Prognostic Value of Body Composition in Therapy-Naive Patients with Non-Small Cell Lung Cancer

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ABSTRACT

The objective of this study was to assess the impact of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), skeletal muscle mass volume (SMMV), and VAT/SAT ratio on the prognosis of therapy naive metastatic non-small cell lung cancer (NSCLC) patients undergoing different therapy regimens. Eighty three patients with stage-IV NSCLC who were received at least one cycle of platinum-based chemotherapy (PBCT) or tyrosine kinase inhibitor (TKI) therapy included in this retrospective study. Pre-treatment multi-slice and single-slice computed tomography images of PET/CT scans were used for the assessment of body composition. The effect of anthropometric measurements on clinical outcomes for advanced NSCLC patients was investigated with survival analysis for each treatment subgroup. In univariate analyses, female gender ($p= 0.03$), presence of bone metastasis ($p= 0.02$), presence of adrenal metastasis ($p< 0.005$), SAT volume ($p= 0.01$), VAT/SAT ratio ($p= 0.02$) and serum albumin levels ($p= 0.01$) were found to be statistically significant for overall survival (OS) in TKI treatment group. In multivariate analyses, only serum albumin level ($p< 0.005$) remained an independent risk factor. No significant results were found in the PBCT treatment group. Single-slice volume calculation method for VAT measurement was highly correlated with a multi-slice method which reflects the entire abdominopelvic region. In conclusion, our study indicates that adipose tissue and muscle mass volume alone do not significantly affect survival in patients with metastatic NSCLC. However, hypoalbuminemia was identified as an independent negative prognostic factor.

Keywords: Body composition, Multi-slice computed tomography, Non-small cell lung cancer, Subcutaneous adipose tissue, Visceral adipose tissue

INTRODUCTION

Lung cancer is one of the leading causes of cancer-related mortality worldwide, with 2.2 million newly diagnosed cases and 1.8 million deaths reported in 2020.[1] Non-small cell lung cancer (NSCLC) accounts for 85% of all cases. At the time of diagnosis, approximately 20% of this subgroup have locally advanced disease (stage III) and about 50% have metastatic (stage IV) disease. The 5-year survival rate for patients with metastatic disease under standard regimen is less than 6%. Targeted therapy (tyrosine kinase inhibitors; TKIs), immune checkpoint inhibitors (ICIs), or platinum-based chemotherapy (PBCT) regimens are used in the treatment of metastatic NSCLC, based on molecular characteristics.[2]

The effect of body mass index (BMI) and body composition on the survival rate is one of the research topics of interest in cancer patients. BMI is often used as a proxy measure of total adiposity and previous studies examining the relationship between BMI and cancer outcomes have shown distinct results.[3] Obese patients with malignancies such as colorectal, breast, and pancreatic cancers, have been shown to have a worse prognosis than normal-weight patients.[4-6]

Nevertheless, obese patients with NSCLC have been observed to have a better clinical outcome than normal/low-weight cancer patients.[7] On the other side, sarcopenia, defined as a loss in skeletal muscle mass volume (SMMV) is associated with poor prognosis in many malignancies as in lung cancer.[8] The term sarcopenia was first used by Baumgartner to describe the age-related loss of muscle mass seen in older adults. Over the last decade, the definition of sarcopenia has been adapted in oncology as severe muscle loss and has been associated with adverse outcomes.

While BMI is a simple and reproducible measure that is used to allocate the weight of study participants into broad groups, typically underweight, normal weight, overweight, and obese, it does not clearly reflect body composition, adipose tissue (AT) distribution, and total body SMMV.[3] Although there is no standard procedure for determining the distribution of AT and SMMV, studies have consistently reported that computed tomography (CT) and magnetic resonance imaging (MRI) can delineate these structures.

Body AT has traditionally been divided into two main groups: visceral AT (VAT) and subcutaneous AT (SAT).[9] Currently, CT is one of the most widely used imaging modalities for differentiating VAT from SAT; and both the volumes of VAT and SAT, and SMMV can be estimated using the single slice method.[10] This technique has been questioned and its limitations are highlighted in the literature.[11] A variety of multiple-slice volume calculation methods have been applied in different studies and some of them used the entire abdominal area of the body to solve these limitations.[12] Such a comparative study has not been published before for these volume calculation methods in the literature.

Based on all the information in the literature, as the primary aim, we here evaluated the impact of VAT, SAT, SMMVs, and VAT/SAT ratio on the prognosis of therapy-naïve metastatic NSCLC patients undergoing different therapy regimens. The secondary aim of this research was to investigate the usefulness of single-slice CT assessment of visceral abdominal adiposity and the consistency of the results obtained with the multi-slice volume calculation method for the entire abdominal area.

