ОРИГІНАЛЬНЕ ДОСЛІДЖЕННЯ
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Clinicoradiomic model incorporating orbital adipose tissue radiomic features for predicting response to immunotherapy in patients with metastatic non-small cell lung cancer

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Conflict of interest: none

BACKGROUND. Host-related biomarkers may improve prediction of response to immune checkpoint inhibitors. However, the predictive value of radiomic features derived from orbital adipose tissue remains unknown.
OBJECTIVE. To evaluate the prognostic significance of orbital adipose tissue radiomic features and develop a combined clinicoradiomic model for predicting objective response to immunotherapy.
MATERIALS AND METHODS. This study included 86 patients with stage IV non-small cell lung cancer (NSCLC) treated with immunotherapy. Baseline head computed tomography scans were used for segmentation of bilateral orbital adipose tissue. Radiomic features (Variance, Entropy, and Size Zone Non-Uniformity) were extracted using PyRadiomics. Independent predictors were identified by multivariable logistic regression, and predictive performance was evaluated using receiver operating characteristic analysis.
RESULTS. Objective response was significantly associated with lower radiological density (≥-77 HU; p=0.001), lower Entropy (p<0.001), and lower Size Zone Non-Uniformity (p=0.011). Radiological density (p=0.0001), Variance (p=0.002), and Entropy (p=0.029) were also associated with disease control. Multivariable analysis identified first-line immunotherapy, PD-L1 expression, radiological density, and Entropy as independent predictors of objective response. The combined clinicoradiomic model demonstrated the highest predictive accuracy (area under the curve 0.896).
CONCLUSIONS. Radiomic features of orbital adipose tissue are independent predictors of immunotherapy response in metastatic NSCLC.

КЛЮЧОВІ СЛОВА: metastatic non-small cell lung cancer, immunotherapy, orbital adipose tissue, radiomics, clinicoradiomic model, entropy.

Клініко-радіомічна модель, що включає радіомічні характеристики орбітальної жирової тканини для прогнозування відповіді на імунотерапію в пацієнтів з метастатичним недрібноклітинним раком легень

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ОБҐРУНТУВАННЯ. Біомаркери, пов'язані з організмом хазяїна, можуть покращити прогнозування відповіді на терапію інгібіторами контрольних точок імунної відповіді. Проте прогностичне значення радіомічних характеристик орбітальної жирової тканини залишається невивченим.
МЕТА. Оцінити прогностичне значення радіомічних характеристик орбітальної жирової тканини та розробити комбіновану клініко-радіомічну модель прогнозування об'єктивної відповіді на імунотерапію.
МАТЕРІАЛИ ТА МЕТОДИ. У дослідження було включено 86 хворих на недрібноклітинний рак легень (НДРЛ) IV стадії, які отримували імунотерапію. На вихідних комп'ютерно-томографічних зображеннях голови виконували сегментацію двобічної орбітальної жирової тканини. Радіомічні характеристики (Variance, Entropy та Size Zone Non-Uniformity) вилучали за допомогою програмного забезпечення PyRadiomics. Незалежні предиктори визначали методом багатофакторного логістичного регресійного аналізу, а прогностичну ефективність моделей оцінювали за допомогою ROC-аналізу.

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РЕЗУЛЬТАТИ. Досягнення об'єктивної відповіді було статистично значуще асоційоване з нижчою радіологічною щільністю (≥-77 HU; p=0,001), нижчими значеннями Entropy (p<0,001) та Size Zone Non-Uniformity (p=0,011). Радіологічна щільність (p=0,0001), Variance (p=0,002) та Entropy (p=0,029) також були пов'язані з досягненням контролю над захворюванням. За результатами багатофакторного аналізу незалежними предикторами об'єктивної відповіді були імунотерапія першої лінії, експресія PD-L1, радіологічна щільність та Entropy орбітальної жирової тканини. Найвищу прогностичну точність продемонструвала комбінована клініко-радіомічна модель (площа під кривою 0,896).

ВИСНОВКИ. Радіомічні характеристики орбітальної жирової тканини є незалежними предикторами відповіді на імунотерапію у хворих на метастатичний НДРЛ.

KEY WORDS: метастатичний недрібноклітинний рак легень, імунотерапія, орбітальна жирова тканина, радіоміка, клініко-радіомічна модель, ентропія.

