Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) represents approximately 5% of all Hodgkin lymphoma and is recognized to have a more indolent course and potentially an improved prognosis when compared with classical Hodgkin lymphoma (cHL) [1]. While advanced-stage (stages III-IV) NLPHL is treated with upfront chemotherapy, the current standard of care for (stages I-II) NLPHL in the United States includes involved site radiation therapy, as the preferred or standard option, for all stage I and stage II patients [2]. This standard of care for NLPHL is primarily based on retrospective analyses and subgroup analyses of prospective trials [2–8]. In the case of early-stage cHL, there has been a decline in the United States (US) in radiotherapy utilization that has been associated, in some studies, with inferior survival following diagnosis[9]. This trend is largely related to large, prospective randomized trials supporting a chemotherapy alone treatment strategy, but these trials do not exist in the setting of NLPHL [2].

Abstract

Early-stage nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is associated with a favorable prognosis. Our aim was to evaluate the patterns of care of radiotherapy utilization in this disease and to define the relationship between treatment modality and survival. The National Cancer Database was queried for patients with stages I-II NLPHL diagnosed from 2004 to 2012. Patients were compared based on primary therapy into four categories: radiotherapy, chemotherapy, both, or neither. Covariate-adjusted and propensity score-weighted (PS) Cox proportional hazards models were used, adjusting for potential factors confounding survival. After exclusions, 1420 patients were evaluated, 571 (40%) received radiotherapy alone, 318 (22%) received chemotherapy alone, 351 (25%) received both, and 180 (13%) received neither. Younger patient age ($P = 0.001$), female gender ($P = 0.019$), and chemotherapy use ($P < 0.001$) were associated with decreased radiotherapy utilization. On PS, radiation alone (HR = 0.298, $P < 0.001$) and chemoradiotherapy (HR = 0.258, $P < 0.001$) were associated with improved survival compared to no upfront therapy, but the use of chemotherapy alone did not statistically differ compared to no initial therapy (HR = 0.784, $P = 0.078$). In this large database analysis, over one-third of patients with early-stage NLPHL did not receive radiotherapy as a component of initial therapy. The omission of upfront radiotherapy was associated with inferior survival.
Previous retrospective series have shown similar outcomes in patients with early-stage NLPHL treated with radiation therapy with or without chemotherapy with complete response rates of ≥98% and 10-year recurrence-free survival of 68–77% [5, 8]. More recently, a Surveillance, Epidemiology, and End Results (SEER)-based analysis has shown similar results, with a 10-year diseasespecific survival of 93% [1]. The same study showed a decrease in radiation therapy utilization from 1988 to 2010, despite an overall survival benefit associated with the use of radiation therapy on multivariable analysis (hazard ratio, HR = 0.64, \( P = 0.03 \)) [1]. Of note, this study was limited in that it was unable to evaluate the utilization and impact of systemic therapy in this patient population, a topic of considerable interest since the advent of the anti-CD20 antibody rituximab (initially FDA approved in 1997 for relapsed or refractory low-grade CD20-positive non-Hodgkin’s lymphoma), which has demonstrated efficacy as monotherapy in the treatment of NLPHL [1, 10–13].

Our aim was to update and further evaluate the patterns of care of radiotherapy utilization in the treatment of NLPHL in the United States and to define the relationship between treatment modality (i.e., systematic therapy and radiation therapy) and overall survival (OS) following diagnosis.

Methods and Materials

Data source and cohort selection

The National Cancer Database (NCDB) is a prospectively collected database led by the American College of Surgeons that collects patient-level data on patients with cancer diagnoses from participating institutions across the United States and Puerto Rico [14]. It is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons, who execute a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer-accredited hospitals. Established in 1989, the database is a nationwide facility-based comprehensive clinical surveillance resource oncology dataset that accounts for roughly 70% of new cancer diagnoses in the United States annually [14]. This study was approved by our institutional review board prior to initiation.