PATIENTS AND METHODS

Study Design and Patient Selection

Eighty-three patients with stage-IV NSCLC who received at least one cycle of PBCT or TKI therapy and who underwent pre treatment FDG PET/CT from June 2012 to February 2019 were enrolled in this single center retrospective study.

Medical records were reviewed to extract the required clinical data [age, smoking history, height, weight, Eastern Cooperative Oncology Group (ECOG) performance status score, biochemical parameters [C-reactive protein (CRP), albumin, calcium, lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) serum levels], diagnosis date, tumor histology, driver mutations, stage at diagnosis, metastasis regions, treatment type and content, and survival.

Clinical T/N/M stage was determined according to the eight editions of the American Joint Committee on Cancer (AJCC). The BMI of each patient was calculated with the formula of weight/height^2 (kg/m^2) and body surface area ([Height (cm) x Weight (kg)] / 3600) ½ (m^2). Overall survival (OS) was defined as the time (month) from the beginning of the first-line treatment until death or until the present time.

Imaging Analysis

All patients had undergone whole-body 18F-FDG PET/CT (GE Discovery ST; GE Healthcare, Milwaukee, WI) imaging and multi-slice CT was performed with a multidetector ST helical scanner using slip ring technology. All patients fasted for 6 hours before the PET/CT scan. Approximately 1 hour later, a multi-slice CT scan was acquired using a 16-slice multidetector scanner (Parameters: 80 mA, 140kV, table speed: 27 mm/rotation, and slice thickness: 7 mm) of areas from the upper thigh to the skull base. A standard whole body PET scan was performed in 3D mode with an acquisition time of 4 minutes per bed position covering the same field as the CT scan. Acquired data were reconstructed using an iterative algorithm and CT images without contrast enhancement were acquired for attenuation correction. Next, the acquisition data were transferred to a workstation

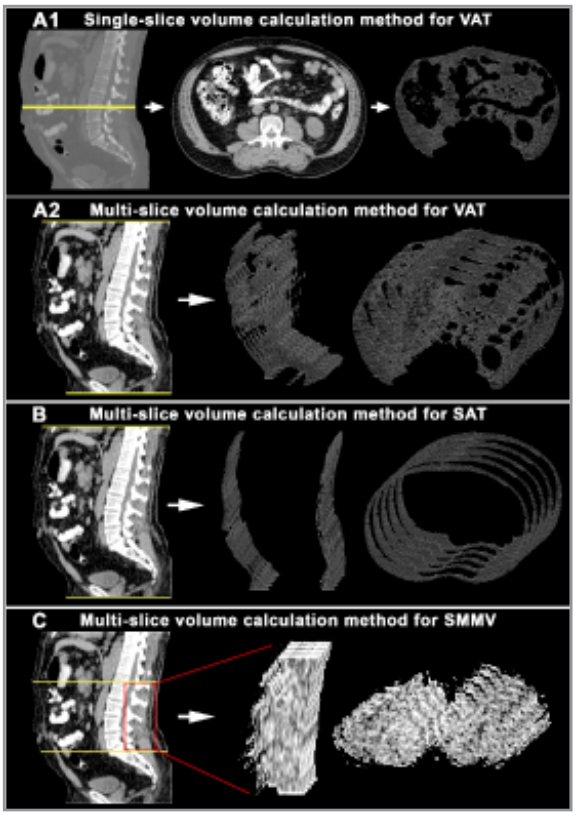

Figure 1. Examples of segmentation of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle mass volume (SMMV).

(Advantage Windows Server 4.5; GE Healthcare) for manual segmentation and interpretation. CT images were reviewed in transaxial, coronal, and sagittal views, and evaluated by two experienced nuclear medicine physicians.

Due to the heterogeneous distribution of VAT, the entire abdominopelvic region from the "diaphragm dome" to the "symphysis pubis" level was determined as the study area (Figure 1 A2, B). For SMMV calculation, paraspinal muscle tissue located between L2-L5 lumbar vertebrae levels was determined (Figure-1 C). "Hounsfield Unit" (HU) values were used for VAT, SAT and SMMV calculations. To isolate tissue voxels, thresholding was applied with HU values between; -190 and -30 HU values for AT and -29 and +150 HU values for muscle tissue, respectively.[10] The excessive breast tissue, pericardial, intermuscular, and deep subcutaneous AT were manually excluded to minimize gender-related bias. Index values were calculated by proportioning VAT, SAT, and SMMVs to body surface area (BSA). For single-slice volume calculation of VAT, the segmentation method was based on measurements obtained from manual segmentation of one CT slice at the spinous process of the