Introduction

In recent years, increasing attention has been directed not only toward the molecular characteristics of tumors but also toward the systemic host response, which plays a crucial role in determining disease progression and the effectiveness of anticancer therapy. The concept of host-related biomarkers is based on the premise that clinical outcomes depend on the interaction between the tumor and the patient's systemic metabolic, immunological, and inflammatory processes rather than solely on the biological characteristics of the tumor itself [1, 2].

Adipose tissue represents one of the key components of this immunometabolic environment and is now recognized as an active endocrine and immunoregulatory organ. It participates in the synthesis of cytokines, adipokines, and other mediators that regulate systemic inflammation, energy homeostasis, and antitumor immune responses [3, 4]. Structural and functional alterations of adipose tissue have been associated with the development of cancer cachexia, chronic systemic inflammation, and unfavorable treatment outcomes in patients with non-small cell lung cancer (NSCLC) [5, 6]. Furthermore, accumulating evidence suggests that adipose tissue characteristics may influence the efficacy of immune checkpoint inhibitor therapy [7].

Unlike conventional anthropometric measures, contemporary medical imaging techniques enable the assessment of individual adipose tissue depots and the analysis of their structural characteristics. In this context, orbital adipose tissue has attracted particular interest because it represents an anatomically distinct fat depot with unique molecular and biological properties. Previous studies have demonstrated that orbital adipose tissue differs substantially from other adipose tissue depots in terms of its transcriptomic profile, lipid composition, and the activity of signaling pathways involved in inflammation and adipogenesis [8, 9]. Moreover, orbital adipose tissue has been proposed as a promising model for investigating white adipose tissue remodeling and its role in systemic metabolic alterations [10]. From a clinical perspective, this approach is particularly attractive because head computed tomography (CT) is routinely performed in patients with metastatic NSCLC before the initiation of systemic therapy to exclude central nervous system metastases, thereby providing an opportunity for the noninvasive assessment of orbital adipose tissue without additional radiation exposure.

Further advances in radiomics have substantially expanded the possibilities for quantitative analysis of medical images. Unlike conventional morphometric parameters, radiomic features enable the assessment of tissue spatial heterogeneity, intensity distribution patterns, and textural organization, all of which may reflect underlying biological processes that are not visually appreciable on routine imaging [11]. In recent years, radiomic analysis of adipose tissue has emerged as a rapidly evolving research area, demonstrating promising results for predicting tumor aggressiveness, patient survival, and treatment outcomes across various malignancies [12, 13]. However, studies investigating the radiomic characteristics of orbital adipose tissue remain scarce and have primarily focused on ophthalmological disorders [14].

Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have become the standard of care for patients with metastatic NSCLC. Nevertheless, response to immunotherapy remains highly variable. Even among patients with high PD-L1 expression, objective responses are not consistently achieved, highlighting the limited predictive performance of currently available biomarkers [2, 6]. Recent evidence has demonstrated that quantitative adipose tissue characteristics derived from CT may be associated with the efficacy of immunotherapy in patients with metastatic NSCLC [15]. However, the potential of radiomic features of orbital adipose tissue as noninvasive predictors of treatment response, as well as their integration into combined clinicoradiomic prediction models, remains largely unexplored.

The aim of this study was to evaluate the association between radiomic features of orbital adipose tissue and the efficacy of immunotherapy, to determine their independent prognostic and clinical significance, and to develop a combined clinicoradiomic model for predicting objective response in patients with metastatic NSCLC.

Materials and methods

Study design and patients

This retrospective single-center study included consecutive patients with histologically confirmed stage IV NSCLC who received anti-PD-1 or anti-PD-L1 immunotherapy at the Sumy Regional Clinical Oncology Center. Eligible patients

were aged 18 years or older and had available pretreatment head CT scans of sufficient quality for orbital fat segmentation, documented PD-L1 expression status, and complete clinical data regarding treatment response. Patients with inadequate CT image quality, unsuccessful orbital fat segmentation, missing clinical information, or unavailable follow-up data were excluded from the analysis. After applying the eligibility criteria, 86 patients were included in the final study cohort.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Bioethics Committee of the Educational and Scientific Medical Institute of Sumy State University (protocol No. 5/04, April 20, 2026). The requirement for written informed consent was waived because of the retrospective study design.

