Baseline Tumor Size as a Predictive and Prognostic Factor of Immune Checkpoint Inhibitor Therapy for Non-small Cell Lung Cancer

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Abstract. *Background/Aim: Immune checkpoint inhibitors (ICI) are a novel medication for non-small cell lung cancer (NSCLC). Recent reports indicated that baseline tumor size (BTS) relates to the efficacy of ICI therapy for melanoma, but no study exists for NSCLC. This study aimed to evaluate the utility of BTS for ICI therapy. Patients and Methods: Data from 58 patients diagnosed with NSCLC who underwent ICI monotherapy, were retrospectively analyzed. Patients were divided into two groups according to BTS (below 101 mm, above 101 mm). The primary endpoint was progression-free survival (PFS) and the secondary endpoint was overall survival (OS). Results: PFS of patients with a large BTS was significantly shorter than that of those with a small BTS (median; 2.07 [95% confidence interval (CI)=0.99-6.77] months versus 6.39 [95%CI=4.17-11.50] months) ($p=0.044$). OS of patients with large BTS was also significantly shorter ($p<0.01$). Conclusion: BTS is a predictive and prognostic negative factor of ICI therapy for NSCLC.*

Lung cancer is one of the leading causes of cancer-related death worldwide (1). Advanced non-small cell lung cancer (NSCLC) is treated using systemic therapies, including chemotherapy, epidermal growth factor receptor-tyrosine

kinase inhibitor (TKI), anaplastic lymphoma kinase-TKI, c-ros oncogene 1 inhibitor, a combination of BRAF/MET inhibitor, and an immune checkpoint inhibitor (ICI) (2). The immune system protects the host against cancer cells *via* seven steps termed the cancer-immunity cycle (3). The seven steps include ‘priming and activation’ and ‘recognition of cancer by T cells’ (3). These processes are regulated and activated by various molecules and cytokines, including programmed death-ligand 1 (PD-L1) and programmed death-1 (PD-1), which suppress the cancer-immune cycle (3, 4). Cancer cells can express PD-L1 on their surfaces, facilitating recognition by PD-1, which is expressed on the surface of T-cells and acts as a PD-L1 receptor. Binding of PD-L1 to T cells has a profound inhibitory effect on immune functions such as cytokine secretion, growth, and cytotoxicity. Hence, PD-1 and PD-L1 are thought to be important target molecules for the control of cancer.

ICI is a novel and promising medication for NSCLC. Nivolumab, a fully human IgG4 anti-PD-1 receptor-blocking monoclonal antibody (5), was the first ICI available for treatment of NSCLC in Japan. The Checkmate 017 and Checkmate 057 studies indicated the superiority of nivolumab over docetaxel for patient progression-free survival (PFS) and overall survival (OS) (6, 7). In addition to nivolumab, various other ICIs are now available, including pembrolizumab (an anti-PD-1 blocking antibody), atezolizumab and durvalumab (anti-PD-L1 blocking antibodies). Use of these ICIs has also been shown to lead to superior PFS and OS (8-10).

Previous studies (Checkmate 017, 057, and Keynote-010) showed that the effects of ICI differed according to PD-L1 expression. As ICI is more effective against NSCLC expressing a higher tumor proportion score (TPS) of PD-L1 (6, 7), TPS of PD-L1 is considered one of the most useful prognostic biomarkers. However, a recent study indicated that the efficacy of ICI did not necessarily depend on PD-L1 expression (9). Hence, investigators seek more reliable

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predictive and prognostic factors. To date, various factors have been proposed as potential prognostic indicators, including tumor mutation burden (11), presence of liver metastasis (12), gut microbiome (13), and neutrophil-to-lymphocyte ratio (14).

Baseline tumor size (BTS), quantified as the sum of the longest dimensions of all measurable target lesions, reflects tumor burden, load, and bulk. In patients undergoing ICI therapy for melanoma, BTS below 102 mm is associated with significantly better predicted OS (15) and is expected as a new prognostic factor. However, in patients with NSCLC, no study has examined the relationship between BTS, PFS and OS. We hypothesized that BTS is a potential predictive and prognostic indicator also in patients undergoing ICI therapy for NSCLC. The aim of this study was to evaluate the utility of BTS as a simple and useful prognostic factor of ICI treatment in NSCLC patients.

