Original Article

What Is the Optimal Management of Early-Stage Low-Grade Follicular Lymphoma in the Modern Era?

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BACKGROUND: Despite international practice guidelines endorsing radiotherapy (RT) as the preferred initial therapy, treatment approaches vary for patients with early-stage follicular lymphoma. The authors engaged the National Cancer Data Base to analyze patterns of care and survival outcomes for patients with early-stage follicular lymphoma in the era of modern therapy. **METHODS:** A National Cancer Data Base retrospective cohort study was conducted of 35,961 patients with lymph node and extranodal, American Joint Committee on Cancer stage I to II, WHO grade 1 to 2 follicular lymphoma who were diagnosed between 1998 and 2012. Univariate and multivariable analyses were performed to identify sociodemographic, treatment, and tumor characteristics that were predictive of overall survival (OS) and treatment use. Propensity score-adjusted Cox proportional hazards ratios for survival in patients treated for follicular lymphoma were used. **RESULTS:** Of the 35,961 patients with follicular lymphoma included in the current study, 63% had stage I disease, 79% were without extranodal disease, and 61% were aged >60 years. RT use decreased from 37% in 1999 to 24% in 2012 ($P<.0001$), with corresponding significant increases in observation and single-agent chemotherapy. Patients who received RT had 5-year and 10-year OS rates of 86% and 68%, respectively, compared with 74% and 54%, respectively, for those who did not receive RT ($P<.0001$). On multivariable survival analysis, including a propensity score to account for potential uncaptured confounding variables due to a lack of randomization, upfront RT remained independently associated with improved OS (hazard ratio of death, 0.54; 95% confidence interval, 0.47-0.63 [$P<.0001$]). **CONCLUSIONS:** RT is an increasingly underused treatment approach in the era of modern therapy for patients with early-stage follicular lymphoma. The use of RT appears to improve OS and should remain standard practice as encouraged by clinical practice guidelines. ***Cancer*** **2015;121:3325-34**. © *2015 American Cancer Society.*

KEYWORDS: National Cancer Data Base (NCDB), follicular lymphoma, radiotherapy, rituximab, National LymphoCare Study.

INTRODUCTION

Indolent low-grade follicular lymphoma represents a challenging disease in which less than one-third of patients present with localized stage I to II disease. Historically, involved-field radiotherapy (RT) (and more recently involved-site or involved-lymph node RT) has been accepted as a standard of care for patients with localized stage I to II follicular lymphoma. Multiple international, single-institutional series have highlighted the primary benefits of RT: high cure rates and limited toxicities.[1-4] A Surveillance, Epidemiology, and End Results (SEER) program analysis from 1973 through 2004 suggested a survival benefit for initial management with RT.[5] However, this analysis was performed before the introduction of rituximab and, due to limitations of SEER, did not include information regarding chemotherapy.

Despite clinical practice guidelines by the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology, which both list initial RT as the preferred management strategy,[6,7] results from the National LymphoCare Study demonstrated that in the era of rituximab, only 23% of patients in the United States with stage I follicular lymphoma received RT.[8] A subsequent analysis of 206 patients with stage I follicular lymphoma from the National LymphoCare Study suggested excellent outcomes for varying treatment approaches and a potential progression-free survival benefit for systemic therapy plus RT or systemic therapy plus rituximab over RT alone.[9] The results from this multicenter observation study challenged the paradigm that RT should be the standard treatment approach.

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Data were submitted in abstract format to the American Society for Therapeutic Radiology Oncology (ASTRO) 57th Annual Meeting, which is to be held October 18 to 21, 2015 in San Antonio, Texas. The data used in the current study were derived from a deidentified National Cancer Data Base file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigators. The interpretation and reporting of these data are the sole responsibility of the authors.

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To provide additional data regarding survival outcomes for the various management approaches in early-stage follicular lymphoma, we engaged the population-based data available in the National Cancer Data Base (NCDB). We hypothesized that despite RT remaining the preferred standard in clinical practice guidelines, the use of RT is decreasing in favor of alternative management strategies (observation, targeted agents, and chemotherapy), which may negatively impact survival.

MATERIALS AND METHODS

A retrospective cohort study was formed with patients with both lymph node and extranodal, stage I to II, World Health Organization (WHO) grade 1 to 2 follicular lymphoma to evaluate the potential impact of treatment use on overall survival (OS). The NCDB is a tumor registry jointly maintained between the American Cancer Society and the American College of Surgeons for >1500 Commission on Cancer-accredited hospitals capturing an estimated 70% of newly diagnosed cancer cases in the United States. This database was queried for adult patients aged ≥18 years who were diagnosed with follicular lymphoma using International Classification of Diseases for Oncology, 3rd revision (ICD-O-3), diagnosis codes 9690, 9691, and 9695 from 1998 through 2012. A Consolidated Standards of Reporting Trials (CONSORT) diagram describing the cohort selection is outlined in Figure 1. The analysis was restricted to patients with NCDB analytic stage group I–II. Patients with grade 3 disease, non-B-cell histology, and those receiving a radiation modality other than external-beam RT were excluded. In addition, patients for whom RT use was unknown were excluded because this group represented only 2.3% of the study population.[10]

