Journal for ImmunoTherapy of Cancer

Radiomics to evaluate interlesion heterogeneity and to predict lesion response and patient outcomes using a validated signature of CD8 cells in advanced melanoma patients treated with anti-PD1 immunotherapy

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To cite: Sun R, Lerousseau M, Briend-Diop J, *et al*. Radiomics to evaluate interlesion heterogeneity and to predict lesion response and patient outcomes using a validated signature of CD8 cells in advanced melanoma patients treated with anti-PD1 immunotherapy. *Journal for ImmunoTherapy of Cancer* 2022;**10**:e004867. doi:10.1136/jitc-2022-004867

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jitc-2022-004867).

Accepted 28 September 2022

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ABSTRACT

Purpose While there is still a significant need to identify potential biomarkers that can predict which patients are most likely to respond to immunotherapy treatments, radiomic approaches have shown promising results. The objectives of this study were to evaluate whether a previously validated radiomics signature of CD8 T-cells could predict progressions at a lesion level and whether the spatial heterogeneity of this radiomics score could be used at a patient level to assess the clinical response and survival of melanoma patients.

Methods Clinical data from patients with advanced melanoma treated in our center with immunotherapy were retrieved. Radiomic features were extracted and the CD8 radiomics signature was applied. A progressive lesion was defined by an increase in lesion size of 20% or more. Dispersion metrics of the radiomics signature were estimated to evaluate the impact of interlesion heterogeneity on patient's response. Fine-tuned cut-offs for predicting overall survival were evaluated after splitting data into training and test sets.

Results A total of 136 patients were included in this study, with 1120 segmented lesions at baseline, and 1052 lesions at first evaluation. A low CD8 radiomics score at baseline was associated with a significantly higher risk of lesion progression (AUC=0.55, p=0.0091), especially for lesions larger than >1 mL (AUC=0.59 overall, p=0.0035, with AUC=0.75, p=0.002 for subcutaneous lesions, AUC=0.68, p=0.01, for liver lesions and AUC=0.62, p=0.03 for nodes). The least infiltrated lesion according to the radiomics score of CD8 T-cells was positively associated with overall survival (training set HR=0.31, p=0.00062, test set HR=0.28, p=0.016), which remained significant in a multivariate analysis including clinical and biological variables.

Conclusions These results confirm the predictive value at a lesion level of the biologically inspired CD8 radiomics score in melanoma patients treated with anti-PD1-based immunotherapy and may be interesting to assess the

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Radiomics have shown promising results to predict response to immunotherapy. However, few studies have evaluated the use of radiomics to assess interlesion heterogeneity. A radiomics score predicting tumor infiltrating CD8 T cells has been previously developed and has shown to be associated with response to immunotherapy or radioimmunotherapy in several cohorts of pan-solid cancer patients. Whether these results apply in a large cohort of melanoma patients remains unknown.

WHAT THIS STUDY ADDS

⇒ This study confirms the association of the previously validated radiomic score of CD8 T cells with response to immunotherapy in melanoma patients, at a lesion level and a patient level.This study highlights the interest of radiomics to assess inter-lesion heterogeneity, and the prognostic value of the least infiltrated lesion according to the radiomic score of CD8 T cells. This study presents in detail the performance of the radiomics score according to the lesion size and location.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study is an independent validation of the radiomic score of CD8 T cell.

⇒ It confirms the potential of radiomics to identify patients most likely to respond to immunotherapy.

⇒ Our data strongly suggest that radiomics studies in metastatic patients should take into account features from several lesions to avoid misleading conclusions.

⇒ This study suggests the potential of radiomics to identify high-risk lesions that could allow directed local treatment.

disease spatial heterogeneity to evaluate the patient prognosis with potential clinical implication such as tumor selection for focal ablative therapies.

INTRODUCTION

The introduction of immune-checkpoint inhibitors (ICI) has undoubtedly been a major breakthrough in cancer treatment over the past decade.[1 2] Nowadays, anti-PD1/PD-L1 antibodies are some of the most widely prescribed anticancer drugs. T cells modulators account for about two-thirds of all cancer clinical trials.[3] Although ICI have revealed long-term remission not seen before in some patients, such responses have only occurred in around 20% of melanoma patients treated with anti-PD1-based immunotherapy.[4 5] Thus, development of effective biomarkers to identify the patients that are most likely to respond to these treatments is of utmost importance.[6]

For this task, quantitative imaging biomarkers and radiomics are of tremendous interest. Unlike traditional biopsy, medical imaging is done through non-invasive techniques and is widely used in everyday clinical practice. Moreover, it depicts the entire tumor load, allowing all lesions to be analyzed.[7] Radiomics, which translates images into high-throughput quantitative data, is a rapidly growing field of research and has shown promising results for predicting response to immunotherapy.[8–11] Using RNA sequencing data, we previously developed a radiomics signature quantifying tumor infiltrating CD8 T cells (CD8-Rscore) which has shown an association with the overall survival (OS) and response in a cohort of advanced pan-solid tumor cancer patients treated with anti-PD1/PD-L1 immunotherapy.[8] However, this proof-of-concept study did not evaluate the impact of patient disease heterogeneity since only one lesion was analyzed per patient. In a second study of pan-solid tumor cancer patients treated with radiotherapy and immunotherapy combinations, we confirmed the association of the CD8-Rscore with lesion response at a lesion level.[12] We have also demonstrated the potential of this signature for assessing patient inter-lesion heterogeneity. Spatial distribution metrics such as the minimal value and the entropy of the distribution of the radiomics score were associated with patient outcomes. Interestingly, Korpics *et al* have independently evaluated this signature with similar results in a cohort of cancer patients treated with stereotactic radiotherapy and pembrolizumab.[13]

However, since this previous study evaluated the CD8-Rscore in pan-solid tumors patients, it is still uncertain whether this can be applied and fine-tuned for a specific tumor type. A few studies have evaluated radiomics to predict outcomes of metastatic melanoma patients,[9 14–16] and only one study has evaluated the use of radiomics at a lesion level to predict their risk of progression, also showing an interest at the patient level to predict OS.[9]

The primary objective of this study was to evaluate the association between the CD8-Rscore of a given lesion and the progression of that same lesion at the first follow-up CT.[8] Secondary objectives were to evaluate the association between the spatial inter-lesion heterogeneity of the CD8-Rscores of the analyzed lesions with progression-free survival (PFS) and OS of advanced melanoma cancer patients treated with anti-PD1, as well as to identify the other clinical and biological predictors of response (PFS, OS).

METHODS

Data and study design

Patients with metastatic melanoma receiving systemic treatment based on anti-PD1 in monotherapy or a combination in our center, were retrospectively screened for inclusion.

Patients with contrast-enhanced CT available at baseline were included for analysis. This non-interventional study was performed in accordance with the General Data Protection Regulation and France Reference Method-004 not requiring patient consent and approved by the local ethical committee. All patients alive at the time of the study were informed of the use of their data. When available, first follow-up (E1) CT scans were included to assess the response of each lesion delineated on the pretreatment CT (E0). Data from patients with only pretreatment CT were used for survival analysis. Baseline clinical and biological data of the patients were collected. The published prognostic Royal Marsden Hospital score[17] (based on albumin, lactate dehydrogenase (LDH) and the number of organs involved) and Gustave Roussy Immune Score[18] (based on the Neutrophil to lymphocyte ratio, LDH and albumin levels) were also computed.

