Improvements in Observed and Relative Survival in Follicular Grade 1-2 Lymphoma Over Four Decades: The Stanford University Experience

Short Title: Survival in Follicular Lymphoma

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Key Points:

- Retrospective analysis of long term outcomes of patients with follicular lymphoma managed at Stanford University over 4 decades

- Significant improvement in overall survival despite no change in event free survival after first line therapy

ABSTRACT

Recent studies report an improvement in overall survival (OS) of patients with follicular lymphoma (FL). Previously untreated patients with grade 1-2 FL referred from 1960-2003 and treated at Stanford were identified. Four eras were considered: era 1, pre-anthracycline (1960-1975, n=180); era 2, anthracycline (1976-1986, n=426), era 3, aggressive chemotherapy/purine analogs (1987-1996, n=471) and era 4, rituximab (1997-2003, n=257). Clinical characteristics, patterns of care and survival outcomes were assessed. Observed OS was compared with the expected OS calculated from Berkeley Mortality Database life tables derived from population matched by gender and age at time of diagnosis. The median OS was 13.6 years. Age, gender and stage did not differ across the eras. Although primary treatment varied, event free survival after the first treatment did not differ between eras (p=0.17). Median OS improved from approximately 11 years in eras 1 and 2 to 18.4 years in era 3 and has not yet been reached for era 4 (p<0.001) with no suggestion of a plateau in any era. These improvements in OS exceeded improvements in survival in the general population during the same time period. Several factors, including better supportive care and effective therapies for relapsed disease, are likely responsible for this improvement.
INTRODUCTION

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma (NHL).\textsuperscript{1} It is characterized by an indolent clinical course and a continuous pattern of relapse. Additionally, there is a risk of transformation to an aggressive lymphoma of approximately 20% at 5 years and 30% at 10 years.\textsuperscript{2-6}

We have previously reported that the natural history of FL was not altered by the use of various management approaches at Stanford between 1960 to 1992.\textsuperscript{7} Recent studies suggest that the overall survival (OS) of patients with grade 1-2 FL has improved due to progress in treatment and supportive care.\textsuperscript{8-16} In this retrospective analysis, we have updated our previous results and extended the period of analysis to 2007. We sought to determine if changes in outcome were attributed to frontline treatment or effective salvage strategies, which varied across four eras reflecting changes in the treatment of FL.

PATIENTS AND METHODS

Previously untreated patients with all stages of grade 1-2 FL who received primary treatment at Stanford University Medical Center between January 1960 – December 2003 were identified from the lymphoma database. All diagnostic specimens were reviewed by pathologists in the Department of Pathology at Stanford and re-classified according to the WHO classification.\textsuperscript{17} Patients with grade 3 FL or composite lymphoma were excluded. Disease characteristics, time to first treatment, type of front-line treatment, and outcomes were evaluated.
retrospectively. Data regarding additional salvage treatment administered at other facilities were recorded when available. ‘Immediate treatment’ was arbitrarily defined as treatment received within 2 months of referral, while ‘no initial therapy’ was expectant management continuing for > 2 months after referral. For survival analysis, we categorized patients according to four eras reflecting changes in treatment of FL: era 1; pre-anthracycline (1960-75), era 2; anthracycline (1976-1986), era 3; aggressive chemotherapy/purine analogs (1987-1996) and era 4; rituximab (1997-2003). Data on therapy received were censored in January 2007. The Social Security Administration Database was searched to obtain current vital status and data censored in December 2007. Since the study cohorts spanned a 43 year period, variables to calculate the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria often were not available. The follicular lymphoma international prognostic index (FLIPI) was calculated for era 4. The study was conducted according to Stanford University’s Institutional Review Board and in accordance with the Declaration of Helsinki.