Consistent with prognostic classifications in follicular lymphoma, age at diagnosis was categorized as aged 18 to 60 years and >60 years.[11] The number of comorbidities was derived from the Charlson-Deyo comorbidity index.[12] Race was categorized as white, African American, or other. Stage was based on American Joint Committee on Cancer TNM staging for lymphoma of the reported pathologic stage group (unless pathologic stage was not reported; then the clinical stage group was used).[13] Socioeconomic data in the patients' residential census tract were provided as quartiles of the percentage of individuals with less than a high school education and median household income. The facility type was assigned according to the Commission on Cancer accreditation category with locations-based typology published by the US Department of Agriculture Economic Research Services. Insurance was the type reported on the patient's admission page. For ease of interpretation, year of diagnosis was categorized into tertiles.

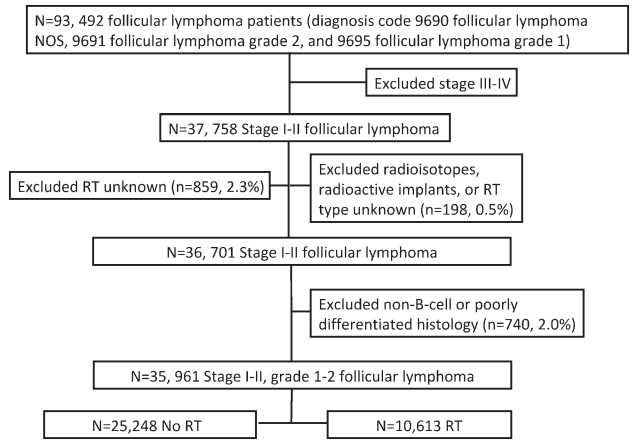

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram for case selection. NOS indicates not otherwise specified; RT, radiotherapy.

Statistical Analysis

Data were analyzed with SPSS statistical software (version 22; IBM Corporation, Armonk, NY). Summary statistics are presented for discrete variables. Chi-square tests compared sociodemographic, treatment, and tumor characteristics between the groups of patients receiving RT and those receiving no RT. Bivariate logistic regression models were used to assess the association between the independent variable of interest and the use of RT. Cases with missing covariate data were excluded from regression analyses.

OS was calculated in elapsed months from the date of diagnosis to the date of last contact or death. Kaplan-Meier curves were used to present the cumulative probability of survival. Log-rank statistics were used to test whether there was a statistically significant difference in the cumulative percentages between the groups.

To account for baseline characteristics that were not equally distributed across those receiving RT and those receiving no RT, a stepwise Cox proportional hazards model was used for multivariable survival analysis. Factors found to be significant on univariate analysis were entered in a hierarchical fashion using forward conditional selection ($P<0.10$ for inclusion). The proportional hazards assumption over time for each covariate in the final Cox model was tested graphically using log-log survival functions confirming the assumption was appropriate for all. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were reported. An α level of .05 was used to indicate statistical significance. Sensitivity analyses

were performed to account for potential time-varying covariates (age and treatment) and for years of diagnosis (to avoid introduction of time bias) confirming the effect of the treatment approaches (results not presented).

In addition, to account for potentially uncaptured confounding variables due to a lack of randomization, a propensity score analysis was conducted.[14] Propensity scores were calculated based on a multivariable logistic regression method to create a score reflective of the conditional probability of patients receiving RT. The propensity model included variables found to be significant for RT use on univariate analysis: sex, race, comorbidity score, insurance status, education, treatment facility type, facility location, age, stage of disease, B-symptoms, extranodal disease, and year of diagnosis. We tested the distribution of the propensity score between those treated with and without RT. We then modeled a Cox proportional hazard adjusting for propensity score and considering baseline differences in covariates in the model separately. The propensity score was incorporated as a continuous covariate; to avoid overcorrection, only those factors found to be significant on univariate survival analysis and not included in the propensity score (treatment, surgery, and income) were included in the propensity score-adjusted model. To further support the assumption of balance between treatment groups, the propensity score was validated by stratification into propensity score-based quintiles, confirming a standardized difference between RT use groups of <0.10.[14,15] Sensitivity analysis was conducted to assess the strength of the findings by excluding covariates with >5% missing values and time-biased covariates confirming the treatment effect (results not presented).

RESULTS

Baseline patient, tumor, and treatment characteristics for the 35,961 patients included in the current study are summarized in Table 1. The majority of patients (63%) had stage I follicular lymphoma, had nodal disease only (79%), and were aged >60 years (61%) at the time of diagnosis. Treatment categories were observation without any initial therapy (13,208 patients; 37%), RT only (7366 patients; 21%), chemotherapy only (11,307 patients; 31%), chemotherapy plus RT (2957 patients; 8%), and unknown (because chemotherapy information missing) (1123 patients; 3%). Trends in the percentage utilization for all the various treatment options as a function of time are summarized in Figure 2A.

