Can Psoas muscle density predict the development of metastasis in non-metastatic adrenocortical carcinomas?

A CT-based AI-assisted automated segmentation analysis study

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Abstract

Aim: Our study aimed to investigate whether artificial intelligence-based body composition analysis can predict metastasis development during follow-up in patients with non-metastatic adrenocortical carcinoma (ACC) at the time of diagnosis.

Methods: Forty-five patients with non-metastatic ACC were included at the time of diagnosis. From the patients' non-contrast computed tomography (CT) scans, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), psoas area, psoas density, total muscle area, and total muscle density were automatically measured from sections taken at the level of the inferior endplate of the L3 vertebra. Patients were followed for developing liver, lung, and lymph node metastases. The relationship between body composition and liver and lymph node metastasis development was investigated. Propensity score matching (PSM) was performed for patients with metastases.

Results: Forty-five patients, 27 of whom were female, with non-metastatic ACC at the time of diagnosis, were included in the study. The mean age of the patients was 53±17.4 years. Significant differences were found between the groups that developed liver metastases and those that did not, and between the groups that developed lymph node metastases and those that did not, in terms of correct Psoas HU, left Psoas HU, PMD, Wall Muscle HU, and age ($p<0.05$). After applying PSM based on age, sex, and T stage, the odds ratio for psoas muscle density in predicting liver metastasis was found to be 0.898, 95% CI(0.828-0.973) in the logistic regression analysis.

Conclusions: Psoas muscle density may be a potential biomarker for predicting metastasis development in patients with non-metastatic ACC.

Keywords: *Adrenocortical carcinoma, sarcopenia, metastasis, psoas muscle density, adipose tissue*

1. Introduction

Adrenocortical carcinoma (ACC) is a rare and lethal malignancy. The incidence of ACC is reported as 1-2 per million population/year.[1,2] Complete surgical resection is the only potentially curative option for localized disease and reported 5-year survival rates following curative resection range from approximately 15-44%.[3] Despite the generally unfavorable prognosis of ACC, there is significant individual variability in disease progression, recurrence, and overall survival. Even in patients with stage 4 disease, survival ranges from a few months to several years. Exceptional cases of long-term survival with ACC diagnosis have been reported.[4] Despite these variations in survival, prognostic factors have not been definitively established. While patient age at diagnosis, tumor surgical resection, tumor growth rate, mitotic index, and high tumor index have been identified as risk factors for poor survival, a well-established system is not yet available.[5, 6]

Although ACC treatment has been advanced over the past years, options for advanced ACC still need to be improved.[7] Chemotherapy with the FIRM-ACT protocol is the current standard treatment.[8] While tyrosine kinase inhibitors and other targeted therapies have shown potential efficacy, novel therapeutic approaches are needed.[7] A better understanding of the molecular profile of ACC has pointed to a limited number of druggable molecular targets. Immunotherapy results are still unclear, as the tumor microenvironment and potential endocrine activity are complex.[3,8] Due to its relative rarity and heterogeneity, personalized treatment is becoming increasingly important.

Sarcopenia, defined as the progressive and generalized loss of muscle mass and function, is typically associated with aging, but ca-

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chexia in malignancy can also contribute to its development[9]. Furthermore, sarcopenia can be viewed as a surrogate for a patient's overall frailty, defined as a syndrome of physiological reserve loss, impaired homeostatic mechanisms, and vulnerability to adverse outcomes.[10] Studies have shown its utility as a tool to determine overall survival and prognosis in many malignancies. However, the number of studies investigating the relationship between sarcopenia and ACC is quite limited compared to other malignancies.[11,12]

In our study, considering the presence of tumor cachexia that can be observed in metastatic patients, we aimed to investigate the relationship between artificial intelligence-based body composition analysis and the development of metastases in non-metastatic ACC patients.

