International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Long-Term Outcomes and Patterns of Relapse of Early-Stage Extranodal Marginal Zone Lymphoma Treated With Radiation Therapy With Curative Intent

Sewit Teckie, MD,* Shunan Qi, MD,* Shona Lovie, MPH,* Scott Navarrett, BS,‡ Meier Hsu, MS,§ Ariela Noy, MD,|| Carol Portlock, MD,|| and Joachim Yahalom, MD*

**Department of Radiation Oncology, §Department of Epidemiology and Biostatistics, and ||Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York; and ‡Weill Cornell Medical College, New York, New York*

Received Dec 19, 2014, and in revised form Jan 23, 2015. Accepted for publication Jan 27, 2015.

Summary

In a cohort of 244 patients treated with curative-intent radiation therapy (RT) for early-stage, extranodal marginal zone lymphoma (MZL), 5-year overall survival was 92%, and 5-year relapse-free survival was 74%. With a median follow-up of 5.2 years, 60 patients (24%) developed MZL relapses, but only 10 patients (4%) relapsed within the RT treatment field. Relapses mostly occurred in distant

Purpose: To report the long-term outcome and patterns of relapse of a large cohort of marginal zone lymphoma (MZL) patients treated with curative-intent radiation therapy (RT) alone.

Patients and Methods: We reviewed the charts of 490 consecutive patients with stage IE or IIE MZL referred between 1992 and 2012 to our institution. Of those, 244 patients (50%) were treated with RT alone. Pathology was confirmed by hematopathologists at our institution. Patient and disease factors were analyzed for association with relapse-free survival (RFS) and overall survival (OS).

Results: Median age of the cohort was 59 years, and median follow-up was 5.2 years. Ann Arbor stage was IE in 92%. Most common disease sites were stomach (50%), orbit (18%), non-thyroid head-and-neck (8%), skin (8%), and breast (5%). Median RT dose was 30 Gy. Five-year OS and RFS were 92% and 74%, respectively. Cumulative incidence of disease-specific death was just 1.1% by 5 years. Sixty patients (24%) developed relapse of disease; 10 were in the RT field. Crude rate of transformation to pathologically confirmed large-cell lymphoma was 1.6%. On multivariable analysis, primary disease site ($P = .007$) was independently associated with RFS, along

Reprint requests to: Joachim Yahalom, MD, Memorial Sloan-Kettering Cancer Center, Department of Radiation Oncology, 1275 York Ave, New York, NY 10065. Tel: (212) 639-5999; E-mail: yahalomj@mskcc.org

Presented in part at the 55th Annual Meeting of the American Society for Radiation Oncology, September 22-25, 2013, Atlanta, GA; and at the 12th International Congress on Malignant Lymphomas, June 18-22, 2013, Lugano, Switzerland.

Supported in part by donations from the Lymphoma Foundation and the Connecticut Sports Foundation.

S.T. was a Dr Mortimer J. Lacher, MD, Lymphoma Fellow at Memorial Sloan Kettering Cancer Center and is presently on staff of the Department of Radiation Medicine, North-Shore-LIJ Health System, Lake Success, NY.

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 130–137, 2015
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2015.01.040

sites unrelated to the RT field. Cumulative incidence of cause-specific death at 5 years was 1.1%.

with age ($P = .04$), presence of B-symptoms ($P = .02$), and International Prognostic Index risk group ($P = .03$). All disease sites except for head-and-neck had worse RFS relative to stomach.

Conclusion: Overall and cause-specific survival are high in early-stage extra-nodal MZL treated with curative RT alone. In this large cohort of 244 patients, most patients did not experience relapse of MZL after curative RT; when relapses did occur, the majority were in distant sites. Stomach cases were less likely to relapse than other anatomic sites. Transformation to large-cell lymphoma was rare.

Introduction

Extra-nodal mucosa-associated lymphoid tissue lymphoma is a subtype of marginal zone B-cell lymphoma (MZL) (1) that can present in a wide variety of organs and sites. Extra-nodal MZL is typically diagnosed at an early, localized stage in 60%-80% of cases (2, 3), making local treatments the preferred initial approach. However, the treatment regimens used in practice are variable, with some patients receiving systemic therapy despite the localized nature of the disease. The existing literature has drawn different conclusions about the optimal treatment regimen for this disease. In addition, there is no consensus on the prognostic value of disease site, stage, risk groups, and other patient characteristics at diagnosis (3-13). Radiation therapy as single-modality treatment is highly effective for local control and organ preservation of early-stage extranodal MZL. However, few studies have consistently assessed the patterns of relapse and disease progression after treatment with radiation therapy (RT) alone, mostly owing to lack of long-term follow-up.

