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Professional article
Stručni članak
UDK 616-006.44-07/-08
https://doi.org/10.2298/MPNS2304092R

INTERIM POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY AS A MAJOR PROGNOSTIC FACTOR OF TREATMENT OUTCOME IN NEWLY DIAGNOSED HODGKIN'S LYMPHOMA AND OPTIMIZATION OF THE THERAPEUTIC APPROACH

INTERIM SKEN POZITRONSKE EMISIONE TOMOGRAFIJE – KOMPJUTERIZOVANE TOMOGRA- FIJE KAO GLAVNI PROGNOSTIČKI FAKTOR U PREDIKCIJI ISHODA LEČENJA NOVODIJAGNOSTIKOVANOG HOČKINOVOG LIMFOMA I OPTIMIZACIJI TERAPIJSKOG PRISTUPA

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Summary

Introduction. During the last decade, the interim positron emission tomography/computed tomography has emerged as the most important prognostic factor in patients with newly diagnosed Hodgkin's lymphoma. The aim of this study was to analyze the treatment of patients at the Clinic of Hematology, University Clinical Center of Vojvodina, in order to evaluate the prognostic value of key risk factors, with a particular focus on the role of interim positron emission tomography/computed tomography. **Material and Methods.** The study included 22 of 29 patients with a newly diagnosed classic Hodgkin's lymphoma, i.e. all patients in whom the first therapy response assessment was based on positron emission tomography/computed tomography scan results. Relevant data were collected from medical records. Kaplan-Meier curves and log-rank tests were used for survival analysis. Univariate Cox regression was used to assess the predictive value of each variable for progression-free survival. **Results.** The study included 13 women (59.09%) and 9 men (40.91%), aged 18 to 73 years (median 39.5 years). Univariate analysis was used to analyze the statistical significance of three examined variables: gender, presence of B symptoms, and complete remission on interim positron emission tomography/computed tomography. Multivariate analysis was not performed due to the insufficient number of patients for adequate interpretation of results. **Conclusion.** Interim positron emission tomography/computed tomography is the main prognostic factor in predicting treatment response and disease outcome in patients with newly diagnosed Hodgkin's lymphoma.

Key words: Positron Emission Tomography Computed Tomography; Prognosis; Treatment Outcome; Hodgkin Disease; Lymphoma

Sažetak

Uvod. Tokom poslednje decenije interim sken pozitronske emisione tomografije – kompjuterizovane tomografije izdvojen je kao najznačajniji prognostički faktor kod bolesnika sa novodijagnostikovanim Hočkinovim limfomom. Cilj ovog rada bila je analiza lečenja bolesnika na Klinici za hematologiju Univerzitetskog kliničkog centra Vojvodine, u cilju procene prognostičkog značaja glavnih faktora rizika, sa posebnim osvrtom na ulogu interim skena pozitronske emisione tomografije – kompjuterizovane tomografije. **Materijal i metode.** U istraživanje je uključeno 22 od 29 novodijagnostikovanih bolesnika sa klasičnim Hočkinovim limfomom, odnosno svi bolesnici kod kojih je prva procena terapijskog odgovora sprovedena na osnovu nalaza skena pozitronske emisione tomografije – kompjuterizovane tomografije. Relevantni podaci su prikupljeni iz medicinske dokumentacije. Preživljavanje je analizirano Kaplan-Majerovim krivama, a poređeno log-rank testom. Za procenu prediktivne vrednosti pojedinih varijabli u odnosu na vreme bez progresije bolesti korišćena je univarijantna Koksova regresija. **Rezultati.** Uzorak bolesnika se sastojao od 13 žena (59,09%) i 9 muškaraca (40,91%), starosti od 18 do 73 godine (medijana 39,5 godina). Univarijantnom analizom dobijena je statistička značajnost kod tri ispitivane varijable: pol, prisustvo B-simptoma i prisustvo kompletne remisije na interim skenu pozitronske emisione tomografije – kompjuterizovane tomografije. Multivarijantna analiza nije sprovedena s obzirom na nedovoljan broj bolesnika za adekvatno tumačenje rezultata. **Zaključak.** Interim sken pozitronske emisione tomografije – kompjuterizovane tomografije predstavlja glavni prognostički faktor u predikciji terapijskog odgovora i ishoda bolesti kod bolesnika sa novodijagnostikovanim Hočkinovim limfomom.

