

COMMENTARY TO HABILITATION THESIS¹

[text of the commentary]

Optimization of Treatment Strategies and the Significance of Selected Prognostic Factors in Hodgkin Lymphoma

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Brief characteristic of the investigated matter

Hodgkin lymphoma (HL) is currently one of the most curable malignancies in adults, with modern treatment approaches achieving long-term remission in the majority of patients. Despite substantial advances in diagnosis and treatment, however, a number of clinical questions remain unresolved. A proportion of patients experience relapse or develop refractory disease, while long-term survivors may face serious late effects of anticancer treatment, including secondary malignancies. A major objective of current research is therefore to maintain the high efficacy of treatment while reducing its acute and, in particular, long-term toxicity. Over recent decades, the development of treatment strategies for HL has increasingly focused on individualising therapy according to disease stage, prognostic factors, and early treatment response. Metabolic imaging using FDG-PET/CT has assumed an important role in this process, enabling more accurate assessment of treatment response and facilitating PET-adapted treatment strategies. At the same time, additional clinical and biological factors are being investigated to improve the identification of patients at increased risk of treatment failure. Optimisation of HL treatment therefore involves both treatment de-escalation in patients with a favourable prognosis and a good treatment response, and treatment intensification or the use of novel therapeutic approaches in patients with high-risk, relapsed, or refractory disease. An important component of this approach is the evaluation of the prognostic significance of extranodal involvement, metabolic and biological markers,

¹ The commentary must correspond to standard expectations in the field and must include a brief characteristic of the investigated matter, objectives of the work, employed methodologies, obtained results and, in case of co-authored works, a passage characterising the applicant's contribution in terms of both quality and content.

including PD-L1 expression, as well as long-term treatment-related complications. More accurate risk stratification and individualisation of treatment strategies thus represent key prerequisites for further improving outcomes in patients with HL.

Objectives of the work

The aim of the present dissertation is to contribute to the optimisation and individualisation of treatment strategies for patients with Hodgkin lymphoma by evaluating the efficacy of treatment approaches of varying intensity and identifying selected prognostic factors. The publications included in the dissertation focus on the potential for treatment de-escalation in early favourable-stage disease and on optimising treatment intensity in early unfavourable and advanced-stage Hodgkin lymphoma. Other studies evaluate the role of PET/CT in the assessment of treatment response and prognosis, treatment outcomes in relapsed and refractory Hodgkin lymphoma, and the prognostic significance of selected clinical and biological factors, particularly extranodal involvement and PD-L1 expression. The dissertation also addresses the long-term consequences of anticancer treatment, with particular emphasis on the risk of secondary malignancies. The common objective of the presented studies is to contribute to more accurate risk stratification and to the selection of treatment strategies that maintain high therapeutic efficacy while reducing both short- and long-term toxicity.

Employed methodologies

The methodological approaches employed in the publications included in the dissertation can be divided into several main areas. The first comprises prospective multicentre randomised clinical trials conducted by the German Hodgkin Study Group (GHSG), focusing on the optimisation of first-line treatment intensity in early and advanced stages of HL and on the use of PET/CT to guide decisions regarding subsequent radiotherapy. The second area comprises retrospective clinical studies and analyses of real-world clinical data focusing on treatment outcomes in relapsed and refractory HL and on the prognostic significance of PET/CT prior to autologous haematopoietic stem cell transplantation. The third area includes retrospective analyses of clinical and biological prognostic factors, particularly extranodal

involvement and PD-L1 expression assessed by immunohistochemistry. A separate area involves the long-term follow-up of patients after treatment for HL, with a focus on the incidence of secondary malignancies and their association with previous anticancer treatment.

The studies employed standard methods for assessing treatment response, progression-free survival, and overall survival, together with appropriate statistical methods for analysing prognostic factors and comparing treatment strategies. The standardised incidence ratio (SIR) and absolute excess risk (AER) were used to assess secondary malignancies. The combination of prospective clinical trials, retrospective analyses, and real-world clinical data enabled the evaluation of both the efficacy of individual treatment strategies and the prognostic significance of selected clinical, imaging, and biological factors, as well as the long-term consequences of treatment for HL.

