

Review Article

Very Late Relapses in Hodgkin Lymphoma: A Critical Comparison of Major Published Studies

**Athanasios Liaskas¹, Fotios Panitsas¹, Evrydiki Kravvariti², Maria K. Angelopoulou¹,
Gerassimos A. Pangalis³, Theodoros P. Vassilakopoulos¹**

¹Department of Haematology, ²First Department of Propaedeutic Internal Medicine, Joint Rheumatology Academic Program, ³Department of Haematology, Athens Medical Center, Psychikon Branch, Athens, Greece

ABSTRACT:

Despite the excellent long-term outcome of patients with Hodgkin Lymphoma (HL), a minority of patients experience Very Late Relapses (VLRs) occurring ≥ 5 years after treatment initiation. Until recently, the issue of VLRs after chemotherapy or combined modality therapy (CT \pm RT) had been studied inadequately, in the context of small case series. In 2017, the German Hodgkin Study Group (GHSG) first reported on the incidence of VLRs after combined modality approaches, and specifically highlighted the linear pattern of risk of VLRs within 20 years after initial treatment. Our group validated the linear risk within extended follow-up time with the latest VLR recorded at 35.1 years. Notably, significant independent prognostic factors were established in our study including mixed cellularity histology, which may have clinical and biological implications. Finally, Andersen et al presented the incidence and characteristics of late lymphoid recurrences in patients with HL and explored the role of several risk factors, involving certain limitations though. In this mini-review we aim to provide additional information and a critical view on the subject of VLRs in classical Hodgkin lymphoma, based on the results of the recent hallmark studies.

KEY WORDS: *Hodgkin lymphoma, Relapse, very late, 5 years, Chemotherapy, Radiotherapy, Mixed cellularity, Prognosis*

INTRODUCTION

Despite the excellent long-term outcome of patients with Hodgkin Lymphoma (HL), 20% of the cases will be primary refractory or will eventually relapse. Most treatment failures occur within the initial 2 years from diagnosis and thus, typically the disease is considered cured after a 5-year continuous first complete remission. However, very late relapses (VLRs), occurring ≥ 5 years after treatment initiation, are a non-negligible event and

possibly comprise a distinct disease with unique biological and clinical characteristics.

The occurrence of VLRs in HL has been long recognized from 1985¹ and relapses recorded as case reports have occurred as late as 30-32 years after the initial diagnosis.^{2,3} Until recently, the issue of VLRs had been evaluated in rather small patient series including patients with variable definition of VLR, treated with very heterogeneous approaches including RT alone and/or outdated chemotherapy.⁴⁻¹¹ We started the study of VLRs in 2005 trying to qualify the risk and identify relevant risk factors.¹² In 2017, the German Hodgkin Study Group (GHSG) first reported on the incidence of VLRs within the HD7-HD12 randomized trials, among patients treated with combined modality approaches.¹³ Our group, recently presented the results of a retrospective study with extended follow-up time, exceeding 20-years.¹⁴ Simultaneously Andersen et

Corresponding author:

Theodoros P. Vassilakopoulos, MD, PhD,
Professor of Hematology, Department of Hematology and Bone Marrow Transplantation, National and Kapodistrian University of Athens, School of Medicine, Laikon General Hospital, Athens 11527, Greece
Tel.: +30 213 2061702, Fax: +30 213 2061498
e-mail: tvassilak@med.uoa.gr and theopvass@hotmail.com

Received 23 May 2022; Accepted 7 Jun 2022

al, presented the results of their population-based study aiming to describe the characteristics of late lymphoid recurrences in patients with HL.¹⁵

In this mini-review we discuss various important points regarding incidence and risk factors for VLR, as derived from the critical comparison of these three studies and highlight the clinical and biological issues related to VLR.

Issues on the incidence of VLR

The incidence of VLR was not adequately described in the small patient series published before 2017 and in fact, it is characterized by considerable variability even among the various major studies published until now. The completeness of follow-up always remains of paramount importance when reporting on VLR. Additionally, the use of competing-risks analysis, considering death from any cause as a competing event to VLR, by GHSG and our study, is necessary to accurately estimate the incidence of VLR and produce robust results.

