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BRIEF ARTICLE

Clinical outcomes of radiation therapy for early-stage gastric mucosa-associated lymphoid tissue lymphoma

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Abstract

AIM: To evaluate the clinical outcomes of radiation therapy (RT) for early-stage gastric mucosa-associated lymphoid tissue lymphoma (MALToma).

METHODS: The records of 64 patients treated between 1998 and 2011 were analyzed retrospectively. For *Helicobacter pylori* (*H. pylori*)-positive patients (n = 31), chemotherapy or *H. pylori* eradication therapy was the initial treatment. In patients with failure after *H. pylori* eradication, RT was performed. For *H. pylori*-negative patients (n = 33), chemotherapy or RT was the first-line treatment. The median RT dose was 36 Gy. The target volume included the entire stomach and the perigastric lymph node area.

RESULTS: All of the patients completed RT without interruption and showed complete remission on endoscopic biopsy after treatment. Over a median follow-up period of 39 mo, the 5-year local control rate was 89%. Salvage therapy was successful in all relapsed patients. Secondary malignancies developed in three patients. The 5-year overall survival rate was 94%. No patient presented symptoms of moderate-to-severe treatment-related toxicities during or after RT.

CONCLUSION: Radiotherapy results in favorable clinical outcomes in patients with early-stage gastric MALToma who experience failure of *H. pylori* eradication therapy and those who are *H. pylori* negative.

Key words: Gastric mucosa-associated lymphoid tissue lymphoma; Radiation therapy; Treatment response

Core tip: Radiation therapy is an effective salvage treatment for patients with gastric mucosa-associated lymphoid tissue lymphoma (MALToma) who experience failure of *Helicobacter pylori* (*H. pylori*) eradication therapy. For patients with *H. pylori*-negative gastric MALToma, radiation therapy is recommended as the initial treatment. The risk of treatment-related toxicities and secondary malignancies is acceptable.

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INTRODUCTION

Mucosa-associated lymphoid tissue lymphoma (MALToma) was first described by Isaacson in 1983[1]. The World Health Organization (WHO) and the Revised European American Lymphoma Classification (REAL) later categorized it as an independent entity[2,3].

The stomach is the most common extranodal site of MALToma (50%-70% of all cases), and *Helicobacter pylori* (*H. pylori*) infection is the most important risk factor[4]. In numerous studies, *H. pylori* eradication therapy had excellent outcomes for gastric MALToma with a reported complete remission (CR) rate of 70%-80%[4-6]. As a result, *H. pylori* eradication therapy is now employed as the sole first-line treatment[7]. For *H. pylori*-negative patients, radiation therapy (RT) has recently been accepted as a preferred treatment modality. The role of surgery has declined gradually because of the high incidence of postoperative morbidity and mortality[8].

MALToma is characteristically a localized disease[9-11], and it is very sensitive to radiation. Accordingly, MALToma at extranodal sites, such as the orbital adnexa and the parotid and thyroid glands, has been treated with a moderate dose (25-40 Gy) of RT as an initial treatment[12-17]. Retrospective studies have largely confirmed the effectiveness of RT for gastric MALToma[18-27]. However, the low case numbers of previous studies render the evidence of the effectiveness of RT insufficient.

In this study, we investigated the clinical outcomes and associated adverse effects of RT in patients with early-stage gastric MALToma who were unresponsive to *H. pylori* eradication therapy and in *H. pylori*-negative patients.

MATERIALS AND METHODS

Between November 1998 and March 2011, 71 patients who were diagnosed with localized gastric MALToma received RT at Samsung Medical Center. Among them, 7 patients were excluded from this study; 5 patients were excluded because they also had small foci of diffuse large B-cell lymphoma. Two patients were immediately lost to follow up after the completion of RT. We retrospectively analyzed the remaining 64 patients. These patients had stage I or II$_1$ MALToma according to the Lugano staging system[28]. All of the patients were histologically diagnosed with gastric MALToma by endoscopic biopsy. Subsequently, patients underwent a systemic staging workup, including laboratory tests, such as blood cell counts, biochemical profile and lactate dehydrogenase, computed tomography (CT), positron-emission tomography (PET) or bone marrow biopsy.

