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ORIGINAL REPORT

# Treatment Selection and Outcomes in Early-Stage Classical Hodgkin Lymphoma: Analysis of the National Cancer Data Base

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## ABSTRACT

### Purpose
The choice between combined-modality therapy (CMT) and chemotherapy alone for early-stage Hodgkin lymphoma (HL) remains controversial. Our objective was to define factors affecting treatment selection and resulting survival outcomes in the United States.

### Patients and Methods
We identified 20,600 patients treated with CMT or chemotherapy between 2003 and 2011 from the National Cancer Data Base. Factors affecting treatment selection were studied in a mixed-effects logistic model. Survival outcomes were compared using a propensity score analysis to account for indication bias.

### Results
Only 49.5% of patients received CMT, and this proportion steadily declined between 2003 (59.4%) and 2011 (45.2%), particularly in younger patients. Apart from classical prognostic factors (age, stage, tumor location, histology, comorbidities), treatment selection was significantly influenced by sex, black race, distance to facility, and type of insurance. Uninsured patients had the lowest odds of receiving CMT. A significant random effect related to facility-specific treatment preference was also evident. Estimated 5-year overall survival (OS) was 89.6%, and relative survival (RS) was 94.3%. After adjustment for guarantee-time and indication biases, CMT was associated with better OS (hazard ratio [HR], 0.61; 95% CI, 0.53 to 0.70) and RS (excess HR, 0.42; 95% CI, 0.33 to 0.54) than chemotherapy alone. This effect was without significant heterogeneity in subset analysis and was not sensitive to unobserved confounding.

### Conclusion
Socioeconomic factors affect selection of curative treatments in HL. Widespread abandonment of CMT beyond circumstances sanctioned by guidelines may affect survival. Further research should focus on developing strategies that minimize toxicity and access disparities without compromising survival.

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## INTRODUCTION

Classical Hodgkin lymphoma (HL) is a highly curable malignancy with long-term disease-specific survival exceeding 85%.[1] Treatment of early-stage HL with sequential chemotherapy and radiation (combined-modality therapy [CMT]) demonstrated superior survival compared with radiation therapy alone and became standard in the early 2000s.[2-4] Until 2007, the US National Comprehensive Cancer Network (NCCN) guidelines recommended CMT for all patients with early-stage HL.[5] This endorsement was independent of the early favorable or unfavorable designations, which are distinguished by the presence of the following poor prognostic factors: "B" symptoms, bulky tumor, elevated erythrocyte sedimentation rate (ESR), or multisite involvement by lymphoma. Whereas early favorable HL can be treated with shorter chemotherapy and lower radiation dose, overall survival (OS) exceeds 90% even in the unfavorable category treated with CMT.[3,6] Because of the late toxicities of radiation, particularly secondary cancers, there is ongoing interest in identifying groups who can be cured with chemotherapy alone.[7] This strategy remains controversial. One randomized trial suggested superior survival, whereas others indicated worse survival, when radiation therapy was omitted.[8,9] How this uncertainty affects management and outcomes in the United States has not yet been evaluated.

HL often affects young adults; approximately half of cases are diagnosed in patients ≤ 40 years old.[10,11] The employment-driven US health insurance market has limited access to coverage for many young Americans, resulting in lack of insurance among approximately 30% of adults 19 to 29 years old.[12] Inadequate coverage is associated with advanced stage at diagnosis and higher risk of death, but the correlation between socioeconomic factors and treatment selection in HL has not been studied.[13,14] In fact, few data exist on the patterns of care for HL in the United States, although decreasing utilization of radiotherapy in the 1990s had been noted.[15] Our prior study suggested that socioeconomic factors influence utilization of curative radiation therapy in marginal zone lymphoma.[16] The objective of this study was to identify factors determining choice of treatment (CMT or chemotherapy alone) among Americans with early-stage HL and to assess the impact of this choice on survival.

## PATIENTS AND METHODS

### Data Source and Study Cohort

This study used deidentified data and was exempt from human protection oversight by the institutional review board. We conducted a population-based, retrospective analysis using the National Cancer Data Base (NCDB), which is a joint program established in 1989 by the Commission on Cancer of the American College of Surgeons and the American Cancer Society.[17] This comprehensive data set integrates registry records from more than 1,500 accredited hospitals, capturing approximately 70% of all incident cancers in the United States.[18] According to the agreements executed with each accredited facility, data from Veteran Affairs, Department of Defense, Puerto Rican, and certain other programs are removed from research files. The accreditation requires an annual 90% follow-up rate for all eligible patients diagnosed within 5 years. Censoring bias is avoided by releasing survival outcomes (calculated from the date of diagnosis) only after at least 5 years of follow-up. Data are coded using standardized algorithms, and duplicate records are eliminated. Variables include patient demographics, comorbidities, socioeconomic status, tumor histology, stage, and the first course of therapy, defined as all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence. Treatments delivered or withheld because of progression, insufficient response, or other therapy modifications caused by restaging or intercurrent events are not recorded. Details of dose, field, and technique of radiation therapy are collected, but specific chemotherapy regimens, doses, or treatment durations are not.

The NCDB provided records of 52,394 patients with HL diagnosed between 2003 and 2011, with survival data available for the 2003 to 2006 cohort (Fig 1). We excluded patients without histologically confirmed classical HL, patients with HIV infection, or patients with advanced or unrecorded stage. We also excluded patients treated outside of the reporting facility, those who did not receive chemotherapy, and those with unknown treatment status, with a database flag that radiation was contraindicated, or with unusual delays in treatment.

