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Impact of metabolic and nutritional disorders on the synergy between radiotherapy and immunotherapy in non-small-cell lung cancer

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Abstract

Background Patient conditions including metabolic and nutritional status were reported to be prognostic or predictive biomarkers of anti-cancer treatment, while little attention has been paid to its association with the synergistic effect of radiotherapy (RT) and immune checkpoint inhibitors (ICIs).

Methods Metastatic non-small-cell lung cancer (mNSCLC) patients who received concurrent RT and ICIs between 2018 and 2023 were included in this study. In addition, mNSCLC patients treated with ICIs alone were enrolled to confirm the synergetic effect of RT and ICIs. Clinicopathological, metabolic and nutritional factors were collected to analyze their influence on progression-free survival (PFS), overall survival and abscopal control time. Abdominal CT was used to obtain body composition data including abdominal obesity and muscle mass.

Results A total of 96 mNSCLC patients who received RT concurrent with ICIs were included, and a synergistic effect of significantly improved PFS was observed when compared with patients treated with ICIs alone. Among patients undergoing concurrent RT and ICIs, both total adipose area(HR = 2.81,*P* = 0.029) and prognosis nutritional index (HR = 0.24, *P*<0.001) were confirmed as independent positive prognostic markers for PFS. Later-line of immunotherapy (HR = 3.67, *P* = 0.006), low visceral-to-subcutaneous ratio (VSR, HR = 5.53, *P* = 0.002), high total adipose area (HR = 5.21, *P* = 0.0016) and high prognostic nutritional index (HR = 0.24, *P* = 0.002) were independent risk factors for abscopal progression. Then, we established a scoring system consisting of metabolic and nutritional factors to stratify patients

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into three groups. Patients with non-visceral obesity and good nutrition status have the longest PFS and abscopal control survival, while patients with poor nutritional status regardless of body composition represent the worst prognosis.

Conclusion Metabolic and nutritional status, particularly the combined assessment of body composition and nutritional index, serves as a valuable predictor for the synergistic efficacy of concurrent RT and ICIs.

Keywords Non-small-cell lung cancer, Radiotherapy, Immune checkpoint inhibitors, Metabolic disorders, Nutritional disorders

Introduction

For patients with metastatic non-small-cell lung cancer (mNSCLC), immune checkpoint inhibitors (ICIs) have been approved either in first-line or second-line treatment, achieving unprecedented success of prolonged survival [1]. However, not all patients respond to ICIs, and the response rate to ICIs remains unsatisfactory, varying from 14 to 46%. The issue of primary and acquired resistance is still critical [2]. Radiation-induced activation of the immune system and remodeling of the tumor microenvironment have been increasingly recognized, and the combination of radiotherapy (RT) with ICIs, often known as immunoradiotherapy (iRT), can help to overcome immunotherapy resistance [3]. The utilization of iRT not only triggers regression of irradiated tumors, but also induces systemic anti-tumor immune response and kills non-irradiated metastases, known as abscopal effect [4]. But there are still a lot of unanswered problems, and one of the issues right now is how to explore a reliable biomarker to select patients who can potentially benefit from iRT.

Tumor-intrinsic and -extrinsic features, such as tumor mutational burden, microsatellite instability, PD-L1 expression, gene expression profiles, T cell repertoire, tumor-infiltrating immune cells, liquid biopsy, etc., have been widely identified to predict response and resistance to ICIs treatment and some of them have guided clinical use of ICIs, but far from satisfactory [5, 6]. Apart from tumor markers, clinical parameters have been discovered as potential prognostic or predictive biomarkers, including age [7, 8], sex [9], performance status [10] and smoking history [11], by affecting the host's innate and adaptive immunity. Metabolic and nutritional disorders are prevalent among cancer patients [12], especially those in advanced stages. Preclinical and translational data strongly suggest a connection between metabolic and nutritional status and immune function [13, 14]. For example, a meta-analysis [15] recently enrolled 4602 NSCLC patients treated with ICIs and found that overweight and obese patients achieved prolonged progression-free survival (PFS) (hazard ratio (HR) = 0.862, $P = 0.021$) and overall survival (OS) (HR = 0.818, $P < 0.001$) compared with normal-weight patients. Another study [16] with 513 NSCLC patients found that abdominal visceral fat was related to inflammatory transcriptomic signature and impacted PFS and OS.

Besides, metabolic and nutritional disorders also affect RT efficacy. Nutritional status was identified as a potential indicator for OS in small-cell lung cancer patients receiving radiotherapy [17]. Ma et al. [18] found that overweight (Adjusted odds ratio(OR) = 0.86, $P < 0.001$) and obese body mass index (BMI) (Adjusted OR = 0.89, $P = 0.005$) were associated with complete metabolic response after chemoradiotherapy in patients with head and neck cancer. Malnutrition was associated with poorer OS in cervical cancer patients receiving RT [19]. However, to date, few studies have investigated the association between metabolic and nutritional disorders and the efficacy of iRT.

Therefore, in this study, we investigated the impact of metabolic and nutritional disorders on the synergy between RT and ICIs in NSCLC. According to the National Heart, Lung and Blood Institute [20], metabolic factors include abdominal obesity, high blood pressure, impaired glucose, high triglyceride(TG) levels, and low high-density lipoprotein (HDL) cholesterol levels. Nutritional disorders, defined by GLIM criterion [21], involve BMI, muscle mass, and inflammation. Overall, we aimed to explore the associations between these factors and the prognosis of mNSCLC patients receiving iRT.

Materials and methods

Patients

Our retrospective database was queried for mNSCLC patients receiving iRT at the Second Affiliated Hospital of Zhejiang University between January 1, 2018 and January 1, 2023. The inclusion criteria were as follows: (1) patients were pathologically diagnosed as NSCLC with distant metastasis; (2) patients received concurrent RT and ICIs, with ICIs administered within 6 months before or after RT; (3) enrolled patients presented measurable abscopal lesions;4) individuals underwent active follow up procedures. They were excluded if (1) without histological diagnosis of mNSCLC, (2) without routine surveillance and follow-up of measurable lesions, (3) without detailed treatment information (including RT or ICIs dose, time and therapeutic schedule) (Fig. 1A). Besides, mNSCLC patients treated with ICIs alone (Without RT within 6

