

Trends in Survival for Classical Hodgkin Lymphoma (cHL) in the Modern Treatment Era: A SEER Population Study

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Background: Classical Hodgkin lymphoma (cHL) is a highly curable malignancy. However, a subset of patients relapse or remain refractory to first-line therapy. Pembrolizumab, a PD-1 inhibitor, has shown favorable outcomes in clinical trials; this study assessed its impact on overall survival (OS) at the population level.

Methods: We used data from the Surveillance, Epidemiology, and End Results (SEER) program. We included adults aged ≥ 20 years diagnosed with classical Hodgkin lymphoma from 2013 through 2021, excluding cases from 2017. Patients were divided into two groups: before pembrolizumab approval (2013–2016) and after approval (2018–2021). Overall survival (OS) was analyzed using Kaplan–Meier curves and log-rank tests. Multivariable Cox models were used to identify independent predictors of OS.

Results: A total of 2,742 patients were included. Median overall survival was not reached in either cohort due to high survival rates and short follow-up time in the second period; therefore, restricted mean survival time at 60 months was used for comparison. The restricted mean OS was 57.0 months (95% CI: 56.5–57.6) in Period 1 and 56.4 months (95% CI: 55.8–57.0) in Period 2, with no significant difference between groups ($\chi^2=0.490$, $p = 0.484$). Multivariable Cox regression identified female sex (HR = 0.654, $p = 0.003$), younger age ($p < 0.001$), localized (HR = 0.637, $p = 0.011$) or regional disease (HR = 0.600, $p = 0.003$), lymphocyte-rich histology (HR = 0.338, $p = 0.012$) as factors associated with improved survival. Factors associated with increased mortality included not receiving chemotherapy (HR = 2.424, $p < 0.001$) or radiotherapy (HR = 2.205, $p = 0.002$). Time period was not associated with OS ($p = 0.165$).

Conclusion: overall survival in cHL remained excellent and stable over time. While immune checkpoint inhibitors have transformed management of relapsed/refractory disease and offered potential improvements in survival, limitations in treatment-specific data and follow-up length emphasize the need for further research to fully understand the impact of new therapies.

Introduction

Hodgkin lymphoma (HL) accounts for approximately 10% of all lymphomas and remains one of the most common hematologic malignancies in young adults worldwide [1]. Between 2000 and 2019, classical Hodgkin lymphoma occurred at an age-standardized incidence of about 3.6 per 100,000 in men and 2.8 per 100,000 in women, with survival rates that have improved significantly over the past several decades due to advances in chemotherapy and radiotherapy [2, 3]. Classical Hodgkin lymphoma represents about 95% of HL cases [4]. Despite favorable outcomes with conventional therapy, around 5–10% of Hodgkin lymphoma patients are refractory to first-line therapy, while an additional 10–30% relapse after an initial remission [5]. Novel therapeutic approaches have been

developed to address this challenge, most notably immune checkpoint inhibitors targeting the PD-1 pathway, such as pembrolizumab, which have demonstrated significant efficacy [6].

The KEYNOTE-087 and KEYNOTE-204 trials established the role of pembrolizumab in cHL, demonstrating high objective response rates and improved progression-free survival [7, 8]. These findings led to expanded indications and widespread use of PD-1 blockade in cHL. However, it remains unclear whether the introduction of pembrolizumab has translated into improved survival trends at the population level, outside the controlled environment of clinical trials. Therefore, the objective of this study was to compare survival trends among patients with classical Hodgkin lymphoma before (2013-2016) and after (2018-2021) the approval of pembrolizumab, utilizing the Surveillance, Epidemiology, and End Results (SEER) database to assess potential shifts in population-wide outcomes.

Methods

We conducted a retrospective analysis using data from the SEER (Surveillance, Epidemiology, and End Results) program, a population-based cancer registry in the United States providing de-identified patient information for research [9]. Institutional Review Board approval was waived due to the public, deidentified nature of the data. Data were extracted from the SEER Research Plus database, Incidence - SEER Research Data, 17 Registries. Nov 2024 Sub (2000-2022) covering cases through 2021. Adults aged ≥ 20 years diagnosed with classical Hodgkin lymphoma (cHL) between 2013-2016 (pre-pembrolizumab era) and 2018-2021 (post-pembrolizumab era) were included, excluding cases from 2017 because this year represented a transition period during which access to pembrolizumab was inconsistent. Patients with nodular lymphocyte predominant disease were also excluded, as this subtype is not an indication for pembrolizumab use in treatment.

