

Computed tomography texture analysis of response to second-line nivolumab in metastatic non-small cell lung cancer

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Practice points

- Immunotherapy is a valuable new treatment for patient with non-small cell lung cancer.
- Rationalization of appropriate patients for therapy is essential.
- PD-L1 currently only known biomarker with some utility in first-line advanced lung cancer setting.
- Radiomics is a noninvasive procedure with potential utility as a radiological biomarker.
- Our data are suggestive of a correlation between radiomic measurements and progression-free survival (PFS).
- Positive skewness and low entropy are the most relevant measurements in predicting PFS from nivolumab in the second-line setting.
- Combining radiomics with other biological biomarkers could improve our ability to predict the most appropriate patients to receive immunotherapy.
- Larger prospective analysis is warranted in this field with potential of incorporation into clinical trials.

Objectives: Assess computed tomography texture analysis of patients likely to benefit from nivolumab.

Materials & methods: Texture analysis was used to quantify heterogeneity within the largest tumor before immunotherapy. Histogram analysis was classified as hyperdense (positive skewness) or hypodense (negative skewness) and subclassified on median standard deviation value or entropy measurement.

Results: 47 patients were included. At a median follow-up of 18 months, statistical significant differences in progression-free survival were observed when stratified by positive skewness with low entropy, hazard ratio: 0.43 (0.19–0.95); $p = 0.036$, and positive skewness with low standard deviation, hazard ratio: 0.42 (0.18–0.96); $p = 0.04$. **Conclusion:** Patients who derive a clinical benefit to Nivolumab show a computed tomography texture of a hyperdense yet homogenous tumor.

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The introduction of immunotherapy with checkpoint inhibitors targeting PD-1 for the treatment of metastatic non-small cell lung cancer (NSCLC) has resulted in reports of long-term survival in small sub-groups of patients. The use of these agents such as nivolumab have brought a transformational change in the management of metastatic NSCLC with proven effectiveness over chemotherapy in the second-line settings [1]. Despite promising application prospects, the clinical effectiveness to these antibodies have yielded response rates of 20%.

Attempts to isolate reliable predictive biomarkers have shown mixed results for the use of immunotherapy in the treatment of NSCLC. The most widely studied biomarker is PD-L1 expression which has shown mixed results across different cancer types. Subpopulations of patients such as those with PD-L1 50% positive tumors have been used in prospective clinical trials to target patients who will benefit from therapy [2]. However, approximately 25% of patients will respond to immunotherapy with checkpoint inhibitors despite lower PD-L1 staining [3]. An explanation of this finding could be related to sampling issues in heterogeneous tumors. An alternate potential

Total population	n = 47
Male	31 (66%)
Female	16 (34%)
Squamous	16 (34%)
Adenocarcinoma	31 (66%)
Active smoker	15 (32%)
Ex-smoker	29 (62%)
Never smoker	3 (6%)
Reason for discontinuation first-line treatment:	
– Disease progression	46 (98%)
– Toxicity	1 (2%)
Adenocarcinoma molecular profile	n = 31
– EGFR mutant	3
– EGFR wild-type	27
– EGFR unknown	1
– KRAS mutant	4
– KRAS wild-type	5
– KRAS unknown	22

biomarker, tumor mutation burden, has shown promise, however, clinical trials have demonstrated only modest benefit with immunotherapy over chemotherapy in advanced NSCLC [4]. Identification of subpopulations of patients with a greater likelihood of response to immunotherapy would enable treatment to be directed to those most likely to benefit, thereby increasing efficacy and cost–effectiveness.

There is a need for alternative methods for predicting response to immune checkpoint inhibitors. Medical imaging is routinely used in the initial staging of NSCLC and, in view of their ability to characterize human tissue noninvasively, these images represent a rich source of data from which to extract tumor biological features (radiomics) relevant to response to immune checkpoint inhibitors. This noninvasive approach could potentially complement tissue-based methods and include the ability to assess the whole tumor tissues at multiple disease sites and multiple time points.

