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ORIGINAL ARTICLE

FDG PET/CT texture analysis for predicting the outcome of lung cancer treated by stereotactic body radiation therapy

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Abstract
Introduction With ^{18}F-FDG PET/CT, tumor uptake intensity and heterogeneity have been associated with outcome in several cancers. This study aimed at investigating whether ^{18}F-FDG uptake intensity, volume or heterogeneity could predict the outcome in patients with non-small cell lung cancers (NSCLC) treated by stereotactic body radiation therapy (SBRT).
Methods Sixty-three patients with NSCLC treated by SBRT underwent a ^{18}F-FDG PET/CT before treatment. Maximum and mean standard uptake value (SUVmax and SUVmean), metabolic tumoral volume (MTV), total lesion glycolysis (TLG), as well as 13 global, local and regional textural features were analysed. The predictive value of these parameters, along with clinical features, was assessed using univariate and multivariate analysis for overall survival (OS), disease-specific survival (DSS) and disease-free survival (DFS). Cutoff values were obtained using logistic regression analysis, and survivals were compared using Kaplan-Meier analysis.
Results The median follow-up period was 27.1 months for the entire cohort and 32.1 months for the surviving patients. At the end of the study, 25 patients had local and/or distant recurrence including 12 who died because of the cancer progression. None of the clinical variables was predictive of the outcome, except age, which was associated with DFS (HR 1.1, $P = 0.002$). None of the ^{18}F-FDG PET/CT or clinical parameters, except gender, were associated with OS. The univariate analysis showed that only dissimilarity (D) was associated with DSS (HR = 0.822, $P = 0.037$), and that several metabolic measurements were associated with DFS. In multivariate analysis, only dissimilarity was significantly associated with DSS (HR = 0.822, $P = 0.037$) and with DFS (HR = 0.834, $P < 0.01$).
Conclusion The textural feature dissimilarity measured on the baseline ^{18}F-FDG PET/CT appears to be a strong independent predictor of the outcome in patients with NSCLC treated by SBRT. This may help selecting patients who may benefit from closer monitoring and therapeutic optimization.

Keywords ^{18}F-FDG PET/CT · Non-small cell lung cancer · Stereotactic body radiation therapy · Textural analysis · Heterogeneity · Prognostic factor

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Introduction

Lung cancer is the leading cause of cancer death among both men and women [1], and NSCLC represents approximately 80 % of them. The survival rate of lung cancer is poor with a global 5-year survival rate lower than 20 %. The outcome becomes more favorable when the cancer is detected early, thus allowing a curative treatment, with survival rates ranging from 43 % to 79 % [2–5]. Survival is nevertheless variable among groups considered as having the same risks [6] and it is therefore essential to develop new parameters to predict the

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response of a tumor to a specific treatment. Lobectomy is the current standard of care for the treatment of early-stage NSCLC, but many patients are inoperable because of comorbidities, especially chronic obstructive pulmonary disease (COPD). SBRT is an alternative treatment for these patients and it has shown good results on the overall survival and local control with a low toxicity [7, 8].

^{18}F-FDG PET/CT is recognised as an essential tool in the staging of lung cancer [9] and valuable in the tumoral target delineation for radiotherapy [10]. Furthermore, it has been suggested that ^{18}F-FDG PET/CT could be used as a predictor of outcome in patients with NSCLC treated by SBRT [11, 12].

Several studies have shown that textural analysis of baseline ^{18}F-FDG PET/CT has predictive and prognostic significances in several types of cancers, including oropharyngeal [13], esophageal [14, 15] and sarcoma [16]. Cook et al. have shown that high coarseness was associated with a poor prognosis in NSCLC treated by chemoradiotherapy [17]. Tixier et al. also reported an association between shorter survival and high tumour volume, uptake intensity and heterogeneity, in a population of NSCLC treated with surgery, chemotherapy or radiation therapy, alone or in combination [18]. Using models, Fried et al. recently demonstrated the added value of the ^{18}F-FDG PET spatial heterogeneity analysis in the prognostic assessment in a population of 195 patients with stage III NSCLC [19]. Cook et al. showed in a population of 40 patients with NSCLC treated with Erlotinib that a reduced of heterogeneity after 6 weeks of treatment was associated with both the CT response at 12 weeks according to the RECIST criteria and the overall survival [20]. Finally, Pyka et al. recently demonstrated in a population of 45 patients with early stage NSCLC treated by SBRT that FDG-PET texture features had a predictive value on the local control and the disease specific survival [21].