Treatment before RT

Of the 64 patients, 40 patients received treatment related to gastric MALToma before RT. *H. pylori* eradication therapy consisting of a 1-2 wk course of amoxicillin (1000 mg twice daily), clarithromycin (500 mg twice daily) and a proton pump inhibitor (omeprazole or esomeprazole) followed by maintenance of the proton pump inhibitor was performed in 31 patients. Among the patients treated with *H. pylori* eradication therapy, 3 had no evidence of *H. pylori* infection.

Chemotherapy consisting of either a combination of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) every 3 wk or cyclophosphamide, vincristine and prednisolone (CVP) every 3 wk was performed in 15 patients until 2002. Among them, 6 patients received both *H. pylori* eradication therapy and chemotherapy (Figure 1).

Twenty-four patients without *H. pylori* infection did not receive any treatment before RT.

Radiation therapy

All patients underwent simulation using fluoroscopy or a CT simulator. Before simulation, the patients were trained to breathe in a regular and shallow cycle to maintain a constant stomach motion.

The clinical target volume (CTV) was the entire stomach plus the perigastric lymph nodes for stage I gastric MALToma. The CTV for stage II$_1$ patients was determined as the CTV for stage I gastric MALToma plus a generous margin extending from the involved lymph nodes. To cover the perigastric lymph nodes, we included a 2-cm margin from the outline of stomach wall, which was observed on fluoroscopy after the ingestion of a barium suspension. The planned target volume (PTV) was individualized, considering setup error and stomach movement. CT planning was conducted for 39 patients following the introduction of the CT simulator. The entire stomach was defined at every respiratory stage in 4-dimensional CT slices. After the internal target volume (ITV) was defined, the CTV was set as the ITV plus a 1-cm margin to cover the perigastric lymph nodes. The PTV was the CTV plus 1 cm, and the planning geometry consisted of 2 to 4 coplanar or non-coplanar beams using high-photon energy (10-15 MV).

The daily fraction size was either 1.8 Gy or 2.0 Gy. The total radiation dose ranged from 30 Gy to 44 Gy, with a median of 36 Gy.

Treatment response

We assessed the treatment response histologically using endoscopic biopsy after the completion of RT. The first post-RT endoscopic examination was typically performed 1-2 mo after RT. The next endoscopic biopsies were performed every 3 to 6 mo in the first two or three years and annually thereafter. CT findings were not considered to evaluate the treatment response. The response criteria were based on the GELA (Groupe d'Etude des Lymphomes de l'Adulte) histologic grading system[29].

Statistical analysis

The end points were overall survival (OS) and local control (LC). Time was calculated from the initiation of RT to the event of interest. LC was defined as the time in-

