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# Disease, treatment, and outcome differences between men and women with follicular lymphoma in the United States

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## Abstract

We aimed to comprehensively study sex differences in disease and patients' characteristics, treatment and outcomes in patients with follicular lymphoma (FL) in the United States (USA) utilizing the National LymphoCare Study registry (2004–2014). Among evaluable males ($n$ = 1277) and females ($n$ = 1375) with FL, females less commonly received anthracyclines and were more likely to receive rituximab monotherapy. Overall response rates were comparable between sex groups. With a median follow-up of 8.1 years, male sex emerged as an adverse factor for PFS (HR, 0.84, 95% CI, 0.72–0.97). Lymphoma-related mortality (HR, 0.46; 0.23–0.93) and overall survival (HR, 0.63; 0.41–0.97) favored females aged ≤60 years. There are subtle differences in

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Additional Supporting Information may be found in the online version of this article.

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**Author Contributions**

C.N., K.D., J.R.C., B-M.D., J.W.F. and C.R.F. conceived and designed the study. C.N., X.Z., J.R.C., B-M.D., K.D., A.D.Z., J.W.F. and C.R.F acquired, analyzed and interpreted the data. C.N., B-M.D., K.D. and C.R.F. drafted the manuscript. X.Z., B-M.D. and A.D.Z. were responsible for statistical analysis. K.D. obtained funding. B-M.D., K.D., J.R.C. and C.R.F. provided administrative, technical or material support. C.N. supervised the study. All authors critically revised the manuscript for important intellectual content and approved the final version.

outcomes between male and female FL patients diagnosed and treated in the contemporary era. These data represent the largest prospective analysis of FL patients in the USA based on sex and can aid design of clinical trials for this disease.

## Introduction

Follicular lymphoma (FL) accounts for almost 15,000 cases diagnosed annually in the United States (USA) [1]. While age and racial disparities in FL have been described [2,3], differences in disease presentation and treatment choices between men and women in a large cohort of USA patients have not been adequately described. The prognostic role of sex in outcomes is a mixture. Some studies suggested male as a risk factor for overall survival (OS) in FL patients: e.g., sex was one of the six factors included in the prognostic index proposed by Intergruppo Italiano Linfomi 2000 [4]. When developing the Follicular Lymphoma International Prognostic Index (FLIPI), sex was a significant factor identified in both univariate and multivariate analyses, although it was not selected into the final 5 factors constructing FLIPI [5], because the clinical committee of the project asked for an index including no more than 5 factors for easy use in routine practice. It is interesting that in the development of FLIPI2, with approximately 60% of the patient cohort treated with rituximab-containing regimens, sex was not a significant factor for progression-free survival (PFS) [6]. However, other studies suggested male sex was associated with poor PFS [7]. Recent epidemiological studies suggest greater survival improvement in females with increasing rituximab use in Europe and Asia [8,9].

Among patients with diffuse large B-cell lymphoma (DLBCL), women experience better PFS than men despite similar therapy [10,11]. Moreover, in a study of DLBCL, significant sex differences in PFS were found in patients aged 61–80 years, but not in patients aged 18–60 years [12]. We utilized the National LymphoCare Study (NLCS) registry database to assess whether disease, patient characteristics, and treatment choices vary by sex in the USA. We further studied variability in overall response rates (ORRs) to similar treatments between men and women and whether OS, PFS and lymphoma-related mortality (LRM) varied by sex among those treated with rituximab-containing regimens. In a previous investigation in FL patients, chemoimmunotherapy improved PFS compared with rituximab monotherapy in patients aged ≤60 years and 61–80 years, but not in those >80 years [2]. Therefore, and given these noted variations based on age, we conducted our analysis of sex differences in the overall cohort and performed subset analyses for specific age groups to account for inherent variability of studied factors that could emerge due to age.

## Patients and Methods

The NLCS registry is a prospective cohort study of patients with FL, within 6 months of initial diagnosis, in the USA that was developed by Genentech, Inc. (South San Francisco, USA) and Biogen Idec (Cambridge, USA) as previously described [13]. Patients were recruited from academic and community practices in the USA between 2004–2007. All patients signed an institutional review board–approved consent form. Patients were evaluated and treated according to each physician's standard discretion without a study-

specific management protocol. Follow-up data on relapses, new treatments, and vital status (including cause of death) were prospectively collected every 3 months from the treating physician.