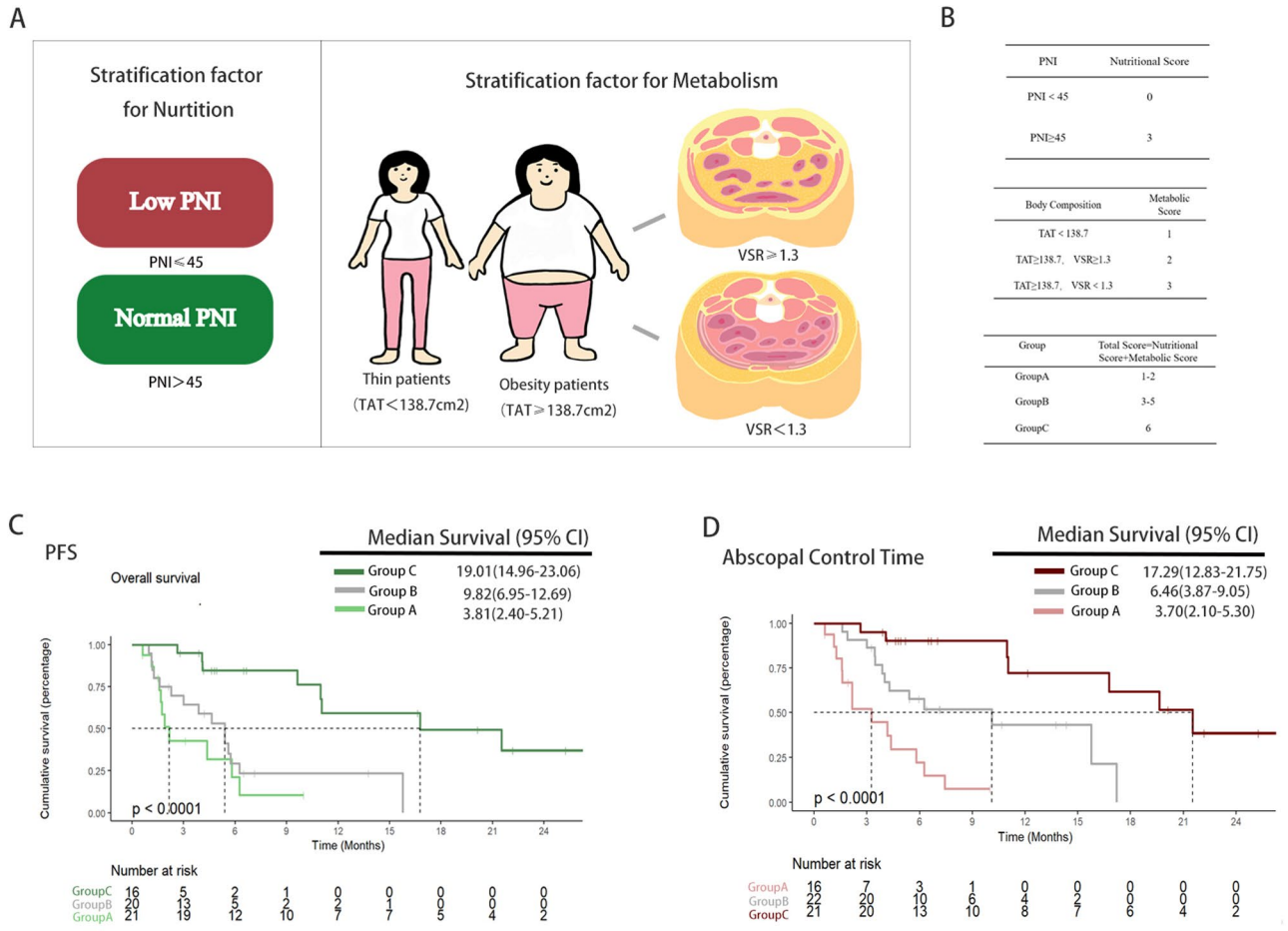

Fig. 1 Patients screened and data extraction process of the study. From left to right displayed the study cohort with key exclusion criteria(**A**), biomarkers related to metabolic and nutritional disorders(**B**), and observation endpoint(**C**)

months before or after ICIs) and active follow-up during January 1, 2018 and January 1, 2023 were also enrolled.

This project was approved by the Independent Ethics Committee of the Second Affiliated Hospital of Zhejiang University (No. I2023409).

Basic clinicopathological data collection

Patient demographic characteristics, including age, sex, smoking history, histology type, combined treatment regimen, radiated lesions, metastasis lesions without RT, detailed RT (including irradiation sites, technique, total dose, and single dose) and ICIs (including cycles, type and line) information were collected on the Electronic Medical Record System.

Metabolic data collection

In accordance with National Heart, Lung and Blood Institute criteria as mentioned above [20], biomarkers reflecting metabolic status were collected, including hypertension, hyperglycemia history, and usage of statin. TG and HDL are reflected by serum blood counts. The normal scope of blood biochemistry biomarkers is listed according to 95% of population mean in China (TG<1.70mmol/L, HDL>0.90mmol/L). Abdominal CT was used to obtain body composition data including abdominal obesity and muscle mass [22], with detailed methods provided below.

Body composition data collection

To gather information on abdominal adipose area and muscle mass, baseline abdominal CT images at the level of the third lumbar vertebra (mid-L3) were obtained. These pretreatment scans were analyzed using sliceOmatic (Tomovision V.5.0) according to previously established methods (Fig. 1B) [22]. We measured the subcutaneous adipose tissue area (SAT) and visceral adipose tissue area (VAT). Total abdominal adipose tissue (TAT) was determined as the sum of VAT and SAT. Visceral-to-subcutaneous ratio (VSR) was applied to reflect the individual fat distribution. Muscle tissue areas were normalized for height in meters squared (m2) and reported as the lumbar skeletal muscle index (SMI) (cm2/m2).

Adipose and muscle tissue were distinguished based on predefined Hounsfield units (HU) ranges: -190 to -30 HU for SAT, -150 to -50 HU for VAT, and − 29 to + 150 HU for SMI. According to the criteria typically employed in Asian patients with cancer based on CT, sarcopenia was defined as SMI ≤ 40.8 cm2 /m2 in men and ≤ 34.9 cm2/m2 in women [23]. R software was used to obtain the best cut-off value for SAT, TAT and VSR. We identified three risk groups (low, intermediate, and high) for SAT, and two risk groups (high and low) for TAT and VSR.

Nutritional data collection

Baseline BMI before the initiation of ICIs was extracted. According to the GLIM criterion, we also collected immuno-nutritional scores, which were calculated based on extracted laboratory markers. Furthermore, we used Prognostic Nutritional Index (PNI) and Glasgow Prognostic Score (GPS) to evaluate nutritional status, which were also widely adopted nutritional assessment tools [24, 25]. PNI was calculated using the following formula: Albumin + 5*lymphocyte count. We utilized a well-established cutoff score of 45, commonly used for Asian patients, to categorize patients into two groups: low PNI (< 45) versus normal PNI (≥ 45) [26, 27]. The GPS was based on a combination of CRP and albumin level. Patients with both an elevated CRP (> 10.0 mg/dl) and hypoalbuminemia (< 3.5 g/dl) were assigned a score of 2, patients with CRP > 10 mg/dL and albumin > 3.5 g/dL got a score of 1, patients with CRP ≤ 10 mg/dL was scored as 0 [28, 29]. Neutrophil/lymphocyte ratio (NLR) was used to describe systemic inflammation.

It is important to note that all these blood biomarkers reflecting metabolic or nutritional status are obtained within 14 days before the initiation of ICIs therapy.

Endpoints

We first compared the PFS and OS between the RT + ICIs group and the ICIs alone group. PFS refers to the interval from the initiation of immunotherapy to tumor progression or death, while OS is the time from immunotherapy initiation to death from any cause. Then, we investigate the impact of nutritional and metabolic disorders on PFS, OS and abscopal control survival in patients receiving RT + ICIs, with all endpoints starting from the initiation of RT. Specially, abscopal control time is defined as the time from radiotherapy initiated to the progression of arbitrary non-irradiated lesions or new distant metastases. As efficacy outcomes, complete response (CR), partial response (PR), stable disease (SD), progression disease (PD) were assessed according to the RECIST 1.1 criteria. Disease control rate (DCR) is defined as the percentage of patients who have achieved CR, PR or SD to a therapeutic intervention, and objective response rate (ORR) Is defined as the proportion of patients who have a CR or PR to therapy.

