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ONCOLOGY

Metastatic melanoma: pretreatment contrast-enhanced CT texture parameters as predictive biomarkers of survival in patients treated with pembrolizumab

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Abstract

Purpose To determine whether texture analysis features on pretreatment contrast-enhanced computed tomography (CT) images can predict overall survival (OS) and progression-free survival (PFS) in patients with metastatic malignant melanoma (MM) treated with an anti-PD-1 monoclonal antibody, pembrolizumab.

Materials and methods This institutional-approved retrospective study included 31 patients with metastatic MM treated with pembrolizumab. Texture analysis of 74 metastatic lesions was performed on CT scanners obtained within 1 month before treatment. Mean gray-level, entropy, kurtosis, skewness, and standard deviation values were derived from the pixel distribution histogram before and after spatial filtration at different anatomic scales, ranging from fine to coarse. Lasso penalized Cox regression analyses were performed to identify independent predictors of OS and PFS.

Results Median OS and PFS were 357 days (range 42–1355) and 99 days (range 35–1185), respectively. Skewness at coarse texture scale (SSF = 6; HR (CI 95%) = 6.017 (1.39, 26.056), $p = 0.016$), Response evaluation criteria in solid tumors (RECIST) conclusion (HR (CI 95%) = 3.41 (1.17, 9.89), $p = 0.024$), and body weight (HR (CI 95%) = 0.96 (0.92, 0.995), $p = 0.026$) were independent predictors of OS. Skewness at coarse texture scale (SSF = 6; HR (CI 95%) = 4.55 (1.46, 14.13), $p = 0.0089$) and RECIST conclusion (HR (CI 95%) = 10.63 (3.11, 36.29), $p = 0.00016$) were independent predictors of PFS. Skewness values above −0.55 at coarse texture scale were significantly associated with both lower OS and lower PFS after administration of pembrolizumab.

Conclusion Pretreatment CT texture analysis–derived tumor skewness may act as predictive biomarker of OS and PFS in patients with metastatic MM treated with pembrolizumab.

Key Points

- *Pretreatment skewness at coarse texture scale in metastases from malignant melanoma was an independent predictor of overall survival and progression-free survival.*
- *Skewness values above −0.55 at coarse texture scale were significantly associated with both lower OS and lower PFS after administration of pembrolizumab.*
- *In patients with metastatic MM, texture analysis performed on pretreatment CT may act as a useful tool to select the best candidates for pembrolizumab therapy.*

Keywords Metastatic melanoma · Pembrolizumab · Tomography, X-ray computed · Biomarkers · Survival

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Abbreviations

CT	Computed tomography
ECOG	Eastern cooperative oncology group
HR	Hazard ratio
LDH	Serum lactate dehydrogenase
MM	Malignant melanoma
OS	Overall survival
PD-1	Program cell death 1
PFS	Progression-free survival
RECIST	Response evaluation criteria in solid tumors
ROI	Region of interest
SD	Standard deviation
SSF	Spatial scale image filtration

Introduction

Malignant melanoma (MM) is the cutaneous malignancy with the highest rate of mortality and represents a public health matter in many countries due to its high incidence [1]. The incidence of MM is estimated to double every 10 to 20 years [2]. The 5-year survival rate of patients with advanced MM is very poor, estimated between 5 and 19% [3].

Recently, two therapeutic approaches have improved survival: targeted therapy blocking BRAF and MEK [4, 5] and immunotherapy, including ipilimumab (CTLA-4 checkpoint inhibitor) and nivolumab and pembrolizumab (PD-1 checkpoint inhibitors) [6, 7]. In contrast with BRAF and MEK inhibitors which are only indicated for the approximately 40% of patients with BRAF V600 mutations, immunotherapy is effective independently of BRAF mutational status. Nivolumab alone, pembrolizumab alone, and the combination of nivolumab and ipilimumab have been found to be associated with longer progression-free survival (PFS) and overall survival (OS) in advanced melanoma than ipilimumab alone [7–9].

Despite these major advances, survival improvement among patients with advanced melanoma treated with anti-PD-1 monoclonal antibodies remains heterogeneous.

