

A Retrospective Study of 5-year Outcomes of Radiotherapy for Gastric Mucosa-associated Lymphoid Tissue Lymphoma Refractory to *Helicobacter pylori* Eradication Therapy

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Background: The favorable response rate of radiotherapy for localized gastric mucosa-associated lymphoid tissue lymphoma refractory to *Helicobacter pylori* eradication has been demonstrated. However, there are limited data available on the long-term outcomes. The aim of this retrospective study was to evaluate the long-term outcomes of radiotherapy for localized gastric mucosa-associated lymphoid tissue lymphoma refractory to *Helicobacter pylori* eradication.

Methods: Thirty-four consecutive patients with localized gastric mucosa-associated lymphoid tissue lymphoma that were refractory to eradication were treated with radiotherapy (a total dose of 30 Gy). The response and adverse events of radiotherapy were retrospectively analyzed as short-term outcomes, and recurrence-free, overall and disease-specific survival rates were calculated as long-term outcomes.

Results: Thirty-three (97.1%) patients achieved complete remission and radiotherapy was well tolerated. One patient underwent emergency gastrectomy due to severe hematemesis. Of the 34 patients during the median follow-up period of 7.5 (1.2–13.0) years, one patient had local recurrence after 8.8 years, one patient underwent surgery for bowel obstruction secondary to small bowel metastasis after 5.1 years and one patient had pulmonary metastasis after 10.9 years. Pathologically, all three recurrences revealed mucosa-associated lymphoid tissue lymphoma without any transformation to high-grade lymphoma. None died of gastric mucosa-associated lymphoid tissue lymphoma. The 5-year recurrence-free survival rate was 97.0%. The 5-year overall survival rates and disease-specific survival rates were 97.0 and 100%, respectively.

Conclusions: Radiotherapy in patients with localized gastric mucosa-associated lymphoid tissue lymphoma refractory to *Helicobacter pylori* eradication can achieve excellent overall survival. However, long-term surveillance is necessary to identify late recurrences.

Key words: mucosa-associated lymphoid tissue lymphoma – stomach – radiotherapy – *Helicobacter pylori* – long-term outcomes

INTRODUCTION

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma is a distinct type of B-cell lymphoma (1). Development of gastric MALT

lymphoma is closely linked to *Helicobacter pylori* infection. Eradication of *H. pylori* leads to complete remission (CR) of the disease in 65–93% of patients with localized gastric MALT lymphoma. Excellent long-term outcomes of gastric

MALT lymphoma after *H. pylori* eradication have also been reported (2–11). Nakamura et al. (11) concluded that the recurrence-free, overall and disease-free survival rates after 10 years in 420 cases were 90, 95, and 86%, respectively. Therefore, eradication has been accepted as the first-line treatment for localized gastric MALT lymphoma (12).

Second-line therapies such as radiotherapy (RT), chemotherapy and a ‘watch and wait’ strategy have been suggested for nonresponders (12). There are several reports that showed the efficacy of RT for gastric MALT lymphoma (13–19). However, only limited data are available on the long-term outcomes of second-line RT (20–22). The aim of this retrospective study was to evaluate the long-term outcomes of RT for localized gastric MALT lymphoma refractory to *H. pylori* eradication therapy.

MATERIAL AND METHODS

PATIENT SELECTION

One hundred and twenty-one patients received *H. pylori* eradication as initial treatment in our hospital even if the test for *H. pylori* was negative from 1993 and 2006, among which 84 patients achieved and sustained CR. Thirty-four did not respond to *H. pylori* eradication and three achieved CR but subsequently relapsed. Another 15 patients who were refractory to initial eradication therapy were referred to our institution.

Of the total 52 patients refractory to or having relapsed after *H. pylori* eradication, 34 consecutive patients who were treated with RT as a second-line therapy were subjects for this analysis. Out of the selected patients, 32 patients did not achieve CR after eradication and 2 patients achieved CR, but thereafter relapsed (Table 1).

Eighteen patients were treated with other modalities instead of RT at their physicians’ discretion. Nine patients were followed up without any further treatment, seven underwent surgery and two underwent gastrectomy followed by chemotherapy.

