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ORIGINAL ARTICLE

Prognostic value of baseline metabolic tumor volume measured on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in melanoma patients treated with ipilimumab therapy

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Abstract

Purpose Ipilimumab induces durable remission in about 15–20% of patients with metastatic melanoma. However, reliable predictors of response to ipilimumab are currently lacking. Whole-body metabolic tumor volume (wMTV) has been shown to be a strong prognostic factor in a variety of malignancies treated with chemotherapy, but few results have been reported for patients treated with immunotherapy. The purpose of this study was to investigate the prognostic value of wMTV and other metabolic parameters from baseline ^{18}F-FDG PET/CT scans in patients with melanoma being treated with ipilimumab.

Methods The prognostic impact of wMTV, as well as mean standardized uptake values and total lesion glycolysis, was evaluated in 142 consecutive patients with melanoma treated with single-agent ipilimumab therapy. Metabolic parameters were dichotomized by their respective medians and correlated with overall survival (OS). In addition, the prognostic value of metabolic parameters combined with known clinical prognostic factors was evaluated in multivariate analyses.

Results The median OS time in all patients was 14.7 months (95% CI 10.45–18.93 months). wMTV was a strong independent prognostic factor for OS ($p = 0.001$). The median survival in patients with a metabolic volume above the median was 10.8 months (95% CI 5.88–15.81 months) as compared with 26.0 months (95% CI 3.02–49.15 months) in patients with an MTV below the median. A multivariate model including wMTV and known clinical prognostic factors, such as age and the presence of brain metastases, further improved the identification of patient subgroups with different OS times.

Conclusion wMTV appears to be a strong independent prognostic factor in melanoma patients treated with ipilimumab, and can be determined semiautomatically from routine ^{18}F- FDG PET/CT scans. wMTV, combined with clinical prognostic factors, could be used to personalize immunotherapy and in future clinical studies.

Keywords CTLA-4 · Metabolic tumor volume · Ipilimumab · Melanoma · PET

Introduction

Treatment with ipilimumab, an anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody, significantly improves survival of patients with metastatic melanoma when compared with chemotherapy [1–3]. Importantly, ipilimumab therapy not only improves the median survival of patients but can also induce long-term tumor

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remission in about 15–20% of patients [4–6]. While this represents a major breakthrough in the treatment of metastatic melanoma, ipilimumab therapy also has known limitations. Ipilimumab is one of the so-called checkpoint inhibitors that block the action of negative regulators of the cellular immune response. Because of its mechanism of action, ipilimumab can also cause immune-related adverse events (irAEs). Severe irAEs—grade 3 or 4 as characterized by the Common Terminology Criteria for Adverse Events (CTCAE)—occur in 20–30% of patients [1, 7]. Treatment has to be discontinued because of these side effects in approximately 20% of patients overall [7, 8].

Combining ipilimumab with the PD1 antibody nivolumab (an immune checkpoint inhibitor with a mode of action different from that of ipilimumab) significantly increases response rates and survival [5, 7]. In a randomized controlled trial in patients with metastatic or unresectable melanoma, the best overall response to ipilimumab was 19%, compared with 58% to a combination of ipilimumab and nivolumab. The 3-year overall survival (OS) rates were 58% and 34%, respectively. However, combination therapy also significantly increased the risk of irAEs. Grade 3 or 4 toxicity occurred in 59% of patients treated with combination therapy, compared with 28% of patients receiving ipilimumab monotherapy [7]. Treatment-related adverse events led to discontinuation of combination therapy in 39% of patients. Interestingly, discontinuation of checkpoint inhibitor therapy due to irAEs is not necessarily associated with decreased efficacy. A pooled analysis of patients in phase II and III studies showed that survival in patients in whom ipilimumab and nivolumab combination therapy was discontinued was not significantly different from that in patients who completed therapy. This raises the question as to whether treatment may be stopped earlier without loss of efficacy [9].

Thus, there is a clear clinical need for better selection of patients for single-agent versus combination immunotherapy, as well as for criteria to determine the optimal duration of immunotherapy. Despite significant effort, no clinical, histological or genetic parameters have so far been identified that reliably predict the success of ipilimumab therapy or of other immunotherapies. The need for such parameters is further emphasized by the high cost of immunotherapy [10].

For several metastatic malignancies, metabolic tumor volume (MTV) derived from ^{18}F-FDG PET/CT studies has been shown to be a strong prognostic factor for OS in patients treated with chemotherapy or radiotherapy [11–15]. However, only limited data exist on the prognostic relevance of MTV for immunotherapy. The purpose of this study was to investigate the prognostic value of metabolic parameters, including MTV from baseline ^{18}F-FDG PET/CT scans, in patients with metastatic melanoma undergoing ipilimumab immunotherapy. We also investigated whether metabolic parameters can be combined with known clinical prognostic parameters to more accurately predict patient outcome after ipilimumab therapy.

