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Title: CT texture analysis as a predictor of favorable response to anti-PD1 monoclonal antibodies in metastatic skin melanoma

Short title: CT texture analysis of metastatic skin melanoma

Authors

Angèle Bonnin^{a,b,c}
Carole Durot^a
Maxime Barat^{b,c}
Manel Djelouah^a
Florent Grange^d
Sébastien Mulé^e
Philippe Soyer^{b,c}
Christine Hoeffel^{a,f,*}

Affiliations

^a Department of Abdominal Radiology, Reims University Hospital, 51092 Reims, France

^b Department of Radiology, Cochin Hospital, AP-HP, 75014 Paris, France

^c Université de Paris, Faculté de Médecine, 75006 Paris, France

^d Department of Dermatology, Valence Hospital, 26000 Valence, France

^e Department of Radiology, Henri Mondor University Hospital, APH-HP, 94000 Créteil, France

^f CRESTIC, Reims Champagne-Ardenne University, 51000 Reims, France

*Corresponding author: choeffel-fornes@chu-reims.fr

CT texture analysis as a predictor of favorable response to anti-PD1 monoclonal antibodies in metastatic skin melanoma

Short title: **CT texture analysis of metastatic skin melanoma**

Abstract:

Purpose. The purpose of this study was to determine whether texture analysis features on pretreatment contrast-enhanced computed tomography (CT) images and their evolution can predict treatment response of metastatic skin melanoma (SM) treated with anti-PD1 monoclonal antibodies.

Materials and methods. Sixty patients (29 men, 31 women; median age, 56 years; age range: 27–91 years) with metastatic SM treated with pembrolizumab (43/60; 72%) or nivolumab (17/60; 28%) were included. Texture analysis of SM metastases was performed on baseline and first post-treatment evaluation CT examinations. 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 variables associated with favorable response to treatment.

Results. A total of 127 metastases were analyzed, with a median of two metastases per patient. Skewness at fine texture scale (spatial scale filtration [SSF] = 2; Hazard ratio [HR]: 3.51; 95% CI: 2.08–8.57; $P = 0.010$), skewness at medium texture scale (SSF = 3; HR: 0.56; 95% CI: 0.11–1.59; $P = 0.014$), variation of entropy at fine texture scale (SSF = 2; HR: 37.76; 95% CI: 3.48–496.22; $P = 0.008$) and LDH above the threshold of 248 UI/L (HR: 3.56; 95% CI: 1.78–21.35; $P = 0.032$) were independent predictors of response to treatment.

Conclusion. Pretreatment CT texture analysis-derived tumor skewness and variation of entropy between baseline and first control CT examination may be used as predictors of favorable response to anti-PD1 monoclonal antibodies in patients with metastatic SM.

Keywords: Biomarkers; Computed tomography; Immunotherapy; Melanoma; Texture analysis

List of abbreviations

CI: Confidence interval;

CT: Computed tomography;

HR: Hazard ratio;

ICI: Immune checkpoint inhibitors;

iRECIST: Immune Response Evaluation Criteria in Solid Tumors;

LDH: Lactate dehydrogenase;

OS: Overall survival;

RECIST: Response Evaluation Criteria In Solid Tumors

SD: Standard deviation;

SM: Skin melanoma;

SSF: Spatial scale filtration;

1. Introduction

Skin melanoma (SM) is an aggressive cutaneous malignancy with a high incidence, which is estimated to double every 10–20 years [1]. SM is the cutaneous cancer that traditionally conveys a high mortality rate [2]. However, recent introduction of immune checkpoint inhibitors (ICI) has led to significant survival improvement [3–5]. ICI are monoclonal antibodies that block co-inhibitory molecules and include ipilimumab, acting as an anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA4), and nivolumab or pembrolizumab that target the programmed-death-I (PD1) pathway [6]. As a limitation, more than 50% of the patients have SM that does not favorably respond to ICI [7]. An early prediction of response to this treatment is thus necessary to identify patients who are more likely to benefit from checkpoint inhibitors. The only known biomarker of response to immunotherapies at baseline, so far, is the serum lactate dehydrogenase (LDH) serum level. However, this biological biomarker appears insufficient to determine therapeutic management and, for now, changes in therapeutic lines are made according to response to treatment on follow-up computed tomography (CT) examinations [8].

As a difficulty, a subset of patients treated with ICI may show an atypical pattern of tumor response either after an increase of tumor burden or appearance of new lesions, a phenomenon termed pseudoprogression. Pseudoprogression is classified as progressive disease by conventional response criteria [9]. To account for this atypical pattern of response, Response Evaluation Criteria In Solid Tumors (RECIST) criteria have been changed for Immune Response Evaluation Criteria in Solid Tumors criteria (iRECIST), which requires confirmation of progressive disease using further assessment three months later [10].

