ABVD PROTOKOL NIJE ADEKVATAN ZA SVE PACIJENTE SA UZNAPREDOVALIM KLASIČNIM HOČKINOVIM LIMFOMOM: PETOGODIŠNJE ISKUSTVO JEDNOG CENTRA IZ SVAKODNEVNE KLINIČKE PRAKSE

ORIGINALNI RAD

ORIGINAL ARTICLE

ABVD DOES NOT FIT ALL ADVANCED-STAGE CLASSICAL HODGKIN LYMPHOMA PATIENTS: REAL-WORLD FIVE-YEAR SINGLE-CENTER EXPERIENCE

Vojin Vuković[1,2], Teodora Karan-Đurašević[3], Tamara Bibić[1], Sofija Kozarac[1], Jelena Ivanović[1], Pavle Tulić[1], Danijela Leković[1,2], Darko Antić[1,2]

[1] Univerzitetski klinički centar Srbije, Klinika za hematologiju, Beograd, Srbija

[2] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

[3] Univerzitet u Beogradu, Institut za molekularnu genetiku i genetičko inženjerstvo, Beograd, Srbija

[1] *University Clinical Center of Serbia, Clinic for Hematology, Belgrade, Serbia*

[2] *University of Belgrade, Medical Faculty, Belgrade, Serbia*

[3] *University of Belgrade, Institute of Molecular Genetics and Genetic Engineering, Belgrade, Serbia*

SAŽETAK

Uvod/Cilj: Uznapredovali klasični Hočkinov limfom (UkHL) predstavlja terapijski izazov zbog značajnog procenta neuspeha prve terapijske linije. Cilj rada je da se opiše lečenje bolesnika sa UkHL-om u svakodnevnoj kliničkoj praksi *ABVD* protokolom.

Metode: U ovoj retrospektivnoj studiji su ispitivani kliničko-laboratorijski parametri, lečenje i ishod bolesnika kod kojih je UkHL dijagnostikovan u periodu od 2016. do kraja 2020. godine.

Rezultati: Kohortu je činilo 49 bolesnika sa UkHL-om čija je medijana praćenja bila 47 meseci (opseg: 1 – 79). Najvažnije kliničko-laboratorijske karakteristike su sumirane u Tabeli 1.

Svi bolesnici su inicijalno lečeni *ABVD* protokolom. Ukupni odgovor je iznosio 72,3% (kompletni odgovor = 61,7%; parcijalni odgovor = 10,6%), dok je ostalih 27,7% pacijenata ispoljilo refraktornost. Još 10,6% bolesnika je relapsiralo naknadno. Od ispitivanih parametara (Tabela 1) samo je povišena sedimentacija eritrocita (SE ≥ 50 mm u prvom satu) uticala na kraće preživljavanje bez progresije (PBP), (medijana PBP = 19 meseci naspram nedostignuta kod bolesnika sa SE < 50mm u prvom satu; $p = 0,039$), dok je prisustvo velike tumorske mase (engl. *bulky tumor mass/bulky disease*) bilo povezano sa kraćim ukupnim preživljavanjem (UP), ($p = 0,044$). Takođe, primarno refraktorni bolesnici su imali značajno kraće UP (medijana UP = 54 meseca naspram nedostignuta kod bolesnika sa postignutom remisijom; $p = 0,004$). Medijana PBP-a i UP-a nije dostignuta; četvorogodišnje PBP i UP iznosili su 61%, odnosno 89%. Pacijenti koji su lečeni autologonom transplantacijom (AT) u relapsiranoj/refraktornoj (R/R) bolesti imali su duže PBP ($p = 0,02$), ali ne i UP. Brentuksimab vedotin (BV) je uspešno primenjen kod četiri od 14 bolesnika, kod troje u konsolidaciji nakon autologne transplantacije.

Zaključak: Značajan broj bolesnika sa UkHL-om ne može da bude izlečen *ABVD* protokolom, već je neophodno za njih obezbediti intenzivnije lečenje ili inovativne terapije.

Ključne reči: uznapredovali Hočkinov limfom, *ABVD*, preživljavanje, autologna transplantacija

ABSTRACT

Introduction/Aim: Advanced-stage classical Hodgkin lymphoma (AScHL) is a therapeutic challenge due to chemoresistance. This study aims to present real-world data on the application of the ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine) in patients with AScHL.

Methods: This retrospective study examines the clinical and laboratory parameters, as well as the treatment and outcome of patients diagnosed with AScHL, in the period between 2016 and 2020.

Results: The cohort consisted of 49 patients with AScHL. Median follow-up was 47 months (range: 1 – 79). The most important clinical and laboratory characteristics are summarized in Table 1.

All patients were initially treated with ABVD. The overall response rate was 72.3% (complete response = 61.7%; partial response = 10.6%), while 27.7% of patients exhibited refractoriness. Additionally, 10.6% relapsed at a later stage. Of the investigated parameters (Table 1), only an elevated erythrocyte sedimentation rate (ESR) ≥ 50 mm in the first hour) was associated with shorter progression-free survival (PFS), (median PFS = 19 months vs. not reached (NR), in patients with ESR < 50 mm in the first hour; $p = 0.039$), while the presence of bulky disease was associated with shorter overall survival (OS), ($p = 0.044$). Also, refractory patients had significantly shorter OS (median OS = 54 months vs. NR in patients who achieved remission; $p = 0.004$). The median PFS and OS were not achieved; four-year PFS and OS were 61% and 89%, respectively. Patients treated with autologous transplantation (AT) in relapsed/refractory disease had a longer PFS ($p = 0.02$), but not a longer OS. Brentuximab vedotin (BV) was successfully used in 4/14 patients, of whom three patients received it as consolidation treatment after AT.

Conclusion: A significant number of patients with AScHL cannot be cured with ABVD, thus more intensive treatment or innovative therapies are warranted.

Keywords: advanced-stage Hodgkin lymphoma, ABVD, survival, autologous transplantation

Autor za korespondenciju:
Vojin Vuković
Klinika za hematologiju, Univerzitetski klinički centar Srbije
Adresa: Koste Todorovića 2, 11000 Beograd, Srbija
Elektronska adresa: vojinvukovic@yahoo.com

Corresponding author:
Vojin Vuković
Clinic for Hematology, University Clinical Center of Serbia
2 Koste Todorovića Street, 11000 Belgrade, Serbia
E-mail: vojinvukovic@yahoo.com

Primljeno • *Received*: July 31, 2024; **Revidirano • *Revised*:** August 22, 2024; **Prihvaćeno • *Accepted*:** August 23, 2024; ***Online first*:** September 25, 2024

DOI: 10.5937/smclk5-52493

UVOD

Klasični Hočkinov limfom (kHL) čini približno 95% svih slučajeva Hočkinovog limfoma. Preostalih 5% su pacijenti sa histološkim podtipom Hočkinovog limfoma sa nodularnom limfocitnom predominacijom, koji zahteva značajno drugačije lečenje i ima drugačiju prognozu. U okviru najnovije klasifikacije limfoidnih maligniteta, Hočkinov limfom sa nodularnom limfocitnom predominacijom je reklasifikovan kao nodularni limfocitno-predominantni B-ćelijski limfom [1,2]. Klasični HL pokazuje bimodalnu starosnu distribuciju i dijagnostikuje se nakon ekscizione biopsije limfnih čvorova i histopatološke i imunohistohemijske potvrde *CD*30-pozitivnih Rid-Šternbergovih i srodnih tumorskih ćelija u okruženju koje obiluje inflamatornim ćelijama [3,4]. Stadijum bolesti i stratifikacija rizika kod pacijenata sa kHL-om oslanjaju se na En Arbor klasifikaciju i prisustvo faktora rizika, različito definisanih u različitim studijskim grupama [5].

Kombinovana hemioterapija (HT) sa ili bez radioterapije (RT) je decenijama bila osnova lečenja kHL-a [6]. Pacijenti se mogu izlečiti u oko 90% slučajeva u ranoj fazi, dok se pacijenti sa uznapredovalim stadijumom klasičnog Hočkinovog limfoma (UkHL) suočavaju sa 25% – 30% rizika od hemorezistencije ili relapsa [3,7]. Modalitet kombinovanog lečenja (HT + RT) nudi bolju dugoročnu kontrolu bolesti nego sama hemioterapija u ranoj fazi bolesti ali po cenu značajno češće kasne toksičnosti, uključujući srčanu i tiroidnu disfunkciju i solidne tumore. Pojava drugih kasnih neželjenih događaja kao što su neplodnost, plućna bolest, akutna leukemija i mijelodisplastični sindrom više zavisi od intenziteta hemioterapije [8–10].

U pogledu bezbednosti i efikasnosti, istorijski postoje dva glavna konkurentna pristupa lečenju UkHL-a: eskalirani *BEACOPP* protokol (*BEACOPPesc*), (bleomicin, etopozid, doksorubicin, ciklofosfamid, vinkristin, prokarbazin i prednizon) Nemačke studijske grupe za Hočkinov limfom (engl. *German Hodgkin Study Group – GHSG*), koji obezbeđuje bolju kontrolu bolesti ali po cenu veće stope i akutne i kasne toksičnosti, i *ABVD* (doksorubicin, bleomicin, vinblastin i dakarbazin) protokol – čvrsto utemeljena kombinovana hemioterapija koja se primenjuje širom sveta, sa manje neželjenih efekata, ali ujedno sa slabijom dugoročnom kontrolom bolesti. Nekoliko kliničkih ispitivanja zasnovanih na lečenju koje je vođeno pozitronskom emisionom tomografijom/kompjuterskom tomografijom (PET/*CT*) bilo je usmereno na smanjenje intenziteta terapije kod privremeno PET negativnih pacijenata sa UkHL-om i, posledično, na smanjenje toksičnosti, uz očuvanu efikasnost lečenja [11–13]. Novi oblici lečenja, kao što je kombinacija brentuksimab vedotina (BV) i tradicional-

INTRODUCTION

Classical Hodgkin lymphoma (cHL) accounts for approximately 95% of all HL cases. The remaining 5% are patients with nodular lymphocyte-predominant Hodgkin lymphoma, a histological subtype with significantly different treatment and prognosis. Within the most recent classification of lymphoid malignancies, nodular lymphocyte-predominant HL has been reclassified as nodular lymphocyte-predominant B-cell lymphoma [1,2]. Classical HL exhibits bimodal age distribution and is diagnosed after excisional lymph node biopsy and histopathological and immunohistochemical confirmation of CD30-positive Reed-Sternberg and related tumor cells in an abundant inflammatory background [3,4]. Disease staging and risk stratification of cHL patients rely on the Ann Arbor classification and the presence of risk factors, defined differently across different study groups [5].

