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# Synergic prognostic value of 3D CT scan subcutaneous fat and muscle masses for immunotherapy-treated cancer

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## ABSTRACT

**Background** Our aim was to explore the prognostic value of anthropometric parameters in a large population of patients treated with immunotherapy.

**Methods** We retrospectively included 623 patients with advanced non-small cell lung cancer (NSCLC) (n=318) or melanoma (n=305) treated by an immune-checkpoint-inhibitor having a pretreatment (thorax)-abdomen-pelvis CT scan. An external validation cohort of 55 patients with NSCLC was used. Anthropometric parameters were measured three-dimensionally (3D) by a deep learning software (Anthropometer3DNet) allowing an automatic multislice measurement of lean body mass, fat body mass (FBM), muscle body mass (MBM), visceral fat mass (VFM) and sub-cutaneous fat mass (SFM). Body mass index (BMI) and weight loss (WL) were also retrieved. Receiver operator characteristic (ROC) curve analysis was performed and overall survival was calculated using Kaplan-Meier (KM) curve and Cox regression analysis.

**Results** In the overall cohort, 1-year mortality rate was 0.496 (95% CI: 0.457 to 0.537) for 309 events and 5-year mortality rate was 0.196 (95% CI: 0.165 to 0.233) for 477 events. In the univariate Kaplan-Meier analysis, prognosis was worse (p<0.001) for patients with low SFM (<3.95 kg/m<sup>2</sup>), low FBM (<3.26 kg/m<sup>2</sup>), low VFM (<0.91 kg/m<sup>2</sup>), low MBM (<5.85 kg/m<sup>2</sup>) and low BMI (<24.97 kg/m<sup>2</sup>). The same parameters were significant in the Cox univariate analysis (p<0.001) and, in the multivariate stepwise Cox analysis, the significant parameters were MBM (p<0.0001), SFM (0.013) and WL (0.0003). In subanalyses according to the type of cancer, all body composition parameters were statistically significant for NSCLC in ROC, KM and Cox univariate analysis while, for melanoma, none of them, except MBM, was statistically significant. In multivariate Cox analysis, the significant parameters for NSCLC were MBM (HR=0.81, p=0.0002), SFM (HR=0.94, p=0.02) and WL (HR=1.06, p=0.004). For NSCLC, a KM analysis combining SFM and MBM was able to separate the population in three categories with the worse prognostic for the patients with both low SFM (<5.22 kg/m<sup>2</sup>) and MBM (<6.86 kg/m<sup>2</sup>) (p<0.0001). On the external validation cohort, combination of low SFM and low MBM was pejorative with 63% of mortality at 1 year versus 25% (p=0.0029).

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Survival outcomes are significantly longer in overweight/obese patients (as determined by higher body mass index) for patients with cancer treated with immune checkpoint inhibitors.

## WHAT THIS STUDY ADDS

⇒ It is shown in this study that an automatic three-dimensional (3D) determination of body composition, more accurate than the body mass index, is possible in clinical routine from diagnostic scans and that 3D-measured low muscle mass is a significant prognosis factor of melanoma treated by immune checkpoint inhibitors while 3D-measured low subcutaneous fat mass and muscle mass are significant prognosis factors of non-small cell lung cancer treated by immune checkpoint inhibitors and both can be combined to improve the prognostic value.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Determination of body composition may help to better define the prognosis of cancers treated with immunotherapy. In the long-term, therapeutic adaptation according to body composition could be possible.

**Conclusions** 3D measured low SFM and MBM are significant prognosis factors of NSCLC treated by immune checkpoint inhibitors and can be combined to improve the prognostic value.

## INTRODUCTION

In 2020, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred worldwide.<sup>1</sup> Among them, lung cancers represented 11.4% of new cases and 18.0% of deaths and melanoma 1.7% of new cases and 0.6% of deaths.<sup>1</sup>

Cancers have the ability to disrupt immune response by interfering with adaptive immunity.<sup>2</sup> Immunotherapy using

immune checkpoint inhibitors (ICI), notably anti-PD-1 (programmed cell death protein-1) and anti-PDL-1 (PD-1 ligand) antibody, has been shown to improve outcome of stage IIIb/IV non-small cell lung cancer (NSCLC) and of high-risk resected stage III/IV melanoma, which made it a new standard of care.<sup>3</sup> Compared with cytotoxic chemotherapy and targeted therapy, ICIs have been shown to induce a durable response (plateau) in a fraction of patients with advanced or metastatic cancer, even after their interruption.<sup>4</sup>

Despite the clinical success of ICI in many patients with cancer, with some durable response, better understanding of determinants affecting response is required, thus ICI response rates in general are around 20% in unselected NSCLC.<sup>5</sup> Some biomarkers are focused on the immune tumor microenvironment<sup>6</sup> or on the gut microbiome while others focus on the disease and/or the host as a whole.

Thus, total tumor burden, as evaluated by positron emission tomography (PET)/CT at the start of treatment, has been shown to be a predictor of patient survival. People with a higher total tumor burden tend to have a worse prognosis and a lower likelihood of surviving compared with those with a lower total tumor burden.<sup>7-9</sup>

Patient-centered parameters also appear to be prognostic for survival. Therefore, body mass index (BMI) was higher in patients with melanoma treated by anti-PD-1 checkpoint inhibitors who had a better survival<sup>10</sup> or had early acute limiting toxicity.<sup>11</sup> Moreover, in a large study involving 976 patients with NSCLC (65.1%) and other cancer types, the response rate was significantly higher and survival outcomes were significantly longer in overweight/obese patients, for both sex.<sup>12</sup>

Although BMI is an interesting parameter to describe the overall mass of patients, it does not describe body composition. Some studies exploring the impact of body composition determined on CT have shown the pejorative prognostic value of low subcutaneous fat mass<sup>13</sup> or sarcopenia<sup>14</sup> for NSCLC treated with ICI. For melanoma, comparable results obtained by body composition analysis were identified with several features with improved clinical outcomes.<sup>15 16</sup>

