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Abstract

BACKGROUND

Given the lower incidence of lymphoma-related death but higher background mortality in patients with early-stage mucosa-associated lymphoid tissue (MALT) lymphoma, it is critically important to examine how age affects a treatment’s survival benefit.

METHODS

9,467 patients with early-stage MALT lymphoma in the Surveillance, Epidemiology, and End Results (SEER) database treated between 2000-2015 were extracted and analyzed. Primary therapy was classified as radiotherapy (n = 3,407), chemotherapy (n = 1,294), and other/unknown treatments including observation (n = 4,766). Inverse probability of treatment weighting (IPTW) was conducted to balance baseline characteristics between groups. Relative survival (RS), standardized mortality ratio (SMR), and transformed Cox regression were conducted to compare survival differences between treatment modalities by controlling for the background mortality. Radiotherapy–age interaction was examined.

RESULTS

Across age-groups, early-stage MALT lymphoma patients were at lower risk of lymphoma-related death than death due to other causes. The 10-year overall survival (OS, 73.8%) and RS (96.6%) rates were significantly higher, and the SMR (1.14) significantly lower, with radiotherapy than with chemotherapy (OS, 61.7%; RS, 86.4%; SMR, 1.54; P < 0.001) or other/unknown treatments (OS, 61.1%; RS, 87.2%; SMR, 1.41; P < 0.001). By multivariable analysis and IPTW, radiotherapy remained an independent predictor of better RS (HR 0.81, 95%CI, 0.73-0.89; P < 0.001). A significant interaction between age and radiotherapy was identified for both RS (Pinteraction = 0.016) and OS (Pinteraction = 0.024), indicating greater benefit in young adults.

CONCLUSION

Radiotherapy can provide significant survival benefit in early-stage MALT lymphoma, especially in young adults.

Background

Mucosa-associated lymphoid tissue (MALT) lymphoma is an indolent malignancy, accounting for 7%-8% of B-cell non-Hodgkin lymphomas.¹ It is commonly seen in older patients (median age, ~ 65 years), who typically present with early-stage disease (60%-90%) and good prognosis. Excellent 5-year overall survival (OS) rates (~ 95%) have been achieved in early-stage disease with moderate-dose irradiation,²⁻⁷ and guidelines recommend radiotherapy as standard of care.[8, 9] However, utilization of other initial therapeutic strategies of early-stage MALT lymphoma remains common including surveillance,
chemotherapy, antibiotic therapy, immunotherapy, or surgical resection. The choice of treatment strategy may be tailored—according to patient age and performance status, primary site and perceived toxicity of radiotherapy extent of disease, and other factors.[7, 10–12]

Despite guideline recommendations, the proportion of patients receiving radiotherapy for upfront management is as low as 40% in the US.[13] The low adoption of radiotherapy may be due to doubts about its net survival benefit particularly for mild or asymptomatic patients, and concerns about long-term toxicity; some physicians may choose to reserve radiotherapy for salvage treatment when the disease progresses or relapses. Due to the paucity of good-quality studies comparing the outcomes of different modalities, it is not known whether the omission of upfront radiotherapy leads to poorer outcomes.

Interpretation of the existent literature associating particular treatment strategies with MALT outcomes is challenging for several reasons. First, patients with early-stage MALT lymphoma have low risk of lymphoma-related death (LRD) but high risk of death from other causes due to the indolent clinical course and older age at diagnosis,[12–14] and so previous studies that focused on assessing OS might have underestimated the survival benefit with radiotherapy.[2, 4, 5, 15] Meanwhile, studies evaluating LRD or disease-specific survival (DSS) may not have taken into account treatment-related deaths, and so could overestimate the survival benefit with radiotherapy.[12, 13, 16] Second, patients with MALT lymphoma are a unique population with long life expectancy but high risk of late relapse, treatment sequelae, or non-lymphoma-related death (non-LRD). In these patients, focusing on 5-year survival as the primary benchmark of treatment success does not adequately reflect the increased risk of morbidity and mortality potentially experienced throughout the lifespan.[1, 7, 20] In previous studies, comparison of effectiveness of treatments was compromised by small patient numbers and few events occurring over relatively short follow-up periods.[16, 21, 22] Third, background mortality rate is not the same in all age-groups; patients over 60 years have high competing mortality risk from other diseases. Therefore, for an indolent lymphoma it is critically important to examine how age affects a treatment's survival benefit. Thus, relative survival (RS) analysis—which controls for background mortality in an age-, sex-, and calendar year–matched general population—could be the appropriate tool to assess the net survival benefit of radiotherapy.[17–19]

