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CHEST

Tumour heterogeneity in non-small cell lung carcinoma assessed by CT texture analysis: a potential marker of survival

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Abstract
Purpose To establish the potential for tumour heterogeneity in non-small cell lung cancer (NSCLC) as assessed by CT texture analysis (CTTA) to provide an independent marker of survival for patients with NSCLC.
Materials and methods Tumour heterogeneity was assessed by CTTA of unenhanced images of primary pulmonary lesions from 54 patients undergoing ^{18}F-fluorodeoxyglucose (FDG) PET-CT for staging of NSCLC. CTTA comprised image filtration to extract fine, medium and coarse features with quantification of the distribution of pixel values (uniformity) within the filtered images. Receiver operating characteristics identified thresholds for PET and CTTA parameters that were related to patient survival using Kaplan-Meier analysis.
Results The median (range) survival was 29.5 (1–38) months. 24, 10, 14 and 6 patients had tumour stages I, II, III and IV respectively. PET stage and tumour heterogeneity assessed by CTTA were significant independent predictors of survival (PET stage: Odds ratio 3.85, 95% confidence limits 0.9–8.09, P=0.002; CTTA: Odds ratio 56.4, 95% confidence limits 4.79–666, p=0.001). SUV was not a significantly associated with survival.
Conclusion Assessment of tumour heterogeneity by CTTA of non-contrast enhanced images has the potential for to provide a novel, independent predictor of survival for patients with NSCLC.
Key Points
• *Computed tomography is a routine staging procedure in non-small cell lung cancer*
• *CT texture analysis (CTTA) can quantify heterogeneity within these lung tumours*
• *CTTA seems to offer a novel independent predictor of survival for NSCLC*
• *CTTA could contribute to disease risk-stratification for patients with NSCLC*

Keywords Lung cancer · Survival · Computed tomography · Positron emission tomography · Texture analysis

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Introduction

Lung cancer is the leading cause of cancer death worldwide [1]. The prevalence of lung cancer is only second to breast cancer in women and prostate cancer in men. 85% of all lung cancers are non-small cell lung carcinoma (NSCLC) [2]. Following diagnosis, determination of prognosis is an important step in lung cancer management, with implications for selection of treatment options. Survival of patients with NSCLC remains relatively poor and is highly variable within groups of patients currently stratified to the same category of risk [3]. More accurate markers of prognosis therefore have the potential to advance the stratification of patients for therapy leading to improvements in health outcomes.

Tumour stage is currently the most important prognostic indicator of survival for patients with NSCLC. Tumour

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stage also indicates the suitability of patients for surgical intervention and other treatment options. Computed tomography (CT) remains an important investigation in the diagnosis of lung cancer [4] and historically CT has been used for initial tumour staging [5]. However, during the last decade, [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) has emerged as a more accurate imaging technique for the diagnosis and staging of NSCLC [6–10]. Furthermore, the intensity of FDG uptake within the primary measured as the standardised FDG uptake value (SUV) has been shown to convey prognostic information on survival [11]. However, a recent systematic review and meta-analysis was unable to confirm that the prognostic ability of SUV measurement was independent of other predictive factors such as tumour stage [11].

There is increasing interest in the use of computer analysis of CT images to improve the detection of lung nodules and their characterisation as benign or malignant [12–17]. However, the ability for computer analysis to provide prognostic information for patients with NSCLC is largely unexplored. The possibility that computer analysis of lung tumour texture could provide prognostic information is suggested by a recent study reporting an association for tumour texture with tumour stage and glucose metabolism, both recognised markers of prognosis as discussed above [18]. Furthermore, texture analysis of CT images has recently been shown to potentially provide prognostic information for patients with colorectal cancer [19]. Thus, our study aims to establish the potential for tumour heterogeneity in NSCLC as assessed by CT texture analysis to provide an independent marker of survival for patients with NSCLC.

Materials & methods

The study comprised retrospective review of archival diagnostic PET-CT imaging data from patients with NSCLC. As this study comprised a retrospective review of existing data with no patient intervention, ethical review was not required under local guidelines.