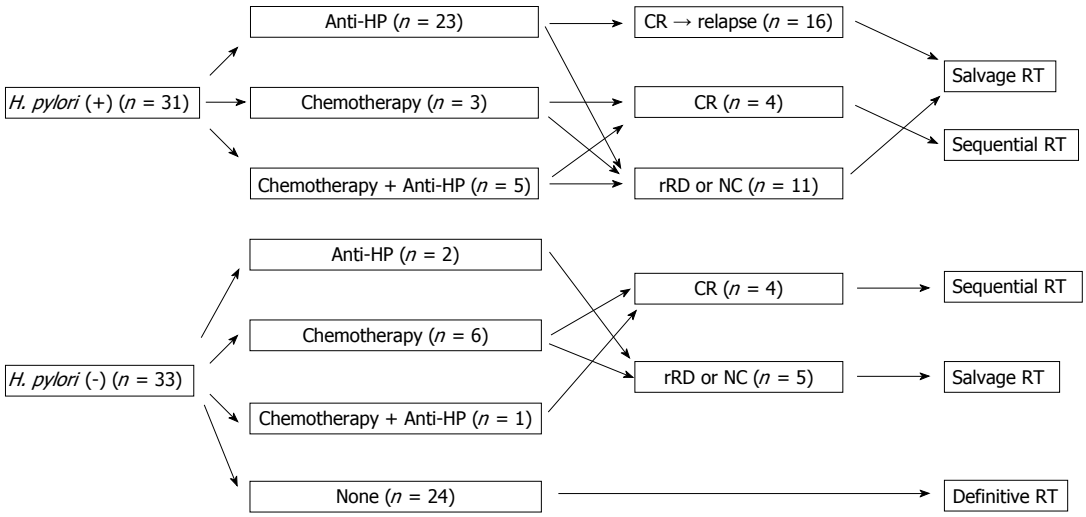

Figure 1 Initial treatment before radiation therapy. *H. pylori*: *Helicobacter pylori*; Anti-HP: anti-*Helicobacter pylori* therapy; CR: Complete remission; rRD: Residual responding disease; NC: No change; RT: Radiation therapy.

Table 1 Patient characteristics *n* (%)

Characteristic	No. of patients (*n* = 64)
Gender	
Male	38 (59)
Female	26 (41)
Age (yr)	
	Median, 49 Range, 24-75
Lugano staging system	
I	53 (83)
II$_1$	11 (17)
Disease location	
Cardia	2 (3)
Fundus	5 (8)
Body	35 (55)
Antrum	7 (11)
Diffuse	15 (23)
H. pylori infection	
Negative	33 (52)
Positive	31 (48)
Prior treatment	
H. pylori eradication	25 (39)
Chemotherapy	9 (14)
Combined	6 (9)
None	24 (38)
Response to prior treatment	
Complete histologic remission (CR)	17
Responding residual disease (rRD)	11
No change (NC)	12
Not evaluable	24
Radiation dose	Median, 36 Gy
≥ 40 Gy	18 (28)
36 Gy	38 (59)
30 Gy	8 (13)
RT technique	
AP/PA	25 (39)
3-D conformal	39 (61)

H. pylori: *Helicobacter pylori*; RT: Radiation therapy; AP/PA: Anteroposterior/posteroanterior.

terval to relapse, which was confirmed by biopsy. OS was defined as the period from diagnosis to the date of last follow up or death. We calculated the LC and OS rates using the Kaplan-Meier method. All analyses were performed using IBM SPSS Statics version 19.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

Patient characteristics are summarized in Table 1. The median age was 49 years, and 53 patients (83%) were stage I . The gastric body was the site most commonly involved, and *H. pylori* infection was detected in 31 patients (48%). As an initial therapy, 31 patients (48%) received *H. pylori* eradication therapy, and 24 patients (38%) received RT.

Seventeen of 40 patients (43%) achieved CR with prior treatment before RT. Nine patients who achieved CR with *H. pylori* eradication therapy relapsed after a median disease-free interval of 19 mo (range: 9 to 56 mo). CR after chemotherapy was achieved in 5 of 9 patients. The combination of *H. pylori* eradication therapy and chemotherapy was successful in 3 patients. Those who achieved CR after chemotherapy received RT as sequential therapy. The remaining 23 patients had persistent disease at the time of referral for salvage RT (Figure 1).

The median interval between the initiation of first treatment and the initiation of RT was 8 mo (range, 1 to 40 mo).

RT response

All patients showed a histological CR at the post-treatment endoscopic biopsy. Three patients had not achieved CR at the first post-treatment endoscopic biopsy, but they had achieved a histological CR at a subsequent evaluation 4 to 5 mo after RT without any further treatment.

Survival

Over a median follow-up period of 39 mo (range, 9-131

Table 2 Patients with local recurrence after achieving complete remission with radiation therapy

	Initial *H. pylori*	Initial Tx before RT	DFI (mo)	*H. pylori* at relapse	Tx after relapse	Final response
Case 1	+	Anti-HP	14	-	Observation	CR
Case 2	-	None	11	-	Observation	CR
Case 3	-	None	26	-	Observation	CR
Case 4	-	None	20	+	Anti-HP	CR
Case 5	-	None	38	+	Anti-HP	CR

H. pylori: *Helicobacter pylori*; anti-HP: anti-*H. pylori* antibiotics; CR: Complete remission; DFI: Disease-free interval; Tx: Treatment.