Serum lactate dehydrogenase (LDH) and sites of metastases (notably the presence of liver or lung metastases) are the only baseline and per-treatment predictors of early response and progression in patients with advanced melanoma treated with pembrolizumab. Reliable markers of response or progression still need to be defined [8–11]. Furthermore, even if anti-PD-1 drugs are usually well-tolerated, adverse events are not infrequent and can be severe [12]. Therefore, identification of patients who are likely to benefit from this therapy would be a major advance.

CT is routinely performed for detection of metastases and treatment monitoring of lesion size according to Response evaluation criteria in solid tumors (RECIST) 1.1 [13]. However, the analysis of the degree of tumor heterogeneity may provide additional information on survival and response to treatment at baseline, as tumors with high heterogeneity seem to be associated with poor prognosis [14]. Texture analysis is an emerging technique that can be applied to quantify tumor heterogeneity [15, 16]. This technique analyzes the distribution and relationship of pixel gray levels in the tumor and identifies spatial variation of individual gray levels or patterns. Most texture parameters are extracted from the histogram of pixel gray levels (mean gray-level intensity (mean), standard deviation (SD), entropy, kurtosis, and skewness, which reflect brightness, scale, irregularity, peak, and asymmetry of the histogram distribution, respectively). Texture analysis of CT images brings information regarding survival in many cancer types such as colorectal [17], esophageal [18, 19], head and neck [20], non-small cell lung [21, 22], lymphomas [23], or hepatocellular carcinoma [24]. It also provides information about response to treatment [25–28]. The only study dealing with CT texture analysis and MM was performed in patients treated with an antiangiogenic therapy, i.e., bevacizumab, and showed that absolute change in mean positive pixels at medium texture scale was predictive of OS [29]. CT texture analysis of target lesions was performed on initial post-therapy CT images. Associated to tumor size changes and baseline serum LDH levels, it allowed accurate prediction of OS. However, the potential of texture analysis as a decision-making or predictive biomarker for efficacy of an anti-PD-1 therapy, i.e., pembrolizumab, in metastatic MM has never been investigated.

In this context, the purpose of this study was to determine whether texture parameters derived from contrast-enhanced CT images acquired before treatment initiation are independently associated with survival in patients with metastatic MM treated with pembrolizumab.

Material and methods

Study population

All patients with metastatic MM who received pembrolizumab between June 2014 and December 2016 at Reims University Hospital were retrospectively identified from the institutional computer database. All patients receiving pembrolizumab for metastatic MM were included. Pembrolizumab was used as a second-line monotherapy. Patients who did not have available pretreatment CT performed within 1 month prior to treatment initiation or without any accurately delineable lesion or with too small metastatic lesions (< 1 cm greatest diameter) were excluded. Recorded demographic, clinical, biological, and radiological data included patients' age, gender, weight, Eastern Cooperative Oncology Group (ECOG) performance status score, serum level of LDH (normal upper limit 430 UI/L), start date of pembrolizumab treatment, date of pretreatment CT examination,

number and size of metastatic lesions chosen for texture analysis, presence of hepatic and/or lung metastases, RECIST 1.1 sum on both pretreatment and 3-month post-treatment CT scans, and 3-month follow-up RECIST 1.1 conclusion (partial response, stable disease, or progressive disease) [30].

In accordance with French law, this retrospective study on medical records was authorized by the "Commission Nationale Informatique et Libertés" (authorization number 1118523), allowing the computerized management of the medical data at Reims University Hospital. The participants were informed of the possibility of using the information concerning them, for biomedical research purposes, and had a right of opposition.

Follow-up and endpoints

All patients underwent clinical, biological, and radiological follow-up according to institution protocol, every 3 months.

Radiological follow-up consisted of contrast-enhanced CT scans covering the brain, thorax abdomen, and pelvis. Additional CT scan was performed in case of clinical suspicion of disease progression or acute complication.

Two endpoints were chosen: OS and PFS. The primary endpoint, OS, was defined as the time from initiation of pembrolizumab therapy to death. The secondary endpoint, PFS, was defined as the time from initiation of pembrolizumab to radiological progression as defined by RECIST 1.1.

