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Prognostic importance of metabolic tumor parameters on initial FDG-PET/CT in patients with isolated infradiaphragmatic Hodgkin's lymphoma

Prognostički značaj metaboličkih tumorskih parametara na inicijalnom FDG-PET/CT kod bolesnika sa izolovanim infradijafragmalnim Hočkinovim limfomom

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Abstract

Background/Aim. Isolated infradiaphragmatic lymph node involvement is not common and makes up 5–13% of stage I-II Hodgkin's lymphoma. Important subjects about prognostic factors and optimal treatment of isolated infradiaphragmatic Hodgkin's lymphoma (II HL) have not been clearly defined. We aimed to evaluate the prognostic value of metabolic tumor indices on initial 18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) through quantitative PET/CT parameters together with the classical predefined risk factors for patients with II HL. **Methods**. This retrospective cohort study conducted between 2004 and 2015 included 21 patients for whom FDG-PET/CT were requested for primary staging. Quantitative PET/CT parameters (maximum standardized uptake value – SUV max) average standardized uptake value – SUV mean, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were used to estimate disease-free survival and overall survival. **Results**. Univariate Cox regression analysis was performed for all potential risk factors impacting metastasis/recurrence of the disease. Factors which had values of $p < 0.2$ after univariate analysis (sex, age, stage, bulky disease, SUV max, SUV mean, MTV, TLG) were processed with the multivariate model. Sex, TLG and bulky disease were found to be statistically significant risk factors for prognosis of outcome in patients with IIHL after multivariate analysis. **Conclusion**. The existence of bulky disease at the diagnosis and high TLG values on primary staging by FDG-PET/CT are potential risk factors for both disease-free survival and overall survival in Hodgkin's lymphoma with isolated infradiaphragmatic lymph node involvement.

Keywords:
hodgkin disease; lymph nodes; diaphragm; positron-emission tomography; fluordeoxyglucose f18; tomography, x-ray computed; prognosis.

Apstrakt

Uvod/Cilj. Prisustvo izolovanih infradijafragmalnih limfnih čvorova kod Hočkinovog limfoma (HL) nije često i javlja se kod 5–15% svih HL I-II stadijuma. Važni podaci o prognostičkim faktorima i optimalnom lečenju izolovanog infradijafragmalnog HL (IIHL) nisu jasno definisani. Cilj ovog ispitivanja bila je procena prognostičke vrednosti pokazatelja metabolizma tumora na inicijalnom pregledu pomoću 18-fluorodeoksiglukoza-pozitron emisione tomografije /kompjuterizovane tomografije (FDG-PET/CT) preko kvanititativnih PET/CT parametara zajedno sa klasičnim predefinisanim faktorima rizika za bolesnike sa II HL. **Metode**. U ovu retrospektivnu kohortnu studiju, sprovedenu između 2004. i 2015. godine, bio je uključen 21 bolesnik, kod kojih je za određenjivanje primarnog stadijuma bolesti primenjena FDG-PET/CT. Kvantitativni PET/CT parametri [vrednost maksimalnog standardizovanog preuzimanja (*maximum standardized uptake value* – SUVmax), prosečna vrednost standardizovanog preuzimanja (*mean standardized uptake value* – SUVmean), metabolički volumen tumora (metabolic tumor valume – MTV), ukupna glikoliza u lezijama (*total lesion glycolysis* – TLG)] korišćeni su za procenu preživljavanja bez prisustva bolesti (*disease-free survival* – DFS) i sveukupnog preživljavanja (*overall survival* – OS). **Rezultati**. Izvršena je univarijantna Cox-ova regresiona analiza svih potencijalnih faktora rizika koji imaju uticaj na metastaze/recidiv bolesti. Faktori koji su imali vrednost $p < 0,2$ posle izvršene univari-

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jante analize (pol, dob, stadijum bolesti, raširena bolest (*bulky disease*), SUVmax, SUVmean, MTV, TLG), potom su obrađeni u multivarijantnom regresionom modelu. Posle multivarijantne regresione analize pol, TLG i raširena bolest prepoznati su kao statistički značajni faktori rizika za prognozu bolesti kod bolesnika sa IIHL. **Zaključak**. Prisustvo raširene bolesti u momentu postavljanja dijagnoze i visoka vrednost TLG kod određivanja primarnog stadijuma bolesti pomoću FDG-PET/CT su potencijalni faktori rizika i za DFS i OS kod bolesnika sa IIHL.

