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Impact of CT-based body composition parameters at baseline, their early changes and response in metastatic cancer patients treated with immune checkpoint inhibitors

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TITLE

Impact of CT-based body composition parameters at baseline, their early changes and response in metastatic cancer patients treated with immune checkpoint inhibitors

ABSTRACT

Purpose: CT-based Body-composition (BC) parameters correlate with the patients' outcome in metastatic cancer patients treated with chemotherapies or targeted therapies. Our aim was to investigate similar associations regarding immune checkpoint inhibitor (CPI).

Methods: Patients were consecutively included as they were treated with CPI at our institution for a metastatic solid cancer with baseline CT-scan (CT0) and early evaluation CT-scan (CT1, 2 months later). At each evaluation, the areas corresponding to psoas muscles alone, skeletal muscle, subcutaneous, visceral and total adipose tissues at L3 vertebral level were extracted and weighted by height², providing PMI, SMI, SATI, VATI and TATI, respectively, and their changes (Δt -) from the first day of treatment to CT1. Correlations between continuous BC-parameters and progression free survival (PFS) were evaluated in men, women and whole population with univariate Cox regressions. After dichotomizing the BC-parameters per whole-population and sex-specific tertiles, uni- and multivariate Cox models were built to identify independent predictors of the PFS.

Results: Between December 2013 and December 2016, 117 patients were included (55 women, mean age: 62.4) and 78 showed a progression (median PFS = 125 days, 95%CI = 87-117). Changes in BC-parameters did not depend on sex. None of the baseline BC-parameters correlated with PFS while Δt -PMI and Δt -SATI did (multivariate HR = 2.41, p = 0.0008 and HR = 2.82, p = 0.0004, respectively).

Conclusions: The occurrence of subcutaneous adipopenia and sarcopenia after beginning CPI treatment, estimated through Δt -SATI and Δt -PMI, correlated with higher risk of progression.

KEY-WORDS

Immunotherapy;

Body composition;

Multidetector computed tomography;
Sarcopenia;
Progression-free survival.

ABBREVIATIONS

95%CI: 94% confidence interval

BC: Body composition

BMI: Body mass index (kg/m^2)

CPI: Checkpoint inhibitors

Δ t: Changes in

HR: Hazard ratio

L3: Third lumbar vertebra level

PFS: Progression-free survival

PMI: Psoas muscle index (cm^2/m^2)

SATI: Subcutaneous adipose tissue index (cm^2/m^2)

SMI: Skeletal muscle index (cm^2/m^2)

TATI: Total adipose tissue index (cm^2/m^2)

VATI: Visceral adipose tissue index (cm^2/m^2)

1. Introduction

Immune checkpoint inhibitors (CPI) have demonstrated remarkable benefits in many subtypes of cancer. Several are now Food and Drug Administration approved and used in clinical practice. However, no marker has been perfectly able to predict the response, toxicity occurrence and outcomes of patients under treatment [1].

Cancer patients demonstrate heterogeneous body composition (BC) parameters that may modify the drug concentration and metabolism. Indeed, BC, particularly sarcopenia (i.e. low muscle mass), body mass index (BMI) and sarcopenic obesity, have emerged as critical parameters, potentially associated with chemotherapies and targeted therapies toxicities but also with patients outcomes [2-5]. In addition to clinical measurements and blood analyses, the nutritional status can be evaluated with CT-scans. Although imaging cannot measure the function of muscles, CT-scans can be used to measure the areas corresponding to skeletal muscle, subcutaneous and visceral adipose tissues [6]. Previous studies have demonstrated that these measurements could reflect the global nutritional status of patients when they were assessed on an axial slice at the 3rd lumbar level and weighted by the patients height², with a good reproducibility [7]. In a recent meta-analysis of 7843 patients with non-hematologic solid tumors from 38 studies, sarcopenia assessed on CT-scan was associated with worse overall survival, cancer-specific survival, disease-free survival and progression-free survival (PFS) [8].

However, there is a lack of consensus regarding the definition of sarcopenia on CT-scan and whether sex-specific thresholds are needed. An alternative could be to consider each patient as his/her own reference. In other words, changes in CT-based BC-parameters could be used to improve the evaluation of the nutritional status during treatments. Blauwhoff et al. demonstrated that the loss of skeletal muscle mass (evaluated with CT-scans) was predictive of worse outcome

for metastatic colorectal patients during chemotherapy [9]. Hence, knowing both the baseline nutritional status and its early change during treatment could help anticipating and strengthening the nutritional cares to patients, and consequently improving the efficacy of treatments. Furthermore, the influence of sex on the value of the prognostic BC-parameters is controversial leading to definitions of sarcopenia that could take into account sex (in the study by Martin et al. for instance), while other definitions did not (in the study by Prado et al. for instance) [3, 18]. The investigation of interactions between BC-parameters and CPI is a growing field of research. High BMI, sarcopenic obesity, sarcopenia and low amount of subcutaneous fat at baseline have been associated with an increasing risk of acute limiting toxicities in melanoma and lung cancer patients treated with ipilimumab or nivolumab [10-13]. Regarding changes in BC-parameters, only one retrospective series has demonstrated that an early loss of skeletal muscle could predict overall survival in metastatic melanoma patients treated with ipilimumab [11]. Therefore, our aim was to investigate correlations between CT-based BC-parameters at baseline and their early changes with the PFS as well as potential interactions with sex, in a retrospective cohort of patients with metastatic solid cancers treated with CPI.

2. Materials and methods

This study was approved by our institutional review board. The informed consent was waived by its retrospective nature.

2.1. Study design

This single-center study enrolled all metastatic solid tumor adult patients who were consecutively treated with CPI at our comprehensive cancer center between December 2013 and December 2016 (n=195). Patients were included if they had: (i) a whole-body baseline CT-scan performed within 28 days before beginning CPI (CT0), (ii) at first evaluation (CT1, within 2 months \pm 28 days after beginning CPI) and (iii) a response evaluation according to the RECIST 1.1 criteria [14]. Seventy-eight patients were excluded because of: lack of CT0 within the appropriate delay (n=51), lack of CT1 within the appropriate delay (n=10), deaths before CT1 (n=10), and cessation of CPI before CT1 due to serious adverse events (n=2) or clinical hyperprogression (n=5) (Fig. 1).

