

## Low Grade MALT Lymphoma of the Stomach: Treatment Outcome with Radiotherapy Alone

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In order to evaluate the role of radiation therapy in the management of low-grade mucosa-associated lymphoid tissue lymphoma of the stomach (MLS), in patients with no evidence of *Helicobacter pylori* (*H. pylori*) or who had not responded to *H. pylori* eradication treatment, we analyzed the treatment outcome of patients who had received radiotherapy alone.

Between Jan 1995 and May 2001, 6 patients with low-grade MLS were treated with radiotherapy alone. The median radiation dose was 30.6 Gy (range; 30-39 Gy) in a daily fractions of 1.5-1.8 Gy. Each patient had an endoscopic esophago-gastro-duodenoscopy with biopsy, 4 weeks after the completion of radiotherapy and every 6 months thereafter.

A complete response was obtained in all patients. All patients were followed-up without evidence of disease, and no patient suffered a relapse. There was neither perforation nor hemorrhage of the stomach in any of the patients. No renal or hepatic toxicity were noted, and no secondary malignancies developed.

In conclusion, radiotherapy should be considered as the preferred treatment method for low-grade MLS, in patients with no evidence of *H. pylori* infection, or who do not respond to antibiotic therapy, due to the significant benefits in gastric preservation and low morbidity.

**Key Words:** Stomach, lymphoma, mucosa-associated lymphoid tissue, *Helicobacter pylori*, radiotherapy, organ preservation

## INTRODUCTION

In the past, primary low-grade mucosa-associated lymphoid tissue lymphomas of the stomach (MLS) were treated with surgery in the same way as high-grade lymphomas. This often necessitated a total gastrectomy due to the multi-focal nature of primary gastric lymphomas. Most surgical studies analyzed their data by stage, rather than by grade, and did not specifically address the management of low-grade MLS.<sup>1</sup> Recently, stomach-conserving strategies have become increasingly importance in the treatment of primary gastric lymphomas as an alternative to surgery; this is due to the advances in non-invasive staging procedures, which reduce the prior dependence on surgery for the diagnosis and staging, and takes advantage of good responses to chemotherapy and radiotherapy. The information from endoscopic ultrasound (EUS) combined with computed tomography (CT) scans, can be analyzed to assess the extent of lymphoma infiltration through the gastric wall, and the status of regional lymph node involvement.<sup>2</sup>

Furthermore, the recognition of the relationship between low-grade MLS and *Helicobacter pylori* (*H. pylori*) infection has brought about extensive changes in their management. The eradication of *H. pylori* infections offered a promising and fascinating therapeutic option as an organ-preserving strategy, especially in cases of localized superficial low-grade MLS associated with *H. pylori* infection. However, in a small percentage of low-grade MLS, with no evidence of *H. pylori*, and in some cases were it is the response to *H. pylori*

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eradication can often be incomplete, and in these cases gastric resection or radiotherapy should be considered.<sup>3</sup>

Although the sensitivity of mucosa-associated lymphoid tissue (MALT) lymphomas to radiation has been known in various sites around the body, radiotherapy has seldom been used in the treatment of low-grade MLS. However, the advances in our comprehensive understanding of the nature of low-grade MLS, and with moves toward non-invasive staging procedures, interest in radiotherapy for gastric preservation has been renewed. In 1997, we reported a case of a low-grade MLS successfully treated with radiotherapy alone, and there have been several reports emphasizing the role of radiotherapy in stomach-conserving treatment for low-grade MLS.<sup>4,7</sup>

It remains to be clarified if operative, or radiation treatment strategies, should be favored in cases where no *H. pylori* exists or where its eradication has not improved the condition of the MLS. In this study, we assessed the outcome of low-grade MLS treated with low-dose involved field radiotherapy, to investigate whether this treatment approach can be applied prior to surgery in cases where *H. pylori* eradication has failed or been irrelevant.