Combined chemotherapy (ChT) with or without radiotherapy (RT) has been the mainstay of treating cHL for decades [6]. Patients can be cured in around 90% of early-stage cases, while patients with advanced-stage classical Hodgkin lymphoma (AScHL) face a 25% – 30% risk of chemoresistance or relapse [3,7]. Combined modality treatment (ChT + RT) offers better long-term disease control than ChT alone in early-stage disease, however, at the cost of significantly more frequent late toxicities, including cardiac and thyroid dysfunction and solid tumors. The occurrence of other late events such as infertility, pulmonary disease, acute leukemia, and myelodysplastic syndrome rather depends on ChT intensity [8–10].

In terms of safety and efficacy, historically there have been two main competing approaches to treating AScHL: the German Hodgkin Study Group (GHSG) BEACOPP escalated regimen (BEACOPPesc) (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), producing better disease control at the cost of higher rates of both acute and late toxicities, and the ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen, a well-established combined ChT applied world-wide, with fewer adverse effects, but also inferior long-term disease control. Several clinical trials based on positron emission tomography/computed tomography (PET/CT) guided treatment were aimed at reducing treatment intensity in interim PET-negative AScHL patients and, consequently, reducing toxicity with preserved treatment efficacy [11–13]. New forms of treatment, such as brentuximab vedotin (BV) combined with traditional ChT have improved progression-free and overall survival, at the same time achieving reduced toxicity [14,15].

ne hemioterapije, poboljšali su preživljavanje bez progresije bolesti kao i ukupno preživljavanje, istovremeno postižući smanjenje toksičnosti [14,15].

Osnova lečenja pacijenata sa relapsiranim/refraktornim (R/R) kHL-om je hemioterapija koja ne ispoljava unakrsnu rezistenciju praćena visokodoznom hemioterapijom (engl. *high-dose chemotherapy – HDC*) i autolognom transplantacijom matičnih ćelija hematopoeze (ATMĆH) kod hemiosenzitivnih pacijenata. Ovaj pristup dovodi do dugotrajne kontrole bolesti u približno 50% slučajeva [16]. Preživljavanje je dodatno poboljšano uvođenjem novih terapija, kao što su BV i inhibitori imunskih kontrolnih tačaka (anti-PD1 antitela). Pokazalo se da je mesto novih terapija u lečenju pacijenata sa relapsiranim/refraktornim (R/R) Hočkinovim limfomom u premošćavanju do ATMĆ i održavanju nakon ATMĆ, kao i u kombinaciji sa hemioterapijom spašavanja (engl. *salvage chemotherapy – salvage ChT*) pre ATMĆ [7]. Monoterapija kod hemiorezistentnih pacijenata i pacijenata koji ne ispunjavaju kriterijume za ATMĆ nije pokazala uspešnost u obezbeđivanju dugoročne kontrole bolesti [17,18].

Postoji nekoliko studija koje opisuju iskustva iz svakodnevne kliničke prakse u primeni *ABVD* protokola kod pacijenata sa UkHL-om [19–22]. Neophodno je prikupiti iskustva iz svakodnevne prakse izvan kliničkih ispitivanja, odnosno kontrolisanih okolnosti, kako bi se dobila šira slika ishoda lečenja kod pacijenata sa UkHL-om.

Ova studija ima za cilj da ispita ishode pacijenata sa UkHL-om koji su lečeni *ABVD* protokolom u našem centru u periodu od pet godina, te da identifikuje faktore rizika za neuspeh lečenja i proceni ishode pacijenata kod kojih lečenje *ABVD* protokolom nije bilo uspešno.

MATERIJALI I METODE

Pacijenti i ishodi lečenja

Sproveli smo retrospektivnu unicentričnu studiju kako bismo analizirali ishode 49 pacijenata sa dijagnozom UkHL-a u skladu sa *GHSG*-om [5]. Ovim pacijentima je dijagnostikovan kHL tokom petogodišnjeg perioda između januara 2016. i decembra 2020. godine. Pacijenti su lečeni su na Klinici za hematologiju Univerzitetskog kliničkog centra Srbije, u Beogradu. Dijagnoza je postavljena nakon biopsije uvećanih limfnih čvorova i histopatološkog pregleda tumorskog tkiva od strane iskusnog hematopatologa. Pacijenti su podvrgnuti standardnim hematološkim pregledima bez inicijalnog PET/*CT* pregleda, dodeljen im je klinički stadijum prema En Arbor klasifikaciji i svrstani su u odgovarajuću terapijsku grupu (engl. *advanced stage – AS*) prema GHSG stratifikaciji rizika [5]. Klinički i laboratorijski parametri pri postavljanju dijagnoze su prikupljeni iz bolničke dokumentacije pacijenata i korelirani sa ishodom lečenja i vremenom preživljavanja. Terapijski od-

The cornerstone of treating relapsed/refractory (R/R) cHL patients is non-cross-resistant ChT followed by high-dose ChT (HDC) and autologous stem cell transplantation (ASCT) in chemosensitive patients. This approach leads to long-term disease control in approximately 50% of cases [16]. Survival is further improved by introducing novel therapies, such as BV and immune checkpoint inhibitors (anti-PD1 antibodies). Bridging to and maintenance after ASCT, as well as combination with salvage ChT prior to ASCT seem to be the most appropriate ways to use these novel therapies in the relapsed/refractory (R/R) setting [7]. Monotherapy in chemoresistant and ASCT-ineligible patients failed to provide long-term disease control [17,18].

There are several studies describing real-world experience with ABVD in patients with AScHL [19–22]. It is necessary to gather experience from daily practice outside trials, i.e., controlled circumstances, in order to get a broader overview of treatment outcomes in AScHL patients.

This study aims to examine the outcomes of AScHL patients treated with ABVD at our center over a period of five years, identify risk factors for treatment failure, and assess the outcomes of patients who had experienced ABVD treatment failure.

MATERIALS AND METHODS

Patients and treatment outcomes

We conducted a single-center retrospective study to analyze the outcomes of 49 patients diagnosed with AScHL as per the GHSG [5]. These patients were diagnosed with cHL during the five years between January 2016 and December 2020 and were treated at the Clinic for Hematology of the University Clinical Center of Serbia, in Belgrade. The diagnosis was established following the biopsy of enlarged lymph nodes and histopathological examination of tumor tissue by an experienced hematopathologist. The patients underwent standard hematological work-up with no initial PET/CT examination. They were assigned an Ann Arbor clinical stage and the appropriate treatment group (advanced stage – AS) according to the GHSG risk stratification [5]. Clinical and laboratory parameters at diagnosis were collected from patient hospital records and correlated with the treatment outcome and survival time. Treatment response and disease relapse were assessed according to the Lugano Criteria [23]. All patients were initially treated with the ABVD regimen which consisted of doxorubicin (25 mg/m^2), (bleomycin 10 mg/m^2), (vinblastine 6 mg/m^2), and dacarbazine (375 mg/m^2). Progression-free survival was calculated as the number of months from treatment initiation to disease relapse

govor i relaps bolesti su procenjeni prema Lugano kriterijumima [23]. Svi pacijenti su inicijalno lečeni *ABVD* protokolom koji se sastojao od doksorubicina (25 mg/m^2), bleomicina (10 mg/m^2), vinblastina (6 mg/m^2) i dakarbazina (375 mg/m^2). Preživljavanje bez progresije je izračunato kao broj meseci od početka lečenja do relapsa bolesti ili smrti usled bilo kojeg uzroka, šta god sa prvo dogodi. Ukupno preživljavanje je definisano kao vreme u mesecima od dijagnoze do smrti ili do datuma cenzorisanja na poslednjoj kontroli. Ispitali smo da li su ključni demografski i klinički parametri povezani sa terapijskim odgovorom, preživljavanjem bez progresije i ukupnim preživljavanjem.

Studija je sprovedena prema Helsinškoj deklaraciji iz 1964. godine i odobrena od strane Etičkog komiteta Medicinskog fakulteta Univerziteta u Beogradu, Beograd, Srbija.

Statistička analiza

Kategoričke varijable su predstavljene kao apsolutni brojevi i frekvencije, dok su kontinuirane varijable predstavljene kao medijana sa opsegom, srednje vrednosti sa standardnom devijacijom (SD) i devedesetpetoprocentni interval poverenja (engl. 95% *confidence interval* – 95% *CI*). Distribucija podataka je procenjena pomoću Šapiro-Vilk testa. Povezanost između kategoričkih varijabli analizirana je Fišerovim egzaktnim testom i Hi-kvadratnim testom. Vreme preživljavanja pacijenata je analizirano prema Kaplan-Majerovom modelu. Razlike u distribuciji preživljavanja među grupama pacijenata na osnovu različitih karakteristika pacijenata definisane su pomoću log-rank testa.

Za statističku analizu korišćen je softver *SPSS 21.0* (*IBM*). Sve analize su izvršene na osnovu dvostranih p vrednosti, a značajnost je definisana kao $p < 0,05$.

REZULTATI

Opis kohorte

Medijana praćenja je bila 47 meseci (opseg: 1 – 79). Medijana starosti pacijenata u trenutku uspostavljanja dijagnoze je bila 34 godine (opseg: 18 – 74). Muškarci su bili zastupljeni u kohorti 1,6 puta više od žena. Učestalosti histoloških podtipova su bile sledeće: nodularna skleroza 73,8%, mešovita celularnost 9,5%, limfocitna deplecija 2,4%, limfocitima bogat 7,1%, kombinovana nodularna skleroza/mešovita celularnost 7,1%, dok je sedam pacijenata bilo neklasifikovano. Pacijenti su klasifikovani na osnovu klasifikacije Evropske organizacije za istraživanje i lečenje raka (engl. *European Organisation for Research and Treatment of Cancer – EORTC*) i Asocijacije za istraživanje limfoma (engl. *Lymphoma Study Association – LYSA*). Sedam (14,3%) pacijenata je

or death from any cause, whatever occurred first. Overall survival was defined as the time in months from diagnosis to death or to the date of censoring at the latest follow-up. We examined whether key demographic and clinical parameters were associated with treatment response, progression-free survival, and overall survival.

The study was conducted per the 1964 Helsinki Declaration and approved by the Ethics Committee of the University of Belgrade School of Medicine, Belgrade, Serbia.