Statistical analysis

We first investigate the synergistic effect between RT and ICIs. To control the effect of potential clinicopathological and treatment-related characteristics on selection bias, propensity score matching (PSM) was applied using the covariates: age, sex, smoking history, histology type of tumor, line of ICIs, combined treatment regimen, with or without hypertension/hyperglycemia, previous usage of statin, with or without liver/brain metastasis. PSM was performed 1:1 using the nearest neighbor matching in RStudio.

Then we use the univariate cox regression model to identify biomarkers with predictive value to local and abscopal control time. Those with $p \le 0.1$ on univariate analysis were finally included in multivariate cox proportional hazards models [30, 31]. Kaplan-Meier analysis was applied to study the prognostic impact of nutritional and metabolic disorders on our primary endpoint and OS. We use restricted cubic spine (RCS) models fit for Cox proportional hazards models with 5 knots at the 5th, 35th, 50th, 65th, and 95th centiles of VSR. Results were adjusted for line of immunotherapy (first or later). To visualize the continuous relationship of the CAR or PNI with the risk of local progression, RCS model with 5 knots was also applied with adjustments of the iRT sequence as reference.

Above analyses were all performed using R software, version 4.2.2 (R Foundation for Statistical Computing). A two-sided $p < 0.05$ was considered statistically significant for the analyses.

Results

Synergistic effect between RT and ICIs

A total of 96 mNSCLC patients who received iRT (RT + ICIs) were included in our study, and the clinicopathological characteristics of these patients are presented in Table 1. To investigate the synergistic effect between RT and ICIs, 203 patients treated with ICIs alone were also enrolled to compare PFS and OS between these two groups. The results showed that patients who underwent iRT exhibited significantly improved PFS (15.04 months vs. 10.33 months, $P = 0.0013$) and comparable OS (33.33 months vs. 29.40 months, $P = 0.2$) compared to those who received ICIs alone (Fig. 2A and B). After PSM, we extracted 61 baseline-matched pairs (Table 1). Radiotherapy details before and after PSM are presented in Supplementary Table 1. In the matched cohort, significantly prolonged PFS (13.91 months vs. 5.94 months, $P < 0.001$) and OS (34.14 months vs. 23.19 months, $P = 0.012$) were observed in the iRT group, indicating a synergistic effect of combining RT and ICIs.

Table 1 Baseline characteristics of mNSCLC patients receiving RT concurrent with ICIs or ICIs alone

	Before PSM ICI (*N* = 203, percentage)			After PSM		
	RT + ICIs (%)	ICIs alone (%)	*P*	RT + ICIs (%)	ICIs alone (%)	*P*
Age			0.06			0.58
≤ 60	33(34.4%)	93(45.8%)		23(37.8%)	26(42.6%)	
>60	63(65.6%)	110(54.2%)		38(62.2%)	35(57.4%)	
Sex			0.35			0.85
male	71(74.0%)	160(78.8%)		41(67.2%)	42(68.9%)	
female	25(26.0%)	43(21.2%)		20(32.8%)	19(31.1%)	
Smoking history			0.73			0.27
ever smoker	60(62.5%)	131(64.5%)		37(60.7%)	31(50.8%)	
non-smoker	36(37.5%)	72(35.5%)		24(39.3%)	30(49.2%)	
Histology type			0.10			0.70
squamous cell carcinoma carcinomacarciom	38(39.6%)	67(33.0%)		20(32.8%)	18(29.5%)	
adenocarcinoma	58(60.4%)	128(63.1%)		41(67.2%)	43(70.5%)	
others	0(0.0%)	8(3.9%)		0(0.0%)	0(0.0%)	
Line of ICIs			0.14			0.12
first	72(75.0%)	168(82.8%)		48(78.7%)	42(68.9%)	
second	13(13.5%)	24(11.8%)		5(8.2%)	13(21.3%)	
Three or more	11(11.5%)	11(5.4%)		8(13.1%)	6(9.8%)	
Combined treatment regimen			0.03			0.87
Chemotherapy	65(67.7%)	145(71.4%)		44(72.1%)	47(77.0%)	
Antiangiogenic therapy	9(9.4%)	9(4.4%)		5(8.2%)	3(4.9%)	
Antiangiogenic + chemotherapy	9(9.4%)	35(17.2%)		5(8.2%)	4(6.6%)	
none	13(13.5%)	14(6.9%)		7(11.5%)	7(11.5%)	
Hypertension			0.07			0.31
with	36(37.5%)	55(27.1%)		19(31.1%)	14(23.0%)	
Without	60(62.5%)	148(72.9%)		42(68.9%)	47(77.0%)	
Hyperglycemia			0.18			0.38
with	14(14.6%)	19(9.4%)		8(13.1%)	5(8.2%)	
Without	82(85.4%)	184(90.6%)		53(86.9%)	56(91.8%)	
Statin use			0.001			0.34
with	15(15.6%)	10(4.9%)		7(11.5%)	4(6.6%)	
Without	81(84.4%)	193(95.1%)		54(88.5%)	57(93.4%)	
Liver metastasis			0.01			0.75
with	6(6.3%)	34(16.7%)		5(8.2%)	6(9.8%)	
Without	90(93.8%)	169(83.3%)		56(91.8%)	55(90.2%)	
Brain metastasis			0.01			0.36
with	40(41.7%)	56(27.6%)		26(42.6%)	31(50.8%)	
Without	56(58.3%)	147(72.4%)		35(57.4%)	30(49.2%)	

Body composition and PNI are predictors for PFS and OS in patients receiving iRT

Among the 96 patients undergoing iRT therapies, 28(29.2%) received RT to lung, 31(32.3%) received treatment to bone, 33(34.4%) underwent RT to brain and the other four patients (4.2%) received RT to liver or abdominal lymph node. The most commonly administered ICIs were Camrelizumab (32/96,33.3%), Tislelizumab (18/96,18.8%), Pembrolizumab (18/96,18.8%) and Sintilimab (18/96,18.8%). The median local control time and abscopal control time were 19.62 and 10.28 months, respectively. Radiated lesions exhibited significantly longer control time compared with abscopal lesions ($P = 0.0062$) (Fig. 2C). Seventeen (17.71%) patients achieved CR or PR for abscopal lesions, and 26 patients (27.08%) achieved CR or PR for local lesions (Fig. 2D).

Sixty of 96(62.5%) patients had baseline abdominal CT and were extracted for adipose and skeletal area. To identify the association between the different body composition features and nutritional factors, we performed correlations between variables (Supplementary Fig. 1). We observed a negative correlation between inflammation index (as indicated by NLR) and better nutritional status (PNI, R=-0.49, P<0.001). We also observed a positive correlation between muscle mass and adipose tissue deposits (SMI vs. VSR: $r = 0.32$; $P = 0.014$).