Patients and Methods

Patients and treatment. A retrospective review of 59 consecutive patients who were diagnosed with NSCLC histologically and treated with ICI monotherapy at Kobe University Hospital in Japan from December 2015 to April 2018 was performed. Collected data included sex, age, Brinkman index, Eastern Cooperative Oncology Group Performance Status (ECOG PS), BTS, metastatic site, and yStage at the time of initiating ICI, driver mutation, history of surgery, history of radiation therapy, histology, TPS of PD-L1, lines of prior therapy, and types of medication. yStage was based on the eighth edition of the Lung Cancer Stage Classification from the Union for International Cancer Control and the American Joint Committee on Cancer (16). TPS of PD-L1 was assessed using the 22C3 antibody.

To clarify the characteristics of ICI, a retrospective review of consecutive patients who were diagnosed with NSCLC histologically or cytologically and started treatment with chemotherapy from December 2015 to January 2017 was also performed. Patients with driver mutations and who have undergone chemoradiotherapy treatment were excluded. Collected data were same as above.

This retrospective analysis was approved by the Institutional Review Board of Kobe University Hospital (permission number: #170023).

BTS. BTS was quantified as the sum of the longest dimensions of all measurable target lesions. We summed the longest major axis of all measurable target lesions, except for metastatic lymph nodes, and the longest minor axis of metastatic lymph nodes. Target lesions were basically assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, but also unmeasurable target was calculated as far as possible to show BTS more accurately. A maximum of five organs were selected and one or two lesions per organ were measured using a computed tomography scan or magnetic resonance imaging within 1 month of initializing therapy. As mentioned above, in patients with NSCLC, no study exists about the relationship between BTS and PFS. Cutoff points for BTS were tested for PFS using the biostatistical tool, cutoff finder (17). Not only in the case of ICI treatment but also in the case of chemotherapy, the cutoff point of BTS was the same, 101 mm.

Endpoints. The best overall response was assessed according to RECIST version 1.1. The follow-up period was from December 2015 to November 2018. Patients who were still alive and free from progression were censored at the time of last follow-up. The primary endpoint was PFS and the secondary endpoint was OS.

Statistical methods. Categorical data are presented as numbers and percentages. Numeric data are presented as median (lower quartile [Q1], upper quartile [Q3]). Univariate analyses were performed using Fisher's exact test for categorical data, and Mann-Whitney U-tests were carried out for analysis of numeric data. PFS and OS curves were estimated using the Kaplan-Meier method and compared using the log-rank test and Cox proportional hazards regression analysis. To investigate prognostic factors for PFS and OS, variables including BTS, ECOG PS, hepatic metastasis, TPS of PD-L1, and lines of prior therapy were analyzed using multivariate Cox proportional hazards regression analysis to test independence in a stepwise procedure with alpha-to-remove, 0.05. All *p*-values were two-sided and values <0.05 were considered statistically significant. All statistical analyses were performed with EZR version 1.37 (Saitama Medical Center Jichi Medical University; <http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html>; Kanda, 2018), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.4.1) (18).

Results

Patient characteristics. Patients (n=59) were treated with ICI monotherapy during the study period. The study included 58 patients, as one patient was excluded because of double primary lung cancers. The baseline characteristics of patients are presented in Table I. The majority of patients (91.4%) were male. The median age was 70.5 (Q1, Q3: 65.25, 74.00) years. ECOG PS was 0 or 1 for 84.5% of patients and 20.7% of patients received ICI as a primary treatment. The median BTS was 84 (Q1, Q3: 15.10, 208.10) mm. The overall response rate (ORR) of all patients to ICI was 26.3%. Next, patients were divided into two groups according to BTS and their characteristics were retrospectively compared. Patients with large BTS (BTS above 101 mm) tended to have hepatic metastasis, poor ECOG PS, and more metastatic sites, but there were no factors with significant differences between the small BTS group and the large BTS group (Table II).

The study included 43 patients treated with chemotherapy. Patients with large BTS tended to have more metastatic sites, there were no factors with significant differences between the small BTS group and the large BTS group (Table III).

Analyses of PFS. The median follow-up time was 9.52 (Q1, Q3: 3.29, 14.77) months at the time of analysis. Median PFS was 5.14 (95%CI=3.32-7.69) months at the time of analysis. The median PFS of patients with large BTS was significantly shorter than that of patients with small BTS (2.07 [95%CI=0.99-6.77] months vs. 6.39 [95%CI=4.17-11.50] months) (*p*=0.044) (Figure 1A). Univariate analysis showed that history of prior chemotherapy, hepatic metastasis, and BTS were significantly associated with PFS (history of prior

Table I. Characteristics of patients treated with immune checkpoint inhibitors (n=58).