This study aimed to analyze the Surveillance, Epidemiology, and End Results (SEER) database to determine whether radiotherapy could provide long-term survival benefit in patients with early-stage MALT lymphoma and to evaluate how this survival benefit is influenced by age at the time of treatment.

**Patients And Methods**

**Data collection and eligibility criteria**

Patients with newly-diagnosed MALT lymphoma were registered in the SEER database between 2000 and 2015. The inclusion criteria were 1) Ann Arbor stage I or II disease; 2) patient age > 20 years; and 3)
availability of follow-up information. The exclusion criteria were 1) stage III-IV or unknown stage disease; 2) unknown cause of death; or 3) initial treatment with implants, isotope, or unknown radiotherapeutic method. Of the 10,255 patients with early-stage MALT lymphoma registered in the database, 9,467 (92.3%) met the eligibility criteria (Supplemental Fig. 1A). Our institutional ethics review board approved this study.

**Definitions**

Variables were defined by International Classification of Diseases (ICD) code provided by the SEER database.[24, 25] The primary sites were classified as lung (ICD-O-3 340–349), stomach (ICD-O-3 160–169), eye and adnexa (ICD-O-3 690–699), salivary gland (ICD-O-3 79–89), skin (ICD-O-3 440–449), other site, and unrecorded site. Year of diagnosis was classified as 2000–2004, 2005–2010, and 2011–2015. Age was categorized as ≤ 40, 41–60, 61–80, and > 80 years, though age was also treated as a continuous variable for some analyses.

Primary therapy was classified as radiotherapy (radiotherapy as one component of primary treatment), chemotherapy (without radiotherapy), and other/unknown treatments (observation, resection, immunotherapy or unknown).

**Primary Endpoint and Statistical analysis**

The primary endpoints were RS and standardized mortality ratio (SMR). Survivals were performed with the Kaplan–Meier method, and compared using the log-rank test. Differences among categorical variables and continuous variables were tested using the Pearson chi-square test and the Kruskal–Wallis test, respectively. The inverse probability of treatment weighting (IPTW) approach based on propensity score, derived from a multinomial logistic regression model,[27] was used to balance the treatment arms. [26] Standardized mean difference was used to evaluate covariate balance, with value < 0.1 considered to indicate acceptable balance (Supplemental Fig. 1B).[27]

RS—the net time-to-event survival in the absence of other causes of death—was calculated using the Ederer II method as the observed OS corrected for the expected OS in an age-, sex-, race-, and calendar year–matched general US population.[17, 18, 28] SMR was the ratio of the observed mortality in the study cohort to the expected mortality in the matched general population; SMR > 1.0 indicated worse-than-expected survival. The US population life table and death rates were acquired from the SEER database. [24, 25] Likelihood ratio tests of Poisson regression models were fitted to test the heterogeneity of SMRs between subgroups. A transformed Cox regression model for RS was fitted to examine excess mortality associated with treatment groups, after adjusting for additional covariates.[19] The model transformed each person's original survival time to the expected death rate at that time by automatically taking account of the population hazard. A lower observed death rate at every expected death rate means better RS. Natural cubic and penalized splines were fitted to smooth out the instantaneous probability (“hazard”) of RS or SMR of different primary treatments according to age as continuous variables; knots of splines were optimized based on the Akaike information criterion. Multivariate Gaussian processes were simulated to graphically assess the interaction between age and the survival benefit of radiotherapy.
Statistical analyses were performed using the `compareGroups`, `survival`, `relsurv`, `popEpi`, `relnsurv`, `survminer`, `simPH`, `smoothHR`, and `maxastat` packages in R version 4.0.4 (https://www.r-project.org/).

