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Comparative outcomes of oncologic therapy in gastric extranodal marginal zone (MALT) lymphoma: analysis of the SEER-Medicare database

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Background: Therapy for gastric marginal zone (MALT) lymphoma is largely based on single-arm trials. This observational study compared survival with radiotherapy, rituximab and combination chemoimmunotherapy in this disease.

Patients and methods: Gastric MALT lymphoma cases diagnosed between 1997 and 2007 were selected from the Surveillance, Epidemiology and End Results-Medicare database. Propensity score analysis and competing risk models were used to compare survival in patients with stage IE treated with radiation or chemotherapy, and in patients of all stages treated with rituximab alone or with chemoimmunotherapy.

Results: Among 1134 patients, 21% underwent radiation and 24% chemotherapy as initial treatment. In the balanced cohort of 347 patients with stage IE, radiotherapy alone was associated with a better cause-specific survival [hazard ratio (HR) 0.27, $P < 0.001$]. Patients receiving systemic therapy had better survival if it incorporated rituximab (HR 0.53, $P = 0.017$). After adjustment for confounding, the outcomes of those who received rituximab alone or combination chemoimmunotherapy were not statistically different ($P = 0.14$).

Conclusions: In elderly patients with stage IE gastric MALT lymphoma, radiotherapy was associated with lower risk of lymphoma-related death than chemotherapy. In those requiring systemic treatment, addition of cytotoxic chemotherapy to rituximab in the first-line regimen was not associated with improved survival.

Key words: chemotherapy, gastric lymphoma, MALT, propensity score, rituximab, SEER-Medicare

introduction

Eradication of *Helicobacter pylori* infection is the cornerstone of treatment of localized gastric extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT) type, leading to durable remissions in over 75% of patients [1]. Conversely, the optimal management of *H. pylori*-negative or recurrent disease is not well defined and relies on single-arm or observational studies of surgery, radiotherapy (RT) or chemotherapy [2]. Expert opinion guidelines recommend stage-dependent approach, favoring RT for localized and chemotherapy for advanced disease [3, 4]. However, clinicians and patients have to balance the risks and benefits of specific treatments without high-level evidence or long-term survival data.

The objective of this observational study was to address two issues using the population-derived Surveillance, Epidemiology and End Results (SEER)-Medicare database. First, we studied the relative benefits of RT and chemotherapy in the Medicare beneficiaries with stage IE gastric MALT lymphoma. Secondly, we evaluated how treatment with rituximab alone compares with combination chemoimmunotherapy in patients requiring systemic treatment.

methods

data source

SEER-Medicare is a database maintained by the National Cancer Institute (NCI), containing high-quality, continuously audited cancer registry data linked to Medicare billing claims [5]. SEER collects clinical, demographic and survival information from 18 registries covering 28% of the US population. Patients aged ≥65 years are matched to their Medicare files for inpatient and ambulatory services, including extensively validated records of surgery, RT and chemotherapy [6]. Data on most oral drugs (such as antibiotics) are not available. This database has been successfully utilized for studying chemoimmunotherapy and survival outcomes in indolent lymphomas [7, 8].

The study was subject to approval by our Institutional Review Board and to a Data Use Agreement with NCI. The study files covered Medicare claims from 1 January 1997 to 31 December 2009. Patients were selected

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using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes for histology (marginal zone B-cell lymphoma) and anatomical location (stomach). We excluded patients without adequate Medicare coverage or those covered by a Health Maintenance Organization, because their billing claims would be absent in the database (Figure 1, supplementary Table S1, available at *Annals of Oncology* online).

definition of variables

Demographic and clinicopathologic characteristics, dates of diagnosis and death were derived from SEER and/or Medicare files. As the database does not contain laboratory or other diagnostic study results, we used the International Classification of Diseases (ICD-9) and Healthcare Common Procedure Coding System (HCPCS) codes from claims to define additional variables, using methods published in the context of SEER-Medicare analyses [9]. The Charlson Comorbidity Index was determined using the validated NCI algorithm in the timeframe between 365 days before and 30 days after the diagnosis [10]. An indicator of poor performance status was constructed based on the utilization of home care services, skilled nursing facility admissions, mobility aids and oxygen therapy supplies [11]. Both indices correlated with patient survival (supplementary Figures S1 and S2, available at *Annals of Oncology* online).

