Received: 23 January 2023 | Accepted: 21 March 2023

DOI: 10.1111/1759-7714.14881

ORIGINAL ARTICLE

WILEY

Prognostic effect of cachexia in patients with non-small cell lung cancer receiving immune checkpoint inhibitors

Norikazu Matsuo[1] | Koichi Azuma[1] | Kenta Murotani[2] | Daiki Murata[1] | Goushi Matama[1] | Akihiko Kawahara[3] | Takashi Kojima[1] | Takaaki Tokito[1] | Tomoaki Hoshino[1]

[1]Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Fukuoka, Japan

[2]Biostatistics Center, Kurume University School of Medicine, Fukuoka, Japan

[3]Department of Diagnostic Pathology, Kurume University Hospital, Fukuoka, Japan

Correspondence
Koichi Azuma, Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan.
Email: azuma@med.kurume-u.ac.jp

Funding information
JSPS KAKENHI, Grant/Award Number: JP20K16317

Abstract

Background: The presence of cachexia in cancer patients negatively affects the quality of life and survival. However, the impact of cachexia on immunotherapy, such as PD-1/L1 inhibitors, is not fully understood. Therefore, we examined whether cancer cachexia affects the prognosis of patients with non-small cell lung cancer (NSCLC) treated with PD-1/PD-L1 inhibitors.

Methods: We retrospectively screened patients with pathologically confirmed advanced or recurrent NSCLC who were treated with PD-1/PD-L1 monotherapy at Kurume University Hospital. We defined cancer cachexia as weight loss of at least 5% during the past 6 months or any degree of weight loss more than 2% and BMI <20.

Results: Among 182 patients, 74 had cancer cachexia. The presence of cachexia was significantly associated with females, poor performance status (PS), never-smokers, and driver mutations. Multivariate analysis revealed that poor PS and being a smoker were associated with the presence of cachexia. Patients with cancer cachexia had significantly shorter progression-free survival (PFS) and overall survival (OS). In the multivariate analysis, PS and sex were significantly correlated with PFS, whereas PS and cachexia were significantly correlated with OS. Subanalysis revealed that patients in the PS0/without cachexia group had longer PFS and OS than those in the cachexia or PS1-3 group.

Conclusions: In NSCLC patients, cachexia was associated with a worse prognosis, irrespective of tumor PD-L1 expression, indicating that cachexia is a predictive factor for NSCLC patients receiving immune checkpoint inhibitors.

KEYWORDS
cachexia, NSCLC, PD-1 inhibitor

INTRODUCTION

Cachexia is a multifactorial syndrome that causes reduced food intake, progressive bodyweight loss via skeletal muscle and adipose tissue loss, and an imbalance in metabolic regulation, resulting in reduced physical function.[1] It is caused by a cancer-associated catabolic state in the systemic circulation as well as physiological factors, such as imbalanced inflammatory activation, proteolysis, autophagy, and lipolysis.[2] Cachexia is a common complication in non-small cell lung cancer (NSCLC), occurring in almost 38.7%–48.1% of patients with advanced or recurrent disease.[3–6] Since the presence of cachexia negatively affects the quality of life and decreases survival, the assessment of cachexia is important in the management of patients with cancer.[7]

Programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors have demonstrated promising clinical outcomes in patients with

NSCLC.[8–11] Notably, a subgroup of NSCLC patients treated with PD-1/PD-L1 inhibitors has long-duration tumor responses.[12] However, PD-1/PD-L1 inhibitors are often ineffective in vulnerable patients, such as those with poor performance status (PS).[13] Given that the presence of cancer cachexia worsens the patient's condition and is associated with altered inflammatory dynamics, the impact of cachexia on immunotherapy efficacy should be clarified. In the present study, we investigated whether cancer cachexia affects the prognosis of patients with NSCLC treated with PD-1/PD-L1 inhibitors. The primary endpoint of this study was to investigate the prognostic impact of cachexia on PD-1/PD-L1 inhibitors treatment, and secondary endpoint was to explore predictors of therapeutic response to PD-1/L1 inhibitors in NSCLC patients with cachexia.