## Statistical methods

Demographics, baseline disease characteristics, treatment, and rituximab dose intensity were summarized by sex using descriptive statistics (frequencies and percentages for categorical variables). The Pearson chi-square test (or Fisher's exact test, if required by small sample size) was performed to assess sex differences. The analysis of maintenance rituximab use was assessed by sex across first-line rituximab-based induction and included only patients who were on the study; achieved complete response, partial response, or stable disease; and had not experienced progression within 215 days after completion of induction therapy with a rituximab-based regimen [14].

Treatment outcomes were compared between male and female patients. The relationship between ORRs and sex overall and for a particular rituximab-based induction treatment was evaluated using the Pearson chi-square test. OS was defined as the number of days from the date of diagnosis to the date of death, from any cause. For patients who were not reported dead, OS was censored at the date that the patient was last known to be alive. PFS was the number of days from the date of diagnosis to the date of the first documented progression or death from any cause, whichever occurred earlier. Patients who had not yet experienced a PFS event were censored at the date of the most recent response assessment. LRM was the number of days from the date of diagnosis to the date of death due to lymphoma treatment–related toxicity or lymphoma-related cause. For patients with reported death due to other causes, LRM was censored at the death date. For patients who were not reported dead, LRM was censored at the last alive date, as OS. Median PFS, OS, and LRM-free survival were estimated using Kaplan-Meier methods by sex and age group. To explore the effect of sex on PFS, OS, and LRM, Cox proportional hazards models were used, which included the following covariates: sex, age group, race/ethnicity, baseline disease characteristics (histology grade, nodal sites, lactate dehydrogenase, hemoglobin, stage, Eastern Cooperative Oncology Group performance score, extra-nodal sites, B-symptoms and bone marrow involvement), geographical region, center type, first-line treatment, rituximab dose intensity, and time-varying rituximab maintenance variable. The interactions between sex, age, and treatment were assessed with a backward selection approach. Considering that the number of deaths was small in some subgroups, interaction terms with $P \leq 0.15$ were retained in the final model, as it may suggest some differentiated effect. This model was used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for an overall sex effect, adjusting for age and other covariates.

To confirm the sex difference seen in NLCS, we assessed OS in FL patients by sex using the SEER (Surveillance, Epidemiology and End Results) program (www.seer.cancer.gov) research data (1973–2012), National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch, released April 2015, based on the November 2014 submission.

## Results

### Patients' characteristics

A total of 2652 evaluable patients were included in this analysis (1277 males and 1375 females). Disease and patient characteristics were similar across sexes except for a difference in distribution of FLIPI scores (36% females with a score of 3–5 vs. 32% males; $P = 0.045$) and in presenting hemoglobin values (Table I). A lower hemoglobin value in women (27% <12 g/dL in females vs. 15% in males; $P < 0.0001$) mirrors what is usually observed in the general USA population [15]. Similar observations were noted regardless of the age group (data not shown).

### Treatment selection

First-line treatment choices varied by sex ($P = 0.003$), as shown in Table II. More females than males received rituximab monotherapy (15% vs. 11%; $P = 0.002$). More men received rituximab plus chemotherapy (51% vs. 46%; $P = 0.021$). Also, men were more likely to receive rituximab plus cyclophosphamide, vincristine, adriamycin and prednisone (R-CHOP) than women (27% vs. 22%). Use of maintenance rituximab was similar between males and females regardless of the induction regimen. Notably, ORRs were similar, regardless of age groups, when identical therapies were received (Supporting Information Table I)

### PFS, OS and LRM

With a median follow-up of 8.1 years, median PFS was 6.3 years for males and 6.9 years for females. After adjusting for baseline characteristics (including age group), first-line treatment, rituximab dose intensity, and rituximab maintenance in a Cox proportional hazards model (see details in the methods section), a sex difference in favor of females was observed for PFS (HR, 0.84; 95% CI, 0.72–0.97; Table III). The age-by-treatment interaction effect was significant as reported previously [2], but we did not observe a meaningful sex-by-treatment or sex-by-age interaction effect (P > 0.15).

