Received: 30 March 2022 | Accepted: 31 March 2022

DOI: 10.1111/bjh.18199

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

COMMENTARY

Late relapses in Hodgkin lymphoma – should we search for the needle in the haystack?

Tarec Christoffer El-Galaly[1,2] | **Ingrid Glimelius**[3]

[1]Department of Hematology, Clinical Cancer Research Center, Aalborg University Hospital, Aalborg, Denmark

[2]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[3]Department of Immunology, Genetics and Pathology, Section of Oncology, Uppsala University, Uppsala, Sweden

Correspondence
Tarec Christoffer El-Galaly, Department of Hematology, Aalborg University Hospital, Aalborg DK-9000, Denmark.
Email: tarec.galaly@gmail.com

Funding information
the Danish Cancer Society

Hodgkin lymphoma is among the most curable cancers. For patients in remission for 24 months, residual lifetime becomes close to that of the background population. However, late relapses can occur after several years and, as shown by Andersen et al., the outcomes are not always good.

Commentary on: Andersen MD, Hamilton-Dutoit S, Modvig L, Vase M, Christiansen I, Christensen JH, et al. Late recurrence of lymphoid malignancies after initial treatment for Hodgkin lymphoma – A study from the Danish Lymphoma Registry. *Br J Haematol* 2022;198:50-61.

KEYWORDS
Hodgkin lymphoma, late toxicity, relapse, survival

In this issue, Andersen et al.[1] describe the risk and outcomes of late relapses (LR) in patients with Hodgkin lymphoma (HL). HL treatment is one of the success stories of modern oncology. Patients with early-stage HL have 5-year progression-free survival (PFS) estimates of >90% with intensive chemotherapy and most relapses occur within the first 2–3 years after completing therapy.[2] For advanced stage disease, the 5-year PFS is also in the range of 90%, again with most events occurring early after diagnosis.[3] Excellent outcomes for patients with HL in continuous complete remission 2 years after therapy were confirmed in a Canadian study of 1402 patients with classical HL (cHL) diagnosed between 1989 and 2012 and treated with ABVD (doxorubicin [adriamycin], bleomycin, vinblastine, dacarbazine) or an equivalent regimen. Almost three-quarters of the relapses occurred within the first 2 years, resulting in a 5-year relapse risk of only 5.6% for the subset of patients without events in the first 2 years. The relative survival (RS) improved over time but did not normalise to the background population.[4] In a Nordic Lymphoma Epidemiology Group study of 2582 patients diagnosed at the ages of 18–49 years, the 5-year risk of relapse was 13.4% (95% confidence interval [CI] 12.1%–14.8%) from diagnosis but decreased to 4.2% (95% CI 3.8%–4.6%) for patients without events in the first 2 years. The 5-year losses in expectation of lifetime were 45 days from diagnosis and only 13 days in patients without events in the first 2 years.[5] These population-based data consistently show that risks of relapse and loss of lifetime are generally very low for patients who are relapse-free in the first years after therapy. The typical post-treatment follow-up accounts for this by closer surveillance for signs of relapse in the early follow-up period. Termination of routine follow-up 2–3 years after completing first-line therapy will often be perceived as cure by patients, but there are exceptions to this rule hidden in the aggregate statistics. We can certainly inform patients that recurrence rates are too low to warrant routine disease surveillance beyond this time point, but can we guarantee that a relapse will not occur after 5 years? According to the results of Andersen et al.[1] based on the Danish Lymphoma Registry (LYFO), we cannot. The study was based on a review of data from 3350 patients with HL diagnosed in Denmark between 1982 and 2018 and investigated pattern of LR of lymphoid malignancies after first-line treatment and their outcomes.

The strength of the study is a very long and complete follow-up in a population-based setting. The LRs were defined as a relapse occurring >5 years after diagnosis, which are events typically not captured by clinical trials where follow-up is limited. In the analyses, LR occurred in 58 of 3350 patients with HL, resulting in cumulative incidences at 10, 15 and 20 years of 2.7%, 4.0% and 5.4% respectively. As expected, LR was more common in patients with nodular lymphocyte-predominant HL (NLPHL) with a hazard ratio (HR) of 4.5. Older age and lymphopenia were general risk factors for LR, but mixed cellularity histological subtype was also a risk factor in females. Generally, the HRs were low, and the absolute risk is still small – in our opinion, not at a level that would warrant longer routine follow-up in the absence of NLPHL histology. Importantly, LRs of cHL were associated with poorer OS as opposed to LRs of NLPHL, where all patients with response data achieved a second CR. The 10-year OS after a LR was 51% (95% CI 25%–71%), not significantly different from the 10-year OS after an early relapse. Thus, this study does not support better outcomes of LRs compared to early relapses. However, only 30/44 patients with cHL with LR relapsed with cHL histology. The study did further not review original tissue biopsies and some of the LRs of non-cHL histology may have been due to initial misclassification or even de novo appearance of a new lymphoid malignancy.

