



Original Article

Long-term Clinical Efficacy of Radiotherapy for Patients with Stage I-II Gastric Extranodal Marginal Zone B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue: A Retrospective Multi-institutional Study

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Purpose This study aimed to evaluate long-term treatment outcomes in patients with localized gastric mucosa-associated lymphoid tissue (MALT) lymphoma treated with radiotherapy (RT).

Materials and Methods A total of 229 patients who received RT in 10 tertiary hospitals between 2010 and 2019 were included in this multicenter analysis. Response after RT was based on esophagogastroduodenoscopy after RT. Locoregional relapse-free survival (LRFS) and disease-free survival (DFS), and overall survival (OS) were evaluated.

Results After a median follow-up time of 93.2 months, 5-year LRFS, DFS, and OS rates were 92.8%, 90.4%, and 96.1%, respectively. LRFS, DFS, and OS rates at 10 years were 90.3%, 87.7%, and 92.8%, respectively. Of 229 patients, 228 patients (99.6%) achieved complete remission after RT. Five-year LRFS was significantly lower in patients with stage IIE than in those with stage IE (77.4% vs. 94.2%, $p=0.047$). Patients with age ≥ 60 had significantly lower LRFS than patients with age < 60 (89.3% vs. 95.1%, $p=0.003$). In the multivariate analysis, old age (≥ 60 years) was a poor prognostic factor for LRFS (hazard ratio, 3.72; confidence interval, 1.38 to 10.03; $p=0.009$). Grade 2 or higher gastritis was reported in 69 patients (30.1%). Secondary malignancies including gastric adenocarcinoma, malignant lymphoma, lung cancer, breast cancer, and prostate cancer were observed in 11 patients (4.8%) after RT.

Conclusion Patients treated with RT for localized gastric MALT lymphoma showed favorable 10-year outcomes. Radiation therapy is an effective treatment without an increased risk of secondary cancer. The toxicity for RT to the stomach is not high.

Key words Radiotherapy, Efficacy, Mucosa, Stomach, Lymphoma

Introduction

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) is composed of B-cells including marginal zone cells, small lymphocytes, monocyte cells, immunoblast, and centroblast-like cells [1]. MALT lymphoma accounts for 7%-8% of all B-cell lymphomas and about half of gastric lymphomas [2,3]. The stomach is the most common site of MALT lymphoma [3]. The majority of patients with gastric MALT lymphoma have *Helicobacter pylori* infection, with antibiotic eradication therapy being usually performed as the first-line treatment [4]. In patients with localized gastric MALT lymphoma who do not have *H. pylori* infection

or do not respond to eradication therapy, radiotherapy (RT) is the standard treatment for them [5]. Gastric MALT lymphoma is an indolent tumor that is responsive to RT. Patients treated with RT generally have a favorable prognosis [6]. There are concerns regarding the development of secondary cancers in patients with gastric MALT lymphoma who typically have a favorable long-term outcome after RT [7,8]. This multi-institutional study aimed to investigate long-term treatment outcomes and prognostic factors for gastric MALT lymphoma patients treated with RT. Treatment-related toxicities and secondary cancer incidence were also evaluated.

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Materials and Methods

Ten tertiary university hospitals participated in this retrospective study. Patients who received RT for localized gastric MALT lymphoma from 2010 to 2019 were included in this analysis. Inclusion criteria were: (1) those with pathologically confirmed gastric MALT lymphoma, (2) those with Ann Arbor stage I or II gastric MALT lymphoma, (3) those aged more than 20 years, (4) those with Eastern Cooperative Oncology Group (ECOG) performance status from 0 to 1, and (5) those with endoscopic evaluation performed before and after RT. Exclusion criteria were: (1) those with previously diagnosed other malignancies except papillary thyroid cancer or breast ductal carcinoma *in situ*; and (2) those with previous history of receiving chemotherapy for gastric MALT lymphoma. Secondary cancers were defined as malignant tumors that developed after RT. Diffuse large B-cell lymphoma (DLBCL) was excluded from this definition because it is difficult to distinguish between treatment-related secondary malignancy and high-grade transformation of MALT lymphoma [9].