We hypothesised that metabolic heterogeneity as assessed by texture analysis is a better predictor of outcome that metabolic volume and intensity in patients with early-stage lung cancer treated by SBRT.

Materials and methods

Patients

The retrospective study was approved by the Ethics Committee of the CHU of Liège. Sixty-three patients (mean age, 72.7 y ; 36 men, 27 women) with newly diagnosed NSCLC treated exclusively with SBRT from April 2010 through January 2013 were included in the study. There were 28 patients with adenocarcinoma, 20 with squamous cell carcinoma, 1 with large cell carcinoma and 14 without pathological confirmation but showing a clinical and radiological pattern highly suggestive of primary lung cancer. According to the AJCC 7th Edition TNM classification, all the patients had stage I disease. There were 30 patients with T1a, 18 with T1b and 15 with T2a. No patient had node involvement or metastatic disease. All these patients were considered inoperable because of comorbidities, mainly COPD. The clinical characteristics of patients are summarised in Table 1. All the patients were exclusively treated by SBRT in our institution using a Cyberknife Robotic Radiosurgery System. They received 45 to 60 Grays (Gy) in 3 to 5 fractions, and the treatment was complete for everyone.

^{18}F-FDG PET/CT acquisition

Every patient underwent ^{18}F-FDG PET/CT prior to any treatment, for tumor staging and target volume delineation. It was performed at a median of 9 days before the first day of SBRT (mean 10, range 3–41). ^{18}F-FDG PET/CT studies were all acquired using a GEMINI TF Big Bore PET/CT system, except one patient on GEMINI TF 16 PET/CT system (Philips Medical Systems, Cleveland, OH, USA); 75 minutes after intravenous injection of 269 MBq of ^{18}F-FDG (range 112–411 MBq; depending on patient's weight). Patients fasted for at least 6 hours before the injection and the median glycemia was 93 mg/dl (range: 73–167). A low dose CT (5 mm slice thickness; tube voltage: 120 kV and tube current–time product: 50 to 80 mAs depending on the patient's weight) was performed without injection of intravenous contrast agent, followed by a PET emission scan of 90 seconds per bed position performed from the upper thigh to the base of skull. Images were reconstructed with standard $4 \times 4 \times 4$ mm^3 voxels using iterative list mode time-of-flight algorithm and corrections for attenuation, dead-time, random and scatter events were applied.

^{18}F-FDG PET/CT analysis

A volume of interest (VOI) was drawn around the tumour by a single observer, who was unaware of the outcome of patients. An automatic segmentation was performed inside this volume using a Fuzzy Locally Adaptive Bayesian (FLAB) algorithm, which has shown both robustness and repeatability [22–24]. Metabolic tumour volume (MTV), SUVmax and SUVmean were measured inside these segmented VOIs, and the total lesion glycolysis (TLG) was calculated according to the formula: TLG = SUVmean x MTV [25].

The texture parameters were obtained using a homemade software implemented with the cross-platform Python language. The algorithms used to obtain these parameters are developed in the supplemental data. We used a resampling of 64 grays-levels for all the analysis, as previously suggested by Hatt et al. [26]. We measured some first-order features based on histogram analysis, which identifies the intensity distribution on the original image: SUVmin, SUVmax, SUVmean, SUV standard deviation (SUVSD), coefficient of variation (COV), skewness and excess kurtosis [27]. Local features were measured using co-occurrence matrices that study the relationships between couples of voxels,

