-L1 expression (Table VII). There was no statistically significant difference between N descriptors and PD-L1 expression ($p = 0.617$, χ^2 test).

Most of the patients with positive PD-L1 expression were classified as stage IIIA, whereas most patients with negative expression were stage IIB (Table VIII). A statistically significant association was observed between PD-L1 expression and the disease stage ($p = 0.012$, χ^2 test).

Discussion

Lung cancer has been the most common carcinoma in terms of both incidence and mortality over the past several decades [9]. As more than 70% of patients are diagnosed at advanced stages of the disease, histological evaluation is frequently limited to small biopsy and/or surgical specimens. Consequently, therapeutic decisions are largely based on the findings obtained from these diagnostic samples.

The most appropriate therapeutic approach is determined based on the diagnostic histological specimen. Immunotherapy has been shown to improve overall survival and disease-free survival while avoiding many of the adverse effects commonly associated with other treatment modalities [4].

Programmed death cell ligand-1 expression analysis was introduced to identify patients with NSCLC

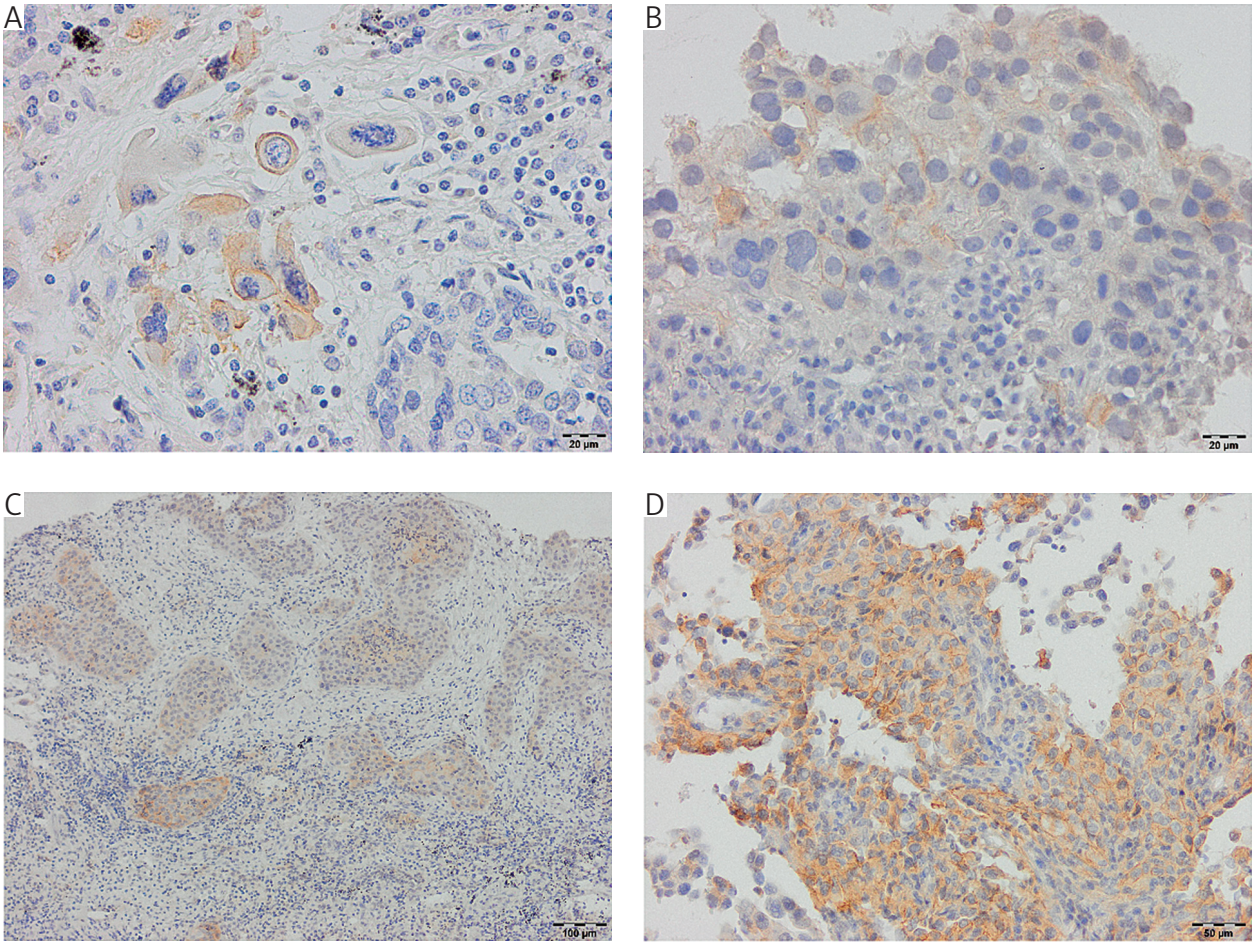

Figure 2. A) Programmed death cell ligand-1 (PD-L1) expression in < 1% of tumour cells. **B**) PD-L1 expression in 1–5% of tumour cells. **C**) PD-L1 expression in 5–10% of tumour cells. **D**) PD-L1 expression in > 10% of tumour cells

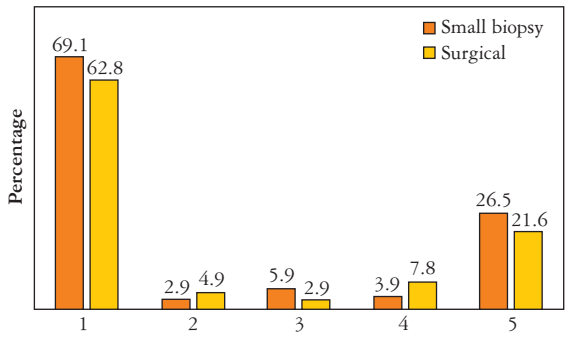

Figure 3. Programmed death cell ligand-1 expression in small biopsy and surgical specimens