In patients with SM, computed tomography (CT) is systematically performed at baseline to detect metastases, and during the follow-up to monitor tumor response to therapy. iRECIST is used to assess tumor response to ICI [11]. Metastases from SM are highly vascular, and immunotherapy induces tumor necrosis, resulting in tumor heterogeneity on contrast-enhanced CT [12]. The analysis of the degree of tumor heterogeneity at baseline and under treatment could bring additional information on survival and treatment response, knowing that a poor prognosis is associated with high heterogeneity tumor [13]. CT texture analysis is an emerging technique, which can quantify tumor heterogeneity [14]. CT texture analysis brings information regarding response to treatment [15–18] and survival in many cancers such as colorectal, hepatocellular carcinoma (HCC), lymphomas, pancreatic cancers, lung and head and neck cancers [9, 15–26].

Regarding SM, two studies have evaluated CT-based texture analysis as a predictive biomarker of survival [12, 27]. However, the potential of CT texture analysis as a predictive biomarker of response to treatment and therapeutic decision-making biomarker has never been investigated. CT texture analysis performed at baseline and on the first CT examination after treatment initiation could allow an earlier prediction of response to treatment, enabling therapeutic adaptations, and discriminating between pseudo progression and actual progression. In this context, we hypothesize that computed tomography-based texture analysis may act as a reliable biomarker able to predict response status as soon as baseline.

The purpose of this study was to determine whether texture parameters derived from contrast-enhanced CT images pre-treatment and acquired three months after treatment initiation are independently associated with response to treatment defined by iRECIST criteria, in patients with metastatic SM treated with anti-PD1 monoclonal antibodies.

2. Materials and methods

2.1. Study population

This retrospective study was approved by institutional review board (AAA-2021-08038) and requirement for written informed consent was waived.

From January 2015 to January 2019, all patients with metastatic SM treated by anti-PD1 monoclonal antibodies (pembrolizumab or nivolumab) were identified from the institutional database and included in this retrospective study. Patients were included when they were treated with pembrolizumab or nivolumab for SM metastases, as a first-line monotherapy or second or more line-therapy, with an age > 18 years. Thirty-one patients treated with pembrolizumab were part of a previous study [27]. The exclusion criteria were: (i), no available CT examination within one month prior to treatment initiation; (ii), no available one month post-treatment CT examination; and (iii), no delineable SM metastases or too small lesion for iRECIST criteria (*i.e.*, < 1 cm in greatest diameter). Recorded demographic variables included: age, sex, weight, Eastern Cooperative Oncology Group (ECOG) performance status, serum level of LDH, date of first infusion of pembrolizumab or nivolumab, date of pretreatment CT examination, date of one month and four-month post-treatment CT examinations, number and largest axial diameter of metastasis chosen for texture analysis, dominant metastasis, RECIST sum on pretreatment and 3-month post-treatment CT examinations, iRECIST conclusion determined on the 6-month post-treatment CT examination.

2.2. Follow-up and endpoints

All patients underwent radiological follow-up according to institution protocol every three months, as well as clinical and biological follow-up. Radiological follow-up consisted of contrast-enhanced CT examinations, covering the brain, thorax, abdomen and pelvis.

The endpoint, response to treatment, was defined using binary coded iRECIST. At 6 months post-treatment evaluation, presence of a response to treatment was defined by complete response, partial response or stable disease. The absence of treatment response was defined by progression according to iRECIST criteria.

2.3. CT examination

CT examinations were performed using a Discovery[®] HD 750 unit (GE Healthcare) and covered the brain, thorax, abdomen and pelvis. Intra-venous administration of non-ionic contrast material (iomeron 350 mg iodine/mL, Iomeron[®] 350, Bracco Imaging) at a dose of 2

mL/kg body weight was performed at a flow rate of 3.5 mL/s followed by 50 mL of saline solution at the same flow rate. Chest CT images were obtained at 35 s after the start of contrast material administration, abdominal and pelvis images at 70 s, and cerebral images at 10 minutes following contrast material administration.

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. Images were reconstructed with a section thickness of 2.5 mm by using 40% adaptive statistical reconstruction (ASiR; GE Healthcare). An automatic tube current modulation technique (Smart mA; GE Healthcare) was used. Mean effective tube current-time product was 336 mAs.

2.4. CT texture analysis

CT texture analysis was performed on the pretreatment CT examination and on the three-month post-treatment initiation CT examination, using the commercially available TexRAD soft-ware (TexRAD Ltd). One radiologist selected from one to five target metastases for each patient following iRECIST criteria. The metastases were contoured by drawing free-hand region of interest (ROI) by a radiologist with 5 years of experience in CT imaging (A.B.), and CT texture analysis was performed in a two-step process (**Figure 1**). First step consisted of image filtration at different spatial scales which allow the extraction of specific features: fine (spatial scale filtration [SSF] = 2), medium (SSF = 3-5) and coarse (SSF = 6). The second step consisted of quantification of the histogram distribution within the ROI with extraction of five texture parameters: mean grey-level intensity (mean) (brightness), standard deviation (SD) (*i.e.*, scale either sd 0 for unfiltered images, sd 2 for fine scale images, sd 4 for medium scale images and sd 6 for coarse scale images), entropy (*i.e.*, irregularity), kurtosis (*i.e.*, peak) and skewness (*i.e.*, asymmetry) [28]. For each patient, the mean value of each texture parameter among lesions and the percentage of variation of the mean value of each texture parameter between pretreatment CT and first control CT (at three months) after initiation of anti-PD1 monoclonal antibodies therapy were calculated.

