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Impact of losing adipose tissue on outcomes from PD-1/PD-L1 inhibitor monotherapy in non-small cell lung cancer

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Abstract

Background: Adipose tissue induces inflammation, which desensitizes the efficacy of immunotherapy. However, several reports show that the therapeutic effect of programed cell death 1 (PD-1)/programed death-ligand 1 (PD-L1) inhibitor(s) monotherapy is significantly better in obese patients. Therefore, the effect of adipose tissue on immunotherapy is unclear.

Methods: In this study, we retrospectively reviewed patients with advanced non-small cell lung cancer (NSCLC) who received PD-1/PD-L1 inhibitor monotherapy between May 2016 and December 2018. We classified patients into total adipose tissue maintenance or loss groups according to adipose tissue change during the 6 months before treatment and compared the therapeutic effect of PD-1/PD-L1 inhibitors between these groups along with the presence or absence of cachexia, a poor prognostic factor.

Results: Of the 74 patients, 40 (54.1%) were cachexic. Among cachexic patients, we found no clear difference in the overall response rate (ORR) and progression-free survival (PFS) between the total adipose tissue maintenance and loss group. However, among noncachexic patients, the total adipose tissue loss group had a higher ORR (64.7% vs. 23.5%, $p < 0.05$) and longer PFS (18.5 months vs. 2.86 months, $p = 0.037$) than the maintenance group.

Conclusions: This study showed that decreasing adipose tissue without cachexia might favor the therapeutic effects of immunotherapy.

KEYWORDS
adipose tissue, cachexia, inflammation, PD-1/PD-L1 inhibitors

INTRODUCTION

Adipose tissue is known to induce chronic inflammation,[1] which is mediated by cytokines, such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and cyclooxygenase-2 (COX-2), secreted by the adipose tissue.[1] Several reports have suggested that inflammation desensitizes the therapeutic efficacy of programed cell death 1 (PD-1)/programed

death-ligand 1 (PD-L1) inhibitors.[2–4] On the other hand, multiple reports indicate that the therapeutic effect of PD-1/PD-L1 inhibitors is significantly better in obese patients, although they have large amounts of adipose tissue, which induces inflammation.[5–7] Considering that inflammation desensitizes the therapeutic efficacy of PD-1/PD-L1 inhibitors, the efficacy of PD-1/PD-L1 inhibitors should be lower in obese patients due to systemic inflammation. Contrarily,

the use of PD-1/PD-L1 inhibitors has better therapeutic outcomes in obese patients.[2-4]

There are several possible causes for this paradox, one of which is cachexia. Cachexia is a multifactorial syndrome that induces excessive inflammation, extreme skeletal muscle loss, and lipoatrophy[8] and occurs in approximately half of the patients with advanced lung cancer.[8,9] Obese patients are less likely to develop cachexia than nonobese patients.[10,11] Therefore, a better response to immunotherapy in obese patients may be explained by the difference in the proportion of patients with cachexia.[5-7]

Another possible cause of this paradox is the inaccuracy of body mass index (BMI) as an index. BMI does not accurately reflect adipose tissue volume and has been correlated with muscle mass to some extent.[12,13] Therefore, the high efficacy of PD-1/PD-L1 inhibitors reported in patients with high BMI may be due to muscle mass in these patients.[14] Furthermore, some results suggest that the therapeutic effect of PD-1/PD-L1 inhibitors is lowered when a certain level of BMI is exceeded, and excessive adipose tissue may indeed reduce the therapeutic effect of PD-1/PD-L1 and overall survival of such patients.[14]

According to Fearon's definition, cachexia, defined by bodyweight change over 6 months, is a strong prognostic factor. Therefore, changes in body composition impact the prognosis and therapeutic effect for patients rather than the state of body composition at any given point in time.[15] Our previous studies have shown that changes in muscle mass affect the therapeutic efficacy of PD-1/PD-L1 inhibitor(s) treatment.[16] However, it is unclear how changes in adipose tissue volume affect the therapeutic efficacy of PD-1/PD-L1 inhibitors. In the case of cytotoxic chemotherapy, it has been reported that the therapeutic efficacy is lower in patients with excessive fat.[17] Furthermore, an increase in BMI above a certain level attenuates the effect of immunotherapy, which led us to hypothesize that a decrease in fat mass may not necessarily have an adverse effect on patients.[14]

In this study, advanced lung cancer patients who received PD-1/PD-L1 inhibitors were classified into four groups according to the combination of total adipose tissue maintenance or loss and the presence or absence of cachexia. We objectively assessed changes in body composition over 6 months using computed tomography (CT) imaging in each group and retrospectively examined how specific changes in adipose tissue volume were related to the effects of PD-1/PD-L1 inhibitors.