Table 1 Clinical characteristics of patients

Characteristics	n
Age (years)	73 ± 8.5 (Range : 56–92)
Sex	
Male	36 (57 %)
Female	27 (43 %)
WHO Performance status	
0	16 (26 %)
1	33 (52 %)
2	14 (22 %)
3	0 (0 %)
Histology	
Adenocarcinoma	28 (44 %)
Squamous cell carcinoma	20 (32 %)
Large cell carcinoma	1 (2 %)
Unknown	14 (22 %)
cT-Stage	
T1a	30 (47.6 %)
T1b	28 (28.6 %)
T2a	15 (23.8 %)
Median time between PET/CT & treatment (days)	9 (Range : 3–41)
Treatment Dose (Gy)	
45	9 (14 %)
50	3 (5 %)
51	2 (3 %)
54	2 (3 %)
60	47 (75 %)
Median follow-up (months)	
Overall	27.1 (Range 5.5–49.1)
Surviving patients	32.1 (Range: 9.3–49.1)

giving the second-order features angular second moment (ASM), contrast, entropy, correlation, homogeneity and dissimilarity [14, 28, 29]. Other local features were obtained with neighbourhood intensity-difference matrix (NGTDM) giving the high-order features coarseness, contrast (contrast NGTDM) and busyness, which describe the differences between each voxel and its neighbours [14, 17, 30]. Finally, we studied 2 regional features of heterogeneity based on intensity-size-zone matrix that study characteristics of homogenous zones: intensity variability and size-zone variability [14].

The ^{18}F-FDG PET/CT results are summarised in Table 2.

Study endpoints

The endpoints were the overall survival (OS), the disease-specific survival (DSS) and the disease-free survival (DFS). DSS was defined as the time from the beginning of the treatment to the time of cancer-related death. DFS was defined as the time from the beginning of SBRT to the time of recurrence. Follow-up of the patients was performed through clinical and imaging means, including chest CT and/or ^{18}F-FDG PET/CT. We retrospectively collected the data of the patient's outcome in the medical records. Patients alive were censored at the time of the last clinical follow-up. Recurrence was defined by the formal progression of the treated lesion and/or by the occurrence of a new metastatic lesion.

Statistical analysis

All statistical analyses were performed using the SAS statistical package (9.3). To identify the predictors of OS, DSS and DFS, all the clinical parameters and the intensity, volume-based and textural ^{18}F-FDG PET/CT parameters were tested using a univariate Cox Proportional Hazard Regression model. A stepwise regression test including only the parameters with univariate *P*-value lower than 0.2 was applied to identify independent parameters in the multivariate analysis. The cutoff, which maximizes the sensitivity (Se) and the specificity (Sp), was calculated by mean of the logistic regression for the parameters that were significant according to the multivariate analysis. Survivals were

Table 2 Values of FDG PET intensity, volume-based and textural analysis features

Feature	Mean	SD	Min	Max
SUVmin	2.6	1.7	0.47	8.35
SUVmax	7.1	5.0	1.1	25.4
SUVmean	4.1	2.7	0.73	13.47
Skewness	0.69	0.24	0.03	1.27
SUV SD	1.14	0.84	0.15	4.36
Excess Kurtosis	−0.40	0.44	−1.17	1.12
COV	0.26	0.05	0.12	0.38
MTV	6.33	5.80	0.70	32.58
TLG	34.56	46.60	0.69	178.37
ASM	0.021	0.027	0.002	0.197
Contrast	551.0	190.08	167.60	1054.30
Entropy	4.32	0.92	1.73	6.39
Correlation	0.138	0.169	−0.314	0.553
Homogeneity	0.119	0.018	0.085	0.198
Dissimilarity	18.67	3.39	9.77	25.87
Coarseness	2.61	1.33	0.36	5.97
Contrast NGTDM	11.61	28.53	0.66	219.50
Busyness	0.058	0.031	0.022	0.238
Intensity variability	2.81	1.76	1.20	10.30
Size-zone variability	0.0206	0.0151	0.0012	0.0909

then compared using Kaplan-Meier curves and log-rank tests. Finally, Spearman's rank correlation coefficients between the variables were calculated. Results were considered statistically significant at the 5 % critical level ($P<0.05$).

Results

Median follow-up was 27.1 months (range: 165–1471 days). It was 32.1 months for the surviving patients (range: 278–1471 days). At the end of the study, 27 patients (42.9 %) died, because of the cancer progression (n = 12, 44.4 %) or another cause (n = 15, 55.6 %).