Ključne reči:
hodžkinova bolest; limfne žlezde; dijafragma; tomografija, positron-emisiona; fluorodeoksiglukoza f18; tomografija, komjuterizovana, rendgenska; prognoza.

Introduction

Hodgkin's lymphoma (HL) comprises roundly 15% of all lymphoma patients and has two main classifications: classic (90–95%) and nodular lymphocyte-predominant Hodgkin's disease (5–10%). Classic HL has 4 subtypes: nodular sclerosing 65–80%), mixed cellular (15-30%), lymphocyte-rich and lymphocyte-depleted Hodgkin's disease [1, 2]. Isolated lymph node (LN) involvement below the diaphragm is a rare form of HL and called infradiaphragmatic Hodgkin lymphoma.

HL with isolated infradiaphragmatic lymph node involvement (IDHL) is not common and makes up 5-13% (usually less than 10% in series) of all stage I-II HL [3–5]. Approximately 90% of patients have painless, mostly inguinal lymphadenopathy (LAP). Fever, night sweats and weight loss (B symptoms) are present in 25–40% of the cases. The diagnosis is established by biopsy of inguinal lymph nodes in a great majority of the cases by the presence of Reed-Sternberg cells which are only specific for HL pathology.

Computed tomography (CT), 18-fluorodeoxyglucose positron emission tomography (FDG-PET) and 18-fluorodeoxy glucose positron emission tomography/computed tomography (FDG-PET/CT) are used to stage HL [6, 7]. FDG-PET/CT is a superior imaging technique with proved utility especially in the oncologic field and widely used in lymphoma patients. FDG is avidly taken up by Reed-Sternberg cells, inflammatory tissue and cells surrounding them. FDG-PET is able to show functional alterations that precede the anatomical changes. Integration of CT to FDG-PET combines anatomical detail with functional information and yields excellent morphological and functional information increasing accuracy and detection capability. All these advantages of FDG-PET/CT potentially make it a superior imaging modality for primary staging, evaluation of treatment response and restaging in IDHL just like in other types of HL and many of non-Hodgkin's lymphomas. Standard therapy regimen for HL is combined modality treatment (CMT) which includes chemotherapy (CT) + irradiation of the involved fields (RT).

Although important subjects about prognostic factors and optimal treatment of isolated infradiaphragmatic HL have not been clearly determined, it is know that IDHL is characterized by higher male/female ratio, older patients' age at diagnosis and higher prevalence of lymphocyte-predominant histologic subtype in relation to supradiaphragmatic HL [8–13]. Whether pure infradiaphragmatic localization has a worse prognosis than stage I/II supradiaphragmatic disease has still remained controversial [9, 14–17]. Most studies pertaining to IDHL contain limited numbers of patients with different treatment approaches and varying outcomes roughly along a mean of 20-year follow-up [18, 19].

We aimed to evaluate the prognostic value of metabolic tumor indices on initial FDG-PET/CT over quantitative PET/CT parameters together with the classical predefined risk factors for patients with IDHL.

Methods

There were 184 patients with HL for whom FDG-PET were performed. From them our retrospective study included 21 patients with IDHL at stage I,II disease for whom FDG-PET/CT was requested for primary staging in the Nuclear Medicine Department between 2004 and 2015. These patients were treated and followed-up at the Medical Oncology Department of our hospital. Ann-Arbor staging system and definitions were used in this study. Information and data were obtained from clinic follow-up files, radiation therapy records, physician records of other departments at our hospital or personal contact with the patients *via* telephone. The majority of the patients referred with palpable inguinal masses and complaints of fever, night sweats, weight loss, itching in some cases. The diagnosis was established by biopsy from these inguinal masses (lymph nodes or conglomerated lymph nodes) or with excisional biopsy by diagnostic laparoscopy from intraabdominal lymph nodes in a few cases. Clinical staging was performed by physical examination, chest X-ray, thoracic and abdominal CT, FDG-PET (between 2004 and 2010) and FDG-PET/CT from June 2010. When the detected lesions were confined below the diaphragm and no supradiaphragmatic pathologic finding was observed neither on diagnostic images nor with physical examination, these cases were accepted as IDHL. Bulky disease was defined as single lymph node or conglomerated nodal mass of size > 5 cm in axial slice [9]. Patients were treated with adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) protocol and irradiation of involved field 30 Gray (Gy). Patients who didn't complete the whole scheduled treatment owing to comorbidities or toxicity and had inadequate follow-up were excluded from the study.