There was a notable decline in RT use, peaking at 37% of patients receiving RT in 1999 to only 24% receiving RT in 2012 ($P<.0001$) (Fig. 2B). Table 2 outlines the comparative use of RT by baseline characteristics. Decreases in RT use were associated with increasing age, female sex, African American race, increasing comorbidity score, treatment at an academic/research program, stage II disease, presence of B-symptoms, absence of extranodal disease, receipt of chemotherapy, and more recent years of diagnosis. Although chemotherapy use as a whole decreased from 43% in 1998 to 36% in 2012, the use of single-agent chemotherapy doubled from a nadir of 5.4% in 1999 to a peak of 11.7% in 2006 ($P=.01$) (Fig. 2C). Correspondingly, there was a 10% absolute increase in the number of patients observed without any initial treatment from 34% in 1998 to 44% in 2012 ($P<.0001$) (Fig. 2D).

The median follow-up for the entire cohort was 58 months (interquartile range, 28 months-93 months) and was 64 months (interquartile range, 34 months-100 months) for surviving patients. There were a total 12,082 deaths in the entire cohort, with an estimated median OS of 149 months (95% CI, 145 months-153 months) and a 5-year and 10-year OS rate of 78% (95% CI, 77%-78%) and 59% (95% CI, 58%-60%), respectively. For patients who received RT, the estimated median OS was 179 months (95% CI, 171 months-186 months) with 5-year and 10-year OS rates of 86% (95% CI, 85%-87%) and 68% (95% CI, 67%-70%), respectively; comparatively, patients who did not receive RT had an estimated median OS of 133 months (95% CI, 130 months-137 months) and 5-year and 10-year OS rates of 74% (95% CI, 74%-75%) and 54% (95% CI, 53%-55%), respectively ($P<.0001$) (Fig. 3A). Conversely, use of chemotherapy was found to have no significant impact on survival when analyzed as a dichotomous variable ($P=.43$) (Fig. 3B). When analyzed by chemotherapy type, single-agent chemotherapy had significantly inferior OS (median OS, 127 months; 95% CI, 118 months-137 months) compared with no chemotherapy use (median OS, 145 months; 95% CI, 140 months-150 months) or multiagent chemotherapy (median OS, 164 months; 95% CI, 156 months-172 months) ($P<.0001$). Those patients observed without any initial treatment had significantly worse OS, with an estimated median OS of 125 months (95% CI, 121 months-130 months) and 5-year and 10-year OS rates of 74% (95% CI, 73%-75%) and 52% (95% CI, 51%-53%), respectively; in comparison, patients who received any initial therapy had an estimated median OS of 165 months (95% CI, 160 months-170 months) and 5-year and 10-year OS rates of 80% (95% CI, 79%-80%) and 62% (95% CI, 61%-63%),

TABLE 1. Baseline Characteristics

Baseline Characteristics	All Patients (N = 35,961) No. (%)
Sex	
Male	17,185 (48)
Female	18,776 (52)
Race	
White	33,244 (92)
African-American	1468 (4)
Other	815 (2)
Unknown	434 (1)
Comorbidity (Charlson-Deyo score)	
0	21,676 (60)
1	3460 (10)
≥2	909 (3)
Unknown	9916 (28)
Insurance	
None	738 (2)
Private payer	16,573 (46)
Government	17,759 (49)
Unknown	891 (3)
Education (% <high school education in patient's zip code)	
≥29%	4355 (12)
20%-28.9%	7388 (21)
14%-19.9%	8534 (24)
<14%	14,173 (39)
Unknown	1511 (4)
Treatment facility type	
Community cancer program	4392 (12)
Comprehensive community cancer program	21,064 (59)
Academic/research program	10,445 (29)
Other	60 (<1)
Treatment facility location	
Metropolitan counties	28,652 (80)
Urban counties	5099 (14)
Rural counties	716 (2)
Unknown	1494 (4)
Income (median household income for patient's zip code)	
<$30,000	3459 (10)
$30,000-$35,000	5712 (16)
$35,000-$45,999	9860 (27)
>$46,000	15,423 (43)
Unknown	1507 (4)
Age, y	
≤60	13,953 (39)
>60	22,008 (61)
AJCC stage of disease	
I	22,765 (63)
II	13,196 (37)
B-symptoms	
Absent	13,098 (36)
Present	1700 (5)
Unknown	21,163 (59)
Extranodal disease	
Absent	28,271 (79)
Present	7690 (21)
Surgery as part of first course of therapy	
None	21,834 (61)
Any	13,938 (39)
Unknown	189 (<1)
Chemotherapy as part of first course of therapy	
None	20,574 (57)
Single-agent chemotherapy	3205 (9)
Multiagent chemotherapy	9462 (27)
Chemotherapy given; type unknown	1597 (4)
Unknown if chemotherapy given	1123 (3)
RT as part of first course of therapy	
None	25,348 (71)
External-beam RT	10,613 (30)
Y of diagnosis	
1998–2002	9916 (28)
2003–2007	12,376 (34)
2008–2012	13,669 (38)

Abbreviations: AJCC, American Joint Committee on Cancer; RT, radiotherapy.

respectively ($P<.0001$) (Fig. 3C). When the treatment options were combined, significant improvements remained with regard to OS for patients receiving either RT alone or combined chemoradiotherapy compared with patients observed without any initial treatment or chemotherapy alone ($P<.0001$) (Fig. 3D).