The NCDB was queried for patients with known stage I or II NLPHL diagnosed from 2004 to 2012. Figure 1 depicts the cohort selection process. Patients with contraindications to radiotherapy, patients who refused radiotherapy, and patients with unknown radiotherapy utilization were excluded, as were patients with unknown OS following diagnosis (lost to follow-up). Patient age,
Table 1. Clinical characteristics of the 1420 patients with early-stage nodular lymphocyte-predominant Hodgkin lymphoma in the National Cancer Database 2004–2012.

| Test                          | No treatment | Radiation only | Chemo only | Both  | Chi-square |
|------------------------------|--------------|----------------|------------|-------|------------|
|                              | n            | %              | n          | %     | n          | %          | P-value |
| **Total number**             | 180          | 13             | 571        | 40    | 318        | 22         | 351     | 25     |
| **Age**                      |              |                |            |       |            |             |         |        |
| ≤60                          | 133          | 74             | 448        | 78    | 239        | 75         | 308     | 88     | <0.001 |
| >60                          | 47           | 26             | 123        | 22    | 79         | 25         | 43      | 12     |        |
| **Year of Diagnosis (median)** |              |                |            |       |            |             |         |        |
| 2004                         | 14           | 8              | 35         | 6     | 23         | 7          | 38      | 11     | 0.052  |
| 2005                         | 18           | 10             | 34         | 6     | 26         | 8          | 43      | 12     |        |
| 2006                         | 10           | 6              | 37         | 6     | 23         | 7          | 32      | 9      |        |
| 2007                         | 17           | 9              | 46         | 8     | 28         | 9          | 38      | 11     |        |
| 2008                         | 20           | 11             | 76         | 13    | 35         | 11         | 36      | 10     |        |
| 2009                         | 22           | 12             | 72         | 13    | 42         | 13         | 41      | 12     |        |
| 2010                         | 24           | 13             | 76         | 13    | 43         | 14         | 46      | 13     |        |
| 2011                         | 31           | 17             | 95         | 17    | 49         | 15         | 38      | 11     |        |
| 2012                         | 24           | 13             | 100        | 18    | 49         | 15         | 39      | 11     |        |
| **Sex**                      |              |                |            |       |            |             |         |        |
| Male                         | 99           | 55             | 372        | 65    | 201        | 63         | 250     | 71     | 0.002  |
| Female                       | 81           | 45             | 199        | 35    | 117        | 37         | 101     | 29     |        |
| **Race**                     |              |                |            |       |            |             |         |        |
| White                        | 102          | 57             | 385        | 67    | 227        | 71         | 259     | 74     | <0.001*|
| Black                        | 59           | 33             | 122        | 21    | 70         | 22         | 65      | 19     |        |
| American Indian              | 0            | 0              | 3          | 1     | 0          | 0          | 2       | 1      |        |
| Asian/Pacific Islander       | 0            | 0              | 11         | 2     | 5          | 2          | 2       | 1      |        |
| Hispanic                     | 16           | 9              | 43         | 8     | 12         | 4          | 21      | 6      |        |
| Unknown                      | 0            | 0              | 7          | 1     | 4          | 1          | 2       | 1      |        |
| **Median income of zip†**   |              |                |            |       |            |             |         |        |
| <$38,000                     | 49           | 27             | 94         | 16    | 51         | 16         | 51      | 15     | 0.021  |
| $38,000–$47,999              | 27           | 15             | 125        | 22    | 64         | 20         | 85      | 24     |        |
| $48,000–$62,999              | 42           | 23             | 151        | 26    | 84         | 26         | 98      | 28     |        |
| $63,000+                     | 58           | 32             | 196        | 34    | 111        | 35         | 108     | 31     |        |
| Unknown                      | 4            | 2              | 6          | 1     | 8          | 3          | 9       | 3      |        |
| **Distance to Hospital†**    |              |                |            |       |            |             |         |        |
| <25 min                      | 146          | 81             | 469        | 82    | 259        | 81         | 267     | 76     | 0.269  |
| 25–100 min                   | 25           | 14             | 75         | 13    | 38         | 12         | 64      | 18     |        |
| >100 min                     | 5            | 3              | 21         | 4     | 14         | 4          | 12      | 3      |        |
| Unknown                      | 4            | 2              | 6          | 1     | 7          | 2          | 8       | 2      |        |
| **Charlson/Deyo Score**      |              |                |            |       |            |             |         |        |
| 0                            | 152          | 84             | 503        | 88    | 275        | 86         | 322     | 92     | 0.117  |
| 1                            | 25           | 14             | 55         | 10    | 35         | 11         | 21      | 6      |        |
| 2                            | 3            | 2              | 13         | 2     | 8          | 3          | 8       | 2      |        |
| **Insurance**                |              |                |            |       |            |             |         |        |
| No                           | 7            | 4              | 25         | 4     | 16         | 5          | 17      | 5      | 0.929  |
| Yes                          | 173          | 96             | 546        | 96    | 302        | 95         | 334     | 95     |        |
| **Stage**                    |              |                |            |       |            |             |         |        |
| Stage I                      | 130          | 72             | 412        | 72    | 126        | 40         | 161     | 46     | <0.001 |
| Stage II                     | 50           | 28             | 159        | 28    | 192        | 60         | 190     | 54     |        |
| **B-symptoms‡**              |              |                |            |       |            |             |         |        |
| No                           | 73           | 41             | 418        | 73    | 143        | 45         | 204     | 58     | <0.001 |
| Yes                          | 6            | 3              | 14         | 2     | 36         | 11         | 32      | 9      |        |
| Unknown                      | 101          | 56             | 139        | 24    | 139        | 44         | 115     | 33     |        |

