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High Level of Irisin as a Marker of Malnutrition in Head and Neck Cancer Patients Subjected to Radiotherapy

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Background: Head and neck cancers (HNC) are the 7th most prevalent neoplasms in the world. In 50% of these patients, body weight loss and malnutrition are observed before the beginning of therapy. It is known that an important role in the pathomechanism of malnutrition and cachexia is played by the development of inflammation, degradation of muscle fibers, and browning of white adipose tissue (WAT). It was demonstrated that even a slight increase in irisin concentration leads to browning of WAT.

Material/Methods: The study group consisted of 50 patients with HNC. The nutritional status of the patients was assessed by the Nutritional Risk Score 2002 (NRS 2002) and Subjective Global Assessment (SGA) scales. Using bioelectrical impedance analysis (BIA), the parameters fat mass (FM) and fat-free mass (FFM) were obtained.

Results: Higher irisin values (1.57 vs 1.18 [ng/ml], *P*=0.0004) were observed in patients with higher nutritional risk (≥3) evaluated according to the NRS scale. In patients assessed as B or C on the SGA scale, higher values of irisin concentration (1.38 vs 1.07 [ng/ml], *P*=0.0139) were noted. It was also observed that the level of irisin before treatment was negatively correlated (rho=-0.30, *p*=0.0350) with FM% and was positively correlated (rho=0.30, *p*=0.0340) with FFM% in BIA measurements performed after the 7th cycle of RTH.

Conclusions: Based on these results, we conclude that patients with malnutrition tend to have higher irisin values compared to normally nourished patients. A high level of irisin may be a useful marker of malnutrition in patients with HNC.

Keywords: Cachexia • FNDC5 Protein, Human • Head and Neck Neoplasms • Malnutrition

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Background

Head and neck cancers (HNC) are the 7th most prevalent neoplasms in the world. Among them, the majority (about 90%) are squamous cell carcinomas (SCCHN). In 50% of these patients, body weight loss and malnutrition occur even before the beginning of therapy. The main methods of SCCHN treatment are surgery, radiotherapy (RTH), chemotherapy (CTH), and combination of these methods. It is estimated that in the course of therapy the proportion of malnourished patients increases to 90%. Nutritional problems in patients with SCCHN are multifactorial. The definition of malnutrition includes progressive loss of muscle and fat tissue. Nutritional problems involve socio-psychological factors, complications of treatment (including dysphagia, xerostomia), or symptoms associated with tumor location. The symptoms associated with tumor location include gastrointestinal obstruction and odynophagia [1,2]. In patients with neoplastic malnutrition or cachexia, various degrees of body weight loss may occur in association with metabolic disturbances, lean body mass loss, and increased lipolysis [2,3]. It should be noted that not all cancer patients, including those with the tumors of the head and neck area (at the same stage of disease, subject to the same treatment method), develop malnutrition or cachexia [3]. Early detection of nutritional disturbances, especially before significant body weight loss, is associated with improved quality of life, longer time to disease progression, and better overall survival (OS) [2,4]. Identification of patients at risk of nutritional disorders may allow for the implementation of appropriate nutritional treatment. Therefore, the search for predictors of malnutrition and/or cachexia seems to be warranted.

Cancer cachexia is not always present in malnourished patients but all cachectic patients experience nutritional disturbances4[5]. Cancer cachexia is a multifactorial syndrome characterized by appetite disorders, body weight loss, metabolic changes, and intensified inflammation [5,6]. Lean and fatty body mass atrophy and skeletal muscle function loss are also observed. These changes lead to steady body weight loss [5]. Knowledge concerning the pathomechanism of malnutrition and cachexia has been expanding in the recent years. However, its complexity still leaves many aspects of these conditions unexplained. It is known that an important role is played by the development of inflammation, degradation of muscle fibers, and browning of white adipose tissue (WAT). One of the most important myokines is irisin, which is a fragment of extracellular domain of FNDC5 protein [5,7]. Irisin is regulated by proliferator-activated receptor-γ coactivator-1α (PGC1α) and the muscles can excrete it into the bloodstream. As a result, irisin can activate adipose tissue thermogenesis and cause browning of WAT [8]. The relationship between irisin and neoplasms is unclear. The level of irisin in patients with different types of cancer may be lower or higher compared to healthy people [9-11]. However, the major aim of research has not been to correlate the level of irisin with the nutritional status of these patients. Perhaps the differences in irisin levels were due to the nutritional status of these patients [11]. Therefore, because irisin is involved in hydrolysis triacylglycerols in WAT and inhibits de novo lipogenesis [12], we hypothesized that irisin may be associated with the development of malnutrition or cachexia in patients with HNC.