Statistical Considerations

For patient characteristics and treatment exposure, P-values < 0.05 were considered to indicate statistical significance. The chi-squared and the t tests were used for comparisons of categorical and continuous variables respectively between the treatment eras. Comparisons of event free survival (EFS) for front-line treatments were restricted to patients with advanced stage (stage III and IV), as those with limited stage disease were usually treated with radiation therapy (RT) alone and the intent of this analysis was to evaluate the impact of changes
in systemic therapies. EFS was calculated from the date of initial treatment to the date of first event defined as progression, relapse, next treatment, or death. All patients were included for OS analysis, which was calculated from date of diagnosis to death related to any cause.

Kaplan-Meier survival curves were estimated for the four eras and compared for statistical differences using the log-rank test in the univariate analyses. Additional analyses were performed for subsets defined by ‘immediate treatment’ versus ‘no-initial therapy’, age ≥ 60 versus <60 years, stage I/II versus stage III/IV, by gender and by excluding patients who received vaccine therapies. We also assessed OS for patients followed at Stanford at time of the first event. For comparison of the observed OS in our patient cohort with that of the general population, patients were matched by diagnosis date, age and gender with single calendar year, single year of age, gender specific life tables from the Berkeley Mortality Database to determine the expected OS for the general population. The latter, accounts for other causes of death and provides an estimate of the cause-specific survival through relative survival analysis.

RESULTS

Patient characteristics

1,334 patients who met predefined criteria were identified. Patient demographics and clinical characteristics are depicted in Table 1. Patients were distributed as: era 1 (n=180), era 2 (n=426), era 3 (n=471), and era 4 (n=257) with a median follow up of 11.1, 8.6, 11.3 and 6.1 years respectively. Over the years, a trend
toward an increasing interval from disease diagnosis to Stanford referral was noted. Median age at diagnosis was 50 years (range 21 – 87) and 77% were ≤ age 60. Approximately 60% had grade 1 FL and > than 80% presented with advanced stage disease. The latter characteristics did not differ significantly across the eras. FLIPI was available for 234 patients (91%) in era 4: 18.8%, 42.7%, and 38.5% had low, intermediate and high risk disease respectively. Histologic transformation of FL to a more aggressive lymphoma proven by subsequent biopsy was seen in 32% of patients, as reported separately.\(^6\)

**Treatment**

The median time from referral to initiation of therapy was longer in eras 3 and 4 compared with earlier eras (\(p=0.001\)) (Table 1). The proportion of patients who had ‘no initial therapy’ in eras 1 to 4 was 16%, 44%, 59%, and 60%, respectively (\(p<0.001\)). The median time to first treatment among these patients was 2.9 years (Appendix Figure 1). For era 4, 11% of patients in whom therapy was deferred had high risk FLIPI compared to 30% in those who received immediate treatment. Front-line therapy of patients with advanced disease was variable (Table 2). Although primary RT was an important modality of treatment for advanced stage disease in the earlier eras, in the later 2 eras, it was used largely for local control or palliation. Cyclophosphamide, vincristine and prednisone (CVP), was the most frequent front-line alkylator-based chemotherapy, whereas CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was used in a minority of patients, mainly in era 3. Upfront rituximab use, either as a single
agent or in combination with CVP or CHOP was introduced in eras 3 and 4. About a quarter of the patients were accrued into FL vaccination trials in combination with chemotherapy in eras 3 and 4. Cumulative treatment exposure according to era is also shown in Table 2. At relapse, patients in eras 1 and 2 were more likely to receive repeated courses of RT or alkylator-based treatments, while patients in eras 3 and 4 had a wider range of therapeutic and salvage options available. The cumulative exposure to rituximab varied considerably. Only 1% and 11% of patients in eras 1 and 2 received rituximab at some point during therapy, compared with 27% in era 3 and 46% in era 4. Due to patterns of referral and the retrospective nature of this analysis, data regarding all additional salvage treatments that patients may have received at other facilities is limited.