Most of the time, these body composition estimates were based on a two-dimensional (2D) basis,<sup>17</sup> with a segmentation at the L3 abdominal level. However, 2D estimates can be less accurate than three-dimensional (3D) multislice measurements.<sup>18</sup> For example, it has been shown that during weight loss, changes in visceral and subcutaneous adipose tissue are poorly evaluated on 2D imaging,<sup>19</sup> while 3D imaging gives good results for intra-abdominal fat.<sup>20</sup> Therefore, multislice segmentation is preferable,<sup>21</sup> but needs automatic processing to avoid a time-consuming manual segmentation.<sup>19</sup>

To accurately assess anthropometric parameters on CT, including CT of PET/CT, automatic, multislice measurement techniques have been developed.<sup>18 22</sup> One of these algorithms has been tested on a limited number of patients with stage IV NSCLC who received immunotherapy. The

results showed that subcutaneous fat mass can be a prognostic factor for this patient population.<sup>13</sup>

The main objective of this study was to evaluate the prognostic value of anthropometric parameters evaluated on CT scan using an automatic 3D deep learning software, on a large database of patients with NSCLC and melanoma treated with ICI.

## MATERIALS AND METHODS

### Population

The study included adult patients with advanced melanoma or NSCLC tumors who received ICI at Gustave Roussy cancer center in France between June 2014 and December 2018. Population characteristics are presented in [table 1](#). Included patients were extracted from a previous database<sup>23</sup> with the condition of having a wide-field CT scan (of PET/CT or thoraco-abdominopelvic or abdominopelvic diagnostic CT scan) within 90 days before immunotherapy. For the external validation, patients with stage IV NSCLC treated by nivolumab after at least one chemotherapy session in pulmonology, thoracic oncology, and respiratory intensive care department of Rouen University Hospital between February 2015 and October 2017 were included.

### Body composition

Height and weight measurements taken just before treatment and within 6 months prior to starting ICI treatment were collected from medical records and used to calculate BMI and weight loss (WL). Anthropometer3DNet, an updated version of Anthropometer3D,<sup>13 24 25</sup> was used to extract body composition parameters from CT images. This software, which is available for research purposes on [www.oncometer3d.com](http://www.oncometer3d.com), can automatically measure 3D fat body mass (FBM), subcutaneous fat mass (SFM), visceral fat mass (VFM), muscle body mass (MBM) and lean body mass (LBM) (in kilograms) on multislice CT scans in less than 5 min (see [figure 1](#)). This software performs a deep learning-based segmentation<sup>26</sup> of fat (visceral and subcutaneous) and muscle voxels. For parts outside the acquisition area, it uses adaptive extrapolation factors<sup>24</sup> for the tissues of interest to determine the whole-body mass. The software is described in a previous publication.<sup>27</sup>

### Endpoints and assessments

The following baseline clinical data were collected: age, sex, type of cancer, and type of ICI. The primary endpoint was overall survival (OS), defined as the time from the beginning of immune therapy to death or last follow-up.

### Statistical analysis

Descriptive statistics were calculated for the study population, with continuous variables reported as mean and SD, and categorical variables as frequencies and percentages. Spearman's correlation coefficient was used to evaluate correlations between the different body composition parameters. The predictive accuracy of the parameters for

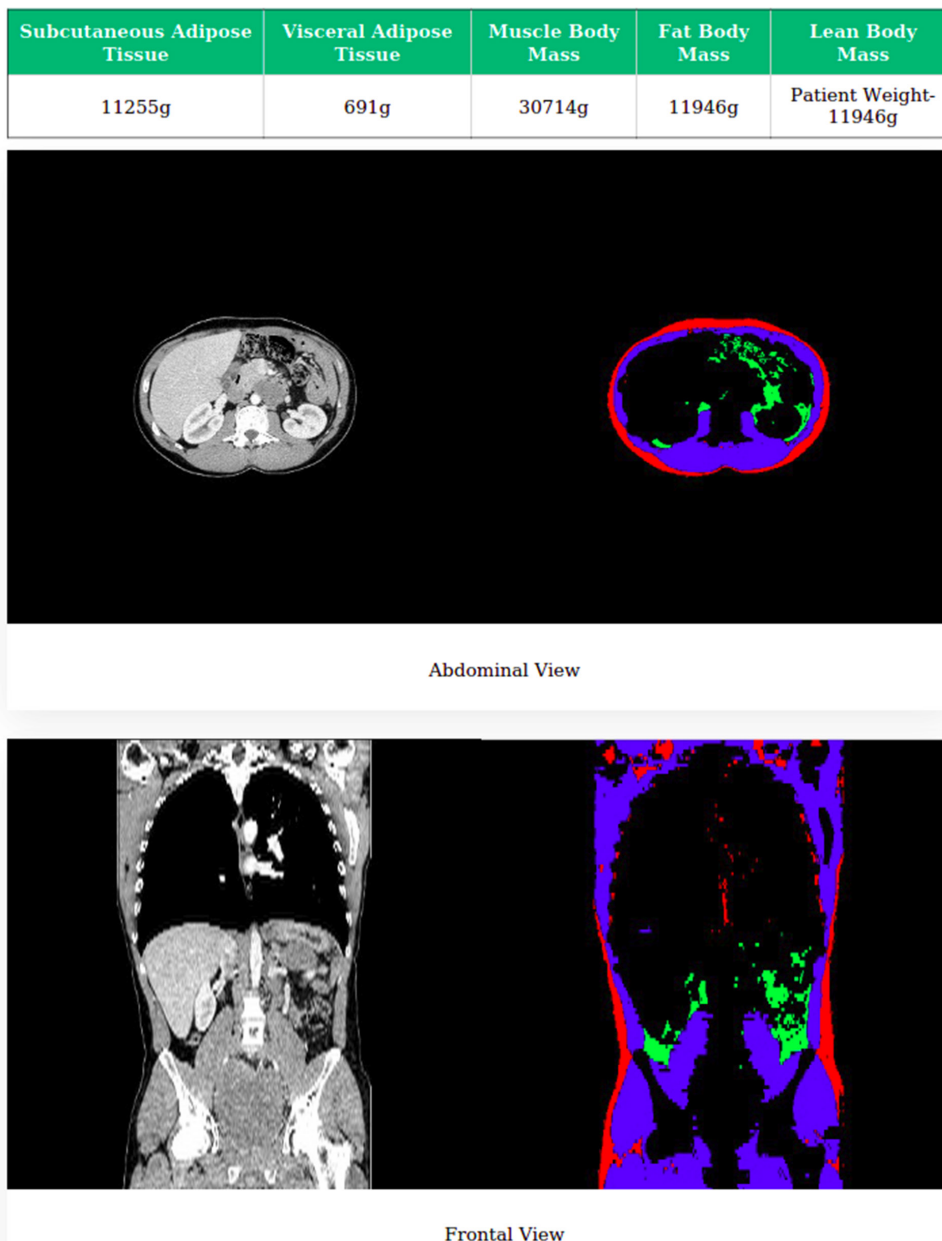
**Table 1** Characteristics of the population

