Comprehensive genomic and immune profiling of non-small cell lung cancer brain metastases reveals low tumor inflammation and elevated cancer testis antigen burden

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Introduction

- Non-small cell lung cancer (NSCLC) accounts for ~50% of brain metastases.
- Many individual biomarkers describe the complexity of each tumor and its interactions with the tumor microenvironment (TME).
- We compare the genomic and immune biomarker landscapes of two cohorts of patients: one with primary NSCLC (pNSCLC) and another with metastatic NSCLC to the brain (mNSCLC).

Methods

- Standard-of-care comprehensive genomic and immune profiling was performed on FFPE tumors representing 39 histologic types, assessing expression levels of 395 immune genes and >500 tumor-associated genes [1,2].
- From this data, three previously published gene expression signatures were calculated: cell proliferation (CP), tumor immunogenic signature (TIGS), and cancer testis antigen burden (CTAB) [3,4,5].
- PD-L1 status of each tumor was assessed by IHC and designated as positive when ≥1% tumor proportion score (TPS), and tumor mutational burden (TMB) was calculated and designated as high when ≥10Mut/Mb was observed.
- We analyzed 137 mNSCLC patient tumors (ages 40-85y [mean 65y], 52% female, 48% male) and 5533 primary NSCLC (pNSCLC) patient tumors (ages 24-100y [mean 71y], 51% female, 49% male) with comprehensive genomic and immune biomarker profiling, including PD-L1 IHC, TMB, TIGS, CP, and CTAB.

Table 1: Biomarker and demographic composition of pNSCLC and mNSCLC cohorts.

Demographics	mNSCLC Cohort (n=137)		pNSCLC Cohort (n=5533)	
	Number of Patients	Percentage of Total Cohort	Number of Patients	Percentage of Total Cohort
	137	100.00%	5533	100.00%
Gender				
Female	71	51.82%	2823	51%
Male	66	48.18%	2710	49%
TMB (≥10Mut/Mb)				
High	77	56.20%	1581	28.57%
Not High	58	42.34%	3134	56.64%
Missing	2	1.46%	818	14.78%
PD-L1 IHC (≥1% TPS)				
Positive	75	54.74%	3678	66.47%
Negative	62	45.26%	1833	33.13%
Missing	0	-	22	0.40%
Tumor Immunogenic Signature (TIGS)				
Strong	34	24.82%	1952	35.28%
Moderate	31	22.63%	1699	30.71%
Weak	72	52.55%	1882	34.01%
Cell Proliferation (CP)				
High	10	7.30%	470	8.49%
Moderate	58	42.34%	2042	36.91%
Poor	69	50.36%	3021	54.60%
Cancer Testis Antigen Burden (CTAB)				
High	94	68.61%	3185	57.56%
Low	43	31.39%	2348	42.44%

Results

- PD-L1 expression (%TPS) for all cases by IHC was not significantly different. However, pNSCLC cases were more likely to be PD-L1 positive (≥1%TPS) (p=0.00506) and mNSCLC cases were more likely to be PD-L1 negative (p=0.0037) [Fig. 1].

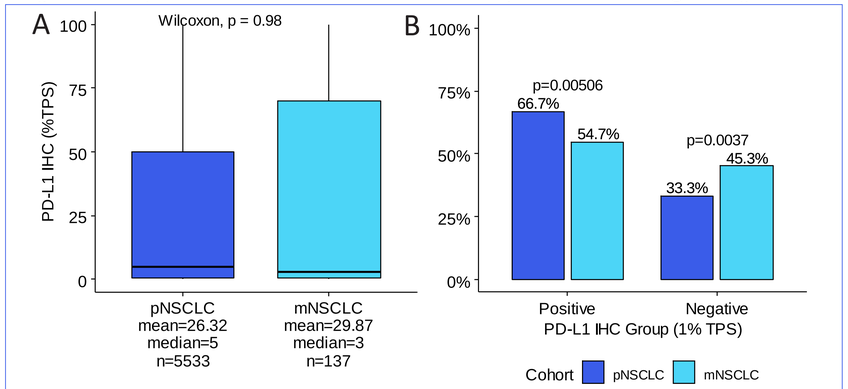

Figure 1: A) PD-L1 IHC distributions (%TPS) in each cohort; B) Bar plot detailing PD-L1 IHC group (Positive: PD-L1 IHC ≥ 1%TPS) composition of each cohort with overrepresentation test p-values indicated.