**Event-free survival**

For patients with advanced disease, the median EFS across eras 1-4 was 2.0 years (range 1.5 - 3.3 years, p=0.4) with no significant differences despite variable initial treatments (Figure 1A). Similarly EFS did not differ for patients receiving ‘immediate treatment’ nor for those with ‘no initial therapy’ [1.6 years (range 0.9-1.8 years, p=0.2), and 2.2 years (range 1.5 - 3.5 years, p=0.4), respectively (Figures 1B and 1C)].

**Overall Survival**

The median OS for the 1,334 patients was 13.6 years; 11.0 years for era 1, 11.0 years for era 2, 18.5 years for era 3 and has not been reached for era 4 (p<0.001) (Figure 2A). The ten-year OS for patients in eras 1 to 4 was 54%, 54%,
68% and 73%, respectively. Gains in OS were seen in both early (stage I-II) and advanced (stage III and IV) FL (Appendix Figure 2A & 2B respectively). Greater gains in OS were observed in patients younger than 60 years compared to patients ≥60 years (Appendix Figure 3A & 3B, respectively).

Patients in eras 3 and 4 had significantly better OS than those in eras 1 and 2, regardless of whether they were in the ‘no initial therapy’ or ‘immediate treatment’ group (Figures 2B and 2C). The median OS for patients assigned to ‘no initial therapy’ and ‘immediate treatment’ was 15.1 and 12.1 years respectively (p=0.007) (Figure 3). The non-inferior OS of patients assigned to ‘no initial therapy’ was observed across all eras despite changes in front-line therapeutic strategies. Therapy choice (or decision for ‘no initial therapy’) did not differ by gender but improvements in OS were greater in women compared to men (p<0.0001 for women and p=0.03 for men) (Appendix Figure 4A & Figure 4B solid lines). Two hundred and nineteen patients (~25%) received vaccine-based therapies in eras 3 and 4. When these patients were excluded from the analysis, the median OS for era 1 and 2 was 11 years, for era 3 16.4 years and not reached for era 4 (p=0.002) (Appendix Figure 5). 86.7% of patients with advanced disease were being followed at Stanford at time of their first event. The median OS following the first event was 4.1 years for era 1, 6 years for era 2, 10.2 years for era 3 and has not been reached for era 4 (p<0.001) (Appendix Figure 6). The magnitude of improvements in OS across eras among patients with FL far exceeded the gains in life expectancy and OS of the general population during the same period of time (Appendix Figure 4C). As expected,
however, in all four eras, the observed OS of patients with FL was significantly inferior to the expected OS of the general population (p<0.0001). The 10-year relative survivals for eras 1 to 4 were 0.61, 0.61, 0.76 and 0.8 respectively (p < 0.001) (Table 3).

DISCUSSION

In this analysis spanning over 50 years, we note a marked improvement in OS of patients with FL. The median OS was 11 years in the first 2 eras, 18.5 years in era 3 and has not yet been reached in era 4, with no plateau observed in any era to date. In our series, there was no detrimental effect on OS in patients who had ‘no initial therapy’ compared to those treated immediately. The EFS was similar across the eras despite variations in the choice of initial therapy, with no significant differences whether patients had ‘no initial therapy’ or ‘immediate treatment’. Although it has been the institutional practice at Stanford to defer the use of anthracycline therapy for treatment after relapse and/or aggressive histologic transformation, the availability of anthracycline beginning in era 2 did not significantly impact the OS of our patients. Similarly, the availability of purine analogue fludarabine for upfront use or for relapsed disease did not appear to have an impact in era 3. Rituximab as a component of initial therapy was used in 4% and 18% of patients in cohort 3 and 4 respectively. The strategy of patient-specific vaccines, designed to provoke a humoral and/or cellular immune response against the clonal surface immunoglobulin (idiotype) unique to each FL patient, was available in the context of clinical trials initiated in era 3. When patients treated with vaccine based therapies were excluded, the OS gains were
similar to the entire cohort. Therefore, the OS seen in eras 3 and 4, which is superior to OS in eras 1 and 2 cannot be attributed to any one particular regimen.