For OS, patients alive at the end of follow-up were censored at that time. For PFS, patients without recurrence at the end of follow-up were censored.

CT examination

All patients underwent a 64-section contrast-enhanced CT scanner (Discovery HD 750; GE Healthcare) covering the brain, chest, abdomen, and pelvis.

A volume of 2 mL/kg body weight of non-ionic contrast material (iomeprol, 350 mg iodine/mL; Iomeron 350, Bracco) was injected into an antecubital vein at a flow rate of 3.5 mL/s followed by 50 mL of saline solution at the same flow rate. Chest images were obtained at an arterial phase 35 s after contrast material administration, abdominal and pelvic images were obtained at a portal-venous phase (70 s), and cerebral images were obtained at a late phase (10 min after injection). Acquisition parameters were as follows: tube voltage, 120 kVp; section collimation, 64 × 1.25 mm; helical pitch, 1.375; scan time per spiral, 0.7 s; image reconstruction thickness, 2.5 mm.

All CT examinations were performed on the same CT scanner; the same tube was applied for all CT exams, while effective tube current values differed between patients due to automatic tube current modulation. Images were reconstructed by using 40% adaptive statistical reconstruction (ASiR, GE Healthcare).

CT texture analysis

CT texture analysis was performed on the pretreatment CT examination using the commercially available TexRAD software (TexRAD Ltd). Two radiologists R1 and R2 with 23-year (R1) and 5-year (R2) experience in oncological imaging selected from one to five target lesions for each patient following RECIST 1.1 criteria in consensus. Afterwards, both radiologists independently placed a free-hand region of interest (ROI) encompassing each entire lesion (Fig. 1). CT texture analysis was performed in a two-step process including image filtration and histogram quantification steps. Spatial scale image filtration (SSF) selectively extracted features with different texture scales, corresponding to fine (SSF = 2, object radius of 2 mm), medium (SSF = 3–5, object radius of 3–5 mm), and coarse (SSF = 6, object radius of 6 mm) scales, by using a Laplacian of Gaussian spatial band-pass filter. Quantification of the histogram distribution within the ROI allowed the extraction of the following five texture parameters: mean gray-level intensity (mean), standard deviation (SD), entropy, kurtosis, and skewness. For each patient, the mean value of each texture parameter among lesions was calculated. Radiologist R2 also repeated texture analysis 2 months later to assess the intrareader reproducibility.

Statistical analysis

Quantitative variables were described as means with standard deviation or medians with minimum-maximum and categorical variables as percentages. Multivariate analysis was performed to identify independent predictors of OS and PFS among clinical and texture parameters. To take into account the correlation between the estimates of each texture parameter from the different filter values as well as the small number of events compared with the number of included covariates, a multivariate L1 (least absolute shrinkage and selection operator—Lasso) penalized Cox regression model was built in order to select texture parameters [31]. The regularization parameter was determined by using tenfold cross-validation. The Lasso method allows variable selection by shrinking down to zero coefficient weights for variables non-related to outcome. Variables with non-zero coefficients were selected as potential predictors of outcome and integrated into a multivariable Cox regression analysis, with clinico-biological and histopathological variables as covariates, in order to estimate associated hazard ratios (HR) and their 95% confidence intervals (CI 95%).

For each texture parameter predictor of outcome, univariate Kaplan-Meier analyses were additionally performed to