The different incidence rates of VLRs in various time-points among the three major studies is presented in Table 1. The GHSG reported 141 VLRs in an analysis of 4935 patients with classical HL (cHL) after a median follow-up of 10.3 years.¹³ Our long-term experience revealed 66 VLRs after a 13.8-year median follow-up in a series of 1143 patients, including 978 cHL patients treated with anthracycline-based chemotherapy.¹⁴ A striking observation in the two studies was the linear pattern of risk of VLRs within 20 years after initial treatment, first noted by the GHSG. We validated the linear risk by further extending this observation and demonstrating that the linear trend of VLRs continues beyond 20 years from diagnosis, up to 25 or even 30 years. Similar findings were observed when the analysis was restricted to patients treated with ABVD or equivalent regimens. This linear risk pattern is similar to the observations made in hormone-receptor-positive early-stage breast cancer.^{16,17} Whilst in breast cancer the development of delayed metastatic disease is almost always relapsing disease and not a new malignancy, the situation is different in HL, where a second primary HL cannot be excluded. However, the 84.5-fold higher risk of HL reported by the GHSG in 5-year relapse-free survivors compared to the general population argues in favor of the relapsing rather than “second primary” nature of late HL events.¹³

Our study reported slightly higher VLR rates than GHSG. However, nearly half of the patients in the German study (~45%) were treated intensively with various BEACOPP schedules \pm RT, whereas 9% of the patients in our study were treated with MOPP or equivalent regimens (mainly before 1988). Hence, possibly BEACOPP-based

strategies not only reduce early relapses but may reduce VLRs as well.

Andersen et al. reported 58 very late lymphoid recurrences in a cohort of 2424 patients of the Danish registry.¹⁵ However, among the 58 events, at least 10 were non-Hodgkin lymphomas including a composite HL/angioimmunoblastic lymphoma (cHL/AILT); interestingly our study also included a single case cHL/AILT as a VLR. Only 31/44 patients with primary cHL relapsed as cHL. The incidence of VLRs was significantly higher in nodular lymphocyte predominant HL (NLPHL) than in cHL. Notably, the cumulative incidence of VLRs in cHL patients of the Danish registry was much lower compared with our data and even with the GHSG. Although the maximum follow-up in the Danish series could have been 37 years (1982-2019), it was 25.5 years, and the most delayed relapse was seen at 18.9 years. In contrast, we observed the latest VLR at 35.1 years and recorded 8 cases of VLRs beyond the 20th year, including 4 occurring beyond the 25th year.¹⁴ Despite the appropriate methodology applied by Andersen et al. in this registry study deriving information from other validated sources as well, the completeness of follow-up may remain an issue. Thus, in order to critically interpret the estimates of the cumulative incidence of VLR the authors should have provided the number of patients at risk at each time point and also report how many patients among the initial patient population, had CR/CRu and follow-up time <5 years, as such patients were not at risk for VLR.

Risk factors for VLR

Various clinical, pathological and laboratory features have been assessed as potential risk factors by the older, moderately-sized series and the three major recent studies, as presented in Table 2. Increasing age remained unanimously a risk factor for late recurrences.¹³⁻¹⁵ Male gender and early stages were independent predictors of higher CI of VLR in the GHSG study.¹³

Our study highlighted the omission of radiotherapy from first-line treatment as a risk factor for VLR which remained significant in multivariate analysis after adjustment for clinical stage (HR:0.35, $p < 0.01$). If VLRs are indeed more frequent in non-irradiated complete responders, the short- and mid-term results of recent randomized trials should be viewed with caution, because non-inferiority may not be valid in the long-term.¹⁸⁻²² Treatment with MOPP vs or equivalent vs anthracycline-based regimens was also associated with higher VLR risk in our study after adjustment for confounding factors (HR:0.49, $p = 0.024$).¹⁴ In this setting it seems that inferior treatment approaches hold higher risk of relapse and this comes in line with the high risk of VLRs in early-stage trials of

TABLE 1. Comparative presentation of the three landmark studies on Very Late Relapses in Hodgkin Lymphoma