Materials and methods

The institutional review board (IRB) approved this retrospective study and waived the requirement for informed consent. The study was compliant with the Health Insurance Portability and Accountability Act. The hospital information system was searched for patients with metastatic melanoma who had been treated with ipilimumab and had received a ^{18}F-FDG PET/CT scan prior to therapy. The search window extended from 2010 to 2016 to ensure that the scans had been performed with similar PET/CT systems and that there was sufficient follow-up to assess OS. Exclusion criteria were as follows: (1) patients with only active brain metastasis; (2) patients with no hypermetabolic lesion on baseline ^{18}F-FDG PET/CT; (3) patients with advanced primary cancers other than melanoma; and (4) patients with a follow-up time of less than 3 months after starting ipilimumab therapy. For the included patients, the following parameters were recorded: age at treatment initiation, gender, serum lactate dehydrogenase (LDH) level, start date, type of other treatments (surgery, radiotherapy, and systemic chemotherapy), primary site of melanoma, *BRAF* mutation status, reasons for discontinuation of ipilimumab therapy, and date and cause of death (whether disease-specific or not) or date of last documented visit.

^{18}F-FDG PET/CT protocol

Before injection of ^{18}F-FDG, all patients fasted for at least 6 hours. If the plasma glucose level was <200 mg/dl, the patient was injected intravenously with 444–555 MBq of radiotracer. After approximately 60–90 min uptake time, patients were scanned while in the supine position. In most patients, images were obtained from the skull vertex to the feet on PET/CT systems of the GE Discovery series (VCT, ST, STE, 600, and 690). Cross-calibration between the dose calibrator and PET scanners was performed monthly. Low-dose CT images obtained during PET/CT were used for attenuation correction of the PET emission scan and for anatomical orientation. PET/CT images were reconstructed using an ordered-subsets expectation maximization algorithm and a gaussian filter using the standard manufacturer-supplied reconstruction software. The acquisition and reconstruction parameters were harmonized to minimize differences in standardized uptake values (SUV) between scanners and keep them within 10%, as tested using measurements of the IEC image quality phantom. Specifically, the scan duration per bed position for first-generation bismuth germanate (BGO) scanners was set at 5 min, and for second-generation lutetium yttrium

oxyorthosilicate (LYSO) detector scanners at 3 min. Secondly, for reconstruction of images from the BGO scanners four iterations were used (with 20 subsets and an 8 mm postreconstruction transaxial gaussian filter), and two iterations and 20 subsets were used for the LYSO scanners. This resulted in images of comparable smoothness and an acceptable level of discrepancies (<10%) among SUVs in the phantom studies.

Scans were generally acquired with an axial field of view from the vertex to the toes (in 118 of 142 patients). In 24 patients, images from the base of the skull to the mid-thighs were obtained because no relevant lesions in the extremities were expected clinically.

Image analysis

One experienced physician, board-certified in radiology and nuclear medicine, reviewed all ^{18}F-FDG PET/CT images on a GE Advantage workstation using PET VCAR software. The CT scan, along with clinical information from the patients' files, was used to help differentiate between benign and treatment-related findings and metastatic disease. Image interpretations were confirmed by another board-certified nuclear medicine physician and any discrepancies were resolved by consensus between the two investigators.

^{18}F-FDG PET/CT uptake was quantified in terms of SUVs normalized by lean body mass (SUL). As a measure of tumor metabolic activity, the maximum SUL of all lesions in each patient (SULmax) was determined. To assess tumor burden, MTV was defined as the volume enclosed by a 42% isocontour around the tumor lesion voxel with the maximum uptake on PET, as described previously [16]. Occasional manual adjustments were made if the volume defined by the 42% threshold extended beyond the lesion borders as seen on CT. Whole-body MTV (wMTV) was defined as the sum of the individual MTVs of all lesions analyzed. Total lesion glycolysis (TLG) was obtained by multiplying the MTV of each focal lesion by the mean SUL of the MTV. Whole-body TLG (wTLG) was defined as the sum the of TLGs of all lesions. In addition, we determined the sum of SULpeak in up to five target lesions (maximum two per organ) as a simplified measure of tumor burden and metabolic activity. To measure SULpeak, a sphere or cube was drawn around the target lesions. Within this volume of interest, the AW software searches for the 1.0 cm^3 sphere that encompasses the voxels with the highest average SUL [17].

Statistical analysis

Statistical analysis was performed using SPSS, version 24 (IBM Corp., Armonk, NY) in all analyses. Continuous variables are summarized as medians and interquartile ranges (IQR) or means and standard deviations (SD), and categorical variables are summarized as frequencies and percentages. For continuous variables, statistical significance was determined using Student's *t* test. A *p* value of 0.05 or less was considered significant. The Kaplan-Meier method was used to determine whether there was an association between treatment response and OS. The log-rank test was used to evaluate differences between Kaplan-Meier curves. Bonferroni correction was used to adjust for multiple comparisons among risk groups. Univariate analysis was used to identify factors associated with OS. Factors identified as being significant in the univariate analysis ($p < 0.05$) were then entered into a Cox multivariate regression analysis model. Forward stepwise multivariate regression analysis was then carried out to identify factors that were correlated with OS. In each step, variables with a *p* value <0.05 were entered and those with a *p* value >0.10 were removed.