Disease stage was classified using SEER summary staging, integrating clinical and pathological information as localized, regional, or distant. Median overall survival (OS) was estimated using the Kaplan-Meier method, with survival curves compared via log-rank tests. Because more than half of the cohort remained alive at the end of the follow up, the median overall survival could not be calculated. Therefore, we report the 60-month restricted mean survival time (RMST). Multivariate Cox proportional hazards models evaluated the impact of age, sex, race, histologic subtype, stage, chemotherapy, and radiotherapy on OS. Crude survival percentages were calculated for the full cohort, while KM and hazard analyses were restricted to 60 months to account for differences in follow-up. Cause-specific survival was determined using SEER cause of death codes, which are derived from death certificates and may be at risk of misclassification. Statistical significance was defined as $p < 0.05$. All analyses were performed using IBM SPSS Statistics version 27.

Results

A total of 2,742 patients diagnosed with classical Hodgkin lymphoma were included in this analysis, excluding nodular lymphocyte-predominant cases. Of these, 1,245 (45.4%) were female and 1,497 (54.6%) were male. The majority of patients were White (82.5%), followed by Black (9.6%), Asian/Pacific Islander (7.5%), and American Indian/Alaska Native (0.4%).

Nodular sclerosis was the most common histologic subtype (51.6%), while lymphocyte-rich (5.1%) and lymphocyte-depleted (0.4%) were least frequent. At diagnosis, most patients presented with regional disease (57.7%), followed by localized (24.8%) and distant involvement (17.5%). The majority of patients received chemotherapy (93.6%) and beam radiotherapy (95.6%). Refusal of radiotherapy was rare (3.6%), though slightly higher in the post-pembrolizumab era (Period 2: 4.4%) compared to the pre-pembrolizumab era (Period 1: 2.9%) as illustrated in Table 1.

Variable	Period 1 n (%)	Period 2 n (%)	Survival % (P1)	Survival % (P2)	P-value
Sex					0.259
Female	726 (46.8)	519 (43.5)	88.80	94.60	
Male	824 (53.2)	673 (56.5)	86.30	94.50	
Race/Ethnicity					
Asian/Pacific Islander	104 (6.7)	101 (8.5)	94.20	93.10	
American Indian/Alaska Native	9 (0.6)	3 (0.3%)	55.60	100	0.015
White	1300 (83.9)	961 (80.6)	87.30	94.50	
Black	137 (8.8)	127 (10.7)	86.10	96.10	
Subtype					
Lymphocyte-rich	66 (4.3)	75 (6.3)	92.40	98.70	
Mixed cellularity	142 (9.2)	101 (8.5)	83.80	93.10	
Lymphocyte-depleted	6 (0.4)	4 (0.3)	66.70	75.00	<0.001
Nodular sclerosis	871 (56.2)	545 (45.7)	90.40	96.10	
Classical Hodgkin, NOS	465 (30.0)	467 (39.2)	82.80	92.50	
Stage					
Localized	354 (22.8)	325 (27.3)	81.90	92.60	
Regional extension	909 (58.6)	673 (56.5)	90.90	97.50	<0.001
Distant	287 (18.5)	194 (16.3)	83.60	87.60	
Radiotherapy					
Beam radiation	1485 (95.8)	1137 (95.4)	87.90	94.70	
Refused	45 (2.9)	53 (4.4)	71.10	90.60	0.039
NOS/Other methods	20 (1.3)	2 (0.2)	≥94	100	
Chemotherapy					
Yes	1451 (93.6)	1116 (93.6)	90.40	96.00	<0.001
No/Unknown	99 (6.4)	76 (6.4)	45.50	73.70	

Table 1. Patient Characteristics and Survival Rates.

At the time of analysis, 2,483 patients (90.6%) were alive. Period 1 (2013–2016) included 1,550 patients (56.5%) with 194 deaths, while Period 2 (2018–2021) included 1,192 patients (43.5%) with 65 deaths. To account for differences in follow-up duration, survival was restricted to 60 months. The estimated mean survival was 57.0 months (95% CI: 56.5–57.6) in Period 1 and 56.4 months (95% CI: 55.8–57.0) in Period 2, with an overall mean of 57.1 months (95% CI: 56.7–57.5). Median survival was not reached due to high censoring (92.7%), and the reported 56–57 month values represent the restricted mean survival time (RMST) over the 60-month follow-up period and should not be interpreted as median survival.