2. Materials and methods

2.1. Patient Selection

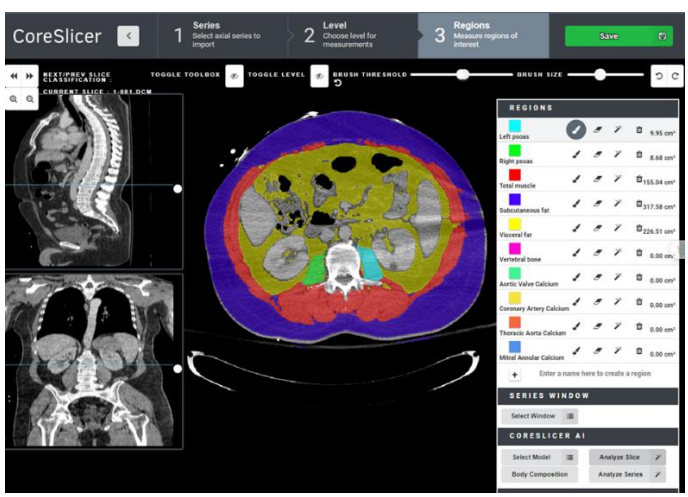
ACC patients from the Adrenal-ACC-Ki67-Seg dataset were included in the study (https://www.cancerimagingarchive.net). Patients with metastatic disease at the time of diagnosis were excluded. All 45 patients were included in the study. Patients in the dataset were followed between 2006 and 2018. The development of liver, lung, and lymph node metastases during follow-up was investigated. Local ethics committee approval was obtained (67-2024).

2.2. Body Composition Analysis

Contrast-enhanced CT images of the patients were uploaded to the open-source, web-based "CoreSlicer" tool [13]. Measurements were performed at the level of the L3 vertebra inferior endplate. Visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), psoas area, psoas density, total muscle area, and total muscle density were automatically measured. The measurements were performed by a radiologist with 10 years of experience. You can view the system interface in Figure 1.

Table 1

CoreSLicer user interface



2.3. Statistical Analysis

Continuous variables were reported as means (± standard deviation) and categorical variables as numbers (proportion). Normality tests were performed for continuous variables Kolmogorov-Smirnov and Shapiro-Wilk test. Comparisons between groups were performed using the following statistical tests: chi-square test for categorical variables, Student's t test for normal-distributed continuous variables, Mann-Whitney U test for non-normal-distributed continuous variables.

To minimize selection bias and adjust for imbalances between groups, we used 1:1 propensity score matching (PSM). The SPSS R plugin (SPSS R Essentials) was implemented for matching[14]. We used the SPSS 'PS Matching' feature to perform the propensity score-matched analysis. Matching factors included age, sex, and T stage. Patients who developed liver and lymph node metastases during follow-up and those who did not were 1:1 matched in a multivariate logistic analysis using stepwise regression based on a greedy matching algorithm with a caliper of 0.05 times the logit's standard deviation (SD).

Using logistic regression after PSM, the association between the development of metastases during follow-up and body composition parameters was investigated.

Table 1

Results of body composition analysis in patient groups with and without liver metastasis development during follow-up.

	Group	Mean± Sd	P value
Left psoas area (cm^2)	No (n:32)	9.71 ±2,99	0.148
	Yes (n:13)	8.28 ± 2,81	
Left psoas density (HU)	No (n:32)	46.11±10.40	**0.006**
	Yes (n:13)	36.66 ±8.71	
Right psoas area (cm^2)	No (n:32)	9.58±2.97	0.127
	Yes (n:13)	8.06±2.97	
Right psoas density (HU)	No (n:32)	46.12±9.395	**0.004**
	Yes (n:13)	36.70±9.01	
Abdominal wall muscle area (cm^2)	No (n:32)	123.06±24.91	0.939
	Yes (n:13)	122.32±37.99	
Abdominal wall muscle density (HU)	No (n:32)	32.84±12.57	**0.014**
	Yes (n:13)	22.37±12.24	
Subcutaneous adipose tissue area (cm^2)	No (n:32)	264.48±161.460	0.882
	Yes (n:13)	271.67±95.42	
Subcutaneous adipose tissue density (HU)	No (n:32)	-98.29±12.73	0.509
	Yes (n:13)	-100.82±7.70	
Visseral adipose tissue area (cm^2)	No (n:32)	174.15±114.11	0.119
	Yes (n:13)	234.18±116.40	
Visseral adipose tissue density(HU)	No (n:32)	-83.49±23.90	0.336
	Yes (n:13)	-90.19±9.94	
Psoas muscle density (HU)	No (n:32)	45.93±9.62	**0.005**
	Yes (n:13)	36.79±8.54	
Age	No (n:32)	50.47±13.32	**0.041**
	Yes (n:13)	59.46±12.05	

