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Potential impact of texture analysis in contrast enhanced CT in non-small cell lung cancer as a marker of survival

A retrospective feasibility study

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Abstract

The objective of this feasibility study was to assess computed tomography (CT) texture analysis (CTTA) of pulmonary lesions as a predictor of overall survival in patients with suspected lung cancer on contrast-enhanced computed tomography (CECT). In a retrospective pilot study, 94 patients (52 men and 42 women; mean age, 67.2 ± 10.8 yrs) from 1 center with non-small cell lung cancer (NSCLC) underwent CTTA on the primary lesion by 2 individual readers. Both simple and multivariate Cox regression analyses correlating textural parameters with overall survival were performed. Statistically significant parameters were selected, and optimal cutoff values were determined. Kaplan–Meier plots based on these results were produced. Simple Cox regression analysis showed that normalized uniformity had a hazard ratio (HR) of 16.059 (3.861–66.788, $P < .001$), and skewness had an HR of 1.914 (1.330–2.754, $P < .001$). The optimal cutoff values for both parameters were 0.8602 and 0.1554, respectively. Normalized uniformity, clinical stage, and skewness were found to be prognostic factors for overall survival in multivariate analysis. Tumor heterogeneity, assessed by normalized uniformity and skewness on CECT may be a prognostic factor for overall survival.

Abbreviations: 18-FDG-PET/CT = 18-flourdeoxyglucose positron emission tomography/computed tomography, CECT = contrast enhanced computed tomography, CI = confidence interval, CTTA = CT texture analysis, NSCLC = non-small cell lung cancer, ROI = region of interest, TNM = tumor-node-metastasis.

Keywords: computed tomography, non-small cell lung cancer, texture analysis

1. Introduction

NSCLC is one of the most common types of cancer in the western part of the world and continues to be among the most lethal cancers. Over the last few years, the number of new cases and overall mortality have decreased in men, whereas both are increasing in women. In Denmark, 12% of all new cancer cases are diagnosed as lung cancer. The relative 5-year survival rate for the entire group is 11% in men and 14% in women; however, these are highly dependent on the time of diagnosis and stage of disease.[1]

Currently, the morphological features of conventional multi-detector computed tomography (MDCT) are the primary tools for staging lung cancer. 18-flourdeoxyglucose positron emission tomography/computed tomography (18-FDG-PET/CT) is often used in the diagnostic work-up of lung cancer. Evidence supports that the morphological features of multi-detector computed tomography (MDCT) and F18-FDG-PET/CT are equal in the assessment of tumor (T) and lymph node (N) stage.[2,3] However, F18-FDG-PET/CT is superior to CT in the assessment of metastatic spread (M). This is based on the 8th tumor-node-metastasis (TNM) classification, which currently does not include tumor heterogeneity, texture or biomarkers.[4]

CTTA, a noninvasive technique that quantifies the spatial pattern of pixel intensities on imaging, is an objective measure of tumor heterogeneity.[5] Tumor heterogeneity is a key feature of therapeutic resistance, which reflects intra-tumor variations in cell density, necrosis, and angiogenesis.[6] CTTA has been shown to provide prognostic information about survival and predictive

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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information on recurrence and response to chemotherapy in patients with a variety of cancer forms.[7–11] If CT-derived prognostic biomarkers can be identified and incorporated into routine practice, they could potentially increase the utility of CT and provide useful and important information, which could help in making optimal treatment decisions and improve overall clinical outcomes.

For NSCLC specifically, texture analysis has been associated with metastatic spread, genetic mutation, differentiation between malignant and benign lymph nodes, and is a prognostic factor for overall survival.[7,12–16]

Although CTTA has been extensively used in research environments, it lacks adaptation to routine clinical use for diagnosis and prognostication.

The purpose of this feasibility study was to assess CTTA as a prognostic factor for overall survival, in patients with suspected lung cancer on CECT, based on the hypothesis that high heterogeneity in a tumor reflects poor overall survival.

