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ORIGINAL ARTICLE

Metabolic tumor burden quantified on [^{18}F]FDG PET/CT improves TNM staging of lung cancer patients

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Abstract

Purpose The purpose of our study was to test a new staging algorithm, combining clinical TNM staging (cTNM) with whole-body metabolic active tumor volume (MATV-WB), with the goal of improving prognostic ability and stratification power.

Methods Initial staging [^{18}F]FDG PET/CT of 278 non-small cell lung cancer (NSCLC) patients, performed between January/2011 and April/2016, 74(26.6%) women, 204(73.4%) men; aged 34-88 years (mean ± SD:66 ± 10), was retrospectively evaluated, and MATV-WB was quantified. Each patient's follow-up time was recorded: 0.7-83.6 months (mean ± SD:25.1 ± 20.3).

Results MATV-WB was an independent and statistically-significant predictor of overall survival ($p < 0.001$). The overall survival predictive ability of MATV-WB (C index: mean ± SD = 0.7071 ± 0.0009) was not worse than cTNM (C index: mean ± SD = 0.7031 ± 0.007) ($Z = -0.143$, $p = 0.773$). Estimated mean survival times of 56.3 ± 3.0 (95%CI:50.40-62.23) and 21.7 ± 2.2 months (95%CI:17.34-25.98) (Log-Rank = 77.48, $p < 0.001$), one-year survival rate of 86.8% and of 52.8%, and five-year survival rate of 53.6% and no survivors, were determined, respectively, for patients with MATV-WB < 49.5 and MATV-WB ≥ 49.5. Patients with MATV-WB ≥ 49.5 had a mortality risk 2.9-5.8 times higher than those with MATV-WB < 49.5 (HR = 4.12, $p < 0.001$). MATV-WB cutoff points were also determined for each cTNM stage: 23.7(I), 49.5(II), 52(III), 48.8(IV) ($p = 0.029$, $p = 0.227$, $p = 0.025$ and $p = 0.001$, respectively). At stages I, III and IV there was a statistically-significant difference in the estimated mean overall survival time between groups of patients defined by the cutoff points ($p = 0.007$, $p = 0.004$ and $p < 0.001$, respectively). At stage II ($p = 0.365$), there was a clinically-significant difference of about 12 months between the groups. In all cTNM stages, patients with MATV-WB ≥ cutoff points had lower survival rates. Combined clinical TNM-PET staging (cTNM-P) was then tested: Stage I < 23.7; Stage I ≥ 23.7; Stage II < 49.5; Stage II ≥ 49.5; Stage III < 52; Stage III ≥ 52; Stage IV < 48.8; Stage IV ≥ 48.8. cTNM-P staging presented a superior overall survival predictive ability (C index = 0.730) compared with conventional cTNM staging (C index = 0.699) ($Z = -4.49$, $p < 0.001$).

Conclusion cTNM-P staging has superior prognostic value compared with conventional cTNM staging, and allows better stratification of NSCLC patients.

Keywords [^{18}F]FDG PET/CT · Quantification · Tumor burden · Prognostic value · Lung cancer

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Introduction

In non-small cell lung cancer (NSCLC) patients, therapeutic decisions as well as prognostic predictions are based on staging criteria such as those established by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), generically known as the TNM (tumor, node, metastases) classification system [1]. Although secondary to clinical TNM staging (cTNM), clinical and pathological aspects that influence prognosis and may be determinant for the therapeutic orientation, are also evaluated in the staging process. Examples of these aspects are age, gender, tumor histology and molecular characterization, performance status, weight loss, and previous treatments [2, 3].There are wide variations in the overall survival of NSCLC patients, even among those who are included in the same cTNM stage and have similar clinical and pathological features. This finding suggests that cTNM staging is not a precise predictor of prognosis [4, 5]. In cTNM staging, primary lung tumors are measured using only one dimension, and the presence and location of nodal and distant metastases are identified. Only the description "T", referring to the measure of the primary tumor, provides information about the tumor size. However, it is not a volumetric measurement, and it does not take into account the degree of metabolic activity of the lesion. Furthermore, the "N" and "M" indicate the presence of lymph node and distant metastases, respectively, but do not consider the metabolic active metastatic volume [6].