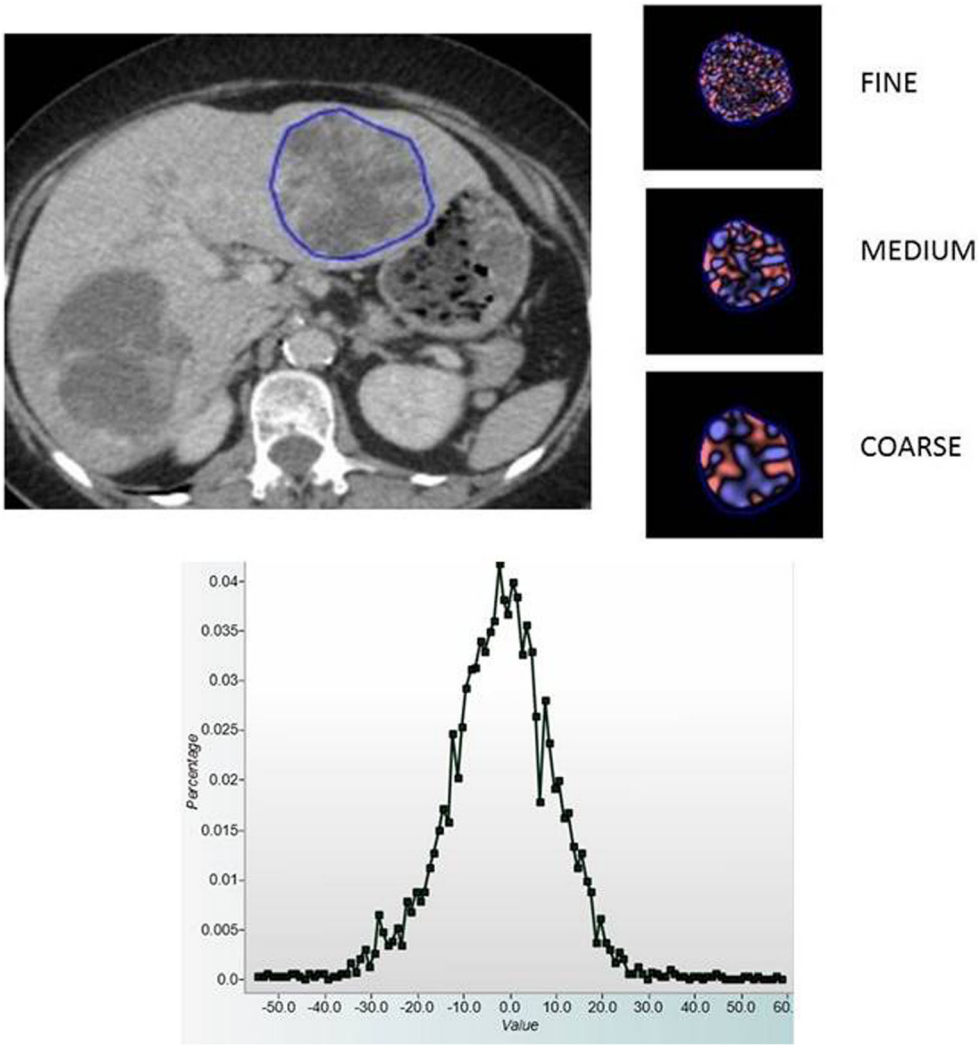

Fig. 1 Illustration of lesion delineation, image filtration at fine, medium, and coarse texture scales, and histogram of pixel gray-level intensities

identify an optimal threshold separating patients with good and poor prognosis, using non-parametric log-rank test.

The intrareader and interreader agreements for the measurements of the texture parameters were assessed using intraclass correlation coefficients (ICC) for each pair of variables. ICC was defined as poor under 0.40, fair between 0.40 and 0.59, good between 0.60 and 0.74, and excellent between 0.75 and 1 [32].

Statistical analyses were performed using R software (version 3.0.1, R Development Core Team, 2013), and p values < 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 52 patients met inclusion criteria. Ten patients without available pretreatment CT evaluation and 11 patients with too small lesions (< 1 cm) or without any accurately delineable lesion were excluded. The final population comprised 31 patients, 14 men and 17 women (median age 60 years, range 27–90 years), with a total of 74 lesions.

The main clinical, biological, and radiological characteristics of patients are shown in Table 1. Serum LDH level was above the normal upper limit in 77% (24/31) of the patients. Target lesion number ranged from 1 to 5, with a median of 2 lesions per patient. Seventy-four percent of patients (23/31) had at least one liver target lesion and 74% (23/31) had no lung lesion.

The median sum of the target lesions on CT before treatment and 3 months after treatment initiation was 38 mm (range 12–208) and 41 mm (range 13–332), respectively, with a median progression at 3 months of + 14% (range − 57, + 180) according to RECIST 1.1, corresponding to partial response in 10% (3/31), stable disease in 45% (14/31), and progressive disease in 45% of patients (14/31).