**Results**

**Baseline characteristics and treatment trends**

Table 1 summarizes the characteristics of the study cohort. Briefly, the majority of patients (61.9%) were >60 years old (median age, 66 years). The male-to-female ratio was 1:1.24. The majority of patients (88.2%) had stage I disease, and the most common tumor site was the stomach, followed by skin, lung, and eye/orbit.
Table 1
Baseline characteristics of patients with early-stage MALT lymphoma, stratified by primary treatment (2000–2015)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All patients</th>
<th>RT</th>
<th>CT without RT</th>
<th>Other/unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td>Total</td>
<td>9467 (100)</td>
<td>3407 (100)</td>
<td>1294 (100)</td>
<td>4766 (100)</td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
<td>66.0 (55.0;76.0)</td>
<td>64.0 (53.0;73.0)</td>
<td>66.0 (56.0;76.0)</td>
<td>67.0 (56.0;77.0)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.310</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4225 (44.6)</td>
<td>1493 (43.8)</td>
<td>568 (43.9)</td>
<td>2164 (45.4)</td>
</tr>
<tr>
<td>Female</td>
<td>5242 (55.4)</td>
<td>1914 (56.2)</td>
<td>726 (56.1)</td>
<td>2602 (54.6)</td>
</tr>
<tr>
<td>Race</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7652 (80.8)</td>
<td>2719 (79.8)</td>
<td>1083 (83.7)</td>
<td>3850 (80.8)</td>
</tr>
<tr>
<td>Black</td>
<td>794 (8.4)</td>
<td>268 (7.9)</td>
<td>102 (7.9)</td>
<td>424 (8.9)</td>
</tr>
<tr>
<td>Other</td>
<td>902 (9.5)</td>
<td>397 (11.7)</td>
<td>102 (7.9)</td>
<td>403 (8.5)</td>
</tr>
<tr>
<td>Unrecorded</td>
<td>119 (1.3)</td>
<td>23 (0.7)</td>
<td>7 (0.5)</td>
<td>89 (1.9)</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000–2005</td>
<td>2282 (24.1)</td>
<td>813 (23.9)</td>
<td>264 (20.4)</td>
<td>1205 (25.3)</td>
</tr>
<tr>
<td>2005–2010</td>
<td>3822 (40.4)</td>
<td>1364 (40.0)</td>
<td>621 (48.0)</td>
<td>1837 (38.5)</td>
</tr>
<tr>
<td>2011–2015</td>
<td>3363 (35.5)</td>
<td>1230 (36.1)</td>
<td>409 (31.6)</td>
<td>1724 (36.2)</td>
</tr>
<tr>
<td>Primary site</td>
<td>&lt; 0.001</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are (%) unless otherwise specified.

Abbreviations: IQR, interquartile range; RT, radiotherapy; CT, chemotherapy; MALT, mucosa-associated lymphoid tissue; LRD, lymphoma-related death.