Factor	Value	Factor	Value
Gender		No. of metastatic sites	
Male	53 (91.4)	0	3 (6.1)
Female	5 (8.6)	1	16 (32.7)
Age (years) [^]	70.50 (65.25, 74.00)	2	16 (32.7)
Brinkman index [^]	967.50 (712.50, 1492.50)	3	8 (16.3)
ECOG PS		4	3 (6.1)
0	1 (1.7)	5	2 (4.1)
1	48 (82.8)	6	1 (2.0)
2	7 (12.1)	Baseline tumor size [^]	84.00 (15.10, 208.10)
3	1 (1.7)	Medication type of ICI	
4	1 (1.7)	Nivolumab	38 (65.5)
Driver mutation		Pembrolizumab	20 (34.5)
EGFR	5 (8.6)	Response	
Negative	52 (89.7)	PR	15 (26.3)
Unexamined	1 (1.7)	SD	23 (39.7)
History of surgery		PD	17 (29.8)
Yes	11 (19.0)	Not evaluated	3 (5.2)
No	47 (81.0)		
History of radiation therapy			
Yes	15 (25.9)		
No	43 (74.1)		
yStage			
IB	1 (1.7)		
IIB	2 (3.4)		
IIIA	1 (1.7)		
IIIB	6 (10.3)		
IIIC	4 (6.9)		
IVA	13 (22.4)		
IVB	22 (37.9)		
Undetermined	9 (15.5)		
Lines of prior therapy			
0	12 (20.7)		
1	15 (25.9)		
2	17 (29.3)		
3	10 (17.2)		
4	3 (5.2)		
6	1 (1.7)		
Type of histology			
Non-Squamous	40 (69.0)		
Squamous	18 (31.0)		
Tumor Proportion Score of PD-L1			
<1%	8 (13.8)		
1%-49%	11 (19.0)		
≥50%	16 (27.6)		
Unexamined	23 (39.7)		
Brain metastases			
Yes	8 (13.8)		
No	42 (72.4)		
Unknown	8 (13.8)		
Hepatic metastases			
Yes	7 (12.1)		
No	43 (74.1)		
Unknown	8 (13.8)		
Bone metastases			
Yes	11 (19.0)		
No	39 (67.2)		
Unknown	8 (13.8)		

Values are presented as n (%), except those variables marked with the symbol [^] which are presented as median (lower quartile, upper quartile). ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: Epidermal growth factor receptor; PD-L1: programmed death-ligand 1; ICI: immune checkpoint inhibitor; PR: partial response; SD: stable disease; PD: progressive disease.

chemotherapy, Hazard Ratio (HR)=2.594 [95%CI=1.093-6.152]; hepatic metastasis, HR=3.286 [95%CI=1.412-7.646]; large BTS, HR=1.818 [95%CI=1.005-3.291]). Multivariate analysis with Cox hazard regression was performed by incorporating ECOG PS, hepatic metastasis, history of prior chemotherapy, TPS of PD-L1, and BTS and showed that history of prior chemotherapy and BTS were significant independent prognostic factors for PFS (history of prior chemotherapy, HR=3.017 [95%CI=1.259-7.229]; large BTS, HR=2.117 [95%CI=1.162-3.859]) (Table IV).

The median PFS of patients between the small BTS group and the large BTS group was not significantly different [4.99 (95%CI=2.69-5.36) months in the small BTS group *vs.* 5.52 (95%CI=1.41-9.49) months in the large BTS group (*p*=0.329)]. Moreover, the Kaplan–Meier (KM) curves between these groups were crossed (Figure 2).

Analyses of OS. Median OS was 14.03 (95%CI=8.51-22.34) months. The median OS of patients with large BTS was significantly shorter than that of patients with small BTS [5.85 (95%CI=2.00-10.68) months *vs.* 22.28 (95%CI=14.03-not reached) months (*p*<0.01)] (Figure 1B). Univariate analysis showed that ECOG PS, hepatic metastasis, and BTS were significantly associated with OS [ECOG PS≥2, HR=2.699 (95%CI=1.074-6.785); hepatic metastasis, HR=4.503 (95%CI=1.700-11.96); large BTS, HR=3.122 (95%CI=1.516-6.426)]. Multivariate analysis with Cox hazard regression was

Table II. Characteristics of patients treated with immune checkpoint inhibitors according to basement tumor size (BTS).