2. Methods

2.1. Design and patients

This study was retrospective, following the STROBE guidelines, and included patients with NSCLC gathered between 2009 and 2011 at Aarhus University Hospital in a previous study. The Danish Board of Health granted permission to access the patient information retrospectively. All patients had previously provided written consent for the use of their images and data for the original study and subsequent analysis using new techniques.[3] The Danish Ethical Committee waived the need for new consent due to the retrospective nature of the study. Survival data were obtained for each patient using the Danish Lung Cancer Registry. Inclusion criteria: pathologically proven NSCLC, available survival data, and CECT suitable for texture analysis. The included patients were randomized for either a feasibility or validity dataset, with half of the cohort assigned to each.

2.2. CECT imaging protocol

CT was performed using a multiple-row detector CT scanner (Philips Brilliance CT 64-channel scanner; Philips Healthcare, Best, The Netherlands). The CT acquisition parameters were 64 × 0.625 mm collimation, kV 120 to 140, mAs/slice 150 to 250, rotation time 0.75, reconstruction thickness 2 mm, increment 1 mm, pitch 1.078, FOV 35 cm, and matrix 512 × 512. CT examinations included the chest and upper abdomen. Iodixanol 270 mg/mL (Visipaque® 270; GE Healthcare, Oslo, Norway), or iohexol 300 mg/mL (Omnipaque® 300; GE Healthcare) was injected intravenously at weight-adjusted doses of 2 mL/kg body weight to adjust for differences in distribution volume with an injection rate of 4 mL/s. A bolus-tracking technique with a region of interest (ROI) in the descending aorta at the level of the carina was used to adjust for differences in cardiac output. CT was performed after a delay of 15 seconds for the chest and upper abdomen (late arterial phase) and 65 seconds for the upper abdomen (portovenous phase) after a threshold of 200 HU was obtained.

2.3. CTTA of primary tumors

CTTA was performed using TexRAD, a research software (TexRAD Ltd, Cambridge, UK).[6] The technique comprised an image filtration-histogram approach; in which an initial filtration step using a Laplacian of Gaussian band-pass filter (non-orthogonal Wavelet) was employed to extract and enhance features of different size based on the spatial scale filter (SSF) values varying from 1.4 to 4.1 mm in diameter. Following image filtration, each filtered image texture map was quantified using histogram parameters such as entropy and uniformity (Fig. 1).

A specialist consultant in radiology with >5 years of experience in the use of the TexRAD software performed the analysis. The radiologists were blinded to all patient identifiers and clinical data, as well as to the CT and tissue sampling results. For each primary tumor, a ROI was drawn on all axial images, in 2D, and the final analysis was performed on the 3D volume of the drawn tumor. A semi-automated approach further refined the ROI enclosing the primary tumor to exclude air and fat using a thresholding procedure that removed pixels with values <–50 HU.

Thirty cases were randomly selected, and a second consultant in Radiology with >5 years of experience in the use