*\(P^*\) of independent Kruskal–Wallis test and chi-square test.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lung</th>
<th>Stomach</th>
<th>Eye</th>
<th>Salivary gland</th>
<th>Skin</th>
<th>Other/unrecorded</th>
<th>Ann Arbor stage</th>
<th>B symptoms</th>
<th>Marital status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>829 (8.8)</td>
<td>3506 (37.03)</td>
<td>779 (8.2)</td>
<td>810 (8.6)</td>
<td>1060 (11.2)</td>
<td>2483 (26.23)</td>
<td>8348 (88.2)</td>
<td>6298 (66.5)</td>
<td>5396 (57.00)</td>
</tr>
<tr>
<td></td>
<td>107 (3.1)</td>
<td>1205 (35.37)</td>
<td>510 (15.0)</td>
<td>344 (10.1)</td>
<td>512 (15.0)</td>
<td>729 (21.40)</td>
<td>3075 (90.3)</td>
<td>2589 (76.0)</td>
<td>2074 (60.87)</td>
</tr>
<tr>
<td></td>
<td>192 (14.8)</td>
<td>431 (33.31)</td>
<td>75 (5.8)</td>
<td>99 (7.7)</td>
<td>60 (4.6)</td>
<td>437 (33.77)</td>
<td>971 (75.0)</td>
<td>782 (60.4)</td>
<td>757 (58.50)</td>
</tr>
<tr>
<td></td>
<td>530 (11.1)</td>
<td>1870 (39.24)</td>
<td>194 (4.1)</td>
<td>367 (7.7)</td>
<td>488 (10.2)</td>
<td>1317 (27.63)</td>
<td>4302 (90.3)</td>
<td>2927 (61.4)</td>
<td>2565 (53.82)</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ann Arbor stage</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8348 (88.2)</td>
<td>3075 (90.3)</td>
<td>971 (75.0)</td>
<td>4302 (90.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1119 (11.8)</td>
<td>332 (9.7)</td>
<td>323 (25.0)</td>
<td>464 (9.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B symptoms</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>6298 (66.5)</td>
<td>2589 (76.0)</td>
<td>782 (60.4)</td>
<td>2927 (61.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>682 (7.2)</td>
<td>207 (6.1)</td>
<td>164 (12.7)</td>
<td>311 (6.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrecorded</td>
<td>2483 (26.3)</td>
<td>611 (17.9)</td>
<td>348 (26.9)</td>
<td>1528 (32.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>5396 (57.00)</td>
<td>2074 (60.87)</td>
<td>757 (58.50)</td>
<td>2565 (53.82)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorced/separated/widowed</td>
<td>2112 (22.31)</td>
<td>720 (21.13)</td>
<td>295 (22.80)</td>
<td>1097 (23.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried/single</td>
<td>1176 (12.42)</td>
<td>433 (12.71)</td>
<td>153 (11.82)</td>
<td>590 (12.38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>783 (8.27)</td>
<td>180 (5.28)</td>
<td>89 (6.88)</td>
<td>514 (10.78)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are (%) unless otherwise specified.

Abbreviations: IQR, interquartile range; RT, radiotherapy; CT, chemotherapy; MALT, mucosa-associated lymphoid tissue; LRD, lymphoma-related death.

*P of independent Kruskal–Wallis test and chi-square test.
### Treatment

<table>
<thead>
<tr>
<th>Insurance</th>
<th>( &lt; 0.001 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insured</td>
<td></td>
</tr>
<tr>
<td>5622 (59.39)</td>
<td>2089 (61.31)</td>
</tr>
<tr>
<td>Uninsured</td>
<td></td>
</tr>
<tr>
<td>103 (1.09)</td>
<td>24 (0.70)</td>
</tr>
<tr>
<td>Unrecorded</td>
<td></td>
</tr>
<tr>
<td>3742 (39.53)</td>
<td>1294 (37.98)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final outcome</th>
<th>( &lt; 0.001 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>6901 (72.9)</td>
<td>2694 (79.1)</td>
</tr>
<tr>
<td>LRD</td>
<td></td>
</tr>
<tr>
<td>497 (5.2)</td>
<td>143 (4.2)</td>
</tr>
<tr>
<td>Other death</td>
<td></td>
</tr>
<tr>
<td>2069 (21.9)</td>
<td>570 (16.7)</td>
</tr>
</tbody>
</table>

Data are (%) unless otherwise specified.