### Variables

For ease of interpretation, we categorized age at diagnosis as 18 to 29, 30 to 49, 50 to 69, and ≥ 70 years. Considering the risk of breast cancer after thoracic irradiation in younger women, interaction between age and sex was included in regression models. Race/ethnicity was categorized as white non-Hispanic, white Hispanic, black, American Indian, and Asian/Pacific Islander. Number of comorbidities was derived from the Charlson/Deyo variation of the Charlson comorbidity index.[19] Stage was based on American Joint Committee on Cancer/Union for International Cancer Control TNM staging for lymphoma. Socioeconomic data were provided as quintiles of median household income and number of persons with less than high school education in

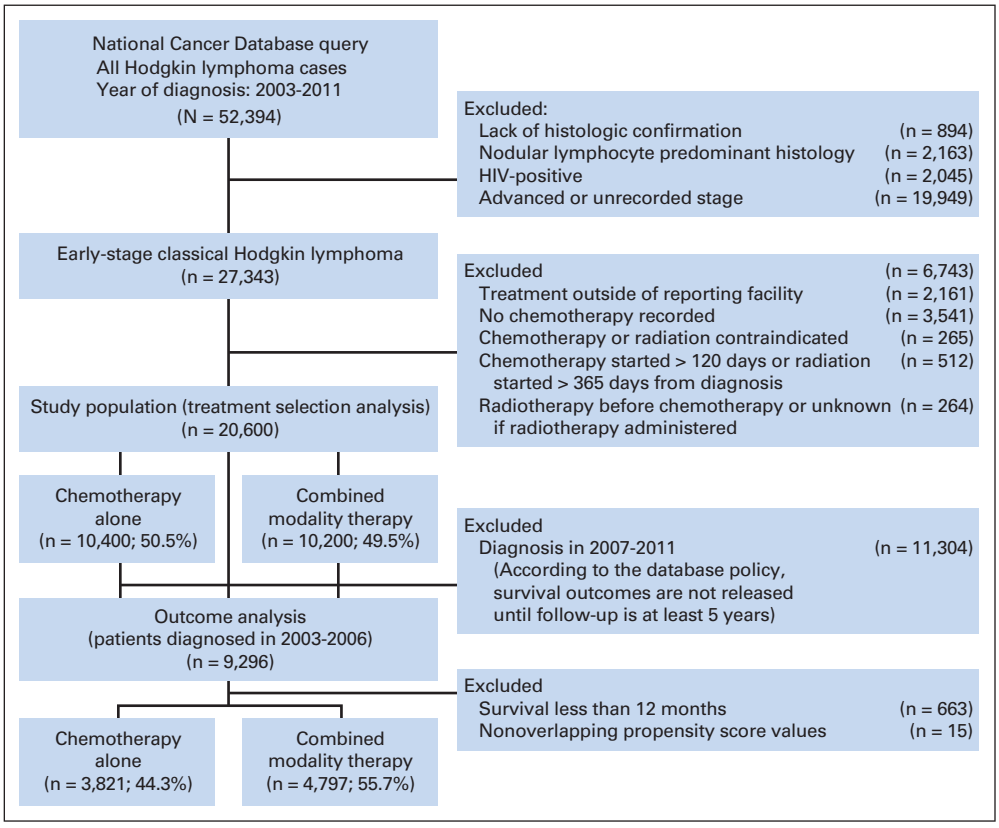


**Fig 1.** CONSORT diagram for cohort selection.

  

patients' census tract of residence. The type of facility was assigned according to the Commission on Cancer accreditation category based on annual case volume and available oncology services. Geographic locations corresponded to the US Census Divisions.

Missing data on race (2.4%), insurance (3.3%), income/education (6.1%), type of area (6.7%), distance to facility (4.9%), and B symptoms (11%) were handled by multiple imputation using chained equations.[20] This method is superior to alternatives (complete case or missing data indicator methods) as far as analytic bias is concerned, under the assumption that data are missing at random conditional on observed variables.[21] Each variable was imputed using a logistic, ordinal, multinomial logistic, or predictive mean matching model, thus creating 50 imputed data sets. The imputation models included the same set of variables present in analysis models, including the age-sex interaction, treatment modality, censoring indicator, and Nelson-Aalen estimate of cumulative hazard function.

### Statistical Analysis

Treatment selection was evaluated in a random-effects logistic regression model that accounted for clustering of treatment patterns by facility.[22,23] Linearized trends in the rates of CMT utilization were summarized as annual percent change derived from log-normal models with robust SE.[24]

For the comparative survival analysis, we used a multistep propensity score methodology. First, the conditional landmark method was used to account for the guarantee-time bias, limiting patients to those with ≥ 12 months of survival (the allowed time frame for starting radiation therapy).[25] Probability of receiving either chemotherapy or CMT was predicted in a logistic model averaged among the imputed data sets and incorporating all variables associated with treatment selection or survival.[26,27] Patients with nonoverlapping probability of treatment were excluded to satisfy the positivity assumption for causal inference.[28] Subsequently, we calculated inverse probability of treatment weights, thus creating a pseudopopulation with a distribution of confounding variables in each treatment arm that was identical to the entire cohort.[29] Covariate balance was evaluated using standardized differences of means.[30] We then fitted adjusted flexible parametric survival models for the two outcomes of OS and relative survival (RS).[31,32] RS was used as a proxy for lymphoma-specific survival and was defined as the ratio of observed survival to expected survival in the general population matched by age, sex, race, and calendar year.[33] Proportional hazards assumption was verified by testing interaction of each variable with time. In addition, we used one-to-one propensity score matching as an alternative approach to assess the sensitivity of our findings to the choice of methodology.

We conducted two types of sensitivity analyses to assess potential residual indication bias. First, we assessed heterogeneity of treatment effects by test of interaction, subset analysis, and progressive propensity score tail trimming.[34] Second, we evaluated the effect of a putative unmeasured binary confounder on the survival model estimates.[35] The prevalence and hazard ratio (HR) for the confounder were derived from a study of prognostic factors in early HL, which were not available in the NCDB data.[36] All analyses were performed using Stata/SE 13.1 (Stata, College Station, TX) with the stpm2 module for survival analysis (version 1.4.9) and report 95% CIs.

## RESULTS

We identified 20,600 patients with early-stage HL who were treated with CMT or chemotherapy alone between 2003 and 2011. Detailed clinical characteristics of the cohort are provided in the Data Supplement. There were 51.3% women, 58.8% of patients were younger than age 40 years at diagnosis, and 9.8% of patients were older than age 65 years at diagnosis. Most patients had stage IIA nodular sclerosis HL. Chemotherapy was initiated at a median of 27 days after diagnosis (interquartile range [IQR], 16 to 41 days), and radiation therapy was initiated at a median of 171 days (IQR, 145 to 209 days). Median dose of radiation was 30.6 Gy (IQR, 30.0 to 36.0 Gy), the same for stage I