| Characteristic            | All patients<br>(n=623, 100%) | Non-small cell lung cancer<br>(n=318, 51.0%) | Melanoma<br>(n=305, 49.0%) |
|---------------------------|-------------------------------|--|----------------------------|
| Sex, n (%)                | 353 (56.7)                    | 201 (63.2)                                   | 152 (49.8)                 |
| Male                      | 270 (43.3)                    | 117 (36.8)                                   | 153 (50.2)                 |
| Female                    |                               |  |                            |
| Age (years)               | 63 (22–92)                    | 63 (34–92)                                   | 62 (22–91)                 |
| Median range              |                               |  |                            |
| Immunotherapy, n (%)      | 318 (51.0)                    | 76 (23.9)                                    | 242 (79.3)                 |
| Pembrolizumab             | 286 (45.9)                    | 233 (73.3)                                   | 53 (17.4)                  |
| Nivolumab                 | 10 (1.6)                      | –  | 10 (3.3)                   |
| Nivolumab+ipilimumab      | 9 (1.4)                       | 9 (2.8)                                      | –                          |
| Durvalumab                |                               |  |                            |
| Stage, n (%)              |                               |  |                            |
| IV                        | 536 (86.0)                    | 276 (86.58)                                  | 260 (85.2)                 |
| III                       | 85 (13.6)                     | 41 (12.9)                                    | 44 (14.4)                  |
| II                        | 2 (0.3)                       | 1 (0.3)                                      | 1 (0.3)                    |
| Metastasis                |                               |  |                            |
| Bone                      | 205 (32.9)                    | 144 (45.3)                                   | 61 (20.0)                  |
| Liver                     | 165 (26.5)                    | 87 (27.4)                                    | 78 (25.6)                  |
| Brain                     | 183 (29.4)                    | 87 (27.4)                                    | 96 (31.5)                  |
| Prior treatment           |                               |  |                            |
| Systemic                  | 431 (69.2)                    | 296 (93.1)                                   | 135 (44.3)                 |
| Radiotherapy              | 275 (44.1)                    | 165 (51.9)                                   | 110 (36.1)                 |
| Prior surgery             | 335 (53.7)                    | 98 (30.8)                                    | 237 (77.7)                 |
| Outcome                   |                               |  |                            |
| 1-year mortality rate     | 0.496                         | 0.411  | 0.582                      |
| 95% CI                    | (0.457 to 0.537)              | (0.359 to 0.47)                              | (0.529 to 0.64)            |
| Events                    | 309                           | 182  | 127                        |
| 5-year mortality rate     | 0.196                         | 0.11   | 0.279                      |
| 95% CI                    | (0.165 to 0.233)              | (0.0762 to 0.158)                            | (0.23 to 0.337)            |
| Events                    | 477                           | 264  | 213                        |
| Overall survival (months) | 11.8                          | 8.7  | 19.7                       |
| Median IQR                | 2.9–37.3                      | 2.1–21.1                                     | 5.6–73.3                   |
| Follow-up (months)        | 10.7                          | 7.0  | 18.8                       |
| Median IQR                | 2.7–32.3                      | 2.0–19.0                                     | 5.3–46.8                   |
| Morphometric data         |                               |  |                            |

Continued

**Table 1** Continued

| Characteristic  | All patients<br>(n=623, 100%) | Non-small cell lung cancer<br>(n=318, 51.0%) | Melanoma<br>(n=305, 49.0%) |
|---|-------------------------------|--|----------------------------|
| BMI (kg/m <sup>2</sup> )<br>Mean (±SD)<br>(min–max)   | 24.1 (±4.7)<br>(13.7–41.4)    | 23.2 (±4.7)<br>(13.7–39.9)                   | 25.0 (±4.5)<br>(16.0–41.4) |
| FBM (kg/m <sup>2</sup> )<br>Mean (±SD)<br>(min–max)   | 5.7 (±3.5)<br>(0.1–21.9)      | 4.9 (±3.2)<br>(0.1–18.3)                     | 6.6 (±3.6)<br>(0.8–21.9)   |
| SFM (kg/m <sup>2</sup> )<br>Mean (±SD)<br>(min–max)   | 4.8 (±3.0)<br>(0.1–20.7)      | 4.1 (±2.7)<br>(0.1–15.7)                     | 5.5 (±3.1)<br>(0.8–20.7)   |
| VFM (kg/m <sup>2</sup> )<br>Mean (±SD)<br>(min–max)   | 0.9 (±0.7)<br>(0.01–3.4)      | 0.9 (±0.7)<br>(0.01–3.4)                     | 1.0 (±0.7)<br>(0.02–3.3)   |
| MBM (kg/m <sup>2</sup> )<br>Mean (±SD)<br>(min–max)   | 5.8 (±1.5)<br>(1.2–14.1)      | 5.4 (±1.4)<br>(1.2–9.9)                      | 6.2 (±1.6)<br>(2.9–14.1)   |
| LBM (kg/m <sup>2</sup> )<br>Mean (±SD)<br>(min–max)   | 18.3 (±2.8)<br>(4.9–36.1)     | 18.2 (±2.6)<br>(4.1–26.6)                    | 18.4 (±3.0)<br>(4.9–36.1)  |
| BMI, body mass index; FBM, fat body mass; LBM, lean body mass; MBM, muscle body mass; SFM, subcutaneous fat mass; VFM, visceral fat mass. |                               |  |                            |