Patients

56 consecutive patients (32 men and 24 women; mean age: 67 years, range: 38–86 years) with NSCLC undergoing staging FDG PET-CT as part of their routine clinical care between April 2006 and November 2006 were included in the study. PET-CT was performed as these patients were considered potentially suitable for surgery or chemotherapy on the basis of an initial CT. The tumour stage for each patient was obtained from the clinical PET-CT reports. All clinical PET-CT examinations had been dual-reported by radiologists/nuclear medicine physicians who had been board certified for a minimum of 5 years. PET images were re-analyzed to obtain SUV_{max} measurements of FDG uptake by an operator blinded to the results of texture analysis. The patient's date of death (from any cause) was obtained from the national registry. The minimum follow-up period to ascertain the survival-time was 30 months following PET-CT, occurring in 27 (50%) patients. The maximum follow-up time was 38 months (median: 30 months). Survival time was defined as the time between the date of the PET-CT and the date of the death.

FDG PET-CT image acquisition

All images had been acquired using a GE Discovery ST PET-CT system (GE Healthcare, Waukesha, WI, USA) with both CT and PET data acquired in one procedure in accordance with a standardised protocol. The use of integrated PET-CT ensured precise spatial correlation between the PET and CT images. Patients had fasted for 6 h before the study and their height, weight and serum glucose level was recorded. PET-CT images had been acquired in the supine position 60 min after an injection of 400 MBq of ^{18}F-FDG. The CT acquisition comprised of an initial digitally acquired radiograph (10 mAs, 120 kVp, fixed rotational speed) followed by a conventional low-dose CT of the neck, chest abdomen and pelvis without contrast material (80 mAs, 140 kVp, rotational speed=0.8 s/rot, pitch=1.5, slice thickness=3.75 mm). The pixel size for the unenhanced CT images used in this study was 0.98 mm x 0.98 mm. Routine PET-CT quality assurance procedures had been carried out in accordance with manufacturer's recommendations. To enable subsequent calculation of tracer uptake expressed as the standardised uptake value, the initial activity and time, administration time, and residual activity and time had been recorded.

PET image analysis

Images from the archive were re-analysed for determination of glucose utilisation within a region of interest (ROI) constructed over the most active axial section of the lung lesion by an operator (EP) blinded to the results of CT texture analysis. The maximal tumour SUV was determined using the expression given below:

$$\mathrm{SUV} = \frac{\text{Activity concentration in the tissue}[\mathrm{Bq/g}]}{\text{Administered activity}[\mathrm{Bq}]\ \text{body weight}[\mathrm{g}]} \qquad (1)$$

In this study the maximum value of the SUV (SUV_{max}) was considered.

CT image analysis

Heterogeneity within lung tumours was assessed using TexRAD (University of Sussex, Brighton, UK), an in-house

software algorithm developed by Ganeshan et al [18]. This CT texture analysis (CTTA) methodology has previously been shown in colorectal cancer to correlate with hepatic physiology [20, 21], disease extent [22, 23] and patient survival [19, 21]. This texture analysis methodology has been shown to have low sensitivity to variations in image acquisition parameters [19].

For each NSCLC patient, the CT image with the largest cross-sectional area of the tumour was selected for texture analysis by a single operator (K.B.) under supervision from a researcher (B.G.) with 6 years' experience in texture analysis of radiographic images performed the images. Both were blinded to the results of the FDG-PET analysis. The CT slice for analysis was comparable in terms of anatomical location to the PET image employed for measuring SUV and the region of interest (ROI) enclosing the lung lesion on CT was drawn using the same guidelines as for PET image analysis. The ROI enclosing the CT lung lesion was further refined by excluding areas of fat and air with a thresholding procedure which removed from analysis any pixels with attenuation values below −50 HU.

CTTA comprised initial band-pass image filtration using a Laplacian of Gaussian (LoG) filter to produce a series of derived images of the lung lesion displaying features at different anatomical, scales from fine to coarse texture (Fig. 1). The scale was selected by altering the filter value in increments of 0.5 (see Table 1) between 1.0 (fine feature width: approximately 4 pixels or 3.92 mm) and 2.5 (coarse feature width: approximately 12 pixels or 11.76 mm). Texture features finer than 4 pixels would represent image noise and hence were not evaluated in this study. Following filtration, any pixels with negative values were assigned a value of zero.