One method using computed tomography (CT) texture analysis may allow clinicians to measure intratumoral heterogeneity which refers to the existence of a nonuniform distribution of cell subpopulations, with distinct phenotypes and genotypes within a single tumor site. Intratumor heterogeneity on diagnostic images can be quantified using texture analysis which provides metrics that reflect the distribution and intensity of individual picture elements within a tumor region. Filtered image CT texture features may be extracted allowing us to identify spatial heterogeneity in cellular density, angiogenesis and necrosis. This heterogeneity may increase effectiveness of immune checkpoint inhibitors, as more heterogeneous tumors with increased tumor mutation burden may lead to a greater number of neo-antigens to present to antigen-presenting cells [5].

This study assessed whether intratumoral heterogeneity as measured by quantitative CT texture analysis is associated with an improved efficacy to immune checkpoint inhibition in NSCLC.

Materials & methods

A single center retrospective analysis was undertaken of patients with metastatic NSCLC previously treated with platinum doublet chemotherapy who underwent nivolumab 3 mg/kg immunotherapy. The presence of a tumor focus of at least 10 mm diameter on an arterial phase contrast enhanced CT of the chest, and upper abdomen was required for inclusion in the analysis. Patient demographics and tumor histological features are outlined in Table 1.

- Inclusion criteria:
 - Advanced/unresectable NSCLC – all histological subtypes eligible;
 - Previous treatment with platinum doublet chemotherapy;
 - Confirmed progression postplatinum doublet chemotherapy based on CT imaging;
 - Received at least one dose of nivolumab in second-line and above setting;
 - Tumor focus ≥ 10 mm in diameter on CT imaging;
 - Follow-up imaging available for comparison.
- Exclusion criteria:
 - Small cell lung cancer;

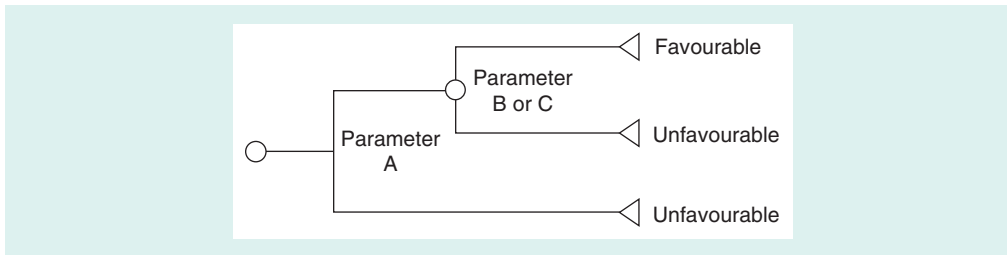


Figure 1. General model for combining pairs of texture parameters.

- Patients who did not receive platinum-based chemotherapy;
- Tumor focus <10 mm in diameter on CT imaging.

The need to obtain consent from individual patients for this nonintervention study had been waived by the local ethics committee (HREC/15/QPAH/735). Time-to-progression on follow-up was determined according to RECIST 1.1. Primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS) and percentage alive at 12 months.

Image analysis

Quantitative CT texture analysis was used to quantify heterogeneity within the single largest tumor site identified on the last clinically indicated contrast enhanced CT of the thorax and upper abdomen performed prior to commencement of immunotherapy. CT texture analysis comprised an image filtration-histogram technique as reported previously [6,7] in which a filtration step that enhances image features of a specified size is followed by quantification of the filtered texture maps using histogram parameters. The filter was set to highlight features of 4 mm radius as this approach has previously been shown to provide prognostic information for patients with NSCLC when implemented in a clinical environment [8]. The histogram descriptors comprised: mean value (a measure of average brightness), mean of positive picture elements, (MPP, the average value of bright regions), standard deviation (SD, a measure of variation from the mean), entropy (E, a measure of the average amount of information in the filtered image), kurtosis (K, a measure of the peakedness and tailedness of the histogram) and skewness (S, a measure of histogram asymmetry). The relationship between these values and characteristics of the original unfiltered image have been previously described in detail elsewhere.