Obtained results

The first area of research focused on the optimisation of first-line treatment for HL. In patients with early-stage favourable disease, reducing treatment to two cycles of ABVD followed by radiotherapy at a dose of 20 Gy was shown to maintain high treatment efficacy while reducing toxicity [1]. In early-stage unfavourable disease, moderate intensification of chemotherapy by incorporating two cycles of escalated BEACOPP improved disease control, although at the cost of increased toxicity [2]. In advanced-stage disease, reducing treatment from eight to six cycles of escalated BEACOPP, together with PET-guided restriction of subsequent radiotherapy, was shown to maintain high treatment efficacy while reducing toxicity [3]. Long-term follow-up subsequently confirmed the favourable outcomes of this treatment strategy [4].

The second area focused on the treatment of relapsed and refractory HL and the prognostic significance of PET/CT. An analysis of real-world clinical data from the Czech Republic and Slovakia confirmed the efficacy of brentuximab vedotin in previously treated patients with relapsed or refractory HL, with higher complete remission rates achieved in patients who had received fewer prior lines of therapy [5]. PET/CT assessment prior to autologous haematopoietic stem cell transplantation

demonstrated significantly better progression-free survival and overall survival in patients with negative PET findings compared with PET-positive patients, thus confirming the importance of metabolic treatment response for prognostic stratification before transplantation [6].

The third area of research focused on prognostic factors and the long-term consequences of treatment for HL. Extranodal involvement was associated with significantly worse progression-free and overall survival, with liver involvement being associated with a particularly unfavourable prognosis [7]. PD-L1 expression on Hodgkin and Reed–Sternberg cells was demonstrated in the majority of evaluated patients, and its association with clinical and pathological characteristics and disease prognosis was analysed [8]. Long-term follow-up of patients treated for HL further demonstrated an almost threefold higher incidence of secondary malignancies compared with the general population (SIR = 2.9). Lung cancer (17.5 %) and breast cancer (15.6 %) accounted for the largest proportions of secondary malignancies, while a markedly increased relative risk was also observed for haematological malignancies, particularly non-Hodgkin lymphoma (SIR = 13.1) and leukaemia (SIR = 5.8). Previous radiotherapy was an important risk factor for the development of secondary malignancies [9].

The results of the presented studies contributed to the optimisation of treatment intensity across different stages of Hodgkin lymphoma, confirmed the importance of PET/CT and selected clinical and biological factors for prognostic stratification, and highlighted the need to consider the long-term toxicity of treatment. Taken together, these findings support the current concept of individualised treatment for HL, with the aim of maintaining a high probability of long-term disease control while reducing both early and late treatment-related adverse effects.

Applicant's contribution

Of the nine published articles included in the thesis, the applicant was the first and/or corresponding author of three (33%). In these studies, the applicant made a substantial contribution to the study design, analysis and interpretation of the results, and preparation of the manuscript. In the remaining publications, as a co-author, the applicant contributed primarily to patient enrolment, collection of clinical data,

interpretation of the results, and critical review of the manuscripts. Some of these publications resulted from international collaboration with the German Hodgkin Study Group (GHSg).

Bibliographic record of a published scientific results included in the habilitation thesis

Accessibility and Web of Science (WoS) classifications

[1]² ENGERT, Andreas, Annette PLUETSCHOW, Hans Theodor EICH, Andreas LOHRI, Bernd DOERKEN, Peter BORCHMANN, Bernhard BERGER, Richard GREIL, Kay C. WILLBORN, Martin WILHELM, Juergen DEBUS, Michael J. EBLE, Martin SOEKLER, Antony HO, Andreas RANK, Arnold GANSER, Lorenz TRUEMPER, Carsten BOKEMEYER, Hartmut KIRCHNER, Joerg SCHUBERT, **Zdenek KRAL**, Michael FUCHS, Hans-Konrad MUELLER-HERMELINK, Rolf-Peter MUELLER and Volker DIEHL. Reduced Treatment Intensity in Patients with Early-Stage Hodgkin's Lymphoma. *New England Journal Of Medicine* [online]. 2010, **363**(7), 640–652. ISSN 1533-4406. Available at: doi:10.1056/NEJMoa1000067