Tumour heterogeneity was then assessed by quantifying the distribution of pixel values in each image with and without filtration as image uniformity (u), using the expression given below:

$$u = \sum_{l=1}^{k} [p(l)]^2 \tag{2}$$

where l is the grey-level (for example l=1 to k indicates grey-level from 1 to k) and $p(l)$ the probability of the

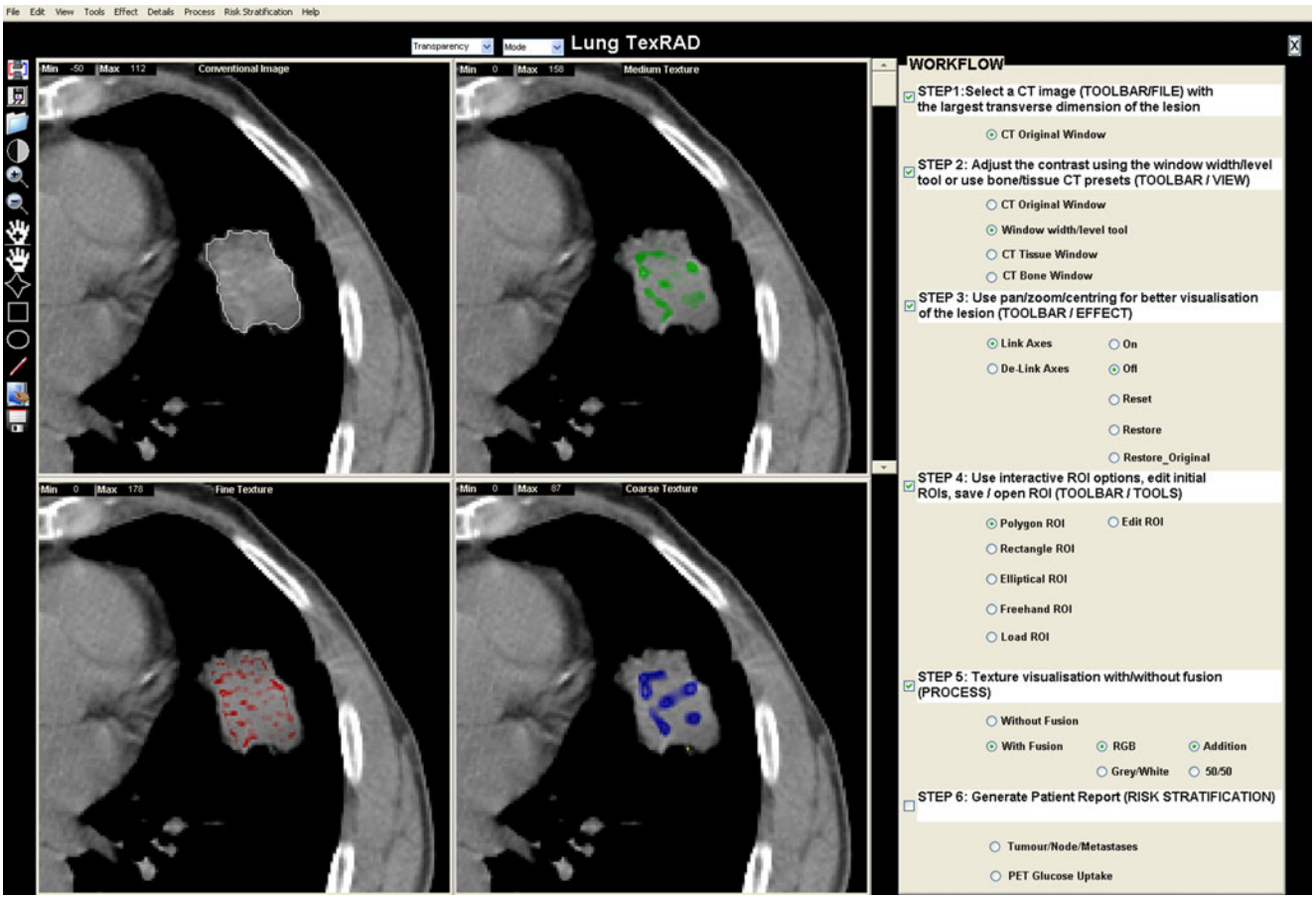

Fig. 1 Screenshot of the CTTA clinical software prototype for a NSCLC patient. This highlights the conventional CT image of the lung lesion (*top-left*), followed by the derived lung lesion filtered texture maps superimposed on the CT image—fine (*red*), medium (*green*) and coarse (*blue*) filtered texture not easily perceptible from the conventional CT image

Table 1 Filter values and the corresponding approximate widths of the filter in pixels and mm