Median OS and PFS were 357 days (range 42–1095) and 99 days (range 35–968), respectively. Death occurred in 65% of patients (20/31).

Table 1 Main baseline demographics and clinical characteristics of patients in the cohort

Characteristics	Value
LDH level (%)	
Normal	7 (23)
Elevated	24 (77)
Number of target lesions (%)	
1	12 (39)
2	8 (26)
3	2 (6)
4	5 (16)
5	4 (13)
Dominant lesion (%)	
Lymphadenopathy	9 (39)
Liver	7 (23)
Lung	4 (13)
Adrenal gland	2 (6.5)
Subcutaneous nodule	2 (6.5)
Mesenteric nodule	2 (6.5)
Spleen	1 (3.5)
Esophagus	1 (3.5)
Brain	1 (3.5)
Bone	1 (3.5)
Liver lesion (%)	
No	8 (26)
Yes	23 (74)
Lung lesion	
No	23 (74)
Yes	8 (26)
Sum of the target lesions before treatment	
Median, mm (range)	38 (12–208)
Sum of the target lesions after treatment	
Median, mm (range)	41 (13–332)
RECIST 1.1	
Median, % (range)	+ 14 (− 57, + 180)
RECIST conclusion (%)	
Partial response	3 (10)
Stable disease	14 (45)
Progression	14 (45)
Median survival, days (range)	
Overall survival	357 (42–1355)
Progression-free survival	99 (35–1185)
Death (%)	
No	11 (35)
Yes	20 (65)

Overall survival analysis

The Lasso penalized Cox regression analysis identified two texture parameters as potential predictors of OS: mean (coefficient weight, − 0.0036) and skewness (coefficient weight, 0.57) at coarse scale (SSF = 6). Three clinical parameters also highlighted non-zero coefficient weights: presence of hepatic metastases (coefficient weight, 0.19), RECIST conclusion (coefficient weight, 0.020), and body weight (coefficient weight, − 0.0020). Multivariate Cox regression analysis confirmed skewness at coarse scale (SSF = 6; HR (CI 95%) = 6.017 (1.39, 26.056), $p = 0.016$), RECIST conclusion (HR (CI 95%) = 3.41 (1.17, 9.89), $p = 0.024$), and body weight (HR (CI 95%) = 0.96 (0.92, 0.995), $p = 0.026$) as independent predictors of OS (Table 2).

When dichotomized at the optimal threshold identified in Kaplan-Meier analysis, skewness above − 0.375 at coarse scale (SSF = 6; $p = 0.0003$) was significantly associated with lower survival time after administration of pembrolizumab (Fig. 2).

Progression-free survival analysis

The Lasso penalized Cox regression analysis identified three texture parameters as potential predictors of PFS: entropy without filtration (SSF = 0; coefficient weight, − 0.28), kurtosis at medium scale (SSF = 5; coefficient weight, − 0.19), and skewness at coarse scale (SSF = 6; coefficient weight, 0.41). Four clinical parameters also highlighted non-zero coefficient weights: presence of hepatic metastases (coefficient weight, 0.65), RECIST conclusion (coefficient weight, 1.00020), age (coefficient weight, 0.00040), and body weight (coefficient weight, − 0.085). Multivariate Cox regression analysis confirmed skewness at coarse texture scale (SSF = 6; HR (CI 95%) = 4.55 (1.46, 14.13), $p = 0.0089$) and RECIST conclusion (HR (CI 95%) = 10.63 (3.11, 36.29), $p = 0.00016$) as independent predictors of PFS (Table 3).

When dichotomized at the optimal threshold identified in Kaplan-Meier analysis, skewness above − 0.74 at coarse scale (SSF = 6; $p = 0.0044$) was significantly associated with lower progression-free survival time after administration of pembrolizumab (Fig. 3). Patients with skewness above − 0.55 at SSF = 6 showed both significantly poorer OS and PFS (Fig. 4).