For OS, the results suggested some differentiated sex effect across age groups worthy of further exploration. As shown in Table III, it is notable that no significant sex difference was observed in patients aged 61-80 years in OS or LRM. For those aged > 80 years, OS (HR, 0.50; 95% CI, 0.31–0.82) was significantly worse in males than females, but is consistent with the survival expectation in the general population. This is supported by the lack of significant sex difference for LRM (HR, 0.84; 95% CI, 0.38–1.87) for age > 80 years.

The interesting finding is that females aged ≤ 60 years had better OS (HR, 0.63; 95% CI, 0.41–0.97) and LRM (HR, 0.46; 95% CI, 0.23–0.93) than males. This sex difference is not explained by variables we measured. In an exploratory analysis to investigate whether hormonal effects could play a role in the observed sex differences, we divided patients aged ≤ 60 years into two age groups: 51–60 years and ≤ 50 years. We found that females aged ≤ 50 years have a better LRM than their male counterparts while this was not observed in the group aged 51–60 years (Fig. 1).

Finally, and to validate our findings, we examined 10,278 adult patients in the SEER database who had a diagnosis of FL from 2004–2007 with a follow-up to 2012. Supporting Information Table II shows OS differences between our cohort and SEER. In all age-gender subgroups, the OS observed from SEER is similar to NLCS except that >80 years female patients in NLCS appear to have a better OS.

## Discussion

In this prospective analysis of 2652 USA-based FL patients diagnosed and treated in the contemporary era, we show minimal treatment selection differences between females and males. Nonetheless, after adjusting for multiple potential confounding variables, we observed better OS and LRM in females <60 years of age, while PFS was similar. This observation was more pronounced in females <50 years of age than in those aged 51–60 years. Also, females >80 years of age had better PFS and OS than their male counterparts, but the sample size was small in this cohort. Our observations are in contrast to patients with DLBCL where sex differences have been reported only in older patients [11].

Relatively little has been published about the impact of sex on outcomes in patients with lymphoid malignancies. Pfreundschuh *et al.* showed that older males with DLBCL had a HR of 1.6 ($P = 0.004$) compared with females, despite receiving comparable therapy [12]. To evaluate whether altering the rituximab delivery schedule is safe and affects outcomes, 124 DLBCL patients were treated prospectively with R-CHOP-14, but rituximab was given on days 0, 1, 4, 8, 15, 22, 29, 43, 57, 85, and 99 [12]. This dose-dense rituximab regimen resulted in higher serum levels during the first 50 days of treatment, but exposure time was not prolonged. In this study, male hazard ratios decreased (PFS: from 1.7 to 1.1 and OS: from 1.4 to 1.0). A larger study in 189 DLBCL patients utilized 6 cycles of R-CHOP-14 with rituximab given on days −4, 0, 10, 29, 57, 99, 155, and 239. This led to identical OS and event-free survival (EFS) in men and women [11]. A preplanned historical comparison suggested that this dose schedule of rituximab improved EFS in patients with poor prognosis based on the International Prognostic Index (IPI) [16].

In view of observations in DLBCL, and as the prognosis of FL patients has markedly improved over the past decade, understanding whether this improvement has transcended both sexes is critical. Despite similar disease characteristics, a few treatment differences emerged. Younger and older women were more likely to receive rituximab monotherapy than men. Also, women were less likely to receive R-CHOP when chemoimmunotherapy was given. At present, differences in anthracycline-based first-line therapy for FL patients are less meaningful given the randomized trials showing non-inferior PFS with bendamustine and rituximab compared with R-CHOP [17,18].

There are few studies of the impact of sex on outcomes in FL. In a cohort of 110 FL patients treated with chemoimmunotherapy, female patients had better PFS (68% vs. 52% at 4 years; $P = 0.036$); reasons for this advantage were not identified [19]. A retrospective analysis of the SEER database showed that both males and females experienced improved OS in the contemporary era [20]. Nonetheless, when the sexes were compared, the advantage that females enjoyed before 2002 was mitigated in subsequent years; no data on differences

according to age were provided. These inconsistent observations argue for better examination of sex differences in FL.