Presence of anemia was determined using relevant ICD-9 codes, claims for transfusions or erythropoietin [7]. We used the same procedure to define malnutrition and gastrointestinal hemorrhage/perforation. Diagnostic codes were only considered if they occurred on at least two nonlaboratory claims at least 30 days apart in order to increase their specificity [9]. The recording of *H. pylori* infection was defined over the entire time window.

Gastrectomy was ascertained using the inpatient procedure codes. Radiotherapy was defined using codes for RT-related services and lymphoma diagnosis, thus excluding RT for other indications. Intravenous chemotherapy was defined using HCPCS codes for specific drugs [8]. The regimens were assumed to contain rituximab if it was administered within 180 days of the initial chemotherapy date, thus accounting for consolidation or maintenance strategies. Chemotherapy initiated within 90 days of RT was assumed to be a part of combined modality therapy. Claims with chemotherapy prescribed for other diagnoses were excluded, but the affected patients ($N = 56$) were retained in the analysis, because patients with secondary cancers treated without chemotherapy still contributed to survival data. For the definition of death related to lymphoma, we counted all fatalities attributed to any form of lymphoma/leukemia on death certificates.

statistical analysis

We studied prognostic factors affecting survival using flexible parametric models [12]. Since the majority of deaths were not attributed to lymphoma and oncologic treatments may affect both cancer-related and other events (e.g. cardiovascular or infectious), we used a competing risk survival analysis to compare treatments [13]. Cumulative incidence function curves were compared using Gray's test and subdistribution hazard ratios (HR) were obtained from Fine-Gray regression models [14]. Proportional hazard assumptions were tested using graphical methods and time interactions. All statistical tests are reported with two-tailed P values and 95% confidence intervals (CI), at an alpha level of 0.05 or lower using SAS version 9.3 (Cary, NC), Stata/SE version 12.1 (StataCorp LP, College Station, TX) and R version 2.15.1 (The R Foundation for Statistical Computing, Vienna, Austria).

propensity score analysis

An inherent treatment selection bias was present in this retrospective cohort, related to numerous clinical factors affecting treatment decisions. In order to generate comparable study arms, we conducted a propensity score analysis. In this two-step procedure, the probability of receiving treatment is first calculated and the calculated score is subsequently incorporated as an adjustment in the survival comparison. The methodology can remove systematic bias related to measured variables and enables estimation of treatment effects [15]. One of its advantages over multivariable regression is that it mirrors the design of a randomized study. Patients with extremely low or high treatment probability, who would not be likely to enter a randomized trial, can be excluded. The balance of study arms with regard to all variables can be verified, thus ensuring group comparability before analyzing the outcomes. The propensity score in our study was derived from a logistic regression model fit using variables associated with treatment or outcome (regardless of their statistical significance), so as to achieve maximal group similarity. Covariate balance was evaluated using standardized differences of means (SDM), with SDM of <0.1 (corresponding to <10% difference between the arms) indicative of acceptable balance [16]. For outcome adjustment, we employed the inverse probability of treatment weighting, assigning to all patients stabilized weights corresponding to their probability of receiving specific therapy [17].

results

patient characteristics and survival

The study included 1134 patients with a median 53 months of follow-up data (Table 1). MALT lymphomas constituted 39.7% ($N = 2155$) of all gastric lymphomas in the database; diffuse large B-cell lymphoma (DLBCL) being more prevalent (45.0%, $N = 2443$, supplementary Table S2, available at *Annals of Oncology* online). Half of the studied patients had no record of any oncologic therapy (*H. pylori* eradication data were not available), while 5% underwent surgery ($N = 59$), 21% RT ($N = 236$) and 24% chemotherapy ($N = 276$) as the initial treatment, at a median of 3.4 months from diagnosis (interquartile range 1.7–7.9 months). Younger age, advanced stage, better performance status and diagnosis after 2003 were associated with a higher chance of receiving RT or chemotherapy, but the teaching status of the hospital was not. Patients undergoing gastrectomy or with no record of oncologic treatment had a distinctly shorter survival, likely reflecting their unfavorable baseline features.