Document Type: Article; IF = 53,486; median IF MEDICINE, GENERAL & INTERNAL – 1,104; according to IF MEDICINE, GENERAL & INTERNAL Q1; according to AIS MEDICINE, GENERAL & INTERNAL Q1

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	5	5	5

[2] VON TRESCKOW, Bastian, Annette PLUETSCHOW, Michael FUCHS, Beate KLIMM, Jana MARKOVA, Andreas LOHRI, **Zdenek KRAL**, Richard GREIL, Max S. TOPP, Julia MEISSNER, Josee M. ZIJLSTRA, Martin SOEKLER, Harald STEIN, Hans T. EICH, Rolf P. MUELLER, Volker DIEHL, Peter BORCHMANN and Andreas ENGERT. Dose-Intensification in Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD14 Trial. *Journal Of Clinical Oncology* [online]. 2012, **30**(9), 907–913. ISSN 1527-7755. Available at: doi:10.1200/Jco.2011.38.5807

Document Type: Article; IF = 18,038; median IF ONCOLOGY – 2,610; according to IF ONCOLOGY Q1; according to AIS ONCOLOGY Q1

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	5	5	5

² Bibliographic record of a published scientific result, which is part of the habilitation thesis.

[3]_ENGERT, Andreas, Heinz HAVERKAMP, Carsten KOBE, Jana MARKOVA, Christoph RENNERT, Antony HO, Josee ZIJLSTRA, **Zdenek KRAL**, Michael FUCHS, Michael HALLEK, Lothar KANZ, Hartmut DOEHNER, Bernd DOERKEN, Nicole ENGEL, Max TOPP, Susanne KLUTMANN, Holger AMTHAUER, Andreas BOCKISCH, Regine KLUGE, Clemens KRATOCHWIL, Otmar SCHOBERT, Richard GREIL, Reinhard ANDREESSEN, Michael KNEBA, Michael PFREUNDSCHUH, Harald STEIN, Hans Theodor EICH, Rolf-Peter MUELLER, Markus DIETLEIN, Peter BORCHMANN, Volker DIEHL, GERMAN HODGKIN STUDY GRP, SWISS GRP CLINICAL CANC RES and ARBEITSGEMEINSCHAFT MEDIKAMENTOSE. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet* [online]. 2012, **379**(9828), 1791–1799. ISSN 1474-547X. Available at: doi:10.1016/S0140-6736(11)61940-5

Document Type: Article; IF = 39,060; median IF MEDICINE, GENERAL & INTERNAL – 1,078; according to IF MEDICINE, GENERAL & INTERNAL Q1; according to AIS MEDICINE, GENERAL & INTERNAL Q1

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	5	5	5

[4]_ENGERT, Andreas, Helen GOERGEN, Jana MARKOVA, Thomas PABST, Julia MEISSNER, Josee M. ZIJLSTRA, **Zdenek KRAL**, Dennis A. EICHENAUER, Martin SOEKLER, Richard GREIL, Stefanie KREISSL, Ruth SCHEUVENS, Hans EICH, Carsten KOBE, Markus DIETLEIN, Harald STEIN, Michael FUCHS, Volker DIEHL and Peter BORCHMANN. Reduced-Intensity Chemotherapy in Patients With Advanced-Stage Hodgkin Lymphoma Updated Results of the Open-Label, International, Randomised Phase 3 HD15 Trial by the German Hodgkin Study Group. *Hemasphere* [online]. 2017, **1**(1). ISSN 2572-9241. Available at: doi:10.1097/Hs9.0000000000000005