In this single-institution study, we describe the outcome of single-modality RT for curative-intent treatment of early-stage extranodal MZL. We also describe patterns of relapse with long-term follow-up of this disease. Last, we set forth to find prognostic factors for disease outcomes.

Patients and Methods

Patient selection

We retrospectively analyzed the medical records of 490 consecutive patients treated at a single institution who had biopsy-proven stage IE or IIE extranodal MZL diagnosed between January 1992 and September 2012. Of this group, 244 (50%) received RT alone with curative intent as the planned initial treatment strategy. The institutional review board approved a waiver of written informed consent for this study. All patients had pathologic confirmation of MZL diagnosis by our hematopathologists. We collected information on clinical features, stage, diagnostic studies, Eastern Cooperative Oncology Group performance status, International Prognostic Index (IPI) (14) score, treatment received, follow-up examinations, relapses or progression of disease, and salvage therapies for recurrences.

Treatment

Patients were referred by their medical oncologists for single-modality curative-intent treatment with RT after pathologic confirmation of early-stage extranodal MZL in any anatomic site. In cases of gastric MZL, patients were referred for RT if they failed antibiotic therapy for *Helicobacter pylori* eradication, or if they had *H. pylori*—independent disease. Most patients underwent computed tomography (CT) or positron emission tomography (PET/CT) staging before treatment. Radiation therapy approach was either involved-field RT or involved-site RT without intentional prophylactic treatment of regional nodes unless the nodal drainage fell within the involved field, as previously reported (8, 15). On the basis of disease site and anatomic considerations, patients were treated with a range of RT modalities, from single-field electron beam therapy for skin or other superficial MZL to 3-dimensional conformal RT or intensity modulated RT for gastric or certain head-and-neck cases.

Follow-up

Patients were typically seen 1-4 months after completing treatment for initial response and toxicity assessment. Modality used to assess response was contingent on the disease site treated. Diagnostic imaging was done for most sites, with the exception of skin and orbit, where principally physical examination was used. For gastric MZL, esophagogastroduodenoscopy (EGD) with biopsy was customarily performed every 4-6 months for the first 2 to 3 years, after which annual EGD was performed.

Radiographic response was generally determined according to the International Working Group response criteria (13) at time of first follow-up imaging study; in some cases, retrospective clinical or radiographic response was determined. Responses were categorized as one of the following: complete response (CR), complete response uncertain (CRu), partial response, stable disease, and progression of disease.

Progression or relapse was classified as any measurable, biopsy-proven, or visible increase in existing disease after treatment, or the development of an entirely new site of MZL. Disease that transformed to large-cell lymphoma was also

considered a progression event. Imaging studies, EGD, clinical examination, and/or tissue biopsy were used to identify progression events. In-field failure was classified as any MZL progression or recurrence within the irradiated site.

Statistical analysis

Endpoints of our study were overall survival (OS), relapse-free survival (RFS), disease-specific death rate, and in-field failure rate after RT. Overall survival was defined as the time from diagnosis until the date of death or last contact. Relapse-free survival was the time from diagnosis until the date of progression, relapse in previous or new site, death, or last follow-up. The interval until start of RT was typically minimal, with a median waiting time of <3 months. Median OS and RFS were estimated by Kaplan-Meier methods. The effect of disease factors on RFS was assessed using the log−rank test. Disease-specific death and in-field relapse rates were separately estimated with cumulative incidence functions with non-MZL death or death without in-field relapse considered as a competing risk for each respective endpoint. We further examined the number and types of relapses after initial treatment.

Association of factors with OS and RFS was analyzed by Cox regression. Multivariable analysis was performed on factors with a P value of <.2 on univariate analysis; factors with $P<.05$ were considered statistically significant. Cumulative incidences were estimated using the *cmprsk* package in R version 3.1. All other statistical analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC).