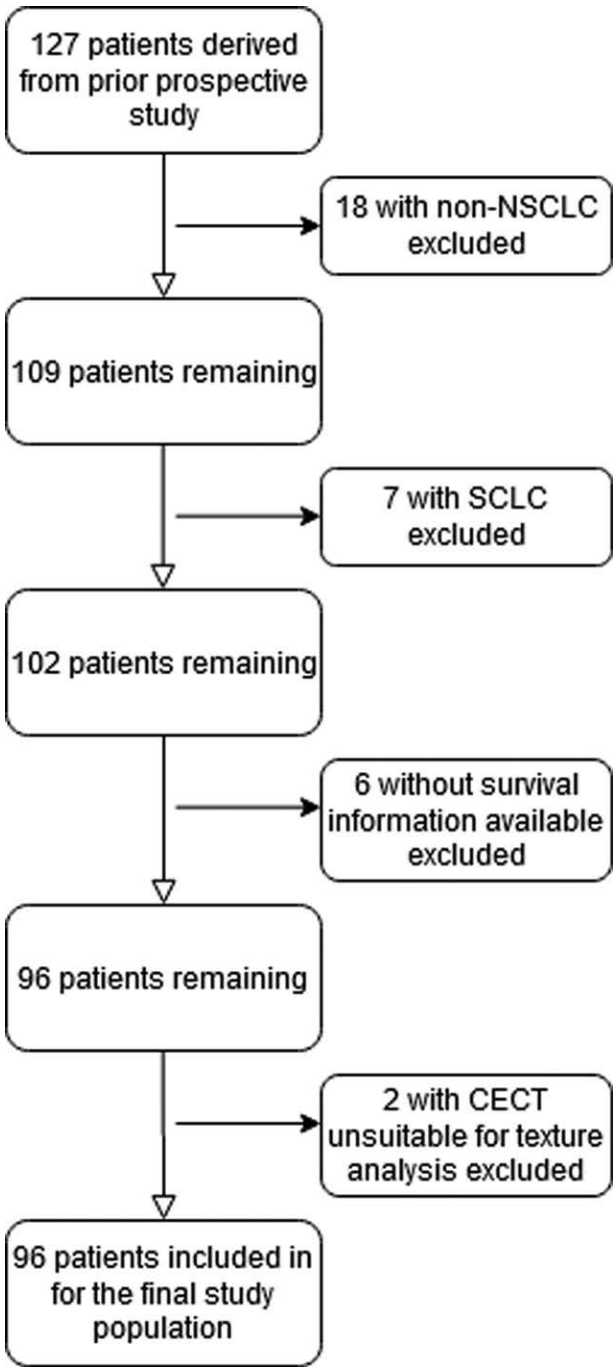

Figure 1. Flowchart for included participants.

Table 1

Patient demographics including age, sex, tumor pathology, clinical stage, smoking history and treatment.

		Demographics		
		Feasibility dataset	**Validity dataset**	**Full dataset**
Age	Yrs of age	67.8 (CI 95% 64.3–71.2)	66.5 (CI 95% 63.6–69.4)	67.2 (CI 95% 64.9–69.4)
Sex	Male	27	25	52
	Female	20	22	42
Pathology	Adenocarcinoma	29	22	51
	Planocellular carcinoma	15	15	30
	Large cell carcinoma	0	6	6
	Blended	3	4	7
Stage	Ia	8	9	17
	Ib	10	9	19
	IIa	6	6	12
	IIb	1	1	2
	IIIa	6	6	12
	IIIb	4	2	6
	IV	11	10	21
	Unknown	1	4	5
Smoking history	Pack yrs	29.9 (CI 95% 23.7–36.1)	37.2 (CI 95% 31.5–42.9)	33.8 (CI 95% 29.6–38.1)
Treatment	Surgery	26	26	52
	Chemotherapy	18	21	39
	Radiation/Chemotherapy	1	0	1
	Missing data	2	0	2