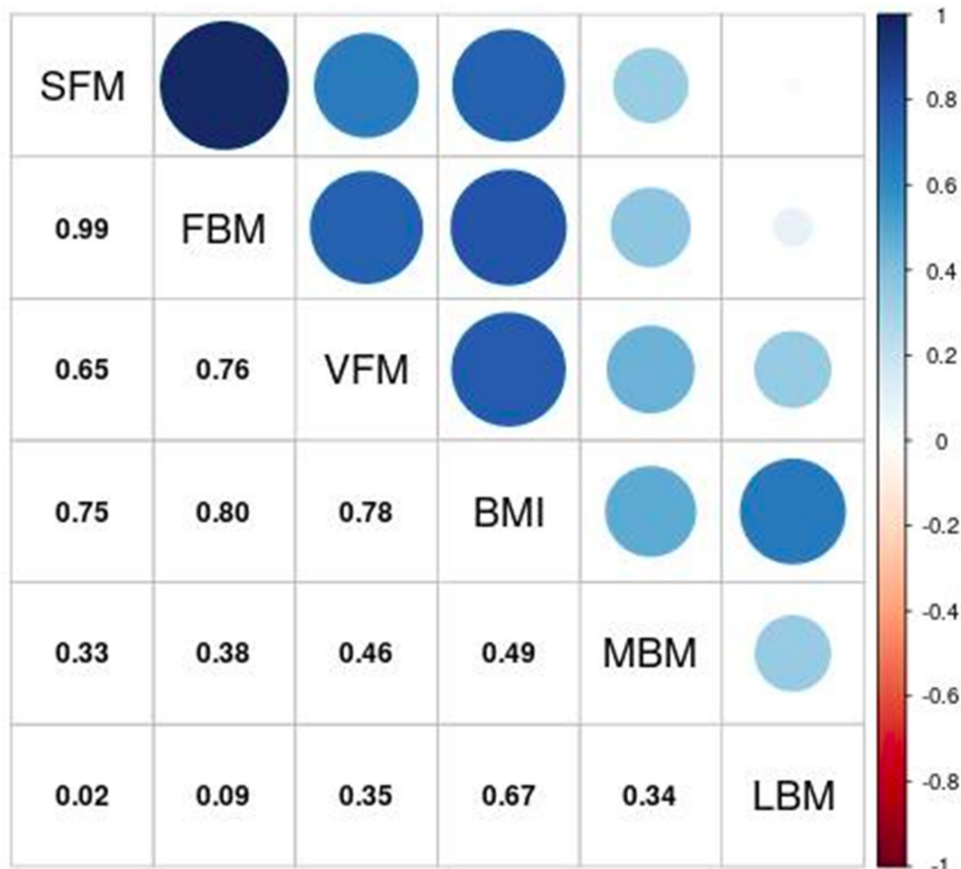
**Figure 1** Graphical representation of the automatic report generated by Anthropometer3DNet with subcutaneous fat (red), muscle (blue) and visceral fat (green) voxels on axial and frontal views.

5-year survival was assessed using receiver operator characteristic (ROC) analysis and the area under the curve (AUC). The optimal cut-off value was determined by maximizing specificity and sensitivity using Youden's Index. Two-sided tests were considered significant at the 5% level. For parameters with an AUC greater than 0.5, the Kaplan-Meier method was used to estimate survival functions, and the log-rank test was used to evaluate significance. Cox proportional hazards models were used to assess the relationship between study variables and survival rates. Analyses were performed in the overall population, as well as in the subgroups of patients with NSCLC or melanoma.

## RESULTS

### Patient characteristics

A total of 623 patients (318 NSCLC and 305 melanoma) were included in this retrospective study; their characteristics, notably according to the tumor type and ICI received, are described in [table 1](#). The average number of days between imaging and the start of immunotherapy was 31 days (median: 26 days), with a minimum of 0 days and a maximum of 90 days. In the overall cohort, 1-year mortality rate was 0.496 (95% CI: 0.457 to 0.537) for 309 events and 5-year mortality rate was 0.196 (95% CI: 0.165 to 0.233) for 477 events. For the external validation, 55 patients with NSCLC treated by nivolumab were included, with details of the population previously published.<sup>13</sup>



**Figure 2** Spearman's correlations between anthropometric parameters (LBM, FBM, MBM, VFM and SFM) and BMI. BMI, body mass index; FBM, fat body mass; LBM, lean body mass; MBM, muscle body mass; SFM, subcutaneous fat mass; VFM, visceral fat mass.

## Whole population analysis

### Correlations

Concerning the body composition parameters and their correlations, as visible in the correlogram (figure 2), FBM and SFM were very highly correlated ( $\rho=0.99$ ), MBM and SFM slightly correlated ( $\rho=0.33$ ) and BMI moderately-to-highly correlated with the other parameters (from  $\rho=0.49$  with MBM to  $\rho=0.80$  with FBM).