FDG-PET/CT imaging protocol

Patients fasted for 6 hours and their blood glucose level had to be under 150 mg/dL before the injection of an activity of 370-555 MBq of 18F-FDG according to patient's weight. Image acquisitions were performed 1 hour later with an integrated PET/CT scanner (Discovery 690-GE Healthcare). Unenhanced low dose CT and PET emission data were acquired from mid-thigh to the vertex of the skull in the su-

pine position with the arms raised overhead. CT data were obtained by automated dose modulation of 120 kVp (maximal 100 mA), collimation of 64×0.625 mm, the measured field of view (FOV) of 50 cm, noise index of 20% and reconstructed to images of 0.625 mm transverse pixel size and 3.75 mm slice thickness. PET data was acquired in 3D mode with a scan duration of 2 min *per* bed position and an axial FOV of 153 mm. The emission data was corrected in a standardized way (random, scatter and attenuation) and iteratively reconstructed (matrix size 256 × 256, Fourier rebinning, VUE Point FX [3D] with 3 iterations, 18 subsets).

Visual and quantitative interpretation

Quantitative PET/CT parameters used in the study were maximum standardized uptake value (SUV max), average standardized uptake value (SUV mean), metabolic tumor volume (MTV) and total lesion glycolysis (TLG). They were calculated according to a standard protocol on a dedicated workstation (Volumetrix for PET-CT and AW volume share 4.5, GE Healthcare, Waukesha, WI, USA). SUV max and SUV mean corrected for body weight were computed by standard methods from the activity at the most intense voxel in three-dimensional tumor region from the transaxial whole body images on attenuation-corrected PET/CT images. MTV (cm3) was measured with semiautomatic PET analysis software using an automatic isocontour threshold method based on a theory of being greater than 42% of the SUV max value within the tumor. TLG values were calculated by multiplying MTV and SUV means.

We retrospectively examined demography, clinic, histology, clinical stage, response to treatment and outcome of the patients. Overall survival (OS) was defined as the time from diagnosis to death of any cause including ones other than the disease itself or last follow-up. Disease-free survival (DFS) was defined as the time from diagnosis to detection of relapse or last follow-up. PET/CT of response to treatment was requested later to detect the relapses. This study was approved by our institutional review Board Committee.

Statistical analysis

The whole data were analyzed using the Statistical Package for the Social Science V.21.0 (IBM Inc.) software. Number, percentage, mean, median, standard deviation (SD), minimum (min) and maximum (max) values were used for the description of the continuous data analysis. Univariate and multivariate Cox regression models were performed to determine related factors with disease free survival time. The variables having a value of $p < 0.20$ were included in multivariate analysis. Backward LR elimination method was used to refine regression model. Receiver operating characteristic (ROC) curve was drawn to evaluate the diagnostic value of TLG. TLG was dichotomized by splitting two groups according to ROC curve. Kaplan-Meier method with log-rank test was used to compare disease free survival times of TLG groups.

Results

A total of 21 patients were enrolled in this study. Mean age of the patients at diagnosis was 33 ± 15 years (6–64). Twenty four percent of the patients were female (n = 5), and 76% (n = 16) male (male/female ratio: 3.2). There were 13/21 (62%) of the patients with nodular sclerosing, 3/21 (14%) with mixed cellular, 1/21 (5%) with lymphocyte-rich, 2/21 (9.5%) with lymphocyte-depleted and 2/21 (9.5%) with nodular lymphocyte-predominant Hodgkin's disease. In relation to the disease stage 14% (3/21) of the patients were at stage IA, 5% (1/21) at stage IB, 38% (8/21) at stage IIA, 43% (9/21) at stage IIB; 47.5% (n = 10) of the cases had B symptoms and 33.3% (n = 7) bulky disease. SUV max was 11.74 ± 5.53 (4–21.3), SUV mean 7.27 ± 2.66 (3.5–12.1), MTV 33.56 ± 17.65 cm^3 (9.8–62.3), and mean TLG was 278.4 ± 214.1 (37.2–754, median = 214.5). The diagnosis was established from the inguinal lymph nodes in 17/21 (81%), and intraabdominal lymph nodes in 4/21 (19%) of the cases. Mean follow-up time was 73.7 ± 37.3 (15–133) months. Three (14%) patients died, 15 (71.5%) developed recurrence and/or metastasis during the follow-up (Figure 1). Patient characteristics and demography, clinicopathologic features and follow-up data were detailed in Table 1.