The primary objective of this study was to determine the response rate of RT, locoregional recurrence rate, and survival rate after RT in patients with gastrointestinal mucosal lymphoma. Secondary objectives included identifying prognostic factors that might affect recurrence and survival and assessing treatment-related toxicity and incidence of secondary malignancies after RT. Locoregional relapse-free survival (LRFS) was defined as the interval from the end date of RT to either the date of locoregional recurrence in the radiation field or patient's death. Disease-free survival (DFS) was defined as the period from the end date of RT to the occurrence of any type of recurrence, distant metastasis or patient's death. Overall survival (OS) was defined as the end date of RT to patient's death or the last date of follow-up when data were censored. Toxicity profiling according to intervention was analyzed with reference to Common Terminology Criteria for Adverse Events ver. 5.0 [10].

To determine prognostic factors for treatment outcomes, statistical analyses were conducted on patient and treatment factors. To analyze differences between groups for non-continuous variables, the chi-square test or Fisher's exact test or linear-by-linear association was applied depending on distribution. Continuous variables between two independent groups were examined using Student's *t* test. Survival analysis was performed using the Kaplan-Meier method. Differences were evaluated using the log-rank test. In the multivariate analysis, independent factors related to recurrence and survival were analyzed using the Cox regression model with hazard ratio (HR) and 95% confidence interval (CI). Statistical significance was considered when *p*-value was less than

Table 1. Patient characteristics

Characteristic	No. of patients (%) (n=229)
Age (yr), median (range)	56 (20-88)
Sex	
Male	109 (47.6)
Female	120 (52.4)
ECOG performance status	
0	146 (63.8)
1	83 (36.2)
<i>Helicobacter pylori</i> infection	
No	109 (47.6)
Yes	116 (50.7)
Unknown	4 (1.7)
B symptom	
No	217 (94.8)
Fever	2 (0.8)
Drenching night sweat	3 (1.2)
Weight loss	10 (4.3)
Ann Arbor stage	
IE	209 (91.3)
IIIE	20 (8.7)
Location in the stomach	
Upper	29 (12.7)
Middle	126 (55.0)
Lower	46 (20.1)
Diffuse	28 (12.2)
Radiation technique	
3D-CRT	203 (88.6)
IMRT	26 (11.4)

ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiation therapy; 3D-CRT, three-dimensional conformal radiation therapy.

0.05. All statistical analyses were performed using SPSS ver. 19.0 (IBM Corp.).

Results

A total of 229 patients were diagnosed as gastric MALT lymphoma. They received RT for it. One hundred sixteen of 229 patients (50.7%) were infected with *H. pylori*. Stage IE (91.3%) was the most frequent clinical stage. There were 12 patients (5.2%) who experienced B-symptoms. One hundred and twenty-six patients (55.0%) had tumors located in the gastric body. Radiation therapy was administered to the entire stomach and any involved lymph nodes with a relevant margin of 1 to 2 cm. Three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) were performed for 203 (88.6%) and 26 (11.4%) patients, respectively. The median radiation dose

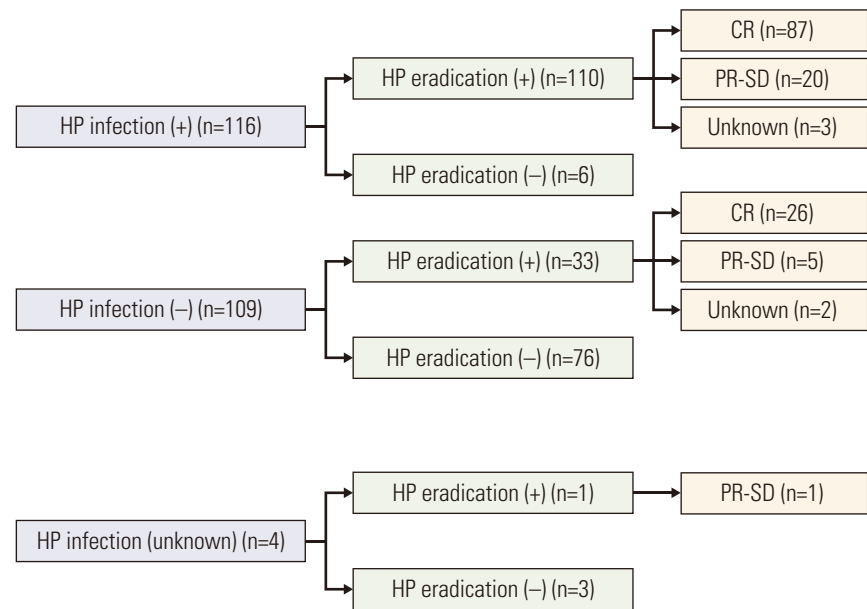


Fig. 1. Clinical response of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue according to the status of *Helicobacter pylori* (HP) infection and eradication treatment. CR, complete response; PR-SD, partial response or stable disease.