Abbreviations: IQR, interquartile range; RT, radiotherapy; CT, chemotherapy; MALT, mucosa-associated lymphoid tissue; LRD, lymphoma-related death.

*P of independent Kruskal–Wallis test and chi-square test.

3,407 (36.0%) were treated with radiotherapy, 1,294 (13.7%) with chemotherapy, and 4,766 (50.3%) with other or unknown treatments. The proportion of patients receiving radiotherapy remained more or less constant (33.4%-37.6%) between 2000 and 2015 (Supplemental Fig. 2A). Use of radiotherapy in initial treatment decreased steadily as patient age increased (63.2%-16.7%; Supplemental Fig. 2B); older patients were less likely to receive radiotherapy (Supplemental Table S1). The proportion of patients receiving chemotherapy remained low (7.7%-17%) across time periods and age subgroups.

## Causes of death

While 497 (5.2%) patients died of the lymphoma, 2,069 (21.9%) patients died of other causes. Over median follow-up of 79 months, the 10-year OS, DSS, and RS rates for the entire cohort were 65.8%, 92.4%, and 90.5%, respectively. Patients were at higher risk of non-LRD, with the risk being particularly high in patients > 60 years. Across the entire cohort, the 10-year cumulative incidence of LRD and non-LRD were 6.6% and 27.6%, respectively; non-LRD included deaths due to cardiovascular disease (8.2%), other cancers (8.3%), and other causes (11.1%; Fig. 1A). With increase in age, the risks of LRD and non-LRD increased dramatically. The 10-year cumulative incidences of LRD and non-LRD in the age-groups of \( \leq 40 \) years, 41–60 years, 61–80 years, and > 80 years were 1.3% and 1.4%, 2.3% and 9.7%, 7.9% and
31.1%, and 14.0% and 66.8%, respectively (Fig. 1B-E). In IPTW and multivariable analyses, older age was an independent predictor of shorter OS (HR 1.08, 95% CI: 1.07–1.09; \( P < 0.001 \); Fig. 1F).

**Absolute OS benefit with radiotherapy**

The unadjusted 10-year OS rate was 73.8% with radiotherapy versus 61.7% with chemotherapy (HR 0.60, 95% CI: 0.53–0.67; \( P < 0.001 \)) versus 61.1% with other/unknown treatments (HR 0.61, 95% CI: 0.56–0.67; \( P < 0.001 \); Fig. 2A). Patients receiving radiotherapy tended to be younger, more likely to have stage I disease, and more likely to have eye, salivary gland, and skin as the site of the primary tumor (Table 1). After IPTW adjustment, prognostic factors and marital status were well balanced between the treatment arms (Supplemental Fig. 1B). The IPTW-adjusted 10-year OS rate was 70.1% for radiotherapy, significantly higher than the 61.3% for chemotherapy (HR 0.68, 95% CI: 0.60–0.78; \( P < 0.001 \)) and 63.5% for other/unknown treatments (HR 0.76, 95% CI: 0.69–0.84; \( P < 0.001 \); Fig. 2B). In multivariable analysis, radiotherapy remained an independent favorable factor for OS (HR 0.80, 95% CI: 0.72–0.88; \( P < 0.001 \); Fig. 2C).