The following factors were also identified to be significant predictors of OS on univariate analysis: sex, race, comorbidity, insurance, education, facility type, facility location, income, age, stage of disease, B-symptoms, extranodal disease, use of surgery, and years of diagnosis. On multivariable Cox proportional hazard analysis, the following factors remained significant for improved OS: RT use, combined chemoradiotherapy use, surgery use, age ≤60 years, stage I disease, absence of B-symptoms, female sex, decreasing comorbidity, private insurance, median income >$46,000, and more recent years of diagnosis (Table 3).

The propensity score-adjusted multivariable analysis identified the following factors as associated with improved OS: RT use, chemotherapy use, combined chemoradiotherapy use, surgery use, and median income >$46,000 (Table 3). Figure 4 highlights OS for the various treatment strategies within the multivariable model without and with the propensity score adjustment to account for imbalances between groups due to a lack of randomization. An identical analysis was completed using a propensity score that was created based on chemotherapy use. In the chemotherapy propensity score-adjusted multivariable model, chemotherapy was found to have no significant impact on OS whereas RT and chemoradiation remained significant predictors of OS.

DISCUSSION

In what to the best of our knowledge is the largest published series of patients with early-stage follicular

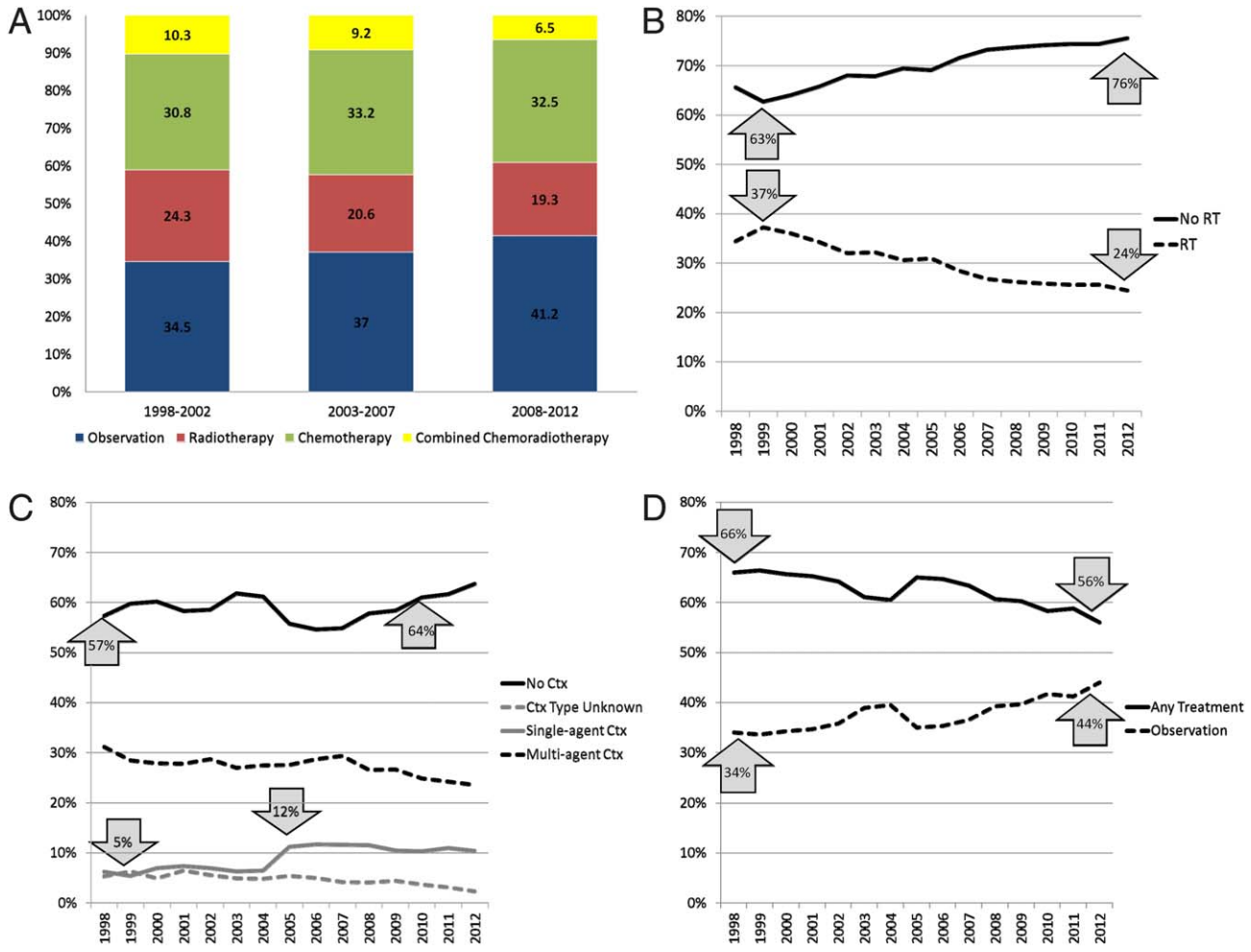

Figure 2. Trends in treatment use over time for (A) all modalities, (B) radiotherapy (RT), (C) chemotherapy (Ctx), and (D) observation.

lymphoma, the use of RT was associated with a significant 12% absolute improvement in the 5-year and a 14% absolute improvement in the10-year OS rate (Fig. 3A) despite a significant decline in use over time. International clinical practice guidelines endorsing involved-site RT as the preferred initial management were not followed for the majority of patients, with only a rate of 30% RT use.[6,7] RT use significantly declined from 37% in 1998 to a nadir of 24% in 2012, with a corresponding 10% absolute increases in observation without any initial therapy and a doubling in single-agent chemotherapy (Fig. 2). These data suggest that even within the context of modern systemic therapy, RT significantly contributes to survival for patients with early-stage low-grade follicular lymphoma and should remain standard practice.