## MATERIALS AND METHODS

### Patients

Between Jan 1995 and May 2001, 6 patients with low-grade MLS were treated with primary

radiotherapy. The patient's ages ranged from 34 to 75 with a median age of 47.5 years, and a male to female ratio of 2:1. All patients were pathologically conformed as low-grade MLS. The initial staging procedures included a complete physical examination, chest PA, abdomino-pelvic CT and EUS. A bone marrow biopsy was performed in 2 patients. The new staging, in accordance with the guidelines of the 1994 consensus conference, was IE in all patients.<sup>8</sup> In one patient, the depth of invasion was beyond the submucosa, and another had a deep ulcerative lesion. The indication for radiotherapy was a failure to gain complete remission after *H. pylori* eradication, which occurred in 4 patients, with no evidence of *H. pylori* infection in 1, and a relapse at the remnant stomach 2 years after the previous partial gastrectomy in the other (Table 1).

### Radiotherapy

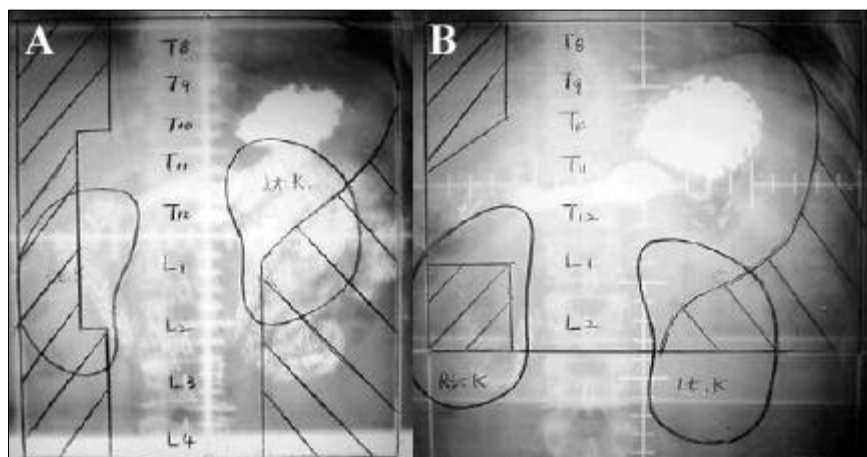
The target volume comprised the stomach and the draining perigastric lymph node groups, with a 2-cm of surrounding margin (Fig. 1). The simulation was performed in the supine position, following fasting; an oral barium mixture was administered to outline the stomach. We confirmed the reproducibility of the empty gastric size, shape and position, in a simulation room, on the first day of treatment. In one patient, a CT simulation, as well as a conventional simulation was performed to analyze the dose-volume histogram (DVH) of the surrounding normal tissues (Fig. 2).

The patients were treated in the early morning,

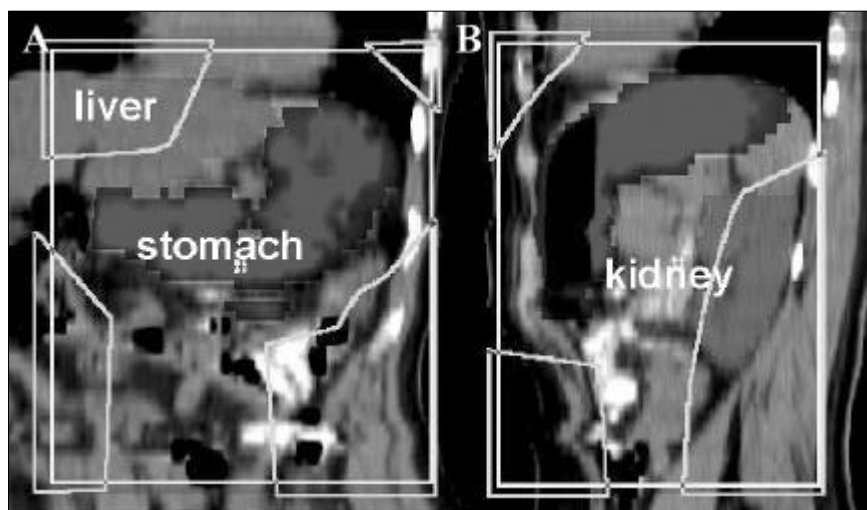
**Table 1.** Patients Characteristics

Case	Age	Gender	Stage	Depth of invasion	Previous treatment	Dose (Gy)	Response	FU* period	FU status
1	47	F	IE	Superficial	No	30.6	CR <sup>§</sup>	65 Months	NED <sup>¶</sup>
2	48	M	IE	