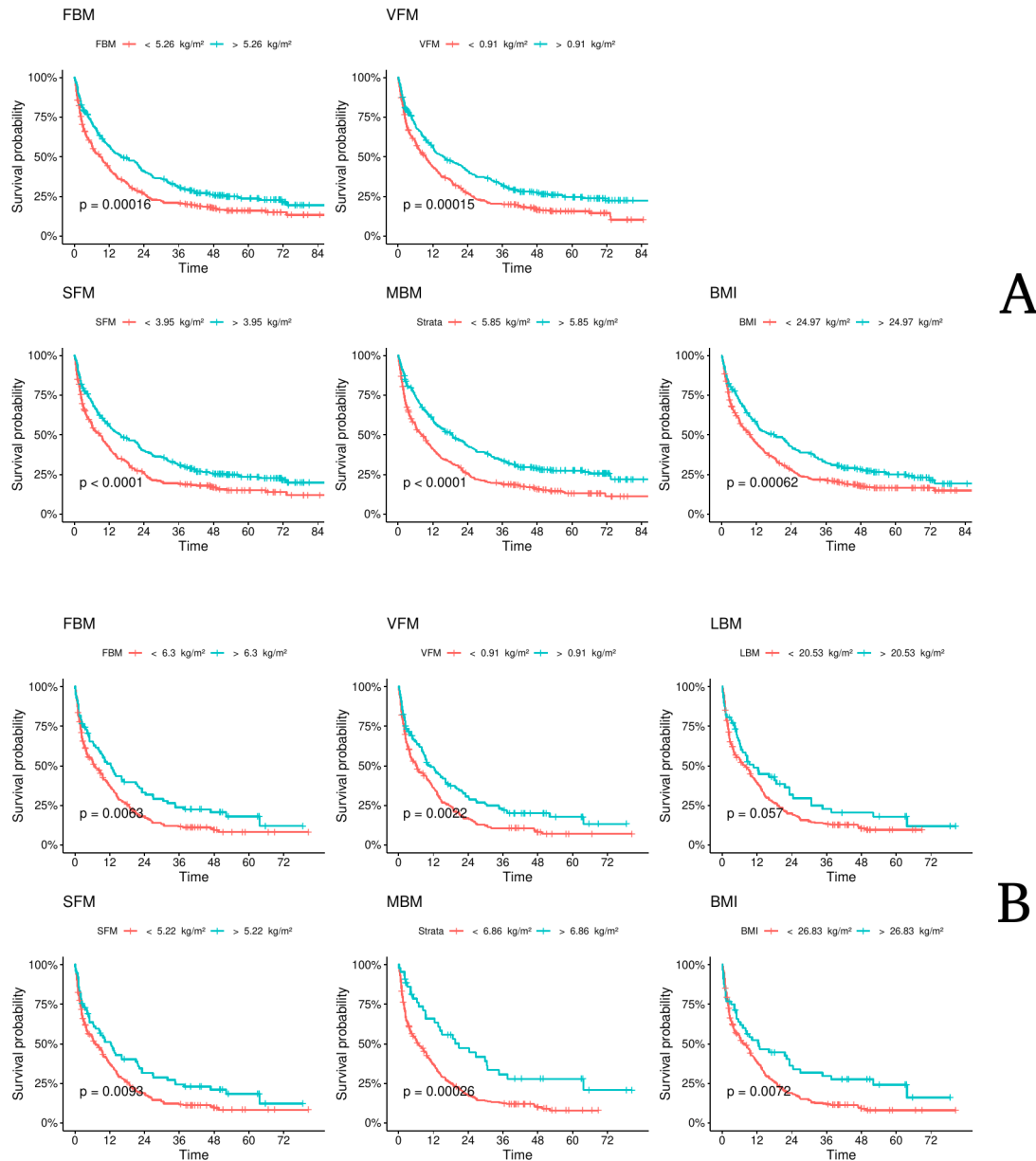
### ROC curve analysis

The ROC curve analysis of the anthropometric parameters for OS are summarized in table 2 with figures in online supplemental data 1. All body composition parameters appear significant, including MBM (AUC=0.69,  $p<0.001$ ) and SFM (AUC=0.60,  $p=0.01$ ). Figure 3 shows the Kaplan-Meier analysis with log-rank tests by using cut-offs determined on the ROC curve analysis for BMI, FBM,

**Table 2** Diagnostic performance, clinical and PET metrics, and anthropometric parameters measured on  $^{18}\text{F}$ FDG PET/CT for 5-year overall survival using an ROC analysis

|                  | Whole population |      |         | NSCLC    |      |         | Melanoma |      |         |
|------------------|------------------|------|---------|----------|------|---------|----------|------|---------|
|                  | Cut-offs         | AUC  | P value | Cut-offs | AUC  | P value | Cut-offs | AUC  | P value |
| Age at diagnosis | NA               | NA   | 0.74    | NA       | NA   | 0.92    | NA       | NA   | 0.51    |
| BMI              | 25.0             | 0.61 | 0.004   | 26.83    | 0.78 | 0.002   | NA       | NA   | 0.57    |
| FBM              | 5.26             | 0.62 | 0.002   | 6.30     | 0.70 | 0.02    | NA       | NA   | 0.41    |
| SFM              | 3.95             | 0.61 | 0.006   | 5.22     | 0.68 | 0.03    | NA       | NA   | 0.56    |
| VFM              | 0.91             | 0.64 | <0.001  | 0.91     | 0.73 | 0.009   | NA       | NA   | 0.06    |
| MBM              | 5.85             | 0.70 | <0.001  | 6.86     | 0.82 | <0.001  | 5.85     | 0.60 | 0.01    |
| LBM              | NA               | NA   | 0.09    | 20.53    | 0.79 | 0.002   | NA       | NA   | 0.59    |

AUC, area under the curve; BMI, body mass index; FBM, fat body mass;  $^{18}\text{F}$ FDG, 18-Fluorodeoxyglucose;  $^{18}\text{F}$ FDG, 18F-Fluorodesoxyglucose; LBM, lean body mass; MBM, muscle body mass; NA, not available; NSCLC, non-squamous cell lung cancer; PET, positron emission tomography; ROC, receiver operator characteristics; SFM, subcutaneous fat mass; VFM, visceral fat mass.



**Figure 3** Kaplan-Meier estimates of overall survival according to the threshold determined on ROC analysis of FBM, SFM, VFM, MBM, LBM and BMI for (A) the whole population and (B) NSCLC. BMI, body mass index; FBM, fat body mass; LBM, lean body mass; MBM, muscle body mass; NSCLC, non-small cell lung cancer; ROC, receiver operator characteristic; SFM, subcutaneous fat mass; VFM, visceral fat mass.