Treatment and response assessment

Patients received anti-PD-1 or anti-PD-L1 immunotherapy as first- or second-line treatment according to contemporary clinical guidelines and routine institutional practice. Treatment selection was based on tumor PD-L1 expression, previous systemic therapy, and the patient's overall clinical condition.

Radiomic analysis was intentionally restricted to baseline head CT examinations obtained before the initiation of immunotherapy. This approach ensured that all imaging biomarkers represented the intrinsic characteristics of orbital adipose tissue prior to exposure to immune checkpoint inhibitors and enabled evaluation of their predictive, rather than response-monitoring, value.

Treatment response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Objective response rate was defined as the proportion of patients achieving complete response (CR) or partial response (PR). Disease control rate was defined as the proportion of patients achieving CR, PR, or stable disease (CR + PR + SD), whereas patients with progressive disease (PD) were classified as having no disease control.

Clinical and laboratory assessment

Clinical data were retrospectively retrieved from medical records and included age, sex, smoking status, body mass index (BMI), histological subtype, line of immunotherapy, and tumor PD-L1 expression.

Baseline laboratory parameters obtained before initiation of immunotherapy were used to calculate the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), where SII was calculated as platelet count × neutrophil count / lymphocyte count.

For statistical analyses, patients were categorized according to the following predefined thresholds: age (<65 vs. ≥65 years), BMI (<24.9, 25.0-29.9, and ≥30.0 kg/m^2), PD-L1 expression (1-49 % vs. ≥50 %), NLR (<3.7 vs. ≥3.7), PLR (<196 vs. ≥196), and SII (<1243 vs. ≥1243).

CT acquisition and orbital adipose tissue segmentation

Baseline head CT examinations acquired before initiation of immunotherapy were retrieved from the institutional picture archiving and communication system (PACS). All scans were performed as part of routine clinical care using a standardized imaging protocol. Images were reconstructed with a slice thickness of 5.0 mm and exported in Digital Imaging and Communications in Medicine (DICOM) format for subsequent analysis.

Orbital adipose tissue was segmented on axial CT images using the Segment Editor module in 3D Slicer software (version 5.8.1, www.slicer.org). Semi-automated segmentation was performed using a predefined attenuation threshold ranging from -200 to -30 Hounsfield units (HU). When necessary, the region of interest was manually refined on consecutive axial slices with additional verification in the sagittal and coronal planes to ensure accurate delineation of orbital adipose tissue and exclusion of adjacent soft tissues, blood vessels, and osseous structures. Upon completion of the segmentation process, a three-dimensional mask of bilateral orbital adipose tissue was generated for subsequent radiomic feature extraction. All segmentations were independently performed by two experienced radiologists blinded to the clinical outcomes. A representative example of orbital adipose tissue segmentation is shown in figure 1.

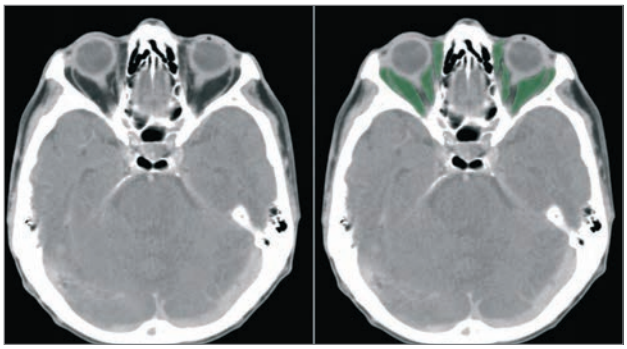

Fig. 1. Representative axial head CT image before (left) and after (right) semi-automated segmentation of bilateral orbital adipose tissue (green overlay) used for radiomic feature extraction

Radiomic feature extraction

Radiomic analysis was performed using the open-source PyRadiomics extension integrated into 3D Slicer (version 5.8.1). Prior to feature extraction, CT images and corresponding segmentation masks underwent standardized preprocessing according to the Image Biomarker Standardisation Initiative (IBSI) recommendations, including image resampling to isotropic voxel spacing and gray-level discretization using a fixed bin width.

The present study focused on three predefined radiomic features describing complementary properties of orbital adipose tissue: Variance, representing the dispersion of voxel intensities; Entropy, reflecting image complexity and randomness of gray-level distribution; and Size Zone Non-Uniformity (SZNU), characterizing spatial heterogeneity of homogeneous intensity zones. These features were selected a priori as candidate imaging biomarkers to evaluate their association with treatment response following immune checkpoint inhibitor therapy.