Ključne reči: PET/CT; prognoza; ishod lečenja; Hočkinova bolest; limfom

Introduction

Clinical stage of the disease and the International Prognostic Score (IPS) have been considered the most important prognostic factors in predicting the disease outcome at the initial diagnosis of Hodgkin's lymphoma for many years. However, during the last decade, interim positron emission tomog-

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Abbreviations

IPS	– International Prognostic Score
PET/CT	– positron emission tomography/computed tomography
CRP	– C-reactive protein
ABVD	– doxorubicin, bleomycin, vinblastine, dacarbazine
PFS	– progression free survival
OS	– overall survival
FDG	– fluorodeoxyglucose
eBEACOPP	– escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
SD	– standard deviation

raphy/computed tomography (PET/CT) has been singled out as the most important prognostic factor and the best early predictor of the therapeutic effect. Accordingly, the latest Hodgkin's lymphoma treatment guidelines recommend the therapy selection and modification based on interim PET/CT scan results [1]. Moreover, several authors have recently challenged the prognostic significance of IPS in the era of therapy optimization based on interim PET/CT scan findings.

Against this backdrop, the aim of the present study was to analyze the treatment provided to patients with newly diagnosed Hodgkin's lymphoma at the Clinic of Hematology, University Clinical Center of Vojvodina, in order to evaluate the prognostic significance of key risk factors in this cohort, as well as the correlation between these factors, with a particular focus on the role of interim PET/CT in the selection and modification of therapeutic modality.

Material and Methods

The study included all patients with a newly diagnosed classic Hodgkin's lymphoma who were treated at the Clinic of Hematology, University Clinical Center of Vojvodina, from the beginning of 2016 to the end of 2020, and in whom the first therapy response assessment was based on PET/CT scan results. Patients in whom the first assessment of therapy response was based on CT scan findings were not included in the study.

Hodgkin's lymphoma was diagnosed by pathohistological and immunohistochemical examination of lymph node, bone marrow, and extranodal organ biopsies, in accordance with the current World Health Organization classification [1, 2]. The clinical stage of the disease was determined according to the Ann-Arbor classification [3] and the IPS was calculated [3]. The following data were collected from patients' medical records: age, gender, presence of B symptoms, evidence of bone marrow infiltration, presence of bulky disease, and values of the laboratory parameters before starting the therapy: blood count with differential blood count, C-reactive protein (CRP), fibrinogen, and serum albumin. Bulky disease was defined as the presence of lymph node conglomerate on the initial CT or PET/CT scan greater than 7 cm in the transverse or frontal plane. In all patients, treatment commenced with 2 cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) and the first revision was performed with PET/CT scan. Progression free survival (PFS) was defined as the time elapsed from diagnosis to disease progression or relapse, or to death from any cause, i.e., to the date of the last contact with a patient in those in whom disease progression did not occur. Overall survival (OS) was defined as the time elapsed from diagnosis to death, i.e., if the patient was still alive, the time period from diagnosis to the last contact with the patient.

Statistical analysis was conducted using the MedCalc Statistical Software version 19.5.1. The D'Agostino-Pearson test was performed to verify the distribution normality of the examined variables. For all normally distributed variables, the data were presented as measures of average values, i.e., as arithmetic mean and standard deviation (SD). The CRP was the only variable that did not conform to the normal distribution; therefore, its values were presented as the median, minimum, and maximum. Limit values for CRP, albumin, and age at diagnosis relative to PFS were determined by receiver operating characteristic curve analysis, whereas Kaplan-Meier curves and log-rank test were used for survival analysis. Univariate Cox regression analysis was conducted to assess the predictive value of each variable for PFS. Hypotheses were accepted or rejected with a risk set at $p < 0.05$ (95% probability).