Table 2 Multivariate Cox proportional hazards regression analyses of MM texture parameters and clinical parameters selected by Lasso penalized Cox regression analysis for predicting overall survival

Clinical and CT parameters	HR (CI 95%)	*p* value
Mean_SSF6	1.00 (0.98, 1.020)	0.90
Skewness_SSF6	6.017 (1.39, 26.056)	0.016*
Presence of hepatic metastases	0.87 (0.18, 4.25)	0.86
RECIST conclusion	3.41 (1.117, 9.89)	0.024*
Body weight	0.96 (0.92, 0.995)	0.026*

*Indicates a significant difference

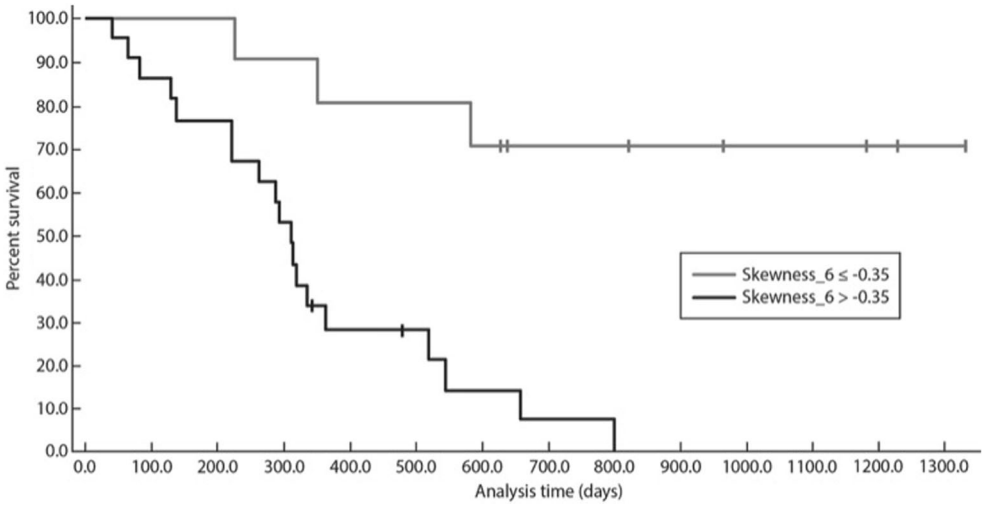

Fig. 2 Kaplan-Meier survival analysis for OS with skewness at SSF = 6

Texture parameter measurement reproducibility

Intrareader agreement regarding texture parameters was excellent for mean (ICC = 0.95), SD (ICC = 0.93), entropy (ICC = 0.95), skewness (ICC = 0.86), and kurtosis (ICC = 0.85).

Interreader agreement was excellent for entropy (ICC = 0.83) and SD (ICC = 0.78), good for mean (ICC = 0.64) and skewness (ICC = 0.62), and fair for kurtosis (ICC = 0.50).

Discussion

Our study suggests that texture features of melanoma metastases on contrast-enhanced CT images acquired before treatment are independent predictors of OS and PFS in patients treated with an anti-PD-1 therapy, i.e., pembrolizumab. Pretreatment skewness values derived from target metastatic lesions were significantly associated with OS and PFS, at coarse texture scale. Filtered coarse texture images highlighted features with a low, coarse scale of details, i.e., features of approximately 6 mm, while minimizing the effects of noise.

Table 3 Multivariate Cox proportional hazards regression analyses of MM texture parameters and clinical parameters selected by Lasso penalized Cox regression analysis for predicting progression-free survival

Clinical and CT parameters	HR (CI 95%)	*p* value
Entropy_SSFO	0.15 (0.017, 1.29)	0.083
Skewness_SSF6	4.55 (1.46, 14.13)	0.0089*
Presence of hepatic metastases	1.69 (0.36, 7.89)	0.50
RECIST conclusion	10.63 (3.11, 36.29)	0.00016*
Sex	0.61 (0.25, 1.49)	0.27
Age	1.0054 (0.97, 1.041)	0.76