METHODS

Patients and clinical analysis

We retrospectively screened patients with pathologically-confirmed advanced or recurrent NSCLC who were treated with PD-1/PD-L1 inhibitors at Kurume University Hospital between February 2016 and December 2020. PD-L1 expression on tumor cells was assessed by the PD-L1 immunohistochemistry (IHC) 22C3 pharm Dx assay (Agilent Technologies) in archived biopsy specimens. The study was performed in accordance with the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board of Kurume University Hospital (IRB No 20100).

Definition of cancer cachexia

The cancer cachexia definition used in our study was derived from the original definition by Fearon et al., which states the presence of weight loss of at least 5% during the past 6 months or any degree of weight loss more than 2% and BMI <20. We did not include skeletal muscle mass in the definition of cancer cachexia.[1]

Statistical analysis

Comparisons for categorical variables were evaluated using the chi-squared or Fisher's exact tests and identified the factors significantly related to cachexia. Multivariate analysis was performed to identify the risk factors for cancer cachexia using the stepwise logistic regression method. With respect to the factors, PS (0 vs. 1–3), age (≥75 years vs. <75 years), sex, smoking status, and driver mutation (positive versus negative) were analyzed.

Objective tumor responses were evaluated in accordance with Response Evaluation Criteria in Solid Tumors

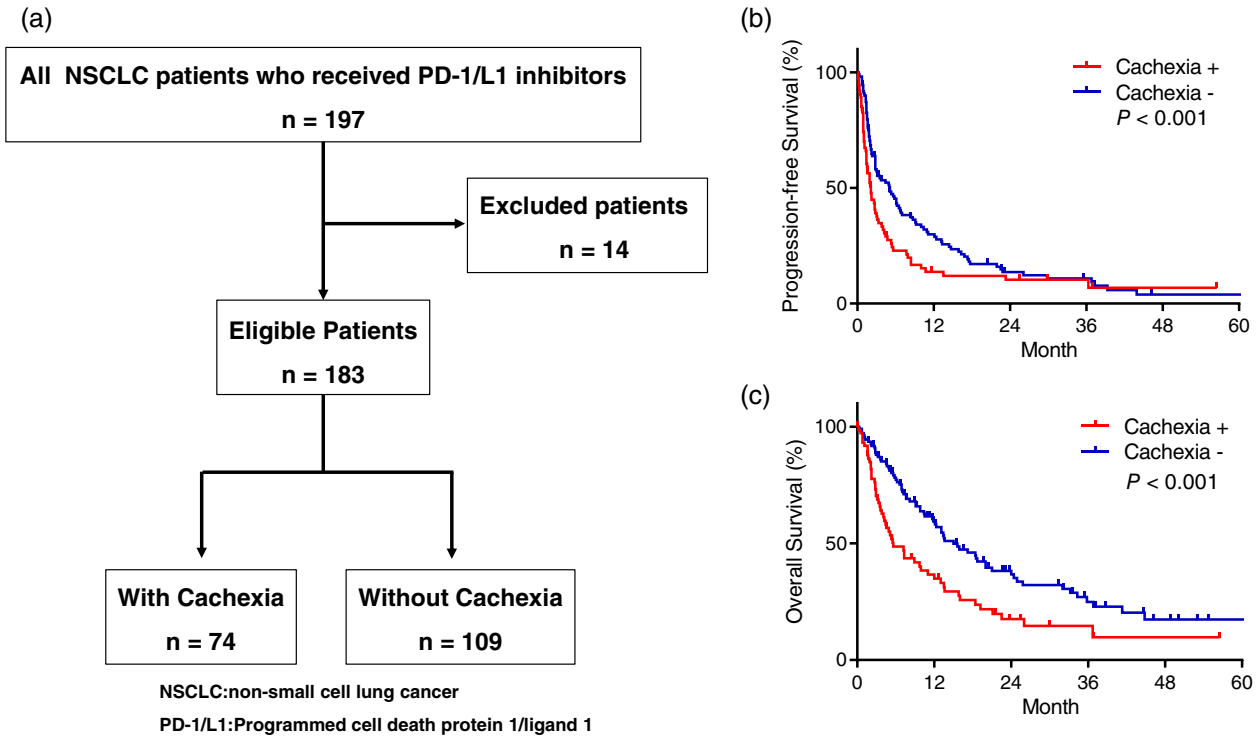

FIGURE 1 (a) A total of 197 patients were identified with advanced or recurrent NSCLC who had been treated with PD-1/PD-L1 inhibitors at Kurume University Hospital between February 2016 and December 2020. Of the 197 patients, 183 were included. Fourteen patients were excluded because their bodyweight before treatment was not recorded and cachexia could not be assessed. Kaplan–Meier curves displaying (b) progression-free survival and (c) overall survival of NSCLC patients receiving PD-1/PD-L1 inhibitors with or without cancer cachexia.