Results

The research sample included 22 of 29 patients with newly diagnosed Hodgkin's lymphoma who were treated at the Clinic of Hematology, University Clinical Center of Vojvodina, during the study period. The sample included 13 women (59.09%) and 9 men (40.91%), aged 18 to 73 years. The average age of patients was 22.4 years (SD 15.14), and the median age was 39.5 years.

The distribution of patients according to the clinical stage of the disease at diagnosis, as well as the prevalence of examined prognostic factors in relation to the clinical stage of the disease, are shown in **Table 1**. Based on the calculated IPS values, which did not exceed 4 **(Table 2)**, there were no patients in the high-risk group. The limit values of the following parameters were identified by ROC analysis: CRP $\leq$ 7.6 mg/L, albumin > 40 g/L, and $\leq$ 57 years old at initial diagnosis. The patient's follow-up time ranged from 7 to 49 months, average 23.68 months (SD 12.77), and median follow-up 21 months. During that period, disease progression occurred in 6 patients (27.27%), on average after 4.5 months (SD 2.98), median 4 months. The mean PFS was 22.4 ± 15.14 months, while the mean OS was 27.7 ± 12.7 months. Considering that only one patient died during the follow-up period, the censored survival time (time elapsed from diagnosis to the last contact with patient) was used when calculating PFS and OS for the remaining 21 patients. The number of patients who progressed in relation to the analyzed prognostic factors for PFS, as well as the

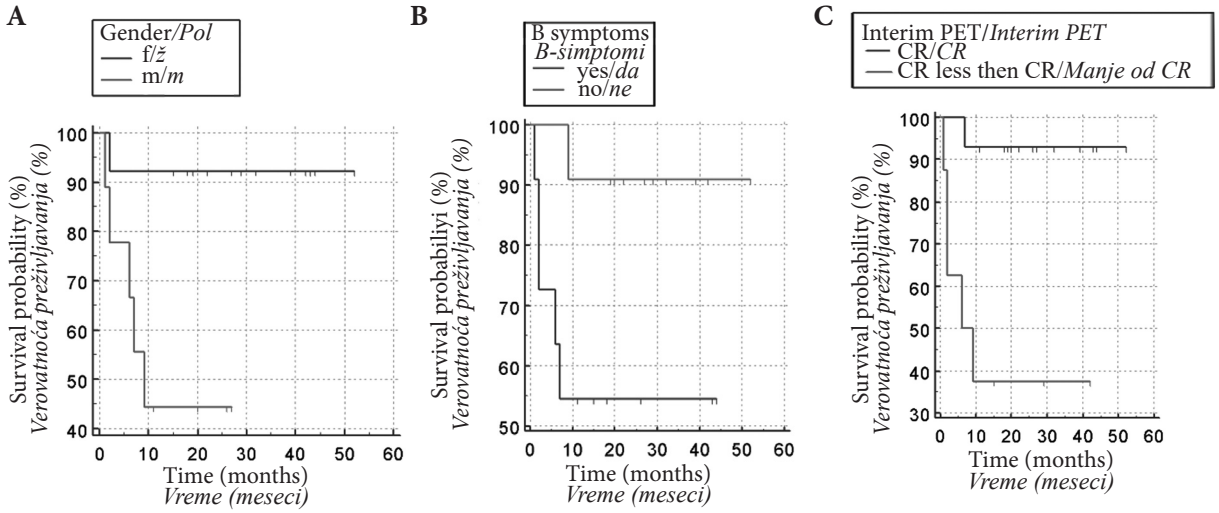
Table 1. Distribution of patients in relation to the clinical stage of the disease at diagnosis and distribution of the prevalence of examined prognostic factors in relation to the clinical stage
Tabela 1. *Raspodela bolesnika u odnosu na klinički stadijum bolesti pri postavljanju dijagnoze i raspodela zastupljenosti ispitivanih prognostičkih faktora u odnosu na klinički stadijum bolesti*