*Indicates a significant difference

Interactions between cancer cells and their environment lead to the neoformation of vascular network. Heterogeneity of the neovascularization inside tumors creates areas of hypoxia which may play a major role in the selection of more aggressive tumor clones, increased risk of invasion and metastasis, unfavorable response to chemotherapeutic agents, and inhibition of immune response [33]. CT is routinely used in oncologic imaging as it is reproducible, standardized, and suitable for analysis of pixel heterogeneity and tumor size. CT texture analysis has recently emerged as a new technique allowing quantitative analysis of tumor heterogeneity, which is an approach to the evaluation of tumor hypoxia and neoangiogenesis. A correlation between CT texture parameters and histopathological markers of hypoxia and/or angiogenesis has been reported in patients with non-small cell lung cancer [34] or soft tissue sarcoma [35]. CT texture analysis has shown the capacity to predict OS in many types of cancer [17–24] and also to predict response to treatment [25–28].

Response to therapy in patients with advanced MM treated with pembrolizumab is usually defined according to RECIST 1.1 criteria on scheduled routine contrast-enhanced CT scans, although atypical responses have been observed [36]. Hodi et al showed that conventional RECIST criteria might underestimate the benefit of pembrolizumab in approximately 15% of patients, leading to premature cessation of treatment [37]. Hence, iRECIST criteria taking into account the possibility of pseudoprogression have been developed but are not yet widely being used in routine practice.

Our study highlights the independent predictive value of pretreatment tumor skewness for both OS and PFS in patients with MM treated with pembrolizumab. In colorectal cancer at various stages, high skewness values were shown to be independent predictors of decreased 5-year OS [17]. Similarly, high skewness on pretreatment contrast-enhanced CT images was associated with reduced OS in locally advanced squamous cell carcinoma of the head and neck treated with

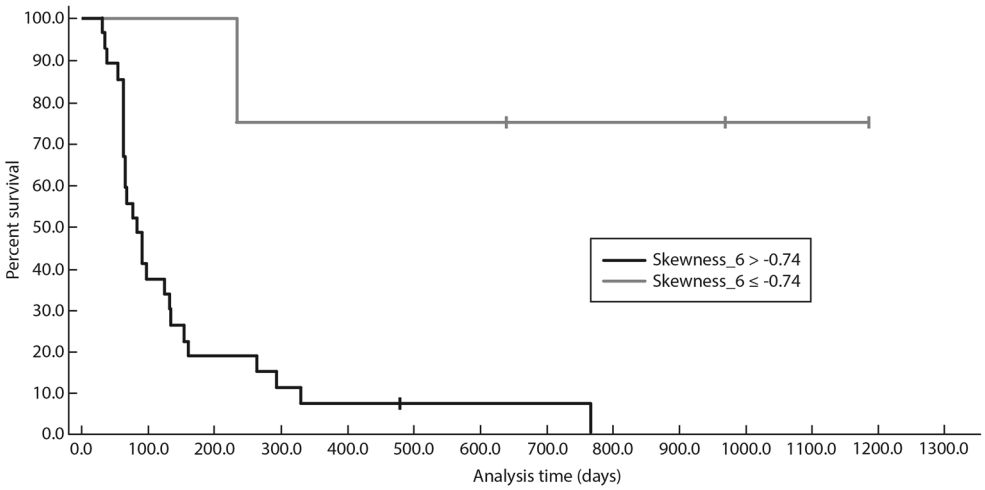

Fig. 3 Kaplan-Meier survival analysis for PFS with skewness at SSF = 6

induction chemotherapy [20], in non-small cell lung cancer treated with chemoradiotherapy [38], and in hepatocellular carcinoma treated by surgical resection.

Skewness reflects the asymmetry of the histogram corresponding to the gray-level values within a predefined ROI. A predominantly bright texture leads to a positive skewness, whereas predominantly dark texture leads to negative skewness [39]. We hypothesize that brightness of metastases may be linked with hypervascularization and thus may reflect tumor angiogenesis. In our study, higher values of skewness were associated with poorer outcomes. Interestingly, we could even define a threshold for skewness values above which patients experienced both significantly poorer OS and PFS.