Kaplan–Meier curves demonstrated overlapping trajectories, and the log-rank test showed no significant survival difference between the two periods ($\chi^2 = 0.490$, $p = 0.484$) Figure 1.

Figure 1. Kaplan-Meier Overall Survival Curves for Patients with Classical Hodgkin Lymphoma Pre-pembrolizumab (2013–2016) and Post Pembrolizumab Approval (2018–2021).

Subgroup analyses showed no survival differences by sex ($p = 0.259$). Survival varied by race ($p = 0.015$), with Asian/Pacific Islander patients having the highest survival in Period 1 (94.2%) but a slight decline in Period 2 (93.1%). White and Black patients demonstrated improved outcomes in

Period 2 (94.5% and 96.1%, respectively), while American Indian/Alaska Native patients had the lowest survival in Period 1 (55.6%) but 100% survival in Period 2, though subgroup numbers were small. Survival was also significantly associated with histologic subtype ($p < 0.001$) and stage at diagnosis ($p < 0.001$), with notable improvements across all stages and subtypes in Period 2. Treatment modality influenced outcomes: survival improved among patients receiving radiotherapy (87.9% to 94.7%, $p = 0.039$), and patients receiving chemotherapy consistently had higher survival compared with untreated patients ($p < 0.001$) Table 1.

Multivariable Cox regression identified several independent predictors of survival. Female sex was associated with improved outcomes (HR = 0.654, 95% CI: 0.496–0.862, $p = 0.003$). Younger age groups demonstrated significantly lower hazards of death ($p < 0.001$). Localized (HR = 0.637, $p = 0.011$) and regional disease (HR = 0.600, $p = 0.003$) predicted improved survival compared with distant disease. Histological subtype influenced prognosis ($p = 0.019$), with lymphocyte-rich cases showing the most favorable outcome (HR = 0.338, $p = 0.012$). Patients not receiving chemotherapy (HR = 2.424, $p < 0.001$) or radiotherapy (HR = 2.205, $p = 0.002$) had significantly higher mortality risk. Time period (Period 2 vs. Period 1) was not independently associated with survival (HR = 0.796, 95% CI: 0.576–1.098, $p = 0.165$).

Cause-specific death classification was highly predictive (HR = 0.065, 95% CI: 0.048–0.088, $p < 0.001$) Table 2.

Variable	Hazard Ratio (95% CI)	P-value
Period		
Pre-Pembrolizumab Era	0.796 (0.576 – 1.098)	0.165
Post-Pembrolizumab Era	Reference	
sex		
Female	0.654 (0.496 – 0.862)	0.003
male	Reference	
Race		
White	0.430 (0.153 – 1.212)	0.11
Black	0.723 (0.237 – 2.206)	0.569
Asian or Pacific Islander	0.357 (0.111 – 1.152)	0.085
American Indian/Alaska Native	Reference	
Age		
20-24	0.04	<0.001
25-29	0.056	<0.001
30-34	0.102	<0.001
35-39	0.055	<0.001
40-44	0.084	<0.001
45-49	0.118	<0.001
50-54	0.247	<0.001
55-59	0.28	<0.001
60-64	0.228	<0.001
65-69	0.383	<0.001
70-74	0.437	<0.001
75-79	0.511	<0.001
80-84	0.54	<0.001
85-89	1.098	<0.001
90+	Reference	
Stage		
Localized only	0.637 (0.451 – 0.900)	0.011
Regional by direct extension only	0.600 (0.430 – 0.838)	0.003
Distant site(s)/node(s) involved	Reference	

Histological subtypes		
Lymphocyte-rich	0.338 (0.145 - 0.788)	0.012
Mixed cellularity	1.326 (0.873 - 2.014)	0.186
Lymphocyte-depleted	2.697 (0.838 - 8.680)	0.096
Nodular sclerosis	1.060 (0.790 - 1.422)	0.699
Classical Hodgkin Lymphoma	Reference	
Chemotherapy (Systemic therapy)		
No/Unknown	2.424 (1.728 - 3.401)	<0.001
Yes	Reference	
Radiotherapy		
No	2.205 (1.326 - 3.668)	0.002
Yes	Reference	
Cause of death		
Dead of other cause	0.065 (0.048 - 0.088)	<0.001
Dead Attributable to this Cancer	Reference	

Table 2. Multivariate Cox-proportional Hazard Analysis.