The involved LN groups in the subdiaphragmatic region according to the order of frequency were inguinal, external iliac, internal iliac, paraaortic, common iliac, aortocaval, femoral, obdurate, paracaval, liver hilus, precaval, paravertebral, sacral, juxtaintestinal, interaortocaval and paraaortocaval lymph nodes. One patient died of cardiac event owing to obesity and diabetes mellitus. The other two patients died of the disease itself (widespread metastasis) and its complications. Most patients 14/15 (93%), with the recurrent/metastatic disease were at stage II; 2/15 (13%) of them had splenic involvement, and 3/15 (20%) had supradiaphragmatic (cervical, axillary, supraclavicular, mediastinal) LN involvement. Overall survival at 5 years was 100%, 90.5% at 10 years (Figure 2). DFS at 5 years was 28.5%. Secondary malignancies were detected in 3 cases (colon adenocarcinoma, squamous cell carcinoma of the left lung, follicular thyroid cancer).

Univariate cox regression was performed for all potential risk factors impacting metastasis/recurrence. Factors which had values of $p < 0.2$ after univariate analysis (sex, age, stage, bulky disease, SUV max, SUV mean, MTV, TLG), were processed with the multivariate model. Sex, TLG and bulky disease were found statistically significant after multivariate analysis. Female sex increases recurrence rate 5.8 times in relation to male sex. Recurrence rate increases 16.6 times in bulky disease. One unit increment of TLG amplifies recurrence in 0.6%. The results of univariate and multivariate Cox regression analyses were shown in Tables 2 and 3, respectively. ROC curve was drawn to evaluate the diagnostic value of TLG (Figure 3). Sensitivity and specificity were calculated 100% and 83.3%, respectively when the cut-off value of TLG was taken as 100. TLG was dichotomized by splitting two groups according to ROC curve. Kaplan-Meier method with log-rank test was used to compare disease free survival times of TLG groups. Kaplan-Meier curve was drawn for TLG with a value of 100 (Figure 4).