*Compares only White, Black, and Hispanic groups because of small samples of other subgroups.

†For variables with a significant amount of unknown data points (income, distance, and B-symptoms), the unknown category was removed in the comparison.
year of diagnosis, sex, race, median income of patient ZIP code, distance from patient home to hospital, Charlson/Deyo comorbidity score, insurance status, stage, and the presence/absence of B-symptoms were extracted from the NCDB dataset for analysis [15]. For interpretation and analysis, patients were then categorized into one of four therapy groups based on treatment modality: radiation alone, chemotherapy alone, chemoradiotherapy, and neither.

### Statistical analyses

Chi-squared tests of independence were performed to compare each categorical demographic and clinical covariate between the four therapy groups. The primary outcome measure of this study was overall survival (OS) following diagnosis of NLPHL based on treatment strategy.

### Results

#### Clinical characteristics

After planned exclusions, 1420 patients with early-stage NLPHL with known therapy and survival information were identified from the NCDB database (Fig. 1). As demonstrated, 571 (40%) patients received radiation therapy alone, 318 (22%) received chemotherapy alone, 351 (25%) received both, and 180 (13%) received neither chemotherapy nor radiation therapy as part of their initial treatment course.

Table 1 describes the patient characteristics of the patient cohort grouped by therapy, with a chi-squared test to evaluate the difference across groups. The median age among patients was 45 years among patients treated with radiation therapy and 48 years among those in whom radiation therapy was omitted. Both groups were male predominant. Most patients identified themselves as white (69%) or black (22%) in both groups. Of evaluated patients, 58% of identified patients were stage I, the remainder stage II (42%), and clinical stage at presentation predicted for the use of a chemotherapy-containing approach (P < 0.001).

#### Factors associated with radiation therapy

Table 2 depicts the analysis of factors associated with receipt of radiation therapy. Because of the large percentage of patients with unknown B-symptoms, this was not included in the utilization model. As demonstrated, factors associated with decreased odds of receiving radiotherapy included younger age (P = 0.001), female sex (P = 0.019), and the use of chemotherapy (P < 0.001) on multivariable analysis. While median household income and

### Table 2. Analysis of factors associated with the receipt of radiotherapy for early-stage nodular lymphocyte-predominant Hodgkin lymphoma in the National Cancer Database 2004–2012.

|                | Univariable | Multivariable |
|----------------|-------------|---------------|
|                | P-value | OR | 95% CI | P-value |
| Patient age*   | <0.001 | 0.987 | 0.980–0.995 | 0.001 |
| Year of diagnosis* | 0.640 | 0.007 | 0.000–0.003 | 0.019 |
| Sex | 0.007 | ref | 0.745 | 0.583–0.952 |
| Race | 0.219 | 0.069 | 0.219 | 0.022 |
| Median income of zip | 0.219 | 0.069 | 0.219 | 0.022 |
| <$38,000 | ref | 1.764 | 1.216–2.557 | 0.003 |
| $38,000–$47,999 | 1.478 | 1.048–2.110 | 0.026 |
| $48,000–$62,999 | 1.487 | 1.048–2.110 | 0.026 |
| $63,000+ | 1.313 | 0.941–1.832 | 0.109 |
| Distance to Hospital | 0.505 | 0.069 | 0.170 |
| Charlson/Deyo Score | 0.069 | 0.069 | 0.069 | 0.170 |
| 0 | ref | 0.703 | 0.479–1.030 | 0.071 |
| 1 | 1.168 | 0.535–2.515 | 0.696 |
| 2 | 0.957 | 0.535–2.515 | 0.696 |
| Insurance No | 0.957 | 0.957 | 0.957 | 0.957 |
| Yes | 0.957 | 0.957 | 0.957 | 0.957 |
| Stage | <0.001 | 0.170 | 0.170 | 0.170 |
| Stage I | ref | 0.844 | 0.663–1.075 | <0.001 |
| Stage II | 0.844 | 0.663–1.075 | <0.001 |
| Chemotherapy No | <0.001 | 0.325 | 0.254–0.415 |
| Yes | 0.325 | 0.254–0.415 |