The median overall survival was 6.7 years (95% CI 6.2–7.5). The cumulative incidence of lymphoma-related death (LRD) at 5 years was 12.1% (95% CI 10.3% to 14.2%), while it was 29.0% (95% CI 26.2% to 31.8%) for competing causes of death (Figure 2A). A simple score incorporating advanced stage (III/IV), B symptoms and poor performance status was strongly prognostic for LRD, with the 5-year risk ranging from 6.5% to 33.5% (Figure 2B, Table 2).

radiation and chemotherapy in stage IE lymphoma

Among patients with stage IE lymphoma, 347 who received RT ($N = 185$) or chemotherapy ($N = 162$) within 2 years of diagnosis were included in the propensity score analysis of comparative outcomes. Twenty-five percent of patients treated with chemotherapy received also RT ($N = 40$), mostly as part of

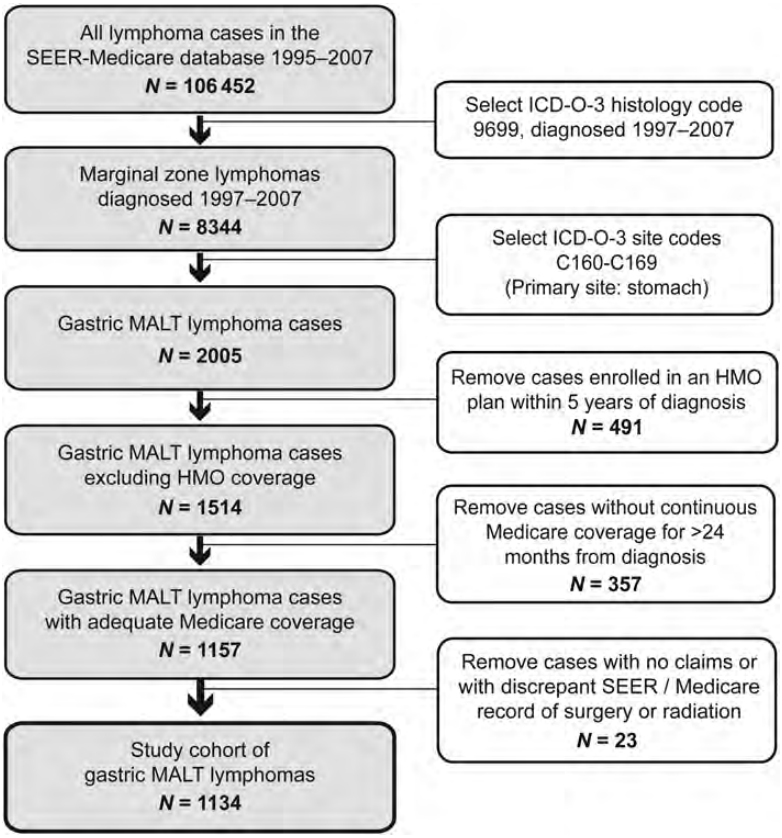

Figure 1. Patient selection flowchart. HMO, health maintenance organization; ICD-O-3, International Classification of Diseases for Oncology, 3rd Edition; MALT, mucosa-associated lymphoid tissue; SEER, Surveillance, Epidemiology, and End Results

their initial treatment plan (median interval of 3 months from the first infusion). Subsequent chemotherapy was applied in only 7% of those initially treated with RT ($N = 13$, median interval 24 months). Patients who underwent combined modality therapy were included in the chemotherapy arm. Radiotherapy alone was a more likely choice in patients without B symptoms, residing in metropolitan areas and with less comorbidities, but did not depend on hospital teaching status. In the unadjusted population, the 5-year cumulative incidence of LRD was 5.3% for RT (95% CI 2.6% to 9.4%) and 19.1% for chemotherapy (95% CI 13.1% to 26.0%, $P < 0.001$, Figure 3A). Conversely, the risk of death from other causes was not different (25.7% and 24.8%, respectively, $P = 0.56$).

The propensity score adequately balanced all variables affecting treatment selection or survival (Figure 3B, supplementary Tables S3 and S4 and Figure S3, available at *Annals of Oncology* online). After the adjustment, the risk of LRD was still significantly lower in patients treated with RT alone (HR 0.27, 95% CI 0.13–0.55, $P < 0.001$). The overall survival was not significantly different (HR 0.73, 95% CI 0.51–1.04, $P = 0.08$). Patients treated with chemotherapy had a higher risk of admission to a hospital [odds ratio (OR) 3.68, 95% CI 2.34–5.81, $P < 0.0001$] or a critical care unit (OR 3.25, 95% CI 1.78–5.92, $P < 0.0001$) within 1 year from treatment.