The following baseline characteristics were retrieved from medical reports: age, sex, performance status, histological type, staging, number of previous chemotherapy lines, presence of visceral metastasis, number of organs with metastases and type of CPI. Weight and height were measured with a medical balance and a stadiometer, respectively, on the first day of CPI to calculate the BMI (kg/m²).

PFS was defined as the number of days until radiological progression (defined as progressive disease according to RECIST 1.1 criteria) [14]. Toxicities were defined using the V4.0 of the Common Terminology Criteria for Adverse Events. Patients were clinically assessed by a

medical oncologist at the beginning of CPI and before any injection. A serious adverse event was defined as: grade III/IV/V, or leading to hospitalization, or leading to CPI discontinuation.

2.2. Assessment of CT-based BC-parameters (Fig. 2)

CT-scans were performed on various systems from 13 radiological centers. Twenty out of the 117 (17.1%) patients had at least one of the 2 examinations without a contrast-agent injection. The characteristics of each system are given in Supplementary Table 1. Overall, the slice thickness ranged from 1 to 2.5 mm; the in-plane resolution ranged from 0.66×0.66 to 0.9×0.9 mm²; the kVp was of 100 or 120; the pitch ranged from 0.825 to 1.75; and the tube currents ranged from 100 to 350 effective mAs.

The analyses were all performed in axial plane. Measurements were extracted from CT0 and CT1 for all patients by a trained senior radiologist (A.C.) and validated by a second senior radiologist (M.K.) blinded to biological and clinical data. The third lumbar vertebra (L3) was used as a standard landmark, as it has been correlated with the whole-body muscle mass in prior studies [7].

Using the Slice-O-Matic software (v4.3, Tomovision, Montreal, Canada), the areas corresponding to the skeletal muscle and the intermuscular, subcutaneous and visceral adipose tissues were manually segmented at L3 level using the following pre-defined thresholds of attenuations: [-29; 150] UH for muscle and [-190; -30] UH for fat. Next, these measurements were indexed for height² (cm²/m²) providing the following CT-based BC-parameters: skeletal muscle index (SMI), visceral adipose tissue index (VATI) and subcutaneous adipose tissue index (SATI). Total adipose tissue index (TATI) was defined as the sum of VATI, SATI and intra muscular adipose tissue index.

Furthermore, the radiologist manually segmented the surfaces of the left and right psoas muscles on a PACS and calculated the average psoas area, which was indexed for height², providing the psoas muscle area index (PMI, in cm²/m²), a simpler alternative for muscular assessment than SMI [15].

The change in each BC-parameters 'X' was calculated as follows: $\Delta t-X = (X_{CT1} - X_{CT0})$ divided by the time from the first day of CPI to CT1, and expressed in mm²/m²/day.

The Table 1 summarizes the definitions and calculations of all the CT-based BC-parameters involved in the study.

2.3. Statistical analysis

Statistical analyses were performed using R (v3.5.2, the R foundation for statistical computing, Vienna, Austria). All tests were two-sided. A p-value ≤ 0.05 was deemed significant. No patients had missing data.

The correlation between each pair of BC-parameters was estimated by using the Spearman rank test. The comparisons between BC-parameters in the men and women subgroups were performed with the Student t-test.

The correlations between continuous BC-parameters and PFS in men, women and in the whole population were assessed with univariate Cox regressions and hazard ratios (HRs, with 95% confidence interval [95%CI]). Next, BC-parameters were dichotomized per sex-specific tertiles and whole-population (or 'global') tertiles and the differences in survival were tested with the log-rank tests. The BC-parameters with a p-value < 0.200 in univariate analysis were entered in backward-forward stepwise Cox regression models in order to select the combination of variables that minimized the Akaike information criterion and that were independently correlated

with the PFS. The following clinical covariables were used in the multivariate models as potential confounding factors, namely: age ($<$ versus \geq median), performance status (0 versus 1-2), tumor type (non-small cell lung cancer versus others), visceral metastases (absent versus present), number of metastatic organs (0-1 versus ≥ 2), number of previous line of treatment (0-1 versus ≥ 2), CPI type (anti-PD1 versus anti-PDL1 versus anti-PD1/anti-CTLA4 combination) and occurrence of serious adverse event (absent versus present). Finally, the prognostic performances of the models were estimated with Harrell concordance indices and compared with a reference model that only included the baseline BMI at baseline and the covariables by using the “survcomp” R package [16,17]. The concordance index ranges from 0 to 1. A concordance index of 0.5 indicates the models predict the PFS as well as chance whereas a concordance index of 1 corresponds to a perfect discrimination.

3. Results

3.1. Study population (Table 2)

Of the 117 included patients, 55 (47%) were women. The median age was 63 years (range: 33.9-84.3). The most frequent histological types were non-small cell lung cancers (65/117, 55.6%). CPIs were anti-PD1, anti-PDL1 and anti-PDL1/CTLA4 association for 89/117 (76%), 12/117 (10.3%) and 16/117 (13.7%) patients, respectively. Initially, 51/117 (43.6%) patients were overweight (BMI > 25kg/m²). There was only one sarcopenic obese at baseline.

Table 3 provides the summary statistics of the BC-parameters at baseline and their early changes in men, women and in the whole population. On average, all CT-based BC-parameters decreased during the first two months of CPI treatment. Excepted SATI, all baseline BC-parameters were significantly different between men and women (range of p-value: <0.0001-0.01). None of the changes in BC-parameters were associated with sex.

There were 78/117 (67.5%) progressions and 36/117 (30.8%) deaths. The median PFS time was 125 days (95%CI = 87-117, Fig. 3).

3.2. Correlations between BC-parameters

Excepted for SMI and SATI, all baseline BC-parameters were significantly correlated with themselves (Fig. 4). In particular, BMI strongly and positively correlated with all CT-based BC-parameters (range of Spearman rho = 0.47 to 0.88).

Regarding correlations between baseline BC-parameters and changes in BC-parameters, correlations were either non significant or weaker. Only correlations between baseline SMI or PMI negatively correlated with their own changes (range of Spearman rho = -0.39 to -0.19), as well as correlations between VATI and Δt -VATI (rho = -0.22).