METHODS

We conducted a retrospective, single-center cohort study of non-small cell lung cancer (NSCLC) patients who received at least one dose of PD-1/PD-L1 inhibitor (pembrolizumab, nivolumab, or atezolizumab) from May 1, 2016, to December 31, 2018. The eligibility criteria were as follows: (1) presence of at least one measurable lesion; (2) histologically proven stage III–IV according to TNM staging (AJCC eighth edition) or postoperative recurrence; and (3) availability of evaluable CT images taken within 1 month of baseline and before PD-1/PD-L1 inhibitor administration, with baseline defined as the heaviest weight between 6 months before PD-1/PD-L1 inhibitor administration and the date of administration. The rationale for patient exclusion was as follows: (1) the presence of driver oncogenes (EGFR/ALK/ROS1); (2) Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\geq$ 2; (3) PD-L1 status not measured or unknown; (4) unknown weight change within 6 months before receiving PD-1/PD-L1 inhibitors; and (5) the absence of CT information at baseline and within 1 month of PD-1/PD-L1 inhibitor administration.

Data collection

The following data were collected from medical records of all eligible patients: sex, age, histology, stage, presence of driver oncogenes (EGFR/ALK/ROS1), ECOG PS at the initiation of immune checkpoint inhibitors, number of prior therapies, PD-L1 tumor proportion score, type of PD-1/PD-L1 inhibitor (nivolumab, atezolizumab, pembrolizumab), BMI, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), lumbar skeletal muscle index (LSMI), total adipose tissue index (TATI), muscle change rate (from baseline to preceding the administration of PD-1/PD-L1 inhibitor), TATI change rate (from baseline to preceding the administration of PD-1/PD-L1 inhibitor), and cachexia (defined as unintentional weight loss of 5% or more in the past 6 months or 2% or more in patients with a BMI less than 20 kg/m^2).[15]

Analysis of adipose tissue quantity and muscle mass

The cross-sectional area of adipose tissue and lumbar skeletal muscle at the third lumbar vertebra (L3) level was analyzed using electronically stored CT images. Adipose tissue and lumbar skeletal muscle area were quantified based on Hounsfield unit (HU) thresholds of −190 to −30 and −29 to +150, respectively.[18] All body composition measurements were analyzed using slice-O-matic software v5.0 (Tomovision). By correcting the lumbar adipose tissue and skeletal muscle area at the L3 level for height, the adipose tissue volume and skeletal muscle volume of the whole body can be assessed, which are referred to as TATI and LSMI, respectively.[19,20]

TATI (cm^2/m^2) = The cross-sectional area of the visceral and subcutaneous adipose tissue (cm^2)/height^2 (m^2).

LSMI (cm^2/m^2) = The cross-sectional area of the skeletal muscle (cm^2)/height^2 (m^2).

Muscle quality (HU) = The mean value of skeletal muscular density (HU) in two consecutive images at the L3 level.

In this study, the population with decreased TATI at the time of PD-1/PD-L1 inhibitor treatment, compared to that at baseline, was defined as the total adipose tissue loss group,

and the other population was defined as the total adipose tissue maintenance group.

Statistical analysis

The primary endpoint was progression-free survival (PFS), defined as the time from the date of initiation of PD-1/PD-L1 inhibitor treatment to the date of tumor progression or death, whichever occurred first. The last follow-up was June 26, 2020. The secondary endpoint was the overall response rate (ORR). The median PFS was assessed by the Kaplan–Meier method. Regarding PFS and duration of response, data for patients who were treated with a new anticancer agent without evidence of tumor progression were censored at the date of their last CT scan for evaluation. PFS was assessed using Cox proportional hazards models, with hazard ratios adjusted for PD-L1 expression (tumor proportion score [TPS] ≥50% or unknown); adjusted hazard ratio was used as a covariate. Based on the Response Evaluation Criteria in Solid Tumors (version 1.1), ORR was measured as the ratio of the sum of complete and partial responses. The Mann–Whitney test was performed for changes in muscle mass and muscle quality between each group. Chi-square or Fisher's exact tests were used to compare categorical variables. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and a graphical user interface for R (The R Foundation for Statistical Computing), and statistical significance was determined at $p < 0.05$.[21]