Positron Emission Tomography/Computed Tomography (PET/CT) with ^{18}F-labeled 2-deoxy-D-glucose ([^{18}F]FDG) has well-established indications for diagnosis, staging, treatment planning, evaluation of response to therapy and follow-up of patients with cancer, including NSCLC [7]. The information provided by [^{18}F]FDG PET/CT result from the visual interpretation of the images complemented with the evaluation of the standardized uptake value (SUV). However, there is growing interest in other data, potentially extractable through the quantitative analysis of these same images. Whole-body metabolic active tumor volume (MATV-WB), measured in cm^3, representing the individual tumor burden of each patient, can be obtained using parameters based on the volume of the primary tumor and the metastatic lesions and on the intensity of their [^{18}F]FDG uptake. This type of information seems to present high prognostic value, regarding patients' overall survival time [8]. Published studies show that MATV-WB has, in NSCLC patients, higher prognostic value than the SUV [9–13], than the secondary prognostic factors, and also possibly than the cTNM staging system [9, 10, 14, 15]. The MATV-WB seems able to provide additional information for the usual evaluation of [^{18}F]FDG PET/CT, allowing for better risk stratification of the patients. This parameter may contribute to the identification of NSCLC patients with worse prognosis and higher risk of relapse and death. It may also contribute to the development of more personalized therapeutic strategies by identifying patients who may benefit from more aggressive treatments, such as complementary therapies to surgery, dose increments in radiotherapy, consolidation chemotherapy, or the addition of new therapies with targeted agents and immunotherapy [16].

Aim

The aim of this study was to investigate, in NSCLC patients, the value of a cTNM-P staging methodology, combining cTNM staging with MATV-WB quantified on the initial staging [^{18}F]FDG PET/CT, testing its stratifying power and comparing its overall survival predictive ability with that of conventional cTNM staging.

Material and methods

Study population

This work was approved by the Institutional Ethics Committee. For this type of retrospective study, formal consent was not required.

Two hundred seventy-eight patients diagnosed with NSCLC who performed [^{18}F]FDG PET/CT for initial staging, between January 2010 and April 2016, were retrospectively evaluated. Seventy-four (26.6%) were female and 204 (73.4%) were male, aged 34 to 88 years (mean ± SD = 66 ± 10). None of the patients included in the study had brain metastases (excluded by magnetic resonance) or a history of other malignancies. The PET/CT scans were performed within 15 days of diagnosis and before any therapeutic intervention. The histological types and cTNM stages of the study population are described in Table 1.

After histological characterization of the lung tumor and its cTNM staging, patients were treated according to the therapeutic strategies most appropriate to their clinical situations, respecting the current good practice guidelines.

[^{18}F]FDG PET/CT acquisition protocol

This was a monocentric study and the [^{18}F]FDG PET/CT scans were conducted according to the institution's existing protocol: patients fulfilled a 6-h fast, and before intravenous [^{18}F]FDG administration their glycaemic levels were below 144 mg/dL. The administered activities ranged from 207 to 573 MBq (mean ± SD: 362.6 ± 59.2). Images were acquired 55 to 110 min after intravenous administration (mean ± SD: 61.8 ± 7.5). The variations observed in the administered activities and times of biodistribution were related to the usual conditions of clinical practice [17]. Patients were positioned in dorsal decubitus with arms above the head and whole body images were acquired using a PET/CT scanner General

Table 1 Histological characterization and cTNM stage of the study population

	Number of patients (n)	%
Histological type		
Adenocarcinoma	172	61.9
Epidermoid carcinoma	61	21.9
Adenosquamous carcinoma	19	6.8
Adenomucinous carcinoma	11	4.0
Pleomorphic carcinoma	9	3.2
Sarcomatoid carcinoma	6	2.2
cTNM stage		
IA	21	7.6
IB	18	6.5
IIA	20	7.2
IIB	11	4.0
IIIA	43	15.5
IIIB	50	18.0
IV	115	41.4

Electric Discovery ST (GE Healthcare, Waukesha, WI, USA). The acquisition parameters of CT for attenuation correction and anatomic mapping were as follows: 120 kV, smart mA (with current values between 10 and 200 mA and noise index 35), pitch 1.5:1, rotation 0.5 s and slice thickness 3.75 mm. The PET emission study was obtained in 3-D mode with 3 min acquisition time per table position, following the manufacturer's recommendations. The collected data were reconstructed with a Field Of View diameter of 70 cm and 256 × 256 matrix using the VUE Point 3-D iterative reconstruction algorithm, with two iterations, 35 subsets and a 4 mm full width at half maximum post-reconstruction filter.

Methodology

The cTNM stage, which was assigned to each patient, was recorded. Given the limited number of patients included in the study, patients belonging to the seven cTNM stages, namely IA, IB, IIA, IIB, IIIA, IIIB and IV, were grouped in stage I (IA and IB) (n = 39), stage II (IIA and IIB) (n = 31), stage III (IIIA and IIIB) (n = 93) and stage IV (n = 115).