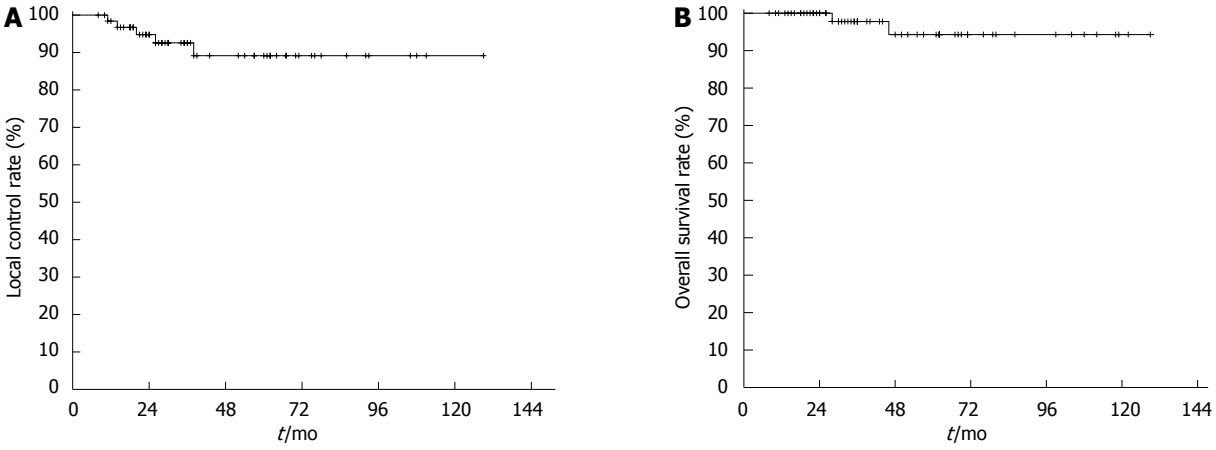

Figure 2 Local control rate (A) and overall survival rate (B) for all patients.

mo), MALToma relapsed in 5 patients (Table 2), and the 5-year LC of all patients was 89% (Figure 2A). Two patients (cases 4 and 5 in Table 2) received *H. pylori* eradication therapy due to positive conversion of *H. pylori* at relapse and finally gained secondary CR. The other three patients (cases 1, 2 and 3) who were not *H. pylori* infected at relapse did not receive any treatment, and MALToma was not detected on subsequent endoscopy.

At the study end point, 62 patients remained alive. One patient died due to relapse following the development of malignant lymphoma involving the mesenteric lymph nodes and bone marrow at 29 mo after RT. Another patient died of intercurrent disease 47 mo after RT. The 5-year overall survival rate was 94% (Figure 2B).

Treatment-related toxicities and secondary malignancies

All patients completed RT without interruptions due to treatment-related toxicities. Some patients experienced mild nausea and epigastric soreness, but these symptoms were managed with anti-emetics or antacids. None of the patients complained of gastrointestinal bleeding or perforations. Neither renal nor hepatic toxicities developed.

One patient with *H. pylori* infection was diagnosed with metachronous gastric cancer 21 mo after RT. He underwent subtotal gastrectomy with Billroth type I reconstruction. On pathologic examination, tubular adenocarcinoma was confined to the mucosa, and metastasis to the regional lymph nodes was not found.

Transformation into malignant lymphoma occurred in two patients at intervals of 26 and 31 mo following the initiation of RT. The sites involved were the mesenteric lymph node and the supraclavicular lymph node, respectively. These patients received 6 cycles of salvage chemotherapy with the CHOP regimen. One patient died of rapid disease progression 6 mo later. The other patient survived in a cured state.