In a sensitivity analysis, consistent results were obtained when extreme values of the propensity score were trimmed at different levels—a procedure shown to partly compensate for unobserved confounding (supplementary Table S5, available at *Annals of Oncology* online) [18]. It was also consistent regardless of inclusion of prognostic factors in the outcome model, omission of the combined modality therapy cases or restriction of the initial treatment timeframe to 6, 12, 36 or 60 months from diagnosis.

rituximab with or without cytotoxic chemotherapy

Among the 321 patients who received any chemotherapy, we restricted the comparative analysis to those treated with regimens incorporating rituximab, cyclophosphamide and/or fludarabine ($N = 307$). Administration of any rituximab was associated with a lower risk of LRD (HR 0.53, 95% CI 0.31–0.89, $P = 0.017$) and its increased application correlated with improved survival observed after 2003.

The cohort of 230 patients who received rituximab was split into groups treated with the monoclonal antibody alone ($N = 139$) or in combination with cytotoxic chemotherapy ($N = 91$). Younger age, stage III/IV disease, presence of B symptoms, lack of comorbidities and residence in nonmetropolitan areas were predictive of the choice of chemoimmunotherapy over rituximab alone. In the unadjusted population, the cumulative incidence of LRD at 5 years for patients treated with rituximab alone was 17.7% (95% CI 11.2% to 25.4%), not significantly different from patients treated with chemotherapy (22.4%, 95% CI 13.8% to 32.4%, $P = 0.46$, Figure 4A). However, there was a significant difference in the risk of death from noncancer-related causes

Table 1. Main clinical characteristics of 1134 patients with gastric MALT lymphoma

Variables	Patients, *N* (%)
Age (years)	
Mean (SD)	76 (9.0)
Median (range)	77 (36–100)
Sex	
Male	544 (48)
Female	590 (52)
Race/ethnicity	
White non-Hispanic	896 (79)
White Hispanic	89 (8)
Black	79 (7)
Asian/Other	70 (6)
Year of diagnosis	
1997–2000	312 (28)
2001–2003	392 (35)
2004–2007	430 (38)
Marital status	
Married	561 (49)
Widowed	340 (30)
Single/divorced	153 (13)
Unrecorded	80 (7)
Prior malignancy	197 (17)
Ann Arbor stage	
I	801 (71)
II	62 (5)
III/IV	107 (9)
Unrecorded	164 (14)
B symptoms	
Absent	436 (38)
Present	111 (10)
Unrecorded	587 (52)
Other recorded diagnoses	
H. pylori infection	210 (19)
Anemia	482 (43)
GI hemorrhage/perforation	341 (30)
Malnutrition	87 (8)
Poor performance status	334 (29)
Charlson Comorbidity Index	
0	636 (56)
1	297 (26)
2	168 (15)
>2	33 (3)
Treatment administered (any date)	
Gastrectomy	72 (6)
Radiotherapy	303 (27)
Chemotherapy	321 (28)
First course of chemotherapy	
Rituximab alone	139 (43)
Chemotherapy alone	84 (26)
Rituximab–chemotherapy	98 (31)
End point status	
Alive	560 (49)
Lymphoma-related death	151 (13)
Other death	423 (37)

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; GI, gastrointestinal; SD, standard deviation.