*Analyzed as a continuous variable. OR, odds ratio of receiving radiotherapy; CI, confidence interval.
Charlson/Deyo score appear to be associated with radiotherapy utilization, a clear trend did not emerge. Of note, stage II NLPHL was not associated with a change in radiotherapy utilization compared to stage I \((P=0.170)\). Figure 2 demonstrates the relatively stable trend in therapy utilization over the study period \((P=0.640)\).

**Overall survival analyses**

Median follow-up among the entire cohort was 48.3 months following diagnosis. Figure 3 provides the unadjusted Kaplan–Meier product limit estimates and PS-weighted survival curves of OS following diagnosis based on therapy received \((P<0.001)\). The 10-year unadjusted OS estimate for the no therapy, radiotherapy, chemotherapy, and chemoradiotherapy groups was 87\%, 93\%, 80\%, and 92\%, respectively. Table 3 provides the detailed analysis of factors associated with survival among the study cohort. As demonstrated, older age \((HR=4.082\) for age \(>60\) years, \(P<0.001)\), Charlson/Deyo score, and omission of initial therapy were associated with shortened time to death on multivariable analysis.

In comparing outcomes based on treatment modality on multivariable PS-weighted analysis, radiation therapy alone and chemoradiotherapy were associated with improved survival as compared to no treatment \((HR=0.298\) and 0.258, respectively, both \(P<0.001)\). In contrast, the use of chemotherapy alone suggested, but failed to confirm, an improvement in OS compared to no treatment \((HR=0.784, P=0.078)\). Additional, similar analyses confirmed these findings through independent groupings of therapy \(\text{radiotherapy vs. no radiotherapy, chemotherapy vs. \text{chemotherapy vs. radiotherapy}}\text{, and radiotherapy vs. chemoradiotherapy, and chemotherapy alone vs. chemoradiotherapy})\). These results are provided in the supplementary materials (Figs S1–S4 and Tables S1–S3).

**Discussion**

In the largest series on NLPHL to date, our findings are consistent with prior studies which have shown an excellent OS after treatment of NLPHL, with 10-year OS between 90\% and 100\% [1, 5, 8]. Our findings are also consistent with prior database studies showing an improvement in OS associated with the receipt of radiation therapy [1, 18]. In a similar recent study, Odei et al. utilized the NCDB to evaluate factors associated with survival among patients will all stages of NLPHL [18]. Their results independently affirm our findings, favoring radiotherapy utilization, in patients with early stage, and also in patients with advanced-stage NLPHL [18]. Given the improvement in OS associated with radiation therapy and chemoradiation seen in these studies, and not in nonradiotherapy containing approaches, there is support of the current
Per the NCCN guidelines, either involved site radiation therapy (preferred) or careful observation (in highly selected patients) is appropriate treatment options for stages IA and IIA NLPHL with combined modality therapy (chemoradiotherapy) for patients with early-stage bulky disease and patients with B-symptoms [2]. The NCCN does not support the use of chemotherapy alone in patients with early-stage NLPHL. Despite this consensus recommendation, 22% of patients in our study were treated with chemotherapy alone.

The cause of these variations in practice patterns is complex [9], but we suspect are related to referral patterns to medical oncologists but not radiation oncologists, lack of recognition of the benefit of radiotherapy in the treatment of NLPHL, and the practice of treating NLPHL patients in the same manner as cHL patients. The lowered utilization of radiotherapy among younger, female patients suggests that the possible late effects of radiotherapy (including cardiovascular disease and secondary malignancies such as breast cancer) are a driver in decision-making in favor of systemic therapy alone approaches. While it does appear that the recent decline in radiotherapy utilization for NLPHL patients identified in previous studies has stabilized [1], our analysis shows that more than 25% of patients receiving treatment for early-stage NLPHL did not receive radiation therapy.