[^{18}F]FDG PET/CT scans were retrospectively evaluated on a dedicated post-processing workstation (Advanced Windows 4.4 GE Medical Systems, Milwaukee, USA). Each patient's lesions were delineated and evaluated using the Volume Computer Assisted Reading (PET_VCAR) software (version vxtl_8_3_65). PET_VCAR software generated whole body 3-D regions of interest, based on the pre-defined threshold SUV value of 2.5. Regions corresponding to physiological uptake and/or uptake in benign lesions were manually excluded based on consensus between two nuclear medicine specialists. After this initial post processing step, 3-D regions of interest, corresponding to the primary lung tumor and all metastatic lesions, were obtained. A quantitative analysis was performed to calculate MATV-WB.

For those who died, the date of death was recorded. The follow-up time calculated from the date of the initial staging [^{18}F]FDG PET/CT scan to the date of death or to the end of the study, was determined. Patient follow-up times ranged from 0.7 to 83.6 months (mean ± SD = 25.1 ± 20.3).

Statistical analysis

A p-value of less than 0.05 was considered statistically significant for all tests performed. The values of the quantitative data were presented with minimum-maximum (mean ± standard deviation) or median (inter quartile range), qualitative data with n (%), and overall survival times with estimated mean.

The SPSS software (version 23; Armonk, NY, USA: IBM Corp) and R (R Foundation for Statistical Computing, Vienna, Austria) software were used for the statistical analysis of the data.

A multivariate Cox regression was run for the total study population to evaluate the influence of MATV-WB, cTNM staging, age, gender and histological type on overall survival time.

The total study population was randomly divided into a training sample containing 80% of the 278 cases under study, and a test sample, for validation purposes, using the remaining cases. From the training sample, 100 random samples with replacement (bootstrapping) were generated [18].

The overall survival time predictive abilities of cTMN staging and MATV-WB were evaluated in the 100 random samples obtained. For that, the respective Harrell-Concordance indexes were calculated using the "cindex" function of the R software package "dynpred". From the values obtained in each of the 100 random samples, it was possible to determine a mean value (and respective 95% confidence interval) for the Harrell-C index as well as for the p-value. Afterwards, the overall survival predictive abilities of cTMN staging and MATV-WB were compared using the "C" function of the same software package [19–21].

A cutoff point for MATV-WB was chosen as the best cutoff value obtained from each one of the 100 random samples, using the "cutp" function of the R software package "survMisc". This cutoff value was validated in the test sample. The overall survival time predictive abilities of MATV-WB and MATV-WB with the cutoff point chosen were determined and compared, using the previously described R software functions.

The total study population was then divided into two groups based on the MATV-WB cutoff point chosen. Kaplan-Meier analysis with the Log-Rank test was used to compare estimated mean overall survival time between the two groups. The one-year and five-year survival rates were

computed and compared between the subjects who were above and below the cutoff point, and the mortality risk was also evaluated trough the determination of the Hazard Ratio (and respective 95% confidence interval).

The same procedures described above were used to choose the best cutoff point for MATV-WB in each subgroup of patients defined by cTNM stages I, II, III and IV, and to compare the estimated mean overall survival times as well as the one-year and five-year survival rates between the subjects who were above and below the cutoff points. In these subgroups, the number of times random samples with replacement (bootstrapping) was extracted from the training samples was as follows: 13 times in stage I, 10 times in stage II, 33 times in stage III and 41 times in stage IV. The number of samples obtained depended on the size of the subgroup under analysis.

Finally, using the total study population, the overall survival time predictive ability of a proposed new cTNM-P staging system was determined and compared with that of the conventional cTMN staging system using the previously described R software functions.

Results

MATV-WB as a predictor of overall survival

The MATV-WB values calculated are presented in Table 2. In the multivariate analysis, preformed through Cox-regression, the independent influence of the MATV-WB, adjusted for cTNM stage and secondary prognostic factors, age, gender and histological type, was evaluated. The Hazard Ratio values obtained revealed that MATV-WB, as well as cTNM stage and age, was an independent and statistically-significant predictor of overall survival time (Table 3).

Given that MATV-WB and cTNM staging were independent and statistically-significant predictors of overall survival time, their respective predictive abilities were compared. The predictive ability of MATV-WB was not worse than cTNM staging (Table 4).