The aim of the study was to evaluate the level of serum irisin in HNC patients subjected to RTH and to assess its correlation with the occurrence of malnutrition.

Material and Methods

The study group consisted of 50 patients (88% male and 12% female) diagnosed with HNC who were treated in the Department of Oncology, Medical University in Lublin. All the patients were informed about the aim of the study and agreed to participate in the study. The study design was approved by the Bioethical Committee (KE-0254/104/2014). Demographic and clinical data were collected before RTH treatment start. Depending on the site of cancer development, we divided patients into 2 groups: upper location (tonsil and nasopharynx cancers), middle location (palatal tonsil, tongue and throat cancers) and lower location (larynx and lower throat cancers). The nutritional status of the patients using the Nutritional Risk Score 2002 (NRS 2002) and Subjective Global Assessment (SGA) scales was assessed before RTH treatment start, while BMI and bioelectrical impedance analysis (BIA) measurements were carried out before the first and the 7th RTH course start. The SGA scale is a recognized clinical method for the assessment of a patient`s nutritional status. It includes information from subjective and objective factors of a patient's medical history [4]. Information about changes in weight, dietary intake, gastrointestinal symptoms, functional capacity, loss of fat tissue, muscle wasting, the appearance of edema, and metabolic stress are obtained from patients. According to the SGA scale patients are divided into 3 groups: well-nourished patients (SGA-A), moderate malnutrition (SGA-B), and severe malnutrition (SGA-C). The NRS-2002 scale is an easy to use and validated instrument used for pre-screening of nutritional status. The NRS-2002 questionnaire consists of 4 questions:
1) Is BMI <20.5;
2) Has the patient lost weight within the last 3 months?
3) Has the patient had a reduced dietary intake in the last week?
4) Has the patient been severely ill?
When at least 1 of these 4 questions is responded to affirmatively, a nutrition assessment is performed (static and dynamic parameters, severity of disease). A score rating from 0 to 3 can be assigned for each parameter. A total score ≥3 indicates that the patient has a risk of nutritional disorder or is

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Table 1. Characteristic of the study group.

Factor		Study group (n=50)	
Gender	Male	44	(88%)
	Female	6	(12%)
Age (years)	≥65	21	(42%)
	<65	29	(58%)
Histopathological diagnosis	Carcinoma planoepitheliale	46	(92%)
	Other	4	(8%)
Tumor location	Upper and middle	11	(22%)
	Lower	39	(78%)
	Lower and middle	45	(90%)
	Upper	5	(10%)
T stage	T1-T2	10	(20%)
	T3-T4	40	(80%)
N stage	N0	16	(32%)
	N1-N3	34	(68%)
M stage	Mx	2	(4%)
	M0	47	(94%)
	M1	1	(2%)
Performance status (ECOG)	1	46	(92%)
	2	4	(8%)
Alcohol consumption	Yes	21	(42%)
	No	29	(58%)
Tobacco smoking	Yes	42	(84%)
	No	8	(16%)

ECOG – Eastern Cooperative Oncology Group; M – metastatic spread; N – lymph node involvement; T – tumor site and size; TNM – Tumor, Node, Metastasis staging.

malnourished [13,14]. Bioimpendance (BIA) analysis was conducted using the SFB7 BioImp device (Pinkenba, QLD, Australia). BIA allows for the direct measurement of body electric parameters – impedance (Z), reactance (Xc), and resistance (R) – by monitoring a voltage drop at the applied current. Based on directly measured electric parameters (at 50 kHz), with the use of the appropriate algorithms of the software (ImpediMed SFB7 Multi Frequency Analysis Software, version 5.4.0.3) included in the BIA device, variables such as fat mass (FM), percent of fat mass (FM%), fat-free mass (FFM), and percent of fat-free mass (FFM%) were estimated automatically. All patients were tested while lying supine with legs apart and arms not touching the body. Four standard electrodes attached to the right hand and foot were used. In all patients, measurements were performed in triplicate (then mean values were calculated) in similar conditions (in the morning, on an empty stomach, after 5 minutes lying on the back to equalize a body level of fluids) [15]. In the study group, 42% of participants were >65 years old. Most (92%) had SCCHN, 80% had T3-T4 stage, and 34% had N1-N3 stage. Most patients (92%) had performance status ≥1 on the ECOG scale. All patients were treated using RTH. Detailed demographic and clinical data and information on the applied treatment schemes are included in **Tables 1 and 2**.