DIAGNOSIS

All gastric MALT lymphomas were histologically proven by hematoxylin and eosin stain, and immunostaining of biopsy specimens. The tumors comprised diffuse proliferation of small-to-medium-sized lymphoid cells with CD20-positive and CD5, CD10 and cyclin D1-negative immunophenotype. The status of *H. pylori* infection was assessed by culture before eradication in all patients. Clinical stage was classified according to the Lugano staging system using clinical examination, esophagogastroduodenoscopy (EGD) and computed tomography (CT) (23). The macroscopic type of MALT lymphoma was classified as superficial, protruded, ulcerative or others based on the report by Nakamura et al. (24). The presence or absence of chromosomal translocation 11q21 and 18q21 corresponding to API2/MALT1 gene fusion was

Table 1. Patient characteristics (n = 34)

Gender, male/female	16/18
Age, median (range)	53.5 (19–73)
Clinical stage I	34
Macroscopic type	
Superficial	26
Ulcerative	5
Protruded	3
<i>H. pylori</i> infection	
Positive	17
Negative	17
API2-MALT1 gene translocation	
Positive	2
Negative	18
Unknown	14
Evaluation of eradication (<i>H. pylori</i> positive/negative)	
Nonresponder	32 (16/16)
Recurrence	2 (1/1)

H. pylori, *Helicobacter pylori*.

retrospectively investigated by interphase fluorescence *in situ* hybridization using the remaining biopsy specimens before treatment (25).

METHOD OF RT

All included patients were treated in opposed anterior and posterior fields or multiple field irradiation. The RT dose was 30 Gy with daily fractions of 1.5 or 2.0 Gy. The clinical target volume (CTV) incorporated the entire affected organ including perigastric lymph nodes. The planning target volume was defined as the CTV with set-up and internal margins. Patients underwent a CT scan or X-ray simulation in the supine position after an overnight fast. The stomach and the organs at risk (spinal cord, kidneys and liver) were defined on the CT slices. Patients were treated under fasting condition.

ASSESSMENT AND FOLLOW-UP

The response of RT was evaluated by EGD and CT. Biopsy specimens after RT were assessed by experienced pathologists according to GELA (Groupe d’Etude des Lymphomes de l’Adult) grading system. CR was defined as the endoscopic disappearance or scarring of the primary lesion without any lymph-node or distant involvement by CT and post-treatment biopsies showing complete histological response (ChR) or pathologically minimal residual disease (pMRD) in two subsequent examinations (26). Adverse events were evaluated according to Common Terminology Criteria for Adverse Events version 4.0 (27).

Those who achieved CR were followed up with surveillance EGD every 4 or 6 months and annual CT for an initial few years. Annual surveillance was done thereafter.

STATISTICAL ANALYSIS

Patient demographics were collected by prospectively stored database. Short and long-term outcome data were retrospectively gathered from the electronic medical record of our institution and analyzed for this study. We evaluated the response and adverse events of RT as short-term outcomes. We calculated the 5-year recurrence-free survival rate, 5-year overall survival rate and 5-year disease-specific survival rate by the Kaplan–Meier method. Recurrence-free survival was measured from the date of last RT to treatment failure or death from any cause. Overall survival was measured from the date of last RT to death from any cause. The study was approved by institutional review boards of our institutions.

RESULTS

Out of the 34 patients included in this study, 17 patients were positive for *H. pylori* infection and 17 patients were negative. Sixteen of the 32 patients who did not achieve CR and 1 of the 2 patients who relapsed after CR had *H. pylori* infection at diagnosis. Two patients had *API2/MALT1* gene translocation, 18 patients were negative, and 14 were unknown (13 were undeterminable due to incomplete specimen or staining and 1 was not investigated). All patients were stage I (Table 1).

RT was well tolerated except for one patient who underwent emergency gastrectomy during treatment period due to grade 4 hematemesis. This patient received only 15 Gy/10Fr of RT and could not be evaluated in terms of the efficacy. But there

was no histological evidence of residual lymphoma in the resected specimen. The remaining 33 patients achieved CR. (Table 2).