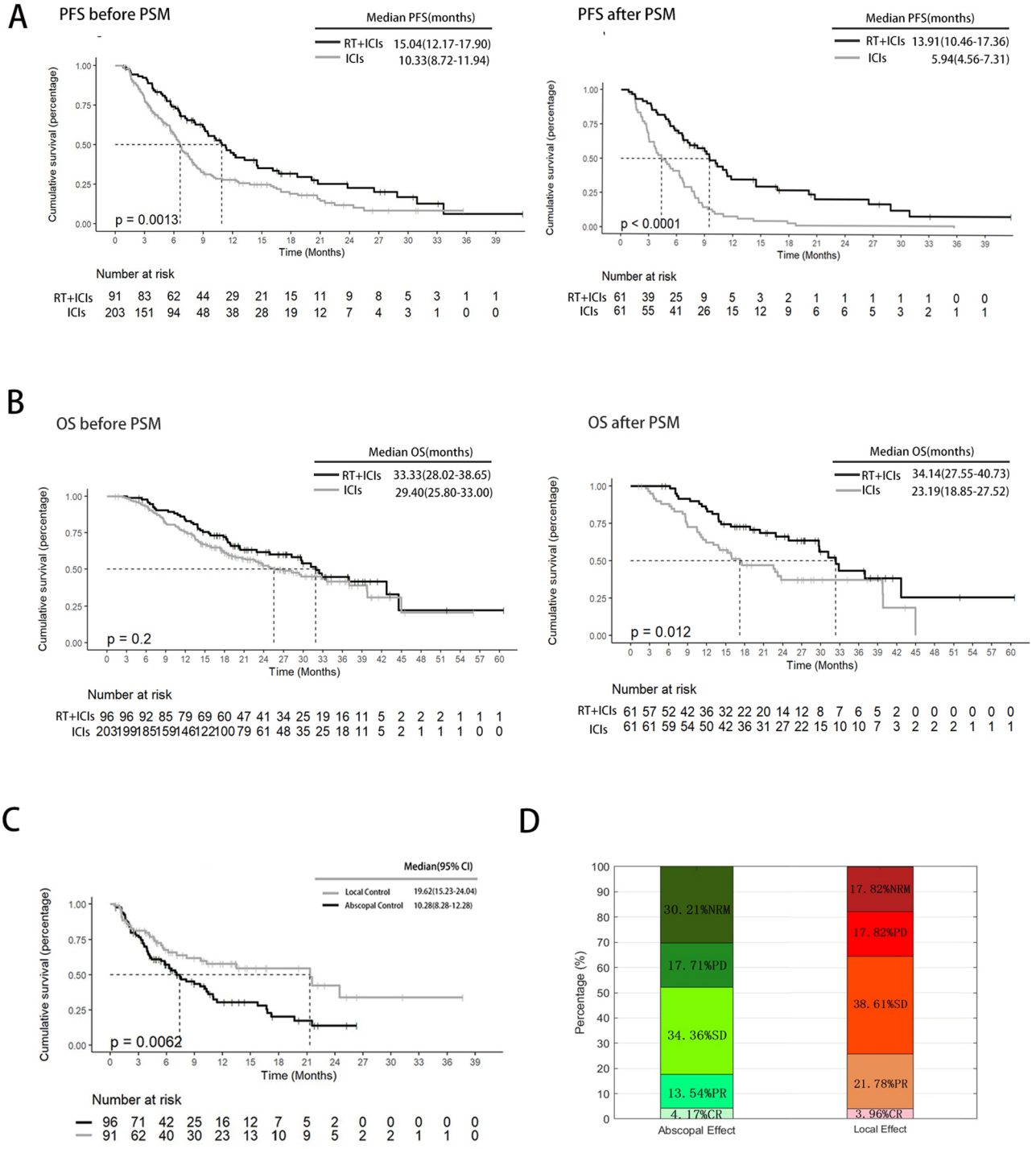

Fig. 2 The synergistic effect between RT and ICIs. A propensity matching analysis between patients receiving iRT and receiving immunotherapy with PFS(**A**), OS(**B**) as endpoints. C, left figure reveals the local control survival(light-gray) and abscopal control survival(dark-gray) for patients receiving iRT. Right figure reveals objective response rate (ORR) after two or three cycles of ICIs after RT

Then, we sought to explore the prognostic value of nutritional and metabolic factors. Multivariate Cox analysis identified TAT (HR = 2.81, 95% CI = 1.11–7.11, $P = 0.029$) and PNI (HR = 0.24, 95% CI = 0.11–0.54, $P<0.001$) as independent prognostic markers for PFS (Table 2). Specifically, patients with TAT < 138.7 cm2 have shorter PFS than those with TAT ≥ 138.7 cm2(4.23 months vs. 11.48 months, $P = 0.019$) (Fig. 3A). Patients with normal PNI obtained longer PFS compared with the low PNI group (Fig. 3B). Patients with low VSR also have

Table 2 Univariate and multivariate COX analysis for PFS in patients receiving iRT

	Univariate regression		Multivariate regression	
Variables*	**HR**	***P***	**HR**	***P***
Baseline characteristics				
Line of ICIs				
Second or further Line vs. first Line	1.5 (0.85-2.66)	0.164		
Histology type				
Adenocarcinoma vs. squamous cell carcinoma	0.88 (0.52-1.5)	0.64		
Sex				
Female vs. male	0.72 (0.4-1.28)	0.26		
Age				
>65 vs. ≤65	1 (0.59-1.7)	0.994		
Smoking history				
Ever smoker vs. non-smoker	1.24 (0.74-2.08)	0.417		
Combined treatment regimen				
Antiangiogenic + chemotherapy vs. chemotherapy	1.18(0.5-2.79)	0.71		
Antiangiogenic therapy vs. chemotherapy	0.73(0.29-1.86)	0.514		
None vs. chemotherapy	0.63(0.27-1.49)	0.295		
Type of immunotherapy				
PD-L1 vs. PD-1	0.96 (0.8-1.16)	0.698		
PS Score				
2-4 vs. 0-1	1.12(0.48-2.61)	0.7966		
Factors reflective of metabolic status				
Hypertension				
With vs. without	0.85(0.5-1.45)	0.554		
Hyperglycemia				
With vs. without	0.99(0.5-1.92)	0.979		
Statin use				
With vs. without	0.63(0.32-1.26)	0.193		
HDL				
High baseline HDL vs. normal	1.83(0.84-4)	0.129		
Triglyceride				
High baseline triglyceride vs. normal	1.05(0.56-1.98)	0.872		
SAT				
80.2≤SAT≤110.9 vs. SAT<80.2	0.74 (0.29-1.87)	0.519		
SAT>110.9	0.54 (0.24-1.23)	0.142		
VSR				
VSR≥1.3 vs. VSR<1.3	1.69 (0.79-3.58)	0.175		
TAT				
TAT<138.7 vs. TAT≥138.7	**2.63(1.14-6.06)**	**0.023**	**2.81(1.11-7.11)**	**0.0293**
Factors reflective of nutritional status				
BMI				
Obese or overweight vs. normal or malnutrition	1.12 (0.66-1.9)	0.676		
Sarcopenia				
With sarcopenia vs. without sarcopenia	1.88 (0.85-4.18)	0.121		
PNI				
PNI>45 vs. PNI≤45	**0.45 (0.27-0.75)**	**0.002**	**0.24(0.11-0.54)**	**<0.001**
GPS				
GPS=1 or 2 vs. GPS=0	1.18 (0.81-1.73)	0.385		
NLR				
NLR≥2.1 vs. NLR<2.1	1.14 (0.77-1.68)	0.525		
Radiotherapy details				
Radiotherapy technique				
IMRT vs. SBRT	0.61(0.26-1.42)	0.254		
Total Dose				

Table 2 (continued)