Samples from patients were obtained before RTH treatment start. The study material was serum obtained from whole blood. The serum was frozen and stored at -80°C until the time of analysis. The level of irisin was evaluated using an enzyme-linked immunosorbent assay (ELISA) kit (SunRed Biotechnology Company cat. no. 201-12-5328) according to the procedure attached by the manufacturer. The detection range was 0.2-60.0 ng/ml and the sensitivity was 0.157 ng/ml). ELISA flat-bottomed plates were filled with 50 µl ml of standard solutions with 50 µl of streptavidin-HRP or 40 µl serum samples, 10 µl of irisin-antibody with 50 µl of streptavidin-HR,P and incubated at 37°C for 60 min. After washing 5 times, the plate was incubated at 37°C for 10 min with 50 µl of chromogen solution A and 50 µl of chromogen solution B. Finally, the reaction

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Table 2. Influence of demographic and clinical factors on irisin level in HNC patients.

Factor		Irisin level median (95% CI)		p
Gender	Male	1.36	(1.22-1.46)	0.1006
	Female	1.12	(0.74-1.50)	
Age (years)	≥65	1.41	(1.21-1.65)	0.1378
	<65	1.27	(1.10-1.41)	
Histopathological diagnosis	Carcinoma planoepitheliale	1.34	(1.17-1.44)	0.4969
	Other	1.22	(–)	
Tumor location	Upper and middle	1.53	(1.05-1.71)	0.7166
	Lower	1.33	(1.17-1.41)	
	Lower and middle	1.33	(1.17-1.42)	0.4869
	Upper	1.55	(–)	
T stage	T1-T2	1.27	(0.79-1.57)	0.2970
	T3-T4	1.34	(1.18-1.45)	
N stage	N0	1.38	(1.22-1.56)	0.5191
	N1-N3	1.24	(1.14-1.44)	
M stage	M0	1.35	(1.20-1.45)	0.2282
	Mx and M1	1.17	(–)	
Performance status (ECOG)	1	1.33	(1.19-1.43)	0.5198
	2	1.47	(–)	
Alcohol consumption	Yes	1.43	(1.14-1.59)	0.2120
	No	1.23	(1.15-1.39)	
Tobacco smoking	Yes	1.38	(1.17-1.51)	0.3543
	No	1.24	(0.99-1.43)	
Treatment	Surgery+RTH	1.39	(1.19-1.46)	0.5936
	Other	1.23	(1.13-1.55)	
	Surgery+chemoradiation	1.22	(1.07-1.53)	0.5701
	Other	1.37	(1.18-1.49)	
	RTH alone	1.13	(–)	0.1796
	Other	1.34	(1.22-1.45)	
	Induction CTH+RTH	1.55	(–)	0.7906
	Other	1.33	(1.18-1.42)	
	Concurrent chemoradiation	1.53	(–)	0.2933
	Other	1.28	(1.17-1.43)	

CTH – chemotherapy; ECOG – Eastern Cooperative Oncology Group; M – metastatic spread; N – lymph node involvement; RTH – radiotherapy; T – tumor site and size; TNM –Tumor, Node, Metastasis staging.

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Table 3. The relationship between factors reflecting malnutrition status and irisin level in HNC patients.

Factor		Cases (n=50)	Irisin level median (95% CI)	*p*
NRS-2002	<3	34 (68%)	1.18 (1.09-1.35)	0.0004*
	≥3	16 (32%)	1.57 (1.36-2.12)	
SGA	A	8 (16%)	1.07 (0.70-1.29)	0.0139*
	B and C	42 (84%)	1.38 (1.23-1.51)	
SGA	A and B	32 (64%)	1.23 (1.14-1.39)	0.0630
	C	18 (36%)	1.45 (1.20-1.74)	
BMI I (kg/m^2)	<18.5	5 (10%)	2.53 (–)	0.0585
	>18.5	45 (90%)	1.33 (1.16-1.42)	
BMI VII (kg/m^2)	<18.5	12 (24%)	1.31 (1.14-2.40)	0.3880
	>18.5	38 (76%)	1.33 (1.16-1.43)	
Total protein	Normal	45 (90%)	1.33 (1.18-1.45)	0.9099
	Abnormal (lowered)	5 (10%)	1.27 (–)	
Albumin	Normal	12 (24%)	1.28 (0.99-1.66)	0.8380
	Abnormal (lowered)	38 (76%)	1.33 (1.17-1.43)	
Transferrin	Norma	41 (82%)	1.33 (1.20-1.45)	0.5034
	Abnormal (lowered)	9 (18%)	1.19 (0.98-1.56)	
Parenteral nutrition	Yes	8 (16%)	1.56 (1.16-4.22)	0.0416*
	No	42 (84%)	1.27 (1.14-1.40)	
Antibiotic	Yes	14 (28%)	1.31 (1.08-1.69)	0.8628
	No	36 (72%)	1.36 (1.17-1.44)	