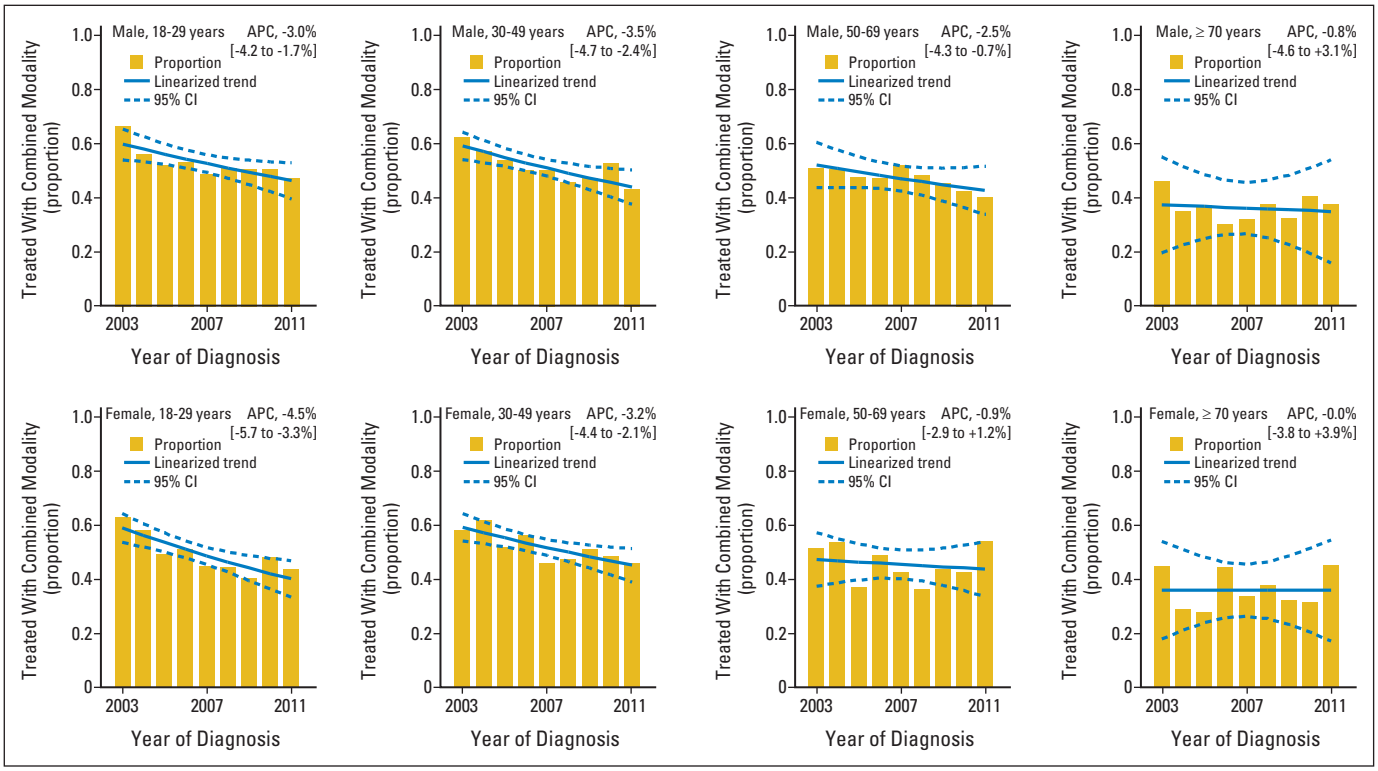


**Fig 2.** Proportion of patients receiving combined-modality therapy in each year by age and sex category. Trends are summarized as annual percent change (APC) with 95% CIs.

**Table 1.** Factors Associated With Treatment Selection Among Patients With Early-Stage Classical Hodgkin Lymphoma in the National Cancer Data Base, 2003 to 2011