RT has historically been considered to be the standard treatment of patients with early-stage, low-grade follicular lymphoma based on long-term follow-up of retrospective single-institutional series demonstrating 10-year freedom-from-recurrence rates of 43% to 51% combined with 10-year OS rates of 62% to 79%.[1-4] The large population-based analysis presented herein demonstrated a comparable 10-year OS rate of 68% for patients receiving RT. Similar trends in RT use and an identical 14% absolute 10-year survival decrement in patients not receiving RT were noted in another population-based analysis from 1973 through 2004 from the SEER data set.[5] Contemporaneously increased adoption of involved-site or involved-lymph node RT and reduced RT dose has notably decreased the RT treatment volume and dose compared with those used in older series, which should translate into an increasing number of patients who are candidates for initial RT by reducing toxicities.[16-18] However, despite lower RT dose, smaller radiation treatment

TABLE 2. Comparative Use of RT by Baseline Characteristics

	No RT (n = 25,348)	RT (n = 10,613)	OR[a]	95% CI	*P*
Sex					
Male	11,887 (69%)	5298 (31%)	1	Reference	
Female	13,461 (72%)	5315 (28%)	0.89	0.85–0.93	<.0001
Race					
White	23,361 (70%)	9883 (30%)	1	Reference	
African-American	1125 (77%)	343 (23%)	0.72	0.64–0.82	<.0001
Other	554 (68%)	261 (32%)	1.11	0.96–1.29	.16
Comorbidity (Charlson-Deyo score)					
0	15,337 (71%)	6339 (29%)	1	Reference	
1	2757 (80%)	703 (20%)	0.62	0.57–0.67	<.0001
≥2	777 (86%)	132 (15%)	0.41	0.34–0.50	<.0001
Insurance					
None	519 (70%)	219 (30%)	1	Reference	
Private payer	11,123 (67%)	5450 (33%)	1.16	0.99–1.36	.07
Government	13,090 (74%)	4669 (26%)	0.85	0.72–0.99	.04
Education (<high school education in patient's zip code)					
≥29%	3220 (74%)	1135 (26%)	1	Reference	
20%-28.9%	5360 (73%)	2028 (27%)	1.07	0.99–1.17	.10
14%-19.9%	5931 (70%)	2603 (31%)	1.25	1.15–1.35	<.0001
<14%	9727 (69%)	4446 (31%)	1.30	1.20–1.40	<.0001
Treatment facility type					
Community cancer program	3172 (72%)	1220 (28%)	1	Reference	
Comprehensive cancer program	14,711 (70%)	6353 (30%)	1.12	1.05–1.21	.002
Academic/research program	7422 (71%)	3023 (29%)	1.06	0.98–1.15	.15
Other	43 (72%)	17 (28%)	1.03	0.58–1.81	.92
Treatment facility location					
Metropolitan counties	20,287 (71%)	8365 (29%)	1	Reference	
Urban counties	3487 (68%)	1612 (32%)	1.12	1.05–1.20	<.0001
Rural counties	505 (71%)	211 (30%)	1.01	0.86–1.19	.87
Income (median household income for patient's zip code)					
<$30,000	2507 (73%)	952 (28%)	1	Reference	
$30,000-$35,000	4052 (71%)	1660 (29%)	1.08	0.98–1.19	.11
$35,000-$45,999	7016 (71%)	2844 (29%)	1.07	0.98–1.16	.14
>$46,000	10,666 (69%)	4757 (31%)	1.17	1.08–1.28	<.0001
Age, years					
≤60	9307 (67%)	4646 (33%)	1	Reference	
>60	16,041 (73%)	5967 (27%)	0.75	0.71–0.78	<.0001
AJCC stage					
I	14,307 (63%)	8458 (37%)	1	Reference	
II	11,041 (84%)	2155 (16%)	0.33	0.31–0.35	<.0001
B-symptoms					
Absent	8136 (62%)	4962 (38%)	1	Reference	
Present	1393 (82%)	307 (18%)	0.36	0.32–0.41	<.0001
Extranodal disease					
Absent	20,756 (73%)	7515 (27%)	1	Reference	
Present	4592 (60%)	3098 (40%)	1.86	1.77–1.96	<.0001
Surgery					
None	15,844 (73%)	5990 (27%)	1	Reference	
Any	9390 (67%)	4548 (33%)	1.28	1.22–1.34	<.0001
Chemotherapy					
None	13,208 (64%)	7366 (36%)	1	Reference	
Single-agent chemotherapy	2706 (84%)	499 (16%)	0.29	0.25–0.33	<.0001
Multiagent chemotherapy	7224 (76%)	2238 (24%)	0.33	0.30–0.37	<.0001
Chemotherapy given; type unknown	1377 (86%)	220 (14%)	0.56	0.53–0.59	<.0001
Year of diagnosis					
1998–2002	6477 (65%)	3439 (35%)	1	Reference	
2003–2007	8697 (70%)	3679 (30%)	0.80	0.75–0.84	<.0001
2008–2012	10,174 (74%)	3495 (26%)	0.65	0.61–0.69	<.0001

Abbreviations: 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; OR, odds ratio; RT, radiotherapy.
[a] Presented are unadjusted odds ratios to treatment use.