SFM, VFM, MBM and LBM. All parameters, except LBM, were found as significant risk factors for OS ( $p < 0.001$ ), considering cut-off values of  $5.26 \text{ kg/m}^2$ ,  $3.95 \text{ kg/m}^2$ ,  $0.91 \text{ kg/m}^2$ ,  $5.85 \text{ kg/m}^2$  and  $24.97 \text{ kg/m}^2$  for FBM, SFM, VFM, MBM and BMI, respectively.

#### Cox analysis

Table 3 shows the results of the Cox analysis. In a univariate study, all body composition parameters, except LBM, were significantly associated with survival. Some clinical parameters (cerebral-meningeal metastasis status and WL) were significant as well. In the multivariate stepwise Cox analysis using only the univariate statistically significant parameters from the univariate study, the significant

parameters were cerebral-meningeal metastasis status, WL, BMI, SFM and MBM.

#### Subgroup analysis : NSCLC

For the subgroup of patients with NSCLC, on the ROC curve analysis (table 2) and in the Kaplan-Meier analysis with log-rank tests (figure 3), all body composition parameters, except LBM, were statistically significant ( $p < 0.05$ ). In the univariate Cox analysis, all of them were statistically significant. In the multivariate analysis, the weight loss, SFM and MBM were statistically significant ( $p = 0.004$ ,  $p = 0.02$  and  $p = 0.0002$ , respectively) (table 3).



**Table 3** Univariate and multivariate Cox analysis using continuous values for clinical and significant PET metrics and anthropometric parameters measured on  $^{18}\text{F}$ FDG PET/CT

|                               | Whole population                   |                     | NSCLC |                     | Melanoma |         |
|-------------------------------|------------------------------------|---------------------|-------|---------------------|----------|---------|
|                               | HR                                 | P value             | HR    | P value             | HR       | P value |
|                               | Univariate Cox analysis            |                     |       |                     |          |         |
| Age                           | 1.00                               | 0.80                | 1.00  | 0.74                | 1.00     | 0.82    |
| Sex                           | 1.12                               | 0.22                | 0.99  | 0.95                | 1.09     | 0.55    |
| Cerebral-meningeal metastasis | 1.25                               | 0.02                | 1.01  | 0.96                | 1.56     | 0.002   |
| BMI                           | 0.96                               | 0.0003              | 0.94  | $8 \times 10^{-05}$ | 1.00     | 0.75    |
| Weight loss                   | 1.07                               | $9 \times 10^{-05}$ | 1.07  | 0.002               | 1.07     | 0.049   |
| FBM                           | 0.95                               | $8 \times 10^{-05}$ | 0.92  | 0.0001              | 0.99     | 0.74    |
| SFM                           | 0.94                               | 0.0002              | 0.91  | 0.0003              | 0.99     | 0.81    |
| VFM                           | 0.79                               | 0.0006              | 0.71  | 0.0005              | 0.94     | 0.53    |
| MBM                           | 0.82                               | $3 \times 10^{-10}$ | 0.80  | $1 \times 10^{-6}$  | 0.89     | 0.01    |
| LBM                           | 0.99                               | 0.44                | 0.94  | 0.02                | 1.02     | 0.38    |
|                               | Multivariate stepwise Cox analysis |                     |       |                     |          |         |
| Cerebral-meningeal metastasis | 1.21                               | 0.053               | NA    | NA                  | 1.50     | 0.004   |
| BMI                           | 1.03                               | 0.10                | NA    | NA                  | 1.03     | 0.06    |
| Weight loss                   | 1.07                               | 0.0003              | 1.06  | 0.004               | 1.06     | 0.10    |
| FBM                           | NA                                 | NA                  | NA    | NA                  | NA       | NA      |
| SFM                           | 0.93                               | 0.013               | 0.94  | 0.02                | NA       | NA      |
| VFM                           | NA                                 | NA                  | NA    | NA                  | NA       | NA      |
| MBM                           | 0.81                               | $3 \times 10^{-08}$ | 0.83  | 0.0002              | 0.90     | 0.02    |

BMI, body mass index; FBM, fat body mass;  $^{18}\text{F}$ FDG,  $^{18}\text{F}$ -fluorodesoxyglucose; LBM, lean body mass; MBM, muscle body mass; MTV, metabolic tumor volume; NA, not available; NSCLC, non-small cell lung cancer; PET, positron emission tomography; SFM, subcutaneous fat mass; VFM, visceral fat mass.

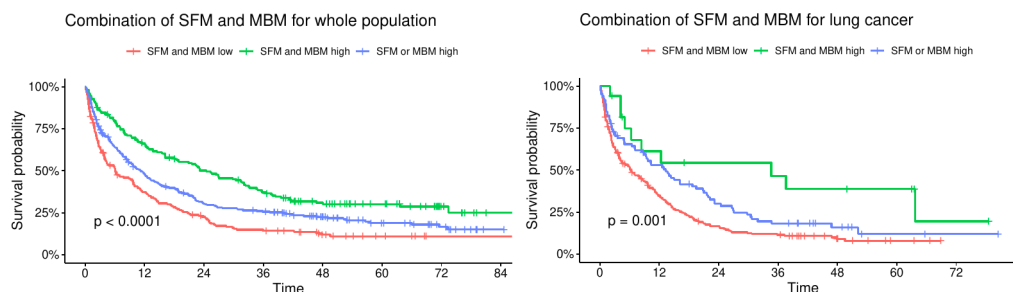
### Subgroup analysis: melanoma

Contrary to the NSCLC subanalyses, only MBM was statistically significant ( $p < 0.05$ ) for melanoma in ROC curve analyses (table 2), Kaplan-Meier analysis with log-rank tests (not shown) and univariate and multivariate Cox analysis (table 3).