In addition to radiomic features, total orbital fat volume and radiological density were included as conventional quantitative imaging biomarkers. For statistical analyses, orbital fat volume (<9.8 vs. ≥9.8 cm^3), radiological density (<-77 vs. ≥-77 HU), Variance (<563 vs. ≥563), Entropy (<2.01 vs. ≥2.01), and SZNU (<52.14 vs. ≥52.14) were analyzed as categorical variables based on predefined cutoff values.

Statistical analysis

Statistical analyses were performed using Stata Statistical Software, version 19.5 (StataCorp LLC, College Station, TX, USA). A two-sided p value <0.05 was considered statistically significant.

Categorical variables were summarized as frequencies and percentages. Differences between groups were evaluated using the Pearson χ^2 test or Fisher's exact test, as appropriate. Clinical variables, laboratory biomarkers, quantitative CT-derived parameters of orbital adipose tissue, and radiomic features were categorized according to predefined cutoff values established before the analysis. Associations between these variables and treatment response were evaluated separately for objective response rate and disease control rate.

To identify independent predictors of objective response, univariable logistic regression analyses were initially performed for all candidate variables. Variables that demonstrated statistical significance in the univariable analysis, together with clinically relevant covariates, were subsequently entered into multivariable logistic regression models. Alternative multivariable models were constructed to assess the independent contribution of individual radiomic features and to identify the final predictive model.

Table 1. Clinical, laboratory, and radiomic characteristics of orbital adipose tissue in patients with metastatic NSCLC stratified according to objective response to immunotherapy

Parameter	Objective response (CR + PR), n=47	No objective response (SD + PD), n=39	p
Demographic and clinical characteristics			
Age, years, n (%) <65 ≥65	 29 (61,7) 18 (38,3)	 29 (74,4) 10 (25,6)	0,212
Sex, n (%) Male Female	 40 (85,1) 7 (14,9)	 30 (76,9) 9 (23,1)	0,332
Smoking, n (%) No Yes	 11 (23,3) 36 (76,6)	 12 (30,8) 27 (69,2)	0,442
BMI, n (%) <24,9 25-29,9 ≥30	 21 (44,7) 11 (23,4) 15 (39,1)	 22 (56,4) 11 (28,2) 6 (15,4)	0,206
Histology, n (%) Adenocarcinoma Squamous cell carcinoma	 21 (44,7) 26 (55,3)	 19 (48,7) 20 (51,3)	0,709
Line of treatment, n (%) First Second	 43 (91,5) 4 (8,5)	 29 (74,4) 10 (25,6)	0,042
PD-L1 expression, n (%) 1-49 % >50 %	 30 (63,8) 17 (36,2)	 37 (94,9) 2 (5,1)	0,001
Laboratory parameters			
NLR, n (%) <3,7 ≥3,7	 30 (63,8) 17 (36,2)	 25 (64,1) 14 (35,9)	0,979
PLR, n (%) <196 ≥196	 33 (70,2) 14 (29,8)	 23 (59,0) 16 (41,0)	0,276
SII, n (%) <1243 ≥1243	 34 (72,3) 13 (27,7)	 27 (69,2) 12 (30,8)	0,752
Quantitative characteristics of orbital adipose tissue			
Total orbital adipose tissue volume, cm^3, n (%) <9,8 ≥9,8	 24 (51,1) 23 (48,9)	 23 (59,0) 16 (41,0)	0,463
Radiological density of orbital adipose tissue, HU, n (%) <-77 ≥-77	 14 (29,8) 33 (70,2)	 26 (66,7) 13 (33,3)	0,001
Radiomic features of orbital adipose tissue			
Variance, n (%) <563 ≥563	 31 (66,0) 16 (34,0)	 18 (46,2) 21 (53,8)	0,065
Entropy, n (%) <2,01 ≥2,01	 43 (91,5) 4 (8,5)	 17 (43,6) 22 (56,4)	0,0001
SZNU, n (%) <52,14 ≥52,14	 31 (66,0) 16 (34,0)	 15 (38,5) 24 (61,5)	0,011

The discriminatory performance of the predictive models was evaluated using receiver operating characteristic (ROC) curve analysis. Three prediction models were developed: a clinical model (line of therapy and PD-L1 expression), a radiomic model (radiological density and entropy of orbital adipose tissue), and a combined clinicoradiomic model incorporating both clinical and radiomic predictors. The primary objective of model development was to determine whether the addition of orbital adipose tissue radiomic features improved prediction of treatment response beyond conventional clinical variables. Model performance was quantified by the area under the ROC curve (AUC) with corresponding 95 % confidence intervals (CI). Differences between ROC curves were assessed using the nonparametric ROC comparison test.