RESULTS

Patient characteristics

Out of 286 consecutive patients with advanced NSCLC who initially received PD-1/PD-L1 inhibitor therapy between May 2016 and December 2018, 74 patients were finally enrolled in this study (Figure 1). The median age of patients was 67.5 (range, 33–84) years (Table 1). The majority of patients were men with stage IV disease and had nonsquamous histology without specific driver oncogenes, and all patients had ECOG-PS 0–1. Thirty-four (45.9%) and 40 (54.1%) patients were non-cachexic and cachaxic, respectively. Thirty (40.5%) and 44 (59.5%) patients had PD-L1 ≥ 50% and PD-L1 < 50%,
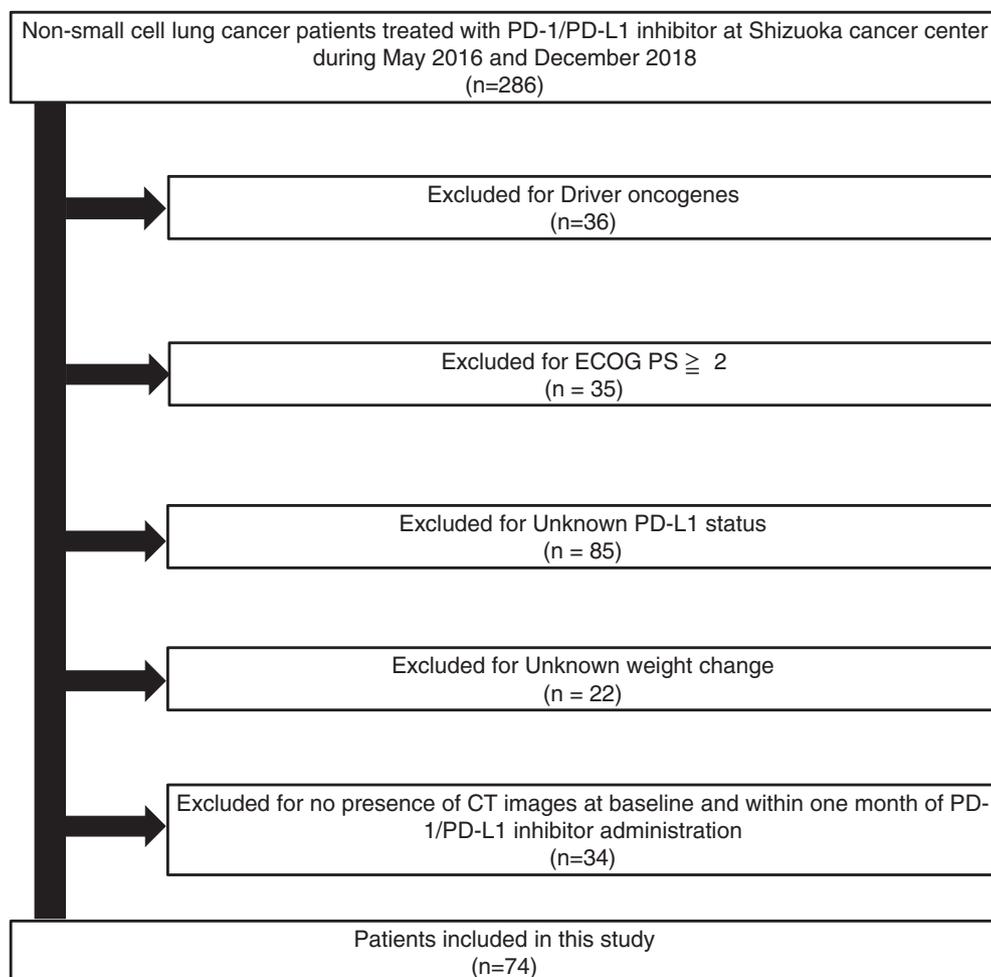
Patient's consort

FIGURE 1 Flow diagram of patient enrollment. A total of 286 patients were enrolled in this study. However, 212 patients were finally excluded for the following reasons: 36 patients had at least one kind of driver oncogene, 35 patients were ECOG-PS >2, 85 patients were not investigated for PD-L1 status, 22 patients did not have their weight changes examined over a six-month duration, and 34 patients had no presence of CT images at baseline and within one month of PD-1/PD-L1 inhibitor administration. Abbreviations: PS, performance status; PD-1, programed cell death 1; PD-L1, programed death-ligand 1; CT, computed tomography