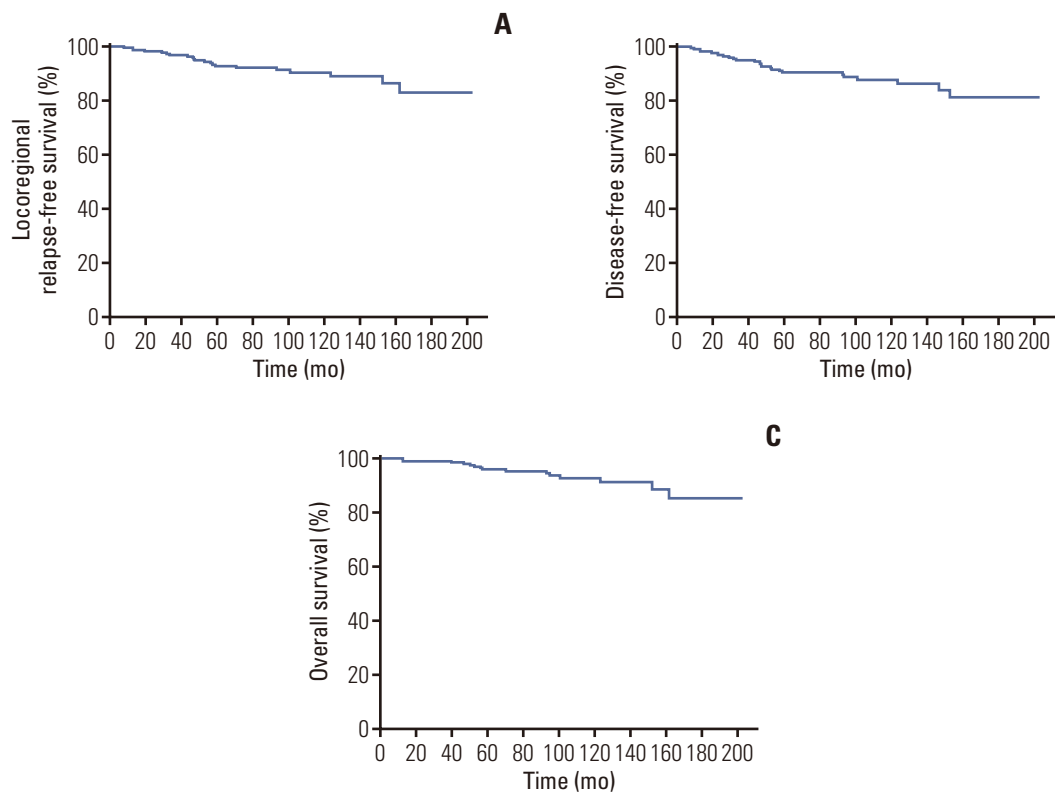


Fig. 2. Locoregional relapse-free survival (A), disease-free survival (B), and overall survival (C) of entire patients.

Table 2. Univariate analysis for recurrence and survival

Variable	No. of patients	5-Year LRFS (%)	p-value	5-Year DFS (%)	p-value	5-Year OS (%)	p-value
Age (yr)							
< 60	134	95.1	0.003 ^{a)}	91.9	0.025 ^{a)}	98.3	< 0.001 ^{a)}
≥ 60	95	89.3		88.2		92.7	
Sex							
Male	109	91.0	0.376	88.0	0.143	95.0	0.358
Female	120	94.4		92.7		97.0	
Location							
Middle	126	91.0	0.425	88.5	0.213	95.5	0.591
Others	103	94.8		92.8		96.7	
<i>Helicobacter pylori</i> infection							
No or unknown	113	95.3	0.298	93.5	0.233	96.2	0.917
Yes	116	90.0		87.1		96.0	
<i>Helicobacter pylori</i> eradication							
No	85	95.1	0.731	91.5	0.779	95.1	0.370
Yes	144	91.2		89.7		96.8	
Ann Arbor stage							
IE	209	94.2	0.047 ^{a)}	91.6	0.166	96.3	0.461
IIE	20	77.4		77.4		93.8	
Radiation technique							
3D-CRT	203	93.3	0.556	90.7	0.929	96.6	0.603
IMRT	26	88.5		88.5		92.3	
Radiation dose (Gy)							
≥ 24 and < 30	21	100	0.309	94.7	0.771	100	0.554
30 or 30.6	159	94.4		91.1		96.5	
> 30.6	49	85.9		85.9		92.9	