Results

Association of clinical, laboratory, and radiomic characteristics of orbital adipose tissue with objective response to immunotherapy

A total of 86 patients with metastatic NSCLC who received immunotherapy were included in the analysis. According to treatment response, patients were stratified into two groups: those who achieved an objective response (CR + PR; n=47) and those without an objective response (SD + PD; n=39). A comparative analysis of the clinical, laboratory, quantitative, and radiomic characteristics of orbital adipose tissue is presented in table 1.

Analysis of demographic characteristics revealed no statistically significant differences between the groups with respect to age, sex, smoking status, BMI, or histological subtype (all p>0.05). However, patients who achieved an objective response were significantly more likely to receive immunotherapy as first-line treatment than those without an objective response (91.5 % vs. 74.4 %; p=0.042). In addition, high PD-L1 expression (>50 %) was significantly more frequent among patients who achieved an objective

response than among those who did not (36.2 % vs. 5.1 %; p=0.001).

Analysis of laboratory parameters showed no statistically significant differences between the groups in terms of NLR, PLR, or SII values (all p>0.05).

Among the quantitative characteristics of orbital adipose tissue, total orbital adipose tissue volume was not associated with the achievement of an objective response (p=0.463). In contrast, the radiological density of orbital adipose tissue demonstrated a statistically significant association with treatment efficacy. Radiological density values ⩾-77 HU were observed more frequently in patients who achieved an objective response than in those without an objective response (70.2 % vs. 33.3 %; p=0.001).

Analysis of radiomic features demonstrated that patients with an objective response were significantly more likely to exhibit lower entropy values (<2.01) (91.5 % vs. 43.6 %; p=0.0001) and lower SZNU values (<52.14) (66.0 % vs. 38.5 %; p=0.011). A trend toward an association between lower Variance values (<563) and the achievement of an objective response was also observed; however, this association did not reach statistical significance (p=0.065).

Association of clinical, laboratory, and radiomic characteristics of orbital adipose tissue with disease control

Following the evaluation of factors associated with the achievement of an objective response, the associations between clinical, laboratory, quantitative, and radiomic characteristics of orbital adipose tissue and disease control were subsequently analyzed. The disease control group (CR+ PR + SD) comprised 76 patients, whereas disease progression (PD) was observed in 10 patients. The results of the comparative analysis are presented in table 2.

Table 2. Clinical, laboratory, and radiomic characteristics of orbital adipose tissue in patients with metastatic NSCLC stratified according to disease control

Parameter	Disease control (CR + PR + SD), n=76	No disease control (PD), n=10	p
Demographic and clinical characteristics			
Age, years, n (%)			0,722
<65	52 (68,4)	6 (60,0)	
⩾65	24 (31,6)	4 (40,0)	
Sex, n (%)			0,904
Male	62 (81,6)	8 (80,0)	
Female	14 (18,4)	2 (20,0)	
Smoking, n (%)			0,805
No	20 (26,3)	3 (30,0)	
Yes	56 (73,7)	7 (70,0)	
BMI, n (%)			0,086
<24,9	35 (46,1)	8 (80,0)	
25-29,9	20 (26,3)	2 (20,0)	
⩾30	21 (27,6)	0 (0,0)	
Histology, n (%)			0,504
Adenocarcinoma	34 (44,7)	6 (60,0)	
Squamous cell carcinoma	42 (55,3)	4 (40,0)	
Line of treatment, n (%)			0,356
First	65 (85,5)	7 (70,0)	
Second	11 (14,5)	3 (30,0)	
PD-L1 expression, n (%)			0,856
1-49 %	59 (77,6)	8 (80,0)	
>50 %	17 (22,4)	2 (20,0)	
Laboratory parameters			
NLR, n (%)			0,672
<3,7	48 (63,2)	7 (70,0)	
⩾3,7	28 (36,8)	3 (30,0)	
PLR, n (%)			0,308
<196	51 (67,1)	5 (50,0)	
⩾196	25 (32,9)	5 (50,0)	
SII, n (%)			0,945
<1243	54 (71,1)	7 (70,0)	
⩾1243	22 (28,9)	3 (30,0)	
Quantitative characteristics of orbital adipose tissue			
Total orbital adipose tissue volume, cm^3, n (%)			0,104
<9,8	39 (51,3)	8 (80,0)	
⩾9,8	37 (48,7)	2 (20,0)	
Radiological density of orbital adipose tissue, HU, n (%)			0,0001
<-77	30 (39,5)	10 (100,0)	
⩾-77	46 (60,5)	0 (0,0)	
Radiomic features of orbital adipose tissue			
Variance, n (%)			0,002
<563	48 (63,2)	1 (10,0)	
⩾563	28 (36,8)	9 (90,0)	
Entropy, n (%)			0,029
<2,01	56 (73,7)	4 (40,0)	
⩾2,01	20 (26,3)	6 (60,0)	
SZNU, n (%)			0,504
<52,14	42 (55,3)	4 (40,0)	
⩾52,14	34 (44,7)	6 (60,0)	