Statistical Analysis

Categorical variables are presented as absolute numbers and frequencies, while continuous variables are presented using medians with ranges, means with standard deviation (SD), and a 95% confidence interval (95% CI). The data distribution was assessed using the Shapiro-Wilk test. The association between categorical variables was analyzed using the Fisher exact test and the Chi-square test. Survival times were analyzed according to the Kaplan-Meier estimator. Survival distribution differences among patient groups based on various patient characteristics were defined using the log-rank test.

SPSS 21.0 software (IBM) was used for statistical analysis. All analyses were performed based on two-tailed p values and significance was defined as $p < 0.05$.

RESULTS

Cohort description

The median follow-up was 47 months (range: 1 – 79). The median age when the diagnosis was established was 34 years (range: 18 – 74). Men were represented in the cohort 1.6 times more than women. The frequencies of histological subtypes were as follows: nodular sclerosis 73.8%, mixed cellularity 9.5%, lymphocyte depletion 2.4%, lymphocyte rich 7.1%, combined nodular sclerosis/mixed cellularity 7.1%, while seven patients were unclassified. The patients were classified based on the European Organisation for Research and Treatment of Cancer (EORTC) and Lymphoma Study Association (LYSA) classification. Seven (14.3%) patients were classified as being in the intermediate stage, while 42 (85.7%) patients were classified as being in the advanced stage (AS). According to the Ann Arbor staging system, seven (14.3%) patients were classified as being in stage II, 26 (53%) patients as being in stage III, and 16 (32.7%) patients were classified as being in stage IV. Thirty-eight (77.6%) patients presented with B symptoms, 58% exhibited a bulky mass ≥ 7 cm, while 30% of the patients had a bulky mass ≥ 10 cm. More than

Tabela 1. Kliničke karakteristike pacijenata sa UkHL-om

Table 1. Clinical characteristics of AScHL patients

Karakteristike / *Characteristics*	***Values***
Starost (godine), medijana (opseg) / *Age (years), median (range)*	34 (18 – 74)
Pol, n (%) / *Gender, n (%)*	
Muški / *Male*	30 (61.2%)
Ženski / *Female*	19 (38.8%)
EORTC/LYSA stadijum, n (%) / *EORTC/LYSA stage, n (%)*	
Intermedijarni / *Intermediate*	7 (14.3%)
Uznapredovali / *Advanced*	42 (85.7%)
En Arbor stadijum, n (%) / *Ann Arbor stage, n (%)*	
II	7 (14.3%)
III	26 (53%)
IV	16 (32.7%)
B simptomi, n (%) / *B symptoms, n (%)*	
A	11 (22.4%)
B	38 (77.6%)
Velika tumorska masa ≥ 7 cm, n (%) / *Bulky disease ≥ 7 cm, n (%)*	25 (58%)
Velika tumorska masa ≥ 10 cm, n (%) / *Bulky disease ≥ 10 cm, n (%)*	12 (30%)
Ekstranodalna bolest, n (%) / *Extranodal disease, n (%)*	15 (34.8)
IPS, n (%) / *IPS, n (%)*	
0 – 2	19 (54.3%)
3 – 7	16 (45.7%)
Hb (g/l), srednja vrednost ± SD / *Hb (g/l), mean ± SD*	118.73 ± 22.90
WBC ($x10^9$/l), medijana (opseg) / *WBC ($x10^9$/l), median (range)*	9.7 (1.6 – 25.0)
Ly ($x10^9$/l), medijana (opseg) / *Ly ($x10^9$/l), median (range)*	1.12 (0.14 – 4.18)
PLT ($x10^9$/l), srednja vrednost ± SD / *PLT ($x10^9$/l), mean ± SD*	348.250 ± 125.662
ESR (mm u prvom satu), medijana (opseg) / *ESR (mm in the 1st hour), median (range)*	59 (14 – 120)
CRP (mg/l), medijana (opseg) / *CRP (mg/l), median (range)*	56.35 (5.6 – 361.7)

UkHL – uznapredovali klasični Hočkinov limfom (engl. *advanced stage classical Hodgkin lymphoma – AscHL*); *EORTC/LYSA* - Evropska organizacija za istraživanje i lečenje raka, engl. *European Organisation for Research and Treatment of Cancer – EORTC*/Asocijacija za istraživanje limfoma, engl. *Lymphoma Study Association* – LYSA; IPS – međunarodni prognostički skor; engl. International Prognostic Score; Hb – hemoglobin; SD – standardna devijacija; *WBC* – bela krvna zrnca, engl. *white blood cells*; Ly – limfociti, engl. lymphocytes; PLT – trombociti, engl. *platelets*; ESR – sedimentacija eritrocita, engl. *erythrocyte sedimentation rate*; CRP – C-reaktivni protein

AScHL – advanced stage classical Hodgkin lymphoma; EORTC/LYSA – European Organisation for Research and Treatment of Cancer/Lymphoma Study Association; IPS – International Prognostic Score; Hb – hemoglobin; SD – standard deviation; WBC – white blood cells; Ly – lymphocytes; PLT – platelets; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein

klasifikovano u grupu onih u intermedijarnom stadijumu, dok je 42 (85,7%) pacijenta klasifikovano u grupu onih koji su u uznapredovalom stadijumu (engl. *advance stage – AS*) bolesti. Prema En Arbor klasifikaciji, sedam (14,3%) pacijenata je bilo u II stadijumu, 26 (53%) pacijenata u III stadijumu, a 16 (32,7%) pacijenata je bilo u IV stadijumu bolesti. Trideset osmoro (77,6%) pacijenata je imalo B simptome, 58% je pokazalo prisustvo velike tumorske mase (engl. *bulky tumor mass/ bulky disease*) dimenzija ≥ 7 cm, dok je 30% pacijenata imalo veliku tumorsku masu dimenzija ≥ 10 cm. Više od 90% slučajeva velike tumorske mase je bilo locirano u medijastinumu. Petnaest (34,8%) pacijenata je imalo

90% of cases of a bulky mass were mediastinal. Fifteen (34.8%) patients presented with extranodal disease (END), of whom 1/3 had two extranodal localizations. Fifteen out of 42 patients (35.7%) exhibited spleen involvement. A low International Prognostic Score (IPS) was calculated in 19/35 (54.3%) patients, and a high IPS was found in 16/35 (45.7%) patients. The basic clinical and laboratory parameters are summarized in Table 1.

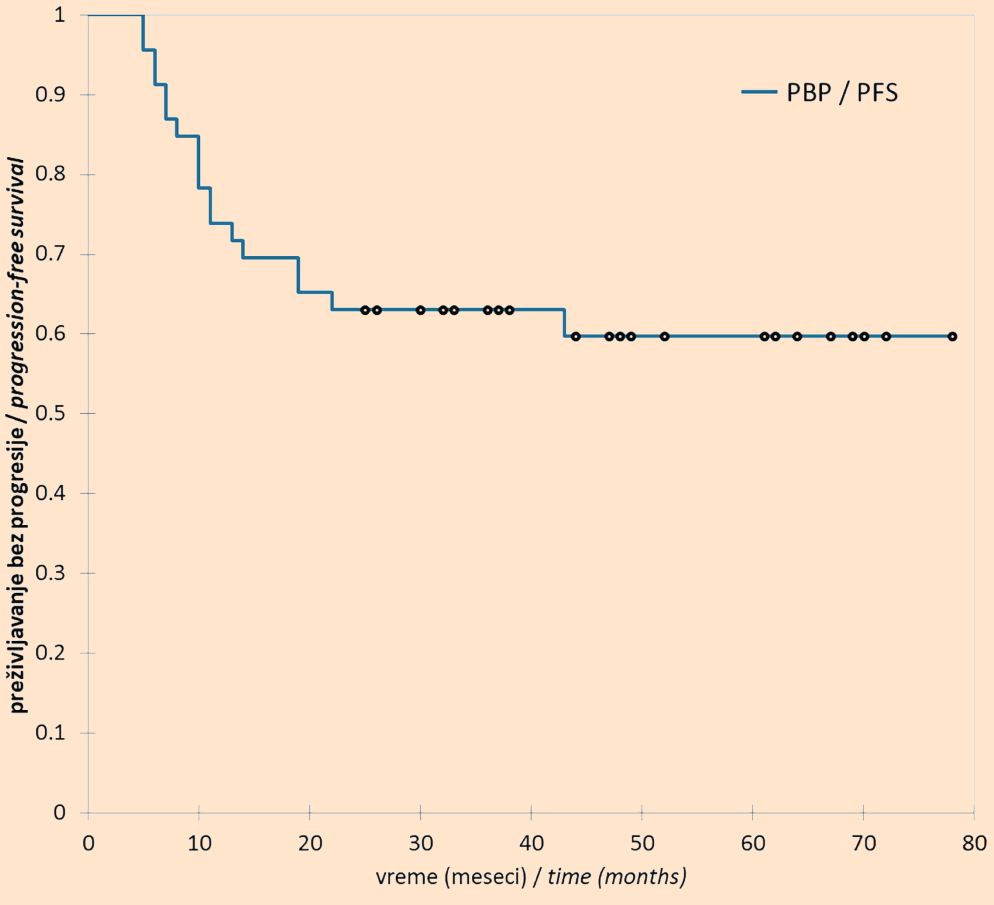
First-line treatment and outcomes

All patients received upfront ABVD treatment. Interim PET/CT was done in 12 patients with modification of further treatment intensity in six patients: three pa-

ekstranodalnu bolest (engl. *extranodal disease – END*), od kojih je 1/3 imala dve ekstranodalne lokalizacije. Petnaest od 42 (35,7%) pacijenta je pokazalo zahvaćenost slezine. Nizak međunarodni prognostički skor (engl. *International Prognostic Score – IPS*) izračunat je kod 19/35 (54,3%) pacijenata, dok je visok *IPS* utvrđen kod 16/35 (45,7%) pacijenata. Sažeti prikaz osnovnih kliničkih i laboratorijskih parametara dat je u Tabeli 1.