Table 1. Patient characteristics (n= 83)

	TKIs, n (%)	PBC, n(%)
Gender		
Male	12 (36.4%)	46 (92%)
Female	21 (63.6%)	4 (8%)
ECOG PS		
PS 0-1	28 (84%)	43 (86%)
PS 2-3	5 (15%)	7 (14%)
Histopathology		
Adenocarcinoma	33 (100%)	35 (70%)
Squamous cell carcinoma	0	15 (15%)
Smoking status		
Non-smoker	20 (61%)	4 (8%)
Smoker	8 (24%)	43 (86%)
Unknown	5 (15%)	3 (6%)
T stage		
T1-2	10 (33%)	15 (30%)
T3-4	22 (66%)	32 (64%)
N stage		
Negative	2 (6%)	5 (10%)
Positive	30 (91%)	45 (90%)
Mutation status		
Positive	33 (100%)	1 (2%)
Negative	0	37 (74%)
Unknown	0	12 (24%)
Mutation type		
EGFR	27 (82%)	1 (2%)
ALK	4 (12%)	0
ROS1	2 (6%)	0
PDL1 expression		
Positive	1 (3%)	2 (4%)
Negative	2 (6%)	3 (6%)
Unknown	30 (91%)	45 (90%)
Metastasis		
Bone	15 (46%)	29 (58%)
Pleura	13 (39%)	17 (34%)
Brain	11 (33%)	24 (48%)
Surrenal gland	6 (18%)	10 (20%)
Liver	3 (9%)	4 (8%)
Metastasis site		
1	22 (67%)	22 (44%)
>1	11 (33%)	28 (56%)

TKIs= Tyrosine kinase inhibitors; PBCT= platinum-based chemotherapy; ECOG PS= Eastern Cooperative Oncology Group Performance Status.

Table 2. Anthropometric measurements

	TKIs median (25-75 percentile)	PBCT median (25-75 percentile)
VAT-L3 volume (cm^3)[a]	122.0 (60.5-205.5)	125.0 (65.0-205.5)
VAT volume (cm^3)[b]	3130.0 (1920.5- 4555.0)	3151.0 (2049.0-4621.0)
SAT volume (cm^3)[b]	3507.0 (1802.5-5733.0)	3750.5 (1835.0- 5970.2)
SMM volume (cm^3)[b]	535.5 (468.7-602.2)	529.5 (443.2-597.5)
VAT/ BSA (cm^3/m^2)	1674.0 (1144.5- 2385.6)	1755.6 (1169.9-2597.9)
SAT/ BSA (cm^3/m^2)	1932.2 (1047.5-3070.5)	2081.9 (1100.6-3256.0)
SMM/ BSA (cm^3/m^2)	298.3 (266.5- 322.5)	293.7 (259.2-321.5)
VAT/SAT (cm^3/ cm^2)	0.9 (0.7- 1.1)	0.9 (0.7-1.1)
BMI (kg/m^2)	25.5 (21.2- 29.2)	23.5 (21.2-28.1)
BSA (m^2)	1.7 (1.5- 1.9)	1.8 (1.6- 1.9)

TKIs, Tyrosine kinase inhibitors; PBCT, platinum-based chemotherapy; VAT-L3, Visseral Adipose Tissue - 3rd lumbar vertebra; VAT, Visseral Adipose Tissue; SAT, Subcutaneous Adipose Tissue; SMM, Skeletal Muscle Mass; BSA, Body Surface Area; BMI, Body Mass Index.

[a] (for single-slice volume calculation method) *[b] (for multi-slice volume calculation method)*

third lumbar vertebra (L3) (Figure 1 A1). The data obtained with the single-slice segmentation method was compared with the results of the multi-slice method for the entire abdominal cavity.

This study was performed with local institutional review board approval –Marmara University School of Medicine Ethics Comitte– (dated December 2019; No: 09.2019.1026).

Statistical Analysis

Statistical analyses were done separately for two treatment subgroups. Descriptive statistics were used to present the characteristics of the study population. Continuous not-normally distributed variables were reported as median (range), while categorical variables were expressed as number of cases and frequencies (percentage). The distribution of numerical data was determined by Kolmogorov-Smirnov and Shapiro-Wilk tests. The correlation of the single slice segmentation method with the multi-slice method for VAT volume calculation was tested with Spearman's correlation analysis. Kaplan-Meier method was used to analyze the effects of anthropometric data and clinicopathological features on survival and compared for significance using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model to determine independent prognostic variables for survival rates. Only variables that showed significance ($p< 0.05$) in univariate analysis were included in the multivariate analysis. All statistical analyses were performed using IBM SPSS® software version 25.0. Results with a 95% Confidence Interval (CI) and two-sided $p< 0.05$ were considered statistically significant.