Three of the 34 patients relapsed during the median follow-up period of 7.5 (1.2–13.0) years. Local and distant relapse rates were 2.9 and 5.9%, respectively. One had local recurrence after 8.8 years, one had pulmonary metastasis after 10.9 years and one underwent surgery for bowel obstruction due to small bowel metastasis after 5.1 years (Table 3). All three recurrences pathologically revealed the same type of MALT lymphoma as at the first presentation without any transformation to high-grade lymphoma. Two of the three patients with recurrence had *H. pylori* infection and none of them were determined to have *API2/MALT1* gene translocation. They have been followed up without any additional treatment (the median follow-up period was 8 months).

There were no serious late adverse events during the median follow-up period of 7.5 years. No patient had metachronous gastric cancer or any secondary malignancy. None died of MALT lymphoma and one patient died of unrelated causes. The 5-year recurrence-free survival rate was 97.0%. Five-year overall and disease-specific survival rates were 97.0 and 100%, respectively (Figs. 1 and 2).

DISCUSSION

MALT lymphoma is characterized by an indolent natural history and has a tendency to stay localized for a long time. In addition, gastric MALT lymphoma has less frequent distant spread than those of other organs (28). Therefore, local treatment approaches for gastric MALT lymphoma are considered reasonable.

The consensus report of the European Gastrointestinal Lymphoma Study group recommended *H. pylori* eradication as a first-line treatment for localized gastric MALT lymphoma, even if the tests for *H. pylori* were negative (12,29). The patients refractory to *H. pylori* eradication as well as those with disseminated or bulky disease require further local or systemic treatment such as surgery, chemotherapy or RT (12). A surgery had been carried out for such patients before introduction of RT. Several studies have demonstrated excellent long-term outcomes of surgery, but a simple partial resection of the stomach cannot be carried out if there is either

Table 2. Short-term outcomes ($n = 34$)

Complete remission, % (n)	97.1% (33)
Not evaluable, % (n)	2.9% (1)
Accomplishment of RT, % (n)	97.1% (33)
Adverse event more than Grade 3, % (n) hematemesis (Grade 4)	2.9% (1)

RT, radiotherapy; CR, complete remission.

Table 3. Clinical characteristics of patients with recurrence ($n = 3$)

	Macroscopic type	<i>H. pylori</i>	Organ	Period from RT (years)	Treatment	Outcome
Case 1	Superficial	–	Stomach	8.8	Watchful wait	Alive
Case 2	Superficial	+	Lung	10.9	Watchful wait	Alive
Case 3	Superficial	+	Ileum	5.1	Surgery	Alive

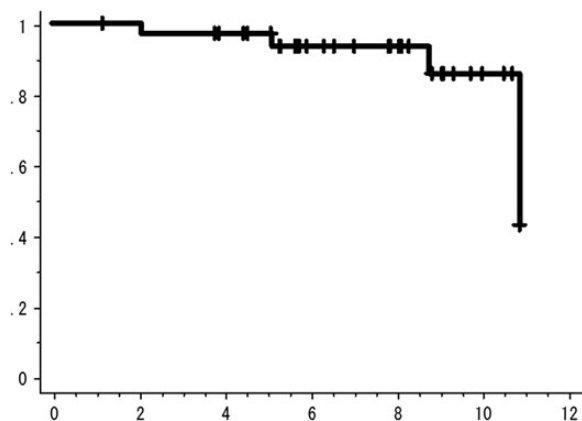


Figure 1. Recurrence-free survival curve calculated by the Kaplan–Meier method.

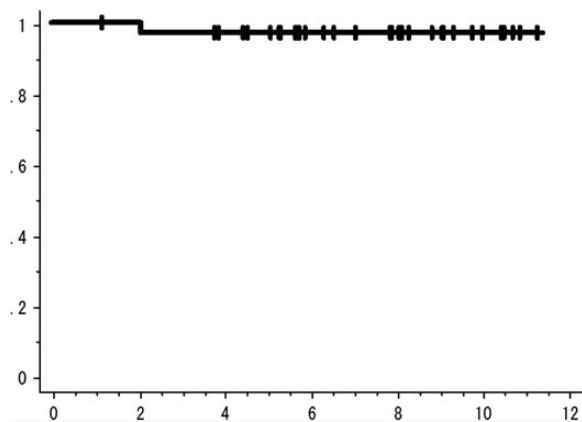


Figure 2. Overall survival curve calculated by the Kaplan–Meier method.

multifocal disease or a fundic location of the tumor. Also, a few prospective studies reported no advantage of surgery compared with organ-preserving treatments (30,31). Therefore, gastrectomy has become uncommon.