Results

Patient characteristics

Median follow-up from diagnosis was 5.2 years (range, 0.2-21.3 years). Median age at diagnosis was 59 years (range, 25-89 years), and 58% of patients were female (Table 1). The majority of patients (92%) had Ann Arbor stage IE disease. Primary site of disease was the stomach in 50%, orbit in 18%, skin in 8%, parotid in 3%, non-parotid head-and-neck in 4%, breast in 5%, and other in 12% (Fig. 1). Eastern Cooperative Oncology Group performance status was 0 or 1 in 93%. International Prognostic Index score was 0 or 1 (low risk) in 95% and 2 (low-intermediate risk) in 4%. Only 4% of patients had B-symptoms at diagnosis.

For staging workup, 55% of patients had PET scans, 87% had CT scans, and 46% had both PET and CT. Esophagogastroduodenoscopy was performed in 55% of patients, and magnetic resonance imaging was done in 23%. Bone marrow biopsy was completed and was negative in 62% of patients; 38% of patients did not undergo bone marrow sampling.

Eleven patients (5%) had one or more documented autoimmune disorders, including Sjogren's disease in 4 patients, Hashimoto's thyroiditis in 4, rheumatoid arthritis in 3, systemic lupus erythematosus in 1, and multiple sclerosis in 1. *H. pylori* infection was diagnosed in 36 patients (15%), of whom 31 had gastric MZL. The majority of *H. pylori*−positive patients (87%) received antibiotic therapy. Patients were referred for RT if found to have persistent gastric MZL after completion of antibiotics and additional observation.

Table 1 Patient characteristics (N = 244)

Characteristic	Result
Age (y), median (range)	59 (25-89)
Gender	
Female	142 (58)
Male	102 (42)
Stage	
IE	225 (92)
IIE	19 (8)
IPI risk group	
Low risk (0-1 points)	232 (95)
Low-intermediate risk (2 points)	10 (4)
Unknown	2 (1)
B-symptoms at diagnosis	
Not present	232 (95)
Present	10 (4)
Not recorded	2 (1)
Bone marrow biopsy	
Performed, negative	152 (62)
Not done or N/A	92 (38)
Autoimmune disease	
No	233 (95)
Yes	11 (5)

Abbreviations: IPI = International Prognostic Index; N/A = not available.

Values are number (percentage) unless otherwise noted. Percentages may not add up to 100 due to rounding.

RT dose and responses

Radiation therapy was initiated at a median of 2.9 months after initial biopsy diagnostic of MZL. Radiation therapy dose delivered was 30 Gy in 65% of patients, <30 Gy in 17%, and >30 Gy in 15%. In 3% of patients, RT was delivered outside of our institution, and dose information is unavailable. Response to RT was CR in 88% of patients, CRu in 5%, partial response in 3%, stable disease in 1%, progression of disease in 1 patient, and unknown response in 2%.

OS and RFS

Thirty-five patients died during the follow-up period. Five-year OS was 92% (95% confidence interval [CI] 88-96%), and 10-year OS was 79% (95% CI 74%-83%) (Fig. 2a). Median OS was not reached. Cumulative incidence of disease-specific death was 1.1% (95% CI 0%-2.7%) by 5 years and 2.0% (95% CI 0%-4.4%) by 10 years (Fig. 2b). Cause of death was MZL related in 4 patients, other