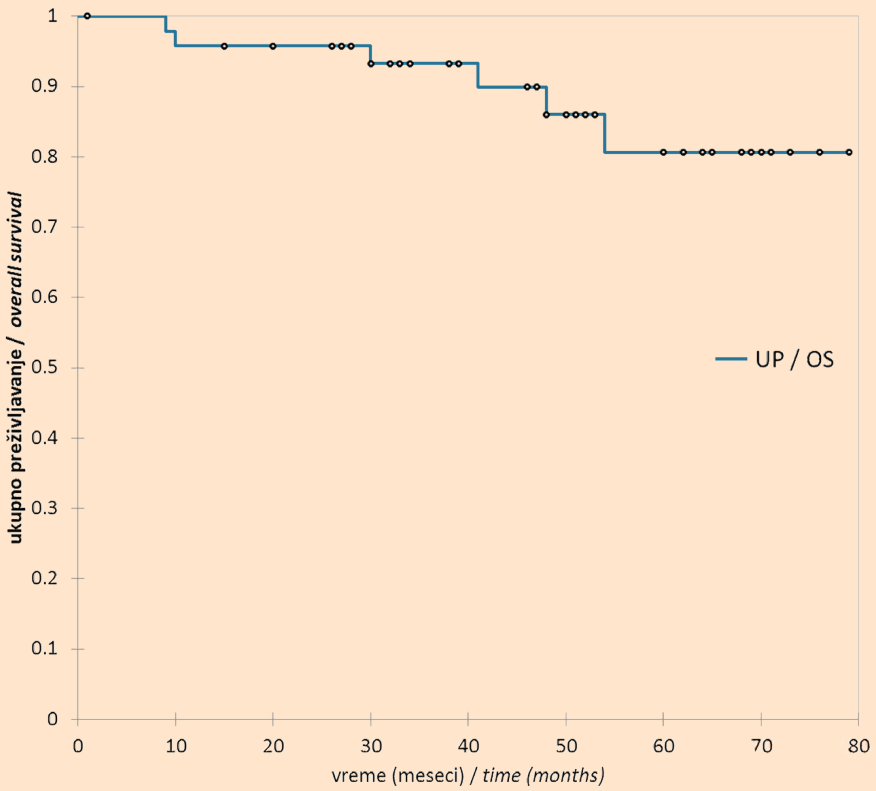
Prva terapijska linija i ishodi lečenja

Svi pacijenti su primili *ABVD* indukcionu terapiju. Kod 12 pacijenata je urađena/učinjena rana procena PET/CT pregledom sa modifikacijom daljeg intenziteta lečenja kod šest pacijenata: tri pacijenta su prešla na *BEACOPPesc*, dok je kod tri pacijenta bleomicin izostavljen i lečenje je nastavljeno *AVD*-om. Sveukupno gledano, medijana broja ciklusa primenjenih u prvoj terapijskoj liniji iznosila je šest ciklusa hemoterapije (opseg: 3 – 8). Deset od 45 (22%) pacijenata je podvrgnuto adjuvantnoj terapiji zračenjem. Ukupni odgovor je potvrđen u 72,3% slučajeva (potpuni odgovor (engl. *complete response – CR*) 61,7%; delimični odgovor (engl. *partial response – PR*) 10,6%), dok je preostalih 27,7%, odnotients switched to BEACOPPesc, while in three patients bleomycin was discontinued and treatment was continued with AVD. Overall, patients received a median of six cycles of chemotherapy (range: 3 – 8) as first-line treatment. Ten out of 45 (22%) patients underwent adjuvant radiation therapy. Overall response was confirmed in 72.3% of the cases (complete response (CR) 61.7%; partial response (PR) 10.6%), while the remaining 27.7%, i.e., 13 patients had primary refractory disease. Additionally, 5 (10.6%) patients relapsed after a median of 19 months (range: 8 – 33). No statistically significant differences in response to first-line treatment regarding gender, age (cut-off value 50 years), Ann Arbor and EORTC/LYSA stage, presence of B symptoms, presence of END, bulky disease (≥ 7 cm), erythrocyte sedimentation rate (ESR) ≥ 50 mm in the first hour, risk group according to IPS, and administered RT were observed. Median PFS (Figure 1) and OS (Figure 2) for the whole cohort were not reached, while the mean PFS and OS were 51.991 months (95% CI 42.290 – 61.692) and 71.017 months (95% CI 64.558 – 77.475), respectively. On the other hand, the four-year PFS was 61%, and the four-year OS was 89%. Patients with ESR



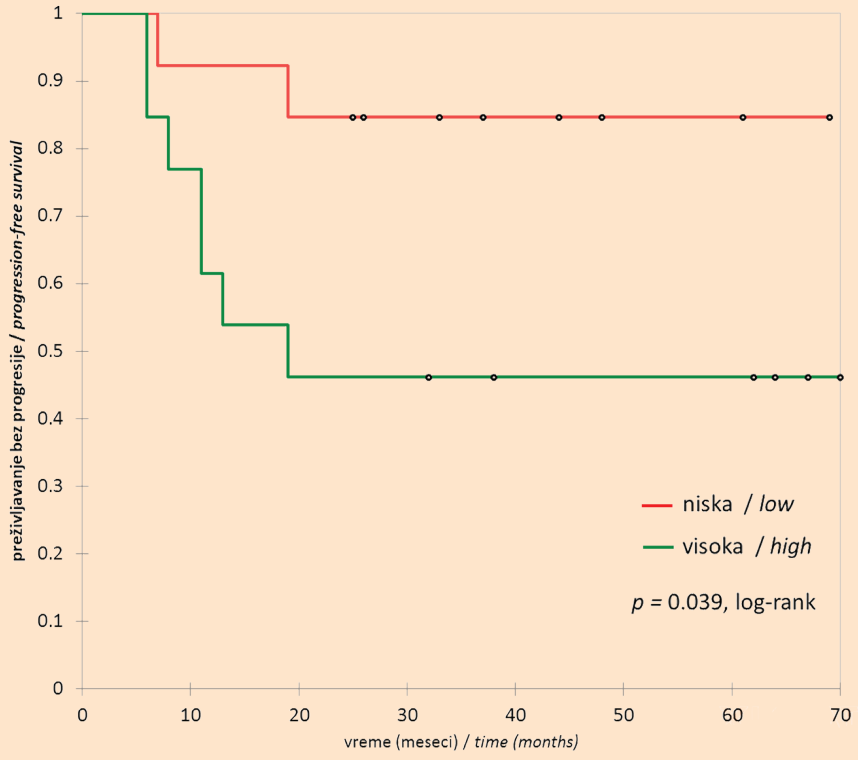
Slika 1. Preživljavanje bez progresije u celoj kohorti
Medijana PBP-a nije dostignuta; srednja vrednost = 51,991 mesec; 95% CI 42,290 – 61,692 meseca; četvorogodišnje PBP iznosilo je 61%

Figure 1. Progression-free survival for the whole cohort
Median PFS was not reached; mean = 51.991 months; 95% CI 42.290 – 61.692 months; four-year PFS was 61%.



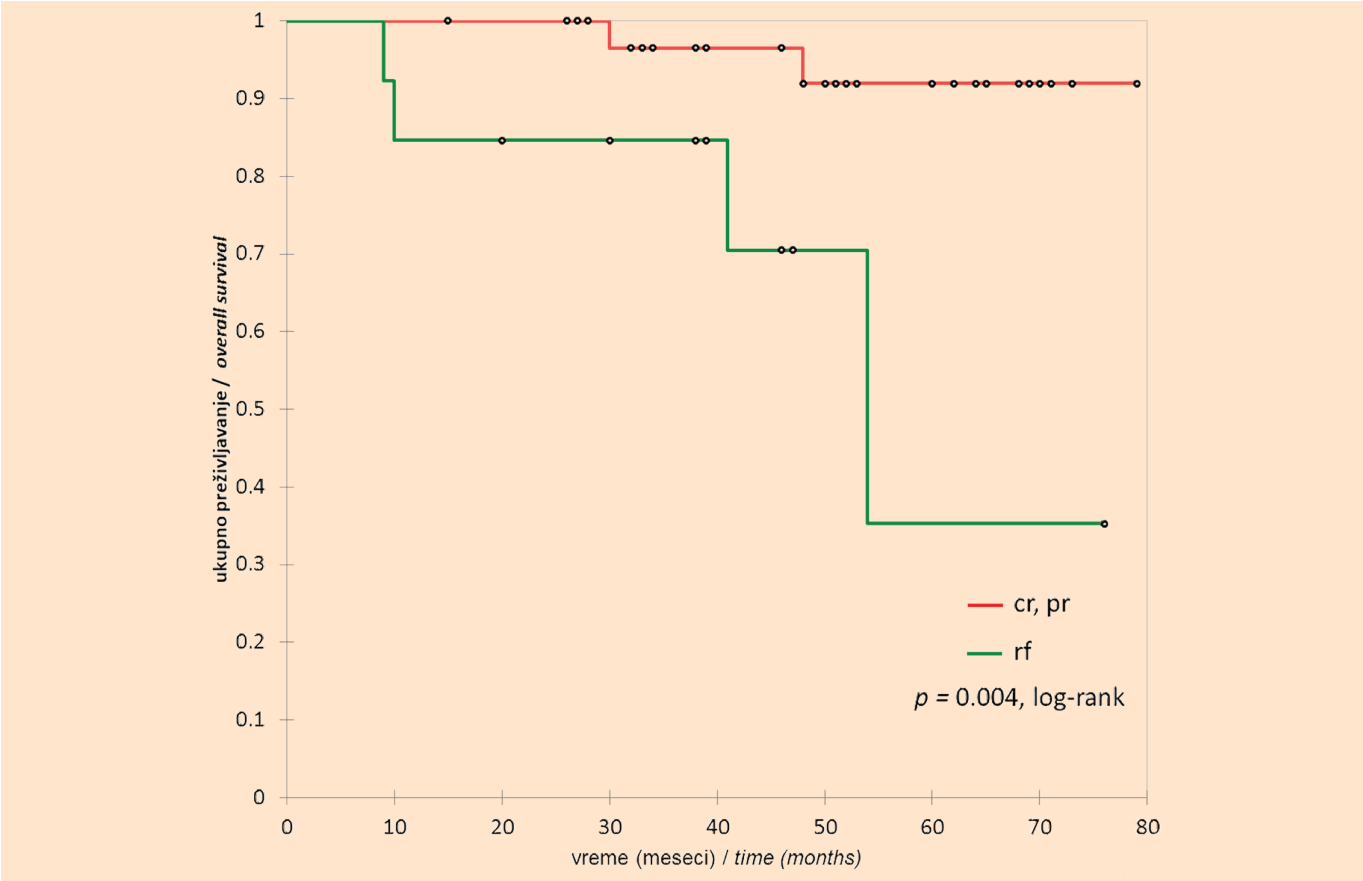
Slika 2. Ukupno preživljavanje u celoj kohorti
Medijana UP-a nije dostignuta; srednja vrednost = 71,017 meseci; 95% CI 64,558 – 77,475 meseci; četvorogodišnje UP je bilo 89%