TABLE 1 Patient characteristics

Characteristics	Cachexia[a]			Noncachexia		
	Total adipose tissue maintenance (n = 7)	Total adipose tissue loss (n = 33)	p-value	Total adipose tissue maintenance (n = 17)	Total adipose tissue loss (n = 17)	p-value
Age (range)	66 (54–78)	68 (53–79)	ns	60 (45–79)	71 (33–84)	ns
Sex (%)						
Men	5 (71.4)	27 (81.8)	ns	12 (70.6)	14 (82.4)	ns
Women	2 (28.6)	6 (18.2)		5 (29.4)	3 (17.6)	
ECOG-PS (%)						
0	0 (0.0)	3 (9.1)	ns	3 (17.6)	4 (23.5)	ns
1	7 (100)	30 (90.9)		14 (82.4)	13 (76.5)	
Histology (%)						
Squamous	0 (0.0)	6 (18.2)	ns	2 (11.8)	3 (17.6)	ns
Nonsquamous	7 (100)	27 (81.8)		15 (88.2)	14 (82.4)	
Stage (%)						
III	0 (0.0)	4 (12.1)	ns	2 (11.8)	3 (17.6)	ns
IV	7 (100)	29 (87.9)		15 (80.2)	14 (82.4)	
PD-L1 Tumor proportion score (%)						
≥50%	2 (28.6)	13 (39.4)	ns	7 (41.2)	8 (47.1)	ns
<50%	5 (71.4)	20 (60.6)		10 (58.8)	9 (52.9)	
Treatment line (%)						
1	2 (28.6)	7 (21.2)	ns	5 (29.4)	3 (17.6)	ns
≥2	5 (71.4)	26 (78.8)		12 (70.6)	14 (82.4)	
Initial PD-1/PD-L1 inhibitor (%)						
Nivolumab	1 (14.3)	8 (24.2)	ns	3 (17.6)	6 (35.3)	ns
Pembrolizumab	5 (71.4)	18 (54.5)		11 (64.8)	10 (58.8)	
Atezolizumab	1 (14.3)	7 (21.2)		3 (17.6)	1 (5.9)	
BMI (kg/m², mean ± SD)	21.1 ± 2.67	20.5 ± 3.32	ns	22.8 ± 3.51	22.9 ± 2.75	ns
Bodyweight change rate (%, mean ± SD)	−8.54 ± 4.06	−9.42 ± 4.19	ns	0.95 ± 3.93	−2.76 ± 1.65	<0.01
NLR	3.87 (2.36–11.01)	3.98 (1.33–14.67)	ns	2.50 (0.79–4.41)	2.94 (1.79–8.23)	ns
CRP	0.47 (0.11–7.51)	1.42 (0.03–20.88)	ns	0.85 (0.04–8.60)	0.44 (0.03–8.01)	ns
LSMI (cm²/m², mean ± SD)						
Men	41.0 ± 6.72	41.8 ± 6.09	ns	44.8 ± 5.62	46.6 ± 5.63	ns
Women	39.2 ± 2.65	34.9 ± 4.91	ns	35.6 ± 7.11	39.6 ± 1.23	ns
TATI (cm²/m², mean ± SD)						
Men	67.3 ± 52.8	50.1 ± 33.4	ns	74.1 ± 35.7	71.7 ± 36.3	ns
Women	66.0 ± 34.3	37.3 ± 35.6	ns	93.7 ± 50.0	33.3 ± 6.01	ns

Note: Cachexia was defined as an unintentional weight loss >5% during the preceding 6 months or >2% in patients with a BMI <20 kg/m² according to consensus criteria.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ECOG-PS, Eastern Cooperative Oncology Group performance status; LSMI, lumbar skeletal muscle index; NLR, neutrophil-to-lymphocyte ratio; ns, not significant; PD-1, programed death-1; PD-L1, programed death-ligand 1; SD, standard deviation; TATI, total adipose tissue index.

[a]Total adipose tissue change was classified into loss or maintenance according to the change rate of TATI from baseline to PD-1/PD-L1 inhibitor treatment. Loss was defined as (pretreatment TATI – Baseline TATI) < 0.0 cm²/m², otherwise considered as maintenance.

respectively. All patients had received PD-1/PD-L1 inhibitors as monotherapy, which included nivolumab in 18 (24.3%) patients, pembrolizumab in 44 (59.5%) patients, and atezolizumab in 12 (16.2%) patients. Seventeen (23%) and 57 (77%) patients had received PD-1/PD-L1 inhibitor therapy as first- and second-line (or higher) therapy, respectively. The median NLR was 3.36 (0.79–14.67), and the median CRP was 0.92 (0.03–20.88). The mean BMI was 21.6 ± 3.33 kg/m², and the mean LSMI was 43.5 ± 6.17 cm²/m² for men and 36.5 ± 5.13 cm²/m² for women. The mean TATI was

TABLE 2 The objective response rate (ORR)