| Variable | % of All Patients (N = 20,600) | Odds Ratio | 95% CI | *P* |
|---|---|---|---|---|
| Sex and age category | | | | |
| Male, 18-29 years | 15.9 | | Reference | |
| Male, 30-49 years | 19.5 | 0.92 | 0.83 to 1.02 | .11 |
| Male, 50-69 years | 9.7 | 0.79 | 0.69 to 0.90 | < .001 |
| Male, ≥ 70 years | 3.6 | 0.58 | 0.47 to 0.72 | < .001 |
| Female, 18-29 years | 19.7 | 0.87 | 0.79 to 0.97 | .0083 |
| Female, 30-49 years | 19.9 | 0.92 | 0.83 to 1.02 | .13 |
| Female, 50-69 years | 8.1 | 0.72 | 0.63 to 0.83 | < .001 |
| Female, ≥ 70 years | 3.6 | 0.55 | 0.44 to 0.68 | < .001 |
| Race/ethnicity | | | | |
| White non-Hispanic | 81.6 | | Reference | |
| White Hispanic | 6.7 | 1.08 | 0.94 to 1.25 | .26 |
| Black | 9.1 | 0.84 | 0.75 to 0.95 | .0043 |
| American Indian | 0.2 | 0.95 | 0.46 to 1.96 | .88 |
| Asian/Pacific Islander | 2.3 | 1.15 | 0.93 to 1.42 | .20 |
| No. of comorbidities | | | | |
| 0 | 90.9 | | Reference | |
| 1 | 7.7 | 0.75 | 0.67 to 0.85 | < .001 |
| ≥ 2 | 1.4 | 0.62 | 0.47 to 0.83 | .001 |
| Stage | | | | |
| IA | 17.4 | | Reference | |
| IB | 5.4 | 0.58 | 0.49 to 0.68 | < .001 |
| IIA | 49.6 | 0.88 | 0.80 to 0.97 | .009 |
| IIB | 27.6 | 0.63 | 0.57 to 0.70 | < .001 |
| Histologic subtype | | | | |
| Nodular sclerosis | 65.8 | | Reference | |
| Mixed cellularity | 10.1 | 1.00 | 0.90 to 1.11 | .95 |
| Lymphocyte depleted | 0.8 | 0.54 | 0.38 to 0.77 | < .001 |
| Lymphocyte rich | 3.7 | 1.35 | 1.15 to 1.60 | < .001 |
| Unspecified classical Hodgkin lymphoma | 19.6 | 0.93 | 0.86 to 1.01 | .096 |
| Anatomic origin | | | | |
| Head/neck | 24.8 | | Reference | |
| Mediastinum/thorax | 12.7 | 1.06 | 0.95 to 1.17 | .32 |
| Abdomen/pelvis | 2.3 | 0.33 | 0.26 to 0.42 | < .001 |
| Axilla/arm | 4.6 | 1.16 | 0.99 to 1.35 | .065 |
| Leg | 2.5 | 0.82 | 0.67 to 1.01 | .062 |
| Extranodal | 1.4 | 0.80 | 0.61 to 1.04 | .096 |
| Nodal, unspecified | 51.7 | 0.86 | 0.79 to 0.93 | < .001 |
| Primary insurance | | | | |
| Private/managed care | 70.8 | | Reference | |
| Uninsured | 7.5 | 0.72 | 0.64 to 0.82 | < .001 |
| Medicaid | 8.7 | 0.86 | 0.76 to 0.96 | .010 |
| Medicare | 11.6 | 0.80 | 0.70 to 0.92 | .0013 |
| Other government | 1.4 | 1.49 | 1.14 to 1.94 | .0035 |
| Median income | | | | |
| < $30,000 | 11.6 | | Reference | |
| $30,000-$34,999 | 16.3 | 0.97 | 0.85 to 1.10 | .64 |
| $35,000-$45,999 | 28.1 | 0.99 | 0.87 to 1.13 | .94 |
| ≥ $46,000 | 44.0 | 0.98 | 0.85 to 1.13 | .79 |
| % with at least high school education | | | | |
| < 14% | 14.4 | | Reference | |
| 14.0%-19.9% | 22.2 | 1.03 | 0.92 to 1.17 | .59 |
| 20.0%-28.9% | 24.0 | 1.10 | 0.96 to 1.25 | .17 |
| ≥ 29% | 39.4 | 0.99 | 0.86 to 1.14 | .91 |
| Year of diagnosis | | | | |
| 2003-2004 | 22.2 | | Reference | |
| 2005-2006 | 22.9 | 0.73 | 0.66 to 0.80 | < .001 |
| 2007-2008 | 23.6 | 0.63 | 0.57 to 0.68 | < .001 |
| 2009-2011 | 31.3 | 0.65 | 0.60 to 0.71 | < .001 |
| Type of facility | | | | |
| Community | 10.1 | | Reference | |
| Comprehensive | 53.9 | 1.12 | 0.97 to 1.30 | .11 |
| Academic/research | 35.1 | 0.81 | 0.69 to 0.96 | .015 |
| Other | 0.9 | 0.70 | 0.46 to 1.07 | .096 |
| Geographical region | | | | |
| Northeast | 6.7 | | Reference | |
| Atlantic | 16.0 | 0.79 | 0.62 to 1.00 | .051 |
| Southeast | 19.3 | 0.67 | 0.53 to 0.84 | < .001 |
| Great Lakes | 18.9 | 1.13 | 0.90 to 1.43 | .30 |
| South | 5.8 | 0.95 | 0.71 to 1.27 | .73 |
| Midwest | 8.5 | 1.21 | 0.92 to 1.59 | .17 |
| West | 6.9 | 0.62 | 0.47 to 0.82 | < .001 |
| Mountain | 4.7 | 1.12 | 0.81 to 1.53 | .50 |
| Pacific | 13.2 | 1.02 | 0.79 to 1.30 | .89 |
| Type of area | | | | |
| Metropolitan | 97.1 | | Reference | |
| Urban | 11.2 | 1.08 | 0.97 to 1.21 | .17 |
| Rural | 1.7 | 1.27 | 0.98 to 1.63 | .068 |
| Distance to facility, miles | | | | |
| < 50 | 92.0 | | Reference | |
| ≥ 50 | 8.0 | 0.75 | 0.66 to 0.86 | < .001 |
| Random effect variance | | | | |
| Treatment facility | | 0.50 | 0.43 to 0.59 | |

(continued in next column)

(continued)

and II HL, and the median number fractions was 17 (IQR, 15 to 20 fractions). The proportion of patients treated with more than 30.6 Gy of radiation decreased from 53.2% in 2003 to 22.7% in 2011 (Data Supplement). The proportion of patients receiving mantle-field radiation also decreased from 29.8% in 2003 to 14.3% in 2011 (Data Supplement). In addition, there was an increase in patients treated using three-dimensional conformal (from 3.4% in 2003 to 11.5% in 2011) or intensity-modulated radiation therapy (from 0.8% in 2003 to 14.3% in 2011).

### *Factors Affecting Treatment Selection*

Only 10,200 patients (49.5%) received CMT, and its use evidently declined from 59.4% in 2003 to 45.2% in 2011 (annual percent change, −3.1%; 95% CI, −3.7 to −2.6%; Data Supplement). This decline was steepest for women younger than age 30 years, whereas the trends for women ≥ 50 and men ≥ 70 years old were not significant (Fig 2).

Treatment selection was associated with both clinical and socioeconomic factors (Table 1). The odds of receiving CMT decreased with age, and in the youngest group, the odds were further significantly lower for women. CMT was less frequently used in patients with B symptoms, subdiaphragmatic tumors, or lymphocyte-depleted histology. Black patients were significantly less likely to receive CMT,

  

even adjusting for insurance, income, and education. Patients with private insurance had significantly higher odds of receiving CMT compared with those who were uninsured or who had Medicaid or Medicare coverage. The utilization of CMT was lower in academic centers, in some geographic regions, and when distance to treatment facility exceeded 50 miles.

A significant random effect related to treatment patterns at individual facilities was also evident (intraclass correlation, 13.3%; 95% CI, 11.6% to 15.2%). Eleven percent of the 1,351 facilities reported a CMT rate of less than 10%, whereas 6% of facilities reported a CMT rate of more than 90% (median, 50%; IQR, 30% to 67%). The number of patients diagnosed at each institution varied from one to 274 patients (median, 10 patients; IQR, five to 20 patients). Facilities reporting less than seven patients had a lower rate of CMT utilization (42%) than those with larger volume (51%).

### *Survival Outcomes*

Median follow-up time for the 9,296 patients with available survival data was 6.1 years. Aggregate OS at 5 years was 89.6% (95% CI, 89.0% to 90.3%), and 5-year RS was 94.3% (95% CI, 93.7% to 94.9%). Despite the NCDB ascertainment mandate, 20% of patients had the date of last contact before 5 years of follow-up, without a significant difference between the CMT and chemotherapy-only groups ($P = .17$). Prognostic factors significantly associated with RS included age greater than 50 years, comorbidities, B symptoms, mediastinal primary, and unfavorable (lymphocyte-depleted) or favorable (lymphocyte-rich) histology (Table 2). Race was not significant after adjustment for income and insurance. Unadjusted 5-year OS estimates were 94.7% (95% CI, 94.0% to 95.3%) after CMT and 83.7% (95% CI, 82.5% to 84.8%) after chemotherapy alone; the respective estimates of RS were 97.6% (95% CI, 97.1% to 98.1%) and 89.2% (95% CI, 88.0% to 90.2%).