	Brockelman PJ et al.		Vassilakopoulos TP et al.		Andersen MD et al.	
Patients in CR1> 5years	4935		1143		2424*	
Number of VLR	141		66		58	
Median follow-up time, years (range)	10.3		13.8 (5-47)		16.0 (5.8-24.3)	
VLRs beyond 20 years [# (%)]	1? (<1%)		8 (12%)		0	
Time to latest VLR (years from diagnosis)	~20.5		35.1		18.9	
Median age at initial diagnosis, years (range)	33 (17-70)		31 (IQR: 23-44)		38 (15-93)	
Gender, male (% of initial population)	54		54		59	
Initial treatment (% of initial population)						
CT alone	16		26		NR	
CT + RT	80		74		NR	
RT alone	4		0		7	
Chemotherapy Regimen (% of initial population)						
ABVD and equivalents	51		91		77	
MOPP and equivalents	0		9		5	
BEACOPP-based	45		0		7	
Histologic Subtype (%)	All pts	VLRs	All pts	VLRs	All pts	VLRs
NLPHL (% of total)	0	0	6	9	6	24
cHL (by definition 100%)	100	100	100	100	100	100
NS (% among cHL)	63	47	69	44	59	55
MC (% among cHL)	26	40	26	50	22	40
Other cHL (% among cHL)	11	13	6	5	19	5
Cumulative incidence [% (95% CI)]	All	cHL	All	cHL (ABVDeq)	All	cHL
at 10 years	NA	2.5 (2.0-3.0)	3.6 (2.5-4.8)	3.0 (2.0-4.3)	2.7 (1.9-3.6)	2.1 (1.5-3.0)
at 15 years	NA	4.3 (3.5-5.1)	5.8 (4.3-7.5)	5.0 (3.5-6.9)	4.0 (3.0-5.2)	3.2 (2.3-3.4)
at 20 years	NA	6.9 (5.0-8.9)	7.9 (5.9-10.3)	7.2 (5.0-9.8)	5.4 (4.0-7.2)	~4.0 (NA - NA)
at 25 years	NA	NA	9.6 (7.1-12.6)	9.2 (6.2-12.8)	NA	NA
at 30 years	NA	NA	12.2 (8.6-16.4)	13.6 (7.4-21.7)	NA	NA

*Potential maximal follow-up 37years

Pts=patients, CR1: first complete remission, VLR: very late relapses, CT: chemotherapy, RT: radiotherapy, cHL: classical Hodgkin Lymphoma, NLPHL: nodular lymphocyte predominant hodgkin lymphoma, NS: nodular sclerosis, MC: mixed cellularity, CMT: combined modality treatment, ABVDeq: ABVD equivalent, 95% CI: 95% Confidence Interval, NA: Not Applicable

TABLE 2. Prognostic factors demonstrated by the three major and four older modestly-sites studies on VLR in HL

	Brockelman PJ et al. 2017	Vassilakopoulos TP et al. 2022	Andersen MD et al. 2022	Garcia- Carbonero R et al. 1998	Provencio M et al. 2010	Markovic O et al. 2017	Pinczés L et al. 2018
Older age	✓	✓	✓	✓	×	NT	✓**
Gender	✓	×	✓	×	×	×	×
Mixed Cellularity	NT	✓	✓	NT	NT	NT	NT
Clinical Stage	✓	×	NT	×	NT	×	✓
Extranodal involvement	×	NT	NT	×	×	×	NT
B-symptoms	×	×	×	×	NT	NT	×
Bulky disease	×	NT	×	×	×	×	NT
Laboratory parameters	NT	Low ESR (<50 mm/h)	Lymphocytopenia	NT	×	×	NT
IPS	×	×	NT	NT	NT	×	NT
Chemotherapy Regimen (MOPP vs ABVD)	NT	✓	NT	NT	NT	NT	NT
CT alone vs CMT	NT	✓	×	NT	✓	NT	✓*
RT only	×	E	NT	✓	NT	NT	✓

VLR: very late relapses, HL: Hodgkin Lymphoma, ✓= significant in multivariate analysis, ×= not significant in multivariate analysis, ✓*= significant in univariate analysis, ✓**=in this study younger age was associated with higher risk of very late relapse, NT= not tested, E= excluded by definition, ESR= erythrocyte sedimentation rate, CT: chemotherapy, RT: radiotherapy, CMT: combined modality treatment

the GHSG (HD7, HD10), in which patients were treated with the least intensive approaches (ABVDx2-4+RT or even RT alone).¹³