Overall survival

Median OS was 38.9 months. Survival probability was 87 % at 1 year, 74 % at 2 years, 55 % at 3 years and 40 % after 4 years. Only the gender was a significant parameter with regard to OS: Men had a shorter survival than women (HR = 2.37, $P=0.04$). None of the other clinical or PET/CT parameters showed a significant association.

Disease specific survival

Median DSS was not reached at the end of the study. Survival probability was 93 % at 1 year, 86 % at 2 years and 75 % after 4 years. None of the clinical parameters showed significant association with DSS. Using the Cox univariate analysis, only dissimilarity (HR = 0.822, $P=0.037$) was a significant predictor of DSS (Table 3). In the multivariate analysis including all the parameters with a P-value lower than 0.2 in the univariate analysis, only dissimilarity was significantly associated with DSS (HR = 0.822, $P=0.037$) (Table 4). Using a cutoff of 18, obtained with a logistic regression analysis, the logrank test with Kaplan-Meier analysis of the dichotomized values only showed a trend towards association between low dissimilarity value and higher risk of death ($P=0.09$). Patients with dissimilarity of 18 or less (n = 28) have a 3-years DSS of 62 %, compared to 87 % for the others (n = 35) (Fig. 1).

Finally, we formed various subgroups of patients according to both dissimilarity and MTV in relation with cutoffs obtained through logistic regression (MTV 7.0 and D 18.0). Only 3 groups were created because there was no patient with a MTV > 7.0 and a dissimilarity > 18.0. The group of patients with MTV ≤ 7 and D ≤ 18 (n = 12) had a 3-years DSS of 58.9 %, compared with 63.8 % in the group with MTV > 7 and D ≤ 18 (n = 16), and 87.4 % in the group with MTV ≤ 7 and D > 18 (n = 35). It is only a trend however, as the relationship was not statistically significant (Cox proportional hazards regression $P=0.24$; and log-rank test $P=0.21$) (Fig. 2).

Disease free survival

At the end of the study, 25 patients had recurrent disease: local sites only (n = 7), both local and distance sites (n = 2), mediastinal nodes only (n = 1), pleura or lung (n = 9) and other distant sites (n = 6). The disease-free-survival probability was 75 % at 1 year, 61 % at 2 years and 57 % after 3 years. Age was the only clinical parameter that was associated with DFS (HR = 1.1, $P=0.002$). Using the Cox univariate analysis, several PET/CT parameters were significantly associated with DFS (Table 3). In the multivariate analysis, only age and dissimilarity were significantly associated with DFS (HR = 1.082, $P=0.01$ and HR = 0.834, $P<0.01$ respectively) (Table 4). A cutoff of 18.4 was found with a logistic regression analysis and the log-rank test confirmed that a low dissimilarity was associated with a higher risk of recurrence ($P=0.003$) (Fig. 1). Patients with dissimilarity lower than 18.4 (n = 30) have a 3-years DFS of 34 %, compared with 79 % for the others (n = 33).

By combining dissimilarity and MTV in relation with cutoffs obtained through logistic regression (MTV 6.4 and D 18.4), 3 groups were created, as there was no patient for the combination between a MTV > 6.4 and a D > 18.4. Median DFS was 785 days for the group with MTV ≤ 6.4 and D ≤ 18.4 (n = 10), 969 days for the group with MTV > 6.4 and D ≤ 18.4 (n = 20), and it was not reached after 1470 days for the group with MTV ≤ 6.4 and D > 18.4 (n = 33). The 3-years DFS of these groups was respectively of 27 %, 40 % and 78 %. Both the Cox proportional hazards regression and the