	Univariate regression		Multivariate regression	
Variables*	**HR**	***P***	**HR**	***P***
≥median total dose(42.79 Gy) vs. < median total dose	0.74 (0.38-1.43)	0.366		
BED				
≥median BED(56.20 Gy) vs. < median BED	0.68 (0.35-1.33)	0.26		
Single dose of radiotherapy				
≥3 Gy vs. <3 Gy	**1.56 (0.92-2.63)**	**0.098**	1.62(0.80-3.29)	0.183
Irradiated lesions				
Bone vs. Lung	0.83(0.4-1.63)	0.589		
Brain vs. Lung	0.98(0.54-1.79)	0.957		
Others (Liver, renicapsule et al.) vs. Lung	0.48(0.11-2.07)	0.327		

*The latter variable was established as a reference

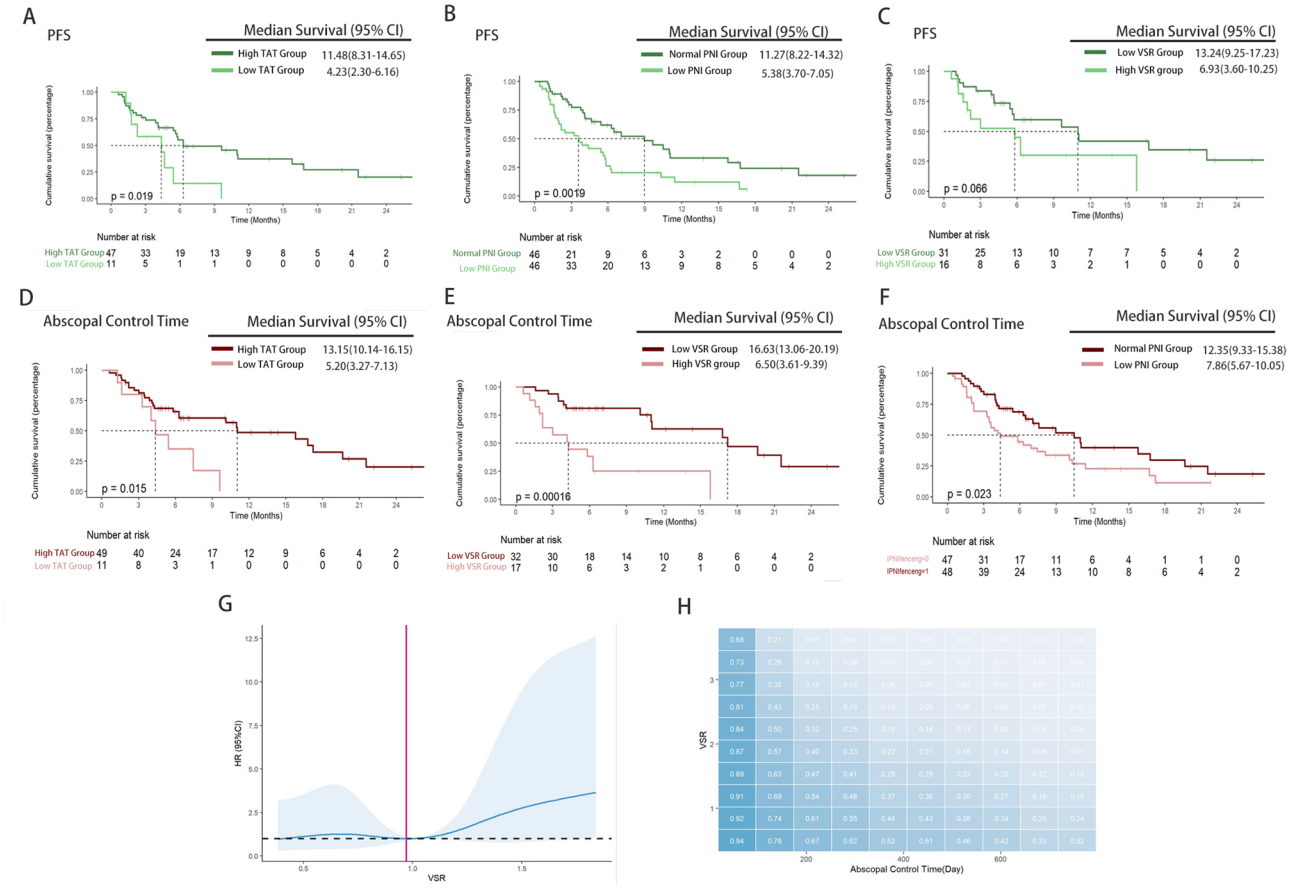

Fig. 3 Body composition and PNI are predictors for PFS and abscopal control survival in patients receiving iRT. Kaplan-Meier curves of TAT(**A**), PNI(**B**), VSR(**C**) for PFS, and TAT(**D**), VSR(**E**), PNI(**F**) for abscopal control survival. Increasing abscopal control risk with increasing VSR by RCS line (**G**) and time-to-event table (**H**)

longer PFS but the difference is not significant (13.24 months vs. 6.93 months, $P = 0.066$) (Fig. 3C). In terms of OS, multivariate Cox regression analysis identified sarcopenia emerged as the only significant factor of worse survival (HR = 4.22, 95% CI = 1.31–13.65, $P = 0.016$) (Table 3).

Given the distinct nature of RT for brain metastases, we conducted a subgroup analysis of these patients (Supplementary Table 2). Multivariate Cox regression identified single-dose radiotherapy (PFS: HR = 0.18, 95% CI = 0.04–0.81, $P = 0.0256$; OS: HR = 0.15, 95% CI = 0.02–0.94, $P = 0.042$) and HDL level (PFS: HR = 2.78, 95% CI = 0.85–9.11, $P = 0.090$; OS: HR = 19.82, 95% CI = 1.97–199.49, $P = 0.011$) as significant factors for both PFS and OS (Supplementary Table 3).

Table 3 Univariate and multivariate COX analysis for OS in patients receiving iRT

	Univariate regression		Multivariate regression	
Variables*	**HR**	***P***	**HR**	***P***
Baseline characteristics				
Line of ICIs				
Second or further Line vs. first Line	**1.85 (1-3.41)**	**0.049**	1.29 (0.44-3.77)	0.637
Histology type				
Adenocarcinoma vs. squamous cell carcinoma	**0.52 (0.28-0.95)**	**0.033**	0.39 (0.13-1.16)	0.092
Sex				
Female vs. male	**0.37 (0.16-0.83)**	**0.016**	0.46(0.11-1.93) 0.0.46 (0.11-1.93)	0.287
Age				
>65 vs. ≤65	1.63(0.9-2.93)	0.104		
Smoking history				
Ever smoker vs. non-smoker	1.41 (0.64-3.13)	0.397		
Combined treatment regimen				
Antiangiogenic + chemotherapy vs. chemotherapy	1.05(0.37-2.98)	0.928		
Antiangiogenic therapy vs. chemotherapy	0.91(0.32-2.58)	0.857		
None vs. chemotherapy	0.68(0.26-1.75)	0.422		
Type of immunotherapy				
PD-L1 vs. PD-1	0.95(0.76-1.17)	0.603		
PS Score				
2-4 vs. 0-1	1.2(0.42-3.4)	0.737		
Factors reflective of metabolic status				
Hypertension				
With vs. without	1.34 (0.74-2.43)	0.342		
Hyperglycemia				
With vs. without	1.06 (0.45-2.52)	0.891		
Statin use				
With vs. without	0.56 (0.22-1.43)	0.227		
HDL				
High baseline HDL vs. normal	1.26 (0.52-3.1)	0.609		
Triglyceride				
High baseline triglyceride vs. normal	1.05 (0.52-2.12)	0.897		
SAT				
80.2≤SAT≤110.9 vs. SAT<80.2	1.16 (0.46-2.96)	0.748		
SAT>110.9	1.14 (0.51-2.56)	0.752		
VSR				
VSR≥1.3 vs. VSR<1.3	0.97 (0.41-2.29)	0.947		
TAT				
TAT<138.7 vs. TAT≥138.7	**2.08 (0.91-4.73)**	**0.082**	0.93 (0.29-2.97)	0.903
Factors reflective of nutritional status				
BMI				
Obese or overweight vs. normal or malnutrition	0.57 (0.25-1.29)	0.176		
Sarcopenia				
With sarcopenia vs. without sarcopenia	**3.14 (1.46-6.75)**	**0.003**	**4.22 (1.31-13.65)**	**0.016**
PNI				
PNI>45 vs. PNI≤45	**0.59 (0.33-1.07)**	**0.084**	0.64 (0.23-1.75)	0.382
GPS				
GPS=1 or 2 vs. GPS=0	**1.46 (0.98-2.16)**	**0.06**	1.1(0.56-2.19)	0.782
NLR				
NLR≥2.1 vs. NLR<2.1	1(0.65-1.53)	0.989		
Radiotherapy details				
Radiotherapy technique				
IMRT vs. SBRT	0.36(0.09-1.51)	0.162		