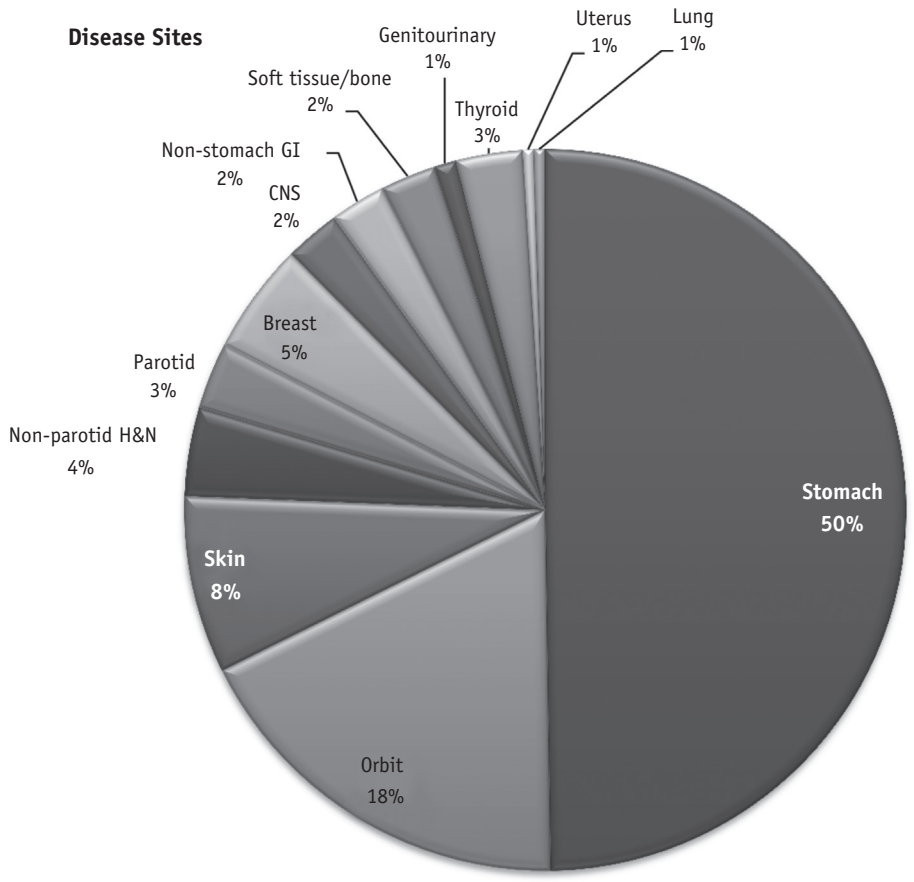

Fig. 1. Initial sites of marginal zone lymphoma (%). CNS = central nervous system; GI = gastrointestinal; H&N = head and neck.

non-MZL causes in 22 patients, and uncertain in 9 patients. The median age at death for patients who died of non-MZL causes was 76 years.

Univariate analysis identified several potential prognostic factors for OS: higher age and higher IPI risk score group were significantly associated with inferior OS (Table 2). Higher stage was marginally associated and also evaluated by multivariable analysis. After multivariable selection, only age (hazard ratio [HR] 1.93; $P<.001$) remained significantly associated with OS.

Seventy-nine patients (32%) experienced relapse or death during the follow-up period. Median RFS was 11.9 years (95% CI 9.5-13.2 years). Five-year RFS was 74% (95% CI 67%-80%), and 10-year RFS was 57% (95% CI 47%-66%) (Fig. 3a). Of the 209 patients alive at last follow-up, 24 are alive with MZL, and 178 have no evidence of disease.

In univariate analysis, age, disease site, and IPI risk group were significantly associated with RFS (Table 3). Presence of B-symptoms was marginally associated and also included in multivariable analysis. Stomach site seems to have superior RFS when compared with all other disease sites (Fig. 3b) and the log−rank test comparing stomach versus all other sites was significant ($P<.001$). By multivariable analysis, age, site of disease, IPI risk group, and B-symptoms remained significantly associated with RFS ($P=.04$, $P=.007$, $P=.03$, and $P=.02$, respectively). Specifically, when compared with stomach site, sites including orbit, skin, breast, and "other" disease sites were all associated with shorter RFS (all HRs >2.4, all individual $P<.05$). Head-and-neck site did not differ significantly from stomach (HR 2.36, $P=.12$).

Patterns of relapse and in-field failure

Of the 60 patients who experienced relapse, 10 were in the radiation field, 23 were in a distant site, 13 were in a regional site outside of the RT field, 9 were in a second skin site (for patients with initial site of MZL in the skin), and 5 were in a paired contralateral organ (3 in the contralateral orbit and 2 in the contralateral breast). Forty-seven percent of patients with skin MZL eventually developed relapse in another skin site, outside of the treatment field. Salvage therapies for relapse included RT in 18 patients (including reirradiation of the stomach in 1 patient), chemotherapy in 12, rituximab monotherapy in 5, surgical resection in 3, and topical steroids in 2. Observation was the selected strategy in 18 patients. On further follow-up of the 60 patients who developed relapse, 19 eventually developed a second relapse, and 8 had a third recorded relapse.