Filter value	Filter width (Pixels)	Filter width (mm)
1.0 (fine)	4	3.92
1.5 (medium)	6	5.88
1.8 (medium)	8	7.84
2 (medium)	10	9.80
2.5 (coarse)	12	11.76

occurrence of the grey-level *l*. Low uniformity values indicate increased tumour heterogeneity.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 16.0 and MedCalc for Windows, version 9.2.0.0 (MedCalc Software, Mariakerke, Belgium). The relationships of PET stage, SUV and tumour heterogeneity with patient survival were assessed using Kaplan-Meier analysis. The thresholds for SUV and CTTA uniformity values used for survival analysis were established from receiver-operating characteristics (ROC) analysis which tested the ability of each parameter to identify patients surviving longer than the minimum follow up period of 30 months. The areas under the ROC curves were recorded and the point on the ROC curve furthest from the line of no-discrimination was considered the optimum threshold. Differences between survival curves were evaluated by a non-parametric log rank test with a *P* value of less than 0.05 considered significant. Following this Cox Regression tested whether any of the imaging parameters (CTTA, SUV or PET stage) were independent predictors of survival.

Results

Two patients were excluded as they were lost in follow-up and no information regarding their survival (alive or dead) was available. The median survival of the remaining 54 patients was 29.5 months. 27 of 54 patients died within 30 months of their PET-CT. The shortest survival time was 1 month. Based on FDG-PET imaging, the number of patients with tumour stages I, II, III and IV were 24, 10, 14 and 6 respectively. Mean (range) tumour SUV for all patients was 13.7 (3.2–34). Furthermore the location (central or peripheral) and size of primary tumour (T-stage) are given as follows. 27 of 54 primary lung tumours were central (based on any contact with the mediastinum or hila). The number of patients with T-stage—T1, T2, T3 and T4 were 11, 25, 9 and 9 respectively. Also as expected centrally located primary tumours were significantly larger in size (higher T-stage) as compared with those located at the periphery ($P<0.005$).

Survival analysis

The median values and distribution statistics for CTTA uniformity at each filter value as well as without filtration and for SUV are shown in Table 2. Table 3 summarises the results of the ROC analysis along with the derived threshold values for texture and SUV parameters and the results of survival curve analysis expressed as the *P*-value. Kaplan-Meier survival curves were significantly different for tumour heterogeneity assessments based on CT image features with a width of either 4 pixels (i.e. filter value 1.0, fine) or 12 pixels (i.e. filter value 2.5, coarse) wide. Patients who had heterogeneous tumours with low uniformity values demonstrated poorer survival. The greatest separation was achieved by a threshold uniformity value of 0.624 using a filter value of 2.5 ($P<0.0014$, Fig. 2a). None of 5 patients with uniformity values below 0.624 survived more than 2.5 years as compared with 26 of 49 patients (53%) above the threshold. Survival analysis based on SUV was not statistically significant (Fig. 2b) while PET stage was significantly associated with survival ($P<0.005$, Fig. 2c). The best CT texture parameter (filter value 2.5) was entered as a predictor into a Cox Regression (due to multicolinearity between the texture parameters) along with

Table 2 Median values and distribution statistics for CT lung lesion texture and PET glucose uptake parameters

Parameter	Median	Range	Kurtosis	Skewness
CT Texture (uniformity)				
Without filtration	0.015	0.008–0.035	6.144	1.743
Filter value=1.0 (fine)	0.509	0.360–0.923	0.591	0.993
Filter value=1.5 (medium)	0.658	0.416–1.000	−0.954	0.285
Filter value=1.8 (medium)	0.750	0.448–1.000	−1.165	−0.139
Filter value=2.0 (medium)	0.839	0.476–1.000	−1.004	−0.476
Filter value=2.5 (coarse)	0.935	0.551–1.000	−0.339	−0.972
PET				
Glucose uptake (SUVmax)	12.6	3.2–34	1.557	1.048

Table 3 Summary of receiver operating characteristics (ROC) analysis results and the *P*-value for the difference in Kaplan-Meier survival curves for each threshold. (AUC=area under ROC curve)

Parameter	AUC	Threshold	Alive/Dead above threshold	Alive/Dead below threshold	*P* – value for survival analysis
CT texture (uniformity)					
Without filtration	0.579	<=0.012	24/22	2/6	0.0892
Filter value=1.0 (fine)	0.583	<=0.431	25/19	1/9	0.0015
Filter value=1.5 (medium)	0.564	<=0.477	25/24	1/4	0.1219
Filter value=1.8 (medium)	0.581	<=0.761	14/12	12/16	0.3869
Filter value=2.0 (medium)	0.601	<=0.924	10/7	16/21	0.2127
Filter value=2.5 (coarse)	0.597	<=0.624	26/23	0/5	0.0014
PET					
Glucose uptake (SUVmax)	0.578	>9.1	18/23	8/5	0.1374
PET Stage	0.703	> II	4/16	22/12	0.002

SUV and PET stage. CT texture and PET stage were significant independent predictors of survival (Table 4). There were no significant interactions between CT texture and PET stage or SUV.