Results

Patient characteristics

Figure 1 shows the flow diagram for the inclusion of potentially eligible patients. Overall, 142 patients were included (median age 69 years, IQR 60.25–77 years). In all patients, 3 mg/kg ipilimumab was administered as a 1-h infusion every 3 weeks for up to four cycles. Baseline ^{18}F-FDG PET/CT scans were performed during the 9 weeks before initiation of ipilimumab therapy (median 3.4 weeks). Patient characteristics are shown in Table 1. Most patients were men with cutaneous melanoma who had undergone wide local excision and had wild-type *BRAF* tumors. Of the 142 patients, 39 had been treated with chemotherapy prior to ipilimumab therapy; the primary drugs were dacarbazine, temozolomide or platinum-based chemotherapy. Of 134 tumors tested for *BRAF* V600 mutations, 27 had this mutation.

Discontinuation of ipilimumab therapy was defined as administration of fewer than four cycles. On this basis, therapy was discontinued in 35 patients. The reasons for discontinuation of ipilimumab therapy were as follows: rapid progression of disease in 20 patients, severe irAEs 13 (colitis in 8, hypophysitis in 2, aseptic meningitis in 2, and hepatitis in 1), ileus requiring surgery in 1, and a cardiovascular event in 1. Survival rates were similar in patients with and without severe irAEs ($p = 0.655$).

Association between ^{18}F-FDG PET/CT parameters and clinical factors and OS

All patients were observed for at least 3 months from the start date of ipilimumab therapy. At the time of data cut-off for the analysis, 95 patients had died. The median OS time in all 142 patients was 14.7 months (95% CI 10.4–18.9 months). The

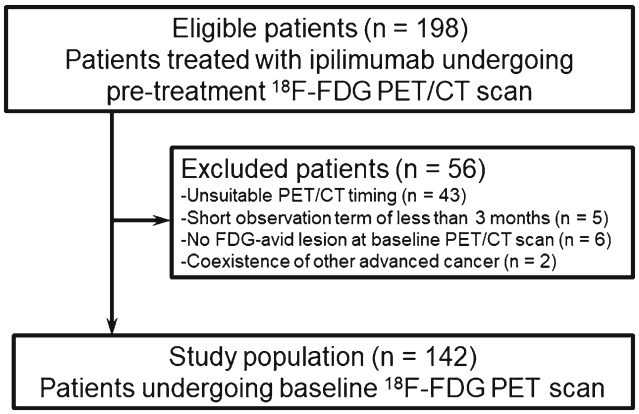

Fig. 1 Flow diagram for the inclusion of potentially eligible patients

median values for SULmax, sum of SULpeak, wTMV, and wTLG were 9.11 (IQR 6.14–13.67), 13.75 (IQR 6.42–24.13), 26.85 cm^3 (IQR 8.21–54.85 cm^3), and 78.74 (IQR 25.60–365.60), respectively. wMTV and wTLG were significantly associated with OS (Fig. 2). The median OS time in patients with wMTV above the median was 10.84 months (95% CI 5.88–5.81 months) as compared with 26.09 months (95% CI 3.02–49.15 months) in patients with wMTV below the median ($p = 0.002$, hazard ratio, HR, 1.9). The corresponding 1-year, 2-year, and 3-year survival rates were 47% vs. 72%, 28% vs. 51%, and 21% vs. 46%, respectively.

The prognostic value of wTLG was similar to that of wMTV. The median OS time in patients with wTLG above the median was 10.84 months (95% CI 5.50–16.19 months) compared with 22.34 months (95% CI 9.36–35.32 months) in patients with wTLG below the median (Fig. 2). SULmax was not a prognostic parameter ($p = 0.60$, HR = 0.90, Fig. 2). Differences in survival between patients with a sum of SULpeak above and below the median were not significant, but a trend was noted ($p = 0.056$, HR = 1.48; Fig. 2).

Combining PET parameters and clinical factors

In a univariate Cox proportional hazards model, age, number of lines of previous chemotherapy, primary site of melanoma, elevated LDH level, and active brain metastases were also significantly associated with OS (Table 2). In a multivariate analysis including the significant clinical and PET parameters, wMTV (HR 1.845, 95% CI 1.180–2.883; $p = 0.007$) remained a significant independent factor associated with OS (Table 2). While the wMTV was larger in patients undergoing PET ≤4 weeks prior to starting therapy (mean ± SD 91.81 ± 153.07 cm^3 vs. 43.42 ± 88.42 cm^3; $p = 0.019$), this time interval was not a prognostic factor ($p = 0.096$) in the univariate analysis.