	Total number of patients *Ukupni broj bolesnika*	Stage I *I stadijum*	Stage II *II stadijum*	Stage III *III stadijum*	Stage IV *IV stadijum*
Clinical stage at diagnosis *Klinički stadijum pri postavljanju dijagnoze*	22	0	11 (50%)	8 (36.36%)	3 (13.63%)
B symptoms/*B-simptomi*	11 (50%)	NA	3	5	3
Bulky disease/*Bulky bolest*	7 (31.81%)	NA	1	4	2
EN localization of the disease *EN lokalizacija bolesti*	7 (31.81%)	NA	2	2	3
Bone marrow infiltration *Infiltracija koštane srži*	2 (9.09%)	NA	0	0	2

Legend: NA – Not applicable; EN - Extranodal/*Legenda: NA – Nije primenjivo; EN – Ekstranodalno*

Table 2. International Prognostic Score values
Tabela 2. *Vrednosti Međunarodnog prognostičkog skora (MPS)*

IPS/*MPS*	0	1	2	3	4	5 - 7	
No/*Broj* (%)	3 (13.64%)	6 (27.27%)	7 (31.82%)	1 (4.54%)	5 (22.73%)	0 (0%)	22 (100%)



Graph 1. Kaplan-Meier curves showing survival analysis in regard to gender (A), B symptoms (B) and complete remission (CR) on interim PET/CT scan (C)
Grafikon 1. *Kaplan-Majerove krive koje prikazuju analizu preživljavanja u odnosu na pol (A), B-simptome (B) i kompletnu remisiju (CR) na interim skenu pozitronske emisione tomografije – kompjuterizovane tomografije (C)*

results of the univariate analysis that estimated the predictive value of each prognostic factor, are shown in **Table 3**. Statistical significance was analyzed for three examined variables, namely gender, presence of B symptoms, and evidence of complete remission on interim PET/CT **(Table 3)**. Survival analysis for these three variables is shown on Kaplan-Meier curves **(Graph 1)**. Adequate multivariate analysis requires at least ten events per prognostic factor, while in this study, disease progression occurred in only six patients. Considering the insufficient number of patients, multivariate analysis was not performed.

Discussion

Retrospective analysis of the disease course in patients with newly diagnosed Hodgkin's lymphoma treated at the University Clinical Center of Vojvodina showed that early assessment of therapy response based on interim PET/CT scan results, as ell as individual therapy adjustments in accordance with these results, is important for achieving and maintaining remission, given that the interim PET/CT scan results were identified as the most statistically significant prognostic factor in predicting disease outcome. The prognostic value of interim PET/CT scan for PFS in patients with Hodgkin's lymphoma has also been reported by other authors [4–

Table 3. Patients with disease progression in relation to prognostic factors; predictive value of prognostic factors for progression free survival
Tabela 3. *Bolesnici kod kojih je došlo do progresije bolesti u odnosu na prognostičke faktore, kao i prediktivna vrednost prognostičkih faktora u odnosu na preživljavanje bez progresije bolesti*