Discussion

The results from our study demonstrate the potential for tumour heterogeneity of lung lesions as assessed by CTTA of unenhanced images to provide a novel, independent predictor of survival for patients with NSCLC. The prognostic information from CTTA appears complementary to tumour stage and, in our series, more predictive that measurements of tumour FDG uptake. The technique could therefore allow risk-stratification of patients within existing tumour stages with possible implications for therapy selection and a move towards 'personalised medicine'.

The use of CTTA as a quantitative prognostic biomarker represents an extension to existing computer-assisted diagnosis (CAD) tools which have largely focused on detection of lung cancer. Although some research studies have used texture analysis to predict whether a lung lesion is benign or malignant [24–26] we are unaware of any previous studies that have related texture analysis of lung lesions to survival. By analysing existing CT images, the prognostic information from CTTA is obtained without additional radiation exposure. CTTA assessments of tumour heterogeneity offer a potential adjunct to routine PET-CT examinations performed for staging of NSCLC. The technique could also be applied to dedicated CT examinations, as not all NSCLC patients necessarily proceed to PET-CT, for example when CT has demonstrated inoperable disease or multiple metastases. However, dedicated CT examinations do not always include acquisition of images without intravenous contrast material and therefore further studies assessing the application of CTTA to contrast enhanced images may be helpful

Heterogeneity is a well recognised feature of malignancy that is associated with adverse tumour biology. Heterogeneity of the tumour blood supply in particular is associated with the presence of hypoxic voids which in turn result in oxidative stress, promotion of survival factors and genomic instability [27]. Tissue responses to hypoxia lead to increased tumour aggression and treatment resistance [28]. A heterogeneous blood supply will also be associated with poor delivery of chemotherapeutic agents to areas of low vascularity leading to impaired treatment response. We hypothesise that this biological heterogeneity is associated with a less uniform distribution of attenuation values within tumours on CT. However, selection of image features of a particular size through image filtration is required to identify heterogeneity at the appropriate anatomical scale and to eliminate heterogeneity due to image noise. We are currently undertaking pathological studies to establish correlations between CTTA assessments of lung tumour heterogeneity and markers of tumour hypoxia. Preliminary results indicate tumour heterogeneity depicted and quantified as CTTA may indirectly reflect areas of tumour hypoxia [29], demonstrating the potential to act as imaging correlates for tumour hypoxia.

Unlike the findings of a recent meta-analysis [11], we did not find tumour uptake of FDG measured as SUV to be a significant predictor of survival in NSCLC. However, not all papers included in the meta-analysis demonstrated a relationship between SUV and survival and our study may have had insufficient statistical power to confirm this association. It is also recognised that SUV measurements are subject to variability due to sensitivity to body composition and habitus, length of uptake period, plasma glucose, PET system performance and partial volume effects [30]. It is feasible that quantitative parameters