Table 3 Cox univariate statistical analysis results

	DSS		DFS	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*
Age	1.064 (0.992–1.142)	0.083	1.100 (1.035–1.169)	0.002
Radiation Dose	0.980 (0.890–1.081)	0.686	0.974 (0.911–1.042)	0.443
Sex	2.881 (0.772–10.76)	0.116	1.277 (0.573–2.846)	0.550
Karnofsky PS	- (*)	0.860	- (*)	0.480
T stage	- (*)	0.205	- (*)	0.330
Histology	- (*)	0.160	- (*)	0.472
SUVmin	1.160 (0.843–1.595)	0.362	1.23 (0.991–1.485)	0.062
SUVmax	1.055 (0.950–1.171)	0.318	1.069 (1.001–1.141)	0.045
SUVmean	1.084 (0.892–1.319)	0.417	1.122 (0.992–1.269)	0.067
Skewness	0.706 (0.057–8.724)	0.786	0.735 (0.133–4.059)	0.724
SUV SD	1.258 (0.651–2.432)	0.494	1.393 (0.936–2.074)	0.102
Excess Kurtosis	1.649 (0.434–6.272)	0.463	1.364 (0.543–3.425)	0.509
COV	0.013 (0.000–2249)	0.479	0.030 (0.000–89.241)	0.390
MTV	1.055 (0.979–1.136)	0.161	1.046 (0.996–1.099)	0.073
TLG	1.008 (0.998–1.017)	0.120	1.008 (1.001–1.015)	0.023
Contrast	0.997 (0.993–1)	0.063	0.996 (0.993–0.999)	0.002
Entropy	1.514 (0.806–2.844)	0.197	1.719 (1.119–2.640)	0.013
Dissimilarity	0.822 (0.683–0.988)	0.037	0.806 (0.706–0.920)	0.001
Coarseness	1.427 (0.956 -2.130)	0.082	1.467 (1.102–1.951)	0.009
Contrast NGTDM	0.940 (0.837 -1.056)	0.299	0.906 (0.823–0.997)	0.043
Busyness	0.695 (0.000–∞)	0.967	0.029 (0.000–∞)	0.619
Intensity variability	1.259 (0.990–1.601)	0.060	1.207 (1.027–1.418)	0.022

(*) No global HR for variables with more than 2 modalities

log-rank test with Kaplan-Meier analysis confirmed the significant difference of DFS between groups ($P = 0.01$ and 0.02, respectively). Multiple comparisons were then made between groups and showed the absence of significant difference between the group with a MTV > 6.4 and D ≤ 18.4 and the group with MTV ≤ 6.4 and D ≤ 18.4 ($P = 0.75$), whereas these groups presented significant differences in DFS with the group with a MTV ≤ 6.4 and D > 18.4 ($P = 0.01$ for both) (Fig. 2).

Correlations among PET parameters

Several PET parameters (intensity, volume-based parameters, heterogeneity) were correlated with each others. The Spearman's correlation coefficients are listed in the supplementary data.

Discussion

SBRT is an alternative treatment for patients with early-stage inoperable NSCLC and shows good results in terms of both local control and survival [7, 8]. In our series, disease specific survival rate was 86 % at 2 years, which is close to values previously reported by others [7]. There is a need to develop reliable prognostic tools that would help personalising the therapeutic management, adapting the radiation dose, and

Table 4 Multivariate statistical analysis results

	DSS		DFS	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*
Dissimilarity	0.822 (0.683–0.988) 0.984)	0.037	0.834 (0.730–0.954)	0.008
Age	1.035 (0.715–1.120)	0.465	1.082 (1.019–1.150)	0.010