Factor	Small (below 101 mm) n=34	Large (above 101 mm) n=24	p-Value	Factor	Small (below 101 mm) n=34	Large (above 101 mm) n=24	p-Value
Gender			0.64	Bone metastases			0.369
Male	32 (94.1)	21 (87.5)		Yes	6 (17.6)	5 (20.8)	
Female	2 (5.9)	3 (12.5)		No	25 (73.5)	14 (58.3)	
Age [^]	71.0 (67.25, 75.75)	70.0 (63.00, 74.00)	0.385	Unknown	3 (8.8)	5 (20.8)	
Brinkman index [^]	970.0 (669.0, 1350)	937.5 (669.0, 1650)	0.782	No. of metastatic sites			0.085
ECOG PS			0.059	0	2 (5.9)	1 (4.2)	
0	1 (2.9)	0 (0.0)		1	12 (35.3)	4 (16.7)	
1	31 (91.1)	17 (70.8)		2	12 (35.3)	4 (16.7)	
2	2 (5.9)	5 (20.8)		3	3 (8.8)	5 (20.8)	
3	0 (0.0)	1 (4.2)		4	1 (3.4)	2 (8.3)	
4	0 (0.0)	1 (4.2)		5	0 (0.0)	2 (8.3)	
Driver mutation			1	6	0 (0.0)	1 (4.2)	
EGFR	3 (8.8)	2 (8.3)		Type of medication			0.165
Negative	30 (88.2)	22 (91.7)		Nivolumab	25 (73.5)	13 (54.2)	
Unexamined	1 (2.9)	0 (0.0)		Pembrolizumab	9 (26.4)	11 (45.8)	
History of surgery			1	Response			0.058
Yes	7 (20.6)	4 (16.7)		PR	11 (32.4)	4 (16.7)	
No	27 (79.4)	20 (83.3)		SD	16 (47.1)	7 (29.2)	
History of radiation therapy			0.552	PD	6 (17.6)	11 (45.8)	
Yes	10 (29.4)	5 (20.8)		unknown	1 (3.4)	2 (8.3)	
No	24 (70.6)	19 (79.2)					
yStage			0.462				
IB	1 (2.9)	0 (0.0)					
IIB	2 (5.9)	0 (0.0)					
IIIA	0 (0.0)	1 (4.2)					
IIIB	4 (11.8)	2 (8.3)					
IIIC	2 (5.9)	2 (8.3)					
IVA	10 (29.4)	3 (12.5)					
IVB	11 (32.4)	11 (45.8)					
Undetermined	4 (11.8)	5 (20.8)					
Lines of prior therapy			0.156				
0	6 (17.6)	6 (25.0)					
1	11 (32.4)	4 (16.7)					
2	12 (35.3)	5 (20.8)					
3	3 (8.8)	7 (29.2)					
4	2 (5.9)	1 (4.2)					
6	0 (0.0)	1 (4.2)					
Type of histology			0.249				
Non-squamous	21 (61.8)	19 (79.2)					
Squamous	13 (38.2)	5 (20.8)					
Tumor proportion score of PD-L1			0.149				
<1%	5 (14.7)	3 (12.5)					
1-49%	9 (26.4)	2 (8.3)					
≥50%	6 (17.6)	10 (41.7)					
Unexamined	14 (41.2)	9 (37.5)					
Brain metastases			0.477				
Yes	5 (14.7)	3 (12.5)					
No	26 (76.5)	16 (66.7)					
Unknown	3 (8.8)	5 (20.8)					
Hepatic metastases			0.075				
Yes	2 (5.9)	5 (20.8)					
No	29 (85.3)	14 (58.3)					
Unknown	3 (8.8)	5 (20.8)					

Values are presented as n (%), except those variables marked with the symbol [^]which are presented as median (lower quartile, upper quartile). **p*<0.05. ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; PD-L1: programmed death-ligand 1; PR: partial response; SD: stable disease; PD: progressive disease.

performed by incorporating ECOG PS, hepatic metastasis, history of prior chemotherapy, TPS of PD-L1, and BTS and showed that ECOG PS ≥2, history of prior chemotherapy, and BTS were significant independent prognostic factors for OS [ECOG PS ≥2, HR=3.407 (95%CI=1.180-9.841); history of prior chemotherapy, HR=4.044 (95%CI=1.273-12.85); large BTS, HR=3.090 (95%CI=1.456-6.558)] (Table V).

Response of ICI therapy and treatment after ICI therapy. Next, to investigate the reason why the OS of patients with small BTS was significantly longer than that of patients with large BTS, we analyzed the differences in the response of ICI therapy and post-treatment between the small BTS group and the large BTS group. The ORR of ICI therapy was not significantly different between the small BTS group and the large BTS group (32.4% in the small BTS group vs. 16.7% in the large BTS group) (*p*=0.231), however the proportion of PD of ICI therapy was significantly larger in the large BTS group (17.6% in the small BTS group vs. 45.8% in the large BTS group) (*p*=0.039). At the time of analysis, the majority of patients with large BTS received best supportive care after getting PD of ICI therapy (*p*<0.01). The response of post chemotherapy was not significantly different between these groups (*p*=0.727) (Table VI).