Analysis of demographic and clinical characteristics revealed no statistically significant differences between the groups with respect to age, sex, smoking status, BMI, histological subtype, line of therapy, or PD-L1 expression (all p>0.05). Likewise, laboratory markers of systemic inflammation (NLR, PLR, and SII) were not significantly associated with disease control.

Among the quantitative characteristics of orbital adipose tissue, total orbital adipose tissue volume was not associated with treatment efficacy (p=0.104). In contrast, the radiological density of orbital adipose tissue emerged as one of the most significant imaging biomarkers. Radiological density values below -77 HU were observed in all patients with disease progression, whereas such values were detected in only 39.5 % of patients who achieved disease control (p=0.0001).

Analysis of radiomic features further demonstrated their association with disease control. Patients who achieved disease control were significantly more likely to exhibit lower Variance values (<563) (63.2 % vs. 10.0 %; p=0.002) and lower Entropy values (<2.01) (73.7 % vs. 40.0 %; p=0.029). In contrast, SZNU was not significantly associated with disease control (p=0.504).

These findings indicate that specific quantitative and radiomic characteristics of orbital adipose tissue are associated not only with the achievement of an objective response but

Table 3. Univariable and multivariable logistic regression analyses of predictors of objective response to immunotherapy in patients with metastatic NSCLC

Predictor	Univariable OR (95 % CI)	p	Multivariable OR (95 % CI)	p
Line of treatment	0.27 (0.08-0.94)	0.040	0.05 (0.01-0.53)	0.012
PD-L1 expression >50 %	10.48 (2.24-49.01)	0.003	41.93 (2.64-665.94)	0.008
Radiological density of orbital adipose tissue ⩾-77 HU	4.71 (1.89-11.75)	0.001	6.49 (1.89-22.37)	0.003
Entropy ⩾2.01	0.07 (0.02-0.24)	<0.001	0.09 (0.02-0.37)	0.001

also with disease control, supporting their potential role as noninvasive predictors of immunotherapy efficacy in patients with metastatic NSCLC.

Given the observed associations of several clinical and radiomic characteristics with both objective response and disease control, the next stage of the study was to evaluate their independent prognostic value using multivariable logistic regression analysis.

Independent predictors of objective response to immunotherapy

To identify independent predictors of objective response to immunotherapy, univariable and multivariable logistic regression analyses were performed. The univariable analysis included the clinical, laboratory, quantitative, and radiomic characteristics of orbital adipose tissue evaluated in the previous stage of the study. The results demonstrated that line of therapy, PD-L1 expression, radiological density of orbital adipose tissue, Entropy, and SZNU were significantly associated with the achievement of an objective response, whereas Variance showed a trend toward statistical significance (p=0.067).

Subsequently, a series of multivariable logistic regression models was constructed by sequentially incorporating clinical and radiomic predictors. A clinical model was first developed, including line of therapy and PD-L1 expression as established clinical predictors of immunotherapy efficacy. Independent radiological and radiomic characteristics of orbital adipose tissue were then added sequentially to the model. To evaluate the contribution of individual texture features, alternative models were constructed incorporating Entropy and SZNU separately, as well as a model including both features simultaneously.