TABLE 1 Clinical characteristics of NSCLC patients receiving PD-1/PD-L1 inhibitors with and without cachexia.

Variable	With cachexia ($N = 74$)	Without cachexia ($N = 109$)	p-value
Age, median (range), years	72 (48–89)	70 (41–87)	0.010
Sex			0.011
Male	47 (62.7)	88 (80.7)	
Female	27 (37.3)	21 (19.3)	
ECOG performance status			<0.001
0	13 (17.6)	59 (54.1)	
1	28 (37.8)	30 (27.5)	
2	21 (28.4)	13 (11.9)	
3	12 (16.2)	7 (6.4)	
Smoking status			0.007
Former or current	49 (66.2)	91 (83.5)	
Never	25 (33.8)	18 (16.5)	
Histology			0.141
Squamous	17 (23.0)	36 (33.0)	
Nonsquamous	57 (77.0)	73 (67.0)	
Driver mutation			0.027
EGFR or ALK	22 (29.7)	17 (15.6)	
Wild-type	52 (70.3)	92 (84.4)	
Treatment line			0.724
First	18 (24.3)	24 (22.0)	
Second or later	56 (75.7)	85 (78.0)	
PD-L1 TPS	($N = 57$)	($N = 82$)	0.566
<1%	16 (28.1)	20 (24.4)	
1%–49%	14 (24.6)	27 (32.9)	
≥50%	27 (42.1)	35 (42.6)	
PD-1/PD-L1 inhibitor			0.085
Nivolumab	42 (56.8)	52 (47.7)	
Pembrolizumab	29 (39.2)	42 (38.5)	
Atezolizumab	3 (4.1)	15 (13.8)	

Note: Data represent numbers (%) unless otherwise indicated.
Abbreviations: ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score.

(RECIST) 1.1.[14] Progression-free survival (PFS) and overall survival (OS) were compared using the log-rank test. Multivariate analysis was performed which factors were associated with PFS and OS using the stepwise logistic regression method. With respect to the factors, cancer cachexia, PS (0 vs. 1–3), age (≥75 years vs. <75 years), sex, smoking status, histology (nonsquamous vs. squamous), driver mutation (positive vs. negative) and PD-L1 tumor proportion score (TPS) (≥50% vs. <50%) were analyzed. All tests were two-sided, and differences were considered statistically significant at $p < 0.05$. Statistical analyses were conducted using JMP version 11 (SAS Institute Inc.) or GraphPad Prism version 6.07 for Windows (GraphPad Software; www.graphpad.com).

TABLE 2 Multivariate analysis of cachexia prevalence.

Variable	p-value	OR (95% CI)
PS ≥1 vs. 0	<0.001	5.441 (2.648–11.179)
Smoker vs.never	0.012	0.375 (0.175–0.805)

RESULTS

Association between cancer cachexia and patient characteristics

We identified 197 patients with advanced or recurrent NSCLC who had been treated with PD-1/PD-L1 inhibitors at Kurume University Hospital between February 2016 and December 2020. Of 197 patients, 183 were included. Fourteen patients were excluded because their bodyweight before treatment was not recorded and cachexia could not be assessed (Figure 1a). All patients received PD-1/PD-L1 inhibitors monotherapy. Of these 183 patients, 74 (40.4%) were diagnosed with cancer cachexia. Relevant patient characteristics related to the presence of cachexia are summarized in Table 1. The presence of cachexia was significantly associated with females ($p = 0.011$), poorer PS ($p < 0.001$), never-smokers ($p = 0.007$), and driver mutations ($p = 0.027$), whereas no significant association was observed with histology, treatment line, PD-L1 expression, or PD-1/L1 inhibitor treatment. Multivariate analysis was performed using step wise regression with factors that were found to be significantly related to cachexia as variables. Multivariate analysis revealed that poorer PS and smoker were ~~was~~ associated with the presence of cachexia (PS 1–3 vs. PS 0, $p < 0.001$, OR = 5.441, and smoker vs. never smoker, $p = 0.012$, OR = 0.375) (Table 2).