DISCUSSION

Currently, *H. pylori* eradication therapy is the only established treatment for low-grade gastric MALToma in *H. pylori*-positive patients[7]. The treatment modality that should be selected for patients who do not respond to *H. pylori* eradication therapy is currently controversial. Recently, many small retrospective studies and a pooled-data analysis[19,21,22,26,30] have demonstrated that RT has excellent clinical outcomes and feasibility. As a result, RT has become a preferred non-invasive local treatment modality. The results of our present study also support the effectiveness of RT for these patients.

The application of salvage RT in this setting depends to a high degree on defining the time at which *H. pylori* eradication failed. Most studies with salvage RT for gastric MALToma have not defined the time to *H. pylori* eradication therapy failure. Our institution also did not have consensus regarding the failure of *H. pylori* eradication therapy. The range of the interval between the initiation of prior treatment and the timing of RT initiation was variable and not homogeneous. Previous studies have demonstrated that 80%-90% of patients may achieve a

histological CR within one year after *H. pylori* eradication therapy[6,20]. The European Society of Medical Oncology has proposed that at least 12 mo be allowed before initiating another treatment in patients who achieve clinical and endoscopic remission in addition to *H. pylori* eradication, albeit with persistent lymphoma at the histological level[7].

In addition, reference data for the evaluation of RT response are lacking. In this study, 3 patients did not show CR at the first post-treatment endoscopy, which was performed 1 to 2 mo after RT, but they had achieved CR at the next endoscopy, which was performed 4 to 5 mo later. We therefore suggest that a minimum follow-up period of 6 mo is needed to evaluate the effects of RT.

For *H. pylori*-negative patients, *H. pylori* eradication therapy can be attempted as an initial treatment because of the possibility of a false-negative test or low bacteria counts. However, the response rate has been reported to vary (0%-83%)[21,27,31]. In contrast, several small retrospective studies reported a response rate of 100% for RT as the initial treatment for *H. pylori*-negative patients with MALToma[18,21,25,27]. In these previous studies, CR was confirmed in all patients at the post-treatment endoscopic biopsy after RT. In the absence of randomized trial data due to the rarity of disease, we cannot directly compare *H. pylori* eradication therapy with RT as an initial treatment for *H. pylori*-negative patients. However, a survey of the literature suggests that RT shows superior performance compared to *H. pylori* eradication therapy in the initial treatment of *H. pylori*-negative patients. Recent evidence indicates that the t(11;18)(q21;q21) translocation in gastric MALToma predicts resistance to *H. pylori* eradication therapy[32]. This same translocation has been detected in nearly half of patients with *H. pylori*-negative gastric MALToma[33]. Therefore, in these subgroups, RT may be an appropriate treatment. As additional data become available, routine testing for the t(11;18)(q21;q21) translocation at the time of MALToma diagnosis may become a useful guide for selecting the initial treatment.

The 5-year LC rate in this study was 89%, which is comparable to those reported by previous studies[13,17,18]. Until 6 mo after the completion of RT, all patients showed histological CR on follow-up endoscopic biopsy. However, 5 patients developed relapse at disease-free intervals of 11 to 38 mo. Three patients achieved histological CR on the subsequent evaluation without any further treatment, which could be due to false-positive results at the initial examinations. The other two patients, who were initially *H. pylori* negative, developed recurrence coincident with *H. pylori* infection, and they were successfully treated with *H. pylori* eradication therapy as a salvage treatment. This example may indicate an important role for *H. pylori* infection in the mechanism of the local recurrence of gastric MALToma.

The major concern regarding stomach irradiation is the risk of perforation and bleeding. A collective review places this risk at 4% or less[34]. Additionally, the risk may be much lower in early-stage and low-grade disease, given the lower radiation doses and target volumes. Another concern is renal toxicity. In the past, the irradiated target volume was the entire abdomen followed by a additional dose to the entire stomach and the perigastric lymph nodes[24]. With increasing knowledge of the spread pattern of low-grade gastric MALToma, the target volume has been reduced to the stomach plus the regional lymphatics[11]. Local RT with the use of three-dimensional conformal or intensity-modulated techniques has the particular advantage of reducing the radiation dose to the kidneys, particularly on the left side[19,35]. Our study, in agreement with numerous other studies, demonstrated no gastric perforation or bleeding and no renal toxicity attributable to RT.