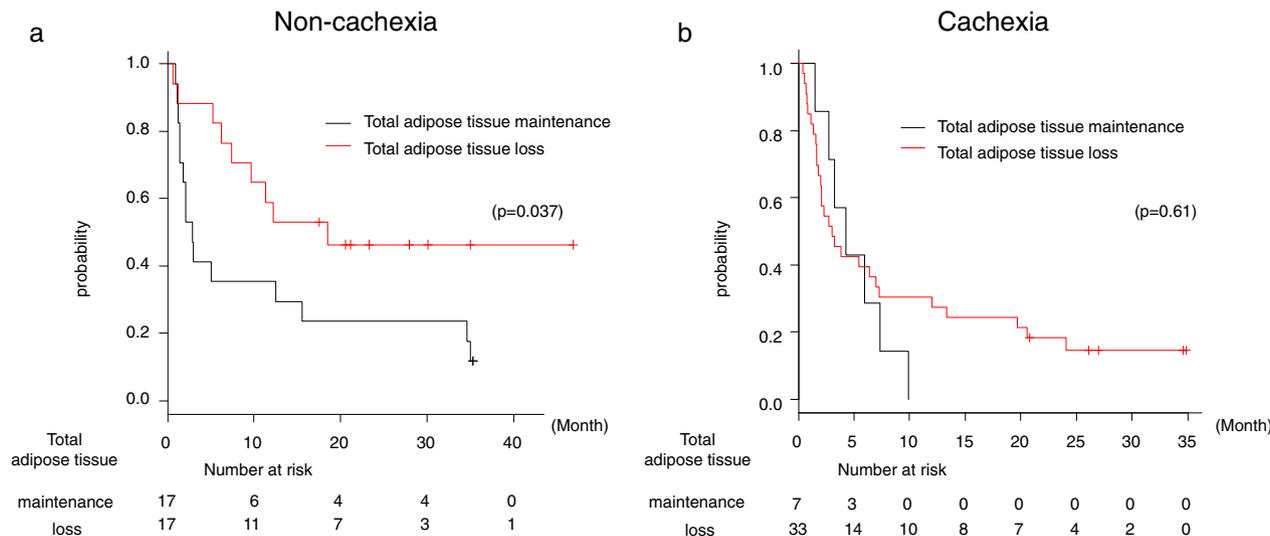|		Cachexia Total adipose tissue			Noncachexia Total adipose tissue		
	All	**Maintenance**	**Loss**	***p*-value**	**Maintenance**	**Loss**	***p*-value**
ORR	28.4%	23.5%	64.7%	0.05	0%	18.1%	ns

Abbreviation: ns, not significant.

FIGURE 2 (a) Kaplan–Meier curves of PFS stratified by total adipose tissue changes in the noncachexia group. (b) Kaplan–Meier curves of PFS stratified by total adipose tissue changes in the cachexia group. Abbreviation; PFS, progression-free survival

61.8 ± 37.1 cm^2/m^2 for men and 57.7 ± 43.6 cm^2/m^2 for women. The mean muscle change rate from baseline to PD-1/PD-L1 inhibitor initiation was $-3.5 \pm 7.49\%$, and the mean adipose tissue change rate from baseline to the time of PD-1/PD-L1 inhibitor was $-9.40 \pm 37.3\%$. Further, we divided these patients into four groups according to the combination of total adipose tissue maintenance or loss and the presence or absence of cachexia and examined the differences among the four groups (Table 1). There were no apparent differences in age, gender, histology, line, TPS, or NLR, and CRP among these groups. There were no significant differences in BMI or LSMI among these groups, but, in men, the group with cachexia and adipose tissue loss had significantly lower TATI than others $(50.13 \pm 33.39$ (cm^2/m^2) vs. 71.92 ± 37.6 (cm^2/m^2), $p = 0.024$). In women, TATI was significantly lower in the adipose tissue loss group, regardless of cachexia $(85.74 \pm 45.22$ (cm^2/m^2) vs. 35.93 ± 28.40 (cm^2/m^2), $p = 0.017$) (Table 1).

Impact of cachexia and total adipose tissue loss on tumor response

The ORR was 28.4% (95% confidence interval [CI]: 18.5–40.1) in all patients. Patients with high tumor PD-L1 expression (TPS $\geq$ 50%) had a higher ORR than those with low PD-L1 expression (46.7% [95% CI: 28.3–65.7] vs. 15.9% [95% CI: 6.6–30.1], $p < 0.05$). Patients with

cachexia had a lower ORR than those with noncachexia (15.0% [95% CI: 5.7–29.8] vs. 44.1% [95% CI: 27.2–62.1] $p < 0.05$). We further assessed the response rate for the cachexia or noncachexia groups. There was no difference in the ORR in the cachexia group between patients with total adipose tissue loss and maintenance (18.1% [95% CI: 7–35.5] vs. 0% [95% CI: 0–34.8] $p = 0.57$) (Table 2). On the other hand, in the noncachexia group, patients with total adipose tissue loss had a significantly higher ORR than those with total adipose tissue maintenance (64.7% [95% CI: 38.3–85.8] vs. 23.5% [95% CI: 6.8–49.9] $p < 0.05$) (Table 2).