DFS, disease-free survival; IMRT, intensity-modulated radiation therapy; LRFS, locoregional relapse-free survival; OS, overall survival; 3D-CRT, three-dimensional conformal radiation therapy. ^{a)}Statistically significant value.

was 30.6 Gy (range, 24.0 to 50.4 Gy) (Table 1). One hundred fifty-nine (69.4%) received either 30.0 Gy or 30.6 Gy. Out of the 21 patients who received a dose less than 30 Gy, 11 were treated with 24 to 25 Gy, and 10 were treated with 27 Gy. One patient, whose biopsy result was confirmed as MALT lymphoma but who needed to rule out high-grade transformation, received radiation dose of 50.4 Gy.

A total of 144 patients underwent eradication treatment for *H. pylori* before RT (Fig. 1). After excluding five patients whose response to eradication treatment could not be measured by endoscopy, remission of MALT lymphoma to eradication treatment was found for 113 patients (78.5%). Among the patients with *H. pylori* infection, there were six patients who received RT without eradication treatment. They had previously undergone *H. pylori* eradication therapy, who initially had achieved complete response (CR), but recurrent gastric MALT lymphoma afterward. Among the 109 patients who were not infected with *H. pylori*, 33 patients received eradication therapy, and 26 patients (78.7%) achieved CR. In

228 of 229 patients (99.5%), CR of gastric MALT lymphoma was observed after RT. One patient who did not respond to RT received chemotherapy and finally achieved CR. During the follow-up period, no evidence of recurrence was observed for this patient.

After a median follow-up period of 93.2 months, 5-year LRFS, DFS, and OS rates were 92.8%, 90.4%, and 96.1%, respectively (Fig. 2). At 10 years, LRFS, DFS, and OS rates were 90.3%, 87.7%, and 92.8%, respectively. By the last follow-up, 15 patients had expired, including three deaths being disease-specific mortality. One patient expired during chemotherapy due to locoregional relapse. Two patients experienced distant metastases (one in the lung and the other in pelvic and abdominal lymph nodes). In the univariate analysis, both age and disease stage were identified as prognostic factors for LRFS (Table 2). Patients with age ≥ 60 years had significantly lower LRFS (89.3% vs. 95.1%, $p=0.003$), DFS (88.2% vs. 91.9%, $p=0.025$), and OS (92.7% vs. 98.3%, $p < 0.001$) rates at 5 years than patients with age < 60 years (Fig.