Association between cancer cachexia and outcomes of PD-1/PD-L1 inhibitor treatment

There was no difference in the overall response rate between patients with (25.4%) or without (28.7%) cancer cachexia ($p = 0.622$). However, the disease control rate tended to be worse in those with cancer cachexia (43.7%) than in those without cachexia (58.3%) (Table S1). The median length of follow-up was 8.5 months (range, 0.1–71.6) for censored cases. The median PFS and OS were 3.0 months (95% CI: 2.2–4.9) and 12 months (95% CI: 9.1–15.0), respectively. Patients with cancer cachexia had significantly shorter PFS (median, 2.1 vs. 5.1 months, $p < 0.001$) and OS (median, 5.6 vs. 15.0 months, $p < 0.001$) (Figure 1b, c).

Multivariate analyses for PFS and OS

We performed multivariate analyses to identify the prognostic importance of clinical characteristics and cancer cachexia. In the multivariate analysis, PS (hazard ratio

[HR] 1.964, 95% CI: 1.403–2.749, $p < 0.001$) and sex (hazard ratio [HR] 0.67, 95% CI: 0.470–0.957, $p < 0.028$) were significantly correlated with PFS (Table 3), whereas PS (hazard ratio [HR] 1.990, 95% CI: 1.344–2.968, $p < 0.001$) and cachexia (hazard ratio [HR] 1.488, 95% CI: 1.018–2.175, $p = 0.040$) were significantly correlated with OS (Table 4).

Exploratory analyses of cachexia and PS

Given the positive association between cancer cachexia and PS, we analyzed the relationship between cachexia and PS. We divided the patients into four groups based on PS 0 or 1–3 as well as the presence or absence of cachexia. The median PFS was 5.6 in the PS 0/with cachexia group, 6.5 months in the PS 0 /without cachexia group, 1.9 months in the PS 1–3/with cachexia group, and 2.8 months in the PS 1–3/without cachexia group ($p < 0.001$, Figure 2a). The median OS was 13.6 months in the PS 0/with cachexia group, 18.5 months in the PS 0 /without cachexia group, 5.4 months in the PS 1–3/with cachexia group, and 11.9 months in the PS 1–3/without cachexia group ($p < 0.001$, Figure 2b).

TABLE 3 Multivariate analysis of progression-free survival (PFS).

Variable	*p*-value	OR (95% CI)
PS ≥1 vs. 0	<0.001	1.964 (1.403–2.749)
Male vs. female	0.028	0.67 (0.470–0.957)

TABLE 4 Multivariate analysis of overall survival (OS).

Variable	*p*-value	OR (95% CI)
Cachexia+ vs. cachexia−	0.040	1.488 (1.018–2.175)
PS ≥1 vs. 0	<0.001	1.990 (1.334–2.968)

DISCUSSION

Cancer cachexia worsens the patient's condition and reduces patient survival due to its high incidence and mortality rate. However, the impact of cachexia on immunotherapy, such as PD-1/L1 inhibitors, is not fully understood. Therefore, we investigated whether cancer cachexia affects the prognosis of patients with NSCLC treated with PD-1/PD-L1 inhibitors. We found that patients with cachexia had a worse prognosis, irrespective of tumor PD-L1 expression, indicating that cachexia is a predictive prognostic factor for NSCLC patients receiving immune checkpoint inhibitors.