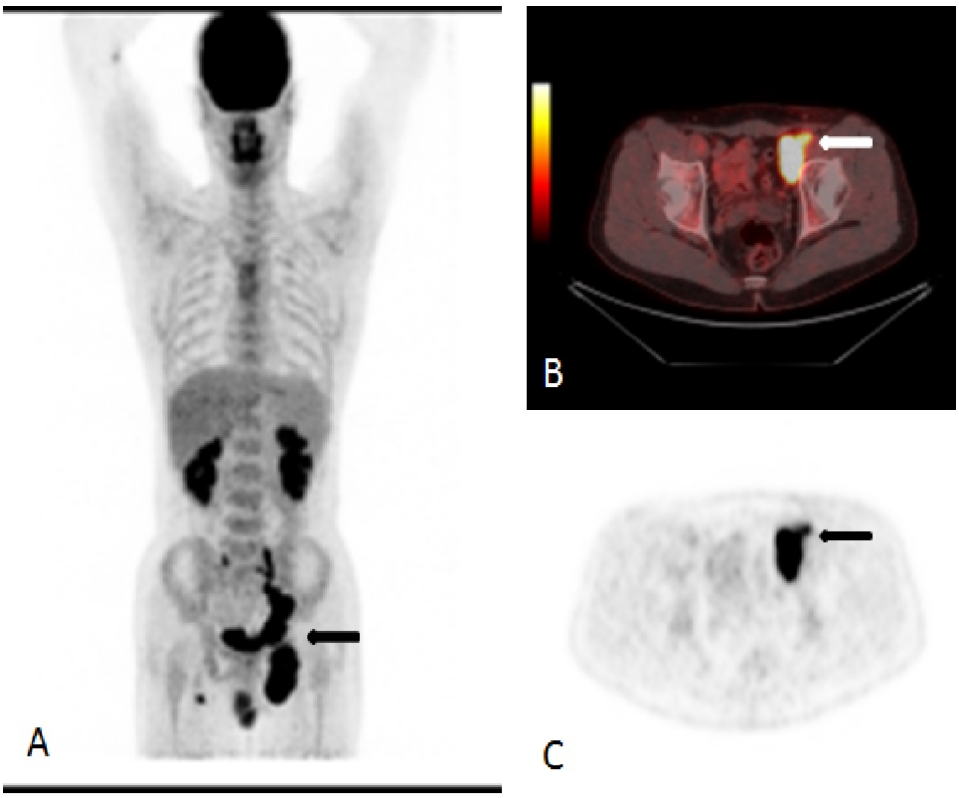

Fig. 1 – A) Maximum intensity projection (MIP); B) 18-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) fusion; C) transaxial slice of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) images of a 25-year old male patient with nodular sclerosing Hodgkin's lymphoma (HL) at stage II B disease. Arrows indicate left femoral, inguinal, external iliac, internal iliac, common iliac and paraaortic conglomerated lymph nodes with maximum standardized uptake value (SUV max) 19.5, mean standardised uptake value (SUV mean) 10.6 and metabolic tumor volume (MTV) 53.8 cm^3. The patient had a high total lesion glycolisis (TLG) value of 572.8 and the disease recurred after 15 months.

Table 1

Patient characteristics, demography, clinical, histological features and follow-up data

Patient no	Age	Gender	Histology	Stage	Presentation site	Bulky disease	B Symptoms	Recurrence	SUV max	SUV mean	MTV	TLG	DFS	OS
1	48	M	NS	IIB	L inguinal	+	+	+	13.5	8.2	36.6	298	11	36
2	21	M	NS	IIB	L inguinal	+	+	+	17.4	9.6	52.5	505	18	38
3	46	F	MC	IA	L inguinal	_	_	+	8	5.3	24.7	130.9	30	72
4	53	M	NS	IIA	L inguinal	_	_	+	5.8	4.6	31.2	143.5	21	74
5	20	M	NS	IA	L inguinal	_	_	_	4.7	3.5	10.8	37.8	75	75
6	35	F	NS	IIA	Paracaval	_	_	+	8.8	5.4	27.8	150	20	82
7	21	M	LR	IA	R inguinal	_	_	_	4	3.8	9.8	37.2	84	84
8	20	M	NS	IB	L inguinal	_	+	_	4	3.8	10	38	78	78
9	20	F	LD	IIB	Paraaortic	+	+	+	15	8.9	56.5	502.8	18	133
10	6	M	NS	IIA	Paraaortic	_	_	+	7.8	5	25.2	126	28	84
11	25	M	NS	IIB	L inguinal	_	+	+	19.5	10.6	53.8	572.8	15	48
12	27	M	MC	IIB	R inguinal	_	+	+	9	6.1	45.5	277.5	36	132
13	27	F	NS	IIA	R inguinal	_	_	+	13.5	8.9	38.3	340	24	120
14	23	M	NLP	IIB	L inguinal	_	+	_	14.7	9.2	15.3	140.7	130	130
15	42	M	NS	IIA	R inguinal	_	_	_	7.2	5	8.4	42	15	15
16	20	M	NS	IIA	R inguinal	+	_	+	17.7	9.8	48.4	475	10	17
17	20	M	NS	IIA	L inguinal	_	_	_	11.4	6.9	15	103.5	35	35
18	59	F	MC	IIB	R inguinal	+	+	+	18.1	10.5	37	389.8	7	32
19	64	M	NS	IIB	Paraaortic	_	+	+	7.3	5.5	39	214.5	36	120
20	42	M	NLP	IIA	R inguinal	+	_	+	17.8	10	56.8	568	10	72
21	50	M	LD	IIB	L inguinal	+	+	+	21.3	12.1	62.3	754	8	70

M – male; F – female; NS – nodular sclerosing; MC – mixed cellular; LR – lymphocyte-rich; LD – lymphocyte-depleted; NLP – nodular lymphocyte-predominant; R – right; L – left; SUV max – maximum standard uptake value; SUV mean – mean standardised uptake value; MTV – metabolic tumor volume; TLG – total lesion glycolysis; DFS – disease free survival; OS – overall survival.