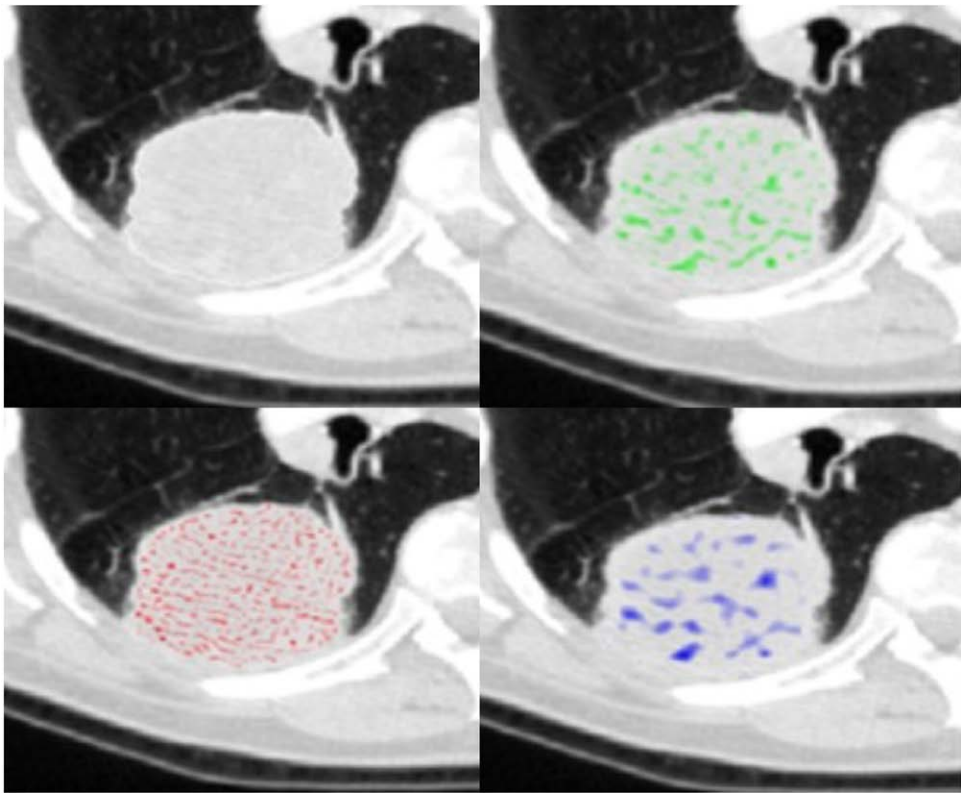

Figure 2. TexRAD research software showing the drawn ROI (Top left) and the representation of fine (Bottom left), medium (Top right) and coarse textures (Bottom right). TexRAD indicates grading of textures in color: red = fine, green = medium and blue = coarse. ROI = region of interest.

of the TexRAD software reanalyzed these for interobserver agreement.

2.4. Statistical analysis

All analyses were conducted using the R software package 4.0.3 (R Core Team, 2022). In R the following packages were used: Dplyr (version 1.0.3, 2021), Survival (version 3.2-7. 2020), Survminer (version 0.4.9, 2021) and SurvMisc (version 0.5.5, 2018).[17–21] Texture parameters were normalized against coarse filters based on a previous publication suggesting that normalized features were more robust and had higher predictive value than standard texture features.[22] Simple Cox regression was used for the entire dataset to determine

the parameters that were prognostic of survival. The feasibility dataset was used to determine the optimal thresholds for normalized and standard CTTA parameters, which were determined based on an algorithm in R using the Fisher exact method.[17] The differences between the survival curves for the groups over or under the threshold were evaluated using a nonparametric log-rank test ($P < .05$, considered significant). Interobserver agreement was assessed using Bland–Altman plots.

3. Results

3.1. Patients

In total, 94 patients were included in the study. Fifty-two males and 42 females with a mean age of 67.2 years (range, 56.4–78.0) were included. The cohort was randomized with 47 patients for the feasibility dataset and 47 patients for the validation dataset (Table 1, Fig. 2). Mean survival was 27.0 months and 27.6 months for the feasibility and validation datasets, respectively. Median survival was respectively 15.0 months and 21.8 months (Fig. 2).

3.2. Texture analysis

The selection of relevant texture parameters was based on a simple Cox regression. Only 2 parameters were prognostic for overall survival with normalized uniformity (HR 16.06, confidence interval [CI] 95: 3.86–66.79, *P*-value < .001) and standard skewness (HR 1.91, CI 95: 1.33–2.75, *P*-value < .001). The remaining texture parameters and clinical parameters, including the total number of voxels, mean intensity, skewness, kurtosis, smoking history, and uniformity, were not associated with overall patient survival (Table 2).

3.3. Optimal cutoffs

Using the Fisher exact method, optimal cutoff points for normalized uniformity were determined to be 0.8602 for the feasibility dataset and 0.1554 for skewness medium filters.

3.4. Kaplan–Meier analysis for both groups

Based on the optimal threshold for both normalized uniformity for medium texture and standard skewness for medium texture, we found similar Kaplan–Meier curves for both the feasibility and validation datasets, thereby validating the model (Figs. 3 and 4).

Accompanying risk tables can be found in Table 3.

3.5. Multiple Cox regression

Multiple Cox regression analysis suggested that standardized uniformity for medium filters (hazard ratio 14.42, CI 95:

Table 2

Results for simple Cox regressions.

	Simple Cox regressions			
Parameters	HR	95% CI	*P*-value	Test of proportional hazards P > chi2
Normalized uniformity (medium/coarse filter)	16.06	3.86–66.79	<.001	0.6802
Treatment	3.10	1.54–6.25	.002	0.1516
Skewness medium filter	1.91	1.33–2.75	<.001	0.1992
Clinical stage	1.33	1.19–1.50	<.001	0.2015
Entropi coarse filter	1.43	1.06–1.95	.02	0.6401