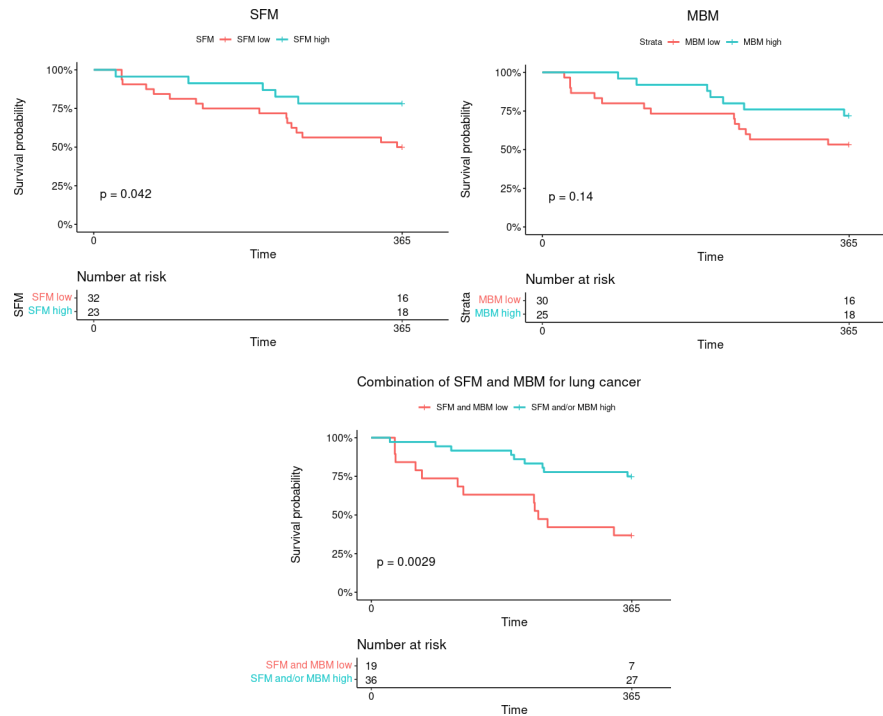
### Combination of MBM and SFM

Because of their relatively low reciprocal correlations and their prognostic values observed in the different univariate and multivariate analyses performed, a combination of two parameters (MBM and SFM) was performed.

Figure 4 shows a Kaplan-Meier survival analysis with a prognostic stratification model combining two adverse parameters: MBM and SFM with three identified risk-groups. For the whole population, a high-risk group comprising patients with low MBM and low SFM had significantly worse prognosis ( $p < 0.001$ ) than low-risk patients with both high MBM/SFM or intermediate-risk patients with only one high parameter. Similar results were observed for NSCLC ( $p < 0.001$ ).



**Figure 4** Kaplan-Meier estimates of overall survival according to a prognostic stratification model combining two adverse parameters: MBM and SFM with three identified risk-groups. MBM, muscle body mass; SFM, subcutaneous fat mass.



**Figure 5** Kaplan-Meier estimates on an external validation cohort of overall survival at 1 year according to SFM, MBM and a prognostic stratification model combining two adverse parameters: MBM and SFM. MBM, muscle body mass; SFM, subcutaneous fat mass.

### External validation

Figure 5 shows a Kaplan-Meier survival analysis on the external database of 55 patients with NSCLC using parameters and their cut-offs (SFM < 5.22 kg/m<sup>2</sup> and MBM < 6.86 kg/m<sup>2</sup>) determined on the NSCLC population. A significant prognostic value was found for SFM alone (p = 0.042) and for the combination of SFM and MBM with a worse prognosis when both SFM and MBM were low with 63% of mortality at 1 year versus 25% (p = 0.0029).

### DISCUSSION

The aim of the present study was to investigate the prognostic value of anthropometric parameters in a large population of patients treated with immunotherapy for NSCLC and melanoma. In a population of 623 patients (n = 318 with NSCLC and n = 305 for melanoma), anthropometric parameters were measured on pretherapeutic 3D CT scan by an automatic 3D software (Anthropometer3DNet). In our study, only MBM was a significant predictor of survival in melanoma, while all of the body composition parameters were significant in NSCLC. In multivariate Cox analysis, the significant predictors of survival in NSCLC were MBM (HR = 0.81, p < 0.0001), SFM (HR = 0.93, p = 0.01), and WL (HR = 1.06, p = 0.004). Kaplan-Meier analysis combining SFM and MBM was able to stratify patients into three prognostic categories, with the worst prognosis observed in those with both low SFM (< 3.95 kg/m<sup>2</sup>) and MBM (< 5.85 kg/m<sup>2</sup>) showing a complementary prognostic value of the combination of

the two parameters. We confirmed the prognostic value of the combination of SFM and MBM in an external validation cohort of 55 patients with NSCLC treated by nivolumab.

Sarcopenia is a condition characterized by age-related loss of muscle mass and function.<sup>28</sup> In a meta-analysis of 2501 patients from 26 studies many cancers treated by ICIs, a negative association between sarcopenia and efficacy of ICI was found with poor survival and poor response in patients with sarcopenia,<sup>29</sup> justifying its assessment in clinical practice to select patients who may respond to ICIs pre-therapeutically.<sup>29</sup> Similar results were observed in another systematic review and meta-analysis where patients with sarcopenia tended to have a lower response rate than those without the disease (30.5% vs 15.9%; p = 0.095) and a significantly shorter 1-year progression-free survival (PFS) rate (32% vs 10.8%; risk ratio (RR), 1.31; p < 0.001) and 1-year OS rate (66 vs 43%; RR, 1.71; p < 0.001).<sup>30</sup> Our results concerning MBM are therefore consistent with those observed in the literature.<sup>31</sup> From a pathophysiological standpoint, that observation could be explained by a vicious circle of chronic inflammation and malnutrition leading up to cachexia and sarcopenia in patients with cancer and affecting immune system and response to therapy.<sup>32</sup>

Many methods exist to measure muscle indices and have proven the impact of sarcopenia for cancers treated by ICI, like two-photon absorptiometry<sup>14</sup> of psoas muscle index measured on 2D CT scan.<sup>33</sup> The use of 3D rather than 2D segmentation to determine body composition on