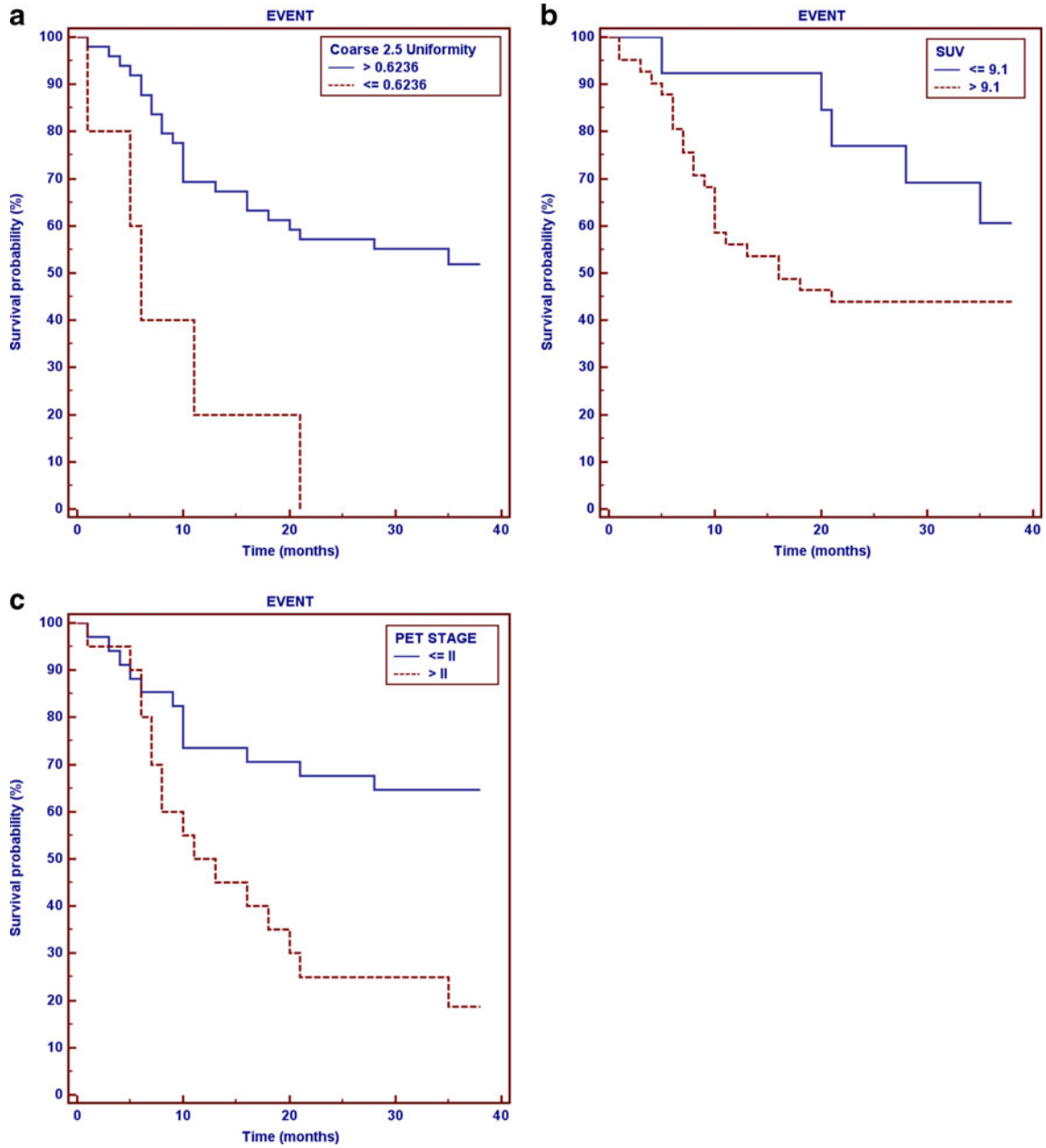

Fig. 2 Kaplan-Meier survival curves for NSCLC patients with lung lesions separated by **a** CT Texture analysis **b** SUV from PET and **c** PET stage. Survival curves were significantly different for CT texture analysis ($P<0.002$), PET stage ($P<0.005$) but not for SUV

Table 4 The results of Cox regression analysis

Parameter	Odds Ratio	95% Confidence Limits	P-value
CT Texture	56.4	4.79–665	0.001
PET Stage	3.85	1.65–8.97	0.002
SUV	2.70	0.9–8.09	0.076
Interactions			
CT texture with PET stage	0.094	0.007–1.18	0.067
CT texture with SUV	0.226	0.011–4.69	0.336

derived from CTTA are less prone to such variability. Indeed, the CTTA methodology used in our study has been shown to be relatively insensitive to variations in CT acquisition parameters, increasing its potential for widespread application [19]. However, there is a need for research to assess the impact of other possible sources of variability on CTTA before broader dissemination. Furthermore unavailability of treatment information for the patients in our study was a limitation. Future studies need to evaluate the ability of CTTA to predict patient survival independent of treatment.

In conclusion, assessment of tumour heterogeneity by CTTA of unenhanced images has the potential to provide a novel, independent predictor of survival for patients with NSCLC. Larger prospective multicentre studies are needed to confirm this potential and to establish the role of CTTA as a prognostic biomarker in oncology.

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