Our prospective data show that after adjusting for multiple potential confounding variables, females had better PFS and OS than males at a median follow-up of 8 years. Analysis of different age groups showed that the survival advantage among FL females occurred specifically in the younger (≤60 years) and older (>80 years) groups. Among younger patients, LRM was better in females, which argues that improved survival in patients aged ≤60 years could be from better FL outcomes. The lack of PFS advantage in this cohort might reflect practice variation in how often imaging and clinical visits are conducted; detecting progression can be delayed when these are done less frequently.

In an exploratory analysis, we divided the cohort of patients aged ≤60 years into 2 cohorts (≤50 years and 51–60 years), hypothesizing a protective hormonal effect. Our data show that females aged ≤50 years have better LRM than males, while those aged 51–60 years do not (Fig. 1). This might suggest a hormonal effect to an extent, but further studies to confirm this are needed especially as other studies did not support a role of estrogen alone or combined with progestin in the development of lymphoma among postmenopausal women [21]. In addition, Teras et al suggested that post-menopausal hormones might play a role in FL etiology and no association with disease-related morality was proposed [22]. Further, agonists of estrogen receptor might induce apoptosis in lymphoid murine models [23]. Collectively, this data along with our findings support further evaluation of hormonal roles in FL outcomes and therapies.

In the older cohort, explaining the better PFS and OS in females is challenging. The total number of patients in this cohort is small, and data on serum rituximab levels, which explained the variations in DLBCL, were not available. Critically, and while data on serum rituximab levels were not captured in our patients, rituximab dose intensity was similar for both sexes.

We validated our data using the SEER database. Similar variations in outcomes were observed among >10,000 patients registered in SEER with a diagnosis of FL from 2004–2007 and followed through 2012 (Fig. 1). These parameters were chosen to select FL patients that reflected our cohort to the extent possible and who had a similar median follow-up.

Our analysis has the limitations of any observational study. Details on other non–lymphoma-related causes of death were not available. The fact that females in the general USA population have a slight survival advantage compared with men might challenge the OS difference observed. Selection bias for enrolling patients on clinical trials might partially explain differences noted in NLCS versus SEER. However, this investigation represents the largest prospective examination of the impact of sex on FL outcomes and prognosis. For the first time, we report that sex can have an impact on outcomes in FL, especially in younger patients. This information is potentially useful as the future generation of clinical trials in this disease is being designed.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015; 65:5–29. [PubMed: 25559415]
2. Nabhan C, Byrtek M, Rai A, et al. Disease characteristics, treatment patterns, prognosis, outcomes and lymphoma-related mortality in elderly follicular lymphoma in the United States. Br J Haematol. 2015; 170:85–95. [PubMed: 25851937]
3. Nabhan C, Byrtek M, Taylor MD, et al. Racial differences in presentation and management of follicular non-Hodgkin lymphoma in the United States: Report from the National LymphoCare Study. Cancer. 2012; 118:2842–4850.
4. Federico M, Vitolo U, Zinzani PL, et al. Prognosis of follicular lymphoma: A predictive model based on a retrospective analysis of 987 cases. Intergruppo Italiano Linfomi Blood. 2000; 95:783–789. [PubMed: 10648386]
5. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood. 2004; 104:1258–1265. [PubMed: 15126323]
6. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: A new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol. 2009; 27:4555–4562. [PubMed: 19652063]
7. Takata K, Okada H, Ohmiya N, et al. Primary gastrointestinal follicular lymphoma involving the duodenal second portion is a distinct entity: A multicenter, retrospective analysis in Japan. Cancer Sci. 2011; 102:1532–1536. [PubMed: 21561531]
8. Junlén HR, Peterson S, Kimby E, et al. Follicular lymphoma in Sweden: Nationwide improved survival in the rituximab era, particularly in elderly women: A Swedish Lymphoma Registry study. Leukemia. 2015; 29:668–676. [PubMed: 25151959]
9. Lim RB, Loy EY, Lim GH, et al. Gender and ethnic differences in incidence and survival of lymphoid neoplasm subtypes in an Asian population: Secular trends of a population-based cancer registry from 1998 to 2012. Int J Cancer. 2015; 137:2674–2687. [PubMed: 26061168]
10. Muller C, Murawski N, Wiesen MH, et al. The role of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. Blood. 2012; 119:3276–3284. [PubMed: 22337718]
11. Pfreundschuh M, Muller C, Zeynalova S, et al. Suboptimal dosing of rituximab in male and female patients with DLBCL. Blood. 2014; 123:640–646. [PubMed: 24297867]
12. Pfreundschuh M, GH SZ, et al. Increased rituximab (R) doses and effect on risk of elderly male patients with aggressive CD20+ B-cell lymphomas: Results from the SEXIE-R-CHOP-14 trial of the DSHNHL. J Clin Oncol. 2014; 32
13. Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: First report of the national LymphoCare study. J Clin Oncol. 2009; 27:1202–1208. [PubMed: 19204203]
14. Nastoupil LJ, Sinha R, Byrtek M, et al. The use and effectiveness of rituximab maintenance in patients with follicular lymphoma diagnosed between 2004 and 2007 in the United States. Cancer. 2014; 120:1830–1837. [PubMed: 24668580]