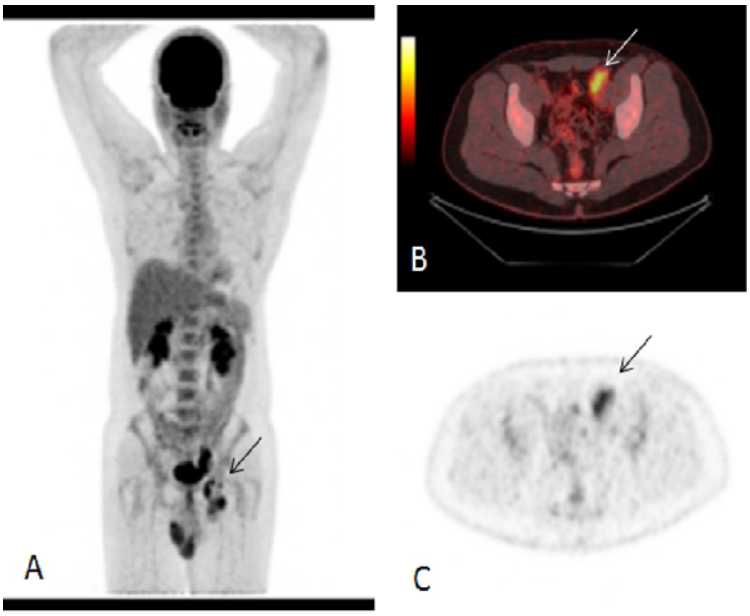

Fig. 2 – A) Maximum intensity projection (MIP); B) 18-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) fusion; C) transaxial slice of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) images of a 42-year old male patient with nodular sclerosing Hodgkin's disease HL at stage II A disease. Arrows indicate left inguinal, external iliac, internal iliac, common iliac and obdurate lymph nodes with maximum standardized uptake value (SUV max) 7.2, mean standardised uptake value (SUV mean) 5 and metabolic tumor volume (MTV) 8.4 cm^3. The patient had a low total lesion glycolisis (TLG) value of 42 and a total remission was observed during a 24-month follow-up.

Table 2

Univariate Cox regression analysis

Factors	*p*	Hazard Ratio	95% CI for Hazard Ratio	
			Lower	Upper
Sex *	0.142	2.332	0.753	7.226
Age	0.107	1.024	0.995	1.054
NS	0.507		Reference	
MC	0.722	1.271	0.339	4.765
LR	0.989	0.000	0.000	
LD	0.086	4.183	0.815	21.471
NLP	0.685	0.651	0.081	5.203
Stage I A	0.460		Reference	
Stage I B	0.990	0.000	0.000	
Stage II A	0.128	5.372	0.616	46.842
Stage II B	0.115	5.343	0.663	43.037
SUV max	0.001	1.253	1.099	1.429
SUV mean	0.001	1.513	1.172	1.953
MTV	0.001	1.080	1.034	1.129
TLG	0.000	1.008	1.004	1.012
Bulky disease**	0.000	20.681	3.898	109.709
Site of diagnosis	0.604	1.356	0.429	4.291
B symptoms	0.567	1.352	0.482	3.787

NS – nodular sclerosing; MC – mixed cellular; LR – lymphocyte-rich; LD – lymphocyte-depleted; NLP – nodular lymphocyte-predominant; SUV max – maximum standard uptake value; SUV mean – mean standardised uptake value; MTV – metabolic tumor volume; TLG – total lesion glycolysis;CI – confidence interval.
***Reference group was males **Reference group was non-bulky disease.**

Table 3

Multivariate Cox regression analysis

Factors	*p*	Hazard Ratio	95% CI for Hazard Ratio	
			Lower	Upper
Sex	0.030	5.866	1.190	28.924
TLG	0.015	1.006	1.001	1.011
Bulky disease	0.012	16.648	1.842	150.452

TLG – total lesion glycolysis; CI – confidence interval.