Kaplan-Meier survival estimates showed high survival in both cohorts, with 60-month survival of 91.1% in Period 1 and 94.5% in Period 2 (Table 3).

Months	Survival % P1 (2013-2016)	Number at Risk P1	Survival % P2 (2018-2021)	Number at Risk P2
0	100	1550	100	1192
12	97.50	1490	98.50	1153
24	95.80	1458	97.30	1130
36	93.50	1418	96.50	1110
48	92.70	1399	95.20	1095
60	91.10	1354	94.50	1070

Table 3. Kaplan-Meier Number at Risk and Survival Estimates.

Discussion

The goal of this study was to determine whether the introduction of pembrolizumab was associated with changes in the overall survival (OS) in patients with classical Hodgkin lymphoma (cHL) from the SEER database. Despite the introduction of a new and highly effective novel therapy in the relapsed/refractory (R/R) lymphoma, no statistically significant improvement was observed in 60-month overall survival between the pre pembrolizumab era (period 1: 2013-2016) and the post pembrolizumab era (period 2: 2018-2021). Kaplan-Meier survival curves of these two periods were nearly overlapping and the log-rank test with a ($p=0.484$) confirmed the absence of a difference. A multivariable Cox proportional hazards modeling further reinforced this observation showing that the period of diagnosis was not an independent predictor of survival (HR for period 2 vs period 1: 0.796, 95% CI: 0.576-1.098, $p=0.165$).

This absence of population-level improvement should not be interpreted as evidence against pembrolizumab effectiveness. In the pivotal phase 3 KEYNOTE204 trial, Pembrolizumab was established as a new standard of care for R/R cHL where it demonstrated a statistically significant and clinically meaningful improvement in PFS over brentuximab vedotin with a median progression-free survival (PFS) of 13.2 months versus 8.3 months, respectively (HR = 0.65, $p=0.0027$). This benefit was robust across key patient subgroups, including those who were ineligible for autologous stem cell transplantation and those with primary refractory disease, firmly

establishing pembrolizumab as a preferred treatment option and a new standard of care in this setting [8]. Similarly, the anti PD 1 antibody nivolumab has shown impressive overall response rates of (69%) and durable responses in heavily pretreated R/R cHL patients in the registrational checkmate 205 trial leading to its regulatory approval and adoption [10]. Such trials have demonstrated evidence that ICIS represents a major therapeutic advance for patients with cHL who have progress on prior therapies.

Unlike many other malignancies where the introduction of novel interventions can lead to substantial and readily detectable improvements in population level survival, cHL is characterized by exceptionally high cure rates with established frontline therapies [11]. For several decades, combination chemotherapy regimens such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) have achieved remissions in over 75% of patients with advanced-stage disease and in over 85% of those with early-stage disease [12]. This creates a so called limit or a “ceiling effect,” where the prognosis baseline is so favourable that slight or small improvements in OS at a population level become statistically challenging to demonstrate over short observational periods. Therefore, the stability of excellent survival outcomes observed in this cohort with a 60-month OS of 91.1% in Period 1 and 94.5% in Period 2 should be viewed as evidence of the constant and consistent effectiveness of standard of care treatments in a real-world setting and not as a lack of progress.

The analysis in this paper revealed that female sex was independently associated with improved survival (HR = 0.654, 95% CI: 0.496–0.862; p=0.003). This finding is consistent with numerous epidemiological studies across various lymphoma subtypes, who have repeatedly shown a survival advantage for the females [13, 14]. The underlying mechanism is not fully understood, but some sources present a potential protective effect of female sex hormones, differences in immune responses and variations in drug pharmacokinetics [15].