2.5. Statistical analysis

Quantitative variables were expressed as means \pm standard deviations (SDs) and ranges or as medians, interquartile ranges (Q1, Q3) and ranges. Qualitative variables were expressed as raw numbers, proportions and percentages. Multivariable analysis was performed to identify variables independently associated with favorable response to treatment

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 covariables, a multivariable L1 (least absolute shrinkage and selection operator—Lasso) penalized Cox regression model was built in order to select texture parameters [29]. The regularization parameter was determined by using 10-fold 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 variables as covariables, in order to estimate associated hazard ratios (HR) and their 95% confidence intervals (CI).

Statistical analysis was performed with *r* software. *P* values < 0.05 were considered to indicate significant differences.

3. Results

3. 1. Patient characteristics

A total of 137 patients treated with pembrolizumab and 71 patients with nivolumab were initially retrieved. Of these, 128 patients without available pre-treatment evaluation within one month prior to initiation of treatment and 20 with diffuse organ infiltration and no delineable metastases were excluded. The final study population comprised 60 patients. There were 29 men and 31 women with a median age of 56 years (range: 27–91 years). Of these, 43 patients (43/60; 72%) were treated with pembrolizumab and 17 (17/60; 28%) were treated with nivolumab. **Figure 2** shows the study flow chart.

The main clinical, biological and radiological characteristics of patients are shown in Table 1. Serum LDH level was above the normal upper limit (*i.e.*, 248 UI/L) in 48/60 patients (80%). The number of target metastases ranged from 1 to 5, with a median of 2.1 metastases per patient. A total of 127 metastases were analyzed.

The mean sum of diameters of the target lesions was 55.2 mm (range: 10–208 mm) on baseline pre-treatment CT and 64.4 mm (range: 0–332 mm) on CT three months after initiation of treatment. The mean progression at 3 months was 11.4% (range: -100– +180%) according to RECIST, corresponding to unconfirmed progression in 24/60 patients (40%), stable disease in 32/60 patients (53%), partial response in 3/60 patients (5%) and complete response in 1/60 patient (2%) (**Table 1**).

At six months after treatment initiation, confirmed progression disease was observed in 26/60 patients (43%), stable disease in 30/60 patients (50%), partial response in 3/60 patients (5%), and complete response in 1/60 patient (2%) according to iRECIST criteria.

3. 2. iRECIST response to treatment analysis

The Lasso penalized Cox regression analysis identified six parameters as potential predictors of response to treatment. They were skewness at fine texture scale (SSF=2) (coefficient weight, 1.18), skewness at medium texture scale (SSF=3) (coefficient weight, -1.52), entropy at medium texture scale (SSF=4) (coefficient weight, -0.98), variation of standard deviation between pre and three months post-treatment CT examinations without any filter (% sd0) (coefficient weight, -0.97), variation of standard deviation (% sd2) (coefficient weight, -1.17) at fine texture scale (SSF=2) and variation of entropy (coefficient weight, 5.51) at fine texture scale (SSF=2) (%entropy 2). LDH serum level was the single bioclinical variable that yielded non-zero coefficient weight (coefficient weight, 3.15).

At multivariable analysis, skewness at fine texture scale (SSF =2; HR = 3.51 [95% CI: 2.08–8.57]; $P = 0.010$), skewness at medium texture scale (SSF = 3; HR = 0.56 [95% CI: 0.11–1.59]; $P = 0.014$), percentage of variation of entropy at fine texture scale (SSF = 2; HR = 37.76 [95% CI: 3.48–496.22]; $P = 0.008$) and LDH serum level above 248 UI/L (HR = 3.56 [95% CI: 1.78–21.35]; $P = 0.032$) were independent variables significantly associated with favorable response to treatment (**Table 2**).

4. Discussion

Our study suggests that texture features of metastases from SM on the baseline CT examination as well as their evolution between the first CT examination at three months after treatment and the baseline CT are independent predictors of response to treatment in patient treated with anti-PDL-1 therapies, either pembrolizumab or nivolumab.

Our study also confirms the independent predictive value of baseline LDH serum level above threshold for response to treatment, in agreement with the literature. As far as immunotherapy is concerned, some studies have confirmed the association between elevated baseline LDH serum levels and poor prognosis and response rates [30, 31]. Monitoring of the LDH serum level has been thus routinely used for years at initial staging and during follow-up [30, 32–34]. However, changes in therapy cannot be initiated on the basis of the LDH serum

level evolution. Indeed, the increase of LDH serum level does not correlate with the type of progression and thus cannot help differentiate pseudoprogression from actual progression [35, 36]. Additional biomarkers predictive of the response to ICI are thus needed, in order to allow an early and quick therapeutic adjustment, owing to the cost and to the potential severe adverse events of immunotherapies.