RESULTS

Characteristics of the Patients

Among the 83 patients included in the study, 50 patients (60.2%) received PBCT as their first line treatment and 33 patients (39.8%) had TKI therapy. The median duration of follow-up in the PBCT and TKI group was 10 months (range 1.5-75 months) and 21 months (range 1.3-84.5 months), respectively. Twelve patients were alive (2 pts for the PBCT group; 10 pts for the TKI group) at the time of writing of this manuscript. The main characteristics of the treatment groups are presented in Table 1.

Table 3. Univariate and multivariate analyses for overall survival

	TKIs						PBCT					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	95% CI			95% CI			95% CI			95% CI		
	HR	HR	p	HR	HR	p	HR	HR	p	HR	HR	p
Gender (female)	0.39	0.17-0.90	<0.05	0.54	0.07-4.14	0.55	1.40	0.49- 3.96	0.52			
ECOG PS (0-1)	0.39	0.14- 1.07	0.69				0.61	0.26- 1.39	0.24			
Histopathology (adenocarcinoma)	1.43	0.19- 10.88	0.72				1.06	0.57- 1.97	0.83			
Smoking status (smoker)	1.68	0.69- 4.09	0.25				1.16	0.41- 3.29	0.76			
T stage	1.00	0.70- 1.42	0.99				1.21	0.94- 1.56	0.13			
N stage	0.71	0.44- 1.15	0.17				1.15	0.84- 1.56	0.36			
Bone metastasis	2.58	1.17- 5.98	<0.05	1.64	0.49-5.50	0.42	1.22	0.68- 2.18	0.48			
Pleura metastasis	0.80	0.33- 1.89	0.61				0.67	0.36-1.23	0.20			
Brain metastasis	1.23	0.52-2.91	0.63				0.75	0.41- 1.34	0.33			
Surrenal metastasis	6.32	2.08- 19.15	<0.001	1.25	0.27-5.69	0.77	1.10	0.54- 2.23	0.78			
Liver metastasis	0.83	0.19-3.58	0.81				1.84	0.64- 5.27	0.25			
Metastasis site	2.06	0.88- 4.85	0.09				0.84	0.47- 1.51	0.57			
VAT-L3 (cm^3)[a]	0.43	0.18-1.05	0.06				0.86	0.48-1.56	0.63			
VAT volume (cm^3)[b]	1.40	0.61- 3.19	0.42				1.28	0.72- 2.27	0.38			
SAT volume (cm^3)	3.16	1.31- 7.61	<0.05	0.69	0.17-2.73	0.59	0.67	0.38- 1.19	0.18			
SMM volume (cm^3)	0.75	0.32- 1.71	0.49				1.01	0.57- 1.79	0.96			
VAT/BSA (cm^3/m^2)	0.98	0.43-2.23	0.96				0.79	0.45- 1.41	0.43			
SAT/BSA (cm^3/m^2)	2.78	1.15- 6.68	<0.05	0.69	0.17-2.73	0.59	0.72	0.41- 1.28	0.27			
SMMV/BSA (cm^3/m^2)	0.76	0.32-1.77	0.76				1.23	0.67-2.25	0.50			
VAT/SAT (cm^3/cm^2)	0.36	0.15- 0.88	<0.05	1.76	0.33-9.38	0.50	1.15	0.65- 2.03	0.62			
BMI (kg/m^2)	1.23	054- 2.80	0.61				0.70	0.39- 1.24	0.22			
BSA (m^2)	1.04	0.45- 2.37	0.92				0.92	0.52- 1.64	0.79			
Albumin (<3.5 mg/dL)	3.99	1.36-11.69	<0.05	0.10	0.02-0.41	<0.001	1.29	0.46-3.64	0.62			
Calcium (<10.5 mg/dL)	1.06	0.36-3.13	0.92				1.02	0.77-1.34	0.91			
ALP (<120 U/L)	1.19	0.37-3.75	0.76				0.97	0.52-1.81	0.93			
LDH (<248 U/L)	1.47	0.53-4.08	0.45				1.00	1.00-1.01	0.44			
CRP (<5 mg/dL)	1.63	0.36-7.41	0.52				1.00	0.99-1.00	0.86			