Age at diagnosis, as expected, emerged as one of the most powerful predictors of mortality, with younger age groups showing significantly lower hazards of death(p<0.001).Younger cHL patients may have a distinct disease biology but more importantly they have a greater capacity to tolerate the intensive multi-agent chemotherapy and consolidative therapies required for cure while older age is strongly associated with higher burden of comorbidities and a reduced physiological reserve, meaning treatment usually requires de-escalation or even stopping or using different treatments than the potentially curative options [13].

The findings revealed that patients presenting with localized (HR=0.637) or regional (HR= 0.6) disease have a significantly better prognosis than those with distant metastatic involvement, underlying the importance of early diagnosis and the constant success of combined modality therapy in achieving high cure rates for patients with limited stage disease [16, 17].

Failure to receive chemotherapy (HR = 2.424) or radiotherapy (HR = 2.205) were powerful independent predictors of mortality. A modest but notable increase in radiotherapy refusal between the two time periods was seen, rising from 2.9% to 4.4%, this may reflect a new and evolving trend towards treatment de-escalation [18], a potential confounder in our comparison.

Histology subtype was also an independent predictor of outcome. The lymphocyte-rich subtype of cHL was associated with the most favourable prognosis, (HR = 0.338, 95% CI: 0.145–0.788; p=0.012), this finding is well supported by the current literature [19]. While not reaching statistical significance, in our model likely due to very small numbers, the lymphocyte depleted subtype is historically associated with a more aggressive clinical course and poorer outcomes [20, 21].

Finally, our study highlighted the persistence of significant demographic disparities in cHL survival. The univariate analysis used revealed that survival varied significantly by race (p=0.015), this adds to the already extensive literature that demonstrated that black and Hispanic patients with HL have historically experienced inferior outcomes compared with their white counterparts,



presenting an important challenge in oncology [22].

Mechanisms driving these disparities are complex and stem to multiple roots, however, recent research presents interesting and important explanatory models. A pooled analysis of patients treated on highly controlled Children's Oncology Group clinical trials, where initial therapy was standardized and access was equalized, found no difference in event-free survival by race or ethnicity. Strikingly, however, OS was significantly worse for the Black and Hispanic children, with this difference being driven entirely by a higher risk of mortality after relapse [23].

This suggests that the survival gap may not be due to differences in the efficacy of frontline chemotherapy but rather to systemic barriers in accessing and benefiting from complex, high cost, and specialized salvage therapies such as ASCT, BV, and PD-1 inhibitors.

Nonetheless, we observed a marked improvement in 5-year survival for Black patients from Period 1 (86.1%) to Period 2 (96.1%), a trend that substantially narrowed the survival gap with White patients (94.5% in Period 2), even though the multivariable model for race was not significant, it may suggest that this improvement could be an early signal or a glimpse of hope of the positive impact of novel agents.

The introduction of more effective and potentially better-tolerated salvage therapies like pembrolizumab, which can be administered in the outpatient setting without the intense toxicities of salvage chemotherapy, may be starting to mitigate the historical disparity in post-relapse outcomes. Even though this is speculative, but it is important hypothesize since this warrants further investigation, suggesting a potential equity enhancing benefit of these new agents that extends beyond just a direct impact on PFS.

This study has several limitations as the SEER database lacks drug-specific and line-of-therapy information, therefore, we cannot identify which patients received pembrolizumab limiting our ability to access treatment-specific effects. Moreover, the approval of pembrolizumab was for relapsed/refractory disease only and the follow-up period was shorter for more recent patients. This may decrease the accuracy of survival estimates by incomplete long-term follow-up and by more advanced disease. Finally, chemotherapy and radiotherapy fields might be incomplete and there may be misclassification of the cause of death which can lead to inaccurate estimates of disease-specific survival.

In conclusion, there was no noticeable change in the overall 60-month survival in cHL in the period following pembrolizumab approval (2018–2021) compared with the earlier period (2013–2016) likely indicating the already excellent outcomes with established frontline therapies. Age, sex, cancer stage, administration of treatment and histologic subtype remained the independent predictors of survival. Racial disparities persisted but the gap in survival differences between groups narrowed in the later period. Limitations in treatment-specific data and follow-up length emphasize the need of further research to fully understand the impact of new therapies.

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None

Declaration of interest statement

The authors declare no competing interests.

Ethics approval

Not applicable. SEER data are de-identified and publicly available.

Data availability

Data used in this study are publicly available from the SEER database <https://seer.cancer.gov/>

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