The association between tumor heterogeneity and increased risk of metastasis, unfavorable response to therapies and inhibition of immune response has been proved [37]. Heterogeneity inside tumors is induced by interactions between cancers cells and their environment, creating neovascularization. CT-based texture analysis is the optimal imaging method to quantify this heterogeneity [38].

Recent trials have reported associations between CT texture parameters and histopathological markers of hypoxia and/or neoangiogenesis [39, 40]. Regarding metastasis of SM, in a study performed on 42 patients treated with an antiangiogenic drug (*i.e.*, bevacizumab), an absolute change in mean positive pixels at medium texture scale was predictive of overall survival (OS) [12]. In another study, pretreatment CT texture analysis-derived tumor skewness was suggested as a predictive biomarker of OS and progression-free survival in patients with metastatic SM treated with pembrolizumab [27]. CT texture analysis has been reported to predict response to treatment in many types of cancer [9, 15–18, 25, 26, 41, 42].

In routine practice, response to treatment in metastatic melanoma under ICI is defined according to iRECIST criteria on contrast-enhanced CT scans. However, atypical responses, particularly pseudo-progression are regularly encountered with anti-PD1 therapies. IRECIST criteria take into account pseudo progression and final response status cannot be stated with certainty until the second control CT examination, six months after treatment initiation. An early prediction of response to treatment would thus allow the identification of the patients who undergo a real progression and thus allow therapeutic adjustments.

Our study highlights the independent predictive value of baseline skewness at fine and medium texture scales for response to treatment according to iRECIST criteria in patients with MM under anti-PD1 inhibitors. Interestingly, high skewness values measured on baseline contrast-enhanced CT examinations were also associated with OS in metastatic melanoma with anti-PD1 inhibitors [27]. Similarly, high skewness values were correlated to decreased 5-

years OS in colorectal cancer [19], reduced OS in small cell lung cancer [43] and in HCC treated by surgical resection [44].

Skewness reflects the asymmetry of the histogram of grey-level pixels distribution within the ROI. High skewness values are associated with poorer prognostic in our study as well as in other previous studies [45]. High skewness values reflect the predominance of bright texture that can be induced by hypervascularization.

It is noteworthy that variation of entropy between baseline and the first CT examination post treatment initiation was also strongly correlated with response to treatment in our study. Entropy reflects the heterogeneity within a determined region of interest. Our results suggest that an important variation of the degree of heterogeneity is associated with response to treatment. We suppose that an early response to treatment translates into a rapid decline of neovascularization, thus inducing important changes of entropy that correspond to the diminution of heterogeneity. Of note, the rate of complete and partial response to treatment was low in our study compared to what is generally achieved with anti-PD1 inhibitors [46, 47]. However, a minority of our patients received the anti-PD1 inhibitors as a first-line therapy, moreover we did not evaluate the best overall response rate but only the response rate at six months after the initiation of the treatment.

Our study has some limitations. First, it was a retrospective, single center study. However, anti-PD1 inhibitors are recent therapies, still mostly used as part as therapeutic trials, which can explain the limited recruitment. Our study is exploratory and more studies, prospective, with a larger number of patients and validation cohort are needed. Second, texture analysis is highly sensitive to technical parameters such as CT acquisition parameters or the type of algorithm that is being used. However, in our study the same CT scanner was used for all patients, with similar acquisition parameters. Moreover, the software which we used has been validated and widely used in the literature [15–17, 25, 26, 48, 49]. Finally, the mean value of each texture parameter among lesions from various organs was calculated. However, SM metastasis can invade various types of organ and this choice appears to be the closest to routine practice.

In conclusion, this retrospective study showed that pretreatment CT texture analysis-derived tumor skewness and variation of entropy between baseline and first CT control may be early predictive biomarkers of response to treatment in patients with metastatic SM treated with anti-PD-1 monoclonal antibodies.

Human rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans. Institutional Review Board approval was obtained.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patients.

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Writing, original draft preparation — Angèle Bonnin, Carole Durot

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Visualization — Angèle Bonnin, Carole Durot

Supervision — Carole Durot, Philippe Soyer, Christine Hoeffel

Project administration — Philippe Soyer, Christine Hoeffel

References

1. Sandru A, Voinea S, Panaitescu E, Blidaru A. Survival rates of patients with metastatic malignant melanoma. *J Med Life* 2014;7:572–576.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012: Globocan 2012. *Int J Cancer* 2015;136:E359–386.
3. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372:320–30.

4. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 2015;372:2521–2532.
5. Schraag A, Klumpp B, Afat S, Gatidis S, Nikolaou K, Eigentler TK, et al. Baseline clinical and imaging predictors of treatment response and overall survival of patients with metastatic melanoma undergoing immunotherapy. *Eur J Radiol* 2019;121:108688.
6. Barat M, Guegan-Bart S, Cottureau AS, Guillo E, Hoeffel C, Barret M, et al. CT, MRI and PET/CT features of abdominal manifestations of cutaneous melanoma: a review of current concepts in the era of tumor-specific therapies. *Abdom Radiol* 2021;46:2219–2235.
7. Lugowska I, Teterycz P, Rutkowski P. Immunotherapy of melanoma. *Contemp Oncol* 2018;22:61–67.
8. Coit DG, Thompson JA, Albertini MR, Barker C, Carson WE, Contreras C, et al. Cutaneous melanoma, Version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw JNCCN* 2019;17:367–402.
9. Lubner MG, Smith AD, Sandrasegaran K, Sahani DV, Pickhardt PJ. CT Texture analysis: definitions, applications, biologic correlates, and challenges. *Radiographics* 2017;37:1483–503.
10. Hamard A, Frandon J, Larbi A, Goupil J, De Forges H, Beregi JP, Greffier J. Impact of ultra-low dose CT acquisition on semi-automated RECIST tool in the evaluation of malignant focal liver lesions. *Diagn Interv Imaging* 2020;101:473–479.
11. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017;18:e143–52.
12. Smith AD, Gray MR, del Campo SM, Shlapak D, Ganeshan B, Zhang X, et al. Predicting overall survival in patients with metastatic melanoma on antiangiogenic therapy and RECIST stable disease on initial posttherapy images using CT texture analysis. *AJR Am J Roentgenol* 2015;205:W283–293.
13. Rao SX, Lambregts DM, Schnerr RS, Beckers RC, Maas M, Albarello F, et al. CT texture analysis in colorectal liver metastases: a better way than size and volume measurements to assess response to chemotherapy? *United Eur Gastroenterol J* 2016;4:257–263.
14. Ganeshan B, Miles KA. Quantifying tumour heterogeneity with CT. *Cancer Imaging* 2013;13:140–149.
15. Ravanelli M, Farina D, Morassi M, Roca E, Cavalleri G, Tassi G, et al. Texture analysis of advanced non-small cell lung cancer (NSCLC) on contrast-enhanced computed tomography: prediction of the response to the first-line chemotherapy. *Eur Radiol* 2013;23:3450–3455.
16. Tian F, Hayano K, Kambadakone AR, Sahani DV. Response assessment to neoadjuvant therapy in soft tissue sarcomas: using CT texture analysis in comparison to tumor size, density, and perfusion. *Abdom Imaging* 2015;40:1705–1712.
17. Yip C, Davnall F, Kozarski R, Landau DB, Cook GJR, Ross P, et al. Assessment of changes in tumor heterogeneity following neoadjuvant chemotherapy in primary esophageal cancer. *Dis Esophagus* 2015;28:172–179.
18. Ahn SJ, Kim JH, Park SJ, Han JK. Prediction of the therapeutic response after FOLFOX and FOLFIRI treatment for patients with liver metastasis from colorectal cancer using computerized CT texture analysis. *Eur J Radiol* 2016;85:1867–1874.
19. Ng F, Ganeshan B, Kozarski R, Miles KA, Goh V. Assessment of primary colorectal cancer heterogeneity by using whole-tumor texture analysis: contrast-enhanced CT texture as a biomarker of 5-year survival. *Radiology* 2013;266:177–184.