MALT lymphoma is sensitive to RT, and several studies showed favorable responses of RT to localized gastric MALT lymphoma not only as first-line therapy, but also as second-line therapy. CR can be achieved in >90% (13–21). In our study, 34 patients received RT as a second-line treatment. All patients achieved CR, except one case with hematemesis. Our study is in line with other previous publications, showing that adverse events are rare (13–22). The prevalence of gastric bleeding and perforation during chemotherapy and/or RT in unresected patients is up to 4%. They occur in advanced stages, and are considered to be comparable with the peri-operative risk of death related to gastrectomy itself (33).

Thieblemont et al. (34) concluded that the probability of 5-year freedom from progression-free survival was 59% for chemotherapy and 85% for surgery alone in patients with localized gastric MALT lymphoma. Mafune et al. (35) reported that 5-year cause-specific survival for surgery was 96.0% in patients with Stage IE gastric non-Hodgkin's

lymphoma (Ann Arbor classification). Although several studies showed favorable short-term outcomes, there are only limited data available on the long-term outcomes of RT for localized gastric MALT lymphoma refractory to *H. pylori* eradication. Okada et al. showed that all 22 patients achieved CR in 30 Gy/20Fr of RT, and 5-year relapse-free survival and 5-year overall survival rates were 84 and 91%, respectively. This study included 14 patients without *H. pylori* infection who received RT as a first-line treatment. It might also exclude some patients with <2 years follow-up (22). Therefore, our study showed excellent 5-year outcomes comparable with surgery or chemotherapy.

Goda et al. reported that gastric and thyroid MALT lymphomas had better clinical outcomes with RT compared with other sites where distant metastases are more common. Eighty percent of the recurrences occurred within 5 years in patients with MALT lymphoma at other sites (orbital adnexa, salivary gland, etc.) (13). On the other hand, in our study, all three relapses were found over 5 years after RT. Considering the results of our study and the previous report, it is possible that gastric MALT lymphoma has a more indolent clinical course after RT compared with other organ sites. Our results support the necessity of life-long follow-up for patients who receive RT (32).

Our study showed excellent 5-year outcomes of RT, but there were a few concerns. First, when to start RT for stable gastric MALT lymphoma still remains unknown, because watchful waiting for >2 years showed acceptable clinical outcomes (36). The clinical course after failure to *H. pylori* eradication might be extremely indolent. Second, it is still controversial whether RT with moderate dosing might increase the risk of a secondary malignancy or not, although our data showed no secondary malignancy after RT (37,38). RT for gastric MALT lymphoma might influence the development of metachronous gastric cancer, which is difficult to distinguish as both are related to *H. pylori* exposure. A more careful observation is needed because secondary cancers might develop after a longer time period.

We tried to predict for relapse after RT by molecular biomarkers that are known to predict response to *H. pylori* eradication in this study, but could not, because *API2/MALT1* gene translocation could not be evaluated in all three patients with relapse. The population of *API2/MALT1* gene translocation was 10% in this study. Because 37–47% of patients refractory to *H. pylori* eradication had *API2/MALT1* gene translocation in other studies, our results might be underestimated due to incomplete specimen or staining (12,39).

The limitations of this study are its retrospective nature and small sample size, even though we evaluated the data collected consecutively in our database as a part of normal clinical care. Further prospective study with a larger sample size is needed to confirm our results and also to compare the long-term outcomes between RT and watchful waiting. It would be useful to ascertain the risk factors for relapse after RT.

RT for patients with localized gastric MALT lymphoma refractory to *H. pylori* eradication can achieve excellent overall

survival. However, long-term surveillance is necessary to identify late recurrences.

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Conflict of interest statement

None declared

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