Table II. Programmed death cell ligand-1 expression in different specimens according to demographic characteristics, smoking habits and tumour types

Parameters	Small biopsy (*p*)	Surgical specimens (*p*)
Age	0.987	0.831
Gender	0.347	0.561
Smoking habits	0.012*	0.019*
Histology	0.036*	0.352

*$p < 0.05$

Table III. Programmed death cell ligand-1 expression in different non-small cell lung cancer types – adenocarcinoma and squamous cell lung cancer

Parameters	Positive, *n* (%)	Negative, *n* (%)
Adenocarcinoma	18 (18)	33 (33)
Squamous cell lung cancer	13 (13)	38 (38)

*$p < 0.05$

Table IV. Programmed death cell ligand-1 expression in different histological types of lung adenocarcinoma

Parameters	Positive, *n* (%)	Negative, *n* (%)
Solid	5 (10)	10 (20)
Acinar	13 (25)	21 (41)
Lepidic	0 (0)	2 (4)

*$p < 0.05$

Table V. Programmed death cell ligand-1 expression in different histological types of squamous cell lung cancer

Parameters	Positive, *n* (%)	Negative, *n* (%)
Keratinizing	6 (12)	20 (39)
Non-keratinizing	8 (16)	17 (33)

** $p < 0.05$)*

Table VI. Programmed death cell ligand-1 expression in different T descriptors of the patients

Parameters	T1a, *n* (%)	T1c, *n* (%)	T2a, *n* (%)	T2b, *n* (%)	T3, *n* (%)	T4, *n* (%)
Positive	2 (2)	5 (5)	4 (4)	5 (5)	9 (8)	6 (6)
Negative	2 (2)	6 (6)	20 (20)	9 (8)	22 (22)	12 (12)

** $p < 0.05$*

Table VII. Programmed death cell ligand-1 expression in different N descriptors of the patients

Parameters	N0, *n* (%)	N1, *n* (%)	N2, *n* (%)	N3, *n* (%)
Positive	19 (19)	6 (6)	5 (5)	0 (0)
Negative	36 (36)	21 (21)	14 (14)	1 (1)

** $p < 0.05$*

Table VIII. Programmed death cell ligand-1 expression in different pathological tumour stages of the disease