15. Guralnik JM, Eisenstaedt RS, Ferrucci L, et al. Prevalence of anemia in persons 65 years and older in the United States: Evidence for a high rate of unexplained anemia. Blood. 2004; 104:2263–2268. [PubMed: 15238427]

16. Pfreundschuh M, Poeschel V, Zeynalova S, et al. Optimization of rituximab for the treatment of diffuse large B-cell lymphoma (II): Extended rituximab exposure time in the SMARTE-R-CHOP-14 trial of the german high-grade non-Hodgkin lymphoma study group. J Clin Oncol. 2014; 32:4127–4133. [PubMed: 25403207]

17. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: The BRIGHT study. Blood. 2014; 123:2944–2952. [PubMed: 24591201]

18. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013; 381:1203–1210. [PubMed: 23433739]

19. Riihijarvi S, Taskinen M, Jerkeman M, et al. Male gender is an adverse prognostic factor in B-cell lymphoma patients treated with immunochemotherapy. Eur J Haematol. 2011; 86:124–128. [PubMed: 20942853]

20. Nabhan C, Aschebrook-Kilfoy B, Chiu BC, et al. The impact of race, age, and sex in follicular lymphoma: A comprehensive SEER analysis across consecutive treatment eras. Am J Hematol. 2014; 89:633–638. [PubMed: 24633911]