Table 2 MATV-WB values, in cm^3, measured in the total sample and in the sub samples divided by cTNM stages I, II, III and IV

	N	Mean ± SD	Min	Max	Median	IQR
Total	278	109.3 ± 177.8	0.1	1181	46.5	10-136.4
Stage I	39	19.8 ± 35.1	0.2	202.6	6.3	2.2-23.7
Stage II	31	31.7 ± 41.3	0.3	176.3	12.7	5.3-49.5
Stage III	93	76.7 ± 92.5	0.2	398.1	40.2	11.5-93.5
Stage IV	115	186.9 ± 240.3	0.1	1181	99.2	33.4-238.1

N-number of patients; SD-standard deviation; Min-minimum; Max-maximum; IQR-inter quartile range

Table 3 Hazard ratio adjusted for MATV-WB, cTNM stage, age, gender and histological type

	HR	CI (95%)	*p*
Age	1.021	1.004-1.038	**0.018**
Gender	0.765	0.512-1.142	0.190
Histological type			0.439
Adenocarcinoma	Reference		
Epidermoid Ca.	1.288	0.854-1.942	0.227
Adenosquamous Ca.	0.891	0.441-1.801	0.748
Pleomorphic Ca.	0.719	0.307-1.681	0.446
Sarcomatoid Ca.	1.897	0.741-4.859	0,182
Adenomucinous Ca.	1.542	0.619-3.840	0,352
cTNM			**<0.001**
I	Reference		
II	3.086	1.099-8.668	**0.032**
III	3.790	1.495-9.605	**0.005**
IV	10.056	4.019-25.161	**<0.001**
MATV-WB	1.002	1.001-1.003	**<0.001**

Statistically significant results are presented in bold

HR-hazard ratio; CI-confidence interval; Ca-carcinoma

MATV-WB with a cutoff point as a predictor of overall survival

In order to find an easy and practical way to use clinically the quantitative parameter MATV-WB, a cutoff point was calculated. The value of 49.5 was identified as the optimal cutoff point ($p = 2.8 \times 10^{-12}$). A new binary variable was created based on this cutoff value: MATV-WB49.5 ("MATV-WB < 49.5"; "MATV-WB ≥ 49.5").

The overall survival time predictive abilities of MATV-WB (C index = 0.687) and MATV-WB49.5 (C index = 0.722) were determined. There was no statistically-significant difference between them (Z = −1260, $p = 0.209$), and the new binary variable was chosen for practical application.

Patients with MATV-WB < 49.5 had an estimated mean overall survival time of 56.31 ± 3.02 months (95% CI: 50.40-62.23), while those with MATV-WB ≥ 49.5 had an estimated mean overall survival time of 21.66 ± 2.20 months (95% CI: 17.34-25.98). There was a statistically significant difference in the estimated mean overall survival times, in months, (Log-Rank = 77.48; $p < 0.001$) between the two groups of patients (Fig. 1).

Also determined was the probability of survival according to the value of MATV-WB, at 1 and 5 years after diagnosis. The one-year survival rate was 86.8% for patients with MATV-WB < 49.5 (standard error = 0.028) and only 52.8% for patients with MATV-WB ≥ 49 (standard error = 0.044). The five-year survival rate was 53.6% for patients with MATV-WB < 49.5 (standard error = 0.057) and there were no survivors for patients with MATV-WB ≥ 49.5. The determined Hazard Ratio was 4.12 ($p < 0.001$), estimating with a

Table 4 Comparison of MATV-WB and cTNM overall survival predictive abilities

	C index			
	Mean ± SD	CI (95%)	*p* (CI 95%)	*Z score* (CI 95%)
MATV-WB	0.7071 ± 0.0009	0.7054-0.7089	0.773	−0.143
cTNM	0.7031 ± 0.007	0.7017-0.7044	(0.741-0.806)	(−0.211 to −0.074)

SD-standart deviation; CI-confidence interval

95% confidence interval that a patient with a MATV-WB value ≥ 49.5 had a mortality risk 2.93 to 5.79 times higher than a patient having a MATV-WB value < 49.5.

MATV-WB with cutoff points as a predictor of overall survival in each cTNM stage

As expected, there was a statistically-significant difference in estimated mean overall survival times between cTNM stages ($p < 0.001$). The survival curves for each cTNM stage are presented in Fig. 2.

Thus, it made sense to look for MATV-WB cutoff points at each cTNM stage patient subgroup. The identified optimal cutoff points were 23.7 for stage I, 52 for stage III and 48.8 for stage IV ($p = 0.029$, $p = 0.025$, $p = 0.001$, respectively). For stage II, there were no cutoff point able to discriminate patients ($p = 0.227$), so the global cutoff point of 49.5 was used. The estimated overall survival times of cTNM stages I, II, III and IV patients, as a function of the respective MATV-WB, are shown in Fig. 3. Patients with MATV-WB values above the cutoff point at each stage had worse prognosis. There was a statistically significant difference in estimated mean overall survival times, in months, between patient groups defined according to the MATV-WB cutoff points at cTNM stages I, III and IV ($p = 0.007$, $p = 0.004$ and $p < 0.001$, respectively). Regarding stage II, although there was no statistically significant difference ($p = 0.365$), the difference between the two groups was clinically significant, given that the difference in estimated mean overall survival times between patients with MATV-WB < 49.5 and patients with MATV-WB ≥ 49.5, which was about 12 months (Table 5). The small number of patients included in stage cTNM II may explain why the difference between groups above and below the cutoff point was not statistically significant.