Parameters	IA1, *n* (%)	IA3, *n* (%)	IB, *n* (%)	IIA, *n* (%)	IIB, *n* (%)	IIIA, *n* (%)	IIIB, *n* (%)	IIIC, *n* (%)
Positive	1 (1)	4 (4)	1 (1)	2 (2)	7 (7)	12 (12)	3 (3)	1 (1)
Negative	1 (1)	3 (3)	0 (0)	18 (18)	24 (24)	22 (22)	3 (3)	0 (0)

** $p < 0.05$*

who may benefit from immunotherapy, with the aim of improving overall survival and disease-free survival [12, 13]. Positive PD-L1 expression is a prerequisite for the administration of immune checkpoint inhibitors. To date, seven different antibodies have been used for PD-L1 assessment, including four approved by the Food and Drug Administration: 28-8, 22C3, SP263, and SP142 [12]. Given that each antibody is associated with a specific cut-off value for PD-L1 positivity, concerns have been raised regarding the comparability of results across studies. Previous investigations have demonstrated that assays using the 28-8, 22C3 and SP142 antibodies show acceptable comparability [4, 6]. Several studies comparing different antibodies and cut-off values reported similar concordance rates, with smaller differences in PD-L1 expression observed when a lower cut-off value of 1% was applied [14]. Notably, results obtained using 28-8 and 22C3 antibodies have been shown to be comparable regardless of selected cut-offs [14, 15].

It the present study, PD-L1 expression was evaluated using the 28-8 antibody in lung adenocarcinoma and squamous cell lung cancer. Programmed death cell ligand-1 positivity, defined by the cut-off value of 1%, was observed in 30% of patients. The proportion of patients without PD-L1 expression in surgical specimens was statistically significantly lower ($p < 0.001$), which is consistent with findings from meta-analysis using the same antibody, where PD-L1 positivity in surgical samples was 17–50%.

Most previous studies have investigated PD-L1 expression either in NSCLC as a whole or specifically in lung adenocarcinoma. In a meta-analysis involving more than 1,000 patients, PD-L1 expression in NSCLC, ranged from 7.4% in Australia to 75% in the United States. In several European countries included in that analysis, PD-L1 expression was reported in approximately 20% of NSCLC cases [16, 17]. These findings were concordant with data from other meta-analysis of surgically resected NSCLC specimens, in which PD-L1 expression assessed by immunohistochemistry was 7–50% [6].

Programmed death cell ligand-1 expression in tumour cells was observed more frequently in male patients in the present study, consistent with the findings reported in previous studies [17–23]. In our cohort, the number of males exhibiting positive PD-L1 expression was approximately three times higher than of females which is comparable to the results reported by Sun *et al*. [22], who found higher proportion of PD-L1 positivity among male patients. Despite this number difference, no statistically significant

association between genders and PD-L1 expression was identified in our study, either in small biopsies ($p = 0.34722$) or in surgical specimens ($p = 0.5614$). A higher proportion of the female patients lacked PD-L1 expression, in agreement with the findings of Tang *et al*. [24]. In contrast, other studied have reported conflicting results, with a higher frequency of PD-L1 positivity observed among female patients, including one study that demonstrated a statistically significant predominance of PD-L1 expression in women [13–25].

No statistically significant association between patient age and PD-L1 expression has been reported in the literature, nor was such an association observed in our study, either in small biopsies ($p = 0.987$) or in surgical specimens ($p = 0.831$) [19–24, 26–29]. However, two studies reported a higher proportion of PD-L1 negative cases among patients younger than 65 [22].

Evaluation of the association between smoking status and PD-L1 expression indicated that PD-L1 positivity tended to be most frequent among current smokers, followed by never-smokers and former smokers. A statistically significant difference in PD-L1 expression according to smoking status was observed in both small biopsy specimens ($p = 0.01208$) and surgical samples ($p = 0.01936$).