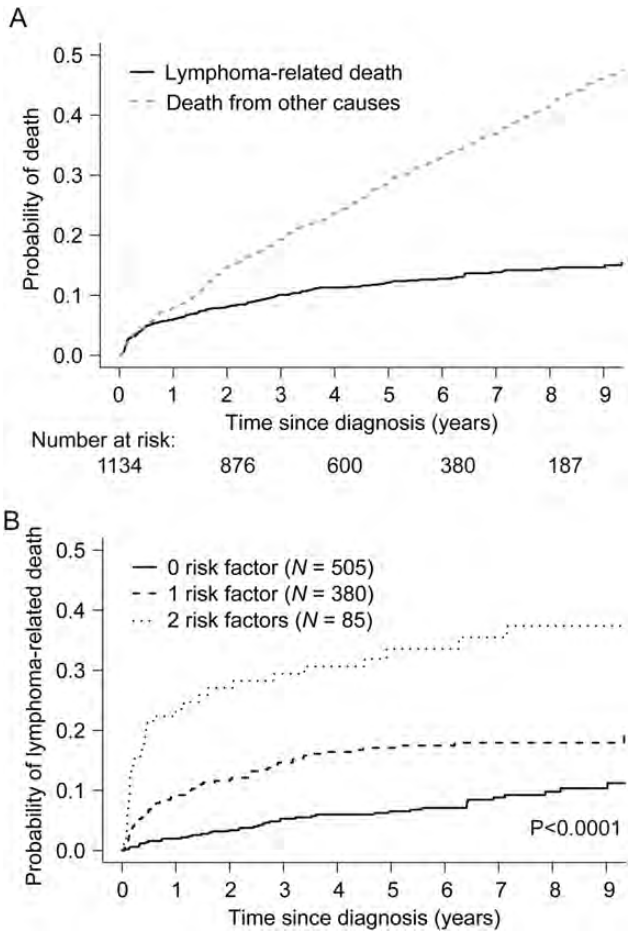

Figure 2. (A) Cumulative incidence of death related to lymphoma and competing causes. (B) Cumulative incidence of lymphoma-related death by the number of high-risk factors (stage III/IV, presence of B symptoms or poor performance status).

(33.1% and 17.8%, respectively, $P = 0.004$). The overlap of the propensity score was weaker, although acceptable matching was achieved (Figure 4B, supplementary Tables S6 and S7 and Figure S4, available at *Annals of Oncology* online).

After the propensity score adjustment, the difference in LRD with administration of combination chemoimmunotherapy was not significant (HR 1.76, 95% CI 0.83–3.73, $P = 0.14$), although the unfavorable HR persisted in the sensitivity analysis (supplementary Table S8, available at *Annals of Oncology* online). The overall survival did not differ (HR 1.02, 95% CI 0.60–1.76, $P = 0.93$). The rates of hospitalization within a year were not significantly different (OR 1.43, 95% CI 0.84–2.43, $P = 0.19$), although the risk of neutropenic infection was higher with combined chemoimmunotherapy (OR 3.79, 95% CI 1.78–8.05, $P = 0.001$).

discussion

This observational study of Medicare patients with gastric MALT lymphomas demonstrates better survival outcomes in early-stage disease with RT and no apparent survival benefit of adding cytotoxic agents to rituximab during the initial course of chemotherapy. Gastric MALT lymphoma has a low

Table 2. Prognostic model for lymphoma-specific survival in 970 patients with gastric MALT lymphoma[a]

Variables	Hazard ratio	95% CI	*P*
Age (10-years increment)	1.76	1.39–2.24	<0.001
Sex			
Female	Reference		
Male	1.49	1.02–2.16	0.037
Race/ethnicity			
White non-Hispanic	Reference		
White Hispanic	0.93	0.47–1.82	0.83
Black	1.14	0.52–2.51	0.75
Asian	2.79	1.62–4.81	<0.001
Marital status			
Married	Reference		
Widowed	1.86	1.21–2.84	0.004
Single/divorced	1.48	0.86–2.55	0.16
Unrecorded	0.85	0.30–2.40	0.76
Hemorrhage/perforation	1.71	1.20–2.44	0.003
Prior malignancy	1.96	1.28–2.99	0.002
B symptoms			
Absent	Reference		
Present	2.13	1.29–3.52	0.003
Unrecorded	1.26	0.85–1.85	0.25
Year of diagnosis			
1997–2000	Reference		
2001–2003	0.85	0.57–1.27	0.43
2004–2007	0.54	0.34–0.87	0.011
Variables with nonproportional hazard[b]			
Stage			<0.001
IE	*Reference*		
II–IV	*5.55 at 6 months*		
	1.31 at 5 years		
Poor performance status			<0.001
	3.43 at 3 months		
	1.51 at 5 years		

[a]Patients with unrecorded Ann Arbor stage were excluded.