Prognostic factor/*Prognostički faktor*						
Gender/*Pol*	DP/*DP*		Total number of patients *Ukupan broj bolesnika*		HR (95% CI)	p/*p*
	Yes/*Da*	No/*Ne*				
Male/*Muški*	5	4	9	22	8.1254 (1.5061 - 43.8356)	0.02
Female/*Ženski*	1	12	13			
B symptoms *B-simptomi*	DP/*DP*		Total number of patients *Ukupan broj bolesnika*		HR (95% CI)	p/*p*
	Yes/*Da*	No/*Ne*				
Yes/*Da*	5	6	11	22	0.1895 (0.03687 - 0.9739)	0.04
No/*Ne*	1	10	11			
CR on interim PET/CT scan *CR na interim PET/CT skenu*	DP/*DP*		Total number of patients *Ukupan broj bolesnika*		HR (95% CI)	p/*p*
	Yes/*Da*	No/*Ne*				
Yes/*Da*	1	13	14	22	14.9818 (2.5039 - 89.6431)	0.003
No/*Ne*	5	3	8			
Age at diagnosis *Starost pri postavljanju dijagnoze*	DP/*DP*		Total number of patients *Ukupan broj bolesnika*		HR (95% CI)	p/*p*
	Yes/*Da*	No/*Ne*				
> 57 years old/> *57 godina*	0	4	4	22	NA	0.21
≤ 57 years old/≤ *57 godina*	6	12	18			
Albumin level *Vrednost albumina*	DP/*DP*		Total number of patients *Ukupan broj bolesnika*		HR (95% CI)	p/*p*
	Yes/*Da*	No/*Ne*				
> 40 g/L	5	8	13	18	0.4789 (0.08461 - 2.7111)	0.41
≤ 40 g/L	1	4	5			
CRP level *Vrednost CRP-a*	DP/*DP*		Total number of patients *Ukupan broj bolesnika*		HR (95% CI)	p/*p*
	Yes/*Da*	No/*Ne*				
≤ 7.6 mg/L	1	7	8	21	2.7232 (0.5247 - 14.1347)	0.23
> 7.6 mg/L	5	8	13			
EN localization of the disease *EN lokalizacija bolesti*	DP/*DP*		Total number of patients *Ukupan broj bolesnika*		HR (95% CI)	p/*p*
	Yes/*Da*	No/*Ne*				
Yes/*Da*	3	4	7	22	2.7044 (0.4616 - 15.8454)	0.27
No/*Ne*	3	12	15			
Bulky disease *Bulky bolest*	DP/*DP*		Total number of patients *Ukupan broj bolesnika*		HR (95% CI)	p/*p*
	Yes/*Da*	No/*Ne*				
Yes/*Da*	2	5	7	19	1.3408 (0.2048 - 8.7782)	0.76
No/*Ne*	3	9	12			
Bone marrow infiltration *Infiltracija koštane srži*	DP/*DP*		Total number of patients *Ukupan broj bolesnika*		HR (95% CI)	p/*p*
	Yes/*Da*	No/*Ne*				
Yes/*Da*	1	1	2	18	3.9877 (0.1813 - 87.7098)	0.38
No/*Ne*	5	11	16			
Advanced stage of the disease *Uznapredovali stadijum bolesti*	DP/*DP*		Total number of patients *Ukupan broj bolesnika*		HR (95% CI)	p/*p*
	Yes/*Da*	No/*Ne*				
Yes/*Da*	6	10	16	22	NA	0.09
No/*Ne*	0	6	6			

Legend: DP - Disease progression; PFS - Progression free survival; HR - Hazard ratio; CI - Confidence interval; p - Probability value ($p < 0.05$ – result is statistically significant); CR - Complete remission; EN - Extranodal; NA - Not applicable
Legenda: DP – progresija bolesti; PFS – preživljavanje bez progresije bolesti; HR – Indeks rizika; CI – interval poverenja; p – vrednost verovatnoće ($p < 0.05$ – postoji statistička značajnost); CR – kompletna remisija; EN – Ekstranodalno; NA – Nije primenjivo

8]. Based on a recent meta-analysis of studies assessing the predictive value of interim PET/CT scan on PFS after two cycles of chemotherapy, Terasawa et al. noted that the three-year PFS in patients with negative interim PET/CT scan results was 90 - 95%, declining to 12 - 30% in patients with positive interim PET/CT scans [9].

High PET/CT predictive value can probably be explained by high sensitivity of Hodgkin's lymphoma to chemotherapy. Therefore, in patients with a good therapy response, a decrease in metabolic activity would manifest on the PET/CT scan immediately after initiation of the chemotherapy protocol [10]. A good fluorodeoxyglucose (FDG) avidity of Hodgkin's lymphoma is attributed to the pathohistological substrate consisting of only 1% of malignant cells, while the majority of tumors comprise a surrounding inflammatory infiltrate with high metabolic activity that is easily registered on PET/CT. Constant cytokine-mediated communication between Reed-Sternberg cells and inflammatory infiltrate is responsible for the maintenance and proliferation of Reed-Sternberg cells, but also for increased metabolic activity of the surrounding inflammatory infiltrate, and consequently increased FDG accumulation [11, 12]. Therefore, soon after starting chemotherapy and reducing the number of Reed-Sternberg cells, the metabolic activity of inflammatory cells decreases rapidly, while in patients resistant to initial chemotherapy, severe FDG avidity will still be detected on the PET/CT scan [13].