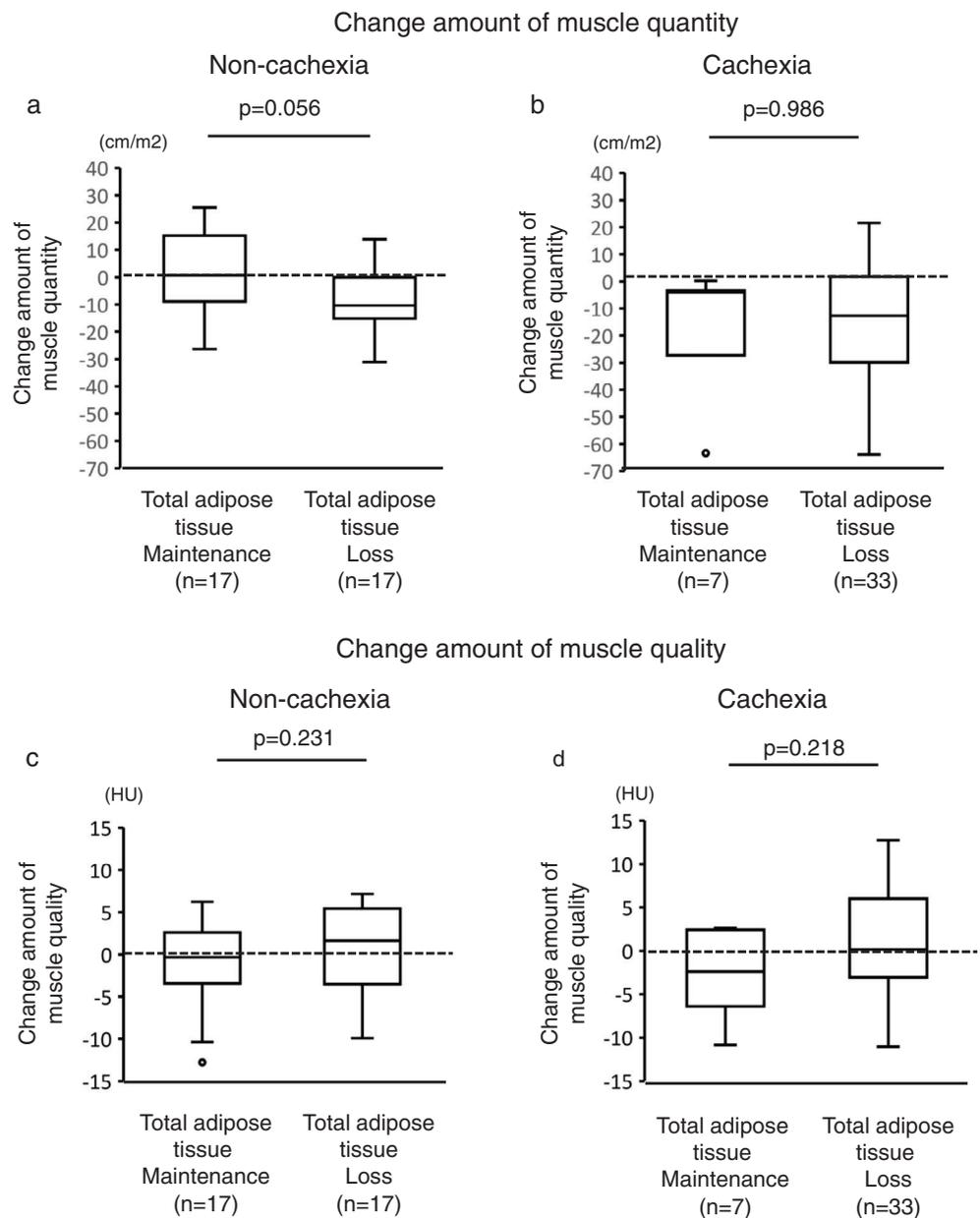## Impact of cachexia and total adipose tissue loss on PFS

Among 74 patients, 59 (79.7%) showed tumor progression up to the cutoff date (June 26, 2020). After a median follow-up of 19.5 months (range, 0.43–48.5 months), among the non-cachexia population, the total adipose tissue loss group had a significantly longer PFS than the total adipose tissue maintenance group (18.5 months [95% CI: 6.21–NA] vs. 2.86 months [95% CI: 1.38–15.6]) $p = 0.037$) (Figure 2a). In the multivariate analyses, total adipose tissue loss was significantly associated with superior PFS values, and the adjusted hazard ratio for total adipose tissue loss was 0.34 (95% CI: 0.14–0.82; $p < 0.05$),