Statistical analysis

Each of the six texture parameters was related to PFS using Kaplan–Meier analysis. The median value of each parameter was adopted as the cut-off value for stratifying patients into prognostic groups apart from skewness for which a cut-off value of zero was used. Skewness values tend to zero as the number of image features highlighted by the filter increases, with positivity or negativity determined by their average brightness [9]. The texture parameters were ranked (A–F) according to the significance of their association with survival determined using the log-rank test.

The prognostic value of combinations of two texture parameters was assessed by sequentially applying the highest rank parameter (A) along with the second or third rank parameter (B or C) using the model shown in Figure 1. The cut-off value for parameter B or C was the median value within the subgroup identified by parameter A. The prognostic values of these models were then subjected to a sixfold cross-validation process in which the patient cohort was randomly partitioned into six subgroups matched for numbers of patients showing progression. A single subgroup was retained as the validation data for testing the model with the other subgroups used as training data. The process was then repeated until each subgroup had been used once as the validation data. The results from each fold were combined to provide an unbiased estimate of prognostic value.

Results

The median follow-up time was 12 months. Nivolumab was discontinued (N = 38) due to progression/mortality, with treatment ongoing in the remaining patients (N = 9). Mortality had occurred in 35 patients (74%). The median PFS was 3 months (95% CI: 1.5–4.5) and median OS was 7 months (95% CI: 2.5–11.5).