**Net survival benefit with radiotherapy based on relative survival analysis**

We evaluated the net survival benefit of radiotherapy relative to the age-, sex-, race, and calendar year-matched general US population. In patients treated with radiotherapy, the RS was only slightly lower than that in the matched general population. The lowest SMR and highest RS were seen in radiotherapy group. The SMR was 1.14 (95% CI: 1.06–1.23; \( P < 0.001 \)) for radiotherapy versus 1.54 (95% CI: 1.40–1.70; \( P < 0.001 \)) for chemotherapy versus 1.41 (95% CI: 1.34–1.49; \( P < 0.001 \)) for other/unknown treatments. The 10-year RS rate was 96.6% for radiotherapy versus 86.4% for chemotherapy (HR 0.73, 95% CI: 0.65–0.83; \( P < 0.001 \)) versus 87.2% for other/unknown treatments (HR 0.80, 95% CI: 0.73–0.88; \( P < 0.001 \); Fig. 3A). After balancing the treatment arms by IPTW and controlling for covariables in multivariable analysis, radiotherapy was still significantly associated with better RS (HR 0.81, 95% CI: 0.73–0.89; \( P < 0.001 \)). The observed death rate is closer to the diagonal line (Fig. 3B), indicating the better RS with radiotherapy than with chemotherapy or other/unknown treatments. Sensitivity analyses showed that the RS benefit of radiotherapy vs. non-radiotherapy was robust and unaffected by sex, race, stage, primary site, surgery, period of diagnosis, medical insurance status and radiotherapy alone (Supplemental Fig. 3–4).

**Age-dependent relative survival benefit of radiotherapy**

As LRD and non-LRD varied between age-groups, we examined how age—as a continuous variable—was associated with RS and SMR (Fig. 4). After adjusting for covariates and treatments using IPTW and multivariable analyses, younger age was found to be an independent predictor of poor RS (HR 0.98, 95% CI: 0.98–0.99; \( P < 0.001 \); Fig. 4A). Considering potential age–treatment interaction, radiotherapy vs. non-radiotherapy was associated with better RS (HR 0.36, 95% CI: 0.19–0.67; \( P = 0.001 \); Fig. 4B). Additionally, a significant interaction between age and radiotherapy was identified in both RS (\( P_{\text{interaction}} = 0.016 \); Fig. 4B) and OS (\( P_{\text{interaction}} = 0.024 \); Supplemental Fig. 5), indicating greater benefit with radiotherapy in
younger rather than in older patients. In natural spline analysis, the SMR with radiotherapy remained lower (approaching 1) than that of other treatments at all ages up to 90 years (Fig. 4C).

Discussion

Because of the indolent behavior of MALT lymphoma and the high competing risk of non-LRD, evaluation of the net survival benefit of radiotherapy is challenging. In this large population-based study, radiotherapy provided a significant and clinically meaningful benefit in terms of long-term OS, RS and SMR. The 10-year RS rate of 96.6% and SMR of 1.14 achieved with radiotherapy was excellent and significantly better than chemotherapy or other/unknown treatments. Radiotherapy was associated with better RS in almost all age-groups and showed a greater benefit of RS in young patients. These findings suggest that there are important age-related survival benefits to be gained from curative-intent radiotherapy in early-stage MALT lymphoma.

Multiple studies have demonstrated that radiotherapy can provide excellent 5-year local control and OS in patients with early-stage MALT lymphoma,[3–6, 15, 30, 31] and that disease-free survival and/or OS are superior with radiotherapy than other treatments.[12–14] However, in these previous studies, the treatments used varied widely (from a wait-and-watch approach to local treatments to systemic treatments, suggesting a similarly favorable 5-year OS or low risk of LRD with these managements.[3, 7, 10, 11, 21, 32, 33] Consistently,[2, 12, 13] only 36% of patients in this study received radiotherapy as initial treatment. Because of the high proportion of older patients at risk of non-LRD,[12, 13] it remains unclear whether the efficacy of initial radiotherapy for early-stage MALT lymphoma translates into definitive survival benefits. The initial treatment strategy should balance survival benefits and toxic effects, and also consider the background mortality, particularly in elderly patients. Previous studies comparing outcomes between treatment modalities were limited by small sample sizes, short follow-up durations, and lack of valid endpoints.[3, 7, 10, 13–16, 21, 22]