Ten patients developed in-field failure after RT, 7 in the stomach and 1 each in the breast, paraspinal soft tissue, and

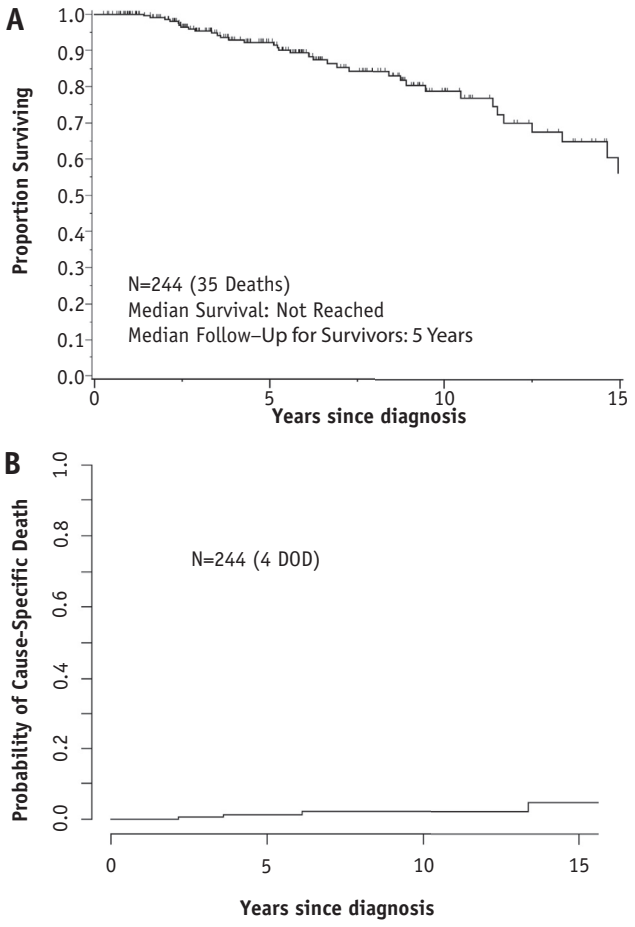

Fig. 2. (a) Overall survival. (b) Cumulative incidence of disease-specific deaths. DOD = died of disease.

orbit. Cumulative incidence of in-field failure by 5 years was 2.8% (95% CI 0.6%-4.9%) and by 10 years was 4.6% (95% CI 0.4%-8.9%) (Fig. 3c). One patient with in-field failure in the stomach had transformation to large-cell lymphoma of the stomach. Patients treated with a lower dose of RT were not overrepresented in this group: dose was <30 Gy in 3 patients, 30 Gy in 6, and >30 Gy in 1.

Only 4 patients experienced transformation of MZL to pathologically confirmed large-cell lymphoma by the end of this study. Of these, 2 died of disease. Transformation occurred at the initial disease site in 1 patient and in a distant site in 3 patients. Cases of transformation were managed with systemic chemotherapy with or without rituximab.

Toxicities and second malignancies

Using the Common Terminology Criteria for Adverse Events version 4 reporting system, acute RT-related toxicities were recorded in 126 (52%) patients. Grade 3 and grade 4 acute toxicities occurred in 6 patients and 1 patient, respectively. Late grade 2 toxicities were recorded in 12 patients, whereas grade 3 late toxicities occurred in 3 patients (duodenal stricture, gastroparesis, and chorioretinopathy). No patients had grade 4 or higher toxicity.

Of the 244 patients treated with RT, 3 developed second malignancies in the radiation field at time points ranging from 4.6 to 11.3 years after RT. Two patients had ductal carcinoma in situ of the breast treated with surgical excision and achieved a complete response. One patient developed adenocarcinoma of the stomach and lung that were not treated and experienced progression of disease.

Table 2 Cox regression analysis for association of factors with overall survival

		Univariate analysis			Multivariable analysis	
Characteristic	Strata	HR (95% CI)	*P*	Overall *P*	HR (95% CI)	*P*
Age (per 10 y)		1.93 (1.44-2.59)	<.001*		1.93 (1.44-2.59)	<.001
Gender	Male	1				
	Female	0.73 (0.37-1.42)	.35			
Stage	IE	1				
	IIE	2.28 (0.80-6.5)	.12*			
Site of disease	Stomach	1		.77		
	Orbit	1.53 (0.69-3.38)	.30			
	Skin	Not estimable†				
	Head and neck	1.01 (0.23-4.33)	.99			
	Breast	1.89 (0.55-6.42)	.31			
	Other	0.64 (0.15-2.78)	.55			
IPI risk group	Low (0-1 points)	1				
	Low-intermediate risk (2 points)	6.4 (1.89-21.7)	.003*			
B-symptoms	Not present at diagnosis	1				
	Present	2.36 (0.31-17.9)	.41			
Bone marrow biopsy	Negative	1				
	Information not available	1.06 (0.553-2.1)	.88			

Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = International Prognostic Index; RT = radiation therapy.
* Included in initial multivariable model.
† No death events.