[b]Variables violating the proportional hazard assumption in the flexible parametric model were modeled using interaction with time. Examples of hazard ratio values (peak and value at 5 years) are listed, italicized.

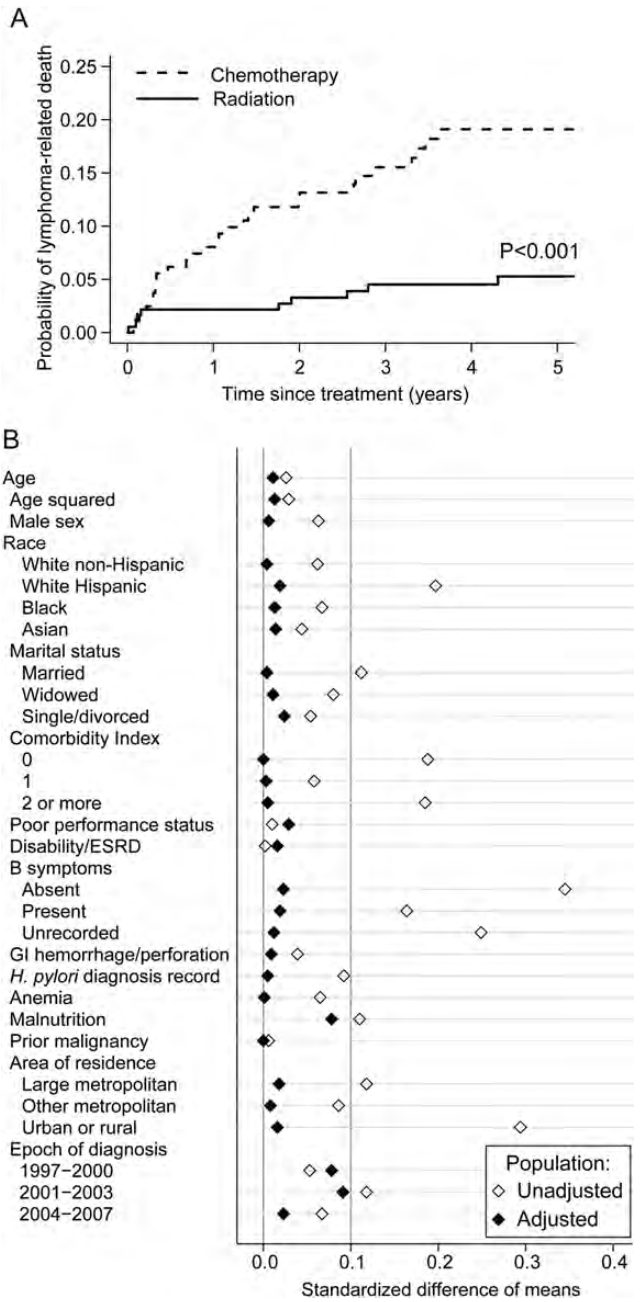

Figure 3. Analysis of patients with stage IE treated with chemotherapy or radiation: (A) Cumulative incidence of lymphoma-related death by treatment arm (unadjusted population); (B) absolute standardized differences of means between treatment arms before and after the propensity score adjustment. ESRD, end-stage renal disease; GI, gastrointestinal.

potential for systemic involvement and <10% risk of dying as a consequence of the disease [19]. Most patients achieve extended remissions after antibiotic eradication of *H. pylori*, and as additional chemotherapy does not improve outcomes, oncologic treatment is reserved for progressive or symptomatic lymphoma [20, 21]. Noncomparative trials report excellent outcomes with either RT or chemotherapy using alkylating agents, purine analogs or rituximab [22–26]. The initial choice should therefore balance benefits and toxic effects, particularly in elderly patients with high noncancer mortality, often focused on the quality of life. The lower risk of death with RT in our study may indicate an advantage of RT in this population. However, a thorough assessment of risks/benefit ratio would require more data on the quality of life, symptom control, toxic effects and progression-free survival. A systematic review of published trials also favored RT, although it evaluated only response rates and did not address treatment selection bias [2]. One randomized study suggested improved event-free survival with chemotherapy (without rituximab), but there was no *H. pylori* assessment or treatment [27].