Image analysis

Definition of analyzed lesions

The analyzed lesions were any tumors (primary or secondary) that were identifiable on baseline CTs. Small lesions <5 mm were also included to assess the impact of lesion size on radiomics prediction. Lesions that could not be accurately discriminated from surrounding tissues (ie, lung nodule adjacent or within atelectasis) or from other adjacent lesions at baseline or follow-up CTs (ie, confluent metastases) were not delineated and excluded.

Feature extraction and computation of the CD8-Rscore

The CD8-Rscore was previously trained and validated using contrast-enhanced CT of patients with solid tumors and RNA-seq genomic data from tumor biopsies to estimate the CD8 T cells density of a lesion based on the *CD8B* gene expression.[8] The radiomics analysis to compute the CD8-Rscore was performed according to the previously described method[8] (figure 1). Contrast-enhanced CTs were used to extract radiomics features. All CT images were reconstructed using soft or standard convolution kernels and had a slice thickness of less than 5 mm. On baseline and follow-up scans, experienced physicians annotated the different lesions. Two volumes of interest (VOIs) were segmented for each lesion, the core tumor

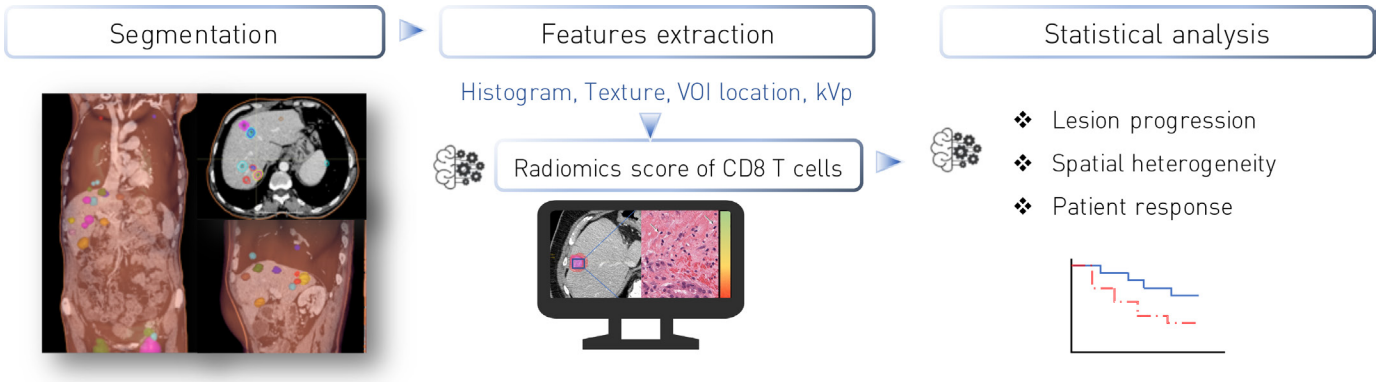

Figure 1 Radiomics workflow. After image preprocessing to discretise the image intensities and to resample the voxel size, features from the radiomics signature of CD8 T-cells published in Sun *et al*,[8] were extracted, allowing the estimation of CD8 T-cells. Analyses were performed at the lesion-level and at the patient-level. VOIs, volumes of interest.

and a peripheral ring of 2 mm on both sides of the tumor boundaries to take into account the peritumoral region as performed in our previous study.[8 19] Images were resized to 1×1×1 mm^3 voxels and resampled into 400 discrete values using absolute discretization from to −1000 and 3000 HU. LIFEx software V.6.67 (Local Image Feature Extraction, freeware, www.lifexsoft.org)[20], which complies with the Image biomarker standardization initiative,[21] was used to extract radiomic features.

The previously validated CD8-Rscore consisted of a linear regression on the basis of eight variables: five radiomics features extracted from each lesion, two variables about lesion location, and one imaging-acquisition related variable—the peak kilovoltage (kVp). The five features from the radiomics signature were extracted and normalized in the range 0–1 according to the data from the training set of the original publication. VOI location was labeled as adenopathy, head and neck, lung, liver, or other. Coefficients from the validated signature were applied to these eight variables to obtain the radiomics score of each analyzed lesion (online supplemental figure S1).

Response evaluation

A lesion-wise evaluation of relative change in diameter between baseline and follow-up was carried out using RECIST V.1.1 criteria. A responding lesion was defined by a decrease in lesion size of at least 30%. A progressive lesion was defined by an increase in lesion size of at least 20%.

Spatial heterogeneity evaluation

To assess the impact of intrapatient interlesion CD8-Rscore heterogeneity, histogram-based distribution metrics such as minimum value, maximal value, mean value, SD using Bessel's correction, skewness, kurtosis and entropy of the pretreatment lesions' CD8-Rscore were retrieved.

Statistical analysis

Comparisons between variables were performed using Wilcoxon signed-rank test or Kruskal-Wallis test for continuous variables, and Fisher test for categorical variables.

To assess the association between radiomics and lesion response, the CD8-Rscore was evaluated as a discrete variable using the previously published cut-off determined in the immunotherapy cohort from the original study (reference cut-off),[8] and also as a continuous variable. Subgroup analyses according to lesion volume were performed as a sensitivity analysis.

To assess the association between radiomics and patient survival, patients were dichotomized into two groups of risk according to the spatial distribution metrics of the CD8-Rscore using the previously published reference cut-off. Fine-tuned cut-offs were also evaluated. To this end, the data were split into a training set and a test set. Optimal cut-points for predicting OS using distribution metrics were determined in the training set using maxstat (maximally selected rank statistics) statistics from the survminer R-package V.0.4.4. The optimized cut-offs were then applied to the test set to assess the association between the distribution metrics of the CD8-Rscore and patient OS. When the CD8-Rscore was evaluated as a binary variable, the cut-off used to define high and low value was specified in the text using either '(ref)' or '(opt)' for reference and optimized cut-off, respectively.

To assess the impact of potential clinical confounding factors, clinical and biological variables were also analyzed in univariate and multivariate analyses. For continuous variables, patients were dichotomized into two distinct groups on the basis of median value, unless there was a validated cut-off (ie, biological variables). A threshold of <0.05 was defined for double-tailed P value's significance. Statistical analyses were performed using R software V.3.6.0 (https://www.r-project.org/).[22] OS and PFS were computed according to the Kaplan-Meier method and Cox proportional-hazards survival estimates. Endpoints were death from any cause for OS, and any recurrence or death for PFS. Multivariate models included the clinically relevant variables that were not redundant with a $p<0.1$ in univariate analysis. A backward stepwise regression was used to identify the most parsimonious model. No imputation was made for the missing data.