Figure 3 shows the survival curves in relation to four other baseline clinical factors, except wMTV, which remained significant after multivariate analysis. The median OS times in good vs. poor prognostic groups dichotomized according to the presence of brain metastases (presence/absence), age (<75/≥75 years), LDH (low/high), and number of lines of prior chemotherapy (none/one or more) were 18.89 vs. 6.80 months, 21.65 vs. 8.87 months, 22.34 vs. 7.36 months, and 20.14 vs. 11.43 months, respectively. Combining these parameters with wMTV further improved patient stratification. Specifically, the following risk groups were identified: (1) low risk (patients with

Table 1 Demographic and disease characteristics of the 142 included patients at the time of ipilimumab therapy

Characteristic	Value
Age (years), median (range)	69 (28–90)
Age ≥75 years, *n* (%)	41 (28.9)
Male sex, *n* (%)	83 (58.5)
Primary site, *n* (%)	
Skin	100 (70.4)
Mucosa[a]	20 (14.1)
Uvea[b]	9 (6.3)
Unknown	13 (9.2)
LDH level above ULN, *n* (%)	38 (26.8)
Prior surgery, *n* (%)[c]	125 (88.0)
Prior radiotherapy, *n* (%)	35 (24.6)
BRAF V600 mutation, *n* (%)	
Positive	27 (19.0)
Negative	107 (75.4)
Unknown[b]	8 (5.6)
Active brain metastases, *n* (%)	22 (15.5)
Status of ipilimumab therapy, *n* (%)	
Discontinued (<4 cycles)	35 (24.6)
Completed (4 cycles)	107 (75.4)
Time between PET and treatment, *n* (%)	
>4 weeks	43 (30.3)
≤4 weeks	99 (69.7)
Lines of previous systemic therapy , *n* (%)	
0	103 (72.5)
1	35 (24.6)
2	4 (2.8)
Type of previous systemic chemotherapy, *n*	
Alkylating agent or platinum-based chemotherapy	25
BRAF or MEK inhibitors or both	7
Other	7

LDH Lactate dehydrogenase, *ULN* Upper limit of the normal range

[a] Vaginal 10, maxillary sinus 5, gastrointestinal tract 2, oral 1, esophageal 1, anal 1

[b] Seven with uveal melanoma harboring *GNAQ* mutation

[c] Most of these operations were wide local excision to cutaneous primary lesions