In the era of rituximab, multiple series have demonstrated that focal radiotherapy is associated with improved disease control compared to systemic therapy [12, 19]. Perhaps related to sample size or uncontrolled confounders, these studies failed to demonstrate a difference in OS between upfront systemic therapy and radiotherapy. In contrast, in the current series, we found that patients treated with chemotherapy alone or with observation had inferior OS compared to those treated with radiotherapy (Fig. 3). An important caveat is that during the study period (2004–2012), the NCDB did not code for cytotoxic chemotherapy and targeted therapies differently. Beginning in 2013, rituximab is now to be classified as an immunotherapeutic agent, not a chemotherapy [15]. As a result, we suspect that the chemotherapy utilized in the patients in this series consists of those treated with both cytotoxic agents and targeted agents.

The primary limitation of our study is the potential for confounding in a retrospective analysis. It is possible that some uncontrolled variable (B-symptoms, bulky disease, and interim metabolic imaging such as PET-CT scans, radiotherapy technique, dose, fractionation, among others) could influence both treatment utilization and survival in this cohort, including treatment bias. However, using propensity score weighting, we adjusted for all confounders that we had available and think have an important effect on treatment decisions and survival. If healthier patients were treated with radiation therapy in ways which were not controlled for in this study, we would overestimate the benefit of radiation therapy.

Of note, the NCDB records the first round of treatment at diagnosis. Therefore, the salvage strategies among this cohort are unknown. However, the OS difference demonstrated here likely includes patients treated with salvage radiotherapy as well as salvage stem cell transplant, raising concern over the potential efficacy of such a salvage strategy on patient survival. Similarly, while OS is reported...
Table 3. Analysis of factors associated with time to death among patients with early-stage nodular-lymphocyte predominant Hodgkin lymphoma in the National Cancer Database 2004–2012.

|                      | Unadjusted Cox model |                         | Multivariable Cox model |                         | Propensity Score weighted |                         |
|----------------------|----------------------|-------------------------|-------------------------|-------------------------|---------------------------|-------------------------|
|                      | HR  | 95% CI  | P-value | HR  | 95% CI  | P-value | HR  | 95% CI  | P-value |
| Therapy              |     |         |         |     |         |         |     |         |         |
| None                 | 1.00 | –       | –       | 1.00 | –       | –       | 1.00 | –       | –       |
| Radiation            | 0.302 | 0.156–0.586 | <0.001 | 0.294 | 0.148–0.583 | <0.001 | 0.298 | 0.211–0.423 | <0.001 |
| Chemotherapy         | 1.023 | 0.571–1.833 | 0.939 | 0.849 | 0.456–1.582 | 0.607 | 0.784 | 0.598–1.028 | 0.078 |
| Both                 | 0.271 | 0.129–0.568 | <0.001 | 0.287 | 0.131–0.627 | 0.002 | 0.258 | 0.179–0.373 | <0.001 |
| Patient age          |     |         |         |     |         |         |     |         |         |
| ≤60                  | 1.00 | –       | –       | 4.082 | 2.521–6.61 | <0.001 |         |           |         |
| >60                  |     |         |         |     |         |         |     |         |         |
| Year of Diagnosis    |     |         |         |     |         |         |     |         |         |
| 2004                 | 1.00 | –       | –       |     |         |         |     |         |         |
| 2005                 | 1.551 | 0.647–3.722 | 0.325 |     |         |         |     |         |         |
| 2006                 | 1.253 | 0.467–3.36 | 0.654 |     |         |         |     |         |         |
| 2007                 | 0.391 | 0.103–1.486 | 0.168 |     |         |         |     |         |         |
| 2008                 | 1.424 | 0.548–3.699 | 0.468 |     |         |         |     |         |         |
| 2009                 | 1.283 | 0.503–2.378 | 0.602 |     |         |         |     |         |         |
| 2010                 | 1.596 | 0.590–4.318 | 0.357 |     |         |         |     |         |         |
| 2011                 | 1.547 | 0.541–4.424 | 0.415 |     |         |         |     |         |         |
| 2012                 | 1.143 | 0.346–3.774 | 0.827 |     |         |         |     |         |         |
| Sex                  |     |         |         |     |         |         |     |         |         |
| Male                 | 1.00 | –       | –       |     |         |         |     |         |         |
| Female               | 0.635 | 0.393–1.028 | 0.065 |     |         |         |     |         |         |
| Race                 |     |         |         |     |         |         |     |         |         |
| White                | 1.00 | –       | –       |     |         |         |     |         |         |
| Black                | 1.254 | 0.703–2.238 | 0.443 |     |         |         |     |         |         |
| American Indian      | 7.464 | 0.937–59.436 | 0.058 |     |         |         |     |         |         |
| Asian/Pacific Islander | 0.000 | NA | 0.996 |     |         |         |     |         |         |
| Unknown              | 0.750 | 0.214–2.63 | 0.653 |     |         |         |     |         |         |
| Hispanic             | 0.000 | NA | 0.997 |     |         |         |     |         |         |
| Median income of zip |     |         |         |     |         |         |     |         |         |
| <$38,000             | 1.00 | –       | –       |     |         |         |     |         |         |
| $38,000–$47,999      | 0.000 | NA | 0.999 |     |         |         |     |         |         |
| $48,000–$62,999      | 1.265 | 0.631–2.538 | 0.508 |     |         |         |     |         |         |
| $63,000+             | 0.714 | 0.339–1.505 | 0.376 |     |         |         |     |         |         |
| Unknown              | 0.601 | 0.290–1.243 | 0.170 |     |         |         |     |         |         |
| Distance to Hospital |     |         |         |     |         |         |     |         |         |
| <25 min              | 1.00 | –       | –       |     |         |         |     |         |         |
| 25–100 min           | 1.001 | 0.515–1.947 | 0.997 |     |         |         |     |         |         |
| >100 min             | 0.898 | 0.210–3.832 | 0.884 |     |         |         |     |         |         |
| Unknown              | NA | NA | 0.999 |     |         |         |     |         |         |
| Charlson/Deyo Score  |     |         |         |     |         |         |     |         |         |
| 0                    | 1.00 | –       | –       |     |         |         |     |         |         |
| 1                    | 1.760 | 0.971–3.189 | 0.062 |     |         |         |     |         |         |
| 2                    | 3.508 | 1.417–8.682 | 0.007 |     |         |         |     |         |         |
| Insurance            |     |         |         |     |         |         |     |         |         |
| No                   | 1.00 | –       | –       |     |         |         |     |         |         |
| Yes                  | 0.809 | 0.235–2.779 | 0.736 |     |         |         |     |         |         |
| Stage                |     |         |         |     |         |         |     |         |         |
| Stage I              | 1.00 | –       | –       |     |         |         |     |         |         |
| Stage II             | 1.539 | 0.955–2.479 | 0.077 |     |         |         |     |         |         |