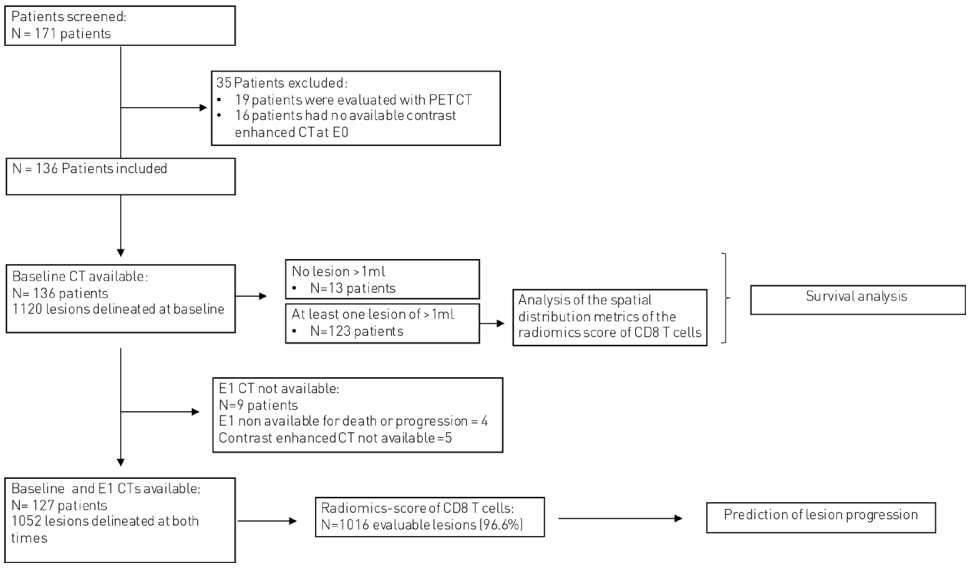

Figure 2 Flow chart of patient.

RESULTS

Patient characteristics and analyzed lesions

A total of 171 patients treated with immunotherapy were screened. Among them, 136 patients treated from May 1, 2012 to February 18, 2019 were included (flow chart in figure 2). Baseline characteristics of the patients are presented in table 1. All patients were diagnosed with metastatic melanoma. Almost all of the patients were metastatic at the initial presentation (92.8%). Median age at baseline was 61.04 (49.55, 68.45). Anti-PD1 consisted in pembrolizumab (n=72, 52.9%) or nivolumab (n=64 patients, 47.1%) (monotherapy or biotherapy), and was administered as the first line of metastatic treatment for 128 patients (94.1%). Pembrolizumab was mostly administered in monotherapy and three patients (2.2%) received a combination with an inhibitor of indoleamine 2,3-dioxygenase-1 (anti-IDO1). Nivolumab was mostly administered in combination with an intravenous or intratumoral anti-CTLA-4 (n=56, 41.2%).

Among the 136 patients, baseline and follow-up CT-scans were available for 127 patients (93.4%), with 1052 lesions delineated on both CTs. The nine other patients accounted for 68 baseline lesions. Overall, 2172 lesions were delineated (table 2, online supplemental table S1 and S2). At baseline, median size of delineated lesions was 0.77 mL (0.26, 2.84). Median time between baseline and follow-up CT was 3.0 months (IQR (2.8–3.4)). Median follow-up was 32.4 months (IQR (15.7–53.6)).

Treatment response

At first evaluation, 6 patients presented a complete response (CR) (4.4%), 49 presented a partial response (PR) (36.0%), 29 (21.3%) a stable disease (SD), and 52 (38.2%) a progressive disease (PD).

The overall response included 52 CR (38.2%), 29 PR (21.3%), 9 SD (6.6%), and 46 PD (33.8%) yielding an overall response rate (ORR) of 59.6% (81 out of 136 patients). Three patients presented a CR (n=2) or PR (n=1) after the initial progression, while three other patients presented an SD after the initial progression (online supplemental table S3). Median OS was 58.7 months (95% CI (34.6 to NA)). Median PFS was 10.9 months (95% CI (3.5 to 6.7)) (online supplemental figure S2).

Lesions response at the first evaluation and association with the CD8-Rscore

Lesion response

A total of 1120 lesions were segmented at baseline (E0). In 1052 lesions, the individual lesion response was evaluable at the first evaluation (E1). The CD8-Rscore was computable for 1084 (96.8%) and 1016 (96.6%) of those lesions at E0 and E1 respectively, because of limitations due to the size of the VOI analyzed.

At baseline, the CD8-Rscore score did not correlate with lesion size (Spearman's r=−0.02, p=0.52).

Using the CD8-Rscore as a discrete variable, the number of lesions with a high (ref)CD8-Rscore was high at E0 (92.8%) and increased after immunotherapy (95.8% at E1, p=0.005) (table 2). Lesions with low (ref) CD8-Rscore at baseline were significantly associated with lesion progression (54% vs 23% for low and high CD8-Rscore scores lesions respectively, OR=3.9, 95% CI (2.1 to 7.5), p<0.0001) (online supplemental figure S3, online supplemental table S4).

When considering the CD8-Rscore as a continuous variable, the radiomics score was only slightly correlated with the variation of the volume of each lesion (Spearman's r=0.062, p=0.049) between baseline and the first evaluation. A subset analysis according to the volume showed a higher correlation when looking at the largest lesions (r=−0.11, p=0.0082 and r=−0.17, p=0.00024, for lesions of more than 0.5 mL and 1 mL, respectively). Despite this, progressive lesions were associated with a lower CD8-Rscore than stable or responding lesions (median=2.18, IQR (1.98–2.40), vs median 2.2 IQR (1.99–2.41), area

Table 1 Patient characteristics

	Level	Overall
n		136
Gender (%)	Female	60 (44.1)
	Male	76 (55.9)
Age (median (IQR))		61.04 (49.55–68.45)
	Age <60	66 (48.5)
	Age >60	70 (51.5)
Type of melanoma (%)	Acrolentiginous melanoma	6 (4.4)
	Desmoplastic melanoma	2 (1.5)
	Dubreuilh melanoma	1 (0.7)
	Mucosal melanoma	9 (6.6)
	Malignant blue nevus	1 (0.7)
	No primitive lesion	14 (10.3)
	Nodular melanoma	27 (19.9)
	Spitz-like melanoma	1 (0.7)
	Superficial spreading melanoma	47 (34.6)
	Unclassifiable	5 (3.7)
	Unknown	23 (16.9)
Breslow (median (IQR))		3.00 (1.84–5.25)
Histollogically proven lymph node (%)	No	26 (56.5)
	Yes	20 (43.5)
Mutations (%)	Wild type	70 (51.5)
	Mutations	66 (48.5)
Initial disease presentation (%)	Metastatic	126 (92.6)
	Adjuvant	10 (7.4)
N local or systemic line before E0 (%)	0	123 (90.4)
	1	6 (4.4)
	2	6 (4.4)
	3	1 (0.7)
N metastatic systemic line before E0 (%)	0	128 (94.1)
	1	3 (2.2)
	2	5 (3.7)
Surgery before E0 (%)	0	84 (61.8)
	1	52 (38.2)
Systemic before E0 (%)	0	121 (89.0)
	1	15 (11.0) (including 7 patients with adjuvant systemic treatment)
Local before E0 (%)	0	130 (95.6)
	1	6 (4.4)
Radiotherapy before E0 (%)	0	126 (92.6)
	1	10 (7.4)
Cryotherapy before E0 (%)	0	136 (100.0)
Radiofrequency ablation before E0 (%)	0	136 (100.0)
Chemotherapy before E0 (%)	0	132 (97.1)
	1	4 (2.9)