The one-year and five-year survival rates for the groups above and below the MATV-WB cutoff points at each cTNM stage were also determined. Patients with MATV-WB values above the cutoff points had lower survival rates than patients with MATV-WB values below them (Table 6).

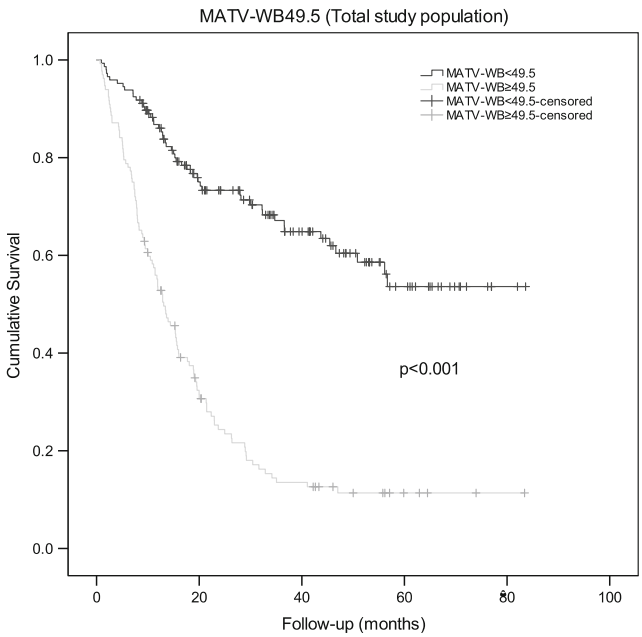

Fig. 1 Kaplan-Meier curves comparing overall survival time between groups as a function of MATV-WB, in the total study population

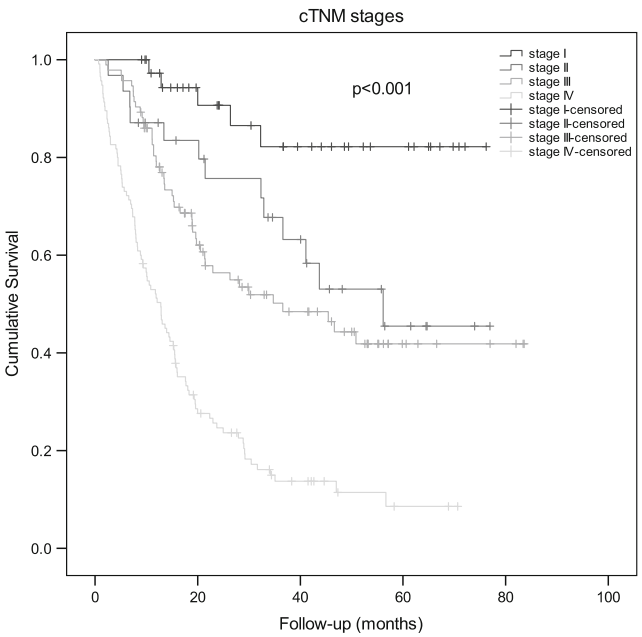

Fig. 2 Kaplan-Meier curves comparing overall survival time between groups as a function of cTNM stages, in the total study population