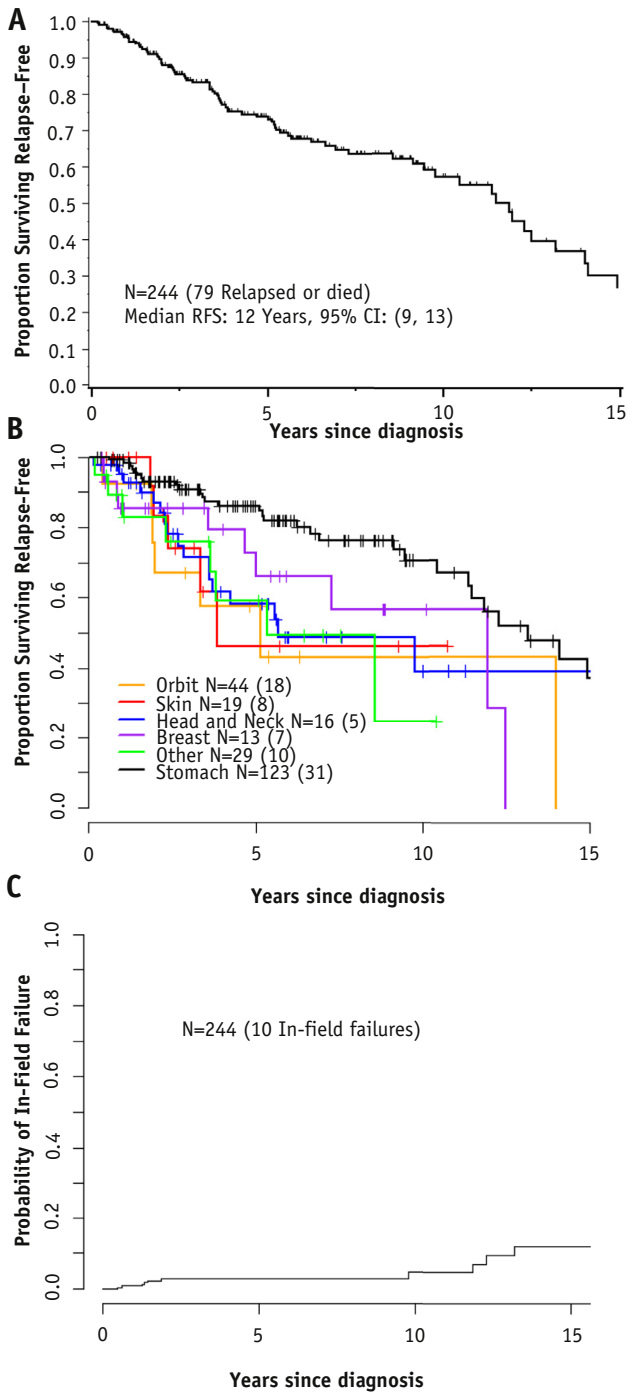

Fig. 3. (a) Relapse-free survival. (b) Relapse-free survival (RFS) by primary disease site. Numbers in parentheses represent relapse or death events for each disease site. (c) Cumulative incidence of in-field failure. CI = confidence interval.

Discussion

We present, to our knowledge, the largest study of early-stage extra-nodal MZL treated with RT as the curative modality. With a median follow-up of more than 5 years, our study presents a comprehensive picture of the long-term natural history of extra-nodal MZL. Extra-nodal MZL is an exquisitely radiosensitive disease with durable long-term responses to local therapy. In our cohort, outcomes are uniformly excellent: complete response rates exceeded 90% after local RT, and disease-specific death is exceedingly low, occurring in only 4 patients. Although progression or relapse occurred in 24% of patients, relapse was almost always a nontransformed MZL emerging in a new extra-nodal site. Distant relapses were most common, but we also observed relapsed disease in paired contralateral organs, the skin, and the initial sites. Disease-specific survival remains high, likely as a result of effective salvage therapies and low rates of progression to more advanced or transformed disease.