* Statistically significant results. BMI – body mass index; NRS-2002 – Nutritional Risk Screening 2002; SGA – Subjective Global Assessment.

was stopped with a stop solution (50 µl). Measurement of the optical density (OD) at 450 nm and calculation of the standard curve linear regression equation and irisin concentration were carried out using a Multiskan FC Multiplate Photometer (Thermo Scientific). A Wellwash Versa (Thermo Scientific) automatic washer was used.

Statistical Analysis

All data were collected in the Excel database and then imported into the MedCalc statistical program (MedCalc Software, Belgium). Since there were no similar studies comparing irisin levels in patients with different nutritional statuses, the sample size was calculated in the acquired data set retrospectively. We decided to use NRS status as a primary outcome. As input data, we used arithmetic means and corresponding standard deviations (SD) of irisin serum concentration. In most medical studies, *P* values below 0.05 are used to reject the null hypothesis, thus a type I error (alpha) of 5% was used. To achieve 80% of statistical power for type II error, we set a cut-off of beta on 0.2. Considering the calculated difference in means, which was equal to 0.89, SD for NRS<3 group equal to 0.30, SD for NRS≥3 equal to 1.21, and the ratio of sample sizes of compared groups equal to 2.125, the minimal sample size of the study group was estimated as 50. Data were expressed as a percentage (for categorized variable), median, and 95% confidence interval (CI) (since continuous variables had not normal distribution). We considered *P* values below 0.05 as statistically significant. Because data were not normally distributed, we used the nonparametric Mann-Whitney U test for comparison of irisin level according to selected categorical variables, as well as Spearman's correlation test for the evaluation of the correlation between irisin and other continuous variables. Odds ratio (with 95% CI) was calculated to evaluate the risk

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Table 4. The correlation between factors reflecting malnutrition status and irisin level in HNC patients.

Factor	Irisin level	
	rho	*p*
Weight (kg) I	-0.1145	p=0.428
Weight (kg) VII	-0.2050	p=0.153
BMI (kg/m^2) I	-0.1193	p=0.409
BMI (kg/m^2) VII	-0.1776	p=0.217
Total Protein (g/dl)	0.1184	p=0.413
Albumin (g/dl)	0.0795	p=0.583
Transferrin (g/l)	-0.0578	p=0.690
Prealbumin (g/dl)	0.2347	p=0.101
Fat mass I	-0.1816	p=0.207
Fat mass % I	-0.1850	p=0.198
Fat mass VII	-0.2412	p=0.092
Fat mass %VII	-0.2990	p=0.035*
Free fat mass I	0.0712	p=0.623
Free fat mass % I	0.2680	p=0.060
Free fat mass VII	-0.0263	p=0.856
Free fat mass % VII	0.2998	p=0.034*

* Statistically significant results. BMI – body mass index.

of abnormal nutrition status (according to SGA scale) or nutritional risk (NRS scale). In addition, we used the analysis of ROC curves (with the area under curve - AUC and its 95% CI) to assess the diagnostic usefulness of irisin in the differential diagnosis of patients with normal and abnormal nutritional status (SGA) and with low and high nutritional risk (NRS).