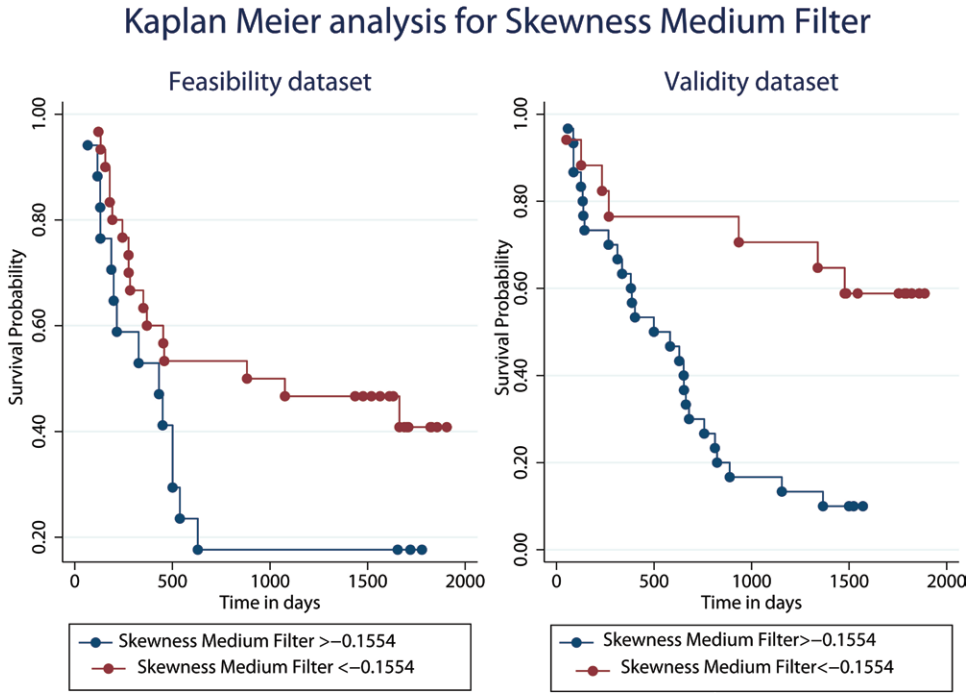

Figure 3. Kaplan–Meier analysis for skewness medium filter, with the determined cutoff value 0.1554, showing similar curves for the feasibility and validity data set.

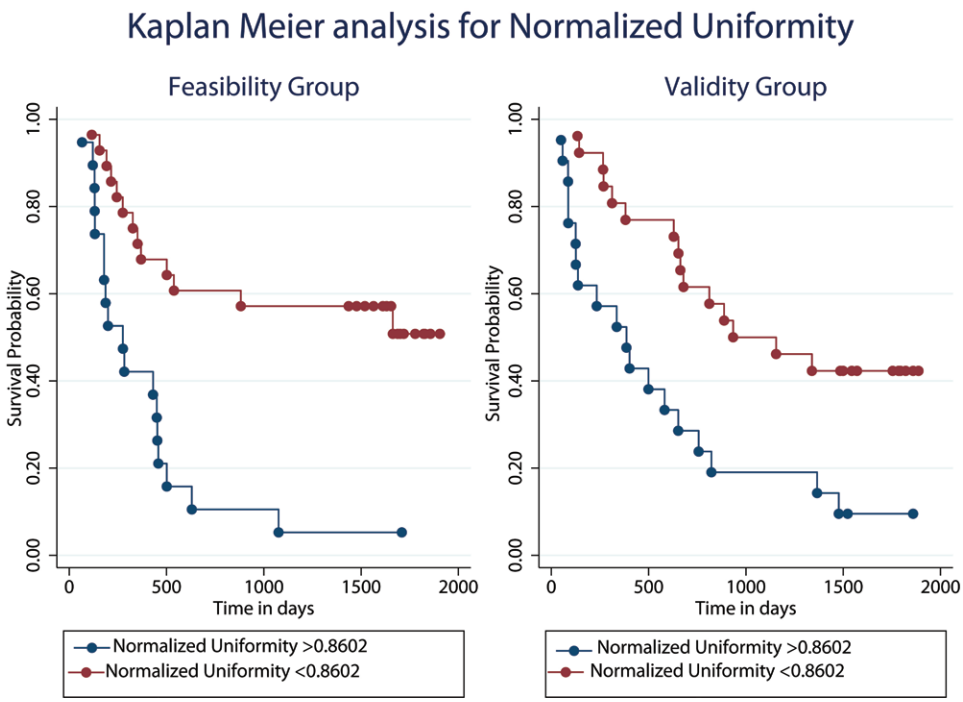

Figure 4. Kaplan–Meier analysis for normalized uniformity, with the determined cutoff value 0.8602, showing similar curves for the feasibility and validity data set.