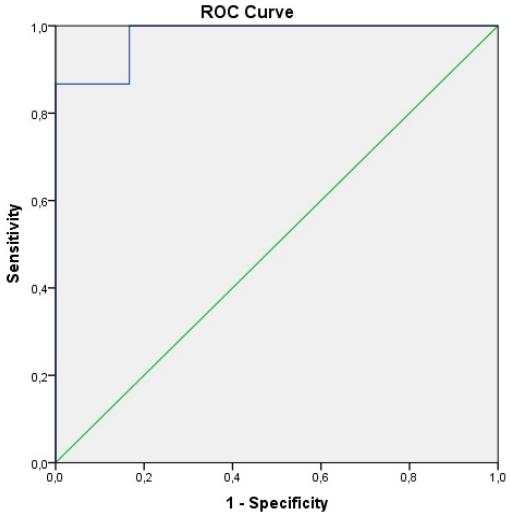

Fig. 3 – Receiver operating characteristic (ROC) curve for total lesion glycolysis (TLG).

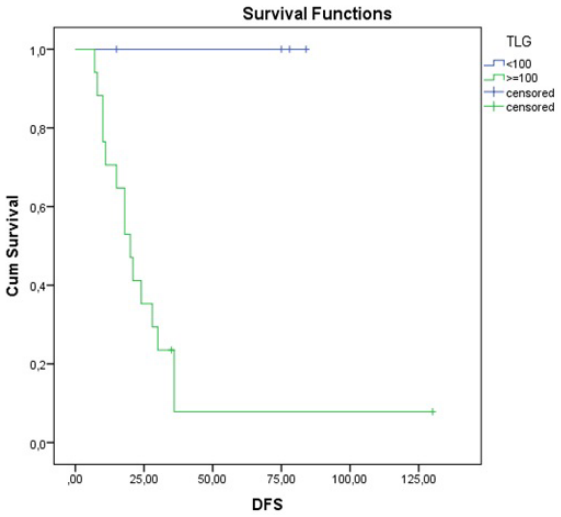

Fig. 4 – Kaplan-Meier curve for total lesion glycolysis (TLG) with a cut-off value of 100.

Discussion

In our patient population with HL 21/184 (11%) had IDHL and this incidence of IDHL is in accordance with literature [3]. IDHL has a higher prevalence of lymphocyte-predominant histologic subtype according to supradiaphragmatic HL. Among 9.5% of our patients with IDHL had nodular lymphocyte-predominant Hodgkin's disease and this is also consistent with the literature (5–10%) [1]. But 5% of supradiaphragmatic HL in our study had nodular lymphocyte-predominant Hodgkin's disease. There is a meaningful difference between them and this is an expected finding according to previous studies. It has been claimed in some studies that the incidence of nodular sclerosing subtype is lower in IDHL in relation to supradiaphragmatic HL [3]. Our incidence of the nodular sclerosing subtype (62%) is a little lower and similar to those ones.

According to literature, IDHL has higher male/female ratio and older age of patients at diagnosis in relation to supradiaphragmatic HL [2, 5]. Mean age of our patients with IDHL at diagnosis was 33 years and male/female ratio was 3.2. Mean age of our supradiaphragmatic HL group was 33 years and male/female ratio 4. There is not a difference between them regarding the age. On the contrary, male/female ratio of our supradiaphragmatic HL patients was higher than that of IDHL patients and this is a disparate finding in relation to literature. Mean age in IDHL patients was declared around 40 years in several studies [14]. Mean age of our IDHL patients (and also of supradiaphragmatic HL ones) were prominently lower than that reported in the literature, because our hospital is serving for recruits aged 18–23 years. Approximately, 30% of our patients were recruits.

The diagnostic site is inguinal lymph nodes in a great majority of the cases and most patients are at stage II [3]. The presentation site was inguinal lymph nodes and patients were at stage II in 81% of our cases and 47.5% of our cases had B symptoms. This is slightly higher incidence than in former studies which is generally between 25–40% [20]. If there is paraaortic LN involvement, careful evaluation of spleen with FDG-PET/CT is very useful [21]. We had two patients with splenic and paraaortic LN involvement. FDG-PET/CT contributed significantly for the delineation of splenic involvement in these patients. Hodgkin's survivors are at increased risk for secondary malignancies [22]. Many secondary malignancies were documented in patients with IDHL during the follow-up in lots of the published series. Hull et al. [18] found 5 secondary malignities in 21 patients during a 32-year follow-up. There were 3 cases of secondary malignancy in 21 patients during the 11-year follow-up in our study.