- Genomic alteration (GA) frequency in mNSCLC and pNSCLC were similar; only KRAS was significantly increased (39.9% vs 25.5%, p<0.0005). Mean TMB was significantly higher in mNSCLC versus pNSCLC (p=7.8e-10). Additionally, mNSCLC cases were more likely to have high TMB (TMB≥10 mut/Mb) (p=3.33e-11) and pNSCLC cases were more likely to not have high TMB (TMB<10 mut/Mb) (p=0.000943) [Fig. 2].

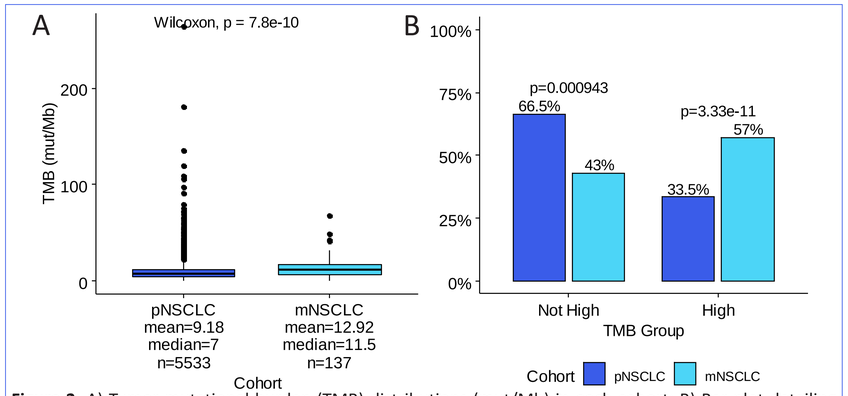

Figure 2: A) Tumor mutational burden (TMB) distributions (mut/Mb) in each cohort; B) Bar plot detailing TMB group (High: ≥10 mut/Mb) composition of each cohort with overrepresentation test p-values indicated.

- mNSCLC cases had a significantly higher mean CP score (p=0.025) [Fig. 3].

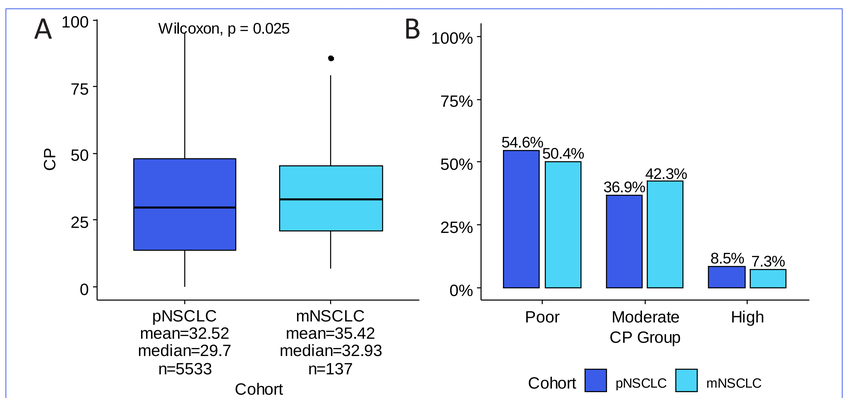

Figure 3: A) Cell proliferation signature (CP) distributions in each cohort; B) Bar plot detailing CP group composition of each cohort with overrepresentation test p-values indicated.