Table 3

Accompanying risk tables for Kaplan–Meyer analysis for normalized uniformity and Skewness medium texture.

Accompanying risk tables for Kaplan–Meyer analysis				
Patients at risk, n				
Normalized uniformity, feasibility group				
19	4	2	1	>0.8602
28	19	16	14	<0.8602
0	500	1000	1500	Survival (d)
Normalized uniformity, validity group				
21	8	4	2	>0.8602
26	20	13	9	<0.8602
0	500	1000	1500	Survival (d)
Skewness medium texture, feasibility group				
17	7	3	3	>–0.1554
30	16	15	12	<–0.1554
0	500	1000	1500	Survival (d)
Skewness medium texture, validity group				
30	15	5	2	>–0.1554
17	13	12	9	<–0.1554
0	500	1000	1500	Survival (d)

2.78–74.92, *P*-value = .001), clinical stage (hazard ratio 1.25, CI 95: 1.03–1.51, *P*-value = .022), and skewness on medium filters (hazard ratio 1.51, CI 95: 1.01–2.27, *P*-value = .044) were prognostic factors for overall survival (Table 4). The proportional hazards assumption was tested in the analysis and showed no violation.

3.6. Interobserver variability

We found good interobserver agreement with narrow limits of agreement, and an even spread around 0. The mean difference between readers for normalized uniformity was –0.023, with limits of ±0.334. For the skewness medium filter, the mean difference between readers was –0.38 with limits of ±0.2.66 (Fig. 5).

4. Discussion

In this retrospective study, we found that normalized uniformity texture parameters, skewness for medium filters, and entropy for coarse filters were significant prognostic factors for patient survival using simple Cox regression and Kaplan–Meier analysis. For normalized uniformity and skewness, the association with overall survival was maintained in the multiple Cox regression.

The publication of the new 8th edition of TNM staging shows that with each new iteration, we gain a new understanding of the factors that influence survival in lung cancer patients; however, TNM staging does not consider imaging biomarkers.[4] Some studies, including the one presented here, have shown a possible impact of texture parameters in the prognostication and staging of lung cancers.[7,14,24,25] An earlier study that focused on unenhanced CT derived from PET/CT examinations

Table 4

Results for multivariate Cox regression.

	Multivariate Cox regression		
Parameters	HR	95% CI	*P*-value
Variables included in the Cox analysis			
Normalized uniformity (medium/coarse filter)	14.42	2.78–74.92	.001
Clinical stage	1.25	1.03–1.51	.022
Skewness medium filter	1.51	1.01–2.27	.044
Parameters	**HR**		***P*-value**
Variables excluded in the Cox analysis			
Age	1.02		.232
Metastatic stage	1.28		.594
Uniformity medium filter	862.87		.503