Figure 2. Overall survival for the whole cohort
Median OS was not reached; mean = 71.017 months; 95% CI 64.558 – 77.475 months; four-year OS was 89%



Slika 3. Sedimentacija eritrocita i preživljavanje bez progresije
Niska (*ESR* < 50 mm u prvom satu): medijana nije dostignuta; srednja vrednost = 60,385 meseci; 95% CI 44,747 – 76,022 meseca
Visoka (*ESR* ≥ 50 mm u prvom satu): medijana = 19 meseci; 95% CI nije utvrđen; *p* = 0,039, log-rank test

Figure 3. Erythrocyte sedimentation rate and progression-free survival
Low (ESR < 50 mm in the 1st hour): median not reached; mean = 60.385 months; 95% CI 44.747 – 76.022 months
High (ESR ≥ 50 mm in the 1st hour): median = 19 months; 95% CI not determined; *p* = 0.039, log-rank test

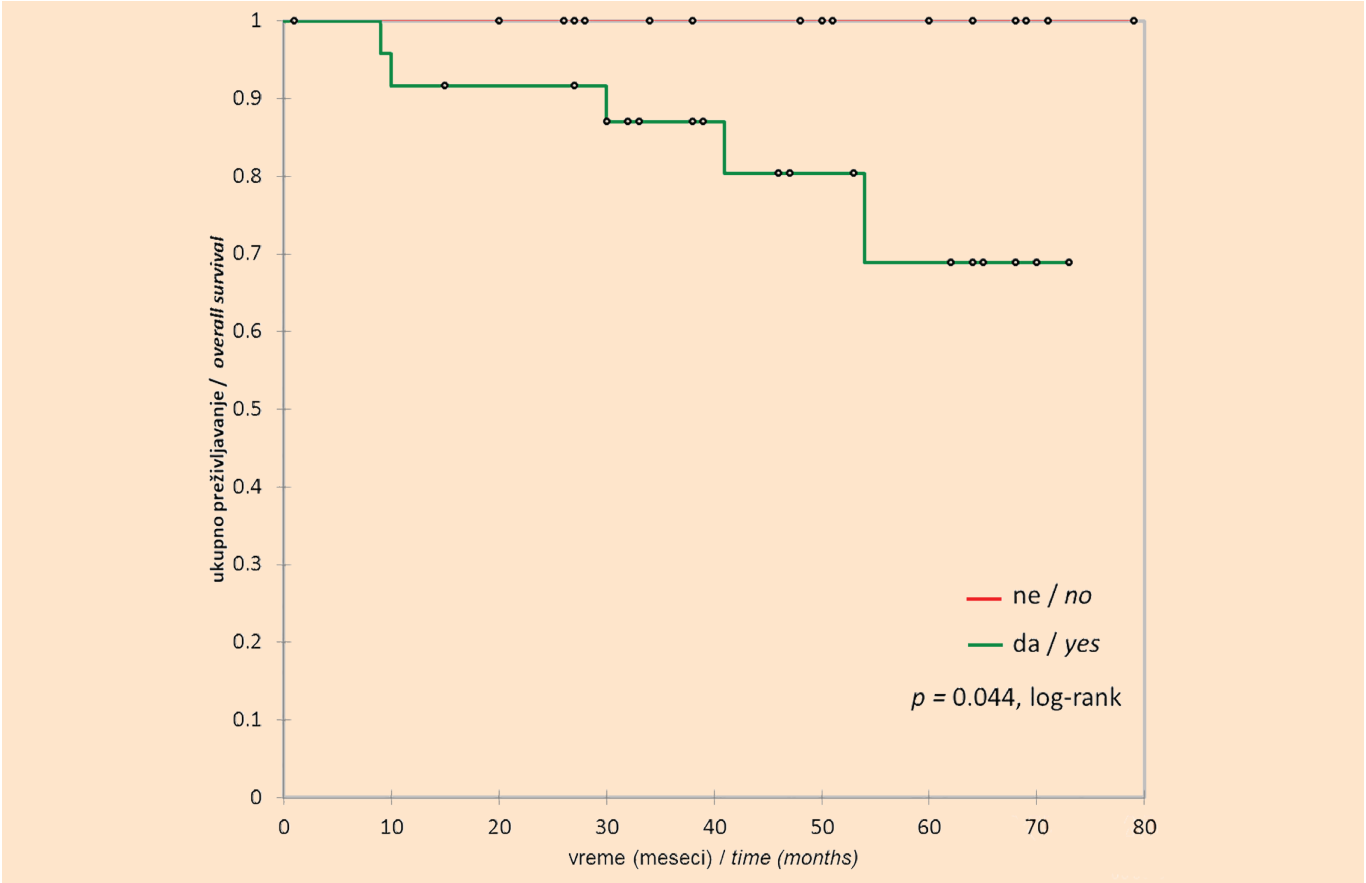


Slika 4. Odgovor na prvu terapijsku liniju i ukupno preživljavanje
Pacijenti koji su dostigli *cr/pr:* medijana nije dostignuta; srednja vrednost = 75,885 meseci; 95% CI 69,987 – 81,783 meseca
Pacijenti sa refraktornom bolešću (rf): medijana = 54 meseca; 95% CI 35,150 – 72,850 meseci; $p = 0{,}004$, log-rank test
cr – kompletni odgovor (engl. *complete response*); pr – parcijalni odgovor (engl. *partial response*); rf – refraktorna bolest

Figure 4. Response to first-line treatment and overall survival
Patients who achieved cr/pr: median not reached; mean = 75.885 months; 95% CI 69.987 – 81.783 months
Patients with refractory disease (rf): median = 54 months; 95% CI 35.150 – 72.850 months; $p = 0.004$, log-rank test
cr – complete response; pr – partial response; rf – refractory disease

sno 13 pacijenata, imalo primarno refraktornu bolest. Nadalje, pet (10,6%) pacijenata je imalo relaps nakon medijane od 19 meseci (opseg: 8 – 33). Nema statistički značajnih razlika u odgovoru na prvu terapijsku liniju u odnosu na pol, starost (granična vrednost 50 godina), En Arbor i *EORTC/LYSA* stadijum, prisustvo B simptoma, prisustvo ekstranodalne bolesti, prisustvo velike tumorske mase (≥ 7 cm), sedimentaciju eritrocita (engl. *erythrocyte sedimentation rate – ESR*) ≥ 50 mm u prvom satu, rizičnu grupa prema *IPS*-u i primenjenu radioterapiju. Medijane PBP-a (Slika 1) i UP-a (Slika 2) za celu kohortu nisu dostignute, dok su srednje vrednosti PBP-a i UP-a bile 51,991 mesec (95% *CI* 42,290 – 61,692), odnosno 71,017 meseci (95% *CI* 64,558 – 77,475). Sa druge strane, četvorogodišnje PBP je bilo 61%, a četvorogodišnje UP je bilo 89%. Pacijenti sa *ESR* ≥ 50 mm u prvom satu su imali kraće PBP nakon *ABVD*, u poređenju sa pacijentima sa *ESR* < 50 mm u prvom satu (medijana PBP = 19 meseci naspram nedostignuta; $p = 0{,}039$, log-rank test), (Slika 3). Pol, starost (granična vrednost 50 godina), *EORTC/LYSA* stadijum (intermedijarni na-

≥ 50 mm in the first hour had shorter PFS after ABVD, as compared to the patients with ESR < 50 mm in the first hour (median PFS = 19 months vs. not reached, respectively; $p = 0.039$, log-rank test) (Figure 3). Gender, age (cut-off value 50 years), EORTC/LYSA stage (intermediate vs. advanced), presence of B symptoms, presence of END, bulky disease, IPS (0 – 2 vs. 3 – 7), and administered RT were not significant regarding PFS. Patients who were refractory to first-line treatment had significantly shorter OS, as compared to the patients who achieved CR/PR (median OS = 54 months vs. not reached; $p = 0.004$, log-rank test), (Figure 4). Additionally, patients who presented with a large tumor mass (bulky mass ≥ 7 cm) experienced significantly decreased OS, as compared to the patients without a bulky mass ($p = 0.044$, log-rank test), (Figure 5). OS did not differ significantly in relation to gender, age (cut-off value 50 years), EORTC/LYSA stage, presence of B symptoms, END at presentation, ESR, IPS (0 - 2 vs. 3 - 7), and RT within first-line treatment.



Slika 5. Prisustvo velike tumorske mase i ukupno preživljavanje
Pacijenti bez prisustva velikih tumorskih masa (Ne): srednja vrednost i medijana nisu utvrđene (bez događaja)
Pacijenti sa velikom tumorskom masom (≥ 7 cm), (Da): medijana nije dostignuta; srednja vrednost = 61,412 meseca; 95% CI 51,435 – 71,389 meseci (značajno kraće UP); $p = 0{,}044$, log-rank test

Figure 5. Bulky disease and overall survival
Patients without bulky disease (No): mean and median not determined (no events)
Patients with bulky mass ≥ 7 cm (Yes): median not reached; mean = 61.412 months; 95% CI 51.435 – 71.389 months (significantly shorter OS); $p = 0.044$, log-rank test

spram uznapredovalog), prisustvo B simptoma, prisustvo ekstranodalne bolesti, prisustvo velike tumorske mase, *IPS* (0 – 2 naspram 3 – 7) i primenjena RT nisu bili značajni za PBP. Pacijenti koji su bili refraktorni na prvu terapijsku liniju su imali značajno kraće UP u poređenju sa pacijentima koji su dostigli *CR/PR* (medijana UP = 54 meseca naspram nedostignuta; $p = 0{,}004$, log-rank test), (Slika 4). Pored toga, pacijenti koji su imali veliku tumorsku masu (≥ 7 cm) su imali značajno smanjeno UP, u poređenju sa pacijentima bez velike tumorske mase ($p = 0{,}044$, log-rank test), (Slika 5). UP se nije značajno razlikovalo u odnosu na pol, starost (granična vrednost 50 godina), *EORTC/LYSA* stadijum, prisustvo B simptoma, prisustvo ekstranodalne bolesti, *ESR*, *IPS* (0 – 2 naspram 3 – 7) i RT u okviru prve terapijske linije.