In this large population-based study, the life expectancy of patients with early-stage MALT lymphoma treated with radiotherapy was only slightly lower than that in the general population. Radiotherapy provided significantly better long-term OS and RS than chemotherapy and other treatments; the SMR and HR for RS were lowest with radiotherapy. The absolute gains of ~10% in 10-year OS and RS rates with radiotherapy suggest that radiotherapy is an essential first-line treatment for early-stage MALT lymphoma. Considering the small effect of indolent lymphoma on life expectancy, RS and SMR are valid endpoints which may be better than disease-specific endpoints for quantitative evaluation of the curative effect of radiotherapy. Cause-of-death analysis such as DSS will not fully account for treatment-related deaths.[34] As patients with MALT lymphoma are at constant risk of relapse[3, 4] and transformation to high-grade lymphoma,[20] the long-term net survival benefit with radiotherapy may be explained by its ability to prevent relapse, systemic dissemination and transformation, without significantly increasing risk of treatment-related death.
Given the median survival time of > 10 years in MALT lymphoma,[12, 14] large sample sizes and long follow-up periods are needed to demonstrate statistically significant survival differences between treatments. In an earlier SEER study of 7,774 patients with early-stage MALT lymphoma followed up for a median of 4.6 years,[13] the risk of LRD after radiotherapy was very low; the survival benefit with radiotherapy versus other treatments was statistically significant only in cutaneous and ocular locations. In another analysis of 347 patients with stage I gastric MALT lymphoma followed up for a median of 53 months,[23] 5-year OS was similar with radiotherapy and chemotherapy, but probability of 5-year LRD was significantly lower with radiotherapy. In a recent larger cohort of 2,996 patients with early-stage gastric MALT lymphoma followed up for a similar duration (5.6 years),[14] both DSS and OS were significantly better with radiotherapy alone than chemotherapy alone, without any increase in cardiac death. In the present study, significant difference in 10-year OS and RS between radiotherapy and other treatments highlights the importance of having large study populations and long follow-up periods when comparing treatment efficacies.

Similarly,[23] we observed higher risk of non-LRD in older patients with early-stage MALT lymphoma. However, after controlling for covariables of background mortality and treatment, older age was a favorable prognostic factor for RS. Previous studies have not specifically examined how age or background mortality influence the treatment benefit of radiotherapy. To our knowledge, this is the first large study to assess the relationship between age and treatment efficacy after controlling for background mortality. Radiotherapy versus non-radiotherapy was associated with better RS and lower SMR in almost all age groups. Furthermore, significant interaction between age and RS suggested that the survival gains provided by radiotherapy were greater in younger patients than in older patients. A probable explanation for this is that a high proportion of younger patients have lymphoma located in the skin and ocular adnexa, which are the locations that respond best to radiotherapy. Additionally, because patients with early-stage MALT lymphoma are at constant risk of relapse after treatment,[3, 4] young patients, with longer life expectancy than older patient, would experience more LRD and therefore are more likely to benefit from definitive control of a localized lesion. Moreover, given the relatively low competing effect of background mortality and the finding that young age is an adverse prognostic factor for RS, controlling the primary lesion is especially important in young patients. However, the long-term RS benefit with radiotherapy versus non-radiotherapy approaches for almost all age-groups should be taken into account and communicated to each patient during selection of the treatment approach.

This study has several strengths. First, this is the largest study to date to assess the long-term efficacy of radiotherapy for early-stage MALT lymphoma. Second, the incorporation of additional valid efficacy endpoints (RS, SMR), with adjustment for background mortality, provides more precise assessment of effectiveness, especially in older patients with indolent lymphoma who have high competing risk of death from other causes. Third, an age-dependent RS benefit of radiotherapy in early-stage MALT lymphoma is a finding that has not been reported previously. This finding is provocative that radiotherapy might be a better option for young patients, a demographic group where fears of longer-term radiotherapy-associated toxicity are likely highest.
This study has several limitations. First, detailed information regarding immunotherapy or chemotherapy regimens and anti-\textit{Helicobacter pylori} therapy was not available. Their effects on survival were not considered in this analysis. Second, treatment and prognosis of MALT lymphoma may vary with the site of the disease. However, sensitivity analyses confirmed that the RS benefit of radiotherapy was robust, regardless of primary site and stage; however, further evaluation of the association between prognosis and primary site is necessary. Third, some important prognostic factors (e.g., performance status and comorbidities) that might be associated with the selection or avoidance of radiotherapy were not accounted for in the analysis.