3. Results

This study included 45 patients, 27 female and 18 male, with non-metastatic disease at the time of diagnosis. The mean age of the patients was 53 ± 17.4 years. At the time of diagnosis, 4 patients were stage T1, 19 were stage T2, and 22 were stage T3. During follow-up, 13 patients developed liver metastases, 6 developed lymph node metastases, 15 developed lung metastases, and 4 developed bone metastases.

No association was found between body composition parameters and the development of lung and bone metastases during follow-up. Significant differences were found between the group that developed liver metastases during follow-up and the group that did not in terms of Right Psoas HU, Left Psoas HU, PMD, Wall Muscle HU, and age (p: 0.004, p: 0.006, p: 0.005, p: 0.041, respectively). Significant differences were found between the group that developed lymph node metastases during follow-up and the group that did not in terms of Right Psoas HU, Left Psoas HU, and PMD (p: 0.037, p: 0.019, p: 0.024, respectively). Please see Tables 1 and 2 for detailed information.

To determine the net effect of psoas muscle density, a logistic regression analysis was performed on 13 patients with liver metastases and 13 without after matching for age, sex, and T stage. The odds ratio was 0.898, 95% CI (0.828-0.973). A similar logistic regression analysis was performed on 6 patients with lymph node metastases and 6 without, resulting in an odds ratio of 0.892, 95% CI (0.803-0.991). Please see Table 3 for details.

Table 2

Results of body composition analysis in patient groups with and without lymph node metastasis development during follow-up

	Group	Mean± Sd	P
Lef psoas area (cm^2)	No (n:39)	9.44±3.12	0.419
	Yes (n:6)	8.37±1.82	
Left psoas density Hu	No (n:39)	44.68±10.48	**0.037**
	Yes (n:6)	34.93±9.16	
Right psoas area (cm^2)	No (n:39)	9.23±2.30	0.618
	Yes (n:6)	8.56±3.38	
Right psoas density (HU)	No (n:39)	44.77±9.52	**0.019**
	Yes (n:6)	34.47±10.35	
Abdominal wall muscle area(cm^2)	No (n:39)	122.89±27.80	0.979
	Yes (n:6)	122.56±37.93	
Abdominal wall muscle density (HU)	No (n39)	30.95±13.15	0.146
	Yes (n:6)	22.46±12.37	
Subcutaneous adipose tissue area (cm^2)	No (n:39)	272.06±151.40	0.521
	Yes (n:6)	230.79±87.13	
Subcutaneous adipose tissue density (HU)	No (n:39)	-98.40±12.084	0.360
	Yes (n:6)	-103.06 ±5.09	
Visseral adipose tissue area (cm^2)	No (n:39)	185.96±117.99	0.424
	Yes (n:6)	227.45±110.94	
Visseral adipose tissue density (HU)	No (n:39)	-83.92±22.03	0.222
	Yes (n:6)	-95.24±6.45	
Psoas muscle density (HU)	No (n:39)	44.61±9.67	**0.024**
	Yes (n:6)	34.69±9.51	
Age	No (n:39)	50.47±3.12	0.358
	Yes (n:6)	59.46±1.82	

Table 3

Logistic regression analysis with matched patients after Propensity-Score Matching

	Odds Ratio (95% CI)	p
Follow up- Liver Metastasis	0.898 %95CI (0.828- 0.973)	0.009
Follow up- Lymph node metastasis	0.892 %95CI (0.803- 0.991)	0.034

4. Discussion

This study investigated the potential utility of artificial intelligence-assisted automated segmentation and body composition analysis in predicting metastatic progression in patients with non-metastatic adrenocortical carcinoma (ACC). Our findings revealed a significant association between psoas muscle density and liver and lymph node metastasis development. These results suggest that psoas muscle density may be a viable biomarker for predicting prognosis in ACC.