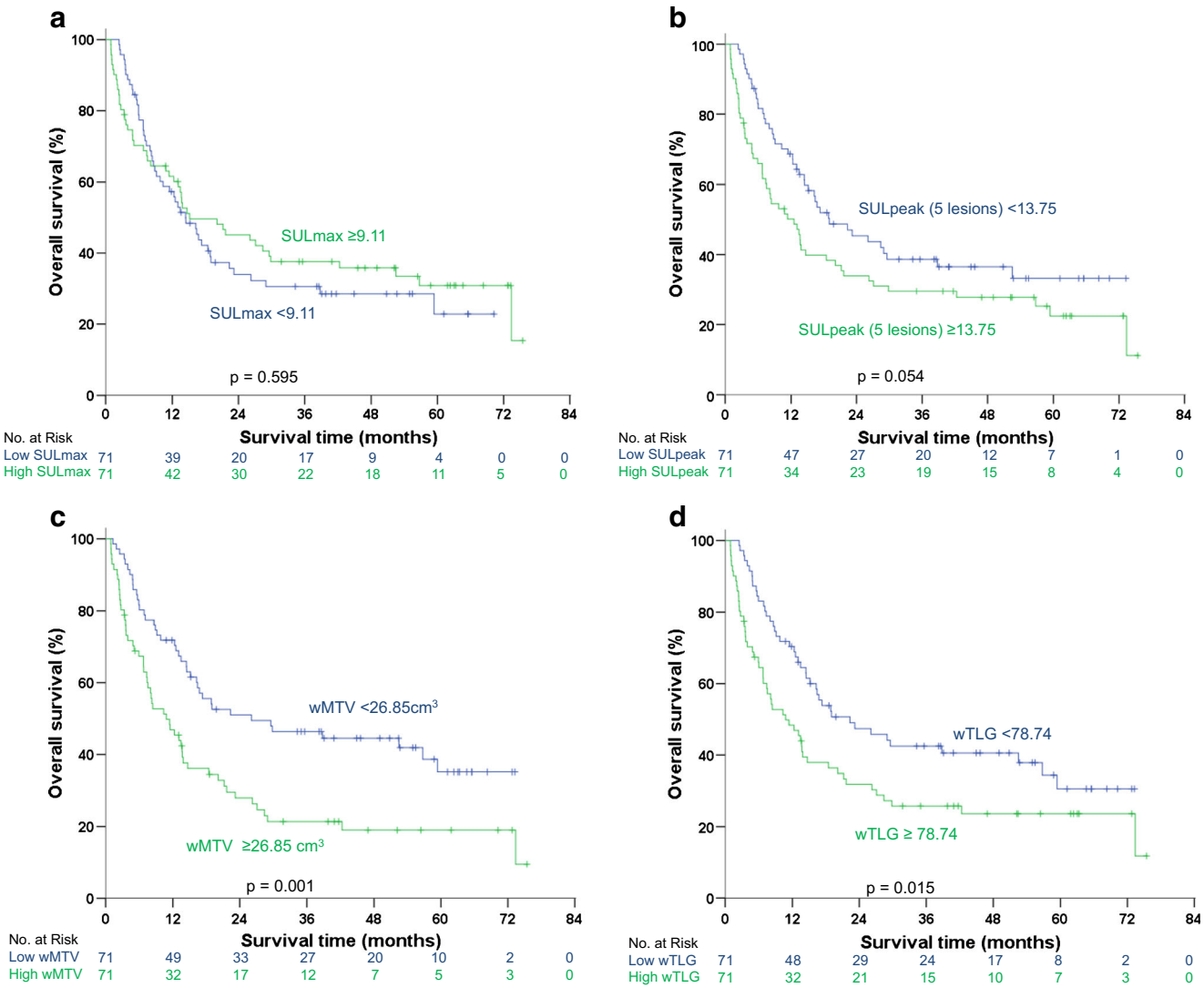

Fig. 2 Kaplan-Meier curves for overall survival in relation to **a** SULmax, **b** sum of SULpeak in five highest uptake lesions, **c** wMTV, and **d** wTLG

low wMTV and favorable clinical risk factors); (2) moderate risk (low wMTV and unfavorable clinical risk factors or high wMTV and favorable clinical risk factors); and (3) high risk (high wMTV and unfavorable clinical risk factors). The survival curves for these three risk groups are shown in Fig. 4. The OS time in the high-risk group was significantly different from those in all other risk groups, and this combined approach to risk stratification differentiated patients according to survival better than wMTV or the clinical parameters alone. The median OS time in all patients with a high wMTV was 10.84 months, but in patients with a high wMTV together with brain metastases, age >75 years, high LDH, or two or more lines of chemotherapy, OS times were 5.95, 7.46, 6.80, and 7.36 months, respectively. Conversely, the median OS time in all patients with low wMTV was 20.09 months, but in those with a low wMTV together with no brain metastases, age <75 years, low LDH, or no prior chemotherapy, OS times were 52.45, 38.80, 52.47, and 29.83 months, respectively.

Discussion

To our knowledge, this is the first study to determine the prognostic value of wMTV in patients with melanoma undergoing immunotherapy. Our findings indicate that wMTV prior to ipilimumab therapy is an independent prognostic factor in patients with advanced melanoma that significantly adds to known clinical prognostic factors including LDH level and the presence of brain metastases.

The prognostic value of wMTV on baseline PET/CT in patients with various malignancies treated with chemotherapy or radiotherapy, including lymphoma [18], breast cancer [19], non-small cell lung cancer [20], and head and neck cancer [21], has been extensively studied. Most studies have indicated that high wMTV or wTLG is strongly correlated with a poor outcome. In contrast, data on the prognostic value of wMTV or wTLG in patients with malignant melanoma or in patients treated with immunotherapy are limited. Son et al.

Table 2 Factors associated with overall survival in patients with advanced melanoma

	Hazard ratio	95% confidence interval	*p* value
Univariate analysis			
Age			
≥75 years	2.018	1.324–3.077	0.001
<75 years	1.000 (reference)		
Sex			
Female	0.793	0.526–1.194	0.267
Male	1.000 (reference)		
Lines of previous chemotherapy			
≥1	1.727	1.130–2.640	0.012
0	1.000 (reference)		
Primary site of melanoma			
Other and unknown	1.645	1.068–2.531	0.024
Skin	1.000 (reference)		
BRAF V600 mutation			
Present	0.954	0.565–1.611	0.861
Absent	1.000 (reference)		
Prior surgery	0.592		
Yes	0.592	0.335–1.046	0.071
No	1.000 (reference)		
LDH level above ULN			
Yes	2.671	1.724–4.140	<0.001
No	1.000 (reference)		
Active brain metastases			
Present	2.800	1.684–4.657	< 0.001
Absent	1.000 (reference)		
Interval from PET to treatment			
>4 weeks	0.670	0.419–1.073	0.096
≤4 weeks	1.000 (reference)		
SULmax			
Greater than median	0.896	0.598–1.344	0.596
Less than median	1.000 (reference)		
Sum of SULpeak in five lesions			
Greater than median	1.484	0.990–2.225	0.056
Less than median)	1.000 (reference)		
wMTV			
Greater than median	1.929	1.282–2.904	0.002
Less than median	1.000 (reference)		
wTLG			
Greater than median	1.644	1.097–2.465	0.016
Less than median	1.000 (reference)		
Multivariate analysis			
Age			
≥75 years	2.147	1.361–3.385	0.001
<75 years	1.000 (reference)		
Lines of previous chemotherapy			
≥1	1.810	1.160–2.823	0.009
0	1.000 (reference)		
Elevated LDH level over ULN			
Yes	2.039	1.269–3.277	0.003

Table 2 (continued)