Continued

Table 1 Continued

	Level	Overall
immnuotherapy IFN CTLA4 beforeE0 (%)	0	124 (91.2)
	1	12 (8.8)
Anti-BRAF before E0 (%)	0	133 (97.8)
	1	3 (2.2)
E0 drug name (%)	Nivolumab	8 (5.9)
	Nivolumab and ipiIT	21 (15.4)
	Nivolumab and IpiIV	35 (25.7)
	Pembrolizumab	69 (50.7)
	Pembrolizumab±epacadostat	3 (2.2)
E0 Anti-PD1-based immunotherapy (%)	Pembrolizumab	72 (52.9)
	Nivolumab	64 (47.1)
E0 immunotherapy combination (%)	Bitherapy	59 (43.4)
	Monotherapy	77 (56.6)
Time between baseline CT and start of treatment, days (median (IQR))		9.00 (5.75–17.00)
Time between baseline CT and follow-up CT, months (median (IQR))		3.0 (2.8–3.4)
Follow-up, months (median (IQR))		32.4 (15.7–53.6)
Performance status (%)	0	119 (87.5)
	1	15 (11.0)
	2	2 (1.5)
Creatinine (median (IQR))		74.00 (61.75–85.25)
LDH (median (IQR))		192.00 (165.00–252.00)
(%)	LDH<ULN	101 (74.3)
	LDH>ULN	35 (25.7)
Hb (median (IQR))		13.70 (12.20–14.70)
lymphocytes (median (IQR))		1.50 (1.20, 1.90)
CRP (median (IQR))		4.40 (1.48–15.02)
(%)	CRP<10	93 (68.4)
	CRP>or=10	43 (31.6)
Neutrophils (median (IQR))		4.80 (3.30–6.03)
(%)	Neutrophils <7	112 (82.4)
	Neutrophils ≥7	24 (17.6)
Platelets (median (IQR))		253.00 (212.00–338.50)
Leucocytes (median (IQR))		6.90 (5.50–8.80)
(%)	Leucocytes <10	121 (89.0)
	Leucocytes ≥10	15 (11.0)
SGPT (median (IQR))		19.00 (12.00–29.00)
(%)	SGPT≤40	125 (91.9)
	SGPT>40	11 (8.1)
SGOT (median (IQR))		21.00 (18.00–27.25)
(%)	SGOT≤40	129 (94.9)
	SGOT>40	7 (5.1)
Least (ref)CD8-Rscore (lesion >1 mL) (%)	High	111 (90.2)
	Low	12 (9.8)
Least (opt)CD8-Rscore (lesion >1 mL) (%)	High	101 (82.1)
	Low	22 (17.9)

Continued

Table 1 Continued

	Level	Overall
BMI (median (IQR))		24.61(22.59–28.11)
(%)	BMI <25	72 (53.7)
	BMI ≥25	62 (46.3)
NLR (median (IQR))		3.19(2.08–4.29)
(%)	NLR <6	121 (89.0)
	NLR >6	15 (11.0)
Albumin (median (IQR))		40.00 (37.00–43.00)
(%)	Albumin ≥35	120 (88.2)
	Albumin <35	16 (11.8)
N organs involved (%)	Organs <3	83 (61.0)
	Organs ≥3	53 (39.0)
RMH (%)	0	63 (46.3)
	1	48 (35.3)
	2	19 (14.0)
	3	6 (4.4)

BMI, body mass index; CRP, C reactive protein; E0, baseline (pretreatment) evaluation; E1, first evaluation; GR, Gustave Roussy; ipilT, intratumoral ipilimumab; ipilV, intraveinous injection of ipilimumab; LDH, lactate dehydrogenase; ND, not determined; NLR, neutrophil-to-lymphocyte ratio; RMH, Royal Marsden Hospital score; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase level; VOI, volume of interest.

under the receiver operating characteristic curve (AUC)=0.55 95% CI (0.51 to 0.60), p=0.0091). The performance of the CD8-Rscore for predicting progressive lesions was better when selecting lesions based on their volume (AUC=0.56, 95% CI (0.5 to 0.62), p=0.025 for lesions >0.5 mL (n=627) and AUC=0.59, 95% CI (0.53 to 0.66), p=0.0035 for lesions >1 mL (n=461) (figure 3A and online supplemental table S5). The predictive performance of the CD8-Rscore varied according to the tumor location, with better performance for subcutaneous lesions (AUC=0.65, 95% CI (0.56 to 0.75), p=0.007 overall, and AUC=0.75, 95% CI (0.61 to 0.90), p=0.002 for lesions of more than 1 mL), liver lesions of more than 0.5 mL (AUC=0.70, 95% CI (0.58 to 0.81), p=0.002) or more than 1 mL (AUC=0.68, 95% CI (0.55 to 0.81), p=0.01) and nodes of more than 1 mL (AUC=0.62, 95% CI (0.51 to 0.73), p=0.03). There was no significant association in the progression of lung lesions with the radiomics score in this cohort (figure 3B).

Baseline CD8-Rscores heterogeneity to predict clinical response

Patient response

To evaluate whether spatial distribution of the CD8 radiomics score may help to predict patient OS, patients with lesions larger than 1 mL were kept for this subsequent radiomics analysis. To note, patients with lesion less than 1 mL tended to have better survival than the rest of the cohort, without reaching statistical significance (online supplemental figure S4).

Patients with high (ref)CD8-Rscore when looking for the lowest infiltrated lesion (the minimal value of the CD8 radiomics score) had better OS than patients with low radiomics score with an HR of 0.35, 95% CI (0.18 to 0.69), p=0.0026, for OS and 0.48, 95% CI (0.25 to 0.93), p=0.030, for PFS (online supplemental figure S5, online supplemental table S6).

To define and evaluate the optimal cut-off for spatial distribution metrics, patients were dichotomized into training set (2/3, n=86 patients) and test set (1/3, n=37 patients) (figure 4). The minimal value of the (opt) CD8-Rscore was shown to have a significant association in both training and test set with OS (HR=0.31, 95% CI (0.16 to 0.61), p=0.00062, and hazard HR=0.28, 95% CI (0.10 to 0.79), p=0.016, respectively). The optimized cut-off allowed the identification of more high-risk patients than with the reference cut-off (22 patients (17.9%) vs 12 patients (9.8%), respectively). This metric was also associated with the occurrence of a PD (OR=5.50 (95% CI 1.86 to 17.74), p=0.0009), and with PFS (HR=0.42, 95% CI (0.25 to 0.7), p=0.00092) (online supplemental figure S6). Survival curves of the whole cohort, including the patients with no lesion of >1 mL, are represented in figure 4D,E (p<0.0001 and p=0.0019 for OS and PFS, respectively).

Entropy of the distribution of the CD8-Rscore, which measures the amount of heterogeneity across the different lesions, was also associated with OS in the test set, despite not being significantly associated in the training set (HR=3.3, 95% CI (1.1 to 9.4), p=0.028

Table 2 Characteristics of the analyzed lesions

	Level	Baseline	First evaluation	P value
No of lesions		1120	1052	
No of patients		136	127	
Locations (%)	Nodes	442 (39.5)	428 (40.7)	1.000
	Brain	12 (1.1)	9 (0.9)	
	Liver	184 (16.4)	152 (14.4)	
	Head and neck	1 (0.1)	1 (0.1)	
	Bone	13 (1.2)	13 (1.2)	
	Other	18 (1.6)	17 (1.6)	
	Peritoneum	43 (3.8)	41 (3.9)	
	Lung	222 (19.8)	213 (20.2)	
	Spleen	9 (0.8)	9 (0.9)	
	Kidney	8 (0.7)	8 (0.8)	
	Breast	2 (0.2)	2 (0.2)	
	Subcutaneous	149 (13.3)	143 (13.6)	
	Adrenal gland	14 (1.2)	13 (1.2)	
	Thyroid	3 (0.3)	3 (0.3)	
Lesions with complete response (%)			61 (100.0)	NA
(ref)CD8-Rscore	High	1006 (92.8)	882 (95.8)	0.005
	Low	78 (7.2)	39 (4.2)	
	Median (IQR)	2.19 (1.98, 2.41)	2.19 (1.99, 2.41)	0.145
KVP (median (IQR))		120.00 (120.00–120.00)	120.00 (120.00–120.00)	0.084
Slice Thickness (median (IQR))		1.25 (1.25–1.25)	1.25 (1.25–1.25)	0.052
Pixel Spacing (median (IQR))		0.77 (0.70–0.87)	0.76 (0.70–0.87)	0.896
Lesion volume (mL) (median (IQR))		0.77 0.26–2.84)	0.62 (0.14–2.61)	<0.001
Lesion largest diameter (median (IQR))		13.42 (9.43–20.22)	12.17 (7.62–20.29)	<0.001
Lesions according to volume (%)	Vol <1 mL	616 (55.0)	631 (60.0)	0.021
	Vol >1 mL	504 (45.0)	421 (40.0)	