Table III. Characteristics of patients treated with chemotherapy according to basement tumor size (BTS).

Factor	Small (below 101 mm) n=30	Large (above 101 mm) n=13	p-Value	Factor	Small (below 101 mm) n=30	Large (above 101 mm) n=13	p-Value
Gender			0.649	Brain metastases			0.649
Male	25 (83.3)	12 (92.3)		Yes	5 (16.7)	1 (7.7)	
Female	5 (16.7)	1 (7.7)		No	25 (83.3)	12 (92.3)	
Age [^]	69.5 (63.5, 73.8)	68.0 (66.0, 70.0)	0.791	Hepatic metastases			0.172
Brinkman index [^]	840.0 (600.0, 1015)	990.0 (810.0, 1040)	0.442	Yes	3 (10.0)	4 (30.8)	
ECOG PS			0.095	No	27 (90.0)	9 (69.2)	
0	8 (26.7)	0 (0.0)		Bone metastases			0.105
1	17 (56.7)	9 (69.2)		Yes	10 (33.3)	8 (61.5)	
2	5 (16.7)	4 (30.8)		No	20 (66.7)	5 (38.5)	
History of surgery			0.681	No. of metastatic sites			0.097
Yes	5 (16.7)	3 (23.1)		0	4 (13.3)	0 (0.0)	
No	25 (83.3)	10 (76.9)		1	8 (26.7)	3 (23.1)	
History of radiation therapy			0.164	2	12 (40.0)	2 (15.4)	
Yes	12 (40.0)	2 (15.4)		3	3 (10.0)	3 (23.1)	
No	18 (60.0)	11 (84.6)		4	2 (6.7)	4 (30.8)	
yStage			0.235	5	1 (3.3)	1 (7.7)	
IB	3 (10.0)	0 (0.0)		6	0 (0.0)	0 (0.0)	
IIB	1 (3.3)	0 (0.0)		Type of medication			0.292
IIIA	2 (6.7)	0 (0.0)		Platinum doublet	22 (73.3)	7 (53.8)	
IIIB	0 (0.0)	2 (15.4)		Non-platinum doublet	8 (26.7)	6 (46.2)	
IIIC	3 (10.0)	1 (7.7)		Response			0.052
IVA	9 (30.0)	2 (15.4)		PR	10 (33.3)	2 (15.4)	
IVB	12 (40.0)	8 (61.5)		SD	12 (40.0)	4 (30.8)	
Type of histology			0.696	PD	8 (26.7)	4 (30.8)	
Non-squamous	22 (73.3)	11 (84.6)		Unknown	0 (0.0)	3 (23.1)	
Squamous	8 (26.7)	2 (15.4)					
Tumor proportion score of PD-L1		1					
<1%	2 (6.7)	1 (7.7)					
1-49%	3 (10.0)	0 (0.0)					
≥50%	0 (0.0)	0 (0.0)					
Unexamined	25 (83.3)	12 (92.3)					

Values are presented as n (%), except those variables marked with the symbol [^]which are presented as median (lower quartile, upper quartile). ECOG PS: Eastern Cooperative Oncology Group Performance Status; PD-L1: programmed death-ligand 1; PR: partial response; SD: stable disease; PD: progressive disease.

Discussion

This study suggests that BTS is a useful negative predictive and prognostic marker not only for PFS but also for OS of NSCLC patients treated with nivolumab or pembrolizumab monotherapy. Among chemotherapy patients, KM curves between the small and the large BTS groups were crossed, suggesting that BTS is a specific marker of ICI monotherapy. To our knowledge, this is the first report of an association between BTS and ICI treatment in NSCLC.

For patients with melanoma, Joseph *et al.* showed that patients with small BTS had significantly better OS compared to those with large BTS (15). Similarly, we showed that patients with NSCLC and a large BTS had significantly inferior PFS and OS.