Since the OS of an indolent malignancy, reflects both the efficacy of initial therapy, and all subsequent treatments, the improvement in OS may be attributable to the sequential application of effective new therapies for relapsed or progressive disease, as well as improved supportive therapy. Our observation of an OS improvement in the absence of a significant change in the EFS supports this concept. This is further supported by the improvements noted in OS across eras after the first event. Increasing exposure to different treatments and lower reliance on repetition of prior therapies is evident in Table 2 that shows increased use of both myeloablative therapy and rituximab-based combination chemotherapy in patients relapsing in era 3 and a declining use of single-agent chlorambucil and RT in the eras 3 and 4. Of note is that the survival curves for eras 2 and 3 start to diverge from that of era 1 around the 20-year and 5-6 year landmarks, respectively. It is likely that patients from eras 2 and 3 who survived past these landmarks entered the era of effective newer therapies. Treatment with rituximab at relapse was rapidly adopted after FDA approval of the agent in 1997, as reflected in eras 3 and 4 in which more patients were exposed to rituximab, predominantly in the relapse setting. It is likely that the overall use of rituximab in our study is underestimated as detailed evaluation of all subsequent treatments, which often occurred at outside facilities, could not be performed.

Our findings are similar to observational studies from the SEER database that reported statistically significant improvement in OS among unselected
patients across consecutive diagnostic eras, as well as to those from a European center that reported improvement in disease-specific survival of FL.\textsuperscript{9,30} Some series suggest that a better response to front-line therapy potentially translates into improved OS for patients with FL in both the pre and post rituximab eras.\textsuperscript{31,32} Reports from the Southwest Oncology Group (SWOG) and MD Anderson Cancer Center attribute the improvement in survival of patients participating in sequential therapeutic trials for FL largely to the incorporation of immunotherapy into front-line regimes.\textsuperscript{8,10} In the SWOG studies, monoclonal antibody trials, included CHOP followed by rituximab (SWOG 9800) and CHOP followed by I\textsubscript{131}I-tositumomab (SWOG 9911). The progression free survival (PFS) and OS were significantly superior in the immunotherapy era (61% and 91% respectively) and superiority was retained after adjusting for differences in prognostic factors between the pre and post immunotherapy study group. In the MD Anderson Cancer Center series an improvement in 5-year OS from 64% to 95% was noted over 5 successive clinical trials, in which rituximab was included in later trials.\textsuperscript{10} Similar observations have been reported in a Cochrane meta analysis evaluating 1,943 patients from 7 randomized clinical trials using rituximab in indolent lymphoma with an improvement in overall response rates and a reduction in the hazard ratio for deaths to 0.63 (95% CI 0.51-0.79, p< 0.001).\textsuperscript{33} Compared to the latter series, in our study only a minority of patients received rituximab in front-line regimens, hence, the potential impact of incorporation of rituximab in EFS could not be determined. Despite this, we observed significant improvements in
OS again supporting the concept that subsequent therapies are just as important as the choice of front-line treatment in defining long-term outcome.\textsuperscript{34}

Although our data are for consecutive patients treated in a single center, a certain degree of inherent selection bias is inevitable since Stanford is a large referral center. This is reflected by a relatively younger median age (50 years) of our patients. Another limitation of this analysis is that staging methods evolved over the study period and there may have been variations in frequency and type of imaging used for follow up care. The concept of lead-time bias i.e., patients with FL in the later eras were diagnosed earlier, which resulted in longer observed OS, is difficult to measure. In our study there was no significant difference in the distribution of stage across eras and OS improvement was noted both for early as well as advanced stage disease (Appendix Figure 2A and 2B, respectively). We note for patients diagnosed in later eras the median time from diagnosis to referral to Stanford was longer (Table 1); however, this trend did not impact OS results when measured from the time of referral (data not shown). Nonetheless, improvements in the observed OS were notable compared to improved life expectancy in the general population and was more marked in women than in men. The latter finding is provocative within the context of the emerging body of literature suggesting that males with B cell lymphoma have an inferior outcome, which might be attributed to differences in metabolism of rituximab between genders.\textsuperscript{35-37}