Ishod kod pacijenata sa relapsiranom/refraktornom bolešću

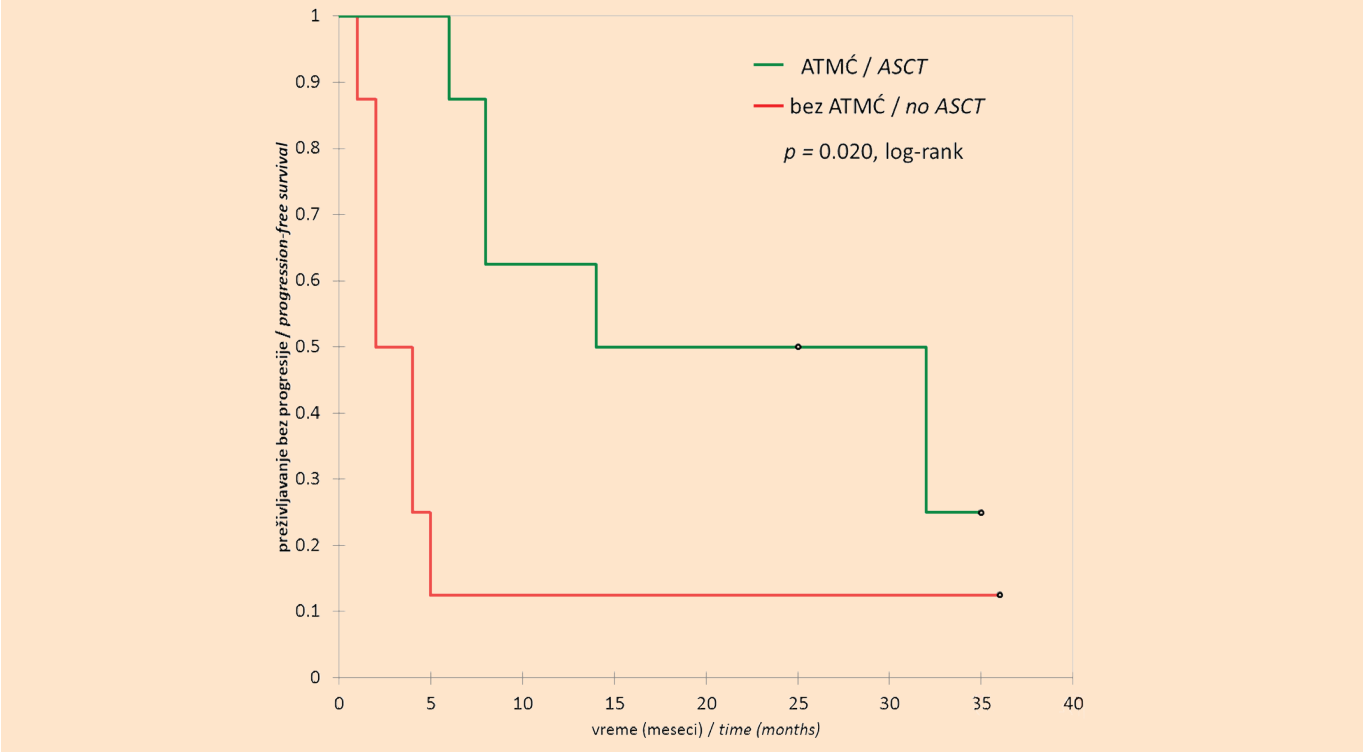
Među 18 bolesnika sa relapsiranom/refraktornom bolešću (od kojih je 13 pacijenata imalo primarni refraktorni HL, a pet je relapsiralo), 17 pacijenata je lečeno

The outcome of relapsed/refractory patients

Among the 18 R/R patients (of whom 13 patients had primary refractory HL and five relapsed), 17 were treated with salvage ChT ± ASCT following HDC. Patients treated with HDC + ASCT after salvage ChT had a significantly longer PFS than those without ASCT ($p = 0.020$, log-rank test), (Figure 6), however, with no confirmed significant advantage in OS. Fourteen patients with R/R disease received BV in monotherapy, of whom three were consolidated after ASCT (all in sustained CR after BV), while 11 patients were treated with BV following a median of three lines of therapy (range: 2 – 4). Of the eleven patients, only one patient achieved CR, one was still on BV at the latest follow-up, while the other nine patients were refractory. The median number of administered BV cycles was 12.

DISCUSSION

Currently, there are various recommendations for the upfront treatment of AScHL [5,24,25]. In keeping with the results of the recent major clinical trials and sub-



Slika 6. Autologna transplantacija matičnih ćelija hematopoeze i PBP kod R/R uznapredovalog Hočkinovog limfoma
ATMĆH: medijana = 14 meseci; 95% CI 8,174 – 36,174 meseci
Bez ATMĆ: medijana = 2 meseca; 95% CI 0,337 – 3,663 meseci
Pacijenti koji su primili *HDC* + ATMĆ nakon hemioterapije spašavanja imali su značajno duže PBP od pacijenata bez ATMĆ ($p = 0,020$, log-rank test).

Figure 6. Autologous stem cell transplantation and PFS in R/R advanced Hodgkin lymphoma
ASCT: median = 14 months; 95% CI 8.174 – 36.174 months
No ASCT: median = 2 months; 95% CI 0.337 – 3.663 months
Patients who received HDC + ASCT after salvage ChT experienced significantly longer PFS than those without ASCT ($p = 0.020$, log-rank test).

hemioterapijom spašavanja ± ATMĆ nakon visokodozne hemioterapije (*HDC*). Pacijenti lečeni pomoću *HDC* + ATMĆ nakon hemioterapije spašavanja su imali značajno duže PBP od onih kod kojih nije primenjena ATMĆ ($p = 0,020$, log-rank test), (Slika 6), međutim, bez potvrđene značajne prednosti za UP. Četrnaest pacijenata sa R/R bolešću je primilo BV u monoterapiji, od kojih je tri konsolidovano nakon ATMĆ (svi sa dugotrajnim *CR*-om nakon BV), dok je 11 pacijenata lečeno BV-om nakon medijane od tri terapijske linije (opseg: 2 – 4). Od tih 11 pacijenata, samo jedan pacijent je postigao *CR*, jedan je još uvek bio na BV-u na poslednjoj kontroli, dok je ostalih devet pacijenata bilo refraktorno. Medijana primenjenih ciklusa BV-a bila je 12.

DISKUSIJA

Trenutno postoje različite preporuke za indukciono lečenje UkHL-a [5,24,25]. U skladu sa rezultatima nedavnih velikih kliničkih ispitivanja i sledstveno ažuriranim relevantnim smernicama za lečenje, kliničari mogu da biraju između konvencionalnih hemioterapijskih opcija (*ABVD* ili *BEACOPPesc*) i kombinacije BV i hemioterapije [15,26]. Ključni cilj lečenja je postizanje maksimalne terapeutske koristi uz izbegavanje akutnih i kasnih

sequently updated relevant treatment guidelines, clinicians can choose between conventional ChT options (ABVD or BEACOPPesc) and a combination of BV and ChT [15,26]. The key objective of the treatment is to get maximal therapeutic benefits while avoiding acute and late side effects that could jeopardize the patients' quality of life and survival.

Lower rates of remission in our study than in other real-world studies can be explained by the fact that a significant number of patients from the cohort were diagnosed in 2019 and 2020 and were treated during the coronavirus disease of 2019 (COVID-19) pandemic with probable treatment delays and subsequent negative impact on outcomes [20,22,27]. However, this is only a speculation as we did not collect information about COVID-19 and treatment delay from the records of the patients in our cohort. Additionally, although most refractory patients were eventually treated at our institution with completely accessible medical records, a number of patients who achieved adequate disease control were subsequently followed up by hematologists in their local area, which removed them from the reach of our institution, making such patients not fully eligible for this study.

After a four-year follow-up of the patients in our cohort, PFS was 61%, and OS was 89%. It is notewor-

neželjenih efekata koji bi mogli da ugroze kvalitet života i preživljavanje pacijenata.

Niže stope remisije u našoj studiji nego u drugim studijama iz svakodnevne kliničke prakse mogu se objasniti činjenicom da je značajan broj pacijenata iz ove kohorte dijagnostikovan 2019. i 2020. godine. Ovi pacijenti su lečeni tokom pandemije koronavirusne bolesti 2019 (KOVID-19), te je kod njih verovatno došlo do odlaganja lečenja i posledičnog negativnog uticaja na ishode [20,22,27]. Međutim, ovo je samo naša pretpostavka jer nismo prikupili informacije o KOVID-19 obolјenju i kašnjenju u lečenju iz dokumentacije pacijenata u našoj kohorti. Osim toga, iako je većina refraktornih pacijenata na kraju lečena u našoj ustanovi sa potpuno dostupnom medicinskom dokumentacijom, jedan broj pacijenata koji je postigao adekvatnu kontrolu bolesti, nakon toga je praćen od strane hematologa na njihovoj teritoriji stanovanja, što ih je učinilo nedostupnim za praćenje od strane naše ustanove, a samim tim oni nisu u potpunosti ispunili kriterijume za ovu studiju.

Nakon četvorogodišnjeg praćenja pacijenata u našoj kohorti, PBP je bilo 61% dok je UP bilo 89%. Važno je napomenuti da je UP bilo duže u našoj studiji nego u prethodnoj velikoj kohortnoj studiji iz naše ustanove, koju su sproveli Anđelić i saradnici (četvorogodišnje UP od 89% naspram petogodišnjeg UP od 76%), najverovatnije zbog dostupnosti novih terapijskih modaliteta za lečenje pacijenata sa R/R kHL-om u Srbiji poslednjih godina [22]. S druge strane, ukupno preživljavanje u našoj studiji je bilo uporedivo sa ukupnim preživljavanjem u većini prospektivnih kliničkih ispitivanja koja su se bavila *ABVD* protokolom u UkHL-u [28–32].