TABLE 3 Predictor for efficacy in PD-1 /PD-L1 inhibitors among the noncachexia patients group

Predictors for PFS	Adjusted HR	95% CI	p-value
Total adipose tissue loss vs. maintenance	0.34	0.14–0.82	<0.05
PD-L1 expressions (TPS ≥ 50% vs. <50% or unknown)	0.36	0.15–0.85	<0.05
ECOG-PS (0 vs. 1)	0.45	0.16–1.25	0.125

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group performance status; PD-L1, programed death-ligand 1; PFS, progression-free survival.

FIGURE 3 (a) Change of muscle quantity from the heaviest weight day in 6 months prior to PD-1/PD-L1 inhibitor administration to the day of PD-1/PD-L1 inhibitor administration among the noncachexia group. (b) Change of muscle quantity from the heaviest weight day in 6 months prior to PD-1/PD-L1 inhibitor administration to the day of PD-1/PD-L1 inhibitor administration among the cachexia group. (c) Change of muscle quality from the heaviest weight day in 6 months prior to PD-1/PD-L1 inhibitor administration to the day of PD-1/PD-L1 inhibitor administration among the noncachexia group. (d) Change of muscle quality from the heaviest weight day in 6 months prior to PD-1/PD-L1 inhibitor administration to the day of PD-1/PD-L1 inhibitor administration among the cachexia group. Abbreviations; PD-1, programed cell death 1; PD-L1, programed death-ligand 1

after adjusting for PD-L1 expression (TPS ≥ 50% vs. <50% or unknown) and PS (0 vs. 1) (Table 3).

However, among patients with cachexia, there was no difference between the total adipose tissue maintenance group and total adipose tissue loss (4.27 months [95% CI: 1.48–7.36] vs. 2.99 months [95% CI: 1.77–7.00], $p = 0.61$) (Figure 2b).

Amount of change in muscle mass and quality

We investigated the amount of change in muscle mass according to the population with the presence or absence of cachexia. In the noncachexia population, although we observed no statistically significant difference in the total adipose tissue loss group compared to that in the total

adipose tissue maintenance group, the total adipose tissue loss group had a greater decrease in muscle mass from baseline (-10.3 cm^2/m^2 [-31.1–13.9] vs. 0.7 cm^2/m^2 [-26.3–25.5], $p = 0.056$). On the other hand, in the cachexia population, there was no significant difference among the total adipose tissue loss and adipose tissue maintenance groups (-12.7 cm^2/m^2 [-63.9–21.6] vs. -4.00 cm^2/m^2 [-63.4–0.2] $p = 0.986$) (Figure 3a,b).

Similarly, we also investigated the amount of change in muscle quality in the patient population due to cachexia. In the noncachexia population, there was no significant difference between the total adipose tissue loss group and the total adipose tissue maintenance group (1.63 HU [-9.92–7.16] vs. -0.32 HU [-12.8%–6.25%], $p = 0.231$) (Figure 3c). In the cachexia population, there was no significant difference between the total adipose tissue loss and total adipose tissue maintenance groups, and both groups had either maintained or reduced muscle quality with respect to baseline (0.15 HU [-11.0–12.7] vs. -2.40 HU [-10.9–2.62] $p = 0.218$) (Figure 3d).

DISCUSSION

In this study, we found no significant difference in PFS in the cachexia group between the total adipose tissue maintenance and loss populations. However, among the noncachexia group, the total adipose tissue loss group showed a significant prolongation of PFS compared to the total adipose tissue maintenance group. In addition, there was no statistical difference in muscle mass and quality between the two populations of noncachexia patients, but the total adipose tissue loss group showed a decreasing trend only in muscle mass relative to the baseline compared to the maintenance group.

Several reports have suggested that adipose tissue adversely affects immunotherapy, and the relationship garnering the most attention in basic research is that between IL-1β and myeloid-derived suppressor cells (MDSCs).[22–27] MDSCs, which promote immunosuppression in tumors, are induced by the inflammatory cytokine IL-1β that exacerbates tumors as their levels increase.[22–25] IL-1β-induced MDSCs are activated by adipose tissues,[26] and inflammatory IL-1β is reportedly activated in the tumor microenvironment of obese breast cancer model mice.[27] Another report indicated that the total frequency of MDSCs in tumors increased significantly in kidney cancer mouse models with food-induced obesity,[25] and inhibition of IL-1β improved tumor immunity.[22] In addition, a clinical trial involving renal cell carcinoma patients who received immunotherapy reported that PFS and overall survival were shorter in patients with BMI ≥ 30 kg/m^2 than in those with BMI < 30 kg/m^2.[24] This study also assessed mice with kidney cancer, and kidney cancer mice with food-induced obesity showed a significant increase in blood levels of IL-1β compared to the control group. Moreover, the increase in IL-1β and MDSC levels in the tumor were positively correlated.[24] Based on these results, it has been reported that

adipose tissue may increase IL-1β levels, induce MDSCs that infiltrate the tumor, and ultimately attenuate the therapeutic effect of PD-1/PD-L1 inhibitors.