The results demonstrated that, after adjustment for clinical factors, first-line therapy (odds ratio, OR 0.05; 95 % CI 0.01-0.53; p=0.012), high PD-L1 expression (>50 %) (OR 41.93; 95 % CI 2.64-665.94; p=0.008), radiological density of orbital adipose tissue ⩾-77 HU (OR 6.49; 95 % CI 1.89-22.37; p=0.003), and Entropy ⩾2.01 (OR 0.09; 95 % CI 0.02-0.37; p=0.001) remained independent predictors of objective response (table 3).

Although SZNU was statistically significant in the univariable analysis, it lost its independent prognostic significance after being entered into the multivariable model together with Entropy (p=0.158). This finding suggests that these two texture features capture partially overlapping biological information, whereas Entropy provides greater independent predictive value for response to immunotherapy.

Predictive performance of the clinical, radiomic, and combined clinicoradiomic models for predicting objective response to immunotherapy

To evaluate the discriminatory performance of the independent predictors of objective response to immunotherapy, three logistic regression models were developed: a clinical model incorporating line of therapy and PD-L1 expression; a radiomic model including radiological density and Entropy of orbital adipose tissue; and a combined clinicoradiomic model integrating both clinical and radiomic predictors.

The results of the ROC curve analysis are presented in figure 2. The clinical model demonstrated satisfactory discriminatory performance for predicting objective response to treatment (AUC 0.718; 95 % CI 0.638-0.799). The radiomic model exhibited superior predictive performance (AUC 0.819; 95 % CI 0.732-0.906), indicating the independent predictive value of quantitative characteristics of orbital adipose tissue.

The combined clinicoradiomic model, incorporating line of therapy, PD-L1 expression, radiological density, and Entropy of orbital adipose tissue, demonstrated the highest discriminatory performance (AUC 0.896; 95 % CI 0.834-0.958), indicating excellent predictive accuracy.

Comparison of the ROC curves revealed statistically significant differences among the three models (χ^2=67.08; p<0.001). The combined clinicoradiomic model exhibited significantly higher predictive accuracy than both the clinical model (χ^2=20.84; p<0.001) and the radiomic model based exclusively on radiomic features (χ^2=6.62; p=0.010). These findings indicate that integrating radiomic features of orbital adipose tissue with conventional clinical predictors provides the most accurate prediction of objective response to immunotherapy.

Taken together, the incorporation of radiomic features of orbital adipose tissue into conventional clinical predictors substantially improved the accuracy of predicting objective response to immunotherapy in patients with metastatic NSCLC.

Discussion

To our knowledge, this is the first study to demonstrate that radiomic features of orbital adipose tissue are associated with the efficacy of immunotherapy in patients with metastatic NSCLC. The principal finding of the present study was the identification of radiological density and Entropy of orbital adipose tissue as independent predictors of objective response to treatment. Furthermore, integrating these imaging biomarkers with established clinical predictors substantially improved the discriminatory performance of the predictive model, as evidenced by an increase in the area under the ROC curve from 0.718 for the clinical model to 0.896 for the combined clinicoradiomic model. These findings suggest that

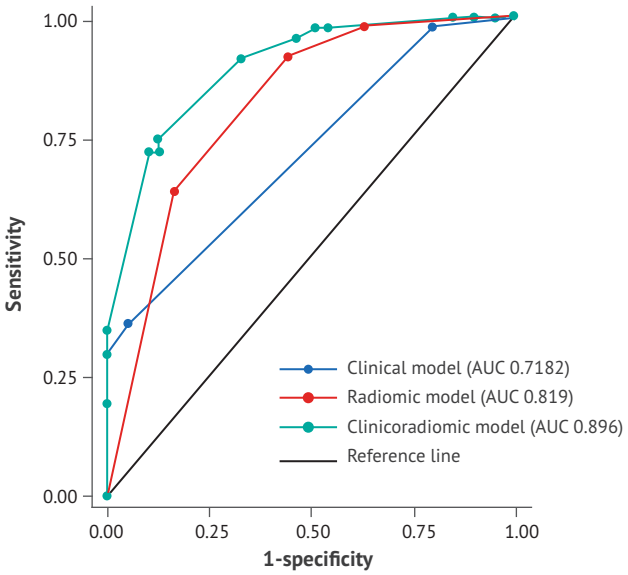

Fig. 2. ROC curves of the clinical, radiomic, and combined clinicoradiomic models for predicting objective response to immunotherapy

radiomic characteristics of orbital adipose tissue not only reflect systemic host-related biological processes but also provide incremental predictive information beyond that offered by conventional clinical variables.