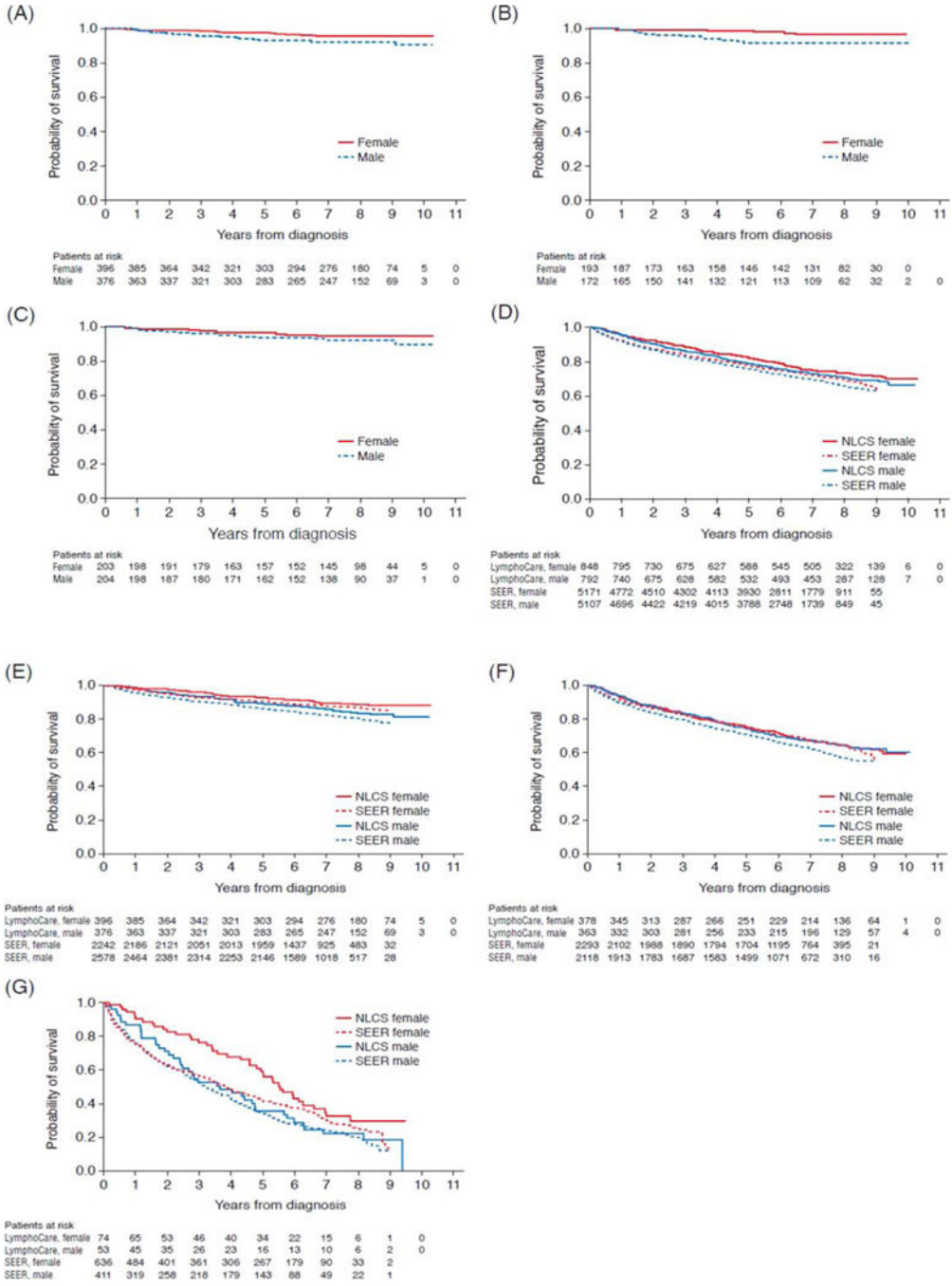


**Figure 1.**

LRM and OS by sex and age group. (A) LRM in patients aged ≤60 years treated with R-based induction therapy ($P = 0.04$). (B) LRM in patients aged ≤50 years treated with R-based induction therapy ($P = 0.04$). (C) LRM in patients aged 51–60 years treated with R-based induction therapy ($P = 0.32$). (D) OS by sex in patients from all age groups (NLCS and SEER).* (E) OS by sex in patients aged ≤60 years (NLCS and SEER).*(F) OS by sex in patients aged 61–80 years (NLCS and SEER).*(G) OS by sex in patients aged >80 years (NLCS and SEER).*LRM, lymphoma-related mortality; OS, overall survival; R, rituximab;

NLCS, National LymphoCare Study; SEER, Surveillance, Epidemiology and End Results program; FL, follicular lymphoma.*SEER adult FL patients diagnosed between 2004 and 2007 were used in this analysis. NLCS patients receiving first-line R-induction treatment were used in this analysis. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