(ref)CD8-Rscore: CD8 radiomics score binarized according to the cut-off from the reference publication.[8]
KVP, kilovoltage peak; NA, not available.

vs HR=1.8, 95% CI (0.97 to 3.4), p=0.064, respectively, figure 4A).

Clinical and biological predictors of outcomes and multivariate analysis

Univariate analyses of OS and PFS are summarized in online supplemental data (table 3). Use of a combination of immunotherapies, male patients, absence of adrenal gland involvement, high minimal value of CD8 radiomics score, absolute count of platelets and leucocytes lower than the median level of the cohort, albumin level greater than 35 g/L, and a low Gustave Roussy Immune Score were associated with better OS in univariate analysis.

In the multivariate analysis using backward stepwise selection of variables, the most parsimonious model for OS retained the sex of the patients (HR=0.35, 95% CI (0.2 to 0.61), p=0.00023), the level of albumin (HR=5.16, 95% CI (2.6 to 10.21)) p<0.0001, and the minimal value of the (opt)CD8-Rscore (HR=0.21, 95% CI (0.11 to 0.4), p<0.0001). The type of the initial disease presentation which was not significant in univariate analysis (p=0.077) was retained as an independent prognosis factor in the multivariate analysis, with patients with non-metastatic disease at initial disease presentation (ie, who have relapsed after adjuvant treatment) having a worse prognosis (HR=4.54, 95% CI (1.8 to 11.44), p=0.0013). Regarding PFS, the most parsimonious model identified was also composed by the (opt)CD8-Rscore (HR=0.38, 95% CI (0.22 to 0.65), p=0.00040), which was the only variable in common with the OS model. The other variables of the PFS multivariate model included the number of lesions delineated, the involvement of adrenal gland, LDH and creatinine level, and the Gustave Roussy Immune Score (table 3). To note, when using the reference cut-off to define high and low scores, (ref)CD8-Rscore was also significantly associated with PFS and OS in multivariate analyses (online supplemental table S7).

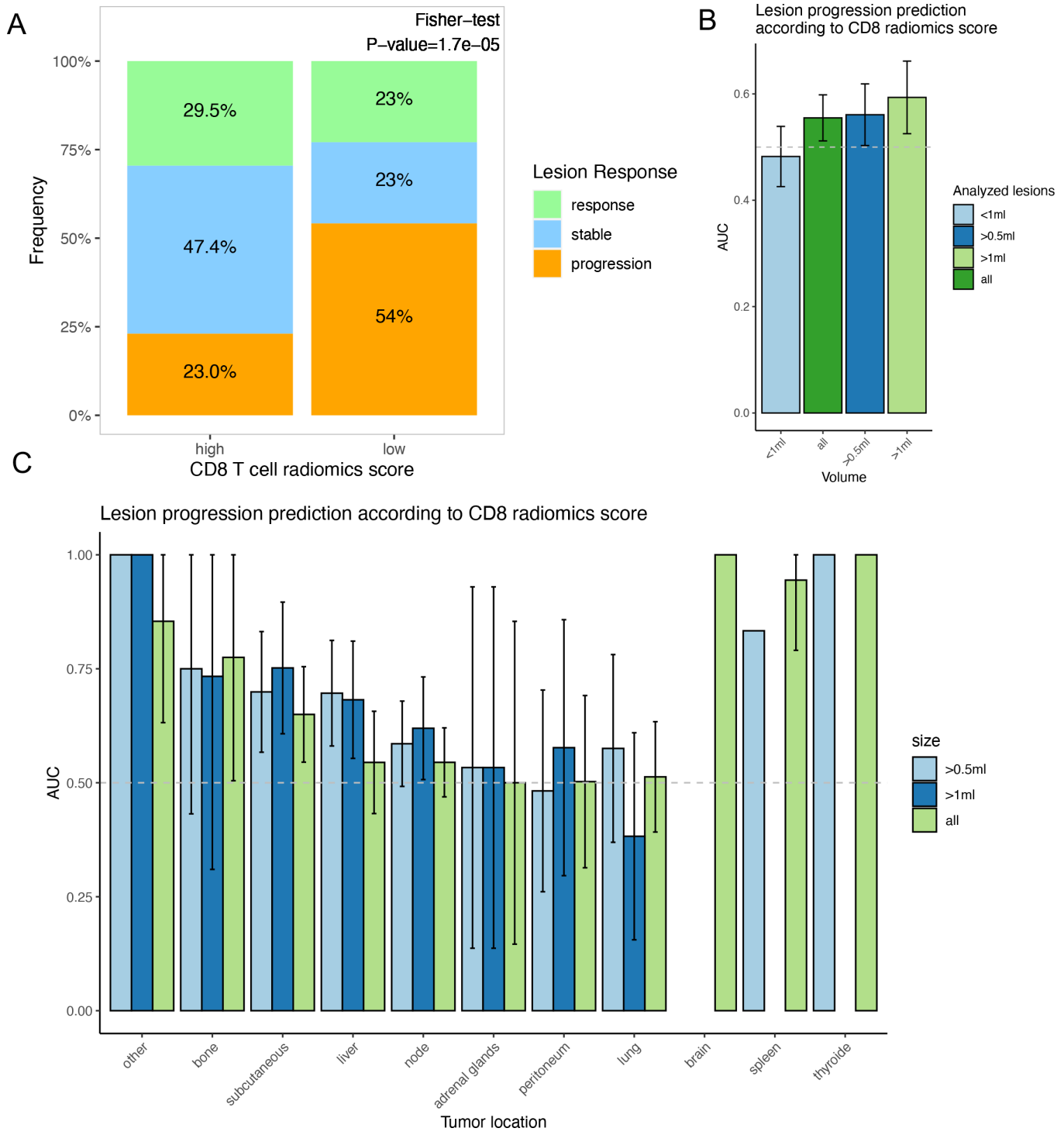

Figure 3 Performance of the radiomics score of CD8 T-cells in predicting lesion progression. (A) Radiomics score of CD8 T-cells evaluated as a discrete variable (high/low) according to previously published cut-off. (B, C) Radiomics score of CD8 T-cells evaluated as a continuous variable, according to the volume (B) and the location of the analyzed lesions (C). AUC, area under the receiver operating characteristic curve