ECOG PS= Eastern Cooperative Oncology Group Performance Status; VAT-L3= Visseral Adipose Tissue - 3rd lumbar vertebra; VAT= Visceral Adipose Tissue; SAT= Subcutaneous Adipose Tissue; SMM= Skeletal Muscle Mass; BSA= Body Surface Area; SMMV= Skeletal Muscle Mass Volume; BMI= Body Mass Index; ALP= Alkaline Phosphatase; LDH= Lactate Dehydrogenase; CRP= C Reactive Protein.
[a] for single-slice volume calculation method [b] for multi-slice volume calculation method

not applicable

not applicable

Body Composition

Table 2 shows anthropometric measures of the study population for each treatment group. It was notable that the data obtained with the single-slice segmentation method and multi slice volume calculation method were highly correlated (spearman Rho 0.972, p< 0.001).

Overall Survival

Univariate and multivariate analyses are shown in Table 3. In univariate analyses, female gender (hazard ratio, HR= 0.39 [0.17-0.90]; p= 0.03), presence of bone metastasis (HR= 2.58 [1.17 5.98]; p= 0.02), presence of adrenal metastasis (HR= 6.32 [2.08-19.15]; p< 0.005), SAT volume (HR= 3.16

[1.31-7.61]; p= 0.01), SAT/BSA ratio (HR= 2.78 [1.15-6.68]; p= 0.02), VAT/SAT ratio (HR= 0.36 [0.15-0.88]; p= 0.02) and serum albumin levels (HR= 3.99 [1.36 11.69]; p= 0.01) were found to be statistically significant for OS in TKI treatment group. Contrary, no significant relationship was observed between VAT volume, SMMV, and OS. In multivariate analyses, only serum albumin level (HR= 0.10 [0.02-0.41]; p< 0.005) remained as an independent risk factor. No significant results were found in the univariate and multivariate analyses in the PBCT treatment group.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the consistency of the results obtained with single-slice and multi-slice volume calculation methods for VAT in therapy-naïve patients diagnosed with advanced-stage NSCLC. The authors wanted to prove, at least in principle, that the multi-slice method for the entire abdominal cavity can yield different results for OS rates in patients with stage IV NSCLC who received PBCT or TKI treatment compared to the single-slice method. Neither single slice nor multi slice method could demonstrate a significant correlation between the volumes of VAT with OS in each treatment group. Interestingly, it was observed that the subjects with a low VAT/SAT ratio and higher SAT volumes were found to have statistically significant increased OS compared to those with lower SAT volumes in the TKI treatment group.

Although several segmentation methods have been proposed for quantifying VAT and SAT, standardization has not yet been achieved, and more validation studies are needed.[13,14] Mourtzakis et al. showed that regional analysis of fat and fat-free tissue at the level of 3rd lumbar vertebrae with CT strongly predicted whole-body fat and fat-free mass.[15] In a recent study, Schaudinn et al. reported that total VAT volume can be rapidly estimated by VAT segmentation of axial CT sections at sex-specific lumbar intervertebral disk spaces.[16] Additionally, newly developed automatic segmentation methods can be used to determine approximate equations for VAT volume measured from segmented VAT areas on all axial CT sections between the diaphragm and pelvic floor.[12,16] In this study, the authors preferred to compare these approaches (single-slice method for one plane vs multiple-slice method for whole abdominal cavity) in the same subgroups of patients who were diagnosed with malignancy. It was found that the measured and calculated volumes of VAT and SAT were not significantly different. These preliminary results showed that a single-slice based approach for assessing the adequacy of acquired VAT volumes worked reasonably well in the case of cancer patients.

In recent years a new direction of research has emerged, which tries to directly explain the role of VAT and SAT in the pathogenesis and therapeutic outcomes of different malignancies. VAT has unique endocrine functions and produces some cancer-promoting factors including adipocytokines, proangiogenic cytokines, proinflammatory cytokines/chemokines such as insulin-like growth factor, fibroblast growth factor-2, tumor necrosis factor alpha, interleukin 6, omentin-1, visfatin, vaspin.[17-23] It has been hypothesized and then proven that VAT produced metabolites may have a direct influence on obesity associated colorectal carcinoma aggressiveness and progression.[18,24] Chakraborty and colleagues reported that VAT promotes ultraviolet radiation (UVR)-induced skin carcinogenesis.[20] Another study demonstrated that VAT modulates the cellular response to radiation in esophageal adenocarcinoma.[25] Furthermore, there are studies in the literature analyzing the relationship between VAT and some malignancies, such as colorectal carcinoma, breast cancer, head and neck cancer, gastric cancer, pancreatic ductal adenocarcinoma, liver cancer, and genitourinary cancers (renal, prostate, ovarian, testicular and endometrial).[23,26-32]