Cachexia is common, with rates of 38.7%–48.1% in patients with NSCLC,[3–6] and it is more common in patients with poor PS.[4,15] Consistent with these results, we also found correlations between cancer cachexia and poorer PS. Cancer patients with cachexia experience numerous complications, including reduced functionality of muscle-dependent systems and mobility. These complications interfere with the patient's ability to perform daily activities, which in turn may be related to a poor PS. Notably, cachexia is also a complication in populations with good PS. Several studies have reported that 18.9%–40% of patients with PS0 have cachexia.[3,4] In accordance with this result, of the patients with cachexia, 17.6% patients had PS0. The survival curves show little difference in patients with cachexia at PS0 treated with ICI from patients without cachexia at PS0 in terms of PFS, but who are worse in terms of OS. These results indicate that patients with PS0 and cachexia are considered to have potentially progressing cachexia, although it does not interfere with their daily activities. This combination of factors can be used to more accurately stratify patients for treatment outcomes of PD-1/PD-L1 inhibitors. It should be noted that cachexia is potentially present even in patients who have the ability to perform daily activities.

We found that patients with cancer cachexia had significantly shorter PFS and OS than those without cachexia. Multivariate analysis has shown that poorer PS and sex are

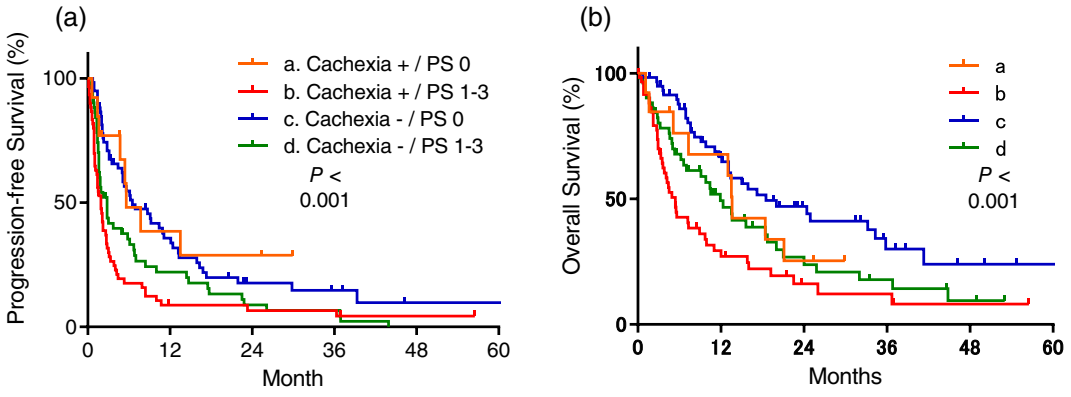

FIGURE 2 (a) The patients were divided into four groups based on PS 0 or 1–3 as well as the presence or absence of cachexia. The median PFS was 5.6 in the PS 0/with cachexia group, 6.5 months in the PS 0 /without cachexia group, 1.9 months in the PS 1–3/with cachexia group, and 2.8 months in the PS 1–3/without cachexia group ($p < 0.001$). (b) The median OS was 13.6 months in the PS 0/with cachexia group, 18.5 months in the PS 0 /without cachexia group, 5.4 months in the PS 1–3/with cachexia group, and 11.9 months in the PS 1–3/without cachexia group.

prognostic factors for shorter PFS, and the presence of cancer cachexia and poorer PS are independently associated with shorter OS. A previous study showed that PFS and OS were significantly shorter in the cachexia than in the noncachexia group.[16] In our analysis, cachexia was not a prognostic factor for PFS, and the possible reasons why cancer cachexia was not significant in the multivariate analysis with respect to PFS, unlike previous reports, could be due to the small number of cases and the fact that this was a retrospective study and the timing of imaging evaluation. Immune checkpoint inhibitors enhance antitumor immunity by blocking a negative regulator of T cell activation, thus promoting the host immune system's ability to attack cancer cells. Cancer cachexia is caused by tumor and host-derived factors that lead to inflammation and systemic metabolism, resulting in catabolism, energy expenditure, and muscle decline.[17–19] Our results may indicate that cancer cachexia promotes tumor progression and resistance to PD-1/L1 inhibitors by interrupting antitumor immunity. Indeed, a previous study reported that patients with cachexia had shorter PFS, irrespective of PD-L1 expression.[16] In accordance with these results, we also found a reduced efficacy of PD-1/L1 inhibitors in patients with cachexia, regardless of PD-L1 expression (Figure S1). Although the mechanisms underlying these effects are not fully understood, several studies have reported that endogenous glucocorticoids and inflammatory cytokines, such as IL-6, TNF-α, and IL-1β, may suppress tumor-infiltrating lymphocytes through the immunosuppressive tumor microenvironment.[20–27] Ghrelin, a peptide secreted by the stomach, is an endogenous agonist of the growth hormone receptor, which regulates energy metabolism by promoting growth hormone secretion.[28] Amamorelin, a ghrelin receptor agonist, is thought to improve cancer cachexia by increasing appetite and insulin-like growth factor-1,[29,30] and has been approved and introduced into clinical practice in Japan. However, because there are few treatment options, further studies to better understand cancer-associated cachexia are needed to assess novel therapeutic strategies for NSCLC patients with cachexia.