The association between the spatial distribution metrics of the CD8-Rscore with the number of lesions delineated, and the number of lesions with a volume of more than 1 mL per patient were analyzed since it could be a potential confounding factor. Except for the maximum value and the mean value of the CD8-Rscore, the different metrics used to assess the spatial distribution of the CD8-Rscores were correlated with the number of the lesions analyzed (online supplemental table S8). The Spearman's correlation coefficient between the minimal value of CD8-Rscore across the lesions of more than 1 mL and their number was −0.25, p=0.0053. However, when including the number of the lesions analyzed in the previous multivariate models of OS and PFS, this variable showed no prognostic value

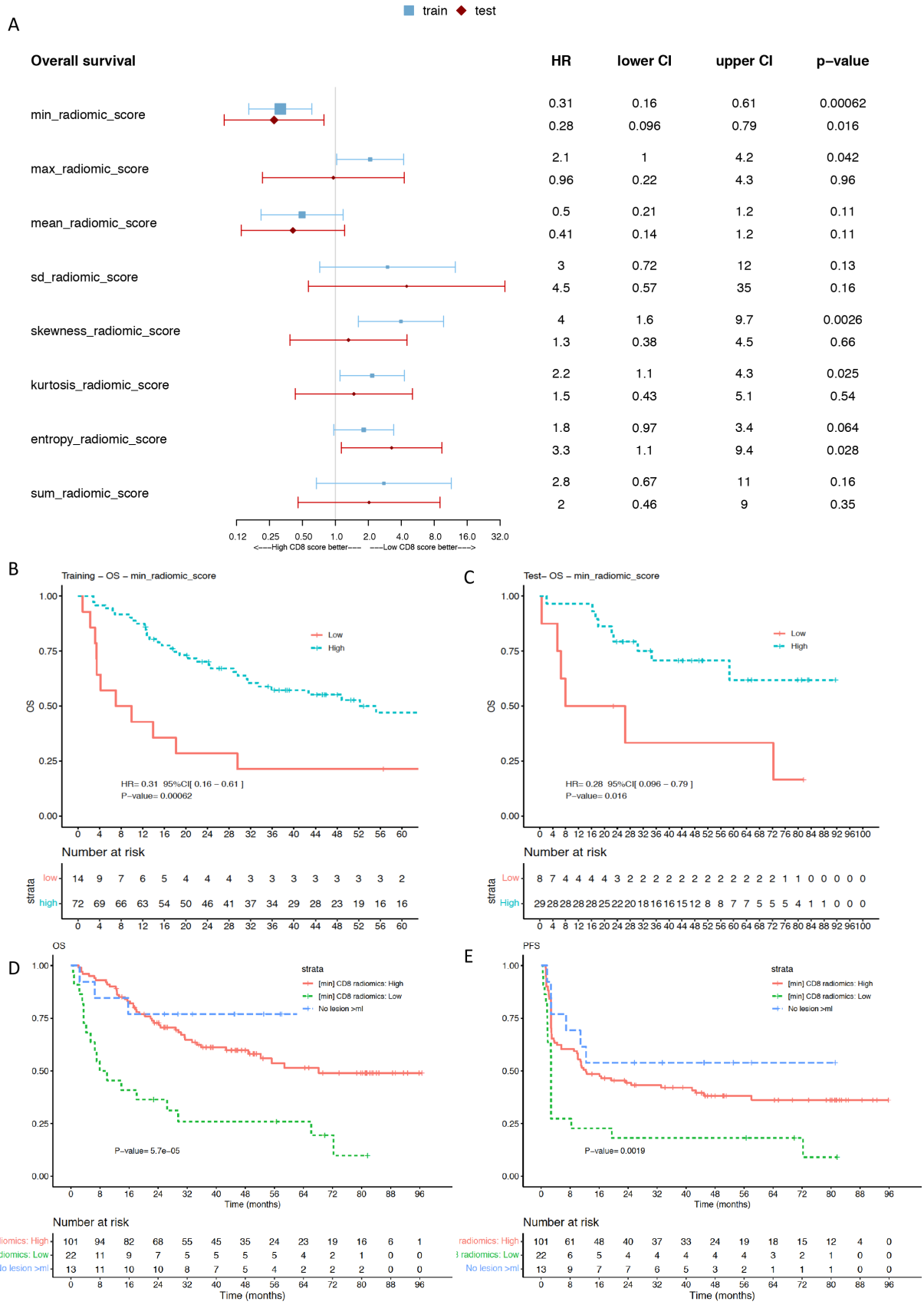

Figure 4 (A) HR (95% CI) of the effect of distribution metrics of the radiomics score of CD8 T-cells on overall survival (OS). (B, C) Kaplan-Meier curves of OS according to the minimal value of the (opt)CD8-Rscore of lesions larger than >1 mL in the training set (B) and the test set (C). (D, E) Kaplan-Meier curves of OS (D) and progression-free survival (PFS) (E) according to three groups: patients without lesions of >1 mL, and patients for whom minimal value of the radiomics score (according to the optimized cut-off) is high or low.

Table 3 Univariate and multivariate analysis of clinical variable and radiomics score, for overall survival (OS) and progression-free survival (PFS)

		OS				PFS			
		Univariate		Multivariate		Univariate		Multivariate	
Variable	Variable test	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	Age >60	0.81 (0.5 to 1.3)	0.42			0.61 (0.4 to 0.93)	0.021	NR	
Gender	**Male**	**0.56 (0.34 to 0.92)**	**0.021**	**0.35 (0.2 to 0.61)**	**0.00023**	0.76 (0.5 to 1.2)	0.21		
Weight	x>74	0.84 (0.51 to 1.4)	0.49			0.95 (0.62 to 1.4)	0.81		
BMI	BMI ≥25	1.4 (0.84 to 2.3)	0.2			1.4 (0.9 to 2.1)	0.14		
PS	PS 1–2	1.8 (0.87 to 3.6)	0.11			1.7 (0.93 to 3.2)	0.083		
Initial disease presentation	**Adjuvant**	**2 (0.93 to 4.5)**	**0.077**	**4.54 (1.8 to 11.44)**	**0.0013**	2.1 (1 to 4.2)	0.036	NR	
Surgery before E0	1	0.63 (0.37 to 1.1)	0.081	0.65 (0.37 to 1.12)	0.12	0.89 (0.57 to 1.4)	0.58		
Systemic before E0	1	1.8 (0.87 to 3.6)	0.12			1.6 (0.89 to 3)	0.11		
Local before E0	1	0.84 (0.26 to 2.7)	0.77			1.5 (0.62 to 3.8)	0.35		
Radiotherapy before E0	1	1.2 (0.46 to 2.9)	0.76	NR		1.5 (0.7 to 3.3)	0.29		
Chemotherapy beforeE0	1	1.2 (0.3 to 5.1)	0.76			1.3 (0.42 to 4.3)	0.61		
Immunotherapy IFN CTLA4 beforeE0	1	1.9 (0.89 to 3.9)	0.1			2 (1 to 3.8)	0.036	NR	
Anti-BRAF before E0	1	3.1 (0.76 to 13)	0.11			1.8 (0.45 to 7.5)	0.39		
Combo versus monotherapy	Monotherapy	2.5 (1.4 to 4.5)	0.0018	1.68 (0.88 to 3.18)	0.11	1.3 (0.87 to 2.1)	0.19	NR	
n organs involved	Organs ≥3	1.3 (0.79 to 2.1)	0.3			1.3 (0.88 to 2.1)	0.17		
Node	1	1.2 (0.69 to 2)	0.56			1.4 (0.86 to 2.2)	0.19		
Brain	1	1.9 (0.61 to 6.2)	0.26			2.2 (0.81 to 6.1)	0.12		
Liver	1	1.3 (0.76 to 2.1)	0.36			1.2 (0.77 to 1.9)	0.42		
Head and neck	1	NC	NC			44 (4.6 to 430)	0.001		
Bone	1	1.8 (0.66 to 5)	0.25			3 (1.3 to 6.9)	0.01	NR	
Other	1	1.3 (0.62 to 2.7)	0.49			1.1 (0.58 to 2.2)	0.74		
Peritoneum	1	1.6 (0.84 to 3)	0.15			1.8 (1 to 3)	0.038	NR	
Lung	1	0.9 (0.55 to 1.5)	0.69			0.94 (0.62 to 1.4)	0.78		
Spleen	1	1.6 (0.51 to 5.2)	0.42			1.5 (0.55 to 4.1)	0.42		
Kidney	1	0.45 (0.062 to 3.3)	0.43			0.75 (0.18 to 3.1)	0.69		
Breast	1	NC	NC			NC	NC		
Subcutaneous	1	1.1 (0.67 to 1.8)	0.73			1.2 (0.82 to 1.9)	0.3		
Adrenal gland	1	2.4 (1.1 to 5)	0.024	NR		**2.5 (1.3 to 4.8)**	**0.0078**	**2.43 (1.16 to 5.08)**	**0.019**
Thyroid	1	2 (0.49 to 8.2)	0.33			1.5 (0.38 to 6.2)	0.55		
No of lesions delineated	x>7	1.6 (0.97 to 2.6)	0.067			1.7 (1.1 to 2.6)	0.011	1.51 (0.95 to 2.4)	0.078