CT is recent<sup>22 24 27</sup> and allows a more accurate measurement of body composition, especially for fat, than the 2D segmentation computed at the L3 abdominal level.<sup>24 27 34</sup> The quality of the 3D measurements compared with the 2D measurements may explain the prognostic value found of the association of muscle mass and subcutaneous fat mass for lung cancer in multivariate analysis despite the addition of weight loss as a covariable that does not cancel out the effect of subcutaneous fat mass in the current study.<sup>23</sup>

Among the studied prognostic factors, ‘sarcopenic obesity’ is a particular entity joining obesity and sarcopenia, with high fat mass and low muscle mass,<sup>35</sup> which has notably been associated with increased toxicity with ICI.<sup>11</sup> This association could be related to the pharmacokinetics of immunotherapy, with a significant variability depending on body composition. Concerning survival, the ‘obesity paradox’ has however been described in renal cell carcinoma,<sup>36</sup> colorectal cancer<sup>37</sup> and NSCLC.<sup>38</sup> It refers to the improved survival among overweight/obese patients compared with normal weight patients, which appears to be related to ICI alone and not to the combination of chemotherapy and ICI.<sup>39</sup> Some authors think that this effect could be explained by visceral obesity<sup>40</sup> as visceral adipose tissue appears to be a prognostic parameter for several cancers, including lung cancer.<sup>41</sup> However, the prognostic value of visceral adipose tissue seems to be observed for patients with lung cancers treated with chemotherapy<sup>42</sup> and not for those treated with immunotherapy.<sup>43 44</sup> In the case of immunotherapy, a team observed recently in a population of 52 patients with NSCLC treated with ICIs that low ‘lumbar skeletal muscle index’ and low ‘subcutaneous fat index’ were predictive of inferior OS.<sup>44</sup> These results are consistent with ours, established on a larger population of 318 patients, plus 55 for the external validation cohort, with a 3D automatic method. While this ‘obesity paradox’ effect is observed in our study for NSCLC, this was not the case for melanoma, possibly due to the fact that melanoma have better OS than NSCLC (in our study, median OS 19.7 months vs 8.7 months, respectively), which could limit the impact of one fat measurement performed before treatment. However, these results are inconsistent with other studies, such the one of McQuade *et al* where, for patients with metastatic melanoma, obesity was associated with improved PFS and OS compared with those outcomes in patients with normal BMI.<sup>10</sup>

One particularly interesting finding of our study was the ability of a combination of SFM and MBM to stratify patients into different prognostic categories. In the whole study population and in NSCLC specifically, Kaplan-Meier analysis combining SFM and MBM was able to stratify patients into three prognostic categories, with the worst prognosis observed in those with both low SFM and MBM. This suggests that a combination of these two body composition variables may provide more prognostic information than either alone.

One of the advantages of the 3D analysis performed by Anthropometer3DNet is that it uses extrapolation factors

to expand on the data beyond the scope of acquisition, resulting in a total mass measurement instead of just an area or index. This total mass measurement has potential therapeutic implications and is obtainable through automatic segmentation and a wide range of Hounsfield units. Furthermore, the software, compatible with both injected and non-injected scanners, is currently accessible for research purposes on the Oncometer3D.com platform through an online service. As the measurements are automatic and take only a few seconds, routine use could be envisaged in the future. For example, these measurements could be taken automatically when a patient undergoes a diagnostic or follow-up CT scan, and recorded in the patient’s report. They would then be available to any clinician who wished to use it.

While our study identified several body composition parameters that were significantly associated with survival in patients with NSCLC treated with ICIs, it is important to consider the potential limitations of these findings. First, we studied morphological parameters prior to treatment and did not perform follow-up measurements of these parameters to see their prognostic value. A recent study showed that, during treatment, visceral adipose tissue increased while subcutaneous adipose tissue and musculature decreased, although this variation did not correlate significantly with survival.<sup>32</sup> However, these results could be studied on a larger population with a 3D measurement. Moreover, with a median delay of 26 days between imaging and the start of immunotherapy, variation in morphological parameters is possible within the interval. Although, in our study, this does not call into question the superiority of anthropometric parameters over BMI measured at the time of treatment, a maximum duration between imaging and the start of immunotherapy will probably have to be considered if these anthropometric parameters are to be taken into account when tailoring treatments. Second, our study population consisted primarily of patients with NSCLC, with no clear effect of body composition parameters, except muscle body mass, for patients with melanoma, and it is not clear if the same body composition parameters would have similar prognostic value in other cancer types.

Despite these limitations, our study shows that 3D-measured SFM and MBM may be useful prognostic factors in patients with NSCLC treated with ICIs. One potential approach to improving the prediction of outcomes in patients with cancer treated with ICIs could be to combine anthropometric parameters with other known prognostic factors. For example, multivariate statistical models or machine learning algorithms could be used to build predictive models based on a combination of multiple factors, including body composition parameters, tumor volume, tumor mutational burden (TMB),<sup>45</sup> microsatellite instability (MSI), neutrophil-to-lymphocyte ratio,<sup>9</sup> and other relevant variables. By considering multiple factors simultaneously, it may be possible to more accurately predict outcomes in patients with cancer treated with ICIs, and to inform personalized treatment decisions in these patients.

In conclusion, the present study suggests that 3D-measured low SFM ( $<5.22 \text{ kg/m}^2$ ) and low MBM ( $<6.86 \text{ kg/m}^2$ ) may be useful prognostic factors in patients with NSCLC treated with ICIs. Further research is needed to validate these findings and to determine the optimal management strategies for patients with low SFM and MBM. In addition to body composition parameters, other factors such as TMB and MSI may also be important prognostic factors in patients with cancer treated with ICIs, and should be considered in the management of these patients. Combining anthropometric parameters with other known prognostic factors may help to improve the prediction of outcomes in patients with cancer treated with ICIs, and could inform personalized treatment decisions in these patients.

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