	Hazard ratio	95% confidence interval	*p* value
No	1.000 (reference)		
Active brain metastases			
Present	3.421	1.967–5.949	<0.001
Absent	1.000 (reference)		
wMTV			
Greater than median	2.015	1.287–3.154	0.002
Less than median	1.000 (reference)		

LDH lactate dehydrogenase, *ULN* upper limit of the normal range, *wMTV* whole-body metabolic tumor volume, *wTLG* whole-body total lesion glycolysis

investigated the relationship between wMTV on pretreatment FDG PET/CT in a heterogenous group of 41 patients with cutaneous melanoma and various tumor stages [11]. wMTV was found to be a significant prognostic factor in a multivariate analysis adjusting for clinical factors including tumor stage. In the study reported here, we confirmed the prognostic value of FDG PET/CT in an almost three-fold larger population of patients with advanced melanoma treated

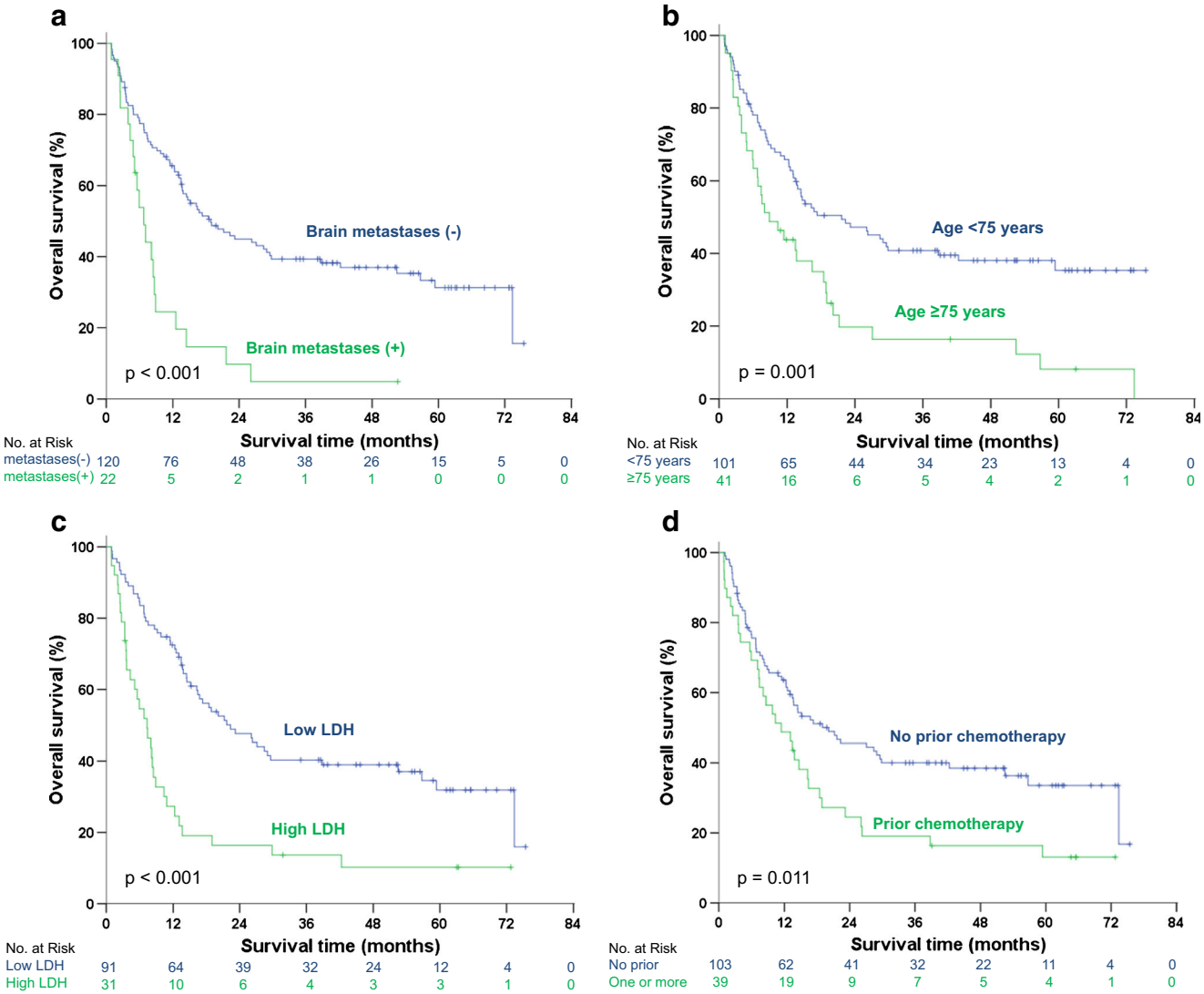

Fig. 3 Kaplan-Meier curves for overall survival in relation to **a** presence of brain metastases, **b** age, **c** LDH level, and **d** number of lines of prior chemotherapy