Excepted for Δt -VATI and changes in muscle-related indices (Δt -PMI and Δt -SMI), all changes in BC-parameters were significantly and positively correlated with themselves (range of Spearman rho = 0.19 to 0.84 to -0.19).

3.3. Univariate analysis

The results of the univariate analysis for BC-parameters are given in Tables 4 and 5 (results regarding the baseline clinical feature are given in Supplementary Table 2). Whatever the cohort (men, women, or whole population), none of the continuous, raw, baseline BC-parameters correlated with the PFS.

However, all the variables assessing the changes in CT-based BC-parameters correlated with PFS in the whole population and in the men cohort (range of p-values = 0.004 to <0.0001 and 0.006 to 0.0001, respectively). In the women cohort, significance was reached for Δt -VATI and Δt -PMI (p=0.004 and 0.01, respectively). Regarding these significant correlations between PFS and changes in CT-based BC-parameters, we found that all HRs were < 1, meaning that the highest and positive changes (i.e. stability or increase) were predictive of a better PFS.

After dichotomizing the whole population according to sex-specific and global tertiles, the same variables remained significantly correlated with the PFS, namely: Δt -PMI (lowest tertile versus others), Δt -SATI (lowest tertile versus others) and Δt -VATI (lowest tertile versus others) (p = 0.002, <0.0001 and 0.002, respectively). In the women subcohort, only Δt -SATI (lowest tertile versus others) was correlated with the PFS (p = 0.005).

3.4. Multivariate analysis

The results of the stepwise Cox regressions are given in Table 6. Tertiles assessed on whole population were used for dichotomization in the modeling. Two BC-parameters were found to be

independent predictors of PFS, i.e. ‘ Δt -SATI < lowest tertile’ (HR = 2.82, 95%CI = 1.58–5.03, p = 0.0004) and ‘ Δt -PMI < lowest tertile’ (HR = 2.41, 95%CI = 1.44 – 4.04, p = 0.0008). Three covariables also independently correlated with the PFS, i.e. the performance status, the presence of visceral metastases and the number of metastatic organs. Figure 5 displays the Kaplan-Meier curves for the BC-parameters included in the final model.

The concordance indices were 0.72 (95%CI = 0.69-0.76) and 0.66 (95%CI = 0.62 - 0.69) for the final model and the reference models, respectively, which was significantly different (p = 0.04).

4. Discussion

In this study, we present a large series examining the relationships between CT-based BC-parameters and response in patients receiving CPI for metastatic solid cancers. Despite the growing interest raised by the BC analysis from CT-scans of cancer patients, few data have been published so far in the field of immuno-oncology. Our results indicate that the early changes in CT-based BC-parameters deserve to be taken into account during CPI treatment, because they could correlate with PFS, while the prognostic value of baseline BC parameters appeared less relevant than for classical chemotherapies and targeted therapies. Moreover, we did not find an added value to sex-specific cutoffs, which suggests that complicating definitions with sex may not be necessary.

In a first exploratory analysis, we simply investigated univariate correlations between continuous BC parameters, without applying any cutoff (either median, tertiles, or previously published – for instance by Prado et al, or Martin et al), and the outcome [3,18]. Regarding the baseline features, we did not find significant correlations between PFS and high BMI or biomarkers of sarcopenia in patients treated with CPI although sarcopenic obesity has previously been identified as an adverse risk factor for patients treated with targeted and cytotoxic therapies [2,10,11,18]. Nevertheless, our results showed a tendency towards lower survivals for patients with high BMI. Furthermore, the BMI at baseline was one of the 3 variables that were selected in the final multivariate Cox model. Interestingly, Heidelberg et al. recently found correlations between sarcopenic overweight (defined as $BMI \geq 25\text{kg/m}^2$ and sarcopenia per Prado et al.) and CPI toxicities in melanoma patients [10]. Hence, a relationship between baseline BC-parameters, toxicity and PFS could be hypothesized. Though the validation of this assumption was not our

primary aim, the occurrence of serious adverse events was systematically included among the confounding covariables in our multivariate analysis. It should be noted that, herein, toxicity did not significantly correlate with the PFS and was an infrequent event.

Interestingly, all the continuous variables assessing the early changes in BC significantly correlated with the PFS in the univariate analysis, both in the whole population and in the men cohort (i.e. occurrence of sarcopenia and subcutaneous and visceral adipopenias). Though similar tendencies were seen in the women cohort, it should be noted that these associations were less important. Our multivariable analysis revealed that Δt -PMI and Δt -SATI were independent prognostic factors of the PFS. These results suggest that patients should be considered as their own reference when investigating the impact of BC parameters on survival. These results are also in agreement with a recent study by Daly et al. in multiple myeloma patients treated by Ipilimumab [11]. Indeed, the authors showed that a significant reduction in PMI (named SMA in this study, without weighting per height² and expressed as %/100days) was an independent predictor of the overall survival. SMI and PMI are both biomarkers of the skeletal muscle mass but the PMI does not require an additional software is a less time-consuming to evaluate. Thus, although less accurate than SMI, PMI correlated well with the PFS and would be easier to assess during daily practice. Finally, the comparisons of predictive models highlighted the added value of assessing the early changes in BC-parameters over a simple baseline assessment alone. These results emphasize the need for a more exhaustive assessment of BC in cancer patients. During their disease, patients generally undergo several CT-scans of which only the response status is extracted while the CT-based BC analysis remains largely unexploited by medical oncologists and radiologists.

The underlying physiopathological explanation of the relationship between BC and survival remains unknown. Not much is known about the impact of adipose and muscle tissues on anticancer treatment distribution and toxicity profile. Only a high intra-abdominal fat volume was associated with greater doxorubicin exposure and hematologic toxicity [19]. Prior studies suggested that sarcopenia and lean body mass could help to predict the occurrence of chemotherapy and targeted therapy toxicities [3-5,20]. These results were explained by the correlations between sarcopenia, cachexia and inflammation, which is known to inhibit the hepatic cytochrome P3A4 – a major actor of the hepatic metabolism of most anticancer therapies [21-23]. However, this explanation cannot be exploited because CPIs are not metabolized by this cytochrome.