Results

No statistically significant differences in the level of irisin were observed in relation to the presence of the analysed demographic and clinical factors (**Table 2**). However, higher irisin values (1.57 vs 1.18 [ng/ml], *P*=0.0004) were observed in patients with higher nutritional risk (≥3) evaluated according to NRS scale. Similarly, in patients assessed as B or C on the SGA scale, higher values of irisin concentration (1.38 vs 1.07 [ng/ml], *P*=0.0139) were noted. Moreover, higher level of irisin (1.56 vs 1.27 [ng/ml], *P*=0.0416) was observed in patients in whom parenteral nutrition was implemented. A trend was noticed toward significantly higher concentrations of irisin in underweight patients (BMI<18.5 vs >18.5: 2.53 vs 1.33, *P*=0.0585). In the remaining studied factors, no statistically significant differences were observed. The influence of selected factors associated with the evaluation of the nutritional status on the level of irisin is presented in **Table 3**. It was also observed that the level of irisin before treatment was correlated negatively (rho=-0.30, *p*=0.0350) with FM% and positively (rho=0.30, *p*=0.0340) with FFM% in the case of BIA measurements performed after the 7th cycle of RTH. A similar correlation was not found in with absolute values of these parameters or with the remaining studied variables (**Table 4**). Among the studied variables, only the performance status (PS) and the level of irisin significantly influenced the risk of occurrence of malnutrition assessed according to the SGA scale. A 20-fold lower risk of occurrence of severe malnutrition (SGA C) was noticed in patients with better performance status (PS<2; OR=0.05, 95% CI: 0.01-0.98, *P*=0.0487), whereas low level of irisin was associated with a 10-fold lower risk of moderate or severe malnutrition (SGA B or C; OR=0.11, 95% CI: 0.01-0.95, *P*=0.0449). Similarly, in the case of nutritional risk assessed using NRS scale, the only factor that affected it was the level of irisin. In patients with low level of irisin, a 5-flod lower nutritional risk was observed (NRS≥3; OR=0.21, 95% CI: 0.05-0.78, *P*=0.0197). The data on the influence of a series of variables on the risk of malnutrition assessed according to SGA or NRS scale are presented in **Tables 5 and 6**. On the basis of analysis of ROCs, it was observed that the level of irisin (with the cut-off point >1.24) significantly differentiated patients with normal nutritional status assessed according to SGA scale (A) from the ones with moderate or severe risk of malnutrition (B or C) (sensitivity: 64.3%, specificity: 87.5%; AUC=0.777 [0.637-0.882]; *P*=0.0029; **Figure 1**). This marker was similarly useful (with the cut-off point >1.43) in the differentiation of patients assessed using SGA scale as normally

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Table 5. Influence of demographic and clinical factors on nutritional status assessed by SGA scale in HNC patients.

Factor		SGA					
		A	B and C	*p* OR (95% CI)	A and B	C	*p* OR (95% CI)
Gender	Male	6 (13.6%)	38 (86.4%)	0.2352; 3.17 (0.47-21.24)	28 (63.6%)	16 (36.4%)	0.8847; 1.14 (0.19-6.95)
	Female	2 (33.3%)	4 (66.7%)		4 (66.7%)	2 (33.3)	
Age (years)	≥65	5 (23.8%)	16 (76.2%)	0.2109; 0.37 (0.08-1.76)	12 (57.1%)	9 (42.8%)	0.3916; 1.67 (0.52-5.36)
	<65	3 (10.3%)	26 (89.7%)		20 (68.9%)	9 (31.1%)	
Histopathological diagnosis	Carcinoma planoepitheliale	6 (13.0%)	40 (86.9%)	0.0822; 6.67 (0.78-56.64)	28 (60.9%)	18 (39.1%)	0.2456; 5.84 (0.30-115.00)
	Other	2 (50%)	2 (50%)		4 (100%)	–	
Tumor location	Upper and middle	2 (18.2%)	9 (81.8%)	0.8234; 0.82 (0.15-4.77)	9 (81.8%)	2 (18.2%)	0.1778; 0.32 (0.06-1.68)
	Lower	6 (15.4%)	33 (84.6%)		23 (59%)	16 (41%)	
	Lower and middle	1 (20%)	4 (80%)	0.7977; 0.74 (0.07-7.61)	5 (100%)	0	0.1843; 0.14 (0.007-2.59)
	Upper	7 (15.6%)	38 (84.4%		27 (60%)	18 (40%)	
T stage	T1-T2	2 (20%)	8 (80%)	0.7007; 0.71 (0.12-4.17)	7 (70%)	3 30%)	0.6594; 0.71 (0.16-3.19)
	T3-T4	6 (15%)	34 (85%)		25 (62.5%)	15 (37.5%)	
N stage	N0	4 (25%)	12 (75%)	0.2433; 0.40 (0.09-1.86)	13 (81.3%)	3 (18.7%)	0.0063; 0.29 (0.07-1.22)
	N1-N3	4 (11.8%)	30 (88.2%)		19 (55.9%)	15 (44.11%)	
M stage	M0	7 (14.9%)	40 (8.5%)	0.4163; 2.85 (0.22-35.91)	30 (63.8%)	17 (36.2%)	0.9210; 1.13 (0.09-13.44)
	Mx and M1	1 (33.3%)	2 (66.7%)		2 (66.7%)	1 (33.3%)	
Performance status (ECOG)	1	8 (17.4%)	38 (82.6%)	0.6553; 0.50 (0.02-10.26)	32 (69.6%)	14 (30.4%)	0.0487*; 0.05 (0.002-0.98)
	2	–	4 (100%)		–	4 (100%)	
Irisin (ng/ml)	Low (<Me)	7 (28%)	18 (72%)	0.0449*; 0.11 (0.01-0.95	18 (72%)	7 (28%)	0.2416; 0.49 (0.15-1.61)
	High (>Me)	1 (4%)	24 (96%)		14 (56%)	11 (44%)	