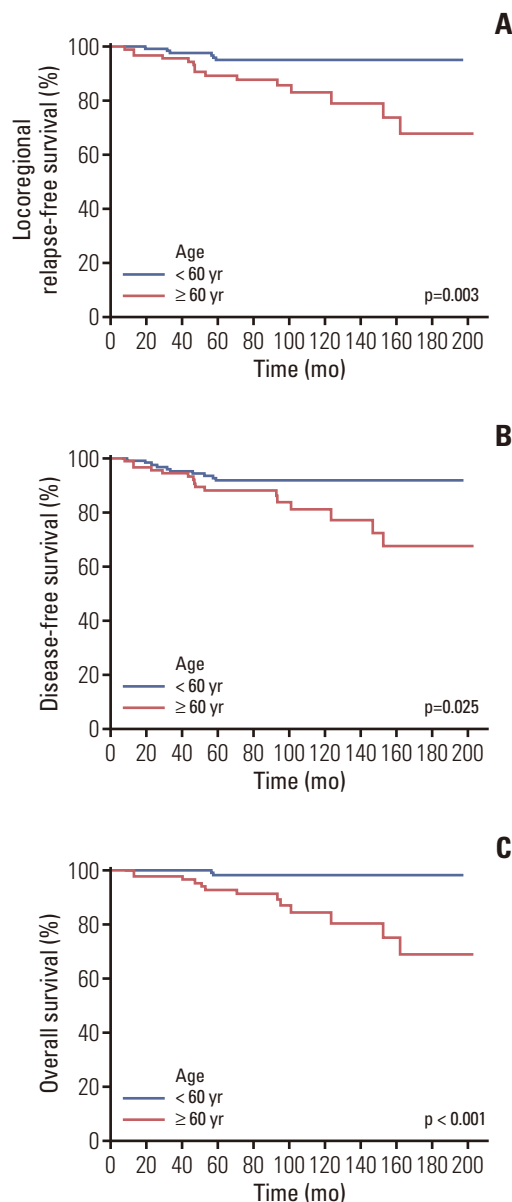


Fig. 3. Locoregional relapse-free survival (A), disease-free survival (B), and overall survival (C) according to the patient's age.

3). Higher radiation dose (> 30.6 Gy) was not a significant factor for LRFS ($p=0.309$), DFS ($p=0.771$), or OS ($p=0.554$) as compared to lower radiation dose (≤ 30.6 Gy). In the multivariate analysis, age was the only significant factor for LRFS (HR, 3.72; 95% CI, 1.38 to 10.03; $p=0.009$) and OS (HR, 9.78; 95% CI, 2.13 to 44.87; $p=0.003$) (Table 3).

A total of 18 patients (7.9%) experienced treatment failure, including eight patients (3.5%) who developed locoregional recurrence, nine patients (3.9%) who had distant metastasis, and one patient (0.4%) who had both locoregional recurrence

and distant metastasis. Among the 209 patients with stage IE, 14 (6.7%) experienced a relapse, whereas among the 20 patients with stage IIE, four (20.0%) experienced a relapse, showing a significant difference between the two groups ($p=0.035$) (Table 4).

There were 132 patients (57.6%) who reported gastrointestinal complications. The most frequent complication was gastritis in 91 patients (39.7%). Observed grade 3 gastrointestinal complications included gastritis in 10 patients (4.4%) and dyspepsia in four patients (1.7%). Grade 4 or 5 complications were not reported (S1 Table). In the 13 patients with grade 3 gastrointestinal complications, median RT dose was 30.6 Gy (range, 27 to 36 Gy). The mean radiation dose for patients with grade 3 complications was 30.6 Gy, and the mean radiation dose for patients without grade 3 toxicity was 31.6 Gy, with no statistically significant difference between the two groups ($p=0.112$). Among patients with *H. pylori* infection, 72 of 110 patients (65.5%) who underwent eradication therapy complained of gastrointestinal complications after treatment, whereas two of six patients (33.3%) who did not undergo eradication therapy reported toxicity after treatment ($p=0.049$).

There were 11 patients (4.8%) who experienced secondary malignancies after RT (Table 5). The most common type of secondary malignancy was adenocarcinoma in stomach, occurring in three patients who had achieved CR after RT. Among the patients who experienced gastric adenocarcinoma, one patient underwent distal gastrectomy due to advanced gastric cancer, while the others received endoscopic submucosal dissection for early gastric cancer. In other patients, secondary cancer occurred at the site where RT was not administered. The median duration from the end of RT to the occurrence of secondary malignancies were 46 months. Secondary cancer occurred in nine of 211 patients (4.3%) who did not experience treatment failure, while two of the 18 patients (11.1%) who had treatment failure developed secondary cancers. Four patients experienced DLBCL with median interval of 27.5 months after RT.

Discussion

In patients with gastric MALT lymphoma who have *H. pylori* infection, antibiotic therapy is suitable as an initial treatment [11]. However, for patients who are either negative for *H. pylori* infection or refractory to *H. pylori* eradication, RT is considered as an optimal treatment [6]. Previous studies have reported CR rates over 95% after RT [12,13]. Studies on long-term outcomes after RT have demonstrated that excellent disease control can be sustained for over 10 years [14,15]. In the present study, 10-year LRFS, DFS, and OS rates