There are a few publications on this topic for NSCLC patients in the literature. Nattemüller et al. found that a higher VAT/SAT ratio was associated with lower survival in this patient group.[33] In a recent study, Durand et al. found that VAT/SAT ratio was an independent predictor of both progression-free survival and OS for NSCLC.[34] Our results were compatible with these published studies for the TKI treatment subgroup. Another two recently published studies focused on stage IV NSCLC

patients, revealed no significantly association between higher VAT volumes and poor survival.[12,35] Additionally, Minami et al. couldn't find any association between the efficacy of ICI therapy and visceral adiposity in pretreated NSCLC patients.[36] Based on these literature findings, including our study, it can be assumed that different treatment approaches and patterns of adipose tissue distribution affect prognosis in different ways in NSCLC.

It is thought that peripheral SAT is less metabolically active than VAT and is the major source of leptin.[37-39] Ebadi et al. reported that lower SAT volume in patients with gastrointestinal, respiratory, and renal cancer was associated with increased overall mortality compared to cancer patients with high SAT volume.[40] Additionally, Lee et al. showed that lower SAT volume was associated with mortality in NSCLC patients.[41] Unlike our research, Lee's study did not include stage IV NSCLC patients and did not focus specifically on therapy naïve patients undergoing different chemotherapy regimens. Taken together, these studies suggested that lower SAT volume was associated with overall mortality in all stages of NSCLC, especially among the subgroup of patients treated with PBCT.

If we focus only on the data acquired for TKI treatment, the most comprehensive study on this topic for NSCLC was published by Minami and colleagues.[36] They found that visceral obesity and high VAT/SAT ratio were not associated with prognosis. The main difference in our study is that it included a small number of patients with a more specific group. We preferred to work with a group of stage IV NSCLC patients who had never received any treatment before. More research studies are needed to further define the prognostic role of visceral obesity in NSCLC patients, especially this type of specialized treatment.

Another aspect of our study was to evaluate the impact of SMMV (unlike other studies, we used VOIs with higher muscle mass volumes instead of cross-sectional ROIs). There are more studies in the literature on this subject for NSCLC patients. In a recently published metanalysis of 11 studies with a total 1544 patients by Yang et al., the authors found that sarcopenia was an independent predictor of shorter OS in both stage I-II NSCLC and stage III-IV NSCLC.[42] Additionally for stage I NSCLC cases, two different studies (n= 215, n= 315, respectively) demonstrated that sarcopenia was significantly associated with unfavorable prognosis.[43,44] Similar results were obtained in another study (n= 69) with stage IIIA NSCLC cases.[45] In this study, sarcopenia was not associated with poor prognosis in therapy-naïve stage IV NSCLC patients undergoing different chemotherapy regimens (neither treated with PBCT nor TKI group). In light of these literature data, it can be concluded that the negative prognostic effects of sarcopenia are seen especially in the first three stages of NSCLC.

Our study showed that hypoalbuminemia was independently associated with shorter survival in metastatic NSCLC patients undergoing TKI treatment. Malnutrition and systemic inflammation are the leading causes of suppression of albumin synthesis, that can contribute to increased chemotherapy toxicity, including anemia, fatigue, and anorexia. Due to these hypotheses, hypoalbuminemia has been demonstrated to have negative prognostic value in cancer patients. Our results were consistent with those of previous studies.[46]

The main limitations of our study include its retrospective and single institutional design. The relatively small sample size is another limitation. The main strength of our study is that, for the first time, various techniques of volume calculation methods were used for a specific research objective. In addition, we also focused on a specific subgroup of NSCLC patients. We hope that this study will shed light on relevant studies in the future.

In conclusion, despite the heterogeneous distribution of VAT, the single-slice volume calculation method was highly correlated with the multi-slice method which reflects the entire abdominopelvic region and it seems that the third lumbar vertebra level can be preferred for VAT volume calculation. Additionally, in this study we have shown that therapy-naïve metastatic NSCLC patients with a low VAT/SAT ratio and higher SAT volumes were found to have statistically significant increased OS compared to those with lower SAT volumes in the TKI treatment group. No significant relationship was observed between the volumes of VAT and SMMV, and OS in therapy-naïve metastatic NSCLC patients. Our study also showed that hy-