These findings are partially consistent with the study of Sun *et al*. [22], who reported a statistically significant association between smoking status and PD-L1 expression, with a higher proportion of smokers demonstrating PD-L1 positivity and an absence of PD-L1 expression among non-smokers. However, although smokers have generally been reported to constitute a larger proportion of PD-L1 positive patients in the literature, several studies have failed to demonstrate a statistically significant difference between smokers and patients with other smoking histories [20, 23–25, 27–29]. In contrast, a limited number of investigations have identified a statistically significant predominance of PD-L1 positivity among smokers [21, 30, 31]. D'Incecco *et al*. [32] reported a statistically higher proportion of patients lacking PD-L1 expression among both smokers and non-smokers, underscoring the heterogeneity of published data. Collectively, these findings suggest that smoking status may influence PD-L1 expression, although this relationship remains incompletely defined and may be affected by confounding factors, including differences in cohort composition, tumour histology, specimen type, and methodological variability in PD-L1 assessment.

In the present study, PD-L1 positivity was significantly more frequent in small biopsy specimens from patients with lung adenocarcinoma compared with those with squamous cell lung cancer ($p = 0.03572$). In contrast, no statistically significant difference in PD-L1 expression between these histological subtypes was observed in surgically resected specimens ($p = 0.35238$). This discrepancy may reflect differences in sample size, tumour heterogeneity, or specimen-related factors inherent to small biopsies vs. surgical material. Overall, lung adenocarcinoma constituted the most common histological subtype among patients with positive PD-L1 expression in our cohort, which is consistent with findings from other previous studies [18, 20, 22, 24, 27–30, 32–35]. However, conflicting results have been reported. Gainor *et al*. [36] observed comparable frequencies of PD-L1 expression in lung adenocarcinoma and squamous cell carcinoma, whereas studies by Munari *et al*. [26] identified squamous cell lung cancer as the predominant type [20, 36]. In contrast, Chang *et al*. [20] reported squamous cell carcinoma as the least frequent histological type among PD-L1 positive cases. These inconsistencies across histological subtypes suggest that histology alone may not reliably predict PD-L1 status, emphasizing the importance of standardized assessment methods and well-defined study populations.

Among patients with lung adenocarcinoma and positive PD-L1 expression, the majority exhibited the acinar type, followed by the solid subtype, whereas no PD-L1 expression was observed in the lepidic subtype, consistent with the previous reports [18]. In most studies, the solid subtype was the predominant histological pattern associated with PD-L1 positivity [14, 28, 29, 37, 38], primarily conducted in Asian populations [22, 39]. These findings suggest that the distribution of PD-L1 expression across adenocarcinoma subtypes may vary by population and study cohort.

In the present study, PD-L1 negativity was more commonly observed among patients with squamous cell lung cancer, with the majority of the cases exhibiting the keratinizing subtype. Data on PD-L1 expression patterns in squamous cell carcinoma are relatively limited; however, our findings are consistent with the results reported by Jin *et al*. [18] Collectively, these observations highlight the potential influence of the histological subtype on PD-L1 expression, while also emphasizing the need for further studies to better characterize expression patterns in less commonly studied subtypes of NSCLC.

Studies worldwide investigating the association between PD-L1 expression and the T descriptor have reported heterogeneous results. Several studies, consistent with our findings, demonstrated that the T descriptor has no significant impact on PD-L1 expression [27–29, 38]. In the present study, none of the T descriptors were associated with a higher proportion of PD-L1-positive compared to PD-L1-negative cases. Among patients with positive PD-L1 expression, the most frequent descriptor was T3.

Conversely, several studies have reported a higher prevalence of positive PD-L1 expression in patients with T descriptors greater than T2 [19–21, 30]. At the same time, a predominance of PD-L1-negative expression has been observed in patients with lower T descriptors, particularly T1 and T2 [20, 22]. In a study by Jin *et al*. [18], a significant association between higher T descriptors and positive PD-L1 expression was identified in lung adenocarcinoma, whereas no such correlation was observed in squamous cell carcinoma.

In approximately half of the published studies, similar to the findings of the present investigation, no statistically significant association was demonstrated between N descriptors and PD-L1 expression ($p = 0.617$) [31, 36, 38–40]. In our cohort, the highest proportion of PD-L1-positive cases was observed among patients with the N0 descriptor. In contrast, the remaining literature supports a correlation between higher N descriptors and increased PD-L1 expression [18–21, 28, 30]. Notably, Pawelczyk *et al*. [27] reported that the highest frequency of PD-L1-positive tumours was identified in patients with the N1 descriptor.