Table 3. Multivariate analysis for recurrence and survival

Variable	LRFS		DFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)						
< 60	Reference	0.009 ^{a)}	Reference	0.068	Reference	0.003 ^{a)}
≥ 60	3.72 (1.38-10.03)		2.16 (0.94-4.97)		9.78 (2.13-44.87)	
Sex						
Male	Reference	0.375	Reference	0.207	Reference	0.349
Female	0.66 (0.26-1.64)		0.58 (0.25-1.34)		0.59 (0.20-1.76)	
Location						
Middle	Reference	0.508	Reference	0.267	Reference	0.630
Others	0.73 (0.29-1.82)		0.62 (0.27-1.42)		0.76 (0.26-2.25)	
<i>Helicobacter pylori</i> infection						
No or unknown	Reference	0.566	Reference	0.323	Reference	0.624
Yes	1.50 (0.37-6.07)		1.84 (0.54-6.23)		1.58 (0.25-9.83)	
<i>Helicobacter pylori</i> eradication						
No	Reference	0.896	Reference	0.709	Reference	0.580
Yes	1.10 (0.26-4.57)		0.79 (0.23-2.71)		0.60 (0.10-3.60)	
Ann Arbor stage						
IE	Reference	0.280	Reference	0.405	Reference	0.883
IIE	1.95 (0.57-6.61)		1.63 (0.51-5.17)		0.88 (0.17-4.58)	
Radiation technique						
3D-CRT	Reference	0.526	Reference	0.891	Reference	0.473
IMRT	1.53 (0.41-5.72)		1.09 (0.30-3.90)		1.81 (0.35-9.26)	
Radiation dose (Gy)						
≥ 24 and < 30	Reference	0.537	Reference	0.764	Reference	0.561
30 or 30.6	0.81 (0.17-3.67)		1.04 (0.23-4.58)		1.23 (0.15-10.01)	
> 30.6	1.45 (0.27-7.66)		1.47 (0.28-7.61)		2.32 (0.24-21.93)	

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; LRFS, locoregional relapse-free survival; OS, overall survival; 3D-CRT, three-dimensional conformal radiation therapy. ^aStatistically significant value.

were 90.3%, 87.7%, and 92.8%, respectively, underscoring the clinical efficacy of RT in patients with localized gastric MALT lymphoma.

Age might be a factor to predict treatment response and treatment failure for patients with gastric MALT lymphoma [16,17]. We found that age was the only independent factor for LRFS and OS. However, there was no statistically significant difference in freedom from treatment failure, with a 5-year rate of 92.8% for those less than 60 years of age and 91.5% for those more than 60 years of age ($p=0.406$). It could be considered that long-term survival after treatment might be influenced by an increased risk of mortality due to old age.

In our study, the recurrence rate after RT was 7.9%, which was comparable to recurrence rates of 0-10.7% reported in other studies [13,15,18,19]. Stage could be an independent prognostic factor for patients with gastric MALT lymphoma [20,21]. A long-term follow-up study on patients treated with RT for localized gastric MALT lymphoma showed that the

10-year freedom from treatment failure rate was 89.6% for stage IE and 79.5% for stage IIE [15]. In our study, the 10-year freedom from treatment failure rate was 92.7% for stage IE and 77.4% for stage IIE, similar to those reported in the above study ($p=0.031$).

There is a concern regarding the development of secondary malignancies since patients with gastric MALT lymphoma are expected to have a long-term survival. Secondary cancers were observed in 35 of 420 patients (8.3%) reported in a Japanese multicenter cohort study [22]. The incidence of secondary cancer might be higher, as the relative risk was 1.3 in patients with non-Hodgkin's lymphoma compared with the general population [23]. However, the incidence of secondary cancer in patients with gastric MALT lymphoma, a subgroup of indolent B-cell lymphoma, remains controversial [7,24]. A population-based study has found an increased risk of secondary malignancies in patients with gastric MALT lymphoma during follow-up [7]. Both RT and chemotherapy for lymphoma might be associated with the development of