Andersen et al, reported lymphocytopenia as a significant independent risk factor for VLR (HR:5.55, p<0.001).¹⁵ Paradoxically in our study elevated ESR ≥50mm/h, which is strongly correlated with advanced stage and B-symptoms, was associated with a significantly lower risk of VLR (HR:0.46, p=0.08).¹⁴ This may be explained on the basis that elevated ESR represents biologically more aggressive disease, which may have a different biology related to primary refractoriness or earlier relapses. This hypothesis is supported by recent data on breast cancer, reporting that grade 1 patients with extensive nodal disease are at highest risk of VLR at 10-35 years.¹⁷

Histologic subtype was also explored as a potential risk factor. Andersen et al reported NLPHL as a significant

risk factor with a frequency of VLR was 9%, as compared with 1.9% in patients with cHL (HR:5.1, p<0.001).¹⁵ This was not confirmed in our study, while GHSG excluded patients with NLPHL histology. However, the most remarkable finding, which was particularly highlighted in our study, is the emergence of mixed cellularity (MC) as a risk factor for developing VLRs. MC was associated with the highest VLR risk followed by NLPHL and finally other cHL subtypes, mainly nodular sclerosis (NS). The association between MC and the probability of VLR was independent from stage, age, ESR, chemotherapy regimen and use of RT (HR=2.84, p=0.001).¹⁴ This was further confirmed when the analysis was restricted to patients diagnosed after 1996 when the histologic classification was not accurate. Andersen et al also found that MC subtype was more likely to be complicated by VLRs but strangely, this was limited to female patients (HR: 5.36, p=0.014).¹⁵

A closer look into the GHSG data reveals that NS and MC accounted for 64% and 26% of 4794 patients with continuous CR versus 47% and 40% in the 141 VLRs.¹³ Although the relative risk was not formally quantified, this clear imbalance provides further support to the findings published by the Danish and our group.^{14,15} In retrospect, we investigated the gender-specific effect of MC (Figure 1) but the risk was higher in males than females. Also, to test for a differential effect of MC histology by gender among cHL patients, the interaction term was included in a Fine&Gray model and was not significant (Wald-test $p=0.9315$). Unexpectedly however we found a higher VRL risk in females with NLPHL. This discrepancy between our study and the Danish one may simply suggest that gender-related differences lack biological significance and appeared just by chance due to the low number of events per gender group. A combined individual-patient data analysis of the published studies would be of value to provide accurate estimates of the impact of each potential risk factor.

In our series independent adverse factors for VLRs were MC, age \geq 45 years, lower ESR $<$ 50 mm/h and treat-

ment with chemotherapy only without RT.¹⁴ Although the risk was low for patients with none of these factors (19.6 % of all patients), the HR for those with 1 (44.3%), 2 (24.6%) or 3-4 (11.4%) factors was 2.68, 6.75 and 11.53 respectively. Thus, a sizeable patient subgroup carries a considerable risk of VLR, which may overweight the risk of treatment-related side effects. Practically, it appears that patients with MC or other multiple risk factors for VLR might require long-term surveillance for the detection of relapsing disease. Although the optimal surveillance procedures remain unknown, it is clear that interrupting follow-up after 5 years may not be prudent.

CONCLUSION

In conclusion, despite the rarity of VLRs, their clinical impact remains significant in the long-term. The linear pattern of relapse, their non-negligible cumulative incidence and the potential risk factors are implying that the optimal surveillance of patients with HL should be reconsidered. More studies with complete and thorough follow-up time are necessary in order to form new poli-