Whether secondary malignancies such as gastric cancer develop years after irradiation is still controversial. Reports of secondary malignancies within the RT field in the treatment of gastric MALToma appear to be rare[13,21,23]. In this study, secondary gastric cancer occurred in one case. For secondary gastric cancer, gastric MALToma itself could be an additional risk factor because of the common pathogenesis, *i.e.*, *H. pylori* infection, irrespective of the treatment modality[34,36-38]. However, the effects of irradiation cannot be neglected. Because the latent period from irradiation to the development of secondary malignancies can reach a few decades and nearly all patients with gastric MALToma are expected to be long-term survivors in a cured state, close, long-term follow up is required to observe the development of radiation-induced secondary cancer.

Malignant transformation in MALToma is uncommon. The transformation rates reported in some studies ranged from 3% to 19% and did not apparently depend on the site involved[10,14,17]. In the present study, transformation developed in 2 patients (3.1%) with a disease-free interval of 26 to 31 mo, which is consistent with other published reports (ranging from 6 to 116 mo)[14,17]. Following malignant transformation, the mortality rate is higher than that for MALT lymphoma.

In conclusion, the results of the present study further support the use of RT for patients with MALToma who experience failure of *H. pylori* eradication therapy and for *H. pylori*-negative patients. The rationale of treating such patients with RT can be summarized as follows. First, gastric MALToma tends to be a localized disease. Second, MALToma is a radio-sensitive tumor. Third, RT has the advantage of stomach preservation. Lastly, RT has low treatment-related morbidity. Although local relapse developed in some cases, all cases were salvaged successfully. Ongoing risks for secondary malignancy or malignant transformation warrant regular long-term follow-up with systemic evaluation and testing for *H. pylori* infection.

COMMENTS

Background

Gastric mucosa-associated lymphoid tissue lymphoma (MALToma) is highly associated with *Helicobacter pylori* (*H. pylori*) infection. Therefore, *H. pylori* eradication therapy is the standard treatment. However, in clinical practice,

persistent disease or recurrence after *H. pylori* eradication therapy are often found. Additionally, a substantial number of gastric MALToma patients are not *H. pylori* positive. Radiation therapy (RT) has been shown to have good clinical outcomes and feasibility for the treatment of gastric MALToma in these patients in many small retrospective studies.

Research frontiers

Some reports from single institutions have shown that RT is effective for patients with gastric MALToma that is resistant to *H. pylori* eradication therapy or that recurs following an initial clinical response. Additionally, in other small reports, patients with *H. pylori*-negative gastric MALToma and low response rates to *H. pylori* eradication therapy were treated successfully with RT.

Innovations and breakthroughs

This study is one of the largest single-institution experiences to report the clinical outcomes of gastric MALToma treated with RT. RT has an excellent role as either a salvage or definitive treatment for gastric MALToma. In particular, for *H. pylori*-negative gastric MALToma patients, in whom the t(11;18)(q21;q21) translocation is frequently found, RT should be applied as the initial treatment because this translocation tends to be resistant to *H. pylori* eradication therapy. With aid of the three-dimensional conformal technique, fatal toxicities related to radiation can be minimized.

Applications

RT is the preferred salvage treatment modality for *H. pylori* infection-associated gastric MALToma patients who are unresponsive to *H. pylori* eradication therapy. Additionally, it can be an effective initial treatment for gastric MALToma patients without *H. pylori* infection.

Terminology

MALToma is a B cell-originating cancer in the marginal zone of the MALT, which is the diffuse system of small areas of lymphoid tissue found in various sites of the body.

Peer review

This paper is well witten. It is acceptable for publication.

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