20. Yip C, Landau D, Kozarski R, Ganeshan B, Thomas R, Michaelidou A, et al. Primary esophageal cancer: heterogeneity as potential prognostic biomarker in patients treated with definitive chemotherapy and radiation therapy. *Radiology* 2014;270:141–148.
21. Ganeshan B, Skogen K, Pressney I, Coutroubis D, Miles K. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: preliminary evidence of an association with tumour metabolism, stage, and survival. *Clin Radiol* 2012;67:157–164.
22. Zhang H, Graham CM, Elci O, Griswold ME, Zhang X, Khan MA, et al. Locally advanced squamous cell carcinoma of the head and neck: CT texture and histogram analysis allow independent prediction of overall survival in patients treated with induction chemotherapy. *Radiology* 2013;269:801v809.
23. Ganeshan B, Panayiotou E, Burnand K, Dizdarevic S, Miles K. Tumour heterogeneity in non-small cell lung carcinoma assessed by CT texture analysis: a potential marker of survival. *Eur Radiol* 2012;22:796–802.
24. Miles KA. How to use CT texture analysis for prognostication of non-small cell lung cancer. *Cancer Imaging* 2016;16:10.
25. Ganeshan B, Miles KA, Babikir S, Shortman R, Afaq A, Ardeshta KM, et al. CT-based texture analysis potentially provides prognostic information complementary to interim FDG/PET for patients with Hodgkin's and aggressive non-Hodgkin's lymphomas. *Eur Radiol* 2017;27:1012–1020.
26. Mulé S, Thieffn G, Costentin C, Durot C, Rahmouni A, Luciani A, et al. Advanced hepatocellular carcinoma: pretreatment contrast-enhanced CT texture parameters as predictive biomarkers of survival in patients treated with sorafenib. *Radiology* 2018;288:445–455.
27. Durot C, Mulé S, Soyer P, Marchal A, Grange F, Hoeffel C. Metastatic melanoma: pretreatment contrast-enhanced CT texture parameters as predictive biomarkers of survival in patients treated with pembrolizumab. *Eur Radiol* 2019;29:3183–3191.
28. Martini K, Moon JW, Revel MP, Dangeard S, Ruan C, Chassagnon G. Optimization of acquisition parameters for reduced-dose thoracic CT: a phantom study. *Diagn Interv Imaging* 2020;101:269–279.
29. Nougaret S, Tardieu M, Vargas HA, Reinhold C, Vande Perre S, Bonanno N, Sala E, Thomassin-Naggara I. Ovarian cancer: an update on imaging in the era of radiomics. *Diagn Interv Imaging* 2019;100:647–655.
30. Diem S, Kasenda B, Spain L, Martin-Liberal J, Marconcini R, Gore M, et al. Serum lactate dehydrogenase as an early marker for outcome in patients treated with anti-PD-1 therapy in metastatic melanoma. *Br J Cancer* 2016;114:256–261.
31. Nosrati A, Tsai KK, Goldinger SM, Tumeh P, Grimes B, Loo K, et al. Evaluation of clinicopathological factors in PD-1 response: derivation and validation of a prediction scale for response to PD-1 monotherapy. *Br J Cancer* 2017;116:1141–1147.
32. Eton O, Legha SS, Moon TE, Buzaid AC, Papadopoulos NE, Plager C, et al. Prognostic factors for survival of patients treated systemically for disseminated melanoma. *J Clin Oncol* 1998;16:1103–1111.
33. Weide B, Elsässer M, Büttner P, Pflugfelder A, Leiter U, Eigentler TK, et al. Serum markers lactate dehydrogenase and S100B predict independently disease outcome in melanoma patients with distant metastasis. *Br J Cancer* 2012;107:422–428.
34. Balch CM, Gershenwald JE, Soong S, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 2009;27:6199–6206.
35. Ferretti GR, Gaj Levra M, Jankowski A, Toffart AC, Moro Sibilot D. Hyperprogressive disease of non-small-cell lung adenocarcinoma under immune-