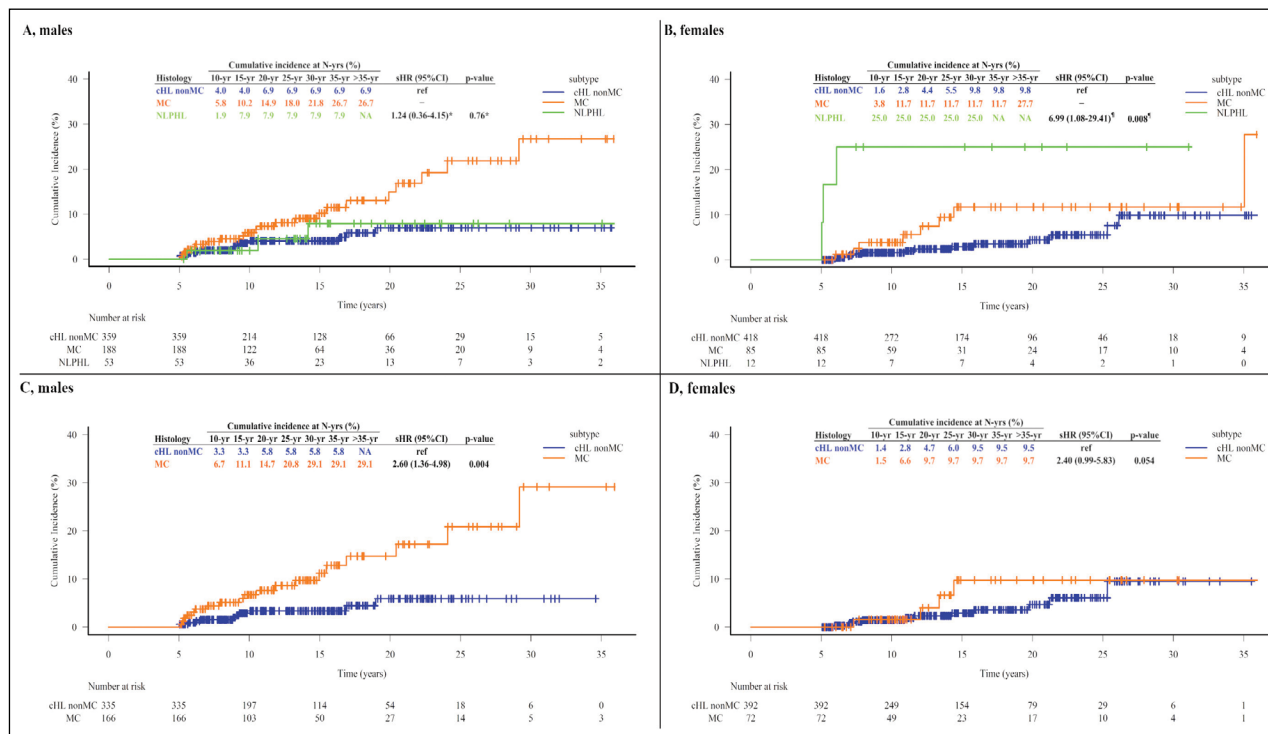


Figure 1. Competing-risks-adjusted Cumulative Incidence at different time-points from diagnosis in the whole male (A) and female population (B), and in male (C) and female (D) patients with classical Hodgkin Lymphoma treated with ABVD or equivalent regimens.

cHL = classical Hodgkin lymphoma, MC= mixed cellularity, NLPHL = nodular lymphocyte predominant Hodgkin lymphoma, HR = hazard ratio, 95%CI= 95% confidence interval

*For NLPHL vs all cHL comparison in males: HR: 0.73 (0.29-2.44), $p=0.63$

[†]For NLPHL vs all cHL comparison in females: HR: 5.92 (1.49-23.26), $p=0.012$

cies. Research should also focus in defining prognostic factors for the outcome and exploring the unique biology of VLRs.²³