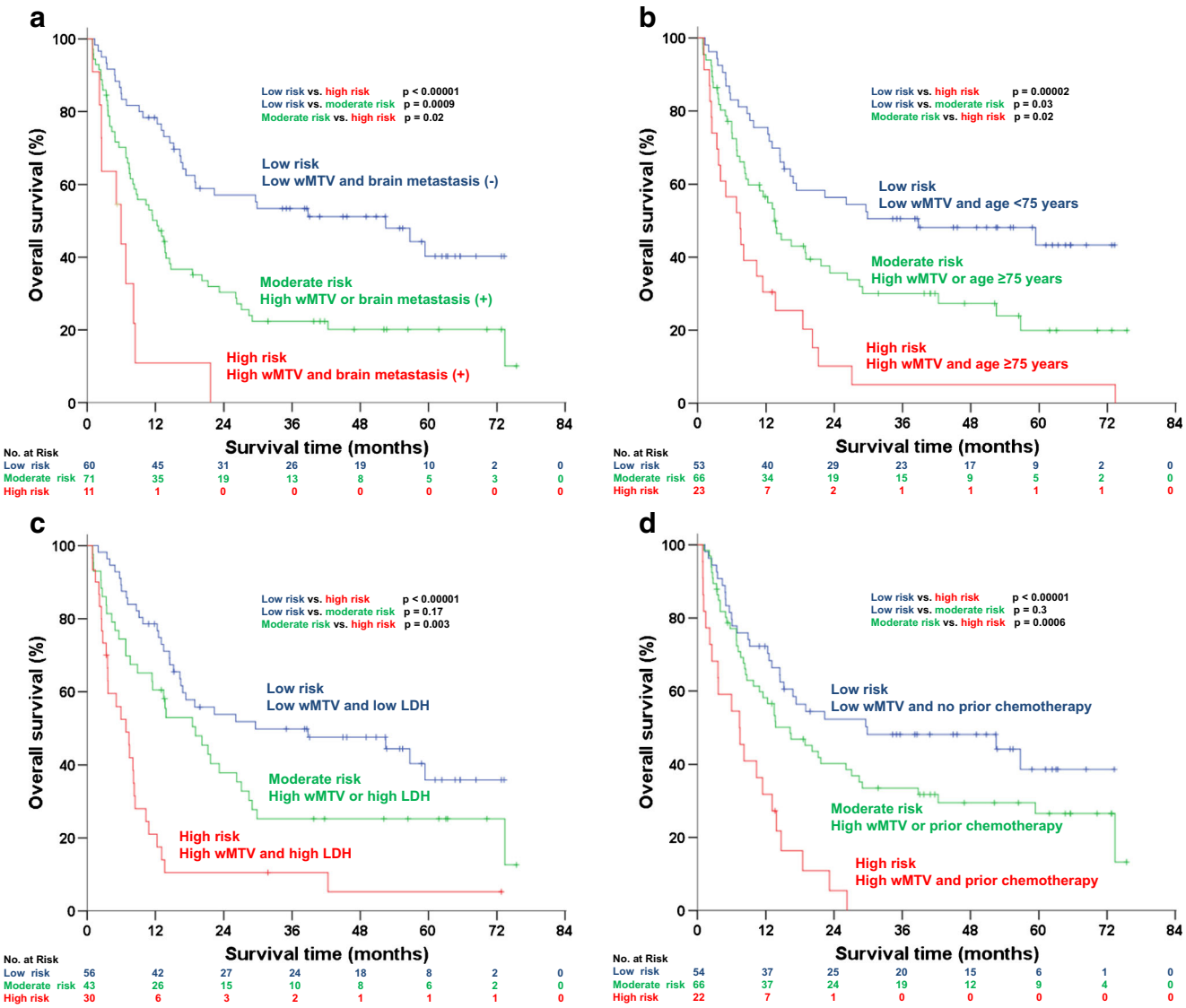

Fig. 4 Kaplan-Meier curves for overall survival in three risk groups stratified according to wMTV combined with the four independent prognostic factors in relation to **a** presence of brain metastases, **b** age, **c** LDH level, and **d** number of lines prior chemotherapy

with ipilimumab, and found that patients with a high wMTV above a cut-off value of 27 cm^3 had a significantly shorter median OS time of 10.84 months. The discrepancy in the results between the studies is probably related to different baseline patient characteristics and methodological differences.

The strong prognostic value of wMTV in patients treated with ipilimumab suggests several potential future clinical applications in patients with melanoma undergoing immunotherapy. As shown in Fig. 2, the difference in median OS times between the higher and lower wMTV groups was approximately 15 months. The difference in median OS times between these two groups is larger than that found in a study comparing treatment with ipilimumab plus dacarbazine and treatment with single-agent dacarbazine [2]. The 3-year OS rates in patients with low and high wMTV were 46% and 21%, respectively. The difference between these survival rates is similar to the difference in 3-year survival rates between patients treated with ipilimumab/nivolumab combination therapy and those treated with ipilimumab monotherapy (53% vs. 32%) [7]. This indicates that wMTV should be considered for patient stratification in randomized clinical trials because imbalances in wMTV could clearly confound comparisons of treatment groups. Currently, clinical factors such as LDH level and history of brain metastases are used to balance the treatment arms in randomized clinical trials [5]. However, our data show that wMTV is an independent prognostic factor that can improve patient stratification.