Kada su u pitanju faktori rizika, u našoj kohorti je utvrđeno da je samo povišena sedimentacija eritrocita povezana sa PBP-om, dok su pacijenti sa velikom tumorskom masom (≥ 7) cm i pacijenti koji su bili primarno refraktorni na prvu terapijsku liniju pokazali značajno kraće UP. U retrospektivnoj studiji koju su sproveli Avigdor i saradnici, a koja opisuje ishod za 221 pacijenta sa UkHL-om lečenog *ABVD* protokolom u prvoj terapijskoj liniji, starosti 60+ godina, visok *IPS* i pozitivan rani PET/*CT* bili su povezani sa kraćim PBP-om [27]. U drugoj studiji iz svakodnevne kliničke prakse, koju su sproveli Anđelić i saradnici u našoj bolnici, viši *IPS* i postojanje više od jedne ekstranodalne lokalizacije bili su povezani sa lošijim PBP-om, dok su visoki *IPS*, *ESR* > 50 mm/h, > 1 ekstranodalna lokalizacija i prisustvo velike tumorske mase bili u korelaciji sa značajno kraćim UP-om [22]. U našoj studiji, samo su povišena sedimentacija, prisustvo velike tumorske mase i primarna refraktornost pokazali prognostički značaj u prvoj terapijskoj liniji, najverovatnije zbog malog broja ispitanika, za razliku od dve gore pomenute studije koje su uključivale

thy that OS was longer in our study than in a previous large cohort study from our institution by Andjelic et al., (four-year OS 89% vs. five-year OS 76%), most probably because of the availability of novel treatment options for R/R cHL patients in Serbia in recent years [22]. On the other hand, OS in our study was comparable to OS in most of the prospective clinical trials dealing with ABVD in AScHL [28–32].

Regarding the risk factors, in our cohort, only elevated ESR was found to be associated with PFS, while patients with bulky disease ≥ 7 cm and patients that were primarily refractory to the first treatment line exhibited significantly shorter OS. In a retrospective study conducted by Avigdor et al., which reports on the outcome of 221 AScHL patients treated with ABVD as first-line therapy and aged 60+ years, a high IPS and positive early PET/CT were associated with a shorter PFS [27]. In another real-world study by Andjelic et al., conducted at our hospital, a higher IPS and more than one extranodal localization were associated with poorer PFS, while high IPS, ESR > 50 mm/h, > 1 extranodal site, and bulky disease correlated with significantly shorter OS [22]. In our study, only elevated ESR, bulky disease, and primary refractoriness showed prognostic significance in first-line treatment, most probably due to the small study sample, as opposed to the other two abovementioned studies which included 221 (Avigdor et al.) and 314 (Andjelic et al.) AScHL patients treated with ABVD, respectively [22,27].

Up to 30% of patients in clinical trials are refractory to combined first-line ChT, while one retrospective study from the United States, which included 167 patients with AScHL, confirmed that 55% of patients were treated with second-line therapy, which makes this number significantly higher in the real-world setting [21]. Our data show that 27.7% of patients were initially refractory to ABVD while an additional 10% relapsed after a median period of 19 months, implying that a certain number of AS patients treated with ABVD will eventually need further treatment. Autologous stem cell transplantation following salvage ChT and HDC remains the standard of care in the R/R setting with a potential for 50% of R/R patients to be cured [16]. The addition of novel therapeutic options, such as BV or checkpoint inhibitors (nivolumab or pembrolizumab) to salvage protocols prior to ASCT, dramatically improves posttransplant survival [7]. Our study confirmed the significance of ASCT in consolidation after salvage ChT in R/R AScHL.

As mentioned above, novel therapies, including BV and anti-PD1 antibodies, have significantly changed the landscape of the contemporary treatment of cHL. Brentuximab vedotin was initially approved in 2011

221 (Avigdor i sar.) i 314 (Anđelić i sar.) pacijenata sa UkHL-om lečenih *ABVD* protokolom [22,27].

Do 30% pacijenata u kliničkim ispitivanjima je refraktorno na kombinovanu hemioterapiju u prvoj terapijskoj liniji, dok je u jednoj retrospektivnoj studiji iz Sjedinjenih Američkih Država, koja je obuhvatila 167 pacijenata sa UkHL-om, potvrđeno da je 55% pacijenata lečeno u drugoj terapijskoj liniji, što čini ovaj broj je znatno većim u svakodnevnoj kliničkoj praksi [21]. Naši podaci pokazuju da je 27,7% pacijenata u početku bilo refraktorno na *ABVD*, dok je dodatnih 10% relapsiralo nakon medijane od 19 meseci, što ukazuje na to da će određenom broju pacijenata sa UkHL-om koji su lečeni *ABVD* protokolom na kraju biti potrebna terapija spašavanja. Visokodozna hemioterapija sa autolognom transplantacijom matičnih ćelija nakon hemioterapije spašavanja ostaje standard lečenja kod R/R pacijenata sa potencijalom da 50% R/R bolesnika bude izlečeno [16]. Dodavanje novih terapijskih opcija, kao što su BV ili inhibitori imunskih kontrolnih tačaka (nivolumab ili pembrolizumab) protokolima spašavanja pre ATMĆ, drastično poboljšava preživljavanje nakon transplantacije [7]. Naša studija je potvrdila značaj ATMĆ u konsolidaciji nakon hemioterapije spašavanja kod R/R UkHL-a.

Kao što je već navedeno, nove terapije, uključujući BV i anti-PD1 antitela, značajno su promenile situaciju u savremenom lečenju kHL-a. Brentuksimab vedotin je prvobitno odobren 2011. godine od strane američke Uprave za hranu i lekove (engl. *Food and Drug Administration*), za pacijente sa relapsom nakon ATMĆ ili za pacijente posle ≥ 2 linije lečenja koji ne ispunjavaju uslove za ATMĆ. Ključno ispitivanje *AETHERA* i iskustvo iz svakodnevne kliničke prakse su potvrdili korist od post-ATMĆ konsolidacije sa BV-om za pacijente visokog rizika, dok njegova upotreba kao monoterapija u kontekstu terapije spašavanja kod pacijenata koji su imali relaps nakon ATMĆ ili nisu ispunjavali kriterijume za ATMĆ, nije pokazala da ostvaruje dovoljnu dugoročnu kontrolu bolesti [17,18,33-35]. Rezultati naše studije po pitanju primene BV-a su u skladu sa ovim nalazima, međutim, mali uzorak (14 pacijenata u našoj kohorti je primilo BV) onemogućio je adekvatnu statističku analizu koja bi donela relevantne zaključke.

Naša studija ima nekoliko ograničenja:

1. Kohorta je premala da bi se napravila poređenja koja bi imala dovoljnu statističku snagu.
2. Ne postoje bezbednosni podaci o toksičnosti *ABVD* protokola tokom i posle terapije i njenom uticaju na ishod.
3. Nema podataka o KOVID-19 statusu onih pacijenata iz kohorte koji su lečeni tokom pandemije bolesti KOVID-19, te njegovom mogućem uticaju na odlaganje lečenja i posledičnim implikacijama na ishod.

by the US Food and Drug Administration, for patients relapsed after ASCT or for patients after ≥ 2 lines of treatment who are not eligible for ASCT. The pivotal AETHERA trial and real-world experience confirmed the benefit of post-ASCT consolidation with BV for high-risk patients, while its use as monotherapy in the salvage setting in patients who had relapsed after ASCT or were not eligible for ASCT did not show sufficient long-term disease control [17,18,33-35]. The results of our study concerning BV are in line with these findings, however, the small sample (14 patients in our cohort received BV) made it impossible to perform an adequate statistical analysis that would have yielded relevant conclusions.

There are several limitations to our study:

1. The cohort is too small to make comparisons that would have enough statistical power.
2. There are no safety data about the toxicity of ABVD during and after treatment and its impact on the outcome.
3. There are no data about the COVID-19 status of the patients from the cohort treated during the COVID-19 pandemic, its possible impact on delaying treatment, and consequent implications for the outcome.

CONCLUSION

In our cohort, patients with higher erythrocyte sedimentation levels had a shorter progression-free survival. Additionally, the presence of a bulky mass and primary refractory disease were associated with shorter overall survival. Patients with relapsed or refractory classical Hodgkin lymphoma showed a significantly better prognosis when they underwent consolidation therapy with autologous stem cell transplantation. Monotherapy with brentuximab vedotin was not beneficial outside the post-transplant consolidation setting. A significant number of advanced-stage classical Hodgkin lymphoma patients can not be cured with ABVD and need more intensive and/or novel therapeutic options in first-line treatment.

ABBREVIATIONS AND ACRONYMS

ABVD – doxorubicin, bleomycin, vinblastine, dacarbazine
AS – advanced-stage
ASCT – autologous stem cell transplantation
AVD – doxorubicin, vinblastine, dacarbasine
BEACOPPesc – bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, escalated
BV – brentuximab vedotin
cHL – classical Hodgkin lymphoma
ChT – chemotherapy

ZAKLJUČAK

U našoj kohorti, pacijenti sa višim vrednostima sedimentacije eritrocita imali su kraće preživljavanje bez progresije bolesti. Pored toga, prisustvo velike tumorske mase i primarna refraktorna bolest su bili povezani sa kraćim ukupnim preživljavanjem. Pacijenti sa relapsom ili refraktornim klasičnim Hočkinovim limfomom pokazali su značajno bolju prognozu kada su bili podvrgnuti konsolidacionoj terapiji sa autolognom transplantacijom matičnih ćelija. Monoterapija sa brentuksimab vedotinom nije bila uspešna van konsolidacije nakon transplantacije. Značajan broj pacijenata sa uznapredovalim klasičnim Hočkinovim limfomom ne može biti izlečen ABVD protokolom i iziskuje intenzivnije i/ili nove opcije lečenja u prvoj terapijskoj liniji.

SPISAK SKRAĆENICA

ABVD – doksorubicin, bleomicin, vinblastin i dakarbazin
AS – uznapredovali stadijum bolesti; engl. *advanced-stage*
ATMĆ – autologna transplantacija matičnih ćelija (engl. *autologous stem cell transplantation – ASCT*)
AVD – doksorubicin, vinblastin i dakarbazin
BEACOPPesc – eskalirani bleomicin, etopozid, doksorubicin, ciklofosfamid, vinkristin, prokarbazin i prednizon
BV – brentuksimab vedotin
kHL – klasični Hočkinov limfom (engl. *classical Hodgkin lymphoma - cHL*)
HT – hemioterapija
KOVID-19 – koronavirusna bolest 2019 (engl. *coronavirus disease of 2019 – COVID-19*)
CR – potpuni odgovor; engl. *complete response*
END – ekstranodalna bolest; engl. *extranodal disease*
EORTC/LYSA - Evropska organizacija za istraživanje i lečenje raka; engl. *European Organisation for Research and Treatment of Cancer – EORTC*/Asocijacija za istraživanje limfoma; engl. *Lymphoma Study Association – LYSA*
ESR –sedimentacija eritrocita; engl. *erythrocyte sedimentation rate*
GHSG – Nemačka studijska grupa za Hočkinov limfom; engl. *German Hodgkin Study Group*
HDC – visokodozna hemioterapija; engl. *high-dose chemotherapy*
IPS – međunarodni prognostički skor; engl. *International Prognostic Score*
UP – ukupno preživljavanje (engl. *overall survival – OS*)
PET/*CT* – pozitronska emisiona tomografija/kompjuterizovana tomografija; engl. *positron emission tomography/computed tomography*
PBP – preživljavanje bez progresije (engl. *progression-free survival – PFS*)
PR – parcijalni odgovor; engl. *partial response*
R/R – relapsiran-a/refraktoran-na (engl. *relapsed/refractory*)
RT – radioterapija
SD – standardna devijacija

Sukob interesa: Nije prijavljen.