This study examined why PFS and OS in the large BTS group is worse than the small BTS group. Table V shows that, compared to the small BTS group, in the large BTS group there was a higher proportion of PD and less patients continued ICI therapy. This may be partly attributed to the fact that BTS reflects tumor burden (*i.e.*, tumor bulk) and high tumor burden is associated with an inferior prognosis and effect of ICI. In contrast, in the current study yStage was not found to be a significant marker for PFS nor OS. These results suggest that BTS contributes to survival because of its relationship with tumor burden, rather than with yStage. Kobayashi H *et al.* reported that the responders to prior chemotherapy with nivolumab had benefited from ICI (19). Although there are no actual data, it is suggested that the tumor burden of responders to prior chemotherapy is less than that of non-responders.

The predictive and prognostic value of BTS for PFS and OS may be due to first, tumor associated antigen (TAA) retention, second, the immunosuppressive effect of the tumor, and third, an imbalance between the immune response and the tumor.

Table IV. Progression-free survival of patients undergoing immune checkpoint inhibitor therapy.

Univariate analysis	n	1-year survival rate (%) (95%CI)	Hazard ratio (95%CI)	p-Value
Gender				0.222
Female	5	20.0 (0.8-58.2)	1	
Male	53	24.9 (14.0-37.4)	0.532 (0.189-1.495)	
Brinkman index				0.933
Below median	29	23.7 (9.5-41.5)	1	
Above median	29	24.1 (10.7-40.5)	0.975 (0.542-1.755)	
ECOG PS				0.366
0, 1	49	24.8 (13.5-37.)	1	
2, 3, 4	9	22.2 (3.4-51.3)	1.450 (0.643-3.268)	
History of surgery				0.947
Yes	11	27.3 (6.5-53.9)	1	
No	47	23.6 (12.3-36.9)	0.974 (0.451-2.105)	
History of radiation therapy				0.074
Yes	15	6.7 (0.4-26.0)	1	
No	43	31.0 (17.7-45.4)	0.562 (0.295-1.069)	
yStage				0.203
IB-IIIC	14	50.0 (22.9-72.2)	1	
IVA, IVB	35	14.2 (4.8-28.7)	2.007 (0.912-4.415)	
Undetermined	9	22.2 (3.4-51.3)	1.559 (0.561-4.337)	
History of prior chemotherapy				0.024*
No	12	45.0 (15.5-71.0)	1	
Yes	46	19.0 (9.1-31.5)	2.594 (1.093-6.152)	
Type of histology				0.462
Non-squamous	40	24.1 (12.2-38.3)	1	
Squamous	18	24.3 (7.1-46.9)	0.789 (0.419-1.488)	
Tumor proportion score of PD-L1				0.208
≥50%	16	41.0 (16.8-64.1)	0.363 (0.139-0.950)	
1%-49%	11	27.3 (6.5-53.9)	0.580 (0.217-1.551)	
<1%	8	not available	1	
Unexamined	23	21.7 (7.9-39.9)	0.622 (0.270-1.432)	
Brain metastasis				0.718
Yes	8	18.8 (1.1-53.5)	1.325 (0.582-3.015)	
No	42	25.4 (13.3-39.4)	1	
Unknown	8	25.0 (3.7-55.8)	0.862 (0.359-2.068)	
Hepatic metastasis				0.011*
Yes	7	not available	3.286 (1.412-7.646)	
No	43	29.9 (16.1-43.1)	1	
Unknown	8	25.0 (3.7-55.8)	0.945 (0.393-2.272)	
Bone metastasis				0.865
Yes	11	9.1 (0.5-33.3)	1.180 (0.544-2.300)	
No	39	30.3 (16.7-45.0)	1	
Unknown	8	25.0 (3.7-55.8)	0.878 (0.350-2.051)	
No. of metastatic sites				0.714
≤2	35	31.4 (17.1-46.8)	0.756 (0.381-1.503)	
≥3	14	8.6 (0.5-31.5)	1	
Unknown	9	22.2 (3.4-51.3)	0.770 (0.302-1.960)	
Baseline tumor size				0.044*
Small (below 101 mm)	34	31.3 (16.5-47.3)	1	
Large (above 101 mm)	24	14.6 (3.8-32.1)	1.818 (1.005-3.291)	
Type of medication				0.097
Nivolumab	38	17.5 (7.4-31.3)	1	
Pembrolizumab	20	38.1 (17.2-58.9)	0.575 (0.296-1.117)	
Multivariate analysis		Hazard ratio	95% CI	p-Value
Large baseline tumor size		2.117	1.162-3.859	0.014*
History of prior chemotherapy		3.017	1.259-7.229	0.013*

Multivariate analysis included the factors ECOG PS, hepatic metastases, baseline tumor size, history of prior chemotherapy, tumor proportion score. CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; PD-L1: programmed death-ligand 1. * $p < 0.05$, † $p < 0.01$.