In the present study, the most common stage among patients with positive PD-L1 expression was stage IIIA, followed by stage IIB. A statistically significant difference in PD-L1 expression was observed in relation to the disease stage ($p = 0.012$). Similarly, Li *et al*. [41] reported a higher proportion of PD-L1-positive patients in stages II, III, and IV of the disease. Additional studies have also demonstrated a greater prevalence of PD-L1-positive expression in patients with advanced-stage disease [19–21, 27, 41, 42]. In most of these investigations, the association between PD-L1 expression and disease stage was analyzed in cohorts of patients with lung adenocarcinoma or NSCLC. Jin *et al*. [18] showed that patients with lung adenocarcinoma and positive PD-L1 expression were more frequently diagnosed at higher disease stages, whereas no such association was observed in patients with squamous cell carcinoma. In contrast to these findings, several studies reported no significant correlation between PD-L1 expression and disease stage, regardless of NSCLC histological subtype [23, 29, 30 32, 38].

Given that NSCLC is frequently diagnosed at advanced stages of disease, a substantial proportion of patients may benefit from immunotherapy targeting the PD-1/PD-L1 axis. However, the marked intratumoural heterogeneity characteristic of NSCLC raises concerns regarding the reliability of PD-L1 assessment in limited tissue samples. Small biopsies and surgical specimens often contain fewer tumour cells and usually represent only a single tumour focus, which may compromise the validity of PD-L1 as an immunohistochemical biomarker in such samples [4, 6, 12, 21, 43–45].

Recent studies have focused on comparing PD-L1 expression across different specimen types, including cytological, small biopsy, and surgical samples. Wang *et al*. [46] reported a high concordance rate in PD-L1 expression between cytological and surgical specimens, as well as between small biopsy and surgical specimens. Notably, higher concordance was observed when lower cut-off values for PD-L1 positivity (1% and 5%) were applied. In their study, PD-L1 expression was detected in 28–42% of cytological specimens, approximately 27% of small biopsy specimens, and 29–36% of surgical specimens, depending on the selected cut-off threshold. Similar findings were reported by Russel-Goldman *et al*. [47]. And a few recent studies demonstrated moderate concordance among cytological, small biopsy, and surgical samples [48, 49]. Heymann *et al*. [25] likewise observed a relatively high level of agreement in PD-L1 expression across these specimen types. In contrast, Ilie *et al*. [50] reported lower concordance rates and considerable discordance in PD-L1 expression between cytological, small biopsy, and surgical specimens. Based on these findings, the authors recommended sampling from multiple tumour sites in small biopsies and surgical samples and evaluating the mean PD-L1 expression value to improve diagnostic accuracy. In the present study, PD-L1 positivity was identified in 26.5% of patients with small biopsy specimens and in 21.6% of those with surgical specimens, findings that are consistent with previously published data. The majority of PD-L1-positive cases demonstrated expression in more than 10% of tumour cells, accounting for 11.8% of small biopsy specimens and 15.7% of surgical specimens. No statistically significant difference in PD-L1 expression was observed between small biopsy and surgical specimens ($p = 0.790$), which agrees with previously published studies [36–38].

Limitations

This study has several limitations that should be considered when interpreting the results. First, the research was conducted at a single center and included only one patient population, which may limit the generalizability of the findings. In addition, the analysis of biopsy specimens was restricted to a single tissue section, potentially reducing the representativeness of PD-L1 assessment. Furthermore, as in other studies, intra-tumoural heterogeneity remains a relevant concern and may have influenced the evaluation of PD-L1 expression. Finally, the relatively small sample size represents an additional limitation and may have affected the statistical power of the study.

Conclusions

Regarding clinicopathological correlations, PD-L1 expression showed no statistically significant associa-

tion with T or N tumour descriptors, whereas a significantly higher rate of PD-L1 positivity was observed in patients with stage IIIA disease. Importantly, the high concordance and the absence of a significant difference in PD-L1 expression between small biopsy and surgical specimens indicate that treatment planning based on small biopsy samples represents a reliable option for patients who are not candidates for surgical resection. At the same time, surgical specimens remain valuable for guiding adjuvant therapy decisions.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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