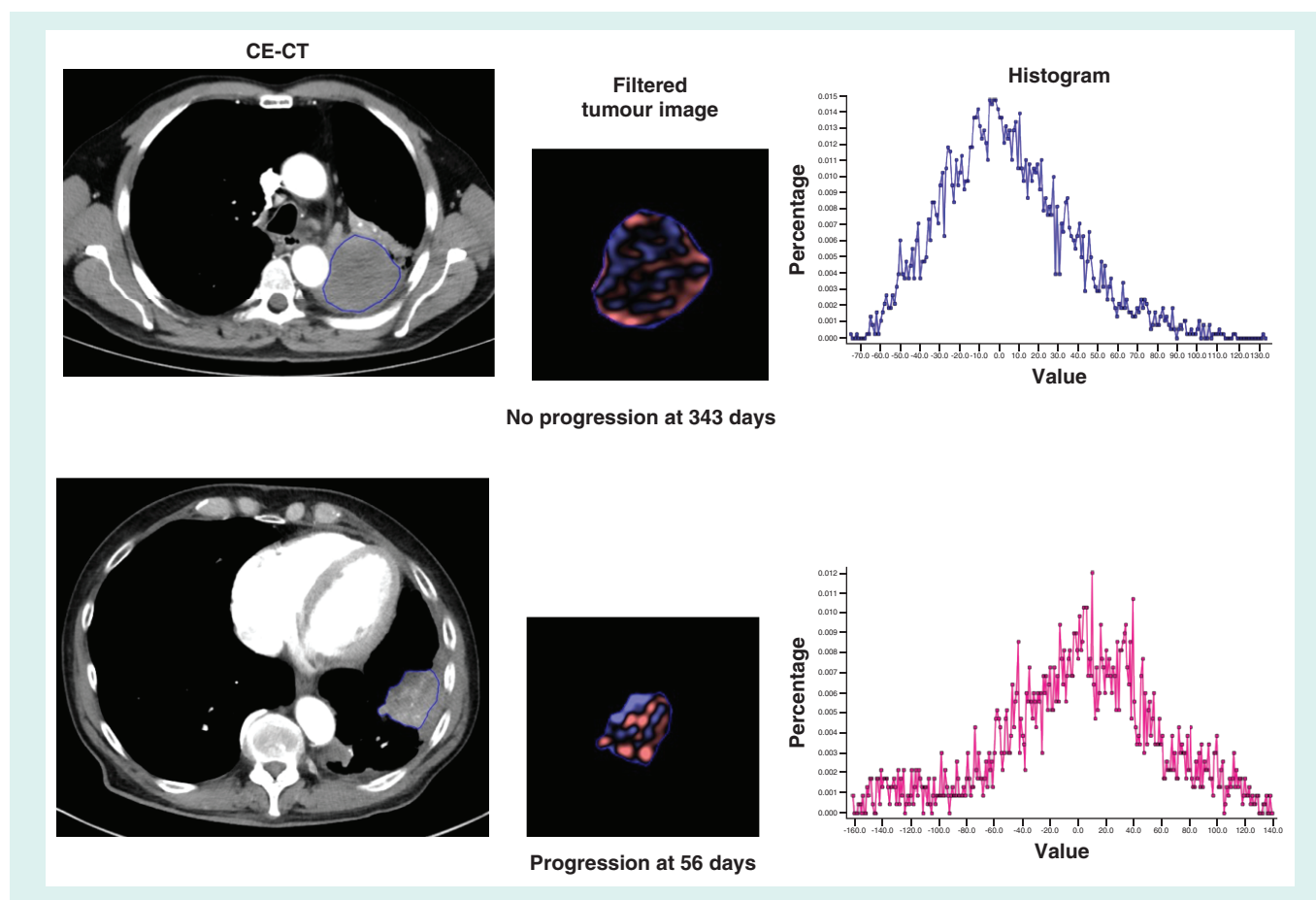


Figure 2. Contrast enhanced computed tomograms, filtered tumor image and corresponding histograms from a patient with no tumor progression at 343 days (top row) and a patient who demonstrated tumor progression at 56 days. CE-CT: Contrast enhanced computed tomograms.

Table 2. Results of progression-free survival analysis for individual texture parameters.			
Rank	Parameter	Cut-off	p-value
A	Skewness	0	0.19
B	SD	45.1	0.28
C	Entropy	4.95	0.31
D	MPP	40.4	0.57
E	Mean	3.90	0.88
F	Kurtosis	0.08	0.92

MPP: Mean positive pixels; SD: Standard deviation.

Examples of texture analyses are given in Figure 2. The histogram derived from the filtered tumor image of a patient who showed no progression at 343 days (top row) shows positive skewness (0.51) and low values for entropy (4.84) and SD (32.2). In comparison, the tumor histogram from a patient who progressed at 56 days shows negative skewness (-0.32) with a higher entropy and SD values (5.36 & 57.2).

Table 2 shows the results for PFS analysis for each texture parameter ranked in order of statistical significance. No single texture parameter showed a statistically significant difference in PFS. The best discriminator for PFS was skewness (positive value: 4 [0.1–7.9] vs negative value: 2 [0.6–3.4] months; p = 0.19) with 28 of 47 patients (60%) showing positive values. The PFS Kaplan–Meier survival curves for this parameter are shown in Figure 3A.