* Statistically significant results. ECOG – Eastern Cooperative Oncology Group; M – metastatic spread; N – lymph node involvement; T – tumor site and size.

nourished or moderately undernourished (A or B) from these with severe malnutrition (C) (sensitivity: 55.6%, specificity: 75%; AUC=0.660 [0.512-0.788]; *P*=0.0487; **Figure 2**). The NRS scale also significantly differentiated the level of irisin (with the cut-off point >1.23) between patients with high and low nutritional risk (NRS>3 vs <3) (sensitivity: 93.7%, specificity: 58.8%; AUC=0.811 [0.675-0.908]; *P*<0.0001; **Figure 3**).

Discussion

Many factors influence the development of malnutrition and cachexia. The initial mechanism leading to hypercatabolism is a systemic inflammation characterized by, among other features, increased secretion of pro-inflammatory cytokines (interferon-γ, TNF-α, NFκβ, IL), catabolic mediators and reactive forms of oxygen, both by the cells of the host and cancer cells [16,17]. Chronic inflammation can cause changes in the metabolism of carbohydrates, fats, and proteins. The main changes in the metabolism of carbohydrates result from the lack of tolerance to glucose, resistance to insulin, and increase of gluconeogenesis. In patients, we can observe an increase of factors, which directly cause lipolysis (including the lipid-mobilizing factor (LMF) and zinc-alpha-2glycoprotein) and raise sensitivity to lipolytic factors, thus contributing to the loss of fat tissue [7,16]. However, one of the main reasons for the decrease

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Table 6. Influence of demographic and clinical factors on nutritional risk assessed by NRS scale in HNC patients.

Factor		NRS		
		<3	≥3	*p* OR (95% CI)
Gender	Male	30 (69.7%)	13 (30.3%)	0.5101 0.58 (0.11-2.96)
	Female	4 (57.1%)	3 (42.8%)	
Age (years)	≥65	13 (61.9%)	8 (38.1%)	0.4333 1.62 (0.49-5.36)
	<65	21 (72.4%)	8 (27.6%)	
Histopathological diagnosis	Carcinama planoepitheliale	32 (69.6%)	14 (30.4%)	0.4311 0.44 (0.06-3.43)
	Other	2 (50%)	2 (50%)	
Tumor location	Upper and middle	6 (54.5%)	5 (45.5%)	0.2843 2.12 (0.54-8.40)
	Lower	28 (71.8%)	11 (28.2%)	
	Lower and middle	2 (40%)	3 (60%)	0.1782 3.69 (0.55-24.73)
	Upper	32 (71.1%)	13 (28.9%)	
T stage	T1-T2	7 (70%)	3 (30%)	0.8796 0.89 (0.20-4.01
	T3-T4	27 (67.5%)	13 (32.5%)	
N stage	N0	8 (50%)	8 (50%)	0.0668 3.25 (0.92-1.46)
	N1-N3	26 (76.5%)	8 (23.5%)	
M stage	M0	32 (68.1%)	15 (31.9%)	0,9593 0,94 (0.07-11.16)
	Mx and M1	2 (66.7%)	1 (33.3%)	
Performance status (ECOG)	1 (n=29)	31 (67.4%)	15 (32.6%)	0.7555 1.45 (0.14-15.16)
	2 (n=1)	3 (75%)	1 (25%)	
Irisin	Low (<Me)	21 (84%)	4 (16%)	0.0197* 0.21 (0.05-0.78)
	High (>Me)	13 (52%)	12 (48%)	

* Statistically significant results. ECOG – Eastern Cooperative Oncology Group; M – metastatic spread; N – lymph node involvement; T – tumor site and size.