Significant differences were observed in factors such as psoas muscle density and age between patients who developed liver and lymph node metastases during follow-up. This observation suggests that muscle density may be sensitive to specific metastatic patterns. Patients who developed liver metastases exhibited significant reductions in right and left psoas HU values (p:0.004 and p:0.006, respectively). Similarly, lower psoas muscle density was observed in patients who developed lymph node metastases (p:0.037 and p:0.019, respectively).

Logistic regression analyses conducted on patients matched for factors such as age, sex, and T stage revealed that psoas muscle density holds potential as a predictor for the development of liver and lymph node metastases. Specifically, the odds ratio for liver metastasis was found to be 0.898 (95% CI: 0.828-0.973), and for lymph node metastasis, it was 0.892 (95% CI: 0.803-0.991). These results suggest that low muscle density is associated with an increased risk of metastasis.

Adrenocortical carcinoma (ACC) is a rare malignancy often associated with a poor prognosis. Treatment options are limited, and significant individual variability is observed in disease progression and survival. Therefore, the identification of novel biomarkers capable of better predicting disease prognosis is of paramount importance. Sarcopenia has been recognized as a significant factor in determining overall survival and prognosis in various malignancies.[15] However, studies investigating the relationship between ACC and sarcopenia are limited.[12] Sarcopenia is a significant factor that can arise in association with malignancies and is known to impact overall survival and prognosis in various cancer types. While often characterized as an age-related condition, sarcopenia is also associated with malignancy-associated cachexia. Loss of muscle mass and function can negatively affect patients' physiological reserves and overall health status, which is linked to poor prognosis in malignancies[15]. In ACC patients, as in other similar malignancies, cancer cachexia typically manifests in the advanced stages of the disease. Cachexia is characterized by progressive loss of body weight, including skeletal muscle mass or sarcopenia, due to systemic inflammation and cannot be fully reversed by conventional nutritional support.[16] The development of sarcopenia in ACC patients, in addition to causing a decrease in muscle mass, also leads to a reduction in muscle density. This decrease in muscle density suggests its potential as a prognos-

tic factor in predicting metastasis development.[17]

A previous study by Miller et al. [11] reported that central sarcopenia was associated with poor survival and that increased intra-abdominal fat reduced survival in ACC patients. This study suggests that psoas muscle density is an essential factor to consider in the prognosis of ACC. De Jong et al.[12] reported that sarcopenia reduced survival after ACC surgery. These findings suggest that muscle density may be associated with the development of metastases. Low psoas muscle density can be associated with decreased physiological reserves and increased patient frailty. This can be considered an adverse prognostic factor for metastasis development and disease progression. Furthermore, the measurement of psoas muscle density is non-invasive and easily applicable, making its integration into clinical practice feasible.

4.1. Limitation

The major limitation of this study is the small sample size. Limited to only 45 patients, this study must be validated in more extensive and diverse populations. Furthermore, due to its retrospective nature, it requires support from prospective studies. Future research should investigate how AI-assisted segmentation methods can be integrated into ACC management in conjunction with other prognostic factors. Fassnacht et al.[8] have highlighted the need for new therapeutic approaches in treating ACC and explored the potential of immunotherapy. Using psoas muscle density as a prognostic biomarker could be crucial for personalizing treatment strategies.

5. Conclusion

In conclusion, psoas muscle density may serve as a biomarker for predicting the development of metastases during follow-up in patients with non-metastatic ACC. This finding could be a significant step towards improving ACC's prognosis and offering patients more personalized treatment approaches. However, validation with more extensive and prospective studies is warranted.

Statement of ethics

The present study protocol was reviewed and approved by Adana City Hospital Ethics Committee ((67-2024)).

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Availability of data and materials

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author contributions

Emin DEMIREL: Conceptualization, Methodology, Software, Data curation, Writing - original draft. Okan DILEK: Formal analysis, Conceptualization, Writing, Supervision,

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