Combination chemotherapy in MALT lymphoma shows a high rate of disease control with acceptable toxicity, but patients in phase II trials are significantly younger (median age 57–63 years) [26, 28, 29]. Therefore, rituximab alone may be attractive in the older population, with durable remission rates of over 75% [24, 30]. Our study reassuringly shows favorable survival with single-agent rituximab as initial therapy in the

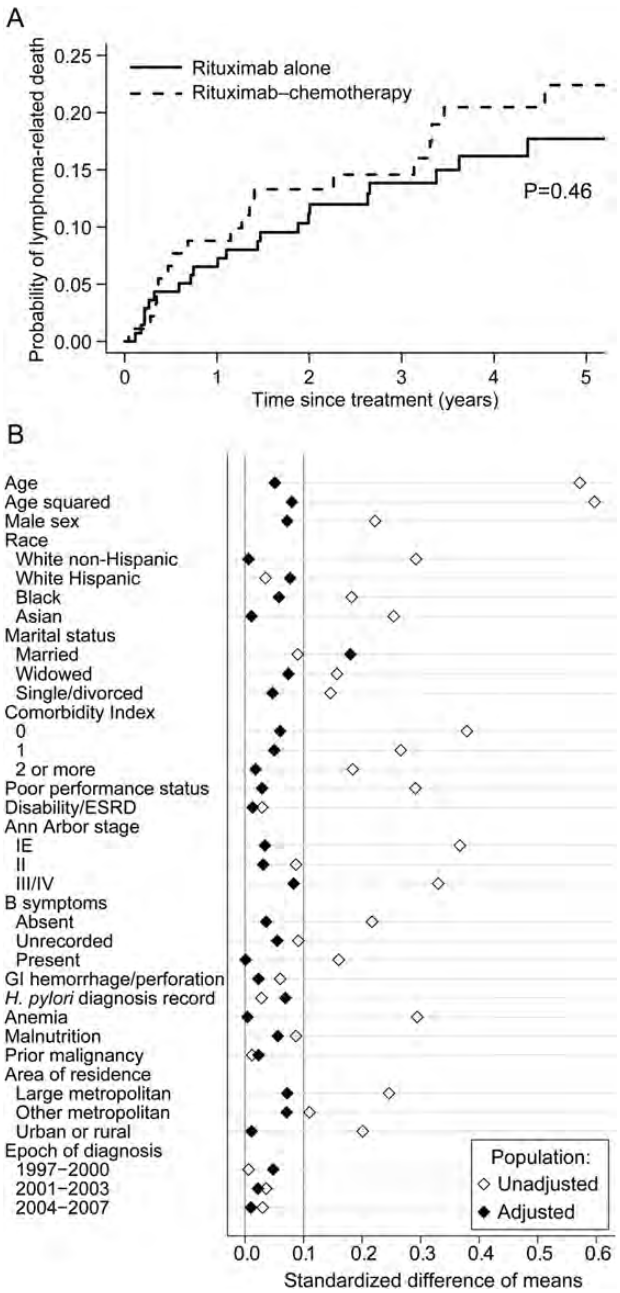

Figure 4. Analysis of patients treated with rituximab with or without cytotoxic chemotherapy: (A) Cumulative incidence of lymphoma-related death by treatment arm (unadjusted population); (B) absolute standardized differences of means between treatment arms before and after propensity score adjustment. *Footnote*: ESRD, end-stage renal disease; GI, gastrointestinal.

largest cohort reported to date. We cannot rule out the possibility that presence of a high-grade histology component or high tumor burden affected the choice of treatment. High-grade gastric MALT lymphomas (correctly classified as DLBCL) may be preferentially treated with anthracycline chemotherapy, although they can respond to *H. pylori*-directed treatment [31]. Our comparison should therefore be interpreted with this limitation in mind. In this cohort of Medicare beneficiaries, treatments with radiation or chemotherapy were highly prevalent (50%). This might indicate that outcomes in this group are not as optimistic as in the published series of younger patients. Transformation to DLBCL was recorded in only 1% of cases, consistent with previous reports [20, 32]. The chromosomal translocations t (11;18) and t(1;14) associated with unresponsiveness to antibiotic therapy do not seem to be more prevalent in older patients [33, 34]. The very low rate of recorded *H. pylori* infection is almost certainly a significant underestimate.