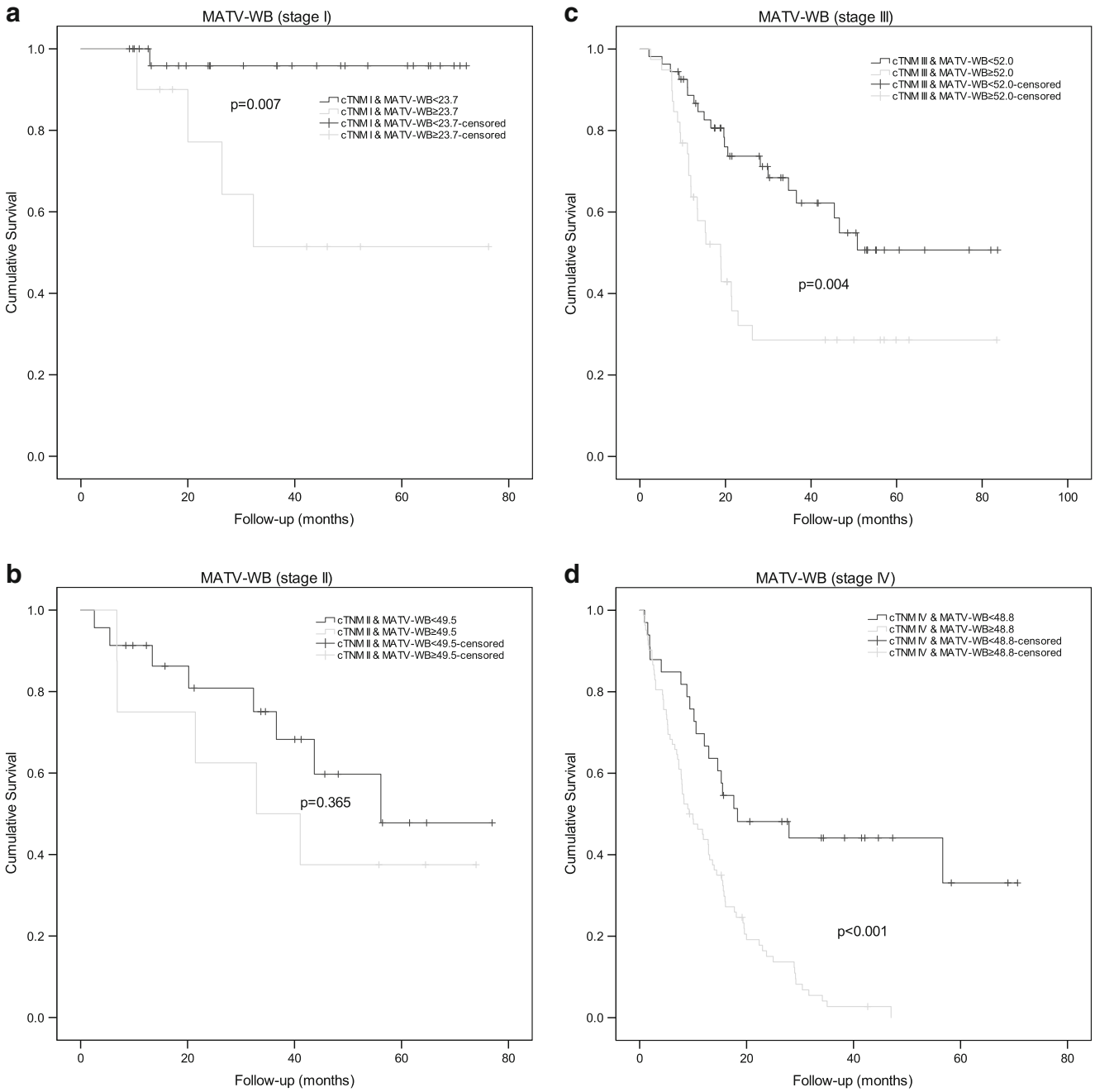

Fig. 3 Kaplan-Meier curves comparing overall survival time between groups as a function of MATV-WB, in cTNM stages I, II, III and IV

Table 5 Estimated mean overall survival time, in months, according to the cutoff point defined for MATV-WB in each cTNM stage

Stage	EMST ± SE	CI (95%)	MATV-WB	EMST ± SE	CI (95%)	*p**
I	66.54 ± 3.97	58.8-74.3	<23.7	69.62 ± 2.42	64.88-74.35	0.007
			≥ 23.7	50.36 ± 9.48	31.79-68.93	
II	50.61 ± 5.39	40.0-61.2	<49.5	53.67 ± 6.27	41.39-65.95	0.365
			≥49.5	41.36 ± 9.72	22.31-60.41	
III	46.35 ± 3.80	39.0-53.8	<52.0	55.04 ± 4.81	45.60-64.47	0.004
			≥52.0	33.76 ± 5.56	22.86-44.66	
IV	19.14 ± 1.98	15.3-23.0	<48.8	35.76 ± 5.20	25.57-45.95	<0.001
			≥48.8	12.95 ± 1.21	10.59-15.32	

*Log-Rank test; EMST-estimated mean survival time; SE standard error; CI-confidence interval

Table 6 Survival rate (%) (mean ± standard error) according to the cutoff point defined for MATV-WB at each cTNM stage

FU	Stage I		Stage II		Stage III		Stage IV	
1 year	**<23.7**	**≥23.7**	**<49.5**	**≥49.5**	**<52**	**≥52**	**<48.8**	**≥48.8**
	100	90 ± 10	91 ± 6	75 ± 15	89 ± 4	64 ± 8	68 ± 8	44 ± 6
5 year	**<23.7**	**≥23.7**	**<49.5**	**≥49.5**	**<52**	**≥52**	**<48.8**	**≥48.8**
	96 ± 4	51 ± 18	48 ± 15	38 ± 17	51 ± 9	29 ± 8	33 ± 11	0