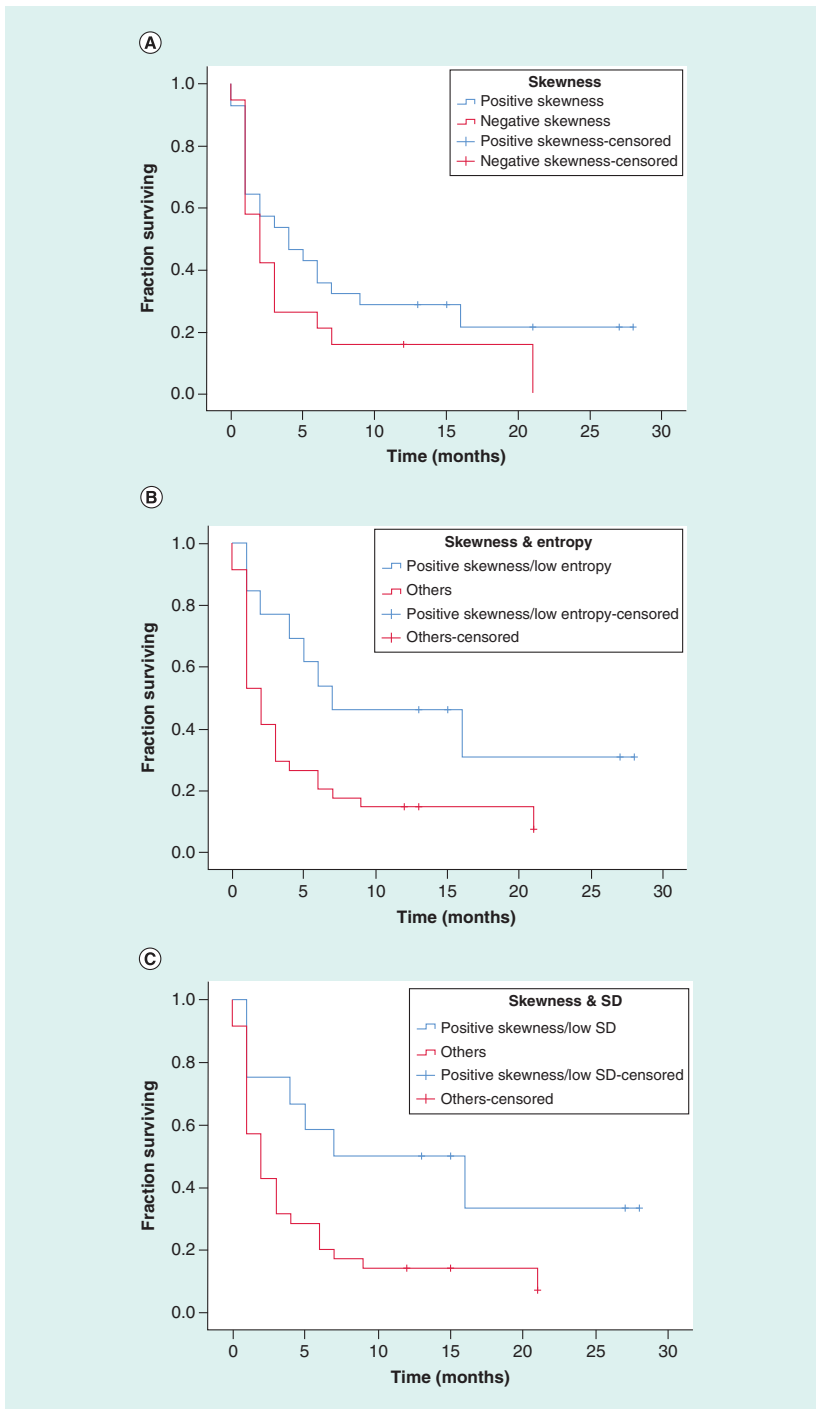


Figure 3. Progression-free survival curves for patients stratified by (A) skewness (positive value: 4 [0.1–7.9] vs negative value: 2 [0.6–3.4] months; $p = 0.19$), (B) skewness with entropy (positive skewness/low entropy: HR: 0.43; 95% CI: 0.19–0.95; $p = 0.036$) and (C) skewness combined with SD (positive skewness/low SD: HR: 0.42; 95% CI: 0.18–0.96; $p = 0.04$). HR: Hazard ratio; SD: Standard deviation.

SD and entropy were ranked second and third and subsequently combined with skewness according to the model in Figure 1.

Following cross-validation, statistically significant differences in PFS were observed when patients were stratified by positive skewness combined with low entropy (hazard ratio [HR]: 0.43; 95% CI: 0.19–0.95; $p = 0.036$) and

Table 3. Results of 12-month landmark survival for texture parameters.

Texture parameter		> 12 months		< 12 months		p-value
		n	(%)	n	(%)	
Skewness	Positive	9	32.1%	19	67.9%	0.968
	Negative	6	31.6%	13	68.4%	
SD	High	9	33.3%	18	66.7%	0.808
	Low	6	30.0%	14	70.0%	
Entropy	High	8	29.6%	19	70.4%	0.696
	Low	7	35.0%	13	65.0%	
Positive skewness & low SD	Present	6	50.0%	6	50.0%	0.119
	Absent	9	25.7%	26	74.3%	
Positive skewness & low entropy	Present	7	53.8%	6	46.2%	0.046
	Absent	8	23.5%	26	76.5%	

SD: Standard deviation.
The bold value p reaches statistically significance whereas the others p values do not.

positive skewness combined with low SD (HR: 0.42; 95% CI: 0.18–0.96; $p = 0.04$). The respective PFS curves are shown in [Figure 3B & C](#).