The longer survivals in recent eras reported in our series likely relate to several other factors including improved supportive care and improved outcome.
of transformed FL.\textsuperscript{6} We have recently reported that the OS of patients with FL after transformation has increased from 0.8 years to 3.3 years.\textsuperscript{6} This may relate to earlier recognition, due to advancement in imaging modalities, such as positron emission tomography, and improved treatment of transformed disease.

In conclusion, in our series, patients with grade 1-2 FL experienced an improvement in OS that was greater than improvements in OS of the general population during the same periods of time. Our data demonstrate that while there has been considerable progress, FL remains an incurable disease. Challenges remain in management and future studies that evaluate tailored sequencing of emerging novel therapeutic agents along with a better understanding of the disease biology, may eventually lead to a cure.
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Authorship Contributions: D.T., S.J.H., and R.H.A. organized the project, assembled data and wrote the manuscript; B.M.S., S.S.H., and S.K.P., provided statistical analysis; and all authors interpreted data and reviewed, edited and approved the final manuscript.

Conflict-of-Interest Disclosures: S.J.H. currently employed by Genentech, and owns Roche stock. The remaining authors declare no competing financial interests.
References


22. Human Mortality Database University of California, Berkeley (USA) and Max Planck Institute for Demographic Research (Germany). Accessed Available at http://www.mortality.org or http://www.humanmortality.de (10/16/11).


Table 1. Patient Demographics and Clinical Characteristics

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<td>51</td>
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<td>24</td>
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<td>Male, (%)</td>
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<td>Median time from referral to first treatment (days)</td>
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<td>61</td>
<td>163</td>
<td>143</td>
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* Follicular and diffuse architecture, grade 1-2 FL, follicular lymphoma
Table 2. Initial and Cumulative Treatment Exposure in Patients with Advanced Stage Grade 1-2 FL

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<td>N=213 N (%)</td>
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<tr>
<td><strong>Initial Therapy</strong></td>
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<tr>
<td>RT only*</td>
<td>37 (25)</td>
<td>46 (14)</td>
<td>11 (3)</td>
<td>6 (3)</td>
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<tr>
<td>Single-agent alkylator*</td>
<td>35 (24)</td>
<td>60 (18)</td>
<td>68 (18)</td>
<td>13 (6)</td>
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<tr>
<td>CVP-like*</td>
<td>68 (46)</td>
<td>150 (45)</td>
<td>125 (33)</td>
<td>110 (52)</td>
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<tr>
<td>CHOP-like*</td>
<td>1 (1)</td>
<td>17 (5)</td>
<td>49 (13)</td>
<td>11 (5)</td>
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<tr>
<td>Fludarabine-based*</td>
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<td>SCT**</td>
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<td>3 (1)</td>
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<td>53 (16)</td>
<td>57 (15)</td>
<td>30 (14)</td>
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**Cumulative treatment exposure in advanced stage patients by era**

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<tbody>
<tr>
<td></td>
<td>N=147 N (%)</td>
<td>N=330 N (%)</td>
<td>N=380 N (%)</td>
<td>N=213 N (%)</td>
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<tr>
<td>RT</td>
<td>59 (40)</td>
<td>86 (26)</td>
<td>46 (12)</td>
<td>17 (8)</td>
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<tr>
<td>Single-agent alkylator</td>
<td>60 (41)</td>
<td>110 (35)</td>
<td>91 (24)</td>
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<tr>
<td>CVP-like</td>
<td>97 (66)</td>
<td>205 (62)</td>
<td>163 (43)</td>
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<tr>
<td>CHOP-like</td>
<td>37 (25)</td>
<td>106 (32)</td>
<td>106 (28)</td>
<td>32 (15)</td>
</tr>
<tr>
<td>Fludarabine-based</td>
<td>2 (1)</td>
<td>10 (3)</td>
<td>87 (23)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>R</td>
<td>1 (1)</td>
<td>36 (11)</td>
<td>103 (27)</td>
<td>98 (46)</td>
</tr>
<tr>
<td>Vaccine trial</td>
<td>1 (1)</td>
<td>10 (3)</td>
<td>99 (26)</td>
<td>60 (28)</td>
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<td>SCT</td>
<td>0</td>
<td>10 (3)</td>
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<tr>
<td>Salvage regimen without SCT</td>
<td>0</td>
<td>3 (1)</td>
<td>11 (3)</td>
<td>6 (3)</td>
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* p < 0.001; ** p =0.001; *** at last follow up