Choosing the optimal therapy based on PET/CT scan results in individuals initially diagnosed at an advanced stage of the disease is important from the aspect of sparing patients from unnecessary exposure to the toxicity of intense therapy modalities, which increases the likelihood of secondary malignancies. Gallamini et al. [14] compared the final therapy effect and the PFS duration in two groups of patients that were diagnosed at an advanced stage of the disease, but were given different initial treatment. The first group received de-escalation therapy according to the escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (eBEACOPP) protocol, while patients in the second group received a standard therapy with two ABVD cycles, after which therapy was escalated only in patients with positive interim PET/CT scan results. The authors reported no statistically significant differences in achieving and maintaining remission between these two groups, suggesting that it is not justified to expose patients to additional toxicity by routine use of eBEACOPP protocol, except when initial resistance to the first-line therapy is confirmed by PET/CT [14].

In our patients, CT was a more frequently adopted radiological method during the initial disease staging than PET or PET/CT (16 versus 6 patients, respectively). However, data reported in pertinent literature indicate that the assessment of FDG avidity on PET or PET/CT scans during the initial disease staging is superior to the assessment of lymph node size and the affection of extranodal structures on CT scans [13, 15]. In several prospective studies [16–25], as a part of which the results of these two radiological methods were compared in the same group of patients, the same specificity and significantly higher sensitivity of PET and PET/CT compared to classical contrast-enhanced CT was verified. The percentage of patients in these studies who were diagnosed at a higher clinical stage of the disease based on the PET or PET/CT scan findings ranged from 9% to 41% (18% on average), while the lower clinical stage of the disease compared to classical contrast-enhanced CT was verified in 0 - 12% of patients (5% on average). The main reason for the diagnosis at a higher clinical stage of the disease was the detection of extranodal lesions on the PET/CT scan, primarily in the bone marrow. These results are consistent with the fact that bone marrow involvement in Hodgkin's lymphoma is mostly focal and more difficult to detect on a pathohistological sample, while high FDG sensitivity of PET/CT scan makes it much easier to detect bone marrow lesions [3, 23]. Accordingly, many authors are questioning the utility of routine bone marrow biopsy if PET/CT is used during the initial diagnosis. Moreover, as their meta-analysis of nine studies including 955 subjects in total confirmed the 87.5 - 100% sensitivity and 86.7 - 100% specificity of PET/CT scan in detecting bone marrow lesions, Adams et al. concluded that routine bone marrow biopsy should be replaced by PET/CT scan at initial diagnosis [26]. Furthermore, international guidelines for treatment of FDG avid lymphomas recommend the use of PET/CT scan during the initial disease staging, while the justification for using classical CT is increasingly being questioned [27].

In the present study, none of the parameters included in the IPS showed to be statistically significant prognostic factors for PFS, countering the prevailing view that IPS is one of the main modalities for disease outcome assessment [28]. Although retrospective studies conducted at the end of 20th century confirmed that these seven factors are independently associated with more adverse disease outcomes, recent investigations suggest that the prognostic significance of IPS exists, but considering that advances in therapy mostly affect patients at the advanced stage of the disease, its predictive value is decreasing. Therefore, the relevance of the IPS in predicting disease outcome when using interim PET/CT scan and optimizing therapy based on the obtained findings is debatable [28–31].

These results in relation to the findings and conclusions yielded by other studies, as well as the fact that the main limitations of our study originate from the retrospective design and a small sample of patients, indicate the need for prospective studies involving a greater number of patients that would be followed over a longer period of time, since it would produce more accurate results.

Conclusion

Interim positron emission tomography/computed tomography is a major prognostic factor in predicting treatment response and disease outcome in patients with newly diagnosed Hodgkin's lymphoma.

Using the interim positron emission tomography/computed tomography and choosing the optimal therapeutic approach based on its results reduces the relevance of International Prognostic Score in predicting the disease outcome.

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Rad je primljen 15. VII 2022.
Recenziran 19. VI 2023.
Prihvaćen za štampu 19. VI 2023.
BIBLID.0025-8105:(2023):LXXVI:3-4:92-98.