In recent years, growing evidence has demonstrated that the response to immunotherapy is determined not only by the molecular characteristics of the tumor but also by host-related biological factors. Consequently, in addition to tumor-specific biomarkers, increasing attention has been devoted to body composition, cancer cachexia, systemic inflammation, and adipose tissue characteristics as potential predictors of treatment efficacy [16, 17]. Adipose tissue is an active endocrine organ that plays a central role in regulating the production of pro-inflammatory cytokines, adipokines, and other mediators involved in modulating the antitumor immune response [18, 19]. Accumulating evidence indicates that adipose tissue remodeling accompanies tumor progression, the development of cancer cachexia, and alterations in systemic immune status, all of which may influence the efficacy of immune checkpoint inhibitor therapy [6, 20]. In this context, our findings support the emerging concept that adipose tissue characteristics may serve as integrated biomarkers of systemic biological processes that determine the host response to anticancer treatment [21].

A distinctive feature of the present study is the use of orbital adipose tissue as the target of radiomic analysis. Unlike visceral or subcutaneous adipose tissue, orbital adipose tissue possesses unique molecular and functional characteristics. Transcriptomic and lipidomic studies have demonstrated substantial differences between orbital adipose tissue and other adipose depots with respect to the expression of genes involved in inflammation, adipocyte differentiation, and cellular metabolism [22]. In addition, orbital adipose tissue contains a unique microenvironment composed of adipocytes, fibroblasts, vascular structures, and immune cells capable of responding to systemic inflammatory stimuli [23]. It can therefore be hypothesized that structural alterations within this adipose depot reflect not only local tissue-specific processes but also the overall immunometabolic status of the host. Another important advantage of this adipose depot is that it can be assessed using routine head CT, which is performed in the majority of patients with metastatic NSCLC before the initiation of immunotherapy, without the need for additional imaging examinations or radiation exposure.

The findings regarding individual radiomic features are of particular interest. Entropy emerged as the strongest independent predictor, reflecting the degree of heterogeneity in the distribution of voxel intensities within the analyzed tissue. Higher Entropy values indicate greater structural complexity and more pronounced microstructural heterogeneity, which may result from adipose tissue remodeling driven by systemic inflammation, metabolic disturbances, or cellular infiltration [24, 25].

Conversely, the lower Entropy values observed in patients who achieved an objective response may reflect a more homogeneous structural organization of orbital adipose tissue and, consequently, a more favorable host immunometabolic phenotype. Similarly, increased radiological density of orbital adipose tissue, which was also retained in the final predictive model, likely reflects structural alterations associated with reduced lipid content, fibrosis, or inflammatory infiltration. Comparable patterns have previously been described in other adipose tissue depots in patients with cancer and have been proposed as potential biomarkers of systemic inflammation and cancer cachexia [26, 27].

This study has several limitations. First, the retrospective single-center design and the relatively small sample size limit the generalizability of the findings and precluded external validation of the proposed clinicoradiomic model. Second, the analysis was based exclusively on baseline CT examinations performed before the initiation of immunotherapy; therefore, longitudinal changes in the radiomic characteristics of orbital adipose tissue during treatment were not evaluated. Furthermore, the potential influence of molecular and genetic biomarkers was not assessed.

Despite these limitations, the present findings have important potential clinical implications. Radiomic features of orbital adipose tissue can be extracted from routine head CT examinations without the need for additional diagnostic procedures, radiation exposure, or financial costs. The proposed combined clinicoradiomic model demonstrated superior predictive performance compared with a model based solely on clinical variables, supporting the integration of radiomic features of orbital adipose tissue into predictive models of response to immunotherapy. Following external validation, this approach may serve as an additional tool for personalizing treatment strategies in patients with metastatic NSCLC.

Conclusions

Radiomic features of orbital adipose tissue are associated with the efficacy of immunotherapy in patients with metastatic NSCLC. Radiological density and Entropy of orbital adipose tissue are independent predictors of objective response to treatment. Integration of radiomic features of orbital adipose tissue with clinical variables provides a statistically significant improvement in the prediction of response to immunotherapy compared with the use of conventional clinical predictors alone. These findings suggest that radiomic analysis of orbital adipose tissue represents a promising noninvasive approach for personalizing treatment in patients with metastatic NSCLC and warrants further validation in prospective multicenter studies.

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