We observed complete remission in 6 patients. Mean follow-up time of this group was 70 (15–130) months. In 10 out of 15 patients with the metastatic/recurrent disease it occured purely in infradiaphragmatic sites which were an involved component before or a new focus. The affected region was supradiaphragmatic lymph nodes plus previously involved infradiaphragmatic sites in 3 cases; 2 patients had splenic involvement plus an involved area before or a new focus. Overall survival at 10 years gathers around 80% in reported series 4, 13. Vassilakopoulos et al. [3] found it 75% in their big cumulative nationwide historical cohort of 131 cases. Our overall survival at 5 years was 100%, and 90.5% at 10 years. These results are excellent according to other studies reported in the literature. But DFS was 28.5%.

There are controversial results about the prognosis of IDHL in comparison to stage I/II supradiaphragmatic disease in the literature. All the studies compared them with their classical prognostic factors with limited numbers of patients and different treatment approaches [10, 12, 15]. After evaluation of all potential risk factors affecting metastasis/recurrence with univariate cox regression analysis and multivariate model sex, TLG and bulky disease were found to be statistically significant risk factors for disease free survival time in our study.

Bulky disease incidence is higher in supradiaphragmatic HL than in IDHL. Although there are different accepted values for bulky disease, ranging from 5–10 cm in studies,

consensus about it is that it is taken as an advanced form of the disease [3, 23]. We chose 5 cm in axial slice as the size for it and one third of our patients had bulky disease. Bulky disease is related to tumor volume and reflects tumor burden. Ergo, its existence means much more tumor cells which could spare themselves getting rid of treating agents and thus have the potential of recurring or metastasizing later [17, 23, 24]. We found bulky disease a meaningful parameter as a predictor of IDHL ($p = 0.12$).

FDG-PET/CT is being widely used in many cancers and lymphoma patients. Some quantitative metabolic parameters derived from initial staging by PET/CT (SUV max, SUV mean) have also been used in prognosis estimation of many cancers and lymphomas. SUV max is the first one used [24, 25]. More lately increasing recognition of volume-based metabolic parameters (MTV and TLG) emerged for this purpose [24]. Gallicchio et al. [25] in their study of 52 patients found these quantitative parameters helpful in the management of diffuse large B-cell lymphoma [25]. Especially TLG proved its utility in this area and came out as a striking predictor in many cancers and lymphomas. As it combines the assessment of tumor volume and metabolism, it can stratify patients or predict the effectiveness of therapy regimens. Ceriani et al. [26] in their cohort study of 103 patients with diffuse large B-cell lymphoma showed TLG is the most powerful predictor on baseline PET/CT. But there are not studies researching the use of these parameters in a specific group of patients with IDHL and almost all evaluations using FDG PET/CT in HL were qualitative. Song et al. [27] evaluated metabolic tumor parameters in early stage HL to determine the appropriate therapeutic modality [27]. To the best of our knowledge, our study is the first one in literature in which the prognosis of IDHL was predicted over these metabolic indicators. Among the examined prognostic metabolic parameters, TLG remained as the only statistically significant pointer ($p = 0.15$) after multivariate model for DFS in this study. There is a similarity between bulky disease and TLG. Both of them are related to tumor volume. But TLG is superior to bulky disease in that it reflects the metabolically active tumor burden. When we evaluated the diagnostic value of TLG over ROC curve, we observed pretty high sensitivity and specificity (100% and 83.3%, respectively) with a cut-off value of 100. No patient whose TLG value was under 126 had recurrence. On the other hand, two patients suspected to have died from the disease had very high TLG values (502 and 754).

The main limitations of our study were the limited patient number and its retrospective design. First impressions show that metabolic tumor parameters, especially TLG may be used in the management of IDHL. However, our results should be supported with studies of large numbered samples in the future. Though our results showed that female sex increases recurrence rate 5.8 times in relation to male sex, this depends on the fact of quite a few sampling number and is no clinically important. Moreover, there are not studies stating that female sex is a risk factor for IDHL or HL yet. On the contrary, male sex was reported as a risk factor in some studies [9, 11].

Conclusion

The existence of bulky disease at the diagnosis and high TLG values (over 126) on primary staging by FDG-PET/CT are potential risk factors for both disease-free survival and overall survival in IDHL patients. Patients with high TLG have an increased risk of recurrence/metastasis and must be followed-up carefully for a possible change of treatment.

Disclosure

The authors declare that they have no conflict of interest.

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