Document Type: Article, IF not available, AIS not available

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
5	5	5	5

[5] **KRAL, Zdenek** **(corresponding author)**, Jozef MICHALKA, Heidi MOCIKOVA, Jana MARKOVA, Alice SYKOROVA, David BELADA, Alexandra JUNGOVA, Samuel VOKURKA, Marie LUKASOVA, Vit PROCHAZKA, Juraj DURAS, Roman HAJEK, Ladislav DUSEK, L'uhos DRGONA, Miriam LADICKA, Veronika BALLOVA and Andrei VRANOVSKY. Treatment of Relapsed/Refractory Hodgkin Lymphoma: Real-World Data from the Czech Republic and Slovakia. *Journal Of Cancer* [online]. 2019, **10**(21), 5041–5048. ISSN 1837-9664. Available at: doi:10.7150/jca.29308

Document Type: Article; IF = 3,565; median IF ONCOLOGY – 3,297; according to IF ONCOLOGY Q2; according to AIS ONCOLOGY Q3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	60	70	70

[6] MOCIKOVA, Heidi, Robert PYTLIK, Jana MARKOVA, Katerina STEINEROVA, **Zdenek KRAL**, David BELADA, Marie TRNKOVA, Marek TRNENY, Vladimir KOZA, Jiri MAYER, Pavel ZAK and Tomas KOZAK. Pre-transplant positron emission tomography in patients with relapsed Hodgkin lymphoma. *Leukemia & Lymphoma* [online]. 2011, **52**(9), 1668–1674. ISSN 1029-2403. Available at: doi:10.3109/10428194.2011.573889

Document Type: Review; IF = 2,580; median IF HEMATOLOGY – 2,606, according to IF HEMATOLOGY Q3; according to AIS HEMATOLOGY Q3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
15	10	10	10

[7] MAULE, Eva, Jozef MICHALKA, Jiri SANA, Lenka RADOVA, Miroslav KOPCIK, Barbora OBADALOVA, Lenka SMARDOVA, Leos KREN, Vaclav KUBES and **Zdenek KRAL** **(corresponding author)**. Extranodal Involvement in Hodgkin's Lymphoma: A Retrospective Analysis of Survival Outcomes and Prognostic Factors at a Single-Center Study. *Bratislava Medical Journal* [online]. 2026. ISSN 1336-0345. Available at: doi:10.1007/s44411-026-00625-y

Document Type: Article; IF = 1,400; median IF MEDICINE, GENERAL & INTERNAL – 1,200; according to IF MEDICINE, GENERAL & INTERNAL Q2; according to AIS MEDICINE, GENERAL & INTERNAL – SCIE Q3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	60	50	70

[8]_KUBES, Vaclav, Leos KREN, Filip SOKOL, Jozef MICHALKA, Jan MUZIK, Tomas ARPAS, Zdenka KRENOVA and **Zdenek KRAL** **(corresponding author)**. Prognostic Significance of Immune-checkpoint Molecule PD-L1 in Classical Hodgkin Lymphoma: A Clinicopathologic Study of 120 Cases. *In Vivo* [online]. 2023, **37**(4), 1735–1742. ISSN 1791-7549. Available at: doi:10.21873/invivo.13261

Document Type: Article; IF = 1,800; median IF MEDICINE, RESEARCH & EXPERIMENTAL – 2,700; according to IF MEDICINE, RESEARCH & EXPERIMENTAL Q3; according to AIS MEDICINE, RESEARCH & EXPERIMENTAL Q3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
25	50	40	60

[9]_PETRAKOVA, Katarina, Jiri VYSKOCIL, Peter GRELL, Ondrej MAJEK, Renata SOUMAROVA, Jiri NOVAK, Petr BURKON, **Zdenek KRAL**, Tomas KAZDA and Rostislav VYZULA. Second cancers in Hodgkin's lymphoma long-term survivals: A 60-year single institutional experience with real-life cohort of 871 patients. *International Journal Of Clinical Practice* [online]. 2018, **72**(9, Article e13235). ISSN 1742-1241. Available at: doi:10.1111/ijcp.13235

Document Type: Article; IF = 2,613; median IF MEDICINE, GENERAL & INTERNAL – 1,570; according to IF MEDICINE, GENERAL & INTERNAL Q2; according to AIS MEDICINE, GENERAL & INTERNAL Q2

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	10	10	10