of FFM (mainly muscular) is the decreased synthesis of new proteins with simultaneous increase of degradation of the existing ones [7,16]. The observed decrease of body weight in malnourished and cachectic patients is mainly associated with lipolysis (mostly WAT) in response to negative energetic balance and anorexia related to the development of cancer [18]. The influence of lipolysis on the development of cancer cachexia was demonstrated in a study in which the inhibition of lipid mobilization improved the patients' condition [19]. Lipolysis of WAT causes loss of adipose tissue and contributes to decreased mass of skeletal muscles. In turn, WAT browning increases the expression of uncoupling protein 1 (UCP1), which leads to increased energy expenditure. Likewise, the activated BAT increases the expression of UCP1 and also increases energy expenditure. Both these processes cause negative energy balance, which contributes to the development and progression of malnutrition and cancer cachexia [19]. PGC1α Participates in many pathways regulating metabolic transformations and energy expenditure. PGC1α stimulates the expression of *FNDC5* and synthesis of transmembrane protein FNDC5, whose sequence contains hydrophobic transmembrane domain, signal peptide, carboxy-terminal domain located in the cytoplasm, and fibronectin III domain. Irisin is released after proteolytic cleavage and glycosylation of FNDC5 and, probably, there is also dimerization of FNDC5 before irisin release. In humans, FNDC5 expression is observed in skeletal muscles and muscular organs (including heart and tongue) and in adipose tissue [20], and is released into the blood, milk, urine follicular fluid, and saliva [21]. However, it is estimated that FNDC5 expression is 100-200 timeshigher in muscular tissue than in adipose tissue, which may suggest that skeletal muscles are the main source of irisin, and low expression of FNDC5 is observed

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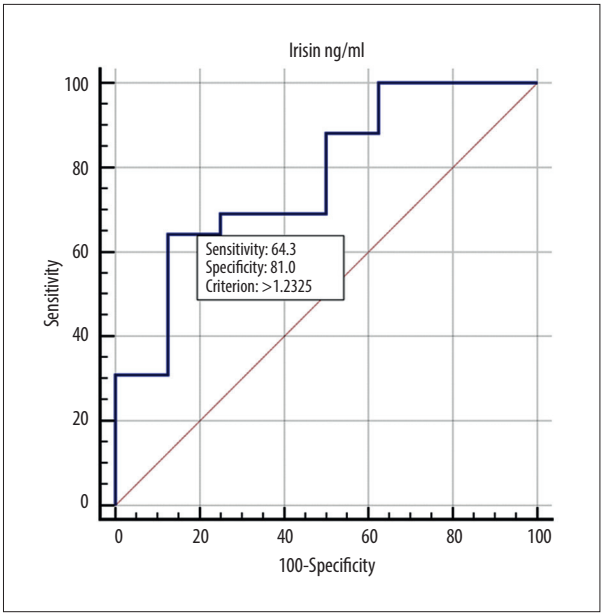

Figure 1. ROC curve showing the diagnostic usefulness of irisin in detecting malnutrition (B or C according to the SGA scale).

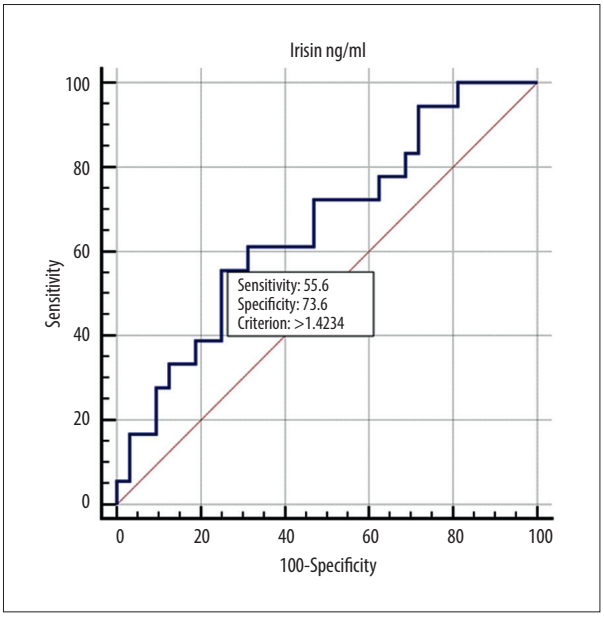

Figure 2. ROC curve showing the diagnostic usefulness of irisin in detecting severe malnutrition (C according to the SGA scale).