Table 3 (continued)

	Univariate regression		Multivariate regression	
Variables*	**HR**	***P***	**HR**	***P***
Total Dose				
≥median total dose(42.79 Gy) vs. < median total dose	1.14 (0.69-1.9)	0.604		
BED				
≥median BED(56.20 Gy) vs. < median BED	1.17 (0.71-1.95)	0.536		
Single dose of radiotherapy				
≥3 Gy vs. <3 Gy	1.01 (0.55-1.86)	0.97		
Irradiated lesions				
Bone vs. Lung	1.09(0.53-2.26)	0.816		
Brain vs. Lung	0.95(0.46-1.98)	0.888		
Others (Liver, renicapsule et al.) vs. Lung	0.42(0.05-3.17)	0.398		

*The latter variable was established as a reference

Body composition and PNI are predictors for abscopal control in patients receiving iRT

After univariate cox regression, biomarkers including lines of immunotherapy, single dose of radiotherapy, statin usage, body composition, PNI and NLR were brought into multivariate cox regression (Table 4). Multivariate regression analysis found that later-line of immunotherapy (HR = 3.67, 95% CI: 1.45–9.3, $P = 0.006$), low VSR (HR = 5.53, 95% CI: 1.91-16, $P = 0.002$), high TAT (HR = 5.21, 95% CI: 1.2-22.71, $P = 0.0016$) and high PNI (HR = 0.24, 95% CI: 0.11–0.56, $P = 0.002$) are independent risk factors for abscopal progression. Specifically, patients with high TAT (Figs. 3D and 13.15 months vs. 5.20 months), low VSR (Figs. 3E and 16.63 months vs. 6.30 months), and normal PNI (Figs. 3F and 12.35 months vs. 7.86 months) obtained a significant longer abscopal survival. No significant factors were identified for abscopal control in patients who received RT for brain metastases (Supplementary Table 4).

Furthermore, we studied the change in abscopal lesion progression risk with the increase of VSR. As is displayed in Fig. 3G, lower abscopal progression risk was observed along with increasing VSR using the RCS curve ($P = 0.037$). Time-To-Event table detailed the specific risk data (Fig. 3H). This indicates that subcutaneous and visceral adipose exert distinct effects on abscopal control time, with increased subcutaneous adipose area as a protective factor while increased visceral adipose area as a risk one.

The impact of combining body composition and PNI on tumor control in patients receiving iRT

It appears that biomarkers reflecting body composition (VSR and TAT) along with PNI hold particular predictive value in the abscopal control of iRT. Tumor regression rates for abscopal and local lesions vary in patients with different nutritional status or with different body compositions. As revealed in Table 5, patients with high PNI have significantly better ORR of both abscopal lesions (27.1% vs. 10.6%, $P = 0.04$) and local lesions (37.5% vs. 17.0%, $P = 0.03$), trends towards higher DCR of abscopal and local lesions were observed in patients with high TAT(67.3% vs. 36.4%, $P = 0.06$ for abscopal lesions, 75.5% vs. 45.5%, $P = 0.05$ for local lesions) and low VSR(69.0% vs. 44.4%, $P = 0.07$ for abscopal lesions, 72.2% vs. 47.6%, $P = 0.08$ for local lesions).We established a scoring system consisting of metabolic and nutritional scores to stratify patients into three groups, as detailed in Fig. 4. With respect to metabolic score, thin patients with TAT < 138.7 cm^2 received one point, while obese patients with TAT ≥ 138.7 cm^2 were assigned two points (if VSR ≥ 1.3) or three points (if VSR < 1.3) based on their VSR values. Additionally, patients with a PNI exceeding 45 garnered three points in the nutritional score, while those with a PNI below 45 received a score of zero. The overall score was calculated as the sum of the metabolic and nutritional scores.

Based on the total score, patients were stratified into groups A, B, and C, with total scores ranging between 1 and 2, 3–5, and 6, respectively. Group C means non-visceral obesity patients with good nutrition status. These patients have significantly longer PFS (19.01 months, 95% CI = 14.96-23.06mo) and abscopal control survival of 17.29 months (95% CI = 12.83-21.75mo) compared with other groups. Group A refers to low PNI groups regardless of body composition, and the median PFS (3.81months, 95% CI = 2.40-5.21mo) and abscopal control survival (3.70months, 95% CI = 2.10-5.30mo) is significantly shorter compared with other groups. In summary, the combined assessment of body composition and nutritional index serves as a valuable predictor for abscopal control in patients receiving iRT.

Discussion

In this study, we investigated the prognostic values of nutritional and metabolic factors. While retrospective series have explored the value of body composition, and PNI on the efficacy of ICIs or RT, none have reported the

Table 4 Univariate and multivariate Cox regression for abscopal control in patients receiving iRT