Table V. Overall survival after immune checkpoint inhibitor therapy.

Factor	n	Overall survival		
		1-year survival rate (%) (95%CI)	Hazard ratio (95%CI)	p-Value
Gender				0.413
Female	5	40.0 (5.2-75.3)	1	
Male	53	51.7 (36.2-65.1)	0.609 (0.183-2.026)	
Brinkman index				0.808
Below median	29	49.6 (28.6-67.5)	1	
Above median	29	52.8 (32.6-69.5)	0.916 (0.450-1.863)	
ECOG PS				0.028*
0, 1	49	54.6 (38.4-68.2)	1	
2, 3, 4	9	29.6 (5.2-60.7)	2.699 (1.074-6.785)	
History of surgery				0.916
Yes	11	42.4 (13.7-69.1)	1	
No	47	52.7 (36.1-66.8)	1.107 (0.415-2.952)	
History of radiation therapy				0.408
Yes	15	41.6 (16.1-65.6)	1	
No	43	54.8 (37.8-69.0)	0.728 (0.342-1.551)	
yStage				0.724
IB-IIIC	14	64.3 (34.3-83.3)	1	
IVA, IVB	35	44.0 (25.3-61.3)	1.329 (0.559-3.162)	
Undetermined	9	53.3 (17.7-79.6)	0.954 (0.279-3.271)	
History of prior chemotherapy				0.116
No	12	72.9 (36.8-90.5)	1	
Yes	46	44.9 (29.0-59.6)	2.276 (0.793-6.531)	
Type of histology				0.384
Non-squamous	40	53.6 (35.8-68.5)	1	
Squamous	18	45.8 (20.9-67.8)	1.371 (0.671-2.805)	
Tumor proportion score of PD-L1				0.801
≥50%	16	54.7 (27.4-75.5)	0.833 (0.242-2.862)	
1%-49%	11	63.6 (29.7-84.5)	0.667 (0.167-2.671)	
<1%	8	56.2 (14.7-84.2)	1	
Unexamined	23	43.7 (22.6-63.2)	1.117 (0.364-3.428)	
Brain metastases				0.771
Yes	8	75.0 (31.5-93.1)	0.688 (0.233-2.030)	
No	42	46.8 (29.8-62.1)	1	
Unknown	8	50.0 (31.5-93.1)	0.837 (0.288-2.433)	
Hepatic metastases				<0.01†
Yes	7	not available	4.503 (1.700-11.96)	
No	43	59.2 (41.9-73.0)	1	
Unknown	8	50.0 (15.2-77.5)	1.085 (0.369-3.198)	
Bone metastases				0.874
Yes	11	38.4 (10.3-66.8)	1.228 (0.516-2.920)	
No	39	54.8 (36.5-69.9)	1	
Unknown	8	50.0 (15.2-77.5)	0.929 (0.316-2.733)	
No. of metastatic sites				0.878
≤2	35	54.4 (35.7-69.8)	1	
≥3	14	41.9 (14.3-67.8)	0.911 (0.393-2.111)	
Unknown	9	53.3 (17.7-79.6)	0.729 (0.215-2.472)	
Baseline tumor size				<0.01†
Small (below 101 mm)	34	71.0 (51.2-83.9)	1	
Large (above 101 mm)	24	23.0 (7.8-42.7)	3.122 (1.516-6.426)	
Type of medication				0.212
Nivolumab	38	44.6 (27.4-60.5)	1	
Pembrolizumab	20	62.2 (35.7-80.4)	0.586 (0.250-1.373)	
Multivariate analysis		Hazard ratio	95%CI	p-Value
ECOG.PS 2,3,4		3.407	1.180-9.841	0.024*
Large baseline tumor size		3.09	1.456-6.558	<0.01†
History of prior chemotherapy		4.044	1.273-12.85	0.017*

Multivariate analysis included the factors ECOG PS, hepatic metastases, baseline tumor size, history of prior chemotherapy, and tumor proportion score. CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; PD-L1: programmed death-ligand 1. * $p < 0.05$; † $p < 0.01$.

Table VI. Response of immune checkpoint inhibitor therapy and post treatment.