poalbuminemia has independently a negative prognostic value in metastatic NSCLC patients undergoing TKI treatment. Further studies with a larger series of patients are warranted to better delineate the clinical relevance of this observation.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines Insights: Non–Small Cell Lung Cancer, Version 2.2021: Featured Updates to the NCCN Guidelines. J Natl Compr Canc Netw 19: 254-266, 2021.
3. Brown JC, Cespedes Feliciano EM, Caan BJ. The evolution of body composition in oncology— epidemiology, clinical trials, and the future of patient care: facts and numbers. J Cachexia, Sarcopenia Muscle 9: 1200-1208, 2018.
4. Widschwendter P, Friedl TW, Schwentner, L et al. The influence of obesity on survival in early, high-risk breast cancer: results from the randomized SUCCESS A trial. Breast Cancer Res 17: 129, 2015.
5. Mathur A, Luberice K, Paul H, et al. Increasing body mass index portends abbreviated survival following pancreatoduodenectomy for pancreatic adenocarcinoma. Am J Surg 209: 969-973, 2015.
6. Doleman B, Mills K, Lim S, et al. Body mass index and colorectal cancer prognosis: a systematic review and meta-analysis. Tech coloproctol 20: 517-535, 2016.
7. Dahlberg SE, Schiller JH, Bonomi PB, et al. Body mass index and its association with clinical outcomes for advanced non-small-cell lung cancer patients enrolled on Eastern Cooperative Oncology Group clinical trials. J Thorac Oncol 8: 1121-1127, 2013.
8. Shachar SS, Williams GR, Muss HB et al. Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. Eur J Cancer 57: 58-67, 2016.
9. Zhang M, Hu T, Zhang S, Zhou L. Associations of different adipose tissue depots with insulin resistance: a systematic review and meta-analysis of observational studies. Sci Rep 5: 18495, 2015.
10. Tokunaga K, Matsuzawa Y, Ishikawa K, Tarui S. A novel technique for the determination of body fat by computed tomography. Int J Obes 7: 437-445, 1983.
11. Thomas EL, Saeed N, Hajnal JV, et al. Magnetic resonance imaging of total body fat. J Appl physiol 85: 1778-1785, 1998.
12. Popinat G, Cousse S, Goldfarb L, et al. Sub-cutaneous Fat Mass measured on multislice computed tomography of pretreatment PET/CT is a prognostic factor of stage IV non-small cell lung cancer treated by nivolumab. Oncoimmunology 8: e1580128, 2019.
13. Ross R, Leger L, Morris D, et al. Quantification of adipose tissue by MRI: relationship with anthropometric variables. J Appl Physiol 72: 787-795, 1992.
14. Lambert L, Novak M, Siklova M, et al. Hybrid and model-based iterative reconstruction influences the volumetry of visceral and subcutaneous adipose tissue on ultra-low-dose CT. Obesity 28: 2083-2089, 2020.
15. Mourtzakis M, Prado CM, Lieffers JR, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 33: 997-1006, 2008.
16. Schaudinn A, Hudak A, Linder N, et al. Toward a Routine Assessment of Visceral Adipose Tissue Volume from Computed Tomographic Data. Obesity 29: 294-301, 2021.
17. Ritter A, Friemel A, Fornoff F, et al. Characterization of adipose-derived stem cells from subcutaneous and visceral adipose tissues and their function in breast cancer cells. Oncotarget 6: 34475, 2015.
18. Ose J, Holowatyj AN, Nattenmüller J, et al. Metabolomics profiling of visceral and abdominal subcutaneous adipose tissue in colorectal cancer patients: results from the ColoCare study. Cancer Causes Control 31: 723-735, 2020.
19. Catalán V, Gómez-Ambrosi J, Rodríguez A, et al. Up-regulation of the novel proinflammatory adipokines lipocalin-2, chitinase-3 like-1 and osteopontin as well as angiogenic-related factors in visceral adipose tissue of patients with colon cancer. The J Nutr Biochem 22: 634-641, 2011.
20. Chakraborty D, Benham V, Bernard JJ. Elucidating the role of adipose tissue secreted factors in malignant transformation. Adipocyte 7: 45-48, 2018.
21. Kan J-Y, Lee Y-C, Lin Y-D, et al. Effect of baseline characteristics and tumor burden on vaspin expression and progressive disease in operable colorectal cancer. Diagnostics 10: 801, 202.
22. Fain JN, Madan AK, Hiler ML, et al. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology 145: 2273-2282, 2004.
23. Shen X-D, Zhang L, Che H, et al. Circulating levels of adipocytokine omentin-1 in patients with renal cell cancer. Cytokine 77: 50-55, 2016.
24. Himbert C, Ose J, Nattenmüller J, et al. Body fatness, adipose tissue compartments, and biomarkers of inflammation and angiogenesis in colorectal cancer: The ColoCare study. Cancer Epidemiol Biomarkers Prev 28: 76-82, 2019.