	Univariate regression		Multivariate regression	
Variables*	**HR**	***P***	**HR**	***P***
Baseline characteristics				
Line of ICIs				
Second or further Line vs. first Line	**2.06(1.18-3.59)**	**0.011**	**3.67 (1.45-9.3)**	**0.006**
Histology type				
Adenocarcinoma vs. squamous cell carcinoma	1.28 (0.74-2.21)	0.378		
Sex				
Female vs. male	**0.57 (0.31-1.05)**	**0.07**	0.83 (0.3-2.27)	0.71
Age				
>65 vs. ≤65	0.93(0.46-1.87)	0.832		
Smoking history				
Ever smoker vs. non-smoker	1.36 (0.81-2.28)	0.248		
Combined treatment regimen				
Antiangiogenic + chemotherapy vs. chemotherapy	2.32(0.86-6.24)	0.1		
Antiangiogenic therapy vs. chemotherapy	1.37 (0.46-4.01)	0.571		
None vs. chemotherapy	0.91 (0.31-2.67)	0.865		
Type of immunotherapy				
PD-L1 vs. PD-1	1.08 (0.9-1.29)	0.41		
PS Score				
2-4 vs. 0-1	1.17(0.5-2.72)	0.717		
Factors reflective of metabolic status				
Hypertension				
With vs. without	1.21 (0.72-2.04)	0.474		
Hyperglycemia				
With vs. without	1.45 (0.77-2.73)	0.255		
Statin use				
With vs. without	**0.47 (0.22-0.99)**	**0.048**	1.2 (0.31-4.67)	0.791
HDL				
High baseline HDL vs. normal	1.53 (0.67-3.5)	0.313		
Triglyceride				
High baseline triglyceride vs. normal	1.33 (0.71-2.47)	0.37		
SAT				
80.2≤SAT≤110.9 vs. SAT<80.2	0.7 (0.28-1.76)	0.451		
SAT>110.9	**0.44 (0.19-0.98)**	**0.046**		
VSR				
VSR≥1.3 vs. VSR<1.3	**2.59 (1.25-5.37)**	**0.011**	**5,53(1.91-16)**	**0.002**
TAT				
TAT<138.7 vs. TAT≥138.7	**2.72 (1.18-6.28)**	**0.019**	**5.21(1.2-22.71)**	**0.0016**
Factors reflective of nutritional status				
BMI				
Obese or overweight vs. normal or malnutrition	1.14 (0.66-1.96)	0.635		
Sarcopenia				
With sarcopenia vs. without sarcopenia	**1.97 (0.88-4.43)**	**0.1**	0.73 (0.21-2.55)	0.627
PNI				
PNI>45 vs. PNI≤45	**0.55(0.33-0.93)**	**0.025**	**0.24 (0.11-0.56)**	**<0.001**
GPS				
GPS=1 or 2 vs. GPS=0	1.02 (0.71-1.45)	0.928		
NLR				
NLR≥2.1 vs. NLR<2.1	**1.47 (1-2.16)**	**0.052**	0.68 (0.34-1.38)	0.285
Radiotherapy details				
Radiotherapy technique				
IMRT vs. SBRT	0.69(0.29-1.62)	0.396		
Total Dose				

Table 4 (continued)

	Univariate regression		Multivariate regression	
Variables*	**HR**	***P***	**HR**	***P***
≥median total dose(42.79 Gy) vs. < median total dose	0.74 (0.38-1.43)	0.366		
BED				
≥median BED(56.20 Gy) vs. < median BED	0.68 (0.35-1.33)	0.26		
Single dose of radiotherapy				
≥3 Gy vs. <3 Gy	1.3 (0.77-2.19)	0.323		
Irradiation lesions				
Bone vs. Lung	1.09(0.53-2.26)	0.816		
Brain vs. Lung	0.97 (0.46-2.03)	0.939		
Others (Liver, renicapsule et al.) vs. Lung	0 (0-Inf)	0.997		

*The latter variable was established as a reference

Table 5 Tumor regression of abscopal and local lesions stratified by TAT, VSR and PNI

Variables	Low TAT	High TAT	*P*	Low VSR	High VSR	*P*	Low PNI	High PNI	*P*
N (%)	11(100%)	49(100%)		42(100%)	18(100%)		47(100%)	48(100%)	
Tumor regression of abscopal lesions after 2–3 cycles of ICIs									
CR	0(0%)	3(6.1%)	-	2(4.8%)	1(5.6%)	-	2(4.3%)	3(6.3%)	-
PR	1(9.1%)	8(16.3%)	-	7(16.7%)	2(11.1%)	-	3(6.4%)	10(20.8%)	-
SD	3(27.3%)	22(44.9%)	-	20(47.6%)	5(27.8%)	-	21(44.7%)	19(39.6%)	-
PD	4(36.4%)	7(14.3%)	-	6(14.3%)	5(27.8%)	-	11(23.4%)	7(14.6%)	-
Not assessed	3(27.3%)	9(18.4%)	-	7(16.7%)	5(27.8%)	-	10(21.3%)	9(18.8%)	-
ORR of abscopal lesions	1(9.1%)	11(22.4%)	0.32	9(21.4%)	3(16.7%)	0.67	5(10.6%)	13(27.1%)	**0.04**
DCR of abscopal lesions	4(36.4%)	33(67.3%)	**0.06**	29(69.0%)	8(44.4%)	**0.07**	26(55.3%)	32(66.7%)	0.26
Tumor regression of local lesions after 2–3 cycles of ICIs									
CR	0(0%)	3(6.1%)	-	1(2.4%)	3(16.7%)	-	1(2.3%)	3(6.3%)	-
PR	3(27.3%)	11(22.4%)	-	9(21.4%)	2(11.1%)	-	7(14.9%)	15(31.3%)	-
SD	2(18.2%)	23(46.9%)	-	10(23.8%)	8(44.4%)	-	20(42.6%)	18(37.5%)	-
PD	3(27.35)	4(8.2%)	-	2(4.8%)	0(0%)	-	6(12.8%)	7(14.6%)	-
Not assessed	3(27.3%)	8(16.3%)	-	2(4.8%)	5(27.8%)	-	13(27.7%)	5(10.4%)	-
ORR of local lesions	3(27.3%)	14(28.6%)	0.93	10(23.8%)	5(27.8%)	0.74	8(17.0%)	18(37.5%)	**0.03**
DCR of local lesions	5(45.5%)	37(75.5%)	**0.05**	20(47.6%)	13(72.2%)	**0.08**	28(59.6%)	36(75%)	0.11

combined efficacy with regard to these factors. This study provides several interesting findings. First, RT enhanced the efficacy of ICIs, as patients in the iRT group exhibited significantly longer PFS and OS compared with those receiving ICIs alone. Second, we discovered that low PNI and TAT were independent predictors for PFS and abscopal control survival for mNSCLC patients undergoing iRT. Besides, lower abscopal progression risk was observed along with increasing VSR. Third, we establish a scoring system that integrates body composition and nutritional index to predict the abscopal control in iRT. The benefit of iRT is maximized in non-visceral obesity patients with high PNI, whereas patients with poor nutritional disorders have the worst iRT efficacy.

Usage of BMI to predict immunotherapy efficacy confronted with confusing results. Some reported that overweight or obese patients have better PFS or OS [32–34], while others found no significant association between baseline BMI and clinical outcomes, regardless of PD-L1 tumor expression, in advanced NSCLC patients [35]. Importantly, BMI is a vague measure of obesity and has been criticized for its inability to distinguish between fat and lean body mass. Previous studies have identified body composition as an independent prognostic factor in patients with various solid tumors receiving immunotherapy [16, 23, 36]. In our study, we also identified an association between VSR and abscopal control in iRT. Visceral or central obesity is increasingly recognized as the primary driver of health outcomes associated with high body fat. Studies have explored the relationship between lung cancer outcomes and central obesity using waist circumference, waist-hip ratio, or imaging, and revealed that central obesity patients obtain worse survival outcomes. For example, Barberio's study [37] included 26,607 participants from Alberta's Tomorrow Project cohort and found that central adiposity appears to be a stronger predictor of overall cancer risk than body size. Yu's pooled analysis [38] of 23,732 incident lung cancer cases revealed that waist circumference and waist-hip ratio were associated with increased risk after controlling for BMI. Similarly, the measurement of visceral adipose tissue has also been associated with poor lung