HR, hazard ratio of death; CI, confidence interval; mi, miles.
herein, other critical considerations such as relapse-free survival, treatment-induced toxicity, and cause of death are not reported in the NCDB and will be of value in future studies.

This large database analysis shows an improvement in OS associated with the use of radiation therapy in early-stage NLPHL. Despite this benefit, 35% of patients with early-stage NLPHL do not receive radiation therapy at diagnosis. Given the rarity of this histologic subtype, we believe that it is unlikely that randomized trials will be conducted in this setting. As a result, we believe that large database analyses, such as the current one, can serve an important role in identifying disparities in care and improving patient outcomes.

Conflict of Interest

The authors declare no disclaimers or conflict of interests.

References

1. Gerber, N. K., C. L. Atoria, E. B. Elkin, and J. Yahalom. 2015. Characteristics and outcomes of patients with nodular lymphocyte-predominant Hodgkin lymphoma versus those with classical Hodgkin lymphoma: a population-based analysis. Int. J. Radiat. Oncol. Biol. Phys. 92:76-83.

2. National Comprehensive Cancer Network Clinical Practice Guidelines: Hodgkin Lymphoma v 1.2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf (accessed May 9, 2017).

3. Lee, A. I., and A. S. LaCasce. 2009. Nodular lymphocyte-predominant Hodgkin lymphoma. Oncologist 14:739-751.

4. Engert, A., P. Schiller, A. Josting, R. Herrmann, P. Koch, M. Sieber, et al. 2003. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J. Clin. Oncol. 21:3601-3608.

5. Nogova, L., T. Reineke, H. T. Eich, A. Josting, H. K. Muller-Hermelink, K. Wingermuhle, et al. 2005. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). Ann. Oncol. 16:1683-1687.

6. Chen, R. C., M. S. Chin, A. K. Ng, Y. Feng, D. Neuberg, B. Silver, et al. 2010. Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. J. Clin. Oncol. 28:136-141.