COVID-19 – coronavirus disease of 2019
CR – complete response
END – extranodal disease
EORTC/LYSA - European Organisation for Research and Treatment of Cancer/Lymphoma Study Association
ESR – erythrocyte sedimentation rate
GHSG – German Hodgkin Study Group
HDC – high-dose chemotherapy
IPS – International Prognostic Score
OS – overall survival
PET/CT – positron emission tomography/computed tomography
PFS – progression-free survival
PR – partial response
R/R – relapsed/refractory
RT – radiotherapy
SD – standard deviation

Conflict of interest: None declared.

LITERATURA / *REFERENCES*

1. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022 Jul;36(7):1720-1748. doi: 10.1038/s41375-022-01620-2.
2. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022;140(11):1229-53. doi: 10.1182/blood.2022015851.
3. Ansell SM. Hodgkin lymphoma: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2022;97(11):1478-88. doi: 10.1002/ajh.26717.
4. Kanzler H, Kuppers R, Hansmann ML, Rajewsky K. Hodgkin and Reed-Sternberg cells in Hodgkin's disease represent the outgrowth of a dominant tumor clone derived from (crippled) germinal center B cells. J Exp Med. 1996;184(4):1495-505. doi: 10.1084/jem.184.4.1495.
5. Eichenauer DA, Aleman BMP, André M, Federico M, Hutchings M, Illidge T, et al.; ESMO Guidelines Committee. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv19-iv29. doi: 10.1093/annonc/mdy080.
6. Johnson PWM. Are we reaching the maximum cure rate for Hodgkin lymphoma? Hematol Oncol. 2023;41 Suppl 1:57-61. doi: 10.1002/hon.3140.
7. Burton C, Allen P, Herrera AF. Paradigm Shifts in Hodgkin Lymphoma Treatment: From Frontline Therapies to Relapsed Disease. Am Soc Clin Oncol Educ Book. 2024;44(3):e433502. doi: 10.1200/EDBK_433502.
8. Radford J, Longo DL. Second Cancers after Treatment for Hodgkin's Lymphoma--Continuing Cause for Concern. N Engl J Med. 2015;373(26):2572-3. doi: 10.1056/NEJMe1511947.
9. Engert A, Diehl V, Franklin J, Lohri A, Dorken B, Ludwig WD, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol. 2009;27(27):4548-54. doi: 10.1200/JCO.2008.19.8820.
10. de Vries S, Schaapveld M, Janus CPM, Daniels LA, Petersen EJ, van der Maazen RWM, et al. Long-Term Cause-Specific Mortality in Hodgkin Lymphoma Patients. J Natl Cancer Inst. 2021;113(6):760-9. doi: 10.1093/jnci/djaa194.
11. Johnson P, Federico M, Kirkwood A, Fossa A, Berkahn L, Carella A, et al. Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma. N Engl J Med. 2016;374(25):2419-29. doi: 10.1056/NEJMoa1510093.
12. Borchmann P, Goergen H, Kobe C, Lohri A, Greil R, Eichenauer DA, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. Lancet. 2017;390(10114):2790-802. doi: 10.1016/S0140-6736(17)32134-7.
13. Zinzani PL, Broccoli A, Gioia DM, Castagnoli A, Ciccone G, Evangelista A, et al. Interim Positron Emission Tomography Response-Adapted Therapy in Advanced-Stage Hodgkin Lymphoma: Final Results of the Phase II Part of the HD0801 Study. J Clin Oncol. 2016;34(12):1376-85. doi: 10.1200/JCO.2015.63.0699.
14. Ansell SM, Radford J, Connors JM, Długosz-Danecka M, Kim WS, Gallamini A, et al.; ECHELON-1 Study Group. Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma. N Engl J Med. 2022 Jul 28;387(4):310-320. doi: 10.1056/NEJMoa2206125.
15. Borchmann P, Ferdinandus J, Schneider G, Moccia A, Greil R, Hertzberg M, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. Lancet. 2024;404(10450):341-52. doi: 10.1016/S0140-6736(24)01315-1.
16. Moskowitz AJ, Perales MA, Kewalramani T, Yahalom J, Castro-Malaspina H, Zhang Z, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol. 2009;146(2):158-63. doi: 10.1111/j.1365-2141.2009.07727.x.
17. Angelopoulou MK, Vassilakopoulos TP, Batsis I, Sakellari I, Gkirkas K, Pappa V, et al. Brentuximab vedotin in relapsed/refractory Hodgkin lymphoma. The Hellenic experience. Hematol Oncol. 2018;36(1):174-81. doi: 10.1002/hon.2383.
18. Ozbalak M, Salihoglu A, Soysal T, Karadogan I, Paydas S, Ozdemir E, et al. Long-term results of brentuximab vedotin in relapsed and refractory Hodgkin lymphoma: multi-center real-life experience. Ann Hematol. 2020;99(2):301-7. doi: 10.1007/s00277-019-03899-1.
19. Wen Q, Ge J, Lei Y, Zhang Y, Kong X, Wang W, et al. Real-world evidence of ABVD-like regimens compared with ABVD in classical Hodgkin lymphoma: a 10-year study from China. J Cancer Res Clin Oncol. 2023;149(7):3989-4003. doi: 10.1007/s00432-022-04321-6.
20. Russell J, Collins A, Fowler A, Karanth M, Saha C, Docherty S, et al. Advanced Hodgkin lymphoma in the East of England: a 10-year comparative analysis of outcomes for real-world patients treated with ABVD or escalated-BEACOPP, aged less than 60 years, compared with 5-year extended follow-up from the RATHL trial. Ann Hematol. 2021;100(4):1049-58. doi: 10.1007/s00277-021-04460-9.
21. Winter A, Liu N, Surinach A, Fanale M, Yu KS, Narkhede M. Real-World Patient Characteristics, Treatment Patterns, and Outcomes for Patients With Stage III or IV Classic Hodgkin Lymphoma Treated With Frontline ABVD: A Retrospective Database Review in the United States. Clin Lymphoma Myeloma Leuk. 2023;23(7):527-34. doi: 10.1016/j.clml.2023.03.015.
22. Andjelic B, Antic D, Jakovic L, Todorovic M, Bogdanovic A, Djurasinovic V, et al. A single institution experience on 314 newly diagnosed advanced Hodgkin lymphoma patients: the role of ABVD in daily practice. Eur J Haematol. 2014;93(5):392-9. doi: 10.1111/ejh.12364.
23. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68. doi: 10.1200/JCO.2013.54.8800.
24. National Comprehensive Cancer Network. Hodgkin Lymphoma (Version 3.2024). [Internet]. [Pristupljeno: 28. jul, 2024.]. Dostupno: https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf
25. Hodgkin Lymphoma. Treatment. 2008 - 2024 German Hodgkin Study Group. [Internet]. Dostupno: https://en.ghsg.org/treatment
26. Straus DJ, Dlugosz-Danecka M, Connors JM, Alekseev S, Illes A, Picardi M, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. Lancet Haematol. 2021;8(6):e410-e21. doi: 10.1016/S2352-3026(22)00009-6.
27. Avigdor A, Trinchese F, Gavini F, Bent-Ennakhil N, Dalal M, Zomas A, et al. First-line treatment of stage IIB to stage IV classical Hodgkin lymphoma in Italy, Israel, and Spain: Patient characteristics, treatment patterns, and clinical outcomes. EJHaem. 2022;3(2):415-25. doi: 10.1002/jha2.426.
28. Hoskin PJ, Lowry L, Horwich A, Jack A, Mead B, Hancock BW, et al. Randomized comparison of the stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol. 2009;27(32):5390-6. doi: 10.1200/JCO.2009.23.3239.

29. Gobbi PG, Levis A, Chisesi T, Broglia C, Vitolo U, Stelitano C, et al. ABVD versus modified stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. J Clin Oncol. 2005;23(36):9198-207. doi: 10.1200/JCO.2005.02.907.
30. Johnson PW, Radford JA, Cullen MH, Sydes MR, Walewski J, Jack AS, et al. Comparison of ABVD and alternating or hybrid multidrug regimens for the treatment of advanced Hodgkin's lymphoma: results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519). J Clin Oncol. 2005;23(36):9208-18. doi: 10.1200/JCO.2005.03.2151.
31. Gordon LI, Hong F, Fisher RI, Bartlett NL, Connors JM, Gascoyne RD, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol. 2013;31(6):684-91. doi: 10.1200/JCO.2012.43.4803.
32. Strati P, Fanale MA, Oki Y, Turturro F, Fayad LE, Bartlett NL, et al. ABVD plus rituximab versus ABVD alone for advanced stage, high-risk classical Hodgkin lymphoma: a randomized phase 2 study. Haematologica. 2019;104(2):e65-e7. doi: 10.3324/haematol.2018.199844.
33. Moskowitz CH, Walewski J, Nademanee A, Masszi T, Agura E, Holowiecki J, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. Blood. 2018;132(25):2639-42. doi: 10.1182/blood-2018-07-861641.
34. Akay OM, Ozbalak M, Pehlivan M, Yildiz B, Uzay A, Yigenoglu TN, et al. Brentuximab vedotin consolidation therapy after autologous stem-cell transplantation in patients with high-risk Hodgkin lymphoma: Multicenter retrospective study. Hematol Oncol. 2021;39(4):498-505. doi: 10.1002/hon.2897.
35. Husi K, Szabo R, Pinczes LI, Foldeak D, Dudley R, Szomor A, et al. Improved survival of autologous stem cell transplantation in primary refractory and relapsed Hodgkin lymphoma in the brentuximab vedotin era - real-world data from Hungary. Ann Hematol. 2023;102(9):2555-63. doi: 10.1007/s00277-023-05354-8.