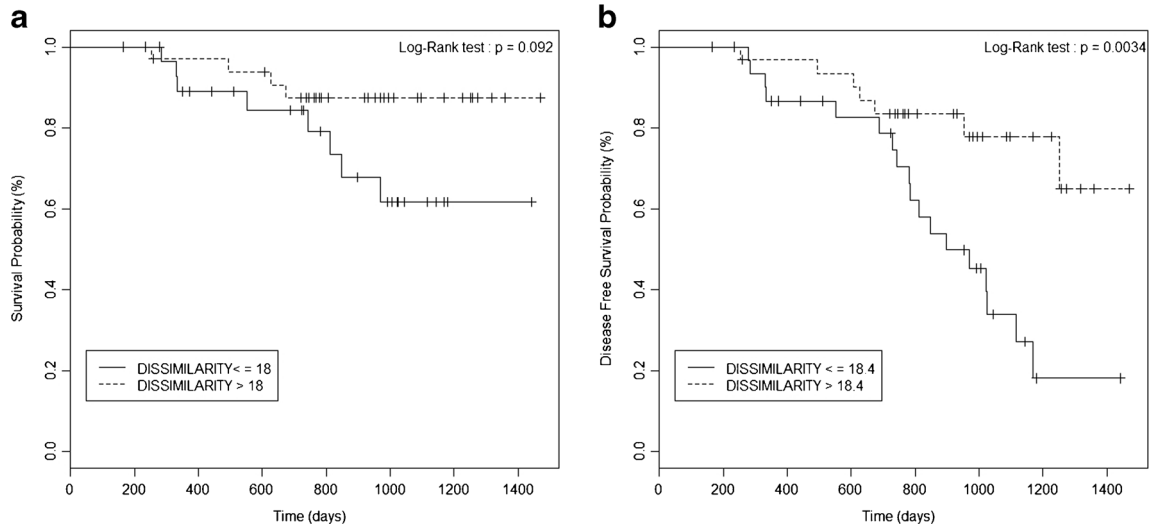

Fig. 1 Kaplan-Meier curves of the dissimilarity which was significantly associated with DSS (**a**) and DFS (**b**). The cutoff values were estimated by logistic regression analysis and *P*-values refer to the log-rank test

guiding the monitoring of patients according to risk of recurrence and specific mortality.

The prognostic value of the baseline ^{18}F-FDG PET/CT for risk stratification in early-stage NSCLC exclusively treated with SBRT has been studied by several investigators, with highly conflicting results. The SUVmax was predictor of the outcome in some studies [11, 12, 31–34] but not in others [35–39]. In those studies, both the outcome measure, i.e. OS, DFS, DSS, local or distant progression and the optimal cutoff value for the SUVmax were variable. These results highlight the many limitations of SUVmax for assessing the metabolic activity of a tumour and predicting the outcome, in particular its variability and its sensitivity to statistical noise. Our results show a similar trend, as the SUVmax was not predictor of DSS and predictor of DFS only in univariate analysis with a *P*-value close to the level of significance, and the cutoff value determined by logistic regression analysis did not allow to reliably differentiate the groups according to their survival. SUVmean was not correlated with OS, DSS or DFS, either.

Volume-based parameters such as MTV and TLG take into account the whole tumour instead of a single voxel, but again, the results available in the literature are very diverse. MTV, using a 2.5 SUVmax threshold and TLG, using 50 % and 60 % intensity thresholds were significant predictors of DFS but not of OS [11]. Conversely, according to Abelson et al., MTV, using SUVmax thresholds of 7 and 10, predicted OS but not DFS [40]. Vu et al. found that MTV and TLG were not correlated with DFS or OS [35]. In our series, volumetric parameters were not predictors of DSS. TLG was predictor of DFS in the univariate analysis only, while MTV