On a patient's perspective, our results suggest that the nutritional status should be carefully monitored during CPI treatments and notably through a quantitative analysis of the CT-scan, for which oncologic radiologists should be sensitized. The lack of correlations between baseline CT-based BC-parameters and their early changes indicate that patients may not be sarcopenic at baseline but may show a strong and early decrease in their muscular mass within 2 months. Hence, nutritional reinforcement should be proposed as soon as a CPI treatment is proposed to a patient, whatever his/her initial nutritional status, in order to prevent the risk of sarcopenia and/or adipopenia.

Our study has limitations. First, this is a retrospective exploratory study. To limit the time-assessment bias, we excluded patients with a CT0 performed more than 28 days before beginning CPI and with a CT1 not within 2 months \pm 28 days later. Moreover, the delay between

CT0 and CT1 was not uniform, which explains why we divided the absolute change in BC-parameters by the time since the first day of CPI treatment to CT1. The iodine contrast-agent injection, which was at risk of measurement bias for the psoas attenuation and explains why we did not investigate the skeletal muscle density [4,24]. In addition, the acquisition protocols were not standardized across the 13 radiological centers involved in the study, leading to changes in in-plane resolution, slice thickness and noise within the images, which could have influenced the value of the CT-based BC-parameters and their changes. Indeed, Fuchs et al. have demonstrated that slice thickness, contrast agent injection and low tube current could significantly modify the skeletal muscle density and skeletal muscle area [25]. Consequently, further studies should consider standardizing the acquisition parameters and/or investigate if voxel size standardization and denoising algorithms could correctly homogenize CT-scans datasets without losing prognostic information. Furthermore, other potentially confusing variables were missing in the medical records such as biological markers of inflammation, sarcopenia, cachexia, or changes in BMI. However, our results were adjusted for the main confusing baseline covariables and notably the cancer histotypes. Moreover, cut-point optimization could have been used to optimally dichotomize BC-parameters but we purposely avoided these methods in our exploratory study because they were at risk of overfitting our findings [26,27]. Tertiles (or median) are classically used in medical statistics in the absence of validation cohort and in exploratory preliminary studies. We purposely did not extensively investigate previously published cut-offs for baseline sarcopenia because our exploratory analysis with continuous BC-parameters did not provide significant results. Furthermore, the existence of correlations between changes in BC-parameters and PFS in cancer patients treated with CPI does not indicate causality. Early occurrence of adipopenia and sarcopenia may just reflect a rapidly progressive

disease resisting to the CPI treatment. Even though, the assessment of the early changes in CT-based BC-parameters could help to distinguish between hyperprogression to pseudo-progression [28]. Finally, the manual segmentation with the slice-O-matic reference method is time-consuming and unfeasible in the routine practice of radiologists. Even if PMI and skeletal muscle density are simpler alternatives, they are prone to measurement bias. Importantly, focusing on only one slice of the CT-scan could also introduce bias, especially for VATI, due to changes in the moment of the respiratory cycle from CT0 to CT1, as also emphasized by Shen et al. [29]. Hence, there is a need for automating the 3D-extraction of BC-parameters from all CT-scan slices so as they could be implemented in clinical practice, enrich radiological reports and could truly reflect the whole BC, this with the help of deep learning approaches [30-33].

To conclude, our study provides evidence that CT-based BC-parameters, and especially their early changes, could correlate with the PFS in patients with metastatic cancers treated with CPI. Our results do not suggest that these changes in BC are different depending on sex. From the beginning of the CPI treatment, we believe that BC-parameters should be carefully monitored, ideally quantified in radiological reports, and nutritional reinforcement should be systematically proposed to these patients.

LEGENDS

Table 1. Definitions and calculations of the CT-based body composition parameters used in the study.

Table 2. Initial characteristics of the study population.

Table 3. Summary statistics of each body composition parameters in men, women and whole study population.

Table 4. Assessment of univariate correlations between progression free survival and continuous body-composition parameters at baseline and their early changes, in men, women and whole population.

Table 5. Univariate survival analysis in men, women and whole population

Table 6. Results of the stepwise multivariate prognostic modeling

Figure 1. Flow-chart of the study.

Figure 2. Assessment of the CT-based body composition parameters at baseline (CT0) and early radiological evaluation (CT1). **(A)** Initial acquisition showing the axial slices at the middle of the third lumbar vertebra (L3) for both examinations. **(B)** Segmentations: The same process was applied to CT0 and CT1. By using Slice-O-matic reference software and pre-defined density threshold, the radiologist manually segmented the area of the skeletal muscle (in red), visceral adipose tissue (in yellow), intermuscular adipose tissue (in green), subcutaneous adipose tissue (in blue) and divided these areas by the height², providing: skeletal muscle index (SMI), visceral adipose tissue index (VATI), intermuscular adipose tissue index (ImATI), subcutaneous adipose tissue index (SATI) and the total adipose tissue index (TATI) as the sum of VATI, TATI and ImATI. Moreover, the radiologist manually segmented the surface of the left and right psoas (in orange) on a PACS and calculated the average area of a psoas divided it by the height², providing the psoas muscle index (PMI).

Figure 3. Kaplan-Meier curve regarding the progression-free survival in the whole study population with 95% confidence interval and risk table.

Figure 4. Correlation matrix between each pair of body composition (BC) parameters. The left-lower diagonal shows the scatterplot with the regression line in red and its 95% confidence interval. The upper diagonal indicates the value of Spearman rho coefficient, from -1 to +1. Colors indicates that the p-value of the Spearman test is below 0.05. Abbreviations: BMI: body mass index, Δt : changes in, PMI : psoas muscle index, SATI: subcutaneous adipose tissue index, SMI: skeletal muscle index, VATI: visceral adipose tissue index, TATI: total adipose tissue index

Figure 5. Kaplan-Meier curves for the progression-free survival depending on the 3 body-composition (BC) parameters selected in the final multivariate model. The 3 variables were (A) the baseline body mass index (BMI); (B) the changes in subcutaneous adipose tissue index (Δ t-SATI); and (C) the changes in psoas muscle index (Δ t-PMI)

§ In men and women subcohorts, the BC parameters were dichotomized according to sex-specific cut-offs. * : $p < 0.05$, ** : $p < 0.005$, *** : $p < 0.001$

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Table 1. Definitions and calculations of the CT-based body composition (BC) parameters used in the study.