**Legend:** FL, follicular lymphoma; RT radiation therapy; CVP, cyclophosphamide-vincristine-prednisolone; RT,Radiotherapy; CHOP, cyclophosphamide-adriamycin-vincristine-prednisolone; R, rituximab; SCT, stem cell transplant.
Table 3. Comparison of Expected Versus Observed Survival by Era of Diagnosis

<table>
<thead>
<tr>
<th>Era</th>
<th>10-year OS Expected (%)</th>
<th>10-year OS Observed (%)</th>
<th>10-year Relative Survival in FL Patients (%)</th>
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<tbody>
<tr>
<td>1965-75</td>
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<td>54</td>
<td>61</td>
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<td>1976-86</td>
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<td>1987-96</td>
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<td>1997-2003</td>
<td>90</td>
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Figure Legends

Figure 1.
Event-free survival (EFS) after first treatment course by era of diagnosis. (A) All patients; (B) Patients with no initial therapy; (C) Patients receiving immediate treatment.

Figure 2.
Overall survival (OS) by era of diagnosis. (A) All patients; (B) Patients with no initial therapy; (C) Patients receiving immediate treatment.

Figure 3.
Overall survival (OS) by time to first treatment.
Figure 1A.

Median EFS:
- Era 1: 3.3 yrs
- Era 2: 2.0 yrs
- Era 3: 1.7 yrs
- Era 4: 1.5 yrs
- Overall: 2.0 yrs

Survival Probability vs. Time (years)

P = 0.2
Figure 1B.

Median EFS

Era 1: 0.9 yrs
Era 2: 1.7 yrs
Era 3: 1.8 yrs
Era 4: 1.5 yrs
Overall: 1.6 yrs
Figure 1C.

Median EFS
Era 1: 3.5 yrs
Era 2: 2.2 yrs
Era 3: 1.7 yrs
Era 4: 1.5 yrs
Overall: 2.2 yrs
Figure 2A.

<table>
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<tr>
<th>Era</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Era 1</td>
<td>11.0 yrs</td>
</tr>
<tr>
<td>Era 2</td>
<td>11.0 yrs</td>
</tr>
<tr>
<td>Era 3</td>
<td>18.5 yrs</td>
</tr>
<tr>
<td>Era 4</td>
<td>Not reached</td>
</tr>
<tr>
<td>Overall</td>
<td>13.6 yrs</td>
</tr>
</tbody>
</table>
Figure 2B.

Median OS
- Era 1: 11.6 yrs
- Era 2: 11.7 yrs
- Era 3: 17.6 yrs
- Era 4: Not reached
- Overall: 15.1 yrs

P < 0.001
Figure 2C.

Median OS
- Era 1: 10.8 yrs
- Era 2: 10.6 yrs
- Era 3: 19.0 yrs
- Era 4: Not reached
- Overall: 12.1 yrs

Survival Probability

Time (years)

P=0.001
No initial therapy
(n=645): Median OS 15.1 yrs

Immediate treatment
(n=688): Median OS 12.1 yrs

Figure 3.
Improvements in observed and relative survival in follicular grade 1-2 lymphoma over four decades: the Stanford University experience

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