In conclusion, compared with other treatment modalities, radiotherapy was associated with better RS and OS and lower SMR in patients with early-stage MALT lymphoma. These results support utilization of radiotherapy for the initial treatment of early-stage MALT lymphoma, especially in younger adults. The findings of this SEER database analysis need to be validated in large institutional cohorts.

**Abbreviations**

SEER, Surveillance, Epidemiology, and End Results; ICD, International Classification of Diseases; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; SMR, standardized mortality ratio; RS, relative survival.

**Declarations**

**Ethics approval and consent to participate**

Our institutional ethics review board approved this study.

**Consent for publication**

Not applicable.

**Availability of data and materials**

All data are available at SEER database under name “Incidence - SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975-2016 varying).”

**Competing interests**

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References


Figures

Figure 1
Cumulative incidence of mortality according to cause of death. (A) Cumulative incidence of death related to lymphoma and other causes in the whole cohort. (B-E) Cumulative incidence of death related to lymphoma and other causes according to age groups: age $\leq$ 40 years (B), age 41-60 years (C), age 61-80 years (D), and age $>$ 80 years (E). (F) Association of age (as a continuous factor) with OS using age 60 years as the reference.

Figure 2
Comparison of OS between treatment arms. (A) Kaplan–Meier analysis of OS in patients treated with initial radiotherapy, chemotherapy, and other/unknown treatments. (B) IPTW-balanced Kaplan–Meier analysis of OS between treatment arms. (C) OS differences between treatment arms after balancing with IPTW and adjusting for age, sex, race, diagnosis year, primary site, Ann Arbor stage, B symptoms, and marital status with Cox multivariable regression. OS, overall survival; IPTW, inverse probability of treatment weighting.
Figure 3

Comparison of RS between treatment arms. (A) RS in patients with early-stage MALT lymphoma who received radiotherapy, chemotherapy, and other/unknown treatments. (B) Adjusted observed death rate in patients with early-stage MALT lymphoma versus the expected death rate in the general US population according to different primary treatments as a result of a transformed Cox proportional hazards model analysis. The observed death rate is close to the diagonal line, indicating lower risk for RS. RS, relative survival.
Figure 4

The relative risk of death by treatment arms and age. (A) Associations of age with HR for RS using age 60 years as the reference. This plot was based on the results of the multivariable transformed Cox regression after IPTW. The mean and 95% CIs of HR are represented by solid and shadow with dashed lines, respectively. (B) HR for RS is presented by radiotherapy versus non-radiotherapy according to age as a continuous variable. The solid line represents the HR estimate, and the shadow with dashed lines
represent 95% CIs. The simulated plot of the interaction between age and RS efficacy of radiotherapy, depicting the HR for RS in patients treated with radiotherapy or non-radiotherapy. This shows the result of the transformed Cox regression testing the interaction of age with the RS benefit of radiotherapy versus non-radiotherapy, after balancing with IPTW and controlling for age, sex, race, diagnosis year, primary site, Ann Arbor stage, B symptoms, and marital status. (C) SMR is presented by radiotherapy, chemotherapy, and other/unknown treatments with natural spline plot according to age at diagnosis. SMR standardized mortality ratio; HR, hazard ratio; RS, relative survival; IPTW, inverse probability of treatment weighting.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- SupFig1.Cohortinformation.pdf
- SupFig2.Primarytreatmentchoice.pdf
- SupFig3.Sensitivityanalysesforsubgroups.pdf
- SupFig4Sensitivityanalysesforinsurance.pdf
- SupFig5.AgehazardcurveforOS.pdf
- SupplementalTable1.Baselinecharacteristicsbyage.docx