BC parameters	Formula	Definition
Baseline parameters		
BMI (kg/m²)	$Weight / Height^2$	Body mass index
SMI (cm²/m²)	$Skeletal\ Muscle\ Area\ on\ CT0 / Height^2$	Surface corresponding to the skeletal muscles on an axial CT-scan slice passing through the middle of the 3 rd lumbar vertebra divided by patient's square of height. Potential biomarker of the muscle mass.
PMI (cm²/m²)	$Average\ Psoas\ Muscle\ Area\ on\ CT0 / Height^2$	Surface corresponding to the psoas muscle on an axial CT-scan slice passing through the middle of the 3 rd lumbar vertebra divided by patient's square of height. Potential biomarker of the muscle mass.
SATI (cm²/m²)	$Subcutaneous\ Adipose\ Tissue\ Area\ on\ CT0 / Height^2$	Surface corresponding to the subcutaneous adipose tissue on an axial CT-scan slice passing through the middle of the 3 rd lumbar vertebra divided by patient's square of height. Potential biomarker of the adipose tissue.
VATI (cm²/m²)	$Visceral\ Adipose\ Tissue\ Area\ on\ CT0 / Height^2$	Surface corresponding to the visceral adipose tissue on an axial CT-scan slice passing through the middle of the 3 rd lumbar vertebra divided by patient's square of height. Potential biomarker of the adipose tissue
TATI (cm²/m²)	$VATI + SATI + Intermuscular\ Adipose\ Tissue\ Index$	Sum of SATI, VATI and the intermuscular adipose tissue index (i.e. surface corresponding to the intermuscular adipose tissue on an axial CT-scan slice passing through the middle of the 3 rd lumbar vertebra divided by patient's square of height). Potential biomarker of the adipose tissue
Change in CT-based BC parameters (mm²/m²/day)		
Δt-SMI	$SMI_{CT1} - SMI_{CT0} / \Delta t$	Absolute change in SMI from 1 st day of CPI treatment to CT1
Δt-PMI	$PMI_{CT1} - PMI_{CT0} / \Delta t$	Absolute change in PMI from 1 st day of CPI treatment to CT1
Δt-SATI	$SATI_{CT1} - SATI_{CT0} / \Delta t$	Absolute change in SATI from 1 st day of CPI treatment to CT1
Δt-VATI	$VATI_{CT1} - VATI_{CT0} / \Delta t$	Absolute change in VATI from 1 st day of CPI treatment to CT1
Δt-TATI	$TATI_{CT1} - TATI_{CT0} / \Delta t$	Absolute change in TATI from 1 st day of CPI treatment to CT1

NOTE. Abbreviations: Δt: early change in, BC: body composition, BMI: body mass index, CPI: check point inhibitor, CT: computed tomography, PMI: psoas muscle index, SMI: skeletal muscle index, SATI: subcutaneous adipose tissue index, VATI: visceral adipose tissue index, TATI: total adipose tissue index.

Table 2. Initial characteristics of the study population.

Characteristics	Patients
Age	63 (33.9-84.3)
Sex	
Woman	55/117 (47%)
Man	62/117 (53%)
Body mass index (kg/m²)	
<20	15/117 (12.8%)
20 - 24.9	51/117 (43.6%)
25 - 29.9	37/117 (31.6%)
≥ 30	14/117 (12%)
Tumor type	
Non-small cell lung cancer	65/117 (55.6%)
Soft-tissue sarcoma	14/117 (12%)
Prostate adenocarcinoma	8/117 (6.8%)
Urothelial carcinoma	6/117 (5.1%)
Cervix cancer	4/117 (3.4%)
Anal carcinoma	3/117 (2.6%)
Cholangiocarcinoma	3/117 (2.6%)
Endometrial adenocarcinoma	3/117 (2.6%)
Gastro-intestinal stromal tumor	3/117 (2.6%)
Others	8/117 (6.8%)
Tumor TNM stages	
Stage 3	6/117 (5.1%)
Stage 4	111/117 (94.9%)
Visceral metastasis	
Absent	46/117 (39.3%)
Present	71/117 (60.7%)
No. of metastatic sites	
0 or 1	39/117 (33.3%)
2 or 3	67/117 (57.3%)
≥ 4	11/117 (9.4%)
Performance status	
PS 0	56/117 (47.9%)
PS 1	54/117 (46.2%)
PS 2	7/117 (6%)
No. of previous chemotherapy line	
0	16/117 (13.7%)
1	50/117 (42.7%)
2	26/117 (22.2%)
≥ 3	25/117 (21.4%)
CPI type	
Anti-PD1	89/117 (76%)
Anti-PDL1	12/117 (10.3%)
Anti-PDL1 + Anti-CTLA4	16/117 (13.7%)

NOTE. Data are numbers of patients with percentage in parentheses except for age, given with median and range. Abbreviations: CPI: check point inhibitor, No: number, PS: performance status.

Table 3. Summary statistics of each body composition parameters in men, women and whole study population.