Conflict of Interest: None

REFERENCES

- Herman TS, Hoppe RT, Donaldson SS, Cox RS, Rosenberg SA, Kaplan HS. Late relapse among patients treated for Hodgkin's disease. *Ann Intern Med.* 1985 Mar;102:292-7.
- Lee KM, Spittle MF. Hodgkin's disease: A case of late relapse. *Clin Oncol (R Coll Radiol).* 1993;5:399.
- Shihabi S, Deutsch M, Jacobs SA. Very late relapse of Hodgkin's disease: A report of five patients. *Am J Clin Oncol.* 2001 Dec;24:576-8.
- Bodis S, Henry-Amar M, Bosq J, Burgers JM, Mellink WA, Dietrich PY, et al. Late relapse in early-stage Hodgkin's disease patients enrolled on European Organization for Research and Treatment of Cancer protocols. *J Clin Oncol.* 1993 Feb;11:225-32.
- Brierley JD, Rathmell AJ, Gospodarowicz MK, Sutcliffe SB, Pintillie M. Late relapse after treatment for clinical stage I and II Hodgkin's disease. *Cancer.* 1997 Apr;79(7):1422-7.
- Garcia-Carbonero R, Paz-Ares L, Arcediano A, Lahuerta J, Bartolome A, Cortes-Funes H. Favorable prognosis after late relapse of Hodgkin's Disease. *Cancer.* 1998 Aug;83:560-5.
- Provencio M, Salas C, Millan I, Cantos B, Sanchez A, Bellas C. Late relapses in Hodgkin lymphoma: A clinical and immunohistochemistry study. *Leuk Lymphoma.* 2010 Sep;51:1686-91.
- Gaudio F, Giordano A, Pavone V, Perrone T, Curci P, Pastore D, et al. Outcome of very late relapse in patients with Hodgkin's Lymphomas. *Adv Hematol.* 2011;2011:707542.
- Viviani S, Mussetti A, Di Bartolo O, Cabras A, Vlagussa P, Bonadonna G, et al. Late relapse in Hodgkin Lymphoma (HL): A retrospective analysis of patients enrolled on clinical trials at the Istituto Nazionale Tumori di Milan (INT-MI). *Blood.* 2015 Dec;126(23):2697 (abstract).
- Markovic O, Andjelic B, Tarabar O, Todorovic M, Filipovic B, Stanisavljevic D, et al. Late relapse of Hodgkin's lymphoma - is it different in clinical characteristics and outcome? *J BUON.* 2017 Mar-Apr;22:481-6.
- Pinczes L, Miltenyi Z, Illes A. Young adults diagnosed with Hodgkin lymphoma are at risk of relapsing late: A comprehensive analysis of late relapse in Hodgkin lymphoma. *J Cancer Res Clin Oncol.* 2018 May;144(5):935-43.
- Vassilakopoulos TP, Angelopoulou MK, Siakantaris MP, Kokoris SI, Dimitriadou EM, Dimopoulou MN, et al. Very late relapses in patients with Hodgkins Lymphoma. 10th Congress of EHA, June 2 - 5, Stockholm, Sweden, Haematologica Abstract Book. 2005;90 (Suppl 2):72 (abstract).
- 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 May;35:1444-50.
- Vassilakopoulos TP, Kravvariti E, Panitsas F, Angelopoulou MK, Liaskas A, Kontopidou FN, et al. Very late relapses in Hodgkin lymphoma treated with chemotherapy with or without radiotherapy: Linear pattern and distinct prognostic factors. *Blood Cancer J.* 2022 Jul;12(7):102.
- 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 Jul;198(1):50-61
- Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *N Engl J Med.* 2017;377:1836-46.
- Pedersen RN, Esen BO, Mellemkjaer L, Christiansen P, Ejlersen B, Lash TL, et al. The incidence of breast cancer recurrence 10-32 years after primary diagnosis. *J Natl Cancer Inst.* 2022 Mar;114(3):391-9
- Fuchs M, Goergen H, Kobe C, Kuhnert G, Lohri A, Greil R, et al. Positron Emission Tomography-Guided Treatment in Early-Stage Favorable Hodgkin Lymphoma: Final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. *J Clin Oncol.* 2019;37:2835-45.
- 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 Jun;35(16):1786-94.
- Aleman BM, Raemaekers JM, Tirelli U, Bortolus R, van 't Veer MB, Lybeert ML, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med.* 2003 Jun;348(24):2396-406.
- von Tresckow B, Kreissl S, Goergen H, Brockelmann PJ, Pabst T, Fridrik M, et al. Intensive treatment strategies in advanced-stage Hodgkin's lymphoma (HD9 and HD12): analysis of long-term survival in two randomised trials. *Lancet Haematol.* 2018 Oct;5:e462-73.
- Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, Johnson P, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med.* 2015 Apr;372(17):1598-607.
- Brockelmann PJ, Angelopoulou MK, Vassilakopoulos TP. Prognostic factors in Hodgkin lymphoma. *Semin Hematol.* 2016 Jul;53(3):155-64.