The study confirms data from 6840 patients with cHL enrolled in the HD7 to HD12 trials; 141 LRs were observed with cumulative incidences at 10, 15, and 20 years of 2.5%, 4.3%, and 6.9% respectively. In contrast to the study by Andersen et al.,[1] the 10-year OS was better for LR than for early relapse (95.8% vs. 86.1%) and better than the 51% in the Danish study despite a median age of 45 years in both.[6] Importantly, the German study showed that the standardised incidence ratio for HL with respect to age- and sex-matched German reference data was 85, revealing that the risk is far beyond random incident cases. While the results do not warrant more disease surveillance, the data suggest that the threshold for investigating relapse suspicious symptoms should be low even after many years in remission. However, looking at the full picture, LRs constitute a minor part of the health-related problems HL survivors face, with some significantly more likely to cause morbidity and mortality. HL survivors face a broad panorama of potential health problems, with increased healthcare use unrelated to HL-relapses up to about 10 years after diagnosis.[7] The risks of secondary cancers,[8] fertility problems[9] and cardiovascular complications[10] after treatment are known, but survivors also face less well-described complications such as eye disorders, asthma, diabetes mellitus and depression.[7] Nearly one-third of HL survivors also perceived HL as affecting their socioeconomic status in a negative way.[11] These are problems faced by many patients and not only a small minority. The need for integrated survivorship care is much greater than additional focus on relapse risk. Primary preventive measures for cardiovascular disorders are starting to get implemented, and screening for secondary malignancies, e.g., breast cancer in females after radiation to the chest, are incorporated in many countries. However, many patients also feel psychological burdened by their disease, depressed, and the availability of care is not always in agreement with the patient-reported problems. We believe that research that identifies modifiable late effects, patients at higher risk, and the effect of preventive measures should be more in focus. However, it is a moving target. Late toxicities occur years after completing therapy and with the constant changes in HL treatment, with better radiotherapy techniques and less chemotherapy for early responders (and escalation in poor responders), todays data on late toxicity and LRs may already be historical.

ACKNOWLEDGEMENTS

Tarec Christoffer El-Galaly: support from the Danish Cancer Society Grant.

CONFLICT OF INTEREST

Tarec Christoffer El-Galaly: previous employment Roche.

ORCID

Tarec Christoffer El-Galaly https://orcid.org/0000-0002-4406-380X
Ingrid Glimelius https://orcid.org/0000-0001-6158-3041

REFERENCES

1. Andersen MD, Hamilton-Dutoit S, Modvig L, Vase M, Christiansen I, Christensen JH, et al. Late recurrence of lymphoid malignancies after initial treatment for Hodgkin lymphoma – a study from the Danish Lymphoma Registry. Br J Haematol 2022;198:50–61.
2. Andre MPE, Girinsky T, Federico M, Reman O, Fortpied C, Gotti M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2017;35(16):1786–94.
3. 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.
4. Hapgood G, Zheng Y, Sehn LH, Villa D, Klasa R, Gerrie AS, et al. Evaluation of the risk of relapse in classical Hodgkin lymphoma at event-free survival time points and survival comparison with the general population in British Columbia. J Clin Oncol Off J Am Soc Clin Oncol. 2016;34(21):2493–500.
5. Biccler JL, Glimelius I, Eloranta S, Smeland KB, Brown PN, Jakobsen LH, et al. Relapse risk and loss of lifetime after modern combined modality treatment of young patients with Hodgkin lymphoma: a Nordic lymphoma epidemiology group study. J Clin Oncol Off J Am Soc Clin Oncol. 2019;37(9):703–13.
6. Brockelmann PJ, Goergen H, Kohnhorst C, von Tresckow B, Moccia A, Markova J, et al. Late relapse of classical Hodgkin lymphoma: an analysis of the German Hodgkin study group HD7 to HD12 trials. J Clin Oncol. 2017;35(13):1444–50.
7. Glimelius I, Eloranta S, Ekberg S, Chang ET, Neovius M, Smedby KE. Increased healthcare use up to 10 years among relapse-free Hodgkin lymphoma survivors in the era of intensified chemotherapy and limited radiotherapy. Am J Hematol. 2017;92(3):251–8.
8. de Vries S, Schaapveld M, van Nimwegen FA, Jozwiak K, Lugtenburg PJ, Daniels LA, et al. High burden of subsequent malignant neoplasms and cardiovascular disease in long-term Hodgkin lymphoma survivors. Br J Cancer. 2018;118(6):887–95.

9. Ovlisen AK, Jakobsen LH, Eloranta S, Kragholm KH, Hutchings M, Frederiksen H, et al. Parenthood rates and use of assisted reproductive techniques in younger Hodgkin lymphoma survivors: a Danish population-based study. J Clin Oncol. 2021;39(31):3463–72.
10. Weibull CE, Bjorkholm M, Glimelius I, Lambert PC, Andersson TML, Smedby KE, et al. Temporal trends in treatment-related incidence of diseases of the circulatory system among Hodgkin lymphoma patients. Int J Cancer. 2019;145:1200–8.
11. Palmarsdottir R, Kiesbye Ovlisen A, Severinsen MT, Glimelius I, Smedby KE, El-Galaly T. Socioeconomic impact of Hodgkin lymphoma in adult patients: a systematic literature review. Leuk Lymphoma. 2019;60(13):3116–31.

How to cite this article: El-Galaly TC, Glimelius I. Late relapses in Hodgkin lymphoma – should we search for the needle in the haystack?. Br J Haematol. 2022;198:11–13. https://doi.org/10.1111/bjh.18199