No single texture parameter showed a statistically significant difference in OS. [Table 3](#) shows 12-month landmark survival data with positive skewness and low entropy showing a significant difference with 54% of cases showing > 12 months survival.

Discussion

In this small retrospective analysis, we analyzed CT texture analysis to effectiveness of nivolumab immunotherapy. Our results indicate that patients who derive a clinical benefit to nivolumab show CT texture features of a positive skewness combined with low entropy or low SD. This CT texture is suggestive of a hyperdense yet homogenous tumor possibly reflective of a dominant sub clonal population of tumor cells.

Radiogenomic research has largely focused on identifying imaging features associated with specific driver gene mutations relevant to malignant progression. Imaging correlates have successfully been identified for a wide range of such mutations [10], confirming the principle of genotype–phenotype relationships that underpins this approach. However, the key genomic feature shown to predict response to immune checkpoint inhibitors (ICI) is tumor mutation burden which leads to tumor-associated inflammation due to increased neoantigenic diversity. Typically, a high mutation burden represents an alternative tumor survival strategy to driver mutations [11], although there are exemptions, for example KRAS mutations in NSCLC. The identification of imaging predictors for response to ICI therapy therefore requires a radiogenomic approach that differs to those applied to date. Imaging correlates for the downstream consequences of high mutation burden such as neoantigenic diversity or clonal heterogeneity are therefore most likely to be predictive for response to ICI. For intratumor heterogeneity on CT texture analysis, to provide a surrogate for genomic heterogeneity, not only does there need to be a correlation between genomic and radiological features but also the scale of genomic heterogeneity has to be sufficiently large for detection by CT.

However, accumulating research data using CT texture analysis alone offers the prospect of a simpler approach based on a small number of imaging parameters derived from a single modality with the benefit of easier incorporation into routine clinical workflow. In particular, a CT texture signature has been reported for NSCLC harboring a KRAS mutation with positive skewness and low kurtosis [12]. The presence of a KRAS mutation within NSCLC is associated with high mutation burden and has been proposed as a potential predictive biomarker in anti-PD-1/PD-L1 immune mediated therapy [11]. Due to our small sample size, subgroup analysis could not be further investigated. Furthermore, CT texture signatures have been reported for NSCLC exhibiting other genetic aberrations such as EGFR mutations and ALK re-arrangements, that represent driver mutations associated with lower mutation burden and poorer response to ICI [13]. To date, no studies directly correlating CT texture and tumor mutation burden have been reported for NSCLC.

In previous reports of CT texture analysis, heterogeneous texture features showing high entropy and low uniformity were associated with poorer OS in esophageal cancer, NSCLC and squamous cell carcinoma of the head and neck [14–17]. Tumor heterogeneity is a well-known character of malignant tumors, which is usually associated with aggressive tumor biology.

Study limitations

The study had several limitations including a relatively small patient population; the fact that it was only a retrospective analysis; it was a single institution experience and the limited radiomic parameters were analyzed in 2D format only.

Future perspective

Although these studies hold promise for the derivation of predictive biomarkers from CT texture analysis, there remains a need for research that relates CT texture in NSCLC to survival outcomes following ICI therapy. Adopting a radiomic approach to identifying patients who will benefit from immune checkpoint inhibitors have the potential advantage of measuring the phenotype of multiple metastatic disease sites across time-points as an adjunct to routine clinical imaging in a non-invasive manner. We identified in this retrospective analysis that a positive skewness with low entropy or SD was associated with improved efficacy to immune checkpoint inhibitors however further validation is required prior to incorporation into routine clinical practice.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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