The significant treatment indication bias between groups was decreased in the propensity score analysis, with residual standardized differences of means for all confounders ≤ 3.5% (Data Supplement). In the adjusted population, OS was significantly better for patients treated with CMT compared with patients treated with chemotherapy alone (Fig 2A), with an HR of 0.61 (95% CI, 0.53 to 0.70; $P < .001$). Estimated 5-year OS (conditional on surviving 12 months according to the landmark analysis cutoff) was 94.6% (95% CI, 93.9% to 95.3%) for CMT and 90.9% (95% CI, 89.9% to 91.7%) for chemotherapy alone. The excess HR in the RS model also favored CMT over chemotherapy (excess HR, 0.42; 95% CI, 0.33 to 0.54; $P < .001$), with estimated 5-year RS rates of 97.5% (95% CI, 96.9% to 98.1%) and 94.1% (95% CI, 93.1% to 94.9%), respectively. These significant differences persisted when the conditional landmark cutoff was varied between 6 and 24 months of minimum survival.

There was no evidence of heterogeneity in the HR for OS (Fig 3B) or RS (data not shown) in subgroups defined by propensity score quintiles or by clinical factors, including the early unfavorable stage IIB stratum. The advantage of CMT was relatively insensitive to further adjustment by a putative unobserved confounder designed to confer an unfavorable HR of 2.3 (corresponding to elevated ESR; Data Supplement). The prevalence of such a confounder would need to be ≥ 50% in the chemotherapy arm and 0% in the CMT arm to render the results statistically insignificant. The outcome analysis was also essentially unchanged using propensity score matching; among the 6,590 matched records, the HR for OS was 0.64 (95% CI, 0.55 to 0.75) and the excess HR for RS was 0.45 (95% CI, 0.35 to 0.59).

**Table 2.** Prognostic Factors for Relative Survival in Patients With Early-Stage Hodgkin Lymphoma (n = 9,296)

| Variable | Excess Hazard Ratio | 95% CI | *P* |
|---|---|---|---|
| Age, years | | | |
| 18-29 | Reference | | |
| 30-49 | 1.31 | 1.03 to 1.65 | .025 |
| 50-69 | 2.84* | 2.18 to 3.71 | < .001 |
| ≥ 70 | 6.04* | 4.19 to 8.71 | < .001 |
| Sex | | | |
| Male | Reference | | |
| Female | 0.89 | 0.75 to 1.04 | .15 |
| Race/ethnicity | | | |
| White non-Hispanic† | Reference | | |
| White Hispanic | 0.98 | 0.70 to 1.37 | .89 |
| Black | 1.22 | 0.93 to 1.60 | .15 |
| Asian/Pacific Islander | 1.53 | 0.87 to 2.69 | .14 |
| No. of comorbidities | | | |
| 0 | Reference | | |
| 1 | 1.95 | 1.56 to 2.44 | < .001 |
| ≥ 2 | 3.05 | 2.14 to 4.35 | < .001 |
| Stage | | | |
| IA | Reference | | |
| IB | 1.43 | 0.98 to 2.09 | .061 |
| IIA | 1.01 | 0.78 to 1.31 | .92 |
| IIB | 1.91 | 1.48 to 2.45 | < .001 |
| Histology | | | |
| Nodular sclerosis | Reference | | |
| Mixed cellularity | 1.01 | 0.78 to 1.30 | .94 |
| Lymphocyte depleted | 2.02 | 1.21 to 3.38 | .0076 |
| Lymphocyte rich | 0.47 | 0.24 to 0.89 | .021 |
| Unspecified classical Hodgkin lymphoma | 1.29 | 1.06 to 1.57 | .012 |
| Anatomic origin | | | |
| Extrathoracic | Reference | | |
| Mediastinum/thorax | 1.41 | 1.13 to 1.76 | .0023 |
| Insurance | | | |
| Private/managed care | Reference | | |
| Uninsured | 1.95* | 1.42 to 2.67 | < .001 |
| Medicaid | 1.98 | 1.50 to 2.63 | < .001 |
| Medicare | 2.24* | 1.68 to 2.99 | < .001 |
| Other government | 1.37 | 0.66 to 2.87 | .40 |
| Median income | | | |
| < $30,000 | Reference | | |
| $30,000-$34,999 | 0.90 | 0.69 to 1.19 | .47 |
| $35,000-$45,999 | 0.92 | 0.71 to 1.18 | .49 |
| ≥ $46,000 | 0.64 | 0.49 to 0.83 | < .001 |
| Year of diagnosis (per year, 2003-2006) | 0.92 | 0.86 to 0.99 | .035 |

*Nonproportional hazard; however, inclusion of a time interaction term did not substantially alter the results.
†Including American Indian category, which was omitted because of few events.

## DISCUSSION

In this first, to our knowledge, analysis of population-based treatment patterns in early-stage HL, we focused on the choice between CMT and chemotherapy alone as primary strategy. The comprehensive NCDB data reveal that the use of CMT is continuously declining, particularly in younger age groups, and currently less than half of patients undergo CMT. We discovered that socioeconomic factors