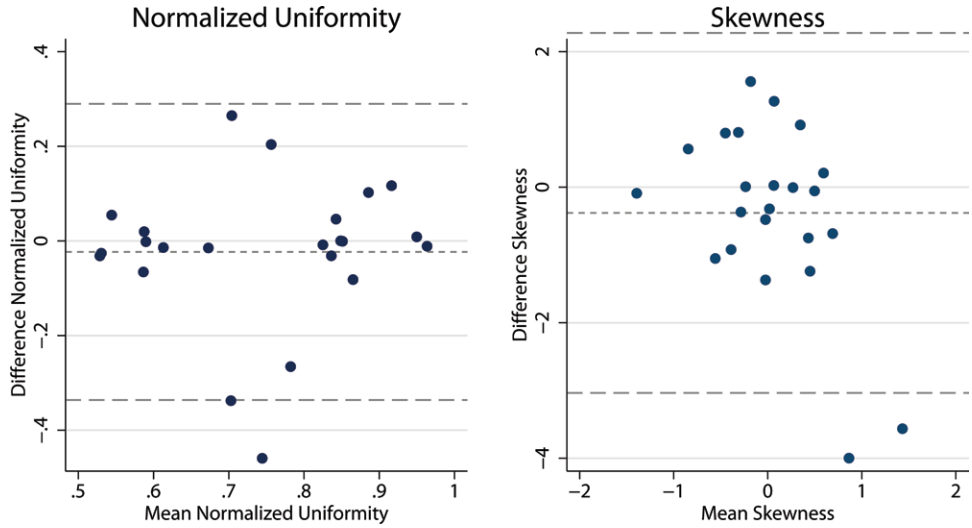

Figure 5. Bland–Altman plots for normalized uniformity and skewness medium filter. (A) Normalized uniformity shows a few outliers, but also very narrow limits of agreement and an even spread around 0. (B) Skewness medium filter showing similar findings with narrow limits of agreement and an even spread around 0.

showed coarse uniformity to be the best prognostic factor for survival.[7] Most likely, the discrepancy between the findings presented in the current study, which found normalized uniformity to be the best predictor, and previous studies was caused by the addition of contrast to the examinations. This indicates that contrast administration can severely affect the texture parameters. Furthermore, differences in acquisition parameters could be another explanation. This suggests that to implement texture analysis in clinical practice, it is imperative to reach a consensus on the international harmonization of scanning protocols and contrast policies.

The reason why tumor heterogeneity is a prognostic factor for survival is currently not understood; however, an explanation might be that aggressive tumors have increased hypoxia and hence increased micro necrosis, giving rise to increased heterogeneity on CECT. It has been previously shown that some texture parameters correlates with tumor hypoxia assessed histopathologically.[5]

Several studies investigating various techniques for assessing tumor heterogeneity have been published.[13,25,26] The most recent technique implemented is radiomics, which uses both histogram analysis, such as the texture analysis presented in this study, and more advanced analysis, including gray-level co-occurrence matrix, run-length matrix, and morphological features of the lesion. In the present study, only histogram analysis was included, as all the parameters were well described and comprehensible. Radiomics features have previously been correlated with survival, the presence of distant metastases, and as a predictor of treatment response.[13,25–27]

As lung cancers are heterogeneous in nature, with multiple cell clones within the same tumor, we chose to assess the full volume of the tumor, even though prior studies and studies of tumors originating in other organ systems have suggested that a single-slice ROI sufficiently accounts for the inherent heterogeneity of lung cancers.

The cohort included patients with a variety of NSCLC pathologies, including adenocarcinomas (ADCs), squamous cell carcinomas (SCCs), large cell carcinomas, and blended tumors. Some studies have suggested that texture analysis/radiomics can differentiate between adenocarcinomas (ADCs) and squamous cell carcinomas (SCCs).[28] Most exhibit almost perfect differentiation on training data, but there is a significant drop in performance on clinical validation data.[29] The differences in texture parameters between various NSCLC pathologies could account for some of the variance in survival found in the current study.

The results presented in this feasibility study, in combination with previous results, show the possible use of imaging biomarkers as part of the prognostication for survival. In particular the current 8th TNM classification only considers morphological features, and the results presented here suggest that imaging biomarkers can further refine the classification of individual groups.

The present study has some limitations. First, the sample size was relatively small for survival analysis. Second, there was selection bias. The reason behind this was to ensure differences in acquisition parameters and contrast media policies, did not affect the measured heterogeneity within the lesions. Finally, a significant limitation is that all CECT come from a single center and from the same CT system.

In conclusion, we showed that for CECT, lung tumor heterogeneity assessed by normalized uniformity can be used as a prognostic factor for survival. It has the potential to be used as a biomarker in future revisions of the TNM classification. The limited sample size warrants further studies investigating various T stages within the TNM classification and in larger groups of patients.

Author contributions

Conceptualization: Michael Brun Andersen, Hans Henrik Torp Madsen, Finn Rasmussen.
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Software: Balaji Ganeshan.
Supervision: Hans Henrik Torp Madsen, Finn Rasmussen.
Writing – original draft: Michael Brun Andersen.
Writing – review & editing: Michael Brun Andersen, Stefan Walbom Harders, Jesper Thygesen, Balaji Ganeshan, Hans Henrik Torp Madsen, Finn Rasmussen.

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