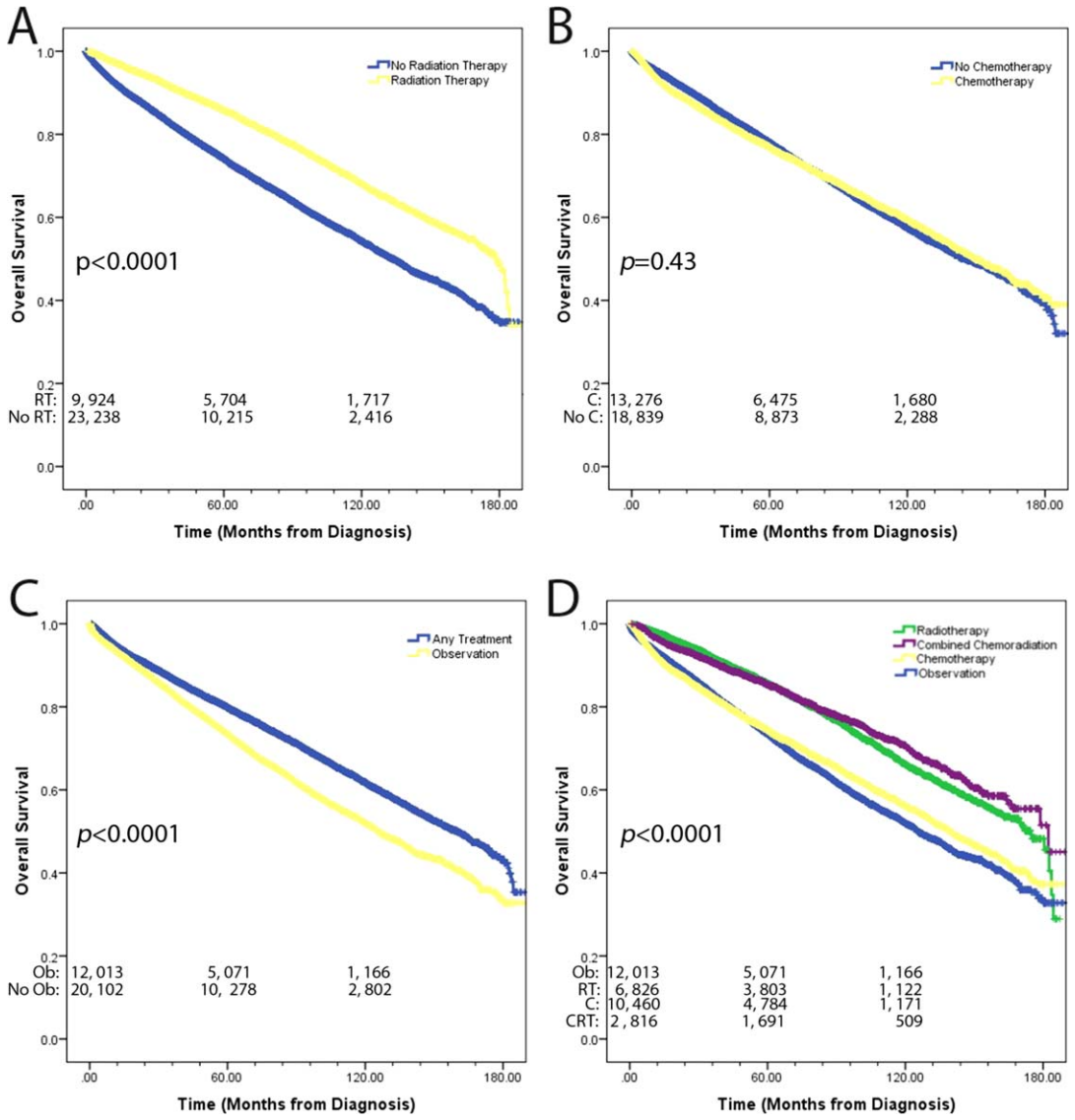

Figure 3. Kaplan-Meier overall survival for the use of (A) radiotherapy (RT), (B) chemotherapy (C), (C) observation (Ob), and (D) all modalities. CRT indicates chemoradiation.

fields, and now 2 large population-based analyses demonstrating a highly significant 14% absolute improvement in 10-year OS for patients receiving RT,[5,16-18] the use of RT has continued to decrease in the era of modern therapy to a nadir of 24% in 2012. Although clinical practice guidelines list RT as the preferred management strategy,[6,7] other options including observation, immunotherapy, and chemotherapy are also listed as acceptable alternatives. These described variations in patterns of care may reflect this ambiguity in clinical guidelines.