Table 4. Characteristic of patients who had treatment failure

Patient No.	Sex	Age (yr)	Stage	<i>H. pylori</i> infection	Radiation to <i>H. pylori</i> eradication	Dose of RT (Gy)	Response to RT	Pattern of failure	Distant site of relapse	Salvage treatment	DFI (mo)	Last status
1	M	63	IE	Negative	-	30.0	CR	LR+DM	Right external iliac LN	Chemotherapy	7.7	Dead
2	F	78	IE	Positive	-	30.0	CR	DM	Both conjunctiva	RT	23.0	Dead
3	F	61	IE	Unknown	-	41.4	CR	DM	Neck LN	Chemotherapy	146.5	Dead
4	M	60	IIE	Negative	-	45.0	CR	DM	Neck LN, paraaortic LN	None	52.7	Dead
5	F	52	IE	Negative	-	30.6	CR	DM	Lung	None	52.5	Dead
6	M	67	IIE	Positive	CR	39.6	CR	LR	-	Local excision	43.5	Dead
7	M	78	IE	Positive	CR	30.0	CR	LR	-	Chemotherapy	47.0	Dead
8	M	52	IE	Positive	CR	30.6	CR	DM	Lung	Chemotherapy	46.0	Alive
9	M	70	IE	Positive	PR-SD	30.6	CR	DM	Neck LN	None	92.8	Alive
10	F	56	IE	Positive	CR	30.6	CR	DM	Bladder	Local excision	9.4	Alive
11	M	36	IE	Negative	-	30.0	CR	DM	Sigmoid colon	RT	22.9	Alive
12	M	47	IE	Negative	-	30.6	CR	DM	Base of tongue	Chemotherapy followed by RT	26.0	Alive
13	M	56	IIE	Positive	PR-SD	34.2	CR	LR	-	Local excision	31.5	Alive
14	M	55	IE	Positive	CR	30.6	CR	LR	-	RT followed by chemotherapy	58.9	Alive
15	M	66	IE	Positive	CR	30.6	CR	LR	-	Chemotherapy	46.4	Alive
16	F	60	IE	Positive	CR	36.0	CR	LR	-	RT	29.0	Alive
17	F	57	IE	Negative	CR	30.6	CR	LR	-	Chemotherapy	19.4	Alive
18	F	52	IIE	Positive	CR	27.0	CR	LR	-	Chemotherapy	33.2	Alive

CR, complete response; DFI, disease-free interval; DM, distant metastasis; *H. pylori*, *Helicobacter pylori*; LN, lymph node; LR, locoregional relapse; PR-SD, partial response or stable disease; RT, radiation therapy.

Table 5. Patients' characteristics for secondary malignancy

Patient No.	Sex	Age (yr)	<i>H. pylori</i> infection	Radiation dose (Gy)	Radiation response	Recurrence site	Type of secondary malignancy	Site of secondary malignancy ^{a)}	DFI (mo)	Last status
1	F	78	Positive	30.0	CR	Conjunctiva	Gastric ADC	In-field	9	Dead
2	F	52	Negative	30.6	CR	Lung	Gastric ADC	In-field	46	Dead
3	F	46	Positive	30.0	CR	None	NSCLC	Out-field	38	Dead
4	M	71	Negative	30.6	CR	None	SCLC	Out-field	24	Alive
5	M	77	Negative	36.0	CR	None	Prostate cancer	Out-field	30	Alive
6	M	63	Positive	30.6	CR	None	NSCLC	Out-field	154	Alive
7	F	72	Negative	30.6	CR	None	MCL	Out-field	72	Alive
8	F	39	Positive	30.6	CR	None	NSCLC	Out-field	59	Alive
9	F	64	Negative	30.6	CR	None	Gastric ADC	In-field	80	Alive
10	F	63	Negative	36.0	CR	None	Breast cancer	Out-field	38	Alive
11	F	49	Negative	30.6	CR	None	Breast cancer	Out-field	62	Alive

ADC, adenocarcinoma; CR, complete remission; DFI, disease-free interval; *H. pylori*, *Helicobacter pylori*; MCL, mantle cell lymphoma; NSCLC, non-small cell lung cancer. ^{a)}If the secondary cancer occurs within the radiation treatment field, it is classified as in-field. Otherwise, it is classified as out-field.

secondary cancers [25]. One study has reported that chemotherapy, not RT, is associated with the development of secondary cancers in patients with gastric MALT lymphoma [7]. In one study, 40% of patients with gastric MALT lymphoma received whole abdominal RT. The incidence of secondary malignancy was 14% at 10 years [14]. In contrast, in our study, RT was administered only to the stomach and involved lymph nodes. The secondary cancer incidence rate was 6.6% including DLBCL, which was lower than that reported in the above study. Therefore, to reduce the risk of secondary cancer, it might be necessary to minimize the irradiated volume, such as irradiating only the involved site while maintaining treatment outcomes [19].