Continued

Table 3 Continued

		OS				PFS			
		Univariate		Multivariate		Univariate		Multivariate	
Variable	Variable test	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Least value of (ref)CD8-Rscore	High (ref cut-off)	0.35 (0.18 to 0.69)	0.0026			0.48 (0.25 to 0.93)	0.03		
Least value of (opt)CD8-Rscore	**High (optimized)**	**0.31 (0.18 to 0.54)**	**0.000035**	**0.21 (0.11 to 0.4)**	**0.0000019**	**0.42 (0.25 to 0.71)**	**0.0012**	**0.38 (0.22 to 0.65)**	**0.00040**
Hemoglobin	x>13.7 (median)	0.81 (0.49 to 1.3)	0.4			1.1 (0.7 to 1.6)	0.77		
Platelets	x>253 (median)	1.8 (1.1 to 2.9)	0.022	NR		1.6 (1 to 2.4)	0.03	NR	
Lymphocytes	x>1.5 (median)	1.2 (0.71 to 1.9)	0.54			1 (0.66 to 1.5)	0.97		
Neutrophils	Neutrophils ≥7	1.7 (0.9 to 3.1)	0.11			1.7 (0.99 to 2.8)	0.057	NR	
Leucocytes	x>6.9 (median)	1.9 (1.1 to 3.1)	0.014	NR		1.8 (1.2 to 2.8)	0.0057	NR	
Leucocytes	Leucocytes ≥10	0.88 (0.38 to 2.1)	0.77			1.1 (0.53 to 2.1)	0.89		
NLR	NLR >6	1.3 (0.61 to 2.9)	0.47			1.9 (1 to 3.5)	0.041	NR	
CRP	CRP ≥10	1.9 (1.1 to 3.1)	0.017	NR		1.5 (0.99 to 2.4)	0.053	NR	
ALT	ALT>40	1.1 (0.44 to 2.7)	0.86			0.89 (0.39 to 2)	0.78		
AST	AST >40	1.5 (0.53 to 4)	0.47			1.8 (0.78 to 4.1)	0.17		
Albumin	**Albumin <35**	**5.2 (2.8 to 9.5)**	**1E-07**	**5.16 (2.6 to 10.21)**	**0.0000025**	3.3 (1.9 to 5.7)	4E-05	NR	
LDH	**LDH >ULN**	1.6 (0.96 to 2.8)	0.073	NR		**1.6 (0.99 to 2.5)**	**0.056**	**0.33 (0.15 t 0.75)**	**0.00810**
Creatinine	**x>74**	0.66 (0.4 to 1.1)	0.1			**0.69 (0.45 to 1.1)**	**0.092**	**0.56 (0.35, 0.89)**	**0.01600**
GRim score	High	1.9 (1.2 to 3.2)	0.0088	NR		**1.9 (1.2 to 2.8)**	**0.0048**	**4.49 (2.1, 9.6)**	**0.00011**
RMH score	RMH 2–3	1.8 (0.98 to 3.2)	0.06			1.9 (1.1 to 3.1)	0.013	NR	

Significant variables according to the multivariate analysis in bold
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C reactive protein; E0, baseline; LDH, lactate dehydrogenase; NC, not computable; NLR, neutrophil to lymphocyte ratio; NR, not retained in the multivariate model; PS, performance status; RMH, Royal Marsden Hospital score; Rscore, radiomics score; Grim score, GR immune score; ULN, upper limit of normal; WT, wild type.

while the minimal value of the CD8-Rscore was still significantly associated with patient outcomes (online supplemental tables S9 and S10).

Finally, when defining high-risk patients as patients with lesions of volume >1 mL and for whom the (opt)CD8-Rscore of the least infiltrated lesion is low, as opposed to low-risk patients with either a high radiomics score or no lesions of >1 mL, sensibility, specificity, positive, and negative predictive value of this radiomics analysis strategy to predict PD was respectively 0.33 (95% CI (0.20 to 0.48)), 0.92 (95% CI (0.85 to 0.97)), 0.68 (95% CI (0.45 to 0.86)), and 0.73 (95% CI (0.64 to 0.81)) (online supplemental table S11). Nomograms predicting 12-month and 24-month OS are presented in online supplemental figure S7.

DISCUSSION

While imaging biomarkers may allow the comprehensive evaluation of a patient's disease, only few studies have tried to integrate disease spatial heterogeneity in the modeling of outcomes in patients with cancer with multifocal tumors. Indeed, the majority of published radiomic studies extracted radiomic features from only one lesion, even in multimetastatic patients. Indeed, analyzing a single lesion is less time-consuming and involves simpler mathematical models. Modeling spatial heterogeneity of the disease is particularly challenging, with the need for an aggregation method to go from the lesion level to the patient level, and a potentially different number of lesions between each patient. However, analyzing only one lesion per patient may lead to misevaluation of the cancer intrapatient interlesion heterogeneity. To date, there is no established methodology regarding the best way to combine radiomic features for patients with multiple lesions.

In this study, the CD8-Rscore was predictive of the outcomes of tumors at a lesion level in advanced melanoma patients treated with anti-PD1, lesions with low radiomics score being more likely to progress under treatment. However, predictivity of lesion response was dependent on the tumor location, with satisfying results for subcutaneous lesions, and large hepatic and nodal metastases, but limited performance for lung lesions. Moreover, we found that performance prediction increased when focused on larger lesions with a volume greater than 1 cc, whereas the radiomics score was not associated with lesion volume. This could have been explained by the inclusion of small lesions, for which the tumorous involvement may have been uncertain (ie, nodes measuring less than 1 cc) and by the technical limits of the imaging modality such as spatial resolution and native spatial sampling. Although these subset analyses should be considered as exploratory, these results identified the most interesting subset of lesions to analyze and a group of patients with a very good prognosis, having only small lesions, and for whom a radiomics analysis may not be necessary. This may suggest that although a comprehensive analysis of all lesions may be a way to capture all the heterogeneity from the patient's disease, the precise choice of relevant lesions, based on size and location, may also be an important step when applying or evaluating an imaging biomarker.