Factor	Baseline tumor size		p-Value
	Small (below 101 mm) n=34	Large (above 101 mm) n=24	
Response of ICI			0.039*
PR/SD/NE	28 (82.4)	13 (54.2)	
PD	6 (17.6)	11 (45.8)	
Post treatment after ICI therapy		0.019*	
Chemotherapy	10 (29.4)	2 (8.3)	
Best supportive care	13 (38.2)	18 (75.0)	
Ongoing ICI therapy	11 (32.4)	4 (16.7)	
Response of post chemotherapy	n=10	n=2	0.727
PR	3 (30.0)	0 (0.0)	
SD	1 (10.0)	0 (0.0)	
PD	4 (40.0)	2 (100.0)	
NE	2 (20.0)	0 (0.0)	

Values are presented as n (%). * $p < 0.05$, † $p < 0.01$. ICI: Immune checkpoint inhibitor; PR: partial response; SD: stable disease; PD: progressive disease; NE: not examined.

Interstitial fluid pressure (IFP) within tumors increases with cancer progression. Raju *et al.* (20) measured lymphatic vessel area using an antibody against lymphatic vessel endothelial hyaluronin acid receptor (LYVE)-1, a lymphatic system specific marker, in rat tongue cancer. Their results demonstrated that the highest IFP values were measured in rats with large tumors and that lymphatic vessel area, determined by LYVE-1 antibody staining, was significantly increased in the peritumoral, compared with the intratumoral, area (20). In addition, when IFP in the tumor is high, intratumoral lymphatic vessels are prone to collapse (21). Consequently, it becomes difficult for antigen-presenting cells recognizing TAAs to migrate into the lymphatic system and remain in the tumor tissue.

Tumors actively suppress the immune response as they grow, using various mechanisms other than the PD-1/PD-L1 pathway. As tumors grow, IFP elevates and the tumor immune microenvironment (TIME) becomes hypoxic with a low pH. Tumor hypoxia leads to expression of hypoxia-inducible factor-1 (HIF-1), which induces vascular endothelial growth factor-A (VEGF-A) (22). VEGF-A promotes the expression of PD-1, T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on cytotoxic T lymphocytes (CTLs), leading to a more immunosuppressive TIME (21, 23). VEGF-A also inhibits dendritic cell maturation and antigen presentation (21). Therefore, high HIF-1 expression levels are associated with poor prognosis for patients with NSCLC (24). Expanding tumors also produce numerous cytokines, including CC chemokine ligand (CCL)2, CCL5, CCL21, and CCL28. These

chemokines induce tumor progression; for example, CCL2 and CCL5 promote tumor cell proliferation and metastasis, respectively (25), while CCL21 and CCL28 attract naïve and regulatory T cells to the TIME (23, 26). Tumors also produce granulocyte colony stimulating factor, which is reported to increase the immunosuppressive function of Gr-1⁺CK11b⁺ myeloid cells (27). Low pH in the TIME induces regulatory T cells and myeloid-derived suppressor cells, while inhibiting natural killer cells and CTLs (28), thereby inducing immunosuppression. These facts demonstrate that a higher tumor burden can induce an immunosuppressive response.

As tumors progress, the immune-cancer balance is shifted. Huang *et al.* (29) found that levels of Ki67⁺ CD8 T cells increase after administration of pembrolizumab and that these cells were strongly correlated with tumor burden, with an even greater correlation observed following pembrolizumab treatment. The authors proposed that Ki67⁺ is a good prognostic marker for OS of melanoma patients treated with pembrolizumab; however, Ki67⁺ expression >6.5% was a poor prognostic marker for PFS and OS, while a Ki67/tumor burden ratio >1.94 was a good prognostic marker (29). These results suggest that T cell surface markers are not useful prognostic markers for patients with high tumor burden and that tumor burden is a more important marker than cell surface molecules.

It should be noted that this study was retrospective and conducted at a single-institution; however, however, our results should be reliable because they reproduce the observations reported for patients with melanoma. In addition, BTS is also likely to be a useful and practical negative marker because clinicians routinely calculate the sum of the diameters of tumors when evaluating RECIST. Furthermore, measurement of BTS does not require a specialist or expensive equipment, as needed to perform next-generation sequencing and immunostaining assays.

In conclusion, BTS is a useful and practical predictive and negative prognostic factor during ICI therapy for NSCLC.

Conflicts of Interest

None of the Authors have any conflict of interest to declare regarding this study.

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Figure 1. Kaplan–Meier (KM) plots grouped by patients with below and above median Baseline Tumor Size. (A) KM plots for progression-free survival (PFS) after starting immune checkpoint inhibitor therapy. (B) KM plots for overall survival (OS) after starting immune checkpoint inhibitor therapy. Mo: Months.

Figure 2. Kaplan–Meier (KM) plots grouped by patients with below and above median Baseline Tumor Size. KM plots for progression-free survival (PFS) after starting chemotherapy. Mo: Months.

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