In the present study, the incidence rate of secondary malignancies or DLBCL in the group with distant recurrence was 30%, which was higher than those in other groups. Genetic mutations such as *API2-MALT1* t(11;18) chromosomal translocation might affect dissemination of gastric MALT lymphoma to distant sites and have an association with the development of secondary malignancies [26,27]. Additionally, the incidence might be increased in patients who are treated with chemotherapy for distant recurrences [7]. Gastric *H. pylori* infection has the potential to cause secondary cancers or DLBCL in the stomach [28,29]. In the present study, four of eight patients (50%) with secondary cancer or DLBCL in the stomach were infected with *H. pylori*, while two of seven patients (28.5%) with secondary cancer at distant sites had *H. pylori* infection.

H. pylori infection could induce gastric mucosal change to atrophy, intestinal metaplasia, and dysplasia and result in gastric malignancy. Eradication of *H. pylori* could prevent gastric malignancy in patients with the infection. Gastric acid

secretion could be increased after eradication for patients with *H. pylori* infection. It might lead to gastroesophageal reflux disease [30]. In our study, 65.5% of patients who underwent eradication for *H. pylori* infection reported higher rate of gastrointestinal complications than other patients ($p=0.049$).

One study has reported that it is feasible to reduce the RT dose from 30-36 Gy to 24-25 Gy without compromising treatment outcomes [19]. In a study comparing two groups treated with 36 Gy and 25.2 Gy, no significant difference in treatment-related toxicities was found [13]. In our study, reducing the RT dose did not have a detrimental effect on treatment outcomes. To avoid long-term complications including secondary malignancies, there is a need to reduce either the RT dose or the irradiated volume. Given that favorable outcomes were observed at a reduced dose of 24-25 Gy, treatment-related complications could be anticipated to be minimized while maintaining efficacy based on an ongoing prospective study employing 4 Gy in 2 fractions (NCT03680586). In our study, three-dimensional RT was performed in 88.6% of patients. However, toxicities could be reduced by utilizing advanced RT technologies such as volumetric modulated arc therapy or IMRT instead of 3D-CRT, which are effective in preserving surrounding normal tissues [18].

H. pylori eradication therapy is important for patients with gastric MALT lymphoma who had *H. pylori* infection, but there is heterogeneity in the clinical response among *H. pylori*-negative patients. In the present study, *H. pylori* eradication was performed on 33 patients without *H. pylori*, resulting in complete remission for 26 patients (78.7%). Genetic abnormalities like translocation t(11;18) are known to be refractory to *H. pylori* eradication, and this genetic fea-

ture is frequently observed in patients who are not infected with *H. pylori* [31]. The exact mechanism by *H. pylori* eradication induces a clinical response in gastric MALT lymphoma for patients without *H. pylori* infection has not been clearly elucidated [16]. It has been suggested that infection by other bacteria like *Helicobacter heilmannii*, may have contributed to the response to eradication therapy [32]. Antibiotics used in *H. pylori* eradication, particularly clarithromycin, may have immunomodulatory effects [33]. In patients with severe gastric atrophy or those taking proton pump inhibitors, *H. pylori* infection might be undetected due to limitations in diagnostic technique, leading a clinical response when treated with eradication therapy.

This study has several limitations that require caution when interpreting its results. This study was retrospective. It inherently limits the ability to control for biases influenced by unexpected and heterogeneous factors that could affect the results. There could be issues with a small sample size and a selection bias which might limit the ability to draw firm conclusions from the study results. Some patients might not have had sufficient longitudinal follow-up to fully assess outcomes such as long-term survival or late onset of treatment-related complications. There were no data on endoscopic ultrasound. It was not possible to determine whether the depth of invasion affected treatment results. Genetic alternations such as t(11;18) translocation are closely related to *H. pylori* eradication therapy and treatment outcomes for patients with gastric MALT lymphoma. However, they were not analyzed in this study.

In conclusion, this study demonstrated the effectiveness of RT in treating patients with gastric MALT lymphoma. Excellent treatment outcomes were shown even in patients who did not have *H. pylori* infection or did not respond to *H. pylori*

eradication. Gastric RT for MALT lymphoma was not associated with severe complications or an increased incidence of secondary cancers.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (<https://www.e-crt.org>).

Ethical Statement

This study is a retrospective multi-institutional study reviewed by the Korean Radiation Oncology Group (KROG 18-08). Approval was obtained from the Institutional Review Boards of each participating institution. A waiver of informed consent was granted for the medical record review.

Author Contributions

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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