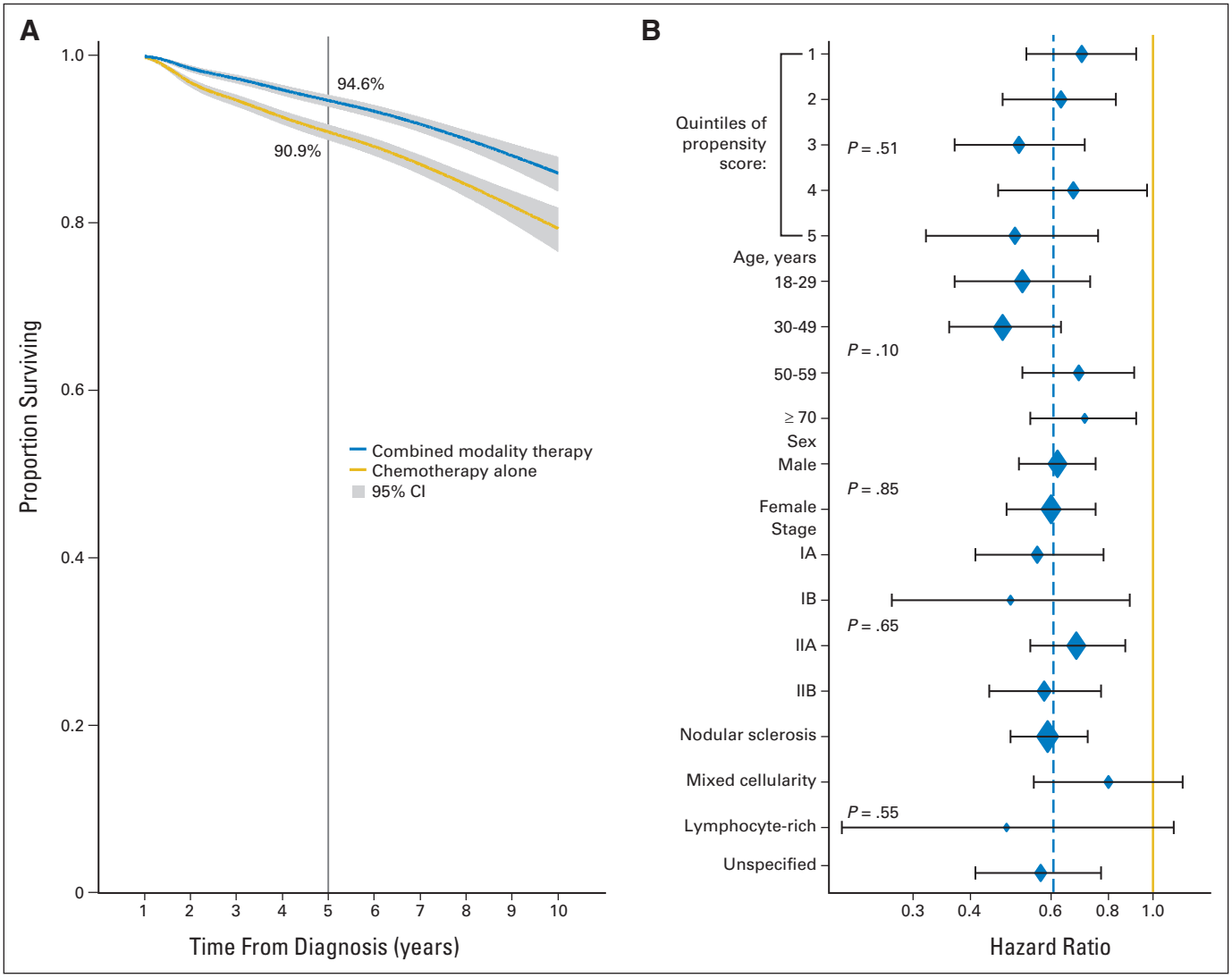


**Fig 3.** Overall survival analysis in the propensity score–weighted population. (A) Overall survival by treatment modality. (B) Forest plot of hazard ratios (HRs) comparing combined-modality therapy with chemotherapy alone in cohort subsets. HRs less than 1.0 favor combined-modality therapy. *P* values are from the subset test of interaction. The lymphocyte-depleted subset was omitted because of the small number of patients. The blue dashed line indicates the aggregate HR (0.61). Propensity score quintiles are ordered by increasing propensity to undergo combined-modality therapy.

such as race and insurance status are significantly associated with the selection of treatment modality. In addition, we found that patients who received CMT in 2003 to 2006 in accordance with contemporary NCCN guidelines had a significant survival advantage.

The association of adherence to guidelines for curative treatment with socioeconomic factors has been demonstrated in solid tumors.[37,38] Similarly, in non-Hodgkin lymphomas, racial and socioeconomic differences in the utilization of treatment modalities exist and parallel observed disparities in survival.[16,39,40] In HL, worse outcomes among racial minorities and economically deprived patients were linked to advanced stage at presentation but not to variations in treatment.[14,41,42] We found that after adjustment for the type of health insurance, other socioeconomic factors including race were no longer significantly associated with excess mortality. The insurance-related differences in CMT utilization are thus concerning in the context of survival disparities. When recommending chemotherapy alone, clinicians are often motivated by long-term toxicities of radiation, but radiation is also costly, requires complex planning, and creates a significant psychosocial burden for patients.[43,44] Although in clinical trials most patients complete the assigned therapy and HL progression during chemotherapy occurs in less than 3% of patients, vulnerable individuals in the community may not pursue radiation because of toxicities of chemotherapy or physician recommendation after interim scans.[3,6,7,45,46] This could contribute to the lower rates of CMT in patients who are older or have comorbidities.

Interim restaging by positron emission tomography (PET), first described in 2006 as predictive of excellent prognosis after CMT, might potentially facilitate the use of chemotherapy alone in HL.[47] However, two randomized trials have not confirmed noninferiority of chemotherapy-only strategies guided by interim PET, even though short-term survival outcomes were excellent.[45,48] We could not distinguish from the NCDB data to what extent interim restaging led to discrepancies between the initial plan for CMT and the actual delivery of radiation, potentially leading to analytic bias. However, the major

  

decline in CMT utilization occurred before 2007 (Data Supplement), so the impact of PET on this trend was not evident. In an observational study, one might expect that individuals with bulky tumors or partial remission after chemotherapy would be more likely to be offered radiation, thus creating a bias in favor of chemotherapy alone, but those few patients who experienced progression during chemotherapy would have likely aborted the planned radiation. We observed a significant survival advantage for CMT that could not be explained by realistic levels of unobserved confounding. The detected HR is quite similar to the Cochrane meta-analysis of randomized trials (HR for OS, 0.40).[8] Nevertheless, expert opinions regarding the relative risks and benefits of CMT remain highly polarized.[49,50] Since 2007, the NCCN guidelines have included an option of therapy with chemotherapy alone. Our study sheds additional light on this uncertainty by excluding significant heterogeneity of treatment effects in subsets defined by age, sex, stage, or histologic subtype. The strategies to limit the radiation field to involved nodes only and to use intensity-modulated radiation therapy may offer alternative approaches to balance the benefits and risks of CMT.[51]

Despite the fact that the NCDB captured a majority of patients with HL diagnosed in the United States in 2003 to 2011, our study is limited by its retrospective design and the nature of the data source. We could not assess the quality of treatment responses or their effect on CMT utilization or compare HL recurrences and progression-free survival. Our surrogate RS end point can measure excess lymphoma-related mortality compared with the general population, but it may be affected by performance status and rates of secondary malignancies, which were unavailable. In addition, we could not identify specific chemotherapy regimens or duration, which may be another source of bias. Potential differences between the number of cycles given with or without radiation may exist. The median time to radiotherapy initiation of nearly 6 months suggests that CMT may have often included fairly long courses of chemotherapy. Some prognostic factors for HL, such as ESR, tumor bulk, and involved nodal areas, were also unrecorded and were addressed through sensitivity analysis, but the question of unobserved confounding always limits interpretation of treatment comparisons from observational data. Some misclassification and treatment underreporting are unavoidable in a large registry-based data set like the NCDB. We found low rates of recorded chemotherapy and radiation among patients treated outside of the reporting facility, which led to exclusion of 8% of patients from the analysis. Still, no treatment was recorded in an additional 9% of patients, likely reflecting significant underascertainment of treatment modalities. The need to exclude those patients limits the interpretation of our results for the population at large. The assumption of administrative censoring for survival analysis could not be independently verified either. Considering further implementation of conditional landmark analysis, we must emphasize that the comparative aspect of our study should be interpreted with caution, recognizing these methodologic assumptions. In addition, longer follow-up will be needed to fully assess the impact of contemporary CMT on the risk of cardiovascular disease, solid tumors, and resulting long-term survival.