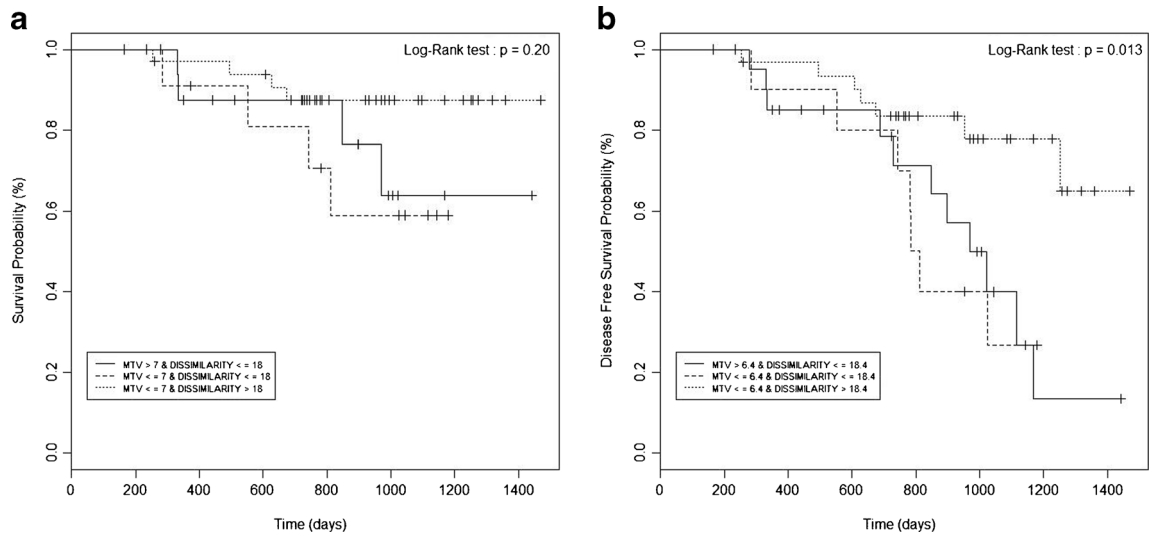

Fig. 2 Kaplan-Meier curves using combination of dissimilarity and MTV for DSS (**a**) and DFS (**b**). The cutoff values were estimated by logistic regression analysis and *P*-values refer to the log-rank test. There was no patient for the combination between a MTV higher than the cutoff and a dissimilarity higher than the cutoff

held no prognostic significance whatsoever. Hence, even though FDG PET/CT plays a major role in the management of NSCLC patients, it is essentially through its impact on staging as the metabolic characteristics of the tumour has currently no clinical role in terms of prognostic information. On the other hand, the evaluation of tumour heterogeneity using textural features has been reported a promising prognostication tool in various types of cancers, but very limited data is available regarding early-stage NSCLC treated by irradiation. The only report in a population of early-stage NSCLC treated with SBRT analysed a limited set of textural features. It showed that tumours with a low level of entropy, i.e. with high heterogeneity, had longer DFS independent from other prognostic factors [21]. Like many other heterogeneity features, entropy is strongly associated to the volume, and negatively correlated to dissimilarity, which in our series, clearly stands out among a large number of parameters. Dissimilarity is the only parameter, whether metabolic or clinical, significantly associated with DSS and DFS in the multivariate analysis. It is a second-order local feature that represents the variation of grey level pairs in an image. The relationship between heterogeneity of the PET signal and either tumour biology or patient outcome is not clear. Higher levels of dissimilarity was described as significantly associated with longer DFS in a population of NSCLC [18], and it was the only parameter significantly associated with longer OS in a cohort of oesophageal cancers [26]. Even though there is a strong negative correlation between MTV and dissimilarity, this relation was not linear as showed by the distribution curve in supplementary data, and dissimilarity appears to bring additional information compared to intensity and volume-based parameters, regarding both the risk of recurrence and the disease-specific mortality. This observation appears even more evident by comparing the survival of patient groups formed by the combination of dissimilarity and MTV values. The patients with low dissimilarity have a similarly poor prognosis regardless of the MTV, in contrast to the group with low MTV and high dissimilarity (Fig. 2). Also, it has been shown in ultrasonography that malignant breast tumours had a lower dissimilarity than benign tumours [41]. Obviously, such results deserve further investigations.

Tumour heterogeneity may be visually assessed but it has been showed that texture analysis improves the reproducibility [18]. In fact, the choice of the segmentation algorithm is a major contributor to the variability of the heterogeneity measurements using texture analysis. With this regard, the FLAB algorithm has showed previously its robustness and reproducibility. On the other hand, respiratory motions cause blurring artefacts which can disturb values of the texture analysis and correction of this phenomenon can improve the results [42].

We find these results quite encouraging, as we could have expected a somewhat lower independent prognostic value for the texture features, as the MTV of the tumours evaluated in the current study was 6.3 cc on average, which is below the threshold of 10 cc previously suggested [26]. Our work confirms in a larger population that PET texture analysis of small-volume NSCLC could predict the response to SBRT, more reliably than the metabolic volume. In view of the strong correlations between local heterogeneity features and MTV for the lesions with small volume, dissimilarity seems to be the best parameter in this indication.

Conclusion

The textural analysis of the baseline ^{18}F-FDG PET/CT appears to be a strong independent predictor of the outcome in patients with NSCLC treated by SBRT. Dissimilarity was the sole parameter associated with both DFS and DSS. The potential clinical implications need to be studied in a prospective fashion.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures were performed in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study design and exemption from informed consent were approved by the Institutional Review Board of Liege University Hospital.

Informed consent For this type of study formal consent is not required.

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