25. Mongan AM, Lynam-Lennon N, Doyle SL, et al. Visceral adipose tissue modulates radiosensitivity in oesophageal adenocarcinoma. Int Med Sci 16: 519, 2019.

26. Lee JW, Son MW, Chung IK, et al. Significance of CT attenuation and F-18 fluorodeoxyglucose uptake of visceral adipose tissue for predicting survival in gastric cancer patients after curative surgical resection. Gastric Cancer 23: 273-284, 2020.

27. Lee JW, Ban MJ, Park JH et al. Visceral adipose tissue volume and CT-attenuation as prognostic factors in patients with head and neck cancer. Head Neck 41: 1605-1614, 2019.

28. Chang H-H, Eibl G. Obesity-induced adipose tissue inflammation as a strong promotional factor for pancreatic ductal adenocarcinoma. Cells 8: 673, 2019.

29. Huang X, Xie C, Tang J et al. Adipose tissue area as a predictor for the efficacy of apatinib in platinum-resistant ovarian cancer: an exploratory imaging biomarker analysis of the AEROC trial. BMC Med 18: 1-10, 2020.

30. Celik E, Kizildag Yirgin I, Goksever Celik H, et al. Does visceral adiposity have an effect on the survival outcomes of the patients with endometrial cancer? J Obstet Gynaecol Res 47: 560-569, 2021.

31. Zhao J, Lawless MW. Stop feeding cancer: pro-inflammatory role of visceral adiposity in liver cancer. Cytokine 64: 626-637, 2013.

32. Willemse P-PM, van der Meer RW, Burggraaf J, et al. Abdominal visceral and subcutaneous fat increase, insulin resistance and hyperlipidemia in testicular cancer patients treated with cisplatin-based chemotherapy. Acta Oncologica 53: 351-360, 2014.

33. Nattenmüller J, Wochner R, Muley T et al. Prognostic impact of CT-quantified muscle and fat distribution before and after first-line-chemotherapy in lung cancer patients. PLoS One 12: e0169136, 2017.

34. Blanc-Durand P, Campedel L, Mule S, et al. Prognostic value of anthropometric measures extracted from whole-body CT using deep learning in patients with non-small-cell lung cancer. Eur Radiol 30: 3528-3537, 2020.

35. Degens J, Sanders KJC, de Jong EEC, et al. The prognostic value of early onset, CT derived loss of muscle and adipose tissue during chemotherapy in metastatic non-small cell lung cancer. Lung Cancer 133: 130-135, 2019.

36. Minami S, Ihara S, Nishimatsu K, et al. Low body mass index Is an Independent prognostic factor in patients with non-small cell lung cancer treated with epidermal growth factor receptor tyrosine kinase Inhibitor. World J Oncol 10: 187, 2019.

37. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev 11: 11-18, 2010.

38. Schlecht I, Gronwald W, Behrens G, et al. Visceral adipose tissue but not subcutaneous adipose tissue is associated with urine and serum metabolites. PloS one 12: e0175133, 2017.

39. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 21: 697-738, 2000.

40. Ebadi M, Martin L, Ghosh S et al. Subcutaneous adiposity is an independent predictor of mortality in cancer patients. Br J cancer 117: 148-55, 2017.

41. Lee JW, Lee HS, Na JO, Lee SM. Effect of adipose tissue volume on prognosis in patients with non-small cell lung cancer. Clin Imaging 50: 308-313, 2018.

42. Yang M, Shen Y, Tan L, Li W. Prognostic value of sarcopenia in lung cancer: A systematic review and meta-analysis. Chest 156: 101-11, 2019.

43. Tsukioka T, Nishiyama N, Izumi N, et al. Sarcopenia is a novel poor prognostic factor in male patients with pathological Stage I non-small cell lung cancer. Jpn J Clin Oncol 47: 363-368, 2017.

44. Takahashi Y, Suzuki S, Hamada K et al. Sarcopenia is poor risk for unfavorable short-and long-term outcomes in stage I non-small cell lung cancer. Ann Transl Med 9: 325, 2021

45. Tsukioka T, Izumi N, Mizuguchi S, et al. Positive correlation between sarcopenia and elevation of neutrophil/lymphocyte ration in pathological stage IIIA (N2-positive) non-small cell lung cancer patients. Gen Thorac Cardiovasc Surg 66: 716-722, 2018.

46. Fiala O, Pesek M, Finek J, et al. Serum albumin is a strong predictor of survival in patients with advanced-stage non-small cell lung cancer treated with erlotinib. Neoplasma 63: 471-476, 2016.

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