In conclusion, treatment selection in Americans with early-stage HL is associated with socioeconomic factors, and deviations from guideline-endorsed pathways may be associated with a survival disadvantage. Further research is needed to compare relative risks of modern CMT using the involved-field techniques with extended anthracycline-based chemotherapy. The insights gained from our population-based analysis support ongoing clinical research efforts in HL, which are necessary to develop treatments that are less toxic without compromising survival and to eliminate socioeconomic disparities in treatment delivery and outcomes.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

## AUTHOR CONTRIBUTIONS

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## REFERENCES


1. Siegel R, DeSantis C, Virgo K, et al: Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 62:220-241, 2012
2. Noordijk EM, Carde P, Dupouy N, et al: Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: Long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. J Clin Oncol 24:3128-3135, 2006
3. Fermé C, Eghbali H, Meerwaldt JH, et al: Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 357:1916-1927, 2007
4. Follows GA, Ardeshna KM, Barrington SF, et al: Guidelines for the first line management of classical Hodgkin lymphoma. Br J Haematol 166:34-49, 2014
5. Hoppe RT, Advani RH, Bierman PJ, et al: Hodgkin disease/lymphoma: Clinical practice guidelines in oncology. J Natl Compr Canc Netw 4:210-230, 2006
6. Engert A, Plutschow A, Eich HT, et al: Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 363:640-652, 2010
7. Canellos GP, Abramson JS, Fisher DC, et al: Treatment of favorable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. J Clin Oncol 28:1611-1615, 2010
8. Herbst C, Rehan FA, Brillant C, et al: Combined modality treatment improves tumor control and overall survival in patients with early stage Hodgkin's lymphoma: A systematic review. Haematologica 95:494-500, 2010
9. Meyer RM, Gospodarowicz MK, Connors JM, et al: ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med 366:399-408, 2012
10. Thomas RK, Re D, Zander T, et al: Epidemiology and etiology of Hodgkin's lymphoma. Ann Oncol 13:147-152, 2002 (suppl 4)
11. Shenoy P, Maggioncalda A, Malik N, et al: Incidence patterns and outcomes for Hodgkin lymphoma patients in the United States. Adv Hematol 2011:725219, 2011
12. US Census Bureau: Health Insurance Coverage of Young Adults Aged 19 to 25: 2008, 2009, and 2011. Washington, DC, US Census Bureau, 2012
13. Aizer AA, Falit B, Mendu ML, et al: Cancer-specific outcomes among young adults without health insurance. J Clin Oncol 32:2025-2030, 2014
14. Smith EC, Ziogas A, Anton-Culver H: Association between insurance and socioeconomic status and risk of advanced stage Hodgkin lymphoma in adolescents and young adults. Cancer 118:6179-6187, 2012
15. Koshy M, Rich SE, Mahmood U, et al: Declining use of radiotherapy in stage I and II Hodgkin's disease and its effect on survival and secondary malignancies. Int J Radiat Oncol Biol Phys 82:619-625, 2012
16. Olszewski AJ, Desai A: Radiation therapy administration and survival in stage I/II extranodal

marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Int J Radiat Oncol Biol Phys 88:642-649, 2014

**17.** Bilimoria KY, Stewart AK, Winchester DP, et al: The National Cancer Data Base: A powerful initiative to improve cancer care in the United States. Ann Surg Oncol 15:683-690, 2008

**18.** Bilimoria KY, Bentrem DJ, Stewart AK, et al: Comparison of commission on cancer-approved and -nonapproved hospitals in the United States: Implications for studies that use the National Cancer Data Base. J Clin Oncol 27:4177-4181, 2009

**19.** Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 45:613-619, 1992

**20.** White IR, Royston P, Wood AM: Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 30:377-399, 2011

**21.** van der Heijden GJ, Donders AR, Stijnen T, et al: Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: A clinical example. J Clin Epidemiol 59:1102-1109, 2006

**22.** Brown H, Prescott R: Generalised Linear Mixed Models, Applied Mixed Models in Medicine. New York, NY, John Wiley & Sons, 2006, pp 107-152

**23.** Hardy D, Chan W, Liu CC, et al: Racial disparities in the use of hospice services according to geographic residence and socioeconomic status in an elderly cohort with nonsmall cell lung cancer. Cancer 117:1506-1515, 2011

**24.** McNutt LA, Wu C, Xue X, et al: Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol 157:940-943, 2003

**25.** Giobbie-Hurder A, Gelber RD, Regan MM: Challenges of guarantee-time bias. J Clin Oncol 31:2963-2969, 2013

**26.** Mitra R, Reiter JP: A comparison of two methods of estimating propensity scores after multiple imputation. Stat Methods Med Res [epub ahead of print on June 11, 2012]

**27.** Armstrong K: Methods in comparative effectiveness research. J Clin Oncol 30:4208-4214, 2012

**28.** Hernán MA: Beyond exchangeability: The other conditions for causal inference in medical research. Stat Methods Med Res 21:3-5, 2012

**29.** Cole SR, Hernán MA: Constructing inverse probability weights for marginal structural models. Am J Epidemiol 168:656-664, 2008

**30.** Austin PC: Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 28:3083-3107, 2009

**31.** Royston P, Parmar MK: Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 21:2175-2197, 2002

**32.** Nelson CP, Lambert PC, Squire IB, et al: Flexible parametric models for relative survival, with application in coronary heart disease. Stat Med 26:5486-5498, 2007

**33.** Rutherford MJ, Dickman PW, Lambert PC: Comparison of methods for calculating relative survival in population-based studies. Cancer Epidemiol 36:16-21, 2012