Trebeschi *et al* developed a radiomics signature to predict tumor progression at a lesion level using a cohort of 203 patients (123 patients with non-small cell lung cancers (NSCLC) and 80 melanoma).[9] In their study, although the radiomic biomarker on 303 lesions from the 70 patients of the test set reached significant predictive performance (0.66 AUC, p<0.01), only a trend toward significance was obtained from the nodal metastases in melanoma patients (AUC=0.64, p=0.05), and application of the signature was not significant for pulmonary and hepatic melanoma lesions (AUC=0.55). Nonetheless, when they combined the predictions made on individual lesions, the pretreatment melanoma patient-wise prediction of immunotherapy response was associated with OS with a significant survival difference at 1 year of 25% (77% vs 52%, log-rank-test, p=0.02), demonstrating the complexity of lesion-wise and patient-wise analyses.[9]

For patient-wise analysis, our study showed an interesting association with patient outcomes and the value of the least infiltrated lesion according to the CD8-Rscore. This cohort study was only conducted in patients with melanoma, in contrast to the previous study evaluating this radiomics signature.[8 12 13] Thus, we were able to identify a cut-off, optimized for high-risk melanoma patients, with the poorest prognosis. To note, the radiomics score of lesions in this cohort were higher than in the previous studies, which seemed concordant with the higher response rate of melanoma patients (median value of CD8-Rscore of 2.19 (1.98, 2.41) here with an ORR of 59.6%, vs median value of CD8-Rscore of 1.75 (1.55, 1.97) and 1.74 (1.54, 1.97) for irradiated and non-irradiated lesions respectively, and an ORR of 29.9%) in Sun *et al*.[12]

This study confirms previous studies evaluating the CD8-Rscore.[8 12 13] In Sun *et al*,[12] we have shown associations between the CD8-Rscore and response of lesions at a lesion level, and suggested the prognosis value of the least infiltrated lesion according to this radiomics score. Interestingly, these results are concordant with the study of Van den Eynde *et al*.[23 24] The Immunoscore scoring system based on the quantification of two T-cell subsets (CD3 and CD8) in two tumor regions (core and invasive margin of tumors),[25] was used to characterize the intrametastatic immune infiltration of 603 resected metastases from 222 stage IV patients undergoing complete curative metastatic resection. They found that the immune phenotype of the least-infiltrated metastasis had a stronger association with patient outcome than other metastases or the average value between the lesions.[23]

Only few other radiomics studies have specifically evaluated aggregating methods from lesion level to patient level. Some studies have tried to address the issue of combining multifocal data at a patient level by using the average value or the median value of radiomic features

extracted from different lesions, but without comparing other methods to integrate spatial heterogeneity.[13 26] Chang *et al* evaluated six different aggregating methods of radiomics features extracted from brain metastases: unweighted average, weighted average, weighted average of largest three metastases, largest+ number of metastases, largest metastasis and smallest metastasis.[27] The 'volume-weighted average of the largest three tumors' model showed the best performance to predict patient survival with C-index of 0.627 (0.595–0.661), 0.628 (0.591–0.666), 0.652 (0.565–0.727) for Cox proportional hazards model, least absolute shrinkage and selection operator regression (LASSO) and random forest, respectively. These findings suggest that there is a need for the development of more advanced tools, to identify the most informative lesions. Liu *et al* evaluated the extraction of radiomic features from either the largest lesion, or the average value of several lesions in lung cancer patients.[28] Using only baseline data, they failed to train a predictive model of patient outcomes, showing that the rationale for modeling patient heterogeneity is of utmost importance.[28]

Overall, our study showed that analysis of interlesion heterogeneity provided relevant information which increase the value of radiomics analyses. In contrast to methods assessing overall tumor burden without specific characterization at a lesion level, our tool may help to identify lesions with the highest risk of progression with a direct impact on the patient prognosis. As suggested in our previous study,[12] these results could be of particular interest for clinical practice. Indeed, this approach is complementary to the current biological biomarkers, biopsies or circulating biomarkers, which do not allow a complete assessment of the patient's disease, both at the lesion-level and at the patient level, and to potentially more advanced imaging approaches such as immune-based PET imaging, for which specific tracers to image CD8, PD-1, or PD-L1 are under investigation, but which may be difficult to use in clinical routine.[29] Finally, the use of this radiomic score may serve in a clinical trial to guide localized ablative treatment on the most at-risk lesions such as stereotactic radiation therapy, shifting the average infiltration of the rest of the lesions upwards to potentially maximize the benefit of systemic immunotherapy.[30]

This study carried some drawbacks due to its retrospective nature. First, the subgroup analyses of lesions to identify those for which the radiomics score were most performant may be biased due to the multiple comparison and the α risk inflation. However, these analyses were mandatory to better understand the limits and the scope of application of the radiomics score. It is noteworthy to mention that the radiomics score was applied without prior fine-tuning, which enhanced the generalizability of our findings. Second, the analysis of different aggregation methods to infer patient outcomes from lesions scores also required multiple analyses due to the lack of known optimal method for assessing spatial heterogeneity. However, we confirmed for the second time the prognostic value of the least infiltrated lesion[12] for which the biological rational is also strong.[23 24] Finally, the identification of an optimal cut-off to discriminate high-risk melanoma patients from low-risk melanoma patients regarding the minimal value of the radiomics score may be biased as it is retrospective, and only validated in one subsample of the cohort (test set). Thus, further validation by independent and prospective studies is necessary.

CONCLUSION

Our findings corroborate the previously published CD8-Rscore's predictive value at a lesion level in melanoma patients treated with anti-PD1-based immunotherapy. Furthermore, the findings confirm the potential interest of this tool to characterize the spatial heterogeneity of the disease, with a prognostic value of the least infiltrated lesion. Overall, this study asserts the role of imaging biomarkers to help clinicians move toward precision medicine.

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Funding Fondation pour la Recherche Médicale (grant DIC20161236437), Fondation ARC pour la Recherche sur le Cancer (grant SIGN'IT20181007805), SIRIC-SOCRATE 2.0 (grant INCa-DGOS-INSERM_12551) and Amazon AWS grant provided funding to INSERM U1030 Radiomics team - Gustave Roussy. Fondation ARC pour la recherche sur le Cancer and Paris-Université Paris-Saclay provided support to RS with a grant for international mobility. Agence Nationale de la recherche provided support to ED with a "Recherche Hospitalo-Universitaire en santé" grant (ANR-21-RHU5-0005) within the FRANCE2030 investment plan. RS received support from Fondation Bettencourt-Schueller (grant CCA Inserm-Bettencourt 2020). Ensemble contre le Mélanome et Crédit Mutuel provided funding to INSERM U981.The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Competing interests ED has declared consulting fees and support from Roche, BMS, Boehringer, Astrazeneca, Lilly Amgen and Merck-Serono. CaR declares consulting fees from Roche, BMS, MSD, AstraZeneca, Pierre Fabre, Sanofi, Novartis.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by institutional review board of our center (IRB-2022-98). Non interventional study It did not request any written consent according to the French MR 004, but all patients were informed.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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