Characteristics	Whole Population cohort		Women cohort		Men cohort		p-value [§]
	Median (range)	Lower Upper tertiles	Median (range)	Lower Upper tertiles	Median (range)	Lower Upper tertiles	
Baseline BC parameters							
BMI	23.78 (16.22 - 35.03)	21.91 26.21	21.84 (16.22 - 31.89)	21.08 23.71	26 (18.61 - 35.03)	23.69 27.54	0.0002***
SMI	44.84 (27.20 - 75.48)	41 48.11	39.11 (27.20 - 54.45)	36.89 41.67	50.49 (34.58 - 75.48)	46.44 54.15	<0.0001***
TATI	100.33 (11.40 - 250.1)	69.31 130.30	75.93 (11.40 - 213.27)	59.71 108.50	122.93 (15.87 - 250.10)	88.85 141.79	0.01*
VATI	27.22 (0.94 - 167.58)	16.54 51.23	16.93 (0.94 - 71.21)	14.03 24.01	57.28 (2.36 - 167.58)	37.67 73.61	<0.0001***
SATI	53.40 (9.11 - 132.01)	42.23 64.59	54.72 (9.10 - 132.01)	45.82 71.44	52.57 (10.01 - 103.70)	41.99 60.86	0.052
PMI	2.12 (0.92 - 4.69)	1.92 2.40	1.89 (0.92 - 2.81)	1.70 2.07	2.46 (1.29 - 4.69)	2.20 2.77	<0.0001***
Change in CT-based BC-parameters (cm²/m²/100days)							
Δt-SMI	-1.65 (-31.36 - 27.17)	- 3.33 0.51	- 0.53 (-21.15 - 27.17)	-2.72 0.87	- 2.4 (-31.36 - 16.66)	-4.38 -0.57	0.07
Δt-TATI	-9.5 (-141.66 - 105.6)	- 22.59 2.96	- 11.7 (-141.66 - 105.6)	-23.7 8.54	- 8.67 (-13.95 - 34.92)	-18.22 -1.97	0.2
Δt-VATI	-2.74 (-100.9 - 34.8)	- 8.06 1.8	- 1.17 (-100.9 - 23.04)	-7.87 2.89	- 3.07 (-99.81 - 34.8)	-8.66 -0.9	0.2
Δt-SATI	-5.27 (-77.94 - 80.94)	- 12.4 0.9	- 7.78 (-56.49 - 80.94)	-16.05 4.2	- 3.52 (-77.94 - 9.11)	-10.36 0.09	0.3
Δt-PMII	-0.07 (-3.74 - 1.27)	- 0.30 0.14	0.07 (-1.69 - 1.17)	-0.22 0.17	- 0.23 (-3.74 - 1.27)	-0.36 0.03	0.07

NOTE. Abbreviations: Δt : early change in, BC: body composition, BMI: body mass index, CT: computed tomography, HR: hazard ratio, PMI: psoas muscle index, SMI: skeletal muscle index, SATI: subcutaneous adipose tissue index, VATI: visceral adipose tissue index, TATI: total adipose tissue index.

§ Differences between men and women were assessed with the Student t-test.

Significant associations are highlighted in bold.

*: p<0.05, **: p< 0.005, ***: p<0.001

Table 4. Assessment of univariate correlations between progression free survival and continuous body-composition parameters at baseline and their early changes, in men, women and whole population.

Characteristics	Whole population cohort		Women cohort		Men cohort	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Baseline BC parameters						
BMI	1.05 (0.99 - 1.11)	0.1	1.02 (0.94 - 1.11)	0.6	1.06 (0.99 - 1.15)	0.1
SMI	1.01 (0.98 - 1.04)	0.6	1.01 (0.95 - 1.08)	0.7	1 (0.95 - 1.04)	0.9
PMI	1 (1 - 1)	0.9	1 (0.99 - 1.01)	0.9	1 (0.99 - 1)	0.6
SATI	1 (0.99 - 1.01)	0.6	1 (0.99 - 1.01)	0.9	1.01 (1 - 1.02)	0.1
VATI	1 (1 - 1.01)	0.1	1 (0.98 - 1.02)	0.8	1.01 (1 - 1.01)	0.1
TATI	1 (1 - 1.01)	0.2	1 (0.99 - 1.01)	0.9	1.01 (1 - 1.01)	0.1
Change in CT-based BC parameters (in mm²/m²/day)						
Δt-SMI	0 (0 - 0.18)	0.004**	0.04 (0 - 12.73)	0.3	0 (0 - 0.16)	0.006*
Δt-PMI	0.45 (0.31 - 0.64)	<0.0001***	0.38 (0.19 - 0.8)	0.01*	0.52 (0.33 - 0.80)	0.003**
Δt-SATI	0.13 (0.04 - 0.43)	0.001**	0.29 (0.07 - 1.27)	0.1	0.03 (0.01 - 0.21)	0.0002***
Δt-VATI	0.09 (0.03 - 0.3)	0.0001***	0.03 (0 - 0.33)	0.004**	0.1 (0.02 - 0.44)	0.002**
Δt-TATI	0.2 (0.1 - 0.41)	<0.0001***	0.29 (0.1 - 0.84)	0.02*	0.15 (0.06 - 0.38)	0.0001***

NOTE. Abbreviations: 95%CI: 95% confidence interval, Δt : early change in, BC: body composition, BMI: bod mass index, CT: computed tomography, HR: hazard ratio, PMI: psoas muscle index, SMI: skeletal muscle index, SATI: subcutaneous adipose tissue index, VATI: visceral adipose tissue index, TATI: total adipose tissue index.

Significant correlations are highlighted in bold.