Decreases in RT use coincided with a 10% absolute increase in patients observed without any initial therapy (Fig. 2). Although observation with therapy deferred until symptomatic disease progression or histologic transformation has been established by multiple randomized controlled trials for patients with stage III to IV follicular lymphoma,[19,20] recommendations for observation without initial therapy in patients with early stage I to II follicular lymphoma is based largely on retrospective single-institutional series subject to inherent selection bias.[21,22] Although highly selected subgroups of patients with early-stage low-grade follicular lymphoma may have excellent survival outcomes with observation and no initial therapy,[21] the inferior OS reported for the group of patients

TABLE 3. Multivariable Cox Proportional Hazard Models for Overall Survival

Cox Model Without Propensity Score		
Significant Characteristic	HR of Death (95% CI)	*P*
Treatment strategy		
Observation	Reference	
RT	0.53 (0.46–0.62)	<.0001
Chemotherapy	0.91 (0.81–1.02)	.09
Chemoradiation	0.69 (0.57–0.83)	<.0001
Surgery		
No surgery	Reference	
Surgery	0.73 (0.66–0.81)	<.0001
Age, years[a]		
≤60	Reference	
>60	2.81 (2.39–3.30)	<.0001
AJCC stage[a]		
I	Reference	
II	1.15 (1.04–1.28)	.006
B-symptoms[a]		
Absent	Reference	
Present	1.42 (1.24–1.63)	<.0001
Sex[a]		
Male	Reference	
Female	0.72 (0.66–0.79)	<.0001
Comorbidity score[a]		
0	Reference	
1	1.64 (1.45–1.86)	<.0001
≥2	3.05 (2.54–3.67)	<.0001
Insurance[a]		
None	Reference	
Private	0.55 (0.37–0.80)	.002
Government	1.25 (0.85–1.84)	.25
Year of diagnosis[a]		
1998–2002	–	
2003–2007	Reference	
2008–2012	0.89 (0.80–1.0)	.05
Income		
<$30,000	Reference	
$30,000-$35,000	1.04 (0.87–1.23)	.69
$35,000-$45,999	0.89 (0.76–1.05)	.16
>$46,000	0.74 (0.63–0.87)	<.001

Cox Model With Propensity Score		
Significant Characteristics	HR of Death (95% CI)	*P*
Treatment strategy		
Observation	Reference	
RT	0.54 (0.47–0.63)	<.0001
Chemotherapy	0.80 (0.72–0.90)	<.0001
Chemoradiation	0.61 (0.50–0.73)	<.0001
Surgery		
No surgery	Reference	
Surgery	0.76 (0.68–0.84)	<.0001
Income		
<$30,000	Reference	
$30,000-$35,000	1.03 (0.87–1.23)	.72
$35,000-$45,999	0.89 (0.76–1.04)	.14
>$46,000	0.68 (0.58–0.79)	<.0001
Propensity score		
Continuous	0.15 (0.11–0.21)	<.0001

Abbreviations: 95% CI, 95% confidence interval; AJCC, American Joint Committee on Cancer; HR, hazard ratio; RT, radiotherapy.
[a] Factors included in the propensity score were excluded from the propensity score-adjusted model to avoid overcorrection.

observed without initial therapy in the current study may suggest overapplication of this approach to a broader, improperly selected patient population (Figs. 3 and 4).

Although the use of chemotherapy decreased from 43% to 36%, use of single-agent chemotherapy doubled from 5.4% in 1999 to 11.7% in 2006 (Fig. 2), which may be related to the promising results noted with single-agent rituximab.[23,24] In the late 1990s to early 2000s, several studies demonstrated the benefits of rituximab, predominantly in patients with advanced or recurrent/refractory follicular lymphoma.[25] Through cases diagnosed in 2012, rituximab was coded as chemotherapy in registry databases. Although others have performed similar analyses that incorporate the use of immunotherapy in patients with non-Hodgkin lymphoma, these analyses are subject to significant recording bias.[26] Thus, we intentionally avoided analysis of use of immunotherapy, and believe that use of immunotherapy alone or with chemotherapy is best reserved for future analyses once these therapies have been more accurately recorded in registry databases. Combined modality regimens including RT plus systemic therapies represented only 5% to 11% of treatment strategies used from 1998 through 2012. Due to limitations in the NCDB, it remains unclear whether this subgroup represented patients treated with rituximab plus RT, which has shown promise in retrospective data sets and is the subject of an ongoing prospective study.[23-25,27] It is interesting to note that, on univariate and multivariable survival analysis, chemotherapy use demonstrated no impact on survival; however, on propensity score-adjusted analysis by RT use, chemotherapy use (part of which may be rituximab) did improve OS but the survival impact was less than that for RT or combined chemoradiation (Figs. 3 and 4). This improvement in OS by chemotherapy use did not hold in a chemotherapy-specific, propensity score-adjusted model. Such results highlight the bias toward the use of chemotherapy in higher-risk subgroups and the power of propensity score analysis to account for the potential imbalances in patient selection inherent to retrospective analyses. Nonetheless, an added limitation of the NCDB is the inability to account for additional factors that may be used to select patients for chemotherapy, including hemoglobin, β_2-microglobulin, Follicular Lymphoma International Prognostic Index (FLIPI) 2 score, lactate dehydrogenase, tumor bulk, disease symptoms, and contiguous versus noncontiguous stage II disease.[28] In addition, missing registry data further limit analysis. For example, B-symptoms (unknown for 59% of patients) and comorbidity score (unknown for 28% of patients) were missing for many patients.