In this cohort of early-stage extra-nodal MZL, we identified several factors associated with relapse-free survival, including disease site, age, presence of B-symptoms, and IPI score. When compared with the stomach, all sites of disease except for head-and-neck were associated with inferior RFS. Stomach site has been reported to have improved relapse-free rates (4, 9). Although almost 50% of patients treated for a skin MZL developed relapse, no patients with cutaneous MZL died during the follow-up period, likely as a result of their younger age at presentation and highly effective therapies (both RT and topical approaches) for relapsed disease. International Prognostic Index score is a well-validated prognostic marker associated with disease-specific and overall survival in aggressive as well as indolent lymphomas (14, 16). In the 10 patients with IPI score >1, we found an association between higher IPI and worse RFS. Although this finding is hypothesis-generating, we interpret it with caution given the small number of patients with IPI score >1. Although B-symptoms are not part of the IPI prognostic criteria, the presence of B-symptoms is a well-known prognostic marker for relapse-free survival in both Hodgkin and non-Hodgkin lymphomas.

Several groups have reported excellent outcomes of early-stage extra-nodal MZL when treated with RT. One study identified 192 patients with stage IE-IIE MZL, 144 of whom received RT alone and another 23 of whom received chemotherapy and RT (4, 9). Median follow-up was 7.4 years, with 99% CR/CRu. Ten-year RFS was 68%, and 10-year cause-specific survival was 98%. Thyroid and stomach sites had >90% 10-year recurrence-free rates. A study of 89 patients with stage IE orbital MZL treated with RT reported 97% local control and 64% RFS (17). A report of 86 patients with stage IE orbital MZL mostly treated with single-modality RT showed 98.7% in-field RFS at 10 years; 6 patients had a contralateral orbital relapse, all salvaged with RT (13). A small, prospective, multicenter phase 2 trial of RT in stage IEA MZL also found that RT was safe and efficacious, with a 3-year OS of 100% and a local control of 97% (5). Other groups have reported outcomes of patients with various MZL stages and subtypes (6, 7, 10-12) without a focus on early-stage extra-nodal MZL treated with RT as curative intent. Our study benefits from having a large,

Table 3 Cox regression analysis for association of factors with relapse-free survival

Characteristic	Strata	Univariate analysis			Multivariable analysis		
		HR (95% CI)	*P*	Overall *P*	HR (95% CI)	*P*	Overall *P*
Age (per 10 y)		1.17 (0.98-1.40)	.08*		1.21 (1.01-1.46)	.04	
Gender	Male	1					
	Female	0.84 (0.53-1.31)	.43				
Stage	IE	1					
	IIE	1.53 (0.73-3.18)	.26				
Site of disease	Stomach	1		.005*			.007
	Orbit	2.40 (1.32-4.37)	.002		2.48 (1.32-4.63)	.005	
	Skin	3.13 (1.41-6.94)	.005		3.22 (1.38-7.55)	.007	
	Head and neck	2.62 (1.00-6.85)	.05		2.36 (0.81-6.88)	.12	
	Breast	3.13 (1.37-7.16)	.007		3.08 (1.33-7.14)	.009	
	Other	2.19 (1.06-4.50)	.03		2.42 (1.16-5.03)	.02	
IPI risk group	Low (0-1 points)	1					
	Low-intermediate risk (2 points)	3.47 (1.39-8.68)	.008*		2.82 (1.08-7.38)	.03	
B-symptoms	Not present at diagnosis	1					
	Present	2.56 (0.79-8.27)	.12*		4.05 (1.21-13.56)	.02	
Bone marrow biopsy	Negative	1					
	Information not available	1.27 (0.81-7.99)	.30				

Abbreviations as in Table 2.
* Included in initial multivariable model.

homogenous cohort of only stage IE and IIE MZL, all treated with RT alone as the definitive modality.

Our study confirms reports that the extra-nodal MZL patient population can have late relapse or progression at time points 5 years or longer after initial diagnosis (18). Rate of transformation to diffuse large B-cell lymphoma is low, <2% in our study, and similar to other studies (4, 6, 7, 10, 19). Notably, no pattern was observed between RT dose received and eventual in-field failure, a finding that supports the results of recent randomized trials examining prescribed RT dose in non-Hodgkin lymphomas (20, 21). The main limitation to our study is its retrospective nature; for example, certain information was not available for all patients, such as the bone marrow sampling status. However, despite the lack of data on bone marrow for more than one-third of patients, there was no relationship between bone marrow sampling at diagnosis and either OS or RFS. The strengths of our study include the large number of patients all treated with RT as definitive therapy, the confirmed diagnoses by dedicated hematopathologists, and the length of follow-up. In addition, the study represents a relatively uniform diagnostic and treatment approach, because all patients were treated and followed up regularly by a small group of physicians at our large tertiary referral cancer center. For example, most patients underwent comprehensive staging with PET and CT scanning for workup and follow-up. Furthermore, because of the large sample, we can draw conclusions about the efficacy and long-term results after RT. Lastly, the length of follow-up provides us with information about relapses, including site of relapse, salvage therapy, transformed disease, and second malignancies. In summary, our retrospective study presents a reassuring picture of the long-term outcomes for clinicians treating patients with early-stage extranodal MZL with primary, curative-intent RT alone.