*: p< 0.05, **: p<0.005, ***: p<0.001

Table 5. Univariate survival analysis in men, women and whole population

Characteristics	Whole population - GLOBAL TERTILES ¹			Whole population - SEX-SPECIFIC TERTILES ²			WOMEN ³			MEN ⁴		
	No. of event / patients	Median PFS (95%CI)	log rank p-value	No. of event / patients	Median PFS (95%CI)	log rank p-value	No. of event / patients	Median PFS (95%CI)	log rank p-value	No. of event / patients	Median PFS (95%CI)	log rank p-value
Baseline BC parameters												
BMI												
Lowest tertile	21/39	229 (86-.)	0.06	22/39	229 (124-.)	0.06	9/18	401 (63-.)	0.4	13/21	225 (124-.)	0.09
Middle tertile	28/39	125 (67-225)	0.2	28/38	98 (62-163)	0.2	12/18	65.5 (61-.)	0.7	16/20	111 (69-.)	0.3
Uppest tertile	29/39	112 (85-163)	<u>0.2</u>	28/40	120 (85-336)	<u>0.2</u>	13/18	106 (63-.)	<u>0.5</u>	15/21	126 (59-.)	<u>0.3</u>
SMI												
Lowest tertile	23/39	172 (64-.)	0.6	25/39	163 (67-322)	0.6	9/18	172 (57-.)	0.9	16/21	124 (67-.)	1
Middle tertile	28/39	122 (86-322)	0.6	26/38	131.5 (69-.)	0.6	12/18	96.5 (61-.)	0.4	14/20	151 (85-.)	0.8
Uppest tertile	27/39	126 (81-225)	<u>0.9</u>	27/40	125 (80-557)	<u>1</u>	13/18	86 (63-.)	<u>0.9</u>	14/21	127 (56-.)	<u>0.7</u>
PMI												
Lowest tertile	23/39	107 (64-.)	0.5	24/39	125 (90-.)	0.5	9/18	86 (57-.)	0.4	15/21	125 (107-.)	0.7
Middle tertile	29/39	122 (85-216)	0.7	27/38	115 (63-216)	0.7	12/18	74.5 (61-.)	0.9	15/20	151 (69-.)	0.4
Uppest tertile	26/39	151 (87-336)	<u>0.5</u>	27/40	126 (80-557)	<u>0.8</u>	13/18	126 (80-.)	<u>0.8</u>	14/21	127 (56-.)	<u>0.6</u>
SATI												
Lowest tertile	26/39	124 (63-322)	0.5	26/39	124 (63-322)	0.5	11/18	71.5 (61-.)	0.6	15/21	182 (64-.)	0.9
Middle tertile	24/39	163 (111-.)	0.2	24/38	160 (107-.)	0.2	9/18	401 (87-.)	0.6	15/20	112 (85-.)	0.1
Uppest tertile	28/39	120 (64-216)	<u>0.2</u>	28/40	120 (64-216)	<u>0.4</u>	14/18	85 (63-.)	<u>0.4</u>	14/21	126 (59-.)	<u>0.9</u>
VATI												
Lowest tertile	23/39	216 (81-.)	0.2	23/39	182 (124-.)	0.2	9/18	126 (63-.)	0.6	14/21	225 (124-.)	0.3
Middle tertile	29/39	122 (63-260)	0.6	25/38	125 (61-.)	0.6	12/18	126 (57-.)	0.6	13/20	125 (69-.)	0.4
Uppest tertile	26/39	120 (87-.)	<u>0.4</u>	30/40	106 (63-163)	<u>0.3</u>	13/18	87 (63-.)	<u>0.8</u>	17/21	112 (59-.)	<u>0.4</u>
TATI												
Lowest tertile	24/39	182 (80-.)	0.5	25/39	165 (67-322)	0.5	11/18	71.5 (61-.)	1	14/21	225 (81-.)	0.3
Middle tertile	26/39	126 (85-.)	0.2	24/38	163 (107-.)	0.2	10/18	401 (64-.)	0.7	14/20	127 (85-.)	0.2
Uppest tertile	28/39	120 (63-163)	<u>0.4</u>	29/40	106 (63-163)	<u>0.2</u>	13/18	87 (63-.)	<u>0.4</u>	16/21	112 (59-.)	<u>0.4</u>
Change in CT-based BC parameters (in cm²/m²/100days)												
Δt-SMI												
Lowest tertile	28/39	80 (57-.)	0.1	27/39	90 (61-.)	0.1	13/18	71.5 (57-.)	0.2	14/21	124 (55-.)	0.4
Middle tertile	28/39	126 (81-182)	0.07	28/38	99 (64-117)	0.07	11/18	104.5 (61-.)	0.5	17/20	98 (60-182)	0.09
Uppest tertile	22/39	225 (126-.)	<u>0.2</u>	23/40	216 (151-.)	<u>0.2</u>	10/18	216 (86-.)	<u>0.7</u>	13/21	225 (126-.)	<u>0.2</u>
Δt-PMI												
Lowest tertile	31/39	61 (55-126)	0.002**	30/39	63 (56-163)	0.002**	13/18	74.5 (54-.)	0.1	17/21	60 (51-.)	0.02*
Middle tertile	24/39	163 (125-.)	0.1	26/38	127 (85-.)	0.1	11/18	86 (64-.)	0.1	15/20	151 (124-.)	0.9
Uppest tertile	23/39	172 (111-.)	0.008*	22/40	216 (120-.)	0.02*	10/18	216 (62-.)	<u>0.3</u>	12/21	160 (112-.)	<u>0.2</u>
Δt-SATI												
Lowest tertile	32/39	59 (54-106)	<0.0001***	31/39	64 (54-112)	<0.0001***	14/18	65 (54-.)	0.005**	17/21	64 (45-151)	0.002**

Middle tertile	24/39	165 (124-.)	0.09	24/38	177 (85-.)	0.09	10/18	126 (61-.)	0.3	14/20	177 (107-.)	0.3
Uppest tertile	22/39	182 (125-.)	<u>0.0004</u>***	23/40	172 (160-.)	<u>0.002</u>**	10/18	216 (87-.)	<u>0.08</u>	13/21	163 (125-.)	<u>0.01</u>*
Δt-VATI												
Lowest tertile	27/39	80 (60-.)	0.1	27/39	80 (60-.)	0.1	13/18	73.5 (60-.)	0.4	14/21	90 (45-.)	0.2
Middle tertile	28/39	151 (124-229)	0.2	26/38	151 (87-260)	0.2	11/18	126 (64-.)	0.3	15/20	151 (124-.)	0.6
Uppest tertile	23/39	216 (85-.)	<u>0.3</u>	25/40	216 (85-.)	<u>0.3</u>	10/18	216 (56-.)	<u>0.7</u>	15/21	225 (107-.)	<u>0.4</u>
Δt-TATI												
Lowest tertile	30/39	64 (57-122)	0.002**	29/39	67 (59-126)	0.002**	13/18	65 (57-.)	0.1	16/21	67 (45-.)	0.002**
Middle tertile	25/39	177 (125-.)	0.3	23/38	165 (111-.)	0.3	11/18	126 (64-.)	0.3	12/20	165 (124-.)	0.5
Uppest tertile	23/39	216 (107-.)	<u>0.007</u>*	26/40	182 (107-336)	<u>0.03</u>*	10/18	216 (63-.)	<u>0.4</u>	16/21	182 (107-343)	<u>0.04</u>*

NOTE. For each CT-based BC parameters, the subgroups were created according to: (1) ‘global’ tertiles assessed on the whole population (without taking into account the sex of patients); (2) sex-specific tertiles (i.e. after pooling together the men and women cohorts previously subdivided according to their sex-specific tertiles); (3) in the women population: per women-specific tertiles, (4) in the men population: per men specific tertiles.