Clinical factors combined with wMTV could also be used to select specific patient populations for experimental therapies. Patients with poor clinical prognostic factors and high wMTV were characterized by very low OS rates. For

example, the median OS time in patients with brain metastases and a high wMTV was 5.9 months, and all patients died within 2 years of starting ipilimumab therapy. Thus, these patients may be candidates for combination immunotherapy or experimental therapies [22]. Conversely, patients with a low wMTV and favorable clinical prognostic factors showed an excellent prognosis after ipilimumab therapy and thus may be potential candidates for less intensive therapies with a lower risk of irAEs. Of course, these hypotheses for future applications of wMTV in clinical practice and research must be properly tested in prospective clinical trials.

A recent study investigated the prognostic value of tumor burden as assessed by CT in patients with melanoma treated with the PD1 antibody pembrolizumab [23]. The baseline CT scans in patients treated with pembrolizumab in the KEYNOTE-1 study were retrospectively analyzed. The sum of the maximum diameters of target lesions on the baseline scan (baseline tumor size, BTS) was used as an index of tumor burden. A BTS above the median was associated with significantly worse OS. Thus, tumor burden appears to be a prognostic factor not only in patients treated with ipilimumab, but also in those treated other immunotherapies. Conceptually, wMTV is a better marker of tumor burden than BTS because it includes all metastases in a patient, whereas BTS is based on up to five index lesions. Furthermore, many metastases, such as bone metastases, are not measurable on CT images. Selection of target lesions is also to a significant extent subjective and is based not only on lesion size, but also on how well the lesions are delineated on CT images. In addition, a one-dimensional measurement of lesions on CT images does not capture the actual tumor volume; irregularly shaped lesions with the same maximum diameter may have very different volumes. In contrast, wMTV from FDG PET/CT is a true measure of tumor volume. Because of the high metabolic activity of malignant melanoma and the resulting high image contrast, in the present study wMTV was determined semiautomatically within 15 min per patient using commercially available software packages. Semiautomatic delineation of lesions on whole-body CT images is technically more challenging due to the much lower contrast between tumor and normal tissues on CT images. Future comparative studies are required to determine if these principal advantages of wMTV as compared with BTS translate into clinically relevant differences in the prognostic value of these two parameters.

We recognize several limitations of this study. FDG PET/CT scans were performed at the discretion of the referring physician, and the patient population may not have been representative of the overall patient population eligible for immunotherapy. The methodology for tumor volume measurements (including all voxels that showed at least 42% of the maximum FDG uptake in the tumor) has been used in several previous studies, but more sophisticated approaches may provide more accurate volume measurements, especially for tumors with relatively low FDG uptake. Nevertheless, we believe that the wMTV determined with our straightforward approach provides a good estimate of whole-body tumor burden and would allow investigators to quantitatively compare tumor burden between individual patients. Finally, further studies are needed to determine the prognostic value of wMTV in patients receiving PD1-directed immunotherapy, which has emerged as the most common treatment for metastatic melanoma in recent years.

In conclusion, our retrospective analysis indicates that tumor burden in patients with advanced melanoma as quantified by ^{18}F-FDG PET/CT is a strong independent prognostic factor for OS after immunotherapy with ipilimumab. Combined with clinical prognostic factors, ^{18}F-FDG PET/CT can potentially identify patient groups with markedly different prognoses. Thus, future prospective validation of ^{18}F-FDG PET/CT for this application is warranted. Ideally, this evaluation should be performed as part of prospective randomized controlled trials to determine not only if tumor burden is a prognostic factor, but also if it can predict the success or failure of specific therapies.

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Compliance with ethical standards

Conflicts of interest Dr. Jedd Wolchok: serves as a consultant for Adaptive Biotech, Advaxis; Amgen, Apricity, Array BioPharma, Ascentage Pharma, Astellas, Beigene, Bristol Myers Squibb, Celgene, Chugai, Elucida, Eli Lilly, F Star, Genentech, Imvaq, Kleo Pharma, MedImmune, Merck, Neon Therapeutics, Ono, Polaris Pharma, Polynoma, Psioxus, Puretech, Recepta, Trienza, Sellas Life Sciences, Serametrix, Surface Oncology, and Syndax; has received research support: from Bristol Myers Squibb, Medimmune, Merck Pharmaceuticals, and Genentech; and has equity in Potenza Therapeutics, Tizona Pharmaceuticals, Adaptive Biotechnologies, Elucida, Imvaq, Beigene, and Trieza. Dr. Wolfgang Weber: has received research support from Ipsen, Piramal, Blue Earth Diagnostics, and Bristol-Myers Squibb; and has served as a consultant for Progenics Pharmaceuticals Inc., Endocyte, Merck, Bayer, and Blue Earth Diagnostics. All other authors declare that they have no conflicts of interest.

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