7. Wirth, A., K. Yuen, M. Barton, D. Roos, K. Gogna, G. Pratt, et al. 2005. Long-term outcome after radiotherapy alone for lymphocyte-predominant Hodgkin lymphoma: a retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. Cancer 104:1221-1229.

8. Wilder, R. B., P. J. Schlembach, D. Jones, G. M. Chronowski, C. S. Ha, A. Younes, et al. 2002. European Organization for Research and Treatment of Cancer and Groupe d'Etude des Lymphomes de l'Adulte very favorable and favorable, lymphocyte-predominant Hodgkin disease. Cancer 94:1731-1738.

9. Parikh, R. R., M. L. Grossbard, L. B. Harrison, and J. Yahalom. 2015. Early-stage classic Hodgkin lymphoma: the utilization of radiation therapy and its impact on overall survival. Int. J. Radiat. Oncol. Biol. Phys. 93:684-693.

10. Advani, R. H., and R. T. Hoppe. 2013. How I treat nodular lymphocyte-predominant Hodgkin lymphoma. Blood 122:4182-4188.

11. Advani, R. H., S. J. Horning, R. T. Hoppe, S. Daadi, J. Allen, Y. Natkunam, et al. 2014. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. J. Clin. Oncol. 32:912-918.

12. Eichnerauer, D. A., A. Plutschow, M. Fuchs, B. von Tresckow, B. Boll, K. Behringer, et al. 2015. Long-term course of patients with stage IA nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin study group. J. Clin. Oncol. 33:2857-2862.

13. Schulz, H., U. Rehwald, F. Morschhauser, T. Elter, C. Driessen, T. Rudiger, et al. 2008. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). Blood 111:109-111.

14. American College of Surgeons, Quality Programs, National Cancer Database. 2016. Available at: https://www.facs.org/quality-programs/cancer/ncdb (accessed December 1, 2016).

15. American College of Surgeons, National Cancer Database: Patient User File Data Dictionary Items. 2011. Available at: http://ncdbpuf.facs.org/?q=node/259 (accessed December 1, 2016).

16. Rosenbaum, P. R., and D. B. Rubin. 1984. Reducing bias in observational studies using subclassification on the propensity score. J. Am. Stat. Assoc. 79:516-524.

17. Mattei, A. 2009. Estimating and using propensity score in presence of missing background data: an application to assess the impact of childbearing on wellbeing. Stat. Methods Appl. 18:257-273.

18. Odei, B., D. Boothe, J. Frandsen, M. M. Poppe, and D. K. Gaffney. 2017. The role of radiation in all stages of
nodular lymphocytic predominant hodgkin lymphoma.
Clin. Lymphoma Myeloma Leuk. 17:819–824.
19. King, M. T., S. S. Donaldson, M. P. Link, Y.
Natkunam, R. H. Advani, and R. T. Hoppe. 2015.
Management of nodular lymphocyte predominant
Hodgkin lymphoma in the modern era. Int. J. Radiat.
Oncol. Biol. Phys. 92:67–75.

Supporting Information
Additional supporting information may be found in the
online version of this article:
Figure S1. Overall survival following diagnosis among
patients with early stage nodular lymphocyte predominant
Hodgkin lymphoma in the National Cancer Database
(2004–2012) comparing radiotherapy use to none.
Figure S2. Overall survival following diagnosis among
patients with early stage nodular lymphocyte predominant
Hodgkin lymphoma in the National Cancer Database (2004–
2012) comparing radiotherapy use to chemotherapy use.
Figure S3. Overall survival following diagnosis among
patients with early stage nodular lymphocyte predominant
Hodgkin lymphoma in the National Cancer Database
(2004–2012) comparing radiotherapy use to chemoradio-
therapy use.
Table S1. Analysis of factors associated with time to
death among patients with early stage nodular lymphocyte
predominant Hodgkin lymphoma in the National Cancer
Database 2004–2012 comparing radiotherapy use to none.
Table S2. Analysis of factors associated with time to
death among patients with early stage nodular lymphocyte
predominant Hodgkin lymphoma in the National Cancer
Database 2004–2012 comparing radiotherapy use to chemora-
diotherapy use.
Table S3. Analysis of factors associated with time to
death among patients with early stage nodular lymphocyte
predominant Hodgkin lymphoma in the National Cancer
Database 2004–2012 comparing radiotherapy use to chemora-
diotherapy use.