Abbreviations: 95%CI: 95% confidence interval, Δt : early change in, BC: body composition, BMI: bod mass index, CT: computed tomography, HR: hazard ratio, PFS: progression free survival, PMI: psoas muscle index, SMI: skeletal muscle index, SATI: subcutaneous adipose tissue index, VATI: visceral adipose tissue index, TATI: total adipose tissue index.

Significant correlations are highlighted in bold.

*: p< 0.05, **: p<0.005, ***: p<0.001.

The underlined p-value corresponds to the log-rank p-value when all modalities were considered altogether. The p-values above correspond to the p-value for the comparisons between (1) lowest tertile vs. middle + uppest tertiles and (2) lowest + middle tertiles vs. uppest tertile.

Table 6. Results of the stepwise multivariate prognostic modeling

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
BC-parameters				
Δ t-SATI (< lowest tertile [§])	2.43 (1.54 – 3.84)	<0.0001***	2.82 (1.58 – 5.03)	0.0004***
Δ t-PMI (< lowest tertile [§])	2.03 (1.28 – 3.2)	0.002**	2.41 (1.44 – 4.04)	0.0008***
BMI (< lowest tertile [§])	0.62 (0.38 – 1.03)	0.06	0.60 (0.35 – 1.04)	0.07
Baseline Covariables				
Age (\geq median)	1.47 (0.94 - 2.31)	0.09	1.24 (0.76 – 2.02)	0.4
Sex (men)	1.15 (0.73 – 1.80)	0.5	0.98 (0.57 – 1.69)	1
Performance status (\geq 2)	1.89 (1.19 - 2.99)	0.006*	1.89 (1.11 – 3.21)	0.02*
Tumor type (non-NSCLC)	1.45 (0.93 - 2.27)	0.1	1.35 (0.81 – 2.24)	0.2
No. of previous lines (\geq 2)	1.24 (0.79 - 1.94)	0.3	0.86 (0.51 – 1.44)	0.6
CPI type (anti-PDL1)	1.26 (0.65 - 2.46)	0.5	1.07 (0.51 – 2.24)	0.9
CPI type (anti-PDL1 + anti CTLA4)	0.52 (0.24 - 1.12)	0.09	0.41 (0.16 – 1.01)	0.052
Presence of visceral metastases	1.03 (0.65 - 1.62)	0.9	1.85 (1.03 – 3.34)	0.04*
No. of metastatic sites (\geq 2)	0.69 (0.44 - 1.1)	0.1	0.40 (0.22 – 0.71)	0.002**
Occurrence of severe adverse event	0.68 (0.31 - 1.49)	0.3	0.51 (0.22 – 1.19)	0.1

NOTE. Abbreviations: 95%CI: 95% confidence interval, Δ t: early change in, BC: body composition, BMI: bod mass index, CPI: checkpoint inhibitor, HR: hazard ratio, NSCLC: non-small cell lung cancer, PMI: psoas muscle index, SMI: skeletal muscle index, SATI: subcutaneous adipose tissue index.

Significant correlations are highlighted in bold.

*: p< 0.05, **: p<0.005, ***: p<0.001

Patients treated with CPI from
December 2013 to December 2016
(N = 195)

◆ 51 patients without baseline CT0 within
28 days before beginning CPI

Patients with baseline CT0
(N = 144)

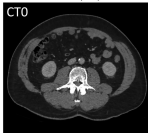
◆ 10 deaths before early evaluation CT1
◆ 2 patients with CPI interruption because
of serious adverse events before early
evaluation CT1
◆ 5 patients with CPI cessation because of
clinical progression before early evaluation
CT1
◆ 10 patients without early evaluation CT1
within 2 months (\pm 28 days)

117 included patients

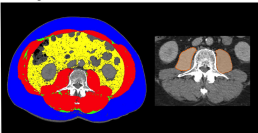
- Extraction of CT BC parameters at
baseline and early evaluation CTs.
- Calculation of the changes in CT BC
parameters.

*Univariate and multivariate prognostic
values of BC parameters and their
changes.*

A. CT-scans (L3)



B. Segmentations



SMI

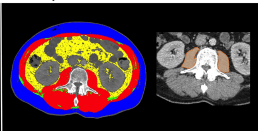
VATI

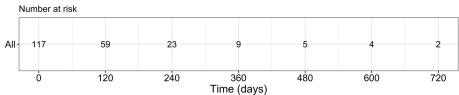
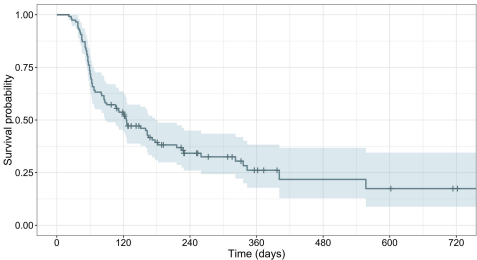
ImATI

SATI

Psoas
PMI

CT1





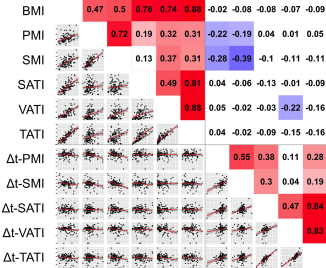
Spearman coefficient



Baseline
BC-parameters

Early changes in
BC-parameters

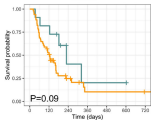
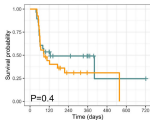
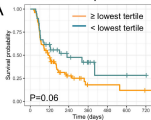
BMI PMI SMI SATI VATI TATI Δ t-PMI Δ t-SMI Δ t-SATI Δ t-VATI Δ t-TATI



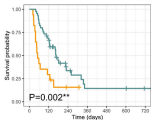
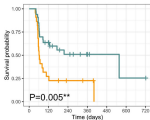
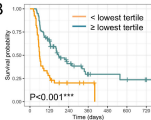
Whole Population

Women[§]Men[§]

A



B



C