In our study, RECIST at 3-month follow-up was a strong predictor of PFS (HR, 10.63; $p = 0.00016$), while its ability to predict OS, although significant, was lower (HR, 3.41; $p = 0.024$). This may be partly due to some pseudoprogression (classified as progression disease according to RECIST 1.1 criteria) not necessarily associated with poor OS [37]. Further studies using iRECIST criteria are thus needed to take into account this phenomenon.

LDH serum level is the only baseline and per-treatment marker that predicts early response and progression in patients with MM treated with pembrolizumab [10]. However, in our study, it was not found to be associated with PFS and OS, probably because of the lack of statistical power in our small sample. The presence of hepatic metastases was selected as a potential predictor of OS by Lasso penalized Cox regression analysis, which is in line with the results found by Tsai et al [10].

Some limitations of this study should be noted. First, it was a retrospective monocentric study, with a relatively small number of patients. Pembrolizumab is a recent second-line treatment after ipilimumab and/or BRAF/MEK inhibitors, which can explain the limited recruitment. Our study should be considered exploratory. Second, CT texture analysis was performed in the largest cross-sectional area of the lesions instead of whole-tumor 3D analysis, which might allow a more precise evaluation of the tumor heterogeneity and also improve reproducibility [23, 35]. Third, the mean value of each texture parameter among lesions was calculated for each patient, including metastases from various organs. However,

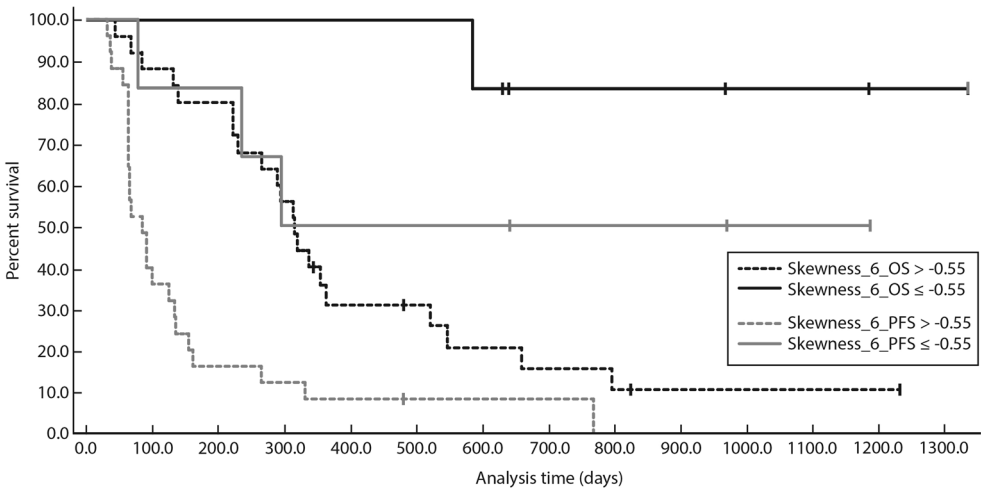

Fig. 4 Combined Kaplan-Meier survival analysis for OS and PFS with skewness at SSF = 6

this choice appeared to be the closest to routine practice, as MM are likely to spread to a wide spectrum of organs. Fourth, heterogeneity due to the variation of contrast distribution and tube current values might influence the validity of the results. To limit these variations inherent to all quantitative imaging analyses, the volume of contrast agent was adapted to the patient body weight and lesions were analyzed at portal-venous phase rather than at arterial phase to limit contrast enhancement heterogeneity among patients. Moreover, all examinations were performed on the same CT scanner with the same CT tube voltage. Finally, it is likely that texture analysis results may vary accordingly to the algorithm that is being used for the evaluation. However, this limit is inherent to all publications dealing with texture analysis. Moreover, the software which we used is commercially available and has been widely used so far, thus allowing comparison of our results with those of the literature [23–27, 40–42].

In conclusion, the results of our study suggest that pretreatment CT texture analysis–derived tumor skewness may be a predictive biomarker of overall survival and progression-free survival in patients with metastatic MM treated with an anti-PD-1 monoclonal antibody, i.e., pembrolizumab.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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