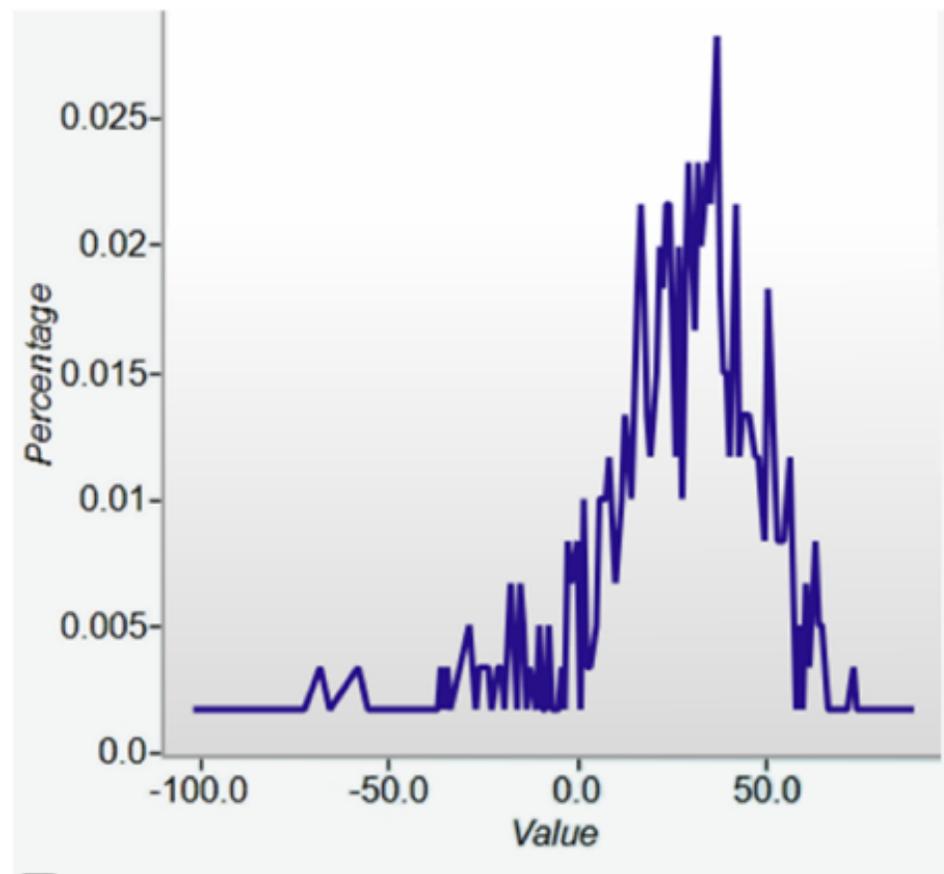
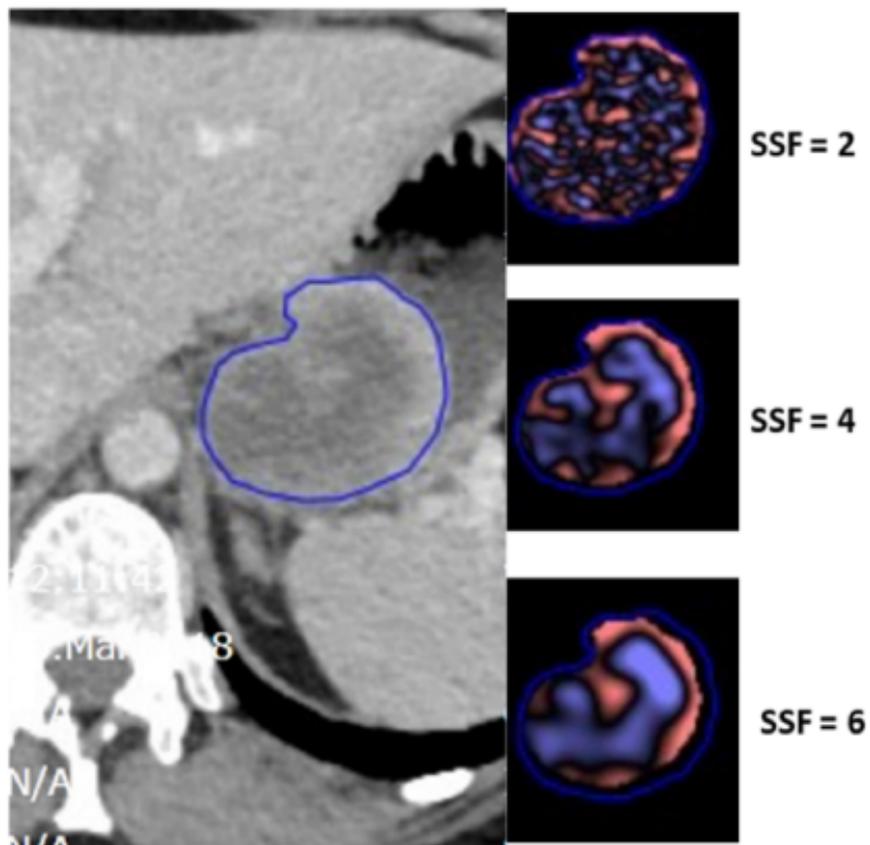
- checkpoint inhibitors: a new response pattern to be recognized by the radiologist. *Diagn Interv Imaging* 2019;100:313–315.
36. Bernard-Tessier A, Baldini C, Castanon E, Martin P, Champiat S, Hollebecque A, et al. Patterns of progression in patients treated for immuno-oncology antibodies combination. *Cancer Immunol Immunother* 2021;70:221–232.
 37. Yun Z, Lin Q. Hypoxia and regulation of cancer cell stemness. *Adv Exp Med Biol* 2014;772:41–53.
 38. Nakaura T, Higaki T, Awai K, Ikeda O, Yamashita Y. A primer for understanding radiology articles about machine learning and deep learning. *Diagn Interv Imaging* 2020;101:765–770.
 39. Ganeshan B, Goh V, Mandeville HC, Ng QS, Hoskin PJ, Miles KA. Non-small cell lung cancer: histopathologic correlates for texture parameters at CT. *Radiology* 2013;266:326–336.
 40. Hayano K, Tian F, Kambadakone AR, Yoon SS, Duda DG, Ganeshan B, et al. Texture analysis of non-contrast-enhanced computed tomography for assessing angiogenesis and survival of soft tissue sarcoma. *J Comput Assist Tomogr* 2015;39:607–612.
 41. Ganeshan B, Skogen K, Pressney I, Coutroubis D, Miles K. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: preliminary evidence of an association with tumour metabolism, stage, and survival. *Clin Radiol* 2012;67:157–164.
 42. Miles KA. How to use CT texture analysis for prognostication of non-small cell lung cancer. *Cancer Imaging* 2016;16:10.
 43. Ahn SY, Park CM, Park SJ, Kim HJ, Song C, Lee SM, et al. Prognostic value of computed tomography texture features in non-small cell lung cancers treated with definitive concomitant chemoradiotherapy. *Invest Radiol* 2015;50:719–725.
 44. Brenet Defour L, Mulé S, Tenenhaus A, Piardi T, Sommacale D, Hoeffel C, et al. Hepatocellular carcinoma: CT texture analysis as a predictor of survival after surgical resection. *Eur Radiol* 2019;29:1231–1239.
 45. Miles KA, Ganeshan B, Hayball MP. CT texture analysis using the filtration-histogram method: what do the measurements mean? *Cancer Imaging* 2013;13:400–406.
 46. Postow M, Chesney J, Pavlick A, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *New Engl J Med* 2015; 372: 2006-17.
 47. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in advanced melanoma. *N Engl J Med* 2015; 372: 2521-32.
 48. Ng F, Kozarski R, Ganeshan B, Goh V. Assessment of tumor heterogeneity by CT texture analysis: can the largest cross-sectional area be used as an alternative to whole tumor analysis? *Eur J Radiol* 2013;82:342–348.
 49. Dohan A, Gallix B, Guiu B, Le Malicot K, Reinhold C, Soyer P, et al; PRODIGE 9 Investigators and PRODIGE 20 Investigators. Early evaluation using a radiomic signature of unresectable hepatic metastases to predict outcome in patients with colorectal cancer treated with FOLFIRI and bevacizumab. *Gut* 2020;69:531–539.