The strengths of our analysis include the cohort size and its comprehensive nature, including both academic and community centers in the covered areas. The propensity score adjustment may have minimized treatment selection bias inherent to retrospective studies. However, our data sources and methodology imposed several important limitations. The analysis involved elderly patients with a median age of 77 years, 8 years higher than in unselected gastric MALT lymphomas, so the results should not be extrapolated to younger populations. The absence of pathology review is another weakness, although the SEER-Medicare classification of gastric lymphoma histologies (45% DLBCL, 39% MALT) is quite consistent with published clinicopathologic reviews [35–37]. One study demonstrated excellent concordance of marginal zone lymphoma diagnosis between SEER and an independent pathology review [38]. We distinguished treatment choices using billing claims, so factors influencing the decisions could only be inferred. We successfully balanced all accessible confounders associated with treatment choices or survival. However, records of prior antibiotic therapy, cytogenetic or laboratory abnormalities (such as lactate dehydrogenase) were not available and their balance between treatment arms could not be ascertained. Limiting the analysis to stage IE lymphomas treated early in the course of the disease makes the impact of such variables on treatment selection less plausible, but also narrows the applicability of our results. It is unlikely that patients treated with chemotherapy experienced systemic progression affecting their outcomes, because the majority initiated therapy within 4 months of diagnosis. Definitions of some variables also relied on billing claims rather than on direct clinical data. A similarly constructed performance score indicator had been previously validated by another group against measures of functional impairment in Medicare beneficiaries [11]. The indicator was strongly associated with treatment selection and survival in our study. Claim-based definitions of other factors, such as anemia or malnutrition, have not been formally validated, although diagnoses constructed from administrative data compare favorably with medical record reviews and are widely used in SEER-Medicare studies [7, 39].

In summary, in the absence of randomized data, the current analysis supports radiotherapy as the initial treatment choice for elderly patients with stage IE gastric MALT lymphoma who need oncologic treatment. For those who require systemic therapy, rituximab alone provides favorable survival compared with combination chemoimmunotherapy. Our findings may guide future prospective studies and help clinicians make more informed decisions while caring for their elderly gastric MALT lymphoma patients.

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disclosure

The authors have declared no conflicts of interest.

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Patients' and physicians' roles in detecting recurrent Hodgkin lymphoma following complete remission†

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Background: Optimal post-treatment surveillance for patients with Hodgkin lymphoma in first complete remission (CR) is unknown. Guidelines are based on consensus rather than high-quality evidence. It is unknown if routine screening leads to earlier relapse detection or translates into better outcomes.
Patients and methods: We identified 258 patients with relapse after CR and determined whether the recurrence was detected as a result of patient-detected symptoms (PT group) or through exams or tests ordered by the physician in the absence of symptoms (MD group).
Results: Of 258 recurrences, 182 (71%) were in the PT group. The median time to diagnosis of recurrence was similar in both groups (PT group = 1.65 years; MD group = 1.95 years; $P = 0.69$). Neither the postrelapse progression-free (PFS, $P = 0.26$) nor overall survival (OS, $P = 0.40$) differed significantly between the groups.
Conclusion: Patients are much more likely to detect recurrence than their physicians employing routine follow-up testing. There is no difference in PFS or OS between patients whose recurrence is self-diagnosed versus those whose recurrence is diagnosed by physician through routine screening. We found no benefit for detection of HL recurrence in asymptomatic patients and thus cannot support the routine use of costly, anxiety-provoking or potentially harmful tests in the absence of symptoms.
Key words: follow-up, Hodgkin lymphoma, recurrence

introduction

Today the prognosis of Hodgkin lymphoma (HL) constitutes one of the best in oncology. As of 2007, the 5-year overall survival is 86% [1] despite a recurrence risk of 10%–15% for early-stage disease and up to 30% for advanced disease [2]. These favorable overall outcomes are explained not only by effective first-line treatments, but also availability of successful secondary interventions for recurrent disease employing high-dose therapy and autologous stem-cell transplantation (ASCT). The latter has an overall cure rate of 50%–60% [2]. Advanced disease stage (stage III and IV) at relapse has been identified as a negative prognostic factor for ASCT [3, 4]. However, several questions remain: Does routine testing in the absence of symptoms lead to earlier diagnosis of recurrent disease? Does

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