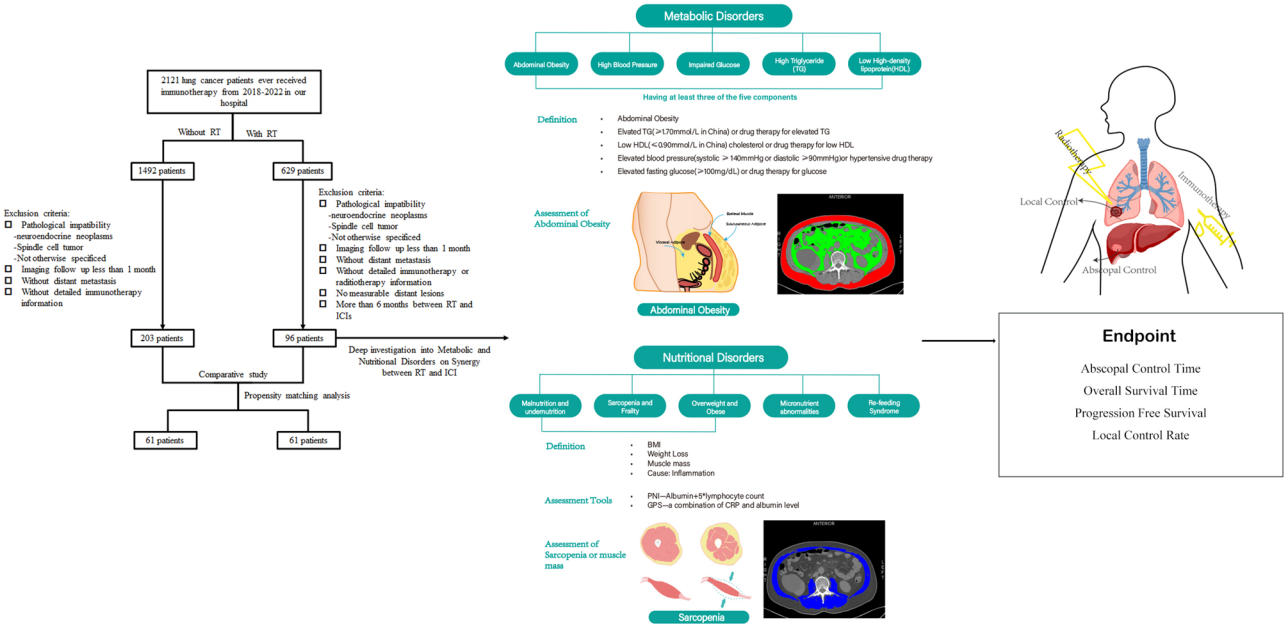

Fig. 4 The combination of body composition and PNI to the synergetic efficacy of RT and ICIs. The sketch map to stratify PNI and body composition (**A**). The detailed score points for PNI and body composition to stratify patients into group A-C (**B**), and K-M estimates of PFS (**C**) and abscopal control time (**D**) stratified by body composition and nutritional scores

cancer prognosis in patients undergoing chemotherapy [39] and immunotherapy [16, 40]. These findings suggest the importance of accurate measures of central obesity in studies of lung cancer.

Why is VSR associated with the efficacy of iRT? Subcutaneous and visceral fat exert distinct effects on the degree of metaflammation and obesity-associated disease. In obese individuals, visceral adipose tissue is linked to the severity of cytokine release syndrome [41]. One side-by-side evaluation [16] of human and murine lung tumors indicated that central obesity in mice reduced transcripts encoding elements of Th1 immunity. Specifically, Th1 chemokines such as CXCL10, CXCL11, and CXCL9, along with Th1 transcription factors STAT1 and Tbx21/Tbet, were underrepresented in samples affected by central obesity. Another study [42] observed significantly higher expression of insulin-like growth factor receptor (IGF-IR) in tumor samples from patients with visceral obesity compared to non-obese patients. Activation of the IGF-IR signaling pathway was implicated in promoting tumor metastasis and proliferation. While subcutaneous adiposity has beneficial effects on metabolic homeostasis and inflammation repression, preclinical experiments [43] have demonstrated that transplantation of subcutaneous adipose tissue into visceral depots can effectively reduce circulating inflammatory cytokine levels and lead to metabolically beneficial outcomes. These findings help explain the observed association between VSR and iRT efficacy.

Besides, we found that PNI was an independent predictor of abscopal control in patients receiving iRT. PNI is an easily obtained inflammation-based prognostic algorithm. A firm relationship between PNI and outcome for immunotherapy was confounded in solid tumors [26, 44, 45]. For NSCLC patients at an advanced stage, a meta-analysis [46] included 1119 stage III-IV NSCLC patients receiving immunotherapy, and found that low PNI was an independent risk factor for worse survival outcomes including both OS (HR = 2.68; $P < 0.0001$) and PFS (HR = 1.84; $P < 0.0001$). A similar positive correlation between PNI and RT efficacy was revealed. A retrospective study [47] enrolled 97 stage I–III NSCLC patients receiving post-operation RT, and found that those with both low pre-RT and low post-RT PNI experienced the worst five-year OS rate of 31.1%. Post-RT PNI was identified as an independent risk factor for mortality (HR 0.92, $P = 0.003$). Another study [48] with 358 Stage IIIB NSCLC patients treated with chemoradiotherapy found that OS ($P < 0.001$), local-progression-free survival ($P < 0.001$) and PFS ($P < 0.001$) were significantly better in high PNI group compared to low PNI group. Our study is the first to demonstrate that the PNI, which is easy to calculate and achievable, holds significant prognostic value for mNSCLC patients undergoing iRT. Furthermore, a randomized controlled clinical trial showed that nutrition therapy can improve OS in a mixed cancer population [49]. This finding suggests that interventions, such as nutritional support aimed at maintaining a normal PNI, could potentially improve survival for these patients.

In addition to the common limitation that our research is a retrospective, single-center study with limited sample size, there are some drawbacks in the study. First, we innovatively use abscopal control time as the progression of abscopal lesions, based on the consideration that the abscopal effect is so rare and difficult to reproduce [50]. Despite the fact that abscopal effect leads to the prevention of cancer recurrence and metastasis [51], no study have verified directly the correlation between complete remission of abscopal lesions with time to progression. Second, subtypes of T cells are reported to be biomarkers with predictive value for iRT efficacy [52]. In our study these biomarkers are not included in because of the retrospective characteristics. Third, the scoring system we developed lacks validation from larger sample sizes and external cohorts.

In conclusion, our study highlights that PNI and body composition assessed through baseline CT are crucial prognostic factors for patients with mNSCLC. Our findings underscore the potential benefits of multimodal clinical management strategies aimed at addressing the loss of subcutaneous adiposity, which could enhance both quality of life and prognosis in advanced NSCLC patients. Further investigation into these strategies is warranted.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14278-7.

Supplementary Material 1: A heat map displaying the correlation between body composition parameters, immuno-nutritional scores, and inflammation indexes(A). Correlation between TAT(B) and VSR(C) with the amount of skeletal muscle measured by SMI

Supplementary Material 2

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Not applicable.

Author contributions
QCW and HJ designed the study. YEY collected patient data, SQZ, JZ, YM, ZFH analyzed and conducted the statistical analysis. HYC and YEY drafted the manuscript, and QCW assisting in the modification. All authors reviewed and approved the final manuscript. YEY and HYC contributed equally to this study.

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Data availability
The raw data supporting the conclusions of this article will be made available by the authors, with undue reservation. HYC or YEY could be contacted to access the data.

Declarations

Ethics approval and consent to participate
The studies were reviewed and approved by Ethics Committee of Second Affiliated Hospital of Zhejiang University School of Medicine in accordance with the Declaration of Helsinki. All patients have signed an informed consent form upon admission, allowing for the collection of medical information in an anonymous and aggregated manner, which may be used for educational and other related activities.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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