Figure legends

Figure 1. Example of feature extraction from CT data in a 39-year-old woman with gastric metastasis from skin melanoma treated with pembrolizumab.

A, Data are extracted after contouring of the metastasis and corresponding resulting image filtration are displayed from fine texture (SSF = 2) to coarsest texture (SSF = 6).
SSF indicates spatial scale filtration
B, Graph shows corresponding histogram of pixel gray-level intensities.

Figure 2. Study flow chart.



A

B

208 patients with skin melanoma metastases treated with anti-PD1 monoclonal antibodies between January 2015 and January 2019

Pembrolizumab (n = 137)

Nivolumab (n = 71)

Excluded patients (n = 148; 71 %)

No available pretreatment CT (n = 128)

Unclear tumor margins (n = 20)

60 eligible patients with skin melanoma metastases and delineable metastases on pretreatment CT

Table 1. Characteristics of 60 patients with metastases from skin melanoma treated with anti-PD1 monoclonal antibodies

Age (years)	58.9 ± 17.4 (56; 46, 72) [17–91]
Received treatment	
Pembrolizumab	43 (43/60; 72%)
Nivolumab	17 (17/60; 28%)
Age > 60 years	29 (29/60; 48%)
Male sex	29 (29/60; 48%)
Weight (kg)	75.6 ± 17.1 (74; 65, 85) [45–130]
ECOG > 1	11 (11/60; 18%)
LDH > 248 (UI/L)	48 (48/60; 80%)
Previous treatment	38 (38/60; 63%)
Number of target metastases per patient	2.1 ± 1.3 (2; 1, 3) [1–5]
1 target metastasis	27 (27/60; 45%)
2 target metastases	16 (16/60; 27%)
3 target metastases	5 (5/60; 8%)
4 target metastases	7 (7/60; 12%)
5 target metastases	5 (5/60; 8%)
Dominant lesion	
Lymphadenopathy	20 (20/60; 33%)
Liver	16 (16/60; 27%)
Lung	11 (11/60; 18%)
Adrenal gland	3 (3/60; 5%)
Subcutaneous nodule	3 (3/60; 5%)
Mesenteric nodule	2 (2/60; 3%)
Peritoneal nodule	2 (2/60; 3%)
Spleen	1 (1/60; 2%)
Stomach	1 (1/60; 2%)
Brain	1 (1/60; 2%)
Sum of target metastasis diameters on pre-treatment CT (mm)	55.2 ± 47.5 (36.4; 19, 81) [10–208]
Sum of target metastasis diameters on the first control CT- (mm)	64.4 ± 69.0 (35.8; 19, 89) [0–332]
Sum target metastasis diameter variation between pre and post treatment CT (%)	11.4 ± 36.6 (9; 0, 33) [-100–180]
RECIST status at three months	
Stable	32 (32/60; 53%)
Progression	24 (24/60; 40%)
Partial response	3 (3/60; 5%)
Complete response	1 (1/60; 2%)
iRECIST status at six months	
Progression	26 (26/60; 43%)
Stable, partial or complete response	34 (34/60; 57%)

Quantitative variables are expressed as means and standard deviations; numbers in parentheses are medians followed by first quartiles and third quartile. Numbers in brackets are ranges. Qualitative variables are expressed as raw numbers; numbers in parentheses are proportions followed by percentages.

CT indicates computed tomography; ECOG indicates Eastern Cooperative Oncology Group; iRECIST indicates Immune Response Evaluation Criteria in Solid Tumors criteria; LDH indicates serum lactate dehydrogenase serum level; RECIST indicates Response Evaluation Criteria In Solid Tumors;

Table 2. Multivariable Cox-proportional hazards regression analyses of texture analysis and clinical parameters selected by Lasso penalized Cox regression analysis for predicting favorable treatment response defined by iRECIST.

Biological and CT texture parameters	HR (95% CI)	<i>P</i> value
LDH	3.56 (1.78–21.35)	0.032
Skewness_2	3.51 (2.08–8.57)	0.010
Skewness_3	0.56 (0.11–1.59)	0.014
Entropy_4	2.31 (0.52–2.49)	0.52
%sd0	0.93 (0.12–6.77)	0.59
%sd2	0.87 (0.60–5.04)	0.19
%entropy2	37.76 (3.48–496.22)	0.008

Bold indicates indicates significant *P* value.

CI: Confidence interval; HR: Hazard ratio; LDH: Lactate dehydrogenase serum level.

sd0 corresponds to unfiltered images and sd2 to fine scale images.