On the other hand, in cachexia patients, we could not find a difference in the therapeutic effect of PD-1/PD-L1 inhibitors between the total adipose tissue loss and total adipose tissue maintenance groups. There are two possible explanations for this finding. First, the impact of cachexia on the therapeutic effect of PD-1/PD-L1 inhibitors might greatly outweigh the impact of changes in the adipose tissue.[28] Second, the presence of inflammation is associated with cachexia. Cachexia-related mediators include IL-6, TNF-α, and IL-1β, associated with the adipose tissue.[22,29,30] Therefore, when cachexia is involved, reducing fat mass may not only fail to reduce IL-1β levels, but also other mediators, such as IL-6, may suppress tumor-infiltrating lymphocytes, meaning that factors other than IL-1β may induce inflammation and ultimately show no difference in the therapeutic effect of PD-1/PD-L1 inhibitors.[22,29] We believe that these two points may explain why there was no difference in the therapeutic effect of PD-1/PD-L1 inhibitors with an increase or decrease in fat mass in the population of patients with cachexia.

There have already been multiple publications, including ours, on the impact of muscle gain/loss on immunotherapy[16,31,32]; therefore, we investigated the impact of increasing or decreasing muscle mass on immunotherapy in this study. Among the noncachexia patients in our study, the adipose tissue loss population experienced a greater therapeutic efficacy of PD-1/PD-L1 inhibitors but tended to have low muscle mass compared to the adipose tissue maintenance population. If we consider previous reports that suggest that reduced muscle mass has a negative impact on the therapeutic effect of PD-1/PD-L1 inhibitors, it is discernible that the effect of immunotherapy on the total adipose tissue loss population in our study was independent of the effect of muscle mass on the therapeutic efficacy of PD-1/PD-L1 inhibitors.[16,31,32] However, this result contradicts previous reports that suggest that a decrease in muscle mass reduces the therapeutic effect of PD-1/PD-L1 inhibitors.[16] Therefore, we suggest that the cause of the decrease in muscle mass may be important to explain why such a phenomenon occurred. In the noncachexia population in this study, the adipose tissue loss group experienced a decrease in muscle mass, albeit not significantly, relative to the patients in the adipose tissue maintenance group (Figure 2). However, even in addition to cancer patients, when someone intending to lose weight performs aerobic exercises, they would lose muscle mass in addition to bodyweight and adipose tissue, which shows that there is mild loss of muscle mass in physiological weight loss that employs training.[33] We believe that noncachexia patients in this study who belonged to the whole adipose tissue loss group were less likely to experience a significant negative impact on immunotherapy because of physiological loss of muscle mass.

We continue to believe that excessive loss of muscle mass is a negative predictor of the therapeutic effect of

immunotherapy. However, since cachexia-induced inflammation also rapidly causes a decline in muscle mass, muscle loss may simply reflect the presence or absence of cachexia. There are very few studies on the relationship between muscle mass and immunotherapy that consider the proportion of patients with cachexia.[34] If loss of muscle mass due to cancer reflects the presence or absence of cachexia, it may be sufficient to evaluate the patient's weight loss for 6 months using a simple calculation, but further research is needed to verify this.

This study had several limitations. First, it was a retrospective study involving a small number of subjects. Second, we did not measure the levels of inflammatory cytokines such as IL-1, IL-6, and TNF-α, which are associated with cachexia. However, previous reports have already indicated that adipose tissue and cachexia are associated with the presence of these inflammatory cytokines, which should be investigated in future prospective studies. Finally, as this was a single-center study involving a small patient population in Japan, there are limitations in generalizing our results to other populations. However, we think that the hypothesis that adipose tissue changes alter the therapeutic efficacy of immunotherapy has rarely been proposed, at least in lung cancer, and may provide clues for improving the therapeutic efficacy of immunotherapy in the future.

In conclusion, this study showed that reduction in the quantity of adipose tissue with suppressed bodyweight loss might be associated with the activation of immunotherapy, at least from an immunotherapy perspective.

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