- The TIGS score was significantly higher for pNSCLC cases (p=3.9e-6). mNSCLC cases were more likely to be weakly inflamed (p=1.19e-5) while pNSCLC cases were more likely to be moderately (p=0.0392) or strongly (p=0.00979) inflamed [Fig. 4].

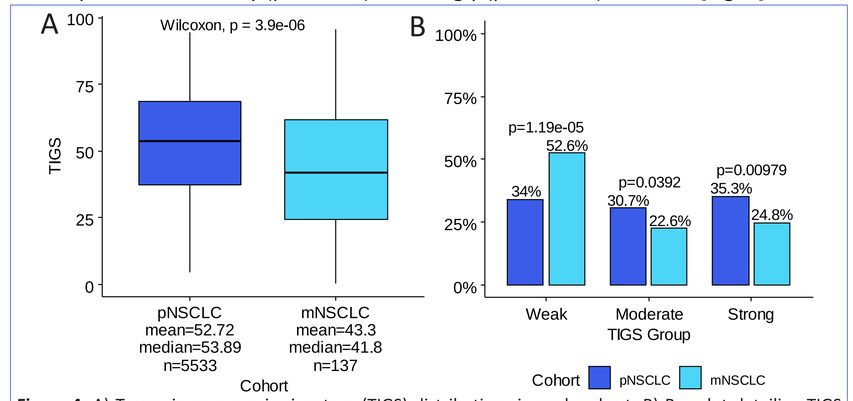

Figure 4: A) Tumor immunogenic signature (TIGS) distributions in each cohort; B) Bar plot detailing TIGS group composition of each cohort with overrepresentation test p-values indicated.

- The CTAB score was significantly higher in mNSCLC cases (p=2e-5). Additionally, mNSCLC cases were more likely to have high (≥171) CTAB (p=0.00902) while pNSCLC cases were more likely to have low (<171) CTAB (p=0.00902) [Fig. 5].

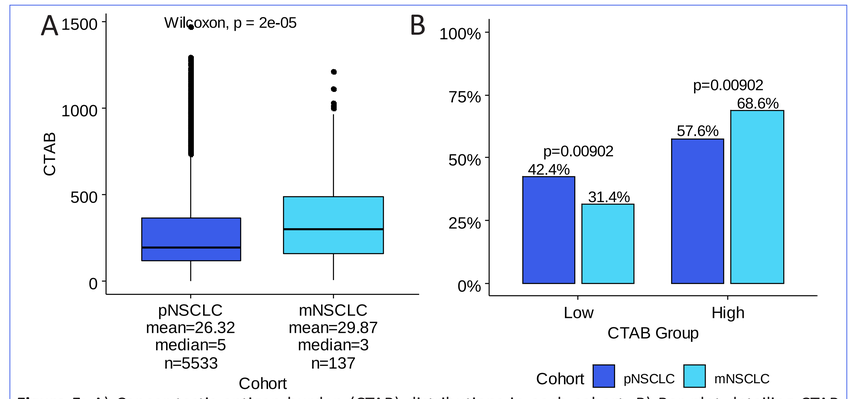

Figure 5: A) Cancer testis antigen burden (CTAB) distributions in each cohort; B) Bar plot detailing CTAB group composition of each cohort with overrepresentation test p-values indicated.

Conclusions

- Comprehensive genomic and immune profiling (CGIP) facilitates the interrogation of tumor immunity biomarkers in real-world NSCLC brain metastasis specimens.
- CGIP reveals that mNSCLC cases have a larger antigen burden, with increased TMB and CTAB, likely due to the immune privileged nature of the brain, which is reflected in the lower TIGS scores and PD-L1 positivity.
- Despite lower overall PD-L1 positivity, mNSCLC with negative PD-L1 IHC may potentially benefit from immunotherapy including cancer vaccine and adoptive cell therapy strategies given the high TMB and CTAB.

References

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