in the liver and pancreas, among other organs. Irisin, which is secreted from a skeletal muscle, stimulates the expression of UCP1 in adipocytes leading to WAT browning by means of the extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase p38 (MAPK) [20]. Studies were also performed to establish a correlation between irisin, cachexia, and cancer in mouse models with experimentally triggered

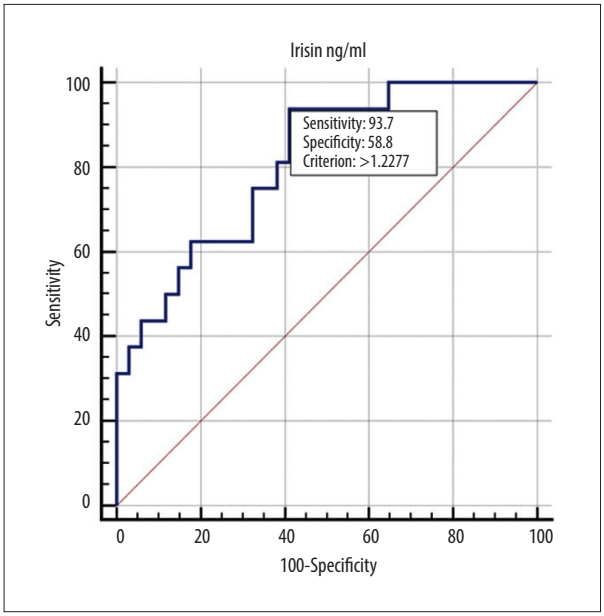

Figure 3. ROC curve showing the diagnostic usefulness of irisin in detecting nutritional risk (according to the NRS scale).

stomach cancer. They demonstrated a correlation between the development of cancer and the increase of FNDC5 expression in subcutaneous adipose tissue, while it was not observed in cancer tissue and skeletal muscles. Significantly higher FNDC5 expression and, in consequence, higher concentration of irisin in BAT was observed in pre-cancer and cancer groups compared to controls. During these studies it was also noticed that the concentration of circulating irisin in the cancer group subjects was higher than in the control group [22]. Studies conducted by Petruzzelli et al, who concentrated of the influence of WAT browning on the development of cancer cachexia, demonstrated that this process leads to increased demand for energy expenditure and lipid mobilization, which leads to progression of cancer cachexia. On the basis of studies in rats, it was noticed that the main factors leading to progression of cachexia are Il-6 and UPC1. Data from the performed studies showed that Il-6 induced WAT browning, which leads to increased UPC1 expression and activation of the process of thermogenesis [12]. Irisin and myostatin are recognized markers of muscle strength/mass described in healthy people or in older people [23]. However, its role in neoplastic diseases has also been recently investigated [9-11]. Panagiotou et al showed a higher level of irisin in both patients with benign breast diseases and malignant tumor of the breast compared to controls [10]. However, Provatopoulou et al found a lower concentration of irisin in patients with breast cancer compared to healthy volunteers (2.47 vs 3.24 μg/ml; $P<0.001$) [9]. Shahidi et al tested irisin levels in gastric cancer patients and healthy controls, finding significantly higher irisin levels in the gastric cancer group compared to healthy controls (0.41 vs 0.35

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ng/ml; *P*=0.032) [11]. Altay et al found higher levels of irisin in renal cancer patients compared to healthy controls (208 vs 110 pg/ml, respectively; *P*=0.0001) [24].

The development of malnutrition and cachexia is associated with the decrease of fat-free and fat body mass as well as a change from WAT to BAT. An active inflammatory process, which is strongly induced at the time of cachexia progression, contributes to the degradation of muscle fibers [24]. The studies that have been conducted so far prove that irisin has a strong impact on the transformation of WAT into BAT. The present study has some limitations. To assess the nutritional status, we used methods such as the NRS and SGA scales, the results of laboratory tests, and BIA to assess body composition. We did not use any subjective anthropometric methods to evaluate muscle mass. We did not evaluate white and brown fat tissue in the patients. We used BIA method to evaluate the fat mass, percent of fat mass, fat-free mass, and percent of fat-free mass.

Conclusions

Patients with cachexia tend to have higher irisin values compared to normally nourished patients. Low level of irisin is associated with low risk of malnutrition in patients with HNC subjected to RTH. High level of irisin may be a useful marker of malnutrition in patients with HNC subjected to RTH.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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