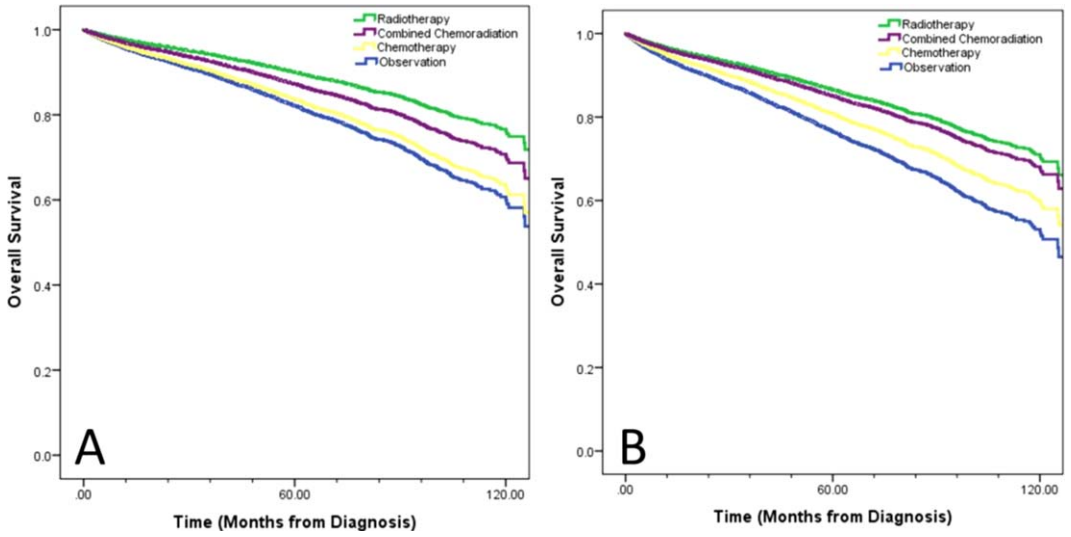

Figure 4. Adjusted overall survival estimate stratified by treatment modality and corrected for significant variables on multivariable cox proportional hazard model analysis (A) without the propensity score and (B) with the propensity score.

In addition to treatment-related factors, we identified several sociodemographic factors associated with decreased RT use including female sex, African American race, increasing comorbidity score, treatment at an academic/research program, and increasing age. Others have similarly highlighted racial and socioeconomic disparities in patterns of care and survival outcomes for patients with follicular lymphoma; continued research is warranted aimed at bridging these disparities.[29-31] The decreased use of RT in academic/research programs may relate to a bias toward increasing integration of novel strategies at this type of treatment facility. Others have similarly demonstrated a wide variation in RT use in patients with early-stage follicular lymphoma within the NCCN centers despite the NCCN guidelines endorsing RT as the preferred initial treatment strategy.[6,32] Sociodemographic factors such as age along with disease-related factors including stage of disease, B-symptoms, and extranodal disease that significantly impacted RT use may relate to these factors having prognostic significance.[11,28]

Although these findings are thought-provoking and powered by large numbers, the presented analysis is subject to inherent biases owing to its retrospective design, a lack of disease-specific or progression outcomes, omission of salvage therapy use, and no information to confirm the extent of staging workup (ie, positron emission tomography/computed tomography, bone marrow biopsy). In addition, we were unable to confirm NCDB treatment use coding with individual patient data, and therefore potential inaccuracies in coding could not be accounted for.[33] Nevertheless, the presented analyses represents to the best of our knowledge the largest outcomes analysis performed in patients with early-stage low-grade follicular lymphoma, with >35,000 patients spanning a 14-year period, validating the results of prior retrospective and population-based analyses by demonstrating that RT use continues to decline in favor of alternative treatment strategies, despite supportive clinical practice guidelines.[1-7] This concerning decline is coupled with improved OS in patients receiving RT, either alone or with chemotherapy. This reduction in OS at the national level is a concerning finding with regard to oncologists' trend of avoiding RT, especially considering that similar findings have just been published with regard to early-stage classical Hodgkin lymphoma.[34]

Conclusions

Despite clinical practice guidelines endorsing RT as the preferred initial management, RT use in patients with early-stage low-grade follicular lymphoma continues to decline in the United States with the increasing use of alternative treatment strategies including observation and single-agent chemotherapy. Even when correcting for sociodemographic, tumor, and treatment factors, the use of RT was found to be associated with a significant improvement in OS. With a lack of randomized evidence and these striking findings, physicians should strongly reconsider excluding RT outside of clinical trials. Continued efforts to increase treatment use in underrepresented subgroups are warranted and prospective validation of

these results is imperative to best define the optimal management strategy in patients with low-grade early-stage follicular lymphoma.

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