References

1. Swerdlow SH, Campo E, Harris NL, et al., editors. WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues. 4th ed. Lyon: International Agency for Research on Cancer; 2008.
2. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: Clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol* 1998;16:2780-2795.
3. Thieblemont C, Berger F, Dumontet C, et al. Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. *Blood* 2000;95:802-806.
4. Goda JS, Gospodarowicz M, Pintilie M, et al. Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy. *Cancer* 2010;116:3815-3824.
5. Isobe K, Kagami Y, Higuchi K, et al. A multicenter phase II study of local radiation therapy for stage IEA mucosa-associated lymphoid tissue lymphomas: A preliminary report from the Japan Radiation Oncology Group (JAROG). *Int J Radiat Oncol Biol Phys* 2007;69:1181-1186.
6. Kalpadakis C, Pangalis GA, Vassilakopoulos TP, et al. Non-gastric extra-nodal marginal zone lymphomas—a single centre experience on 76 patients. *Leuk Lymphoma* 2008;49:2308-2315.
7. Mazloom A, Medeiros LJ, McLaughlin PW, et al. Marginal zone lymphomas: Factors that affect the final outcome. *Cancer* 2010;116:4291-4298.
8. Schechter NR, Portlock CS, Yahalom J. Treatment of mucosa-associated lymphoid tissue lymphoma of the stomach with radiation alone. *J Clin Oncol* 1998;16:1916-1921.
9. Tsang RW, Gospodarowicz MK, Pintilie M, et al. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *J Clin Oncol* 2003;21:4157-4164.
10. Zucca E, Conconi A, Pedrinis E, et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Blood* 2003;101:2489-2495.

11. Tsai HK, Li S, Ng AK, et al. Role of radiation therapy in the treatment of stage I/II mucosa-associated lymphoid tissue lymphoma. *Ann Oncol* 2007;18:672-678.
12. Wirth A, Gospodarowicz M, Aleman BMP, et al. Long-term outcome for gastric marginal zone lymphoma treated with radiotherapy: A retrospective, multi-centre, International Extranodal Lymphoma Study Group study. *Ann Oncol* 2013;24:1344-1351.
13. Harada K, Murakami N, Kitaguchi M, et al. Localized ocular adnexal mucosa-associated lymphoid tissue lymphoma treated with radiation therapy: A long-term outcome in 86 patients with 104 treated eyes. *Int J Radiat Oncol Biol Phys* 2014;88:650-654.
14. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993;329:987-994.
15. Schechter NR, Yahalom J. Low-grade MALT lymphoma of the stomach: a review of treatment options. *Int J Radiat Oncol Biol Phys* 2000;46:1093-1103.
16. López-Guillermo A, Montserrat E, Bosch F, et al. Applicability of the International Index for aggressive lymphomas to patients with low-grade lymphoma. *J Clin Oncol* 1994;12:1343-1348.
17. Goda JS, Le LW, Lapperriere NJ, et al. Localized orbital mucosa-associated lymphoma tissue lymphoma managed with primary radiation therapy: Efficacy and toxicity. *Int J Radiat Oncol Biol Phys* 2011;81:e659-e666.
18. Raderer M, Streubel B, Woehrer S, et al. High relapse rate in patients with MALT lymphoma warrants lifelong follow-up. *Clin Cancer Res* 2005;11:3349-3352.
19. Schechter NR, Yahalom J. Low-grade MALT lymphoma of the stomach: A review of treatment options. *Int J Radiat Oncol Biol Phys* 2000;46:1093-1103.
20. Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomized phase III trial. *Radiother Oncol* 2011;100:86-92.
21. Hoskin P, Kirkwood A, Popova B, et al. 4Gy versus 24Gy radiotherapy for patients with indolent lymphoma (FORT): A randomized phase 3 non-inferiority trial. *Lancet Oncol* 2014;15:457-463.