Statistically significant results are presented in bold

FU-follow up

cTNM-P staging

Based on the results obtained, a new staging methodology, which we called clinical TNM-PET (cTNM-P), was investigated. This new methodology combines the conventional cTNM staging, and the usual interpretation of the [^{18}F]FDG PET/CT, with the MATV-WB quantified from the PET images. Thus, cTNM stages were subdivided into subgroups using the cutoff points determined for MATV-WB. In this way, a new staging system was obtained with patients stratified by eight stages, namely: Stage I(<23.7); Stage I(≥23.7); Stage II(<49.5); Stage II(≥49.5); Stage III(<52); Stage III(≥52); Stage IV(<48.8); Stage IV(≥48.8) (Fig.4 and Table 5).

The overall survival predictive ability of cTNM-P staging (C index = 0.730) was compared to cTNM staging (C index = 0.699). The cTNM-P staging, in which MATV-WB information was associated with cTNM staging, had a higher overall survival time predictive ability compared to the isolated cTNM staging ($Z = -4.49$; $p < 0.001$).

Discussion

The cTNM staging system used to establish the prognosis of NSCLC patients, as well as the therapeutic strategy to which they will be subjected, does not take into account the metabolic active tumor burden of each patient. However, this information is of recognized importance, especially for its prognostic value and its stratifying power, being desirable for its inclusion in the staging of these patients. It is important to identify which patients in stages I and II have worst prognosis. Despite being assigned to in the initial cTNM stages, with surgical indication, some of these patients have high five-year mortality rates. MATV-WB quantified on [^{18}F]FDG PET/CT may contribute to the identification of these patients with surgical indication but with a high risk of recurrence and death and who may, therefore, benefit from more aggressive therapeutic strategies, complementary to surgery [22]. Stage IIIA is a very heterogeneous stage encompassing patients with large variations in size of the primary lung tumor and with large differences in the location and extent of metastatic lymph node disease. The therapeutic strategy adopted for stage IIIA patients is, therefore, controversial, and there is no standardized approach. Chemotherapy, radiotherapy, and surgery, alone or in combination, are the usual therapeutic options, and there is often no consensus on the best solution. Also, in this group of patients, a better stratification will clearly be important, allowing patients with lower risk to be separated (benefiting from an even wider surgical approach) from those at higher risk (indicated for chemotherapy and radiotherapy) [23, 24]. Among IIIB stage patients, without surgical indication, who are treated with chemotherapy and radiotherapy, also those with higher values of MATV-WB have worse prognoses. In these patients, higher doses of radiotherapy, as well as consolidation chemotherapy regimens, may improve survival [16]. Stage IV also consists of a very

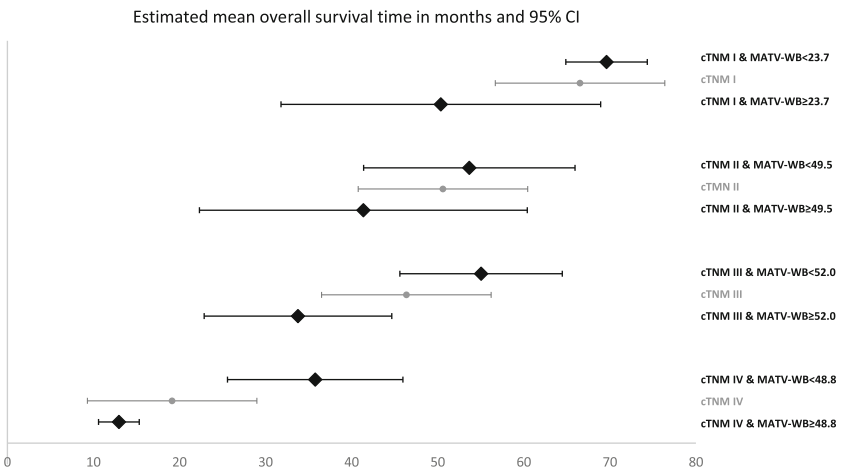

Fig. 4 Estimated mean overall survival time, in months, (and respective 95% confidence interval) for cTNM stages and for subgroups based on the calculated MATV-WB cutoff points in each cTNM stage

heterogeneous group of patients, with very different prognoses [12]. We agree with Winther-Larsen and colleagues who argue that an accurate estimate of the prognosis of patients with advanced NSCLC is essential before starting any palliative treatment strategy, especially second and third line therapy. In the opinion of these authors, the tumor burden of each patient, due to its high prognostic value, presents itself as a very promising clinical tool that allows a better selection of patients for palliative treatments [25]. Thus, we believe that this group of patients will benefit greatly from stratification according to MATV-WB [26].