**34.** Stürmer T, Rothman KJ, Avorn J, et al: Treatment effects in the presence of unmeasured confounding: Dealing with observations in the tails of the propensity score distribution—A simulation study. Am J Epidemiol 172:843-854, 2010

**35.** Lin DY, Psaty BM, Kronmal RA: Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics 54: 948-963, 1998

**36.** Klimm B, Goergen H, Fuchs M, et al: Impact of risk factors on outcomes in early-stage Hodgkin's lymphoma: An analysis of international staging definitions. Ann Oncol 24:3070-3076, 2013

**37.** Hébert-Croteau N, Brisson J, Latreille J, et al: Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. J Clin Oncol 22:3685-3693, 2004

**38.** Chagpar R, Xing Y, Chiang YJ, et al: Adherence to stage-specific treatment guidelines for patients with colon cancer. J Clin Oncol 30:972-979, 2012

**39.** Tao L, Foran JM, Clarke CA, et al: Socioeconomic disparities in mortality after diffuse large B-cell lymphoma in the modern treatment era. Blood 123:3553-3562, 2014

**40.** Flowers CR, Fedewa SA, Chen AY, et al: Disparities in the early adoption of chemoimmunotherapy for diffuse large B-cell lymphoma in the United States. Cancer Epidemiol Biomarkers Prev 21:1520-1530, 2012

**41.** Keegan TH, Clarke CA, Chang ET, et al: Disparities in survival after Hodgkin lymphoma: A population-based study. Cancer Causes Control 20: 1881-1892, 2009

**42.** Evens AM, Antillón M, Aschebrook-Kilfoy B, et al: Racial disparities in Hodgkin's lymphoma: A comprehensive population-based analysis. Ann Oncol 23:2128-2137, 2012

**43.** Ng AK, Kuntz KM, Mauch PM, et al: Costs and effectiveness of staging and treatment options in early-stage Hodgkin's disease. Int J Radiat Oncol Biol Phys 50:979-989, 2001

**44.** Lauzier S, Levesque P, Drolet M, et al: Out-of-pocket costs for accessing adjuvant radiotherapy among Canadian women with breast cancer. J Clin Oncol 29:4007-4013, 2011

**45.** Raemaekers JM, André MP, Federico M, et al: Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol 32:1188-1194, 2014

**46.** Evens AM, Hong F, Gordon LI, et al: The efficacy and tolerability of Adriamycin, bleomycin, vinblastine, dacarbazine and Stanford V in older Hodgkin lymphoma patients: A comprehensive analysis from the North American intergroup trial E2496. Br J Haematol 161:76-86, 2013

**47.** Hutchings M, Loft A, Hansen M, et al: FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 107:52-59, 2006

**48.** Radford J, O'Doherty M, Barrington S, et al: Results of the 2nd planned interim analysis of the RAPID trial (involved field radiotherapy versus no further treatment) in patients with clinical stages 1A and 2A Hodgkin lymphoma and a "negative" FDG-PET scan after 3 cycles ABVD. Blood 112:369, 2008 (abstr)

**49.** Meyer RM, Hoppe RT: Point/counterpoint: Early-stage Hodgkin lymphoma and the role of radiation therapy. Blood 120:4488-4495, 2012

**50.** Yahalom J: Chemotherapy only in early-stage Hodgkin lymphoma: More relapses but "same" (or possibly worse) survival—Reconsidering the misguided trend to omit radiotherapy. Curr Hematol Malig Rep 9:212-216, 2014

**51.** Campbell BA, Hornby C, Cunninghame J, et al: Minimising critical organ irradiation in limited stage Hodgkin lymphoma: A dosimetric study of the benefit of involved node radiotherapy. Ann Oncol 23:1259-1266, 2012

  

## GLOSSARY TERMS

**American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) TNM staging:** a cancer staging system that describes the extent of cancer in a patient?s body. "T" describes the size of the tumor and whether it has invaded nearby tissue; "N" describes regional lymph nodes that are involved; "M" describes distant metastasis (spread of cancer from one body part to another). The TNM Classification of Malignant Tumours was developed and maintained by the UICC to achieve consensus on one globally recognized standard for classifying the extent of spread of cancer. The TNM classification was also used by the AJCC. In 1987, the UICC and AJCC staging systems were unified into a single staging system. Prognosis of a patient is defined by TNM classification.

**Charlson comorbidity index:** a weighted index that takes into account the number and seriousness of 19 comorbid diseases to categorize comorbidity burden. The Charlson comorbidity index has prognostic significance in assessing disease outcomes and health resource use and has been validated in the cancer population.

**confounding variables:** extraneous variables in a statistical model that are associated/correlated with both the independent and dependent variables but are not on the causal pathway between independent and dependent variables. When confounding variables are present, crude (unadjusted) statistical models describing the association between independent and dependent variables are biased (ie, wrong) as the risk estimate includes the effect of the confounding variable as well (type 1 error). As a result, to properly describe the relationship between independent and dependent variables, a multivariable model that includes both the independent variable and all relevant confounding variables as predictors must be executed.

**intensity-modulated radiation therapy:** radiation treatment using beams with nonuniform fluence profiles that shape the dose distribution in the target volume and adjacent normal structures. Beam modulation is typically achieved via multileaf collimators or custom-milled compensators to achieve the appropriate fluence profiles calculated by inverse optimization algorithms. The radiation beam is divided into beamlets of varying intensity such that the sum from multiple beams via inverse planning results in improved tumor targeting and normal tissue sparing. A technique of radiation therapy delivery in which the intensity of each beamlet of radiation coming from a specific angle can be adjusted to provide a desired dose distribution when the doses delivered from all beamlets are added from a single angle and from all dose delivery angles. An advanced type of high-precision radiotherapy, which aims to improve the coverage of the radiotherapy target and/or minimize radiation dose to surrounding normal tissue.

**landmark analysis:** the conditional landmark analysis selects a fixed time during follow-up as the landmark. The subset of patients still in the study at the landmark time is separated into categories described by the classifying event and observed forward in time. Patients who cease follow-up before the landmark time are excluded from the analysis, and membership in the classifying event group is defined at the landmark time regardless of any shifts that may occur later. In essence, the analysis clock is reset at the landmark.

**logistic regression model:** a multivariable prediction model in which the log of the odds of a time-fixed outcome event or other binary outcome is related to a linear equation.

**sensitivity analyses:** analyses that evaluate the impact of missing data and possible differences in interval assessments.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Treatment Selection and Outcomes in Early-Stage Classical Hodgkin Lymphoma: Analysis of the National Cancer Data Base**

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