## TABLE I

Summary of Baseline Patients' Characteristics by Sex

| Variable | Category | Male (*n* = 1277) *n* (%) | Female (*n* = 1375) *n* (%) | *P* value* |
|---|---|---|---|---|
| Age categories (years) | ≤60 | 619 (48) | 636 (46) | 0.119 |
| | 61–80 | 571 (45) | 617 (45) | |
| | >80 | 87 (7) | 122 (9) | |
| Race/ethnicity | White | 1172 (92) | 1223 (89) | 0.102 |
| | African American | 37 (3) | 55 (4) | |
| | Hispanic | 50 (4) | 69 (5) | |
| | Other | 18 (1) | 28 (2) | |
| Grade | 1 or 2 | 906 (80) | 999 (80) | 0.994 |
| | 3a | 232 (20) | 256 (20) | |
| | Missing | 139 | 120 | |
| FLIPI risk category | Good (0–1) | 390 (38) | 360 (33) | 0.045 |
| | Intermediate (2) | 313 (30) | 329 (30) | |
| | Poor (3–5) | 331 (32) | 396 (36) | |
| | Missing | 243 | 290 | |
| Number of nodal sites | <5 | 809 (66) | 871 (66) | 0.958 |
| | ≥5 | 417 (34) | 447 (34) | |
| | Missing | 51 | 57 | |
| LDH level | Normal | 781 (79) | 814 (79) | 0.891 |
| | >ULN | 207 (21) | 219 (21) | |
| | Missing | 289 | 342 | |
| Hemoglobin (g/dL) | <12 | 180 (15) | 340 (27) | <0.0001 |
| | ≥12 | 1014 (85) | 941 (73) | |
| | Missing | 83 | 94 | |
| Stage | I or II | 421 (33) | 441 (32) | 0.681 |
| | III or IV | 846 (67) | 917 (68) | |
| | Missing | 10 | 17 | |
| ECOG PS | 0 | 605 (69) | 630 (66) | 0.133 |
| | 1 | 232 (27) | 273 (29) | |
| | ≥2 | 34 (4) | 53 (6) | |
| | Missing | 406 | 419 | |
| Extra-nodal sites | None | 590 (48) | 617 (46) | 0.548 |
| | 1 | 403 (33) | 462 (35) | |
| | ≥2 | 239 (19) | 250 (19) | |
| | Missing | 45 | 46 | |
| B-symptoms | Yes | 327 (26) | 344 (25) | 0.728 |
| | No | 950 (74) | 1031 (75) | |
| Bone marrow involvement | Yes | 367 (37) | 392 (39) | 0.464 |
| | No | 617 (63) | 616 (61) | |
| | Missing | 293 | 367 | |

| Variable | Category | Male (*n* = 1277) *n* (%) | Female (*n* = 1375) *n* (%) | *P* value* |
|---|---|---|---|---|
| Geographical region | Midwest | 418 (33) | 418 (30) | 0.182 |
| | Northeast | 214 (17) | 246 (18) | |
| | Southeast | 377 (30) | 443 (32) | |
| | Southwest | 108 (8) | 91 (7) | |
| | West | 160 (13) | 177 (13) | |
| Centre type | Academic | 240 (19) | 276 (20) | 0.406 |
| | Community | 1037 (81) | 1099 (80) | |

FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; ULN, upper limit of normal; ECOG PS, Eastern Cooperative Oncology Group performance score.

[a]Pearson chi-square test.

## TABLE II

First-Line Treatment by Sex and Age Group

| First-Line Treatment | Male (*n* = 1277) *n* (%) | Female (*n* = 1375) *n* (%) | Overall *P* Value[a] | Individual *P* Value[b] |
|---|---|---|---|---|
| Watchful waiting | 253 (20) | 302 (22) | 0.003 | 0.174 |
| R-mono | 144 (11) | 212 (15) | | 0.002 |
| R-chemo | 648 (51) | 636 (46) | | 0.021 |
| R-CHOP | 341 (27) | 300 (22) | | |
| R-CVP | 136 (11) | 164 (12) | | |
| R-Fludarabine | 107 (8) | 114 (8) | | |
| R-other | 64 (5) | 58 (4) | | |
| Other treatments | 232 (18) | 225 (16) | | 0.219 |
| Chemotherapy | 39 (3) | 32 (2) | | |
| Investigational therapy | 81 (6) | 77 (6) | | |
| XRT | 62 (5) | 63 (5) | | |
| Other non-investigational therapy | 2 (<1) | 13 (1) | | |
| Combined modality: XRT | 43 (3) | 36 (3) | | |
| Combined modality: BMT | 2 (<1) | 2 (<1) | | |
| Radioimmunotherapy | 3 (<1) | 2 (<1) | | |
| Rituximab dose intensity among patients receiving R-mono, R-chemo[c] | | | 0.496 | |
| <0.9 | 221 (32) | 229 (31) | | |
| ≥0.9–1.1 | 371 (54) | 417 (57) | | |
| >1.1 | 90 (13) | 84 (12) | | |
| Maintenance treatment among patients receiving R-mono, R-chemo | | | 0.988 | |
| R-maintenance | 257 (46) | 282 (46) | | |
| Observation | 304 (54) | 333 (54) | | |
| ≤60 years | *n* = 619 | *n* = 636 | | |
| Watchful waiting | 111 (18) | 128 (20) | 0.042 | 0.322 |
| R-mono | 48 (8) | 74 (12) | | 0.020 |
| R-chemo | 328 (53) | 322 (51) | | 0.403 |
| Other treatments | 132 (21) | 112 (18) | | 0.096 |
| 61–80 years | *n* = 571 | *n* = 617 | | |
| Watchful waiting | 121 (21) | 144 (23) | 0.485 | |
| R-mono | 78 (14) | 96 (16) | | |
| R-chemo | 285 (50) | 282 (46) | | |
| Other treatments | 87 (15) | 95 (15) | | |
| >80 years | *n* = 87 | *n* = 122 | | |
| Watchful waiting | 21 (24) | 30 (25) | 0.092 | |
| R-mono | 18 (21) | 42 (34) | | |
| R-chemo | 35 (40) | 32 (26) | | |
| Other treatments | 13 (15) | 18 (15) | | |