Although our study was retrospective in nature and had a relatively small sample size, our results provide a rationale for future clinical investigations into cancer cachexia as a target for NSCLC patients who receive immune checkpoint inhibitors. Further large-scale studies of patients with similar characteristics are warranted to confirm our findings.

In summary, we have demonstrated that 40.4% of patients who received PD-1/PD-L1 inhibitors had cachexia, which was associated with a poor prognosis. Our subanalysis indicated that the presence of cachexia in combination with poor PS predicts worse survival in these patients. This combination of factors can be used to more accurately stratify patients for treatment outcomes of PD-1/PD-L1 inhibitors. Given the expanding clinical use of immune checkpoint inhibitors, further studies are warranted to evaluate the role cachexia plays in cancer immunotherapy efficacy.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Norikazu Matsuo, Koichi Azuma, Daiki Murata, Goushi Matama, Takashi Kojima, and Takaaki Tokito. Akihiko Kawahara performed Immunohistchemical Staining. Kenta Murotani performed the biostatistics. The first draft of the manuscript was written by Norikazu Matsuo, Koichi Azuma, and Tomoaki Hoshino, and all authors commented on previous versions of the manuscript. All authors reviewed and approved the final version of the manuscript.

ACKNOWLEDGMENTS

We would like to thank the participating patients for their contributions to this study.

This study was supported by the Japan Society for the Promotion of Science. Grant sponsor: JSPS KAKENHI; Grant numbers: JP20K16317.

CONFLICT OF INTEREST STATEMENT

Norikazu Matsuo reports receiving personal fees from Ono Pharmaceutical outside the submitted work; Koichi Azuma reports receiving personal fees from Ono Pharmaceutical, Chugai Pharmaceutical, AstraZeneca, MSD Oncology, and Bristol Myers Squibb, outside the submitted work; Takaaki Tokito reports receiving personal fees from Chugai Pharmaceutical, AstraZeneca, MSD, and Boehringer Ingelheim, outside the submitted work; The remaining authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Koichi Azuma https://orcid.org/0000-0001-5040-5856

REFERENCES

1. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12:489–95.
2. Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. Eur J Cancer. 2008;44:1124–32.
3. Taichi Miyawaki TN, Kodama A, Nishioka N, Miyawaki E, Mamesaya N, Kawamura T. Desensitizing effect of cancer cachexia on immune checkpoint inhibitors in patients with advanced NSCLC. JTO Clin Res Rep. 2020;1:100020.
4. Antoun S, Morel H, Souquet PJ, Surmont V, Planchard D, Bonnetain F, et al. Staging of nutrition disorders in non-small-cell lung cancer patients: utility of skeletal muscle mass assessment. J Cachexia Sarcopenia Muscle. 2019;10:782–93.
5. Vanhoutte G, van de Wiel M, Wouters K, Sels M, Bartolomeeussen L, De Keersmaecker S, et al. Cachexia in cancer: what is in the definition? BMJ Open Gastroenterol. 2016;3:e000097.
6. Schwarz S, Prokopchuk O, Esefeld K, Gröschel S, Bachmann J, Lorenzen S, et al. The clinical picture of cachexia: a mosaic of different parameters (experience of 503 patients). BMC Cancer. 2017;17:130.
7. Bonomi P, Fidler MJ, Shah P, Borgia J. Theoretical and practical implications of treating cachexia in advanced lung cancer patients. Cancers (Basel). 2019;11:1619.

8. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373:1627–39.
9. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373:123–35.
10. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393:1819–30.
11. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389:255–65.
12. Gauci ML, Lanoy E, Champiat S, Caramella C, Ammari S, Aspeslagh S, et al. Long-term survival in patients responding to anti-PD-1/PD-L1 therapy and disease outcome upon treatment discontinuation. Clin Cancer Res. 2019;25:946–56.
13. Friedlaender A, Banna GL, Buffoni L, Addeo A. Poor-performance status assessment of patients with non-small cell lung cancer remains vague and blurred in the immunotherapy era. Curr Oncol Rep. 2019;21:107.
14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
15. Cong M, Song C, Xu H, Song C, Wang C, Fu Z, et al. The patient-generated subjective global assessment is a promising screening tool for cancer cachexia. BMJ Support Palliat Care. 2020;12(e1):e39–46.
16. Jo H, Horinouchi H, Yagishita S, Shinno Y, Okuma Y, Yoshida T, et al. Impact of cachexia in advanced NSCLC patients treated with PD-1 inhibitor. J Clin Oncol. 2020;38:44–4.
17. Brocco D, Di Marino P, Grassadonia A. From cachexia to obesity: the role of host metabolism in cancer immunotherapy. Curr Opin Support Palliat Care. 2019;13:305–10.
18. Schmidt SF, Rohm M, Herzig S, Berriel Diaz M. Cancer cachexia: more than skeletal muscle wasting, trends. Cancer. 2018;4:849–60.
19. Tisdale MJ. Are tumoral factors responsible for host tissue wasting in cancer cachexia? Future Oncol. 2010;6:503–13.
20. Flint TR, Fearon DT, Janowitz T. Connecting the metabolic and immune responses to cancer. Trends Mol Med. 2017;23:451–64.
21. Flint TR, Janowitz T, Connell CM, Roberts EW, Denton AE, Coll AP, et al. Tumor-induced IL-6 reprograms host metabolism to suppress anti-tumor immunity. Cell Metab. 2016;24:672–84.
22. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers. 2018;4:17105.
23. Weber JS, Tang H, Hippeli L, Qian M, Wind-Rotolo M, Larkin JMG, et al. Serum IL-6 and CRP as prognostic factors in melanoma patients receiving single agent and combination checkpoint inhibition. J Clin Oncol. 2019;37:100.
24. Teng MW, Ngiow SF, Ribas A, Smyth MJ. Classifying cancers based on T-cell infiltration and PD-L1. Cancer Res. 2015;75:2139–45.
25. Bertrand F, Montfort A, Marcheteau E, Imbert C, Gilhodes J, Filleron T, et al. TNFα blockade overcomes resistance to anti-PD-1 in experimental melanoma. Nat Commun. 2017;8:2256.
26. Bertrand F, Rochotte J, Colacios C, Montfort A, Tilkin-Mariamé AF, Touriol C, et al. Blocking tumor necrosis factor α enhances CD8 T-cell-dependent immunity in experimental melanoma. Cancer Res. 2015;75:2619–28.
27. Kaplanov I, Carmi Y, Kornetsky R, Shemesh A, Shurin GV, Shurin MR, et al. Blocking IL-1β reverses the immunosuppression in mouse breast cancer and synergizes with anti-PD-1 for tumor abrogation. Proc Natl Acad Sci U S A. 2019;116:1361–9.
28. Koijima N, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999;402:656–60.
29. Katakami N, Uchino J, Yokoyama T, Naito T, Kondo M, Yamada K. Anamorelin (ONO-7643) for the treatment of patients with non-small cell lung cancer and cachexia: results from a randomized, double-blind, placebo-controlled, multicenter study of Japanese patients. Cancer. 2018;124:606–16.
30. Hamauchi S, Furuse J, Takano T, Munemoto Y, Furuya K, Baba H. A multicenter, open-label, single-arm study of anamorelin (ONO-7643) in advanced gastrointestinal cancer patients with cancer cachexia. Cancer. 2019;125:4294–302.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Matsuo N, Azuma K, Murotani K, Murata D, Matama G, Kawahara A, et al. Prognostic effect of cachexia in patients with non-small cell lung cancer receiving immune checkpoint inhibitors. Thorac Cancer. 2023. https://doi.org/10.1111/1759-7714.14881