In our work we propose a new staging methodology in which the conventional cTNM staging is combined with the parameter MATV-WB calculated from the [^{18}F]FDG PET/CT images, obtained at the initial staging. This new classification is an easy way of combining the two pieces of information (cTNM and MATV-WB). The MATV-WB parameter can be obtained in most of the commercially available nuclear medicine equipment. Furthermore, in most of the patients, we spent less than 5 min to perform all the procedures involved. This new methodology can be easily applied in clinical practice, and is a better predictor of overall survival with superior stratifying power compared with conventional cTNM staging, when considered in isolation. It may thus contribute to the optimization of therapeutic decisions for NSCLC patients. In this study, we demonstrated that MATV-WB had prognostic value in NSCLC patients, presenting as a statistically-significant overall survival predictor independent of cTNM stage, age, gender and histological type. We have also shown that its predictive ability was not only independent of the cTNM stage, but was not worse. Using the optimal cutoff point for MATV-WB in the total population including all cTNM stages, and also at each cTNM stage, patients with MATV-WB above the cutoff points presented estimated mean overall survival times and one-year and five-year survival rates lower than those with MATV-WB values below the cutoff points. So, we believe that MATV-WB quantified on [^{18}F]FDG PET/CT may be considered, in the future, as a parameter to be integrated in the initial staging of NSCLC patients. Of course, further studies are needed to assess the best way to integrate this information into established clinical nomograms.

As far as we know, Zhang and colleagues have been the only ones to propose a methodology in which the prognostic values of cTNM and MATV-WB are combined. However, they did so by calculating an index that they denominated as the PET/CT volumetric prognostic (PVP) index [4]. Our methodology is intended to combine the prognostic values of cTNM and MATV-WB in a way that we consider to be easier and more attractive for future clinical application. However, it would be useful and necessary to develop studies comparing the prognostic value and the clinical interest of different methods of applying the parameter MATV-WB. In addition to its application in NSCLC patients, the inclusion of this quantitative information may also be important for other malignant neoplasms staging. Published works show that the tumor burden quantification of each patient has prognostic value in tumors as head and neck cancer [27], breast cancer [28], multiple myeloma [29], follicular lymphoma [30], colorectal cancer [31], cervix carcinoma [32] and pancreatic carcinoma [33].

The prognostic evaluation of MATV-WB should be performed through prospective multicenter studies considering not only overall survival but also disease-free survival or survival without disease progression. In our retrospective analysis, the small number of stage II patients (31 patients) did not allow us to draw statistically-significant conclusions for this stage. A greater number of patients may allow an evaluation for all cTNM stages, namely, IA, IB, IIA, IIB, IIIA, IIIB and IV. In addition, in our study, we used a tomograph with a spatial resolution of about 6 mm and detection sensitivity of 0.2%. State-of-the-art equipment can achieve a spatial resolution of about 4 mm and a detection sensitivity of 0.9% [34]. These devices, with more favorable spatial resolution and detection sensitivity values, would allow more precise quantitative analysis. The widespread clinical use of MATV-WB quantified on [^{18}F]FDG PET/CT implies that this parameter could be comparable between examinations and between patients, regardless of the PET/CT system used. This would require greater attention in relation to all the variables that can influence quantification, such as the activity administered and the time of biodistribution. It will be necessary to standardize protocols and procedures, to harmonize the preparation of patients, as well as the conditions for acquiring, reconstructing and processing images. It will also be fundamental to standardize methodologies for the analysis and quantification of MATV-WB [35].

Nevertheless, based on our experience, the metabolic active tumor burden of each patient is a quantitative parameter with high prognostic value that should be taken into account in the initial staging process of NSCLC patients.

Conclusion

In NSCLC patients, MATV-WB, quantified on initial staging [^{18}F]FDG PET/CT, is an independent and statistically significant predictor of overall survival. The cTNM-P algorithm that we propose combines cTNM staging and MATV-WB. It has superior prognostic value compared to that of conventional cTNM staging considered in isolation, and it allows for improved stratification of patients. The results we present here should be validated in larger populations and through multicenter prospective studies.

Protection of people and animals

The authors declare that all procedures performed in studies involving human participants were in accordance with the

ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Confidentiality of data

The authors state that they have followed the protocols of their work centre on the publication of patient data.

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Compliance with ethical standards

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