R-mono, rituximab monotherapy; R-chemo, rituximab plus chemotherapy; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab plus cyclophosphamide, vincristine and prednisolone; R-Fludarabine, rituximab plus fludarabine with/without other chemotherapy; R-other, rituximab plus other chemotherapy; XRT, radiotherapy; BMT, bone marrow transplantation.

[a] Pearson chi-square test.

[b] *P* values obtained using a 2×2 contingency table for each possible treatment group using Pearson chi-square test.

[c] Rituximab dose intensity less than 1 indicates that the received dose was less intense than expected (1 dose per 7-day cycle for R-mono and 21-day cycle for R-chemo). Missing data were excluded.

## TABLE III

Adjusted HR for Sex Difference in PFS, OS and LRM Among Patients Receiving First-Line R-Based Treatment

| | | Age group | | |
|---|---|---|---|---|
| | | **≤60 years (*n* = 396 F + 376 M)** | **61–80 years (*n* = 378 F + 363 M)** | **>80 years (*n* = 74 F + 53 M)** |
| PFS | Number of events | 151 F+156 M | 199 F+187 M | 48 F+43 M |
| | HR (95% CI) (Female vs. male)[a] | 0.84 (0.72, 0.97) | 0.84 (0.72, 0.97) | 0.84 (0.72, 0.97) |
| OS | Number of events | 39 F+55 M | 127 F+120 M | 41 F+40 M |
| | HR (95% CI) (Female vs. male)[b] | 0.63 (0.41, 0.97) | 0.86 (0.66, 1.11) | 0.50 (0.31, 0.82) |
| LRM | Number of events | 15 F+27 M | 59 F+48 M | 21 F+11 M |
| | HR (95% CI) | 0.46 (0.23, 0.93) (Female vs. male)[c] | 1.06 (0.71, 1.58) | 0.84 (0.38, 1.87) |

F, females; M, males; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; LRM, lymphoma-related mortality; CI, confidence interval; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance score; R, rituximab.

Baseline covariates are sex, age group, race/ethnicity, baseline disease characteristics (histology grade, nodal sites, LDH, hemoglobin, stage, ECOG PS, extra-nodal sites, B-symptoms, bone marrow involvement), geographical region and center type.

[a]Estimations are from the Cox proportional hazards model with baseline covariates, first-line treatment, age-by-treatment interaction ($P < 0.001$), rituximab dose intensity, and time-varying R-maintenance variable.

[b]Estimations are from the Cox proportional hazards model with baseline covariates, sex-by-age interaction ($P = 0.128$), first-line treatment, treatment-by-age interaction ($P = 0.147$), rituximab dose intensity, and time-varying R-maintenance variable.

[c]Estimations are from the Cox proportional hazards model with baseline covariates, sex-by-age interaction ($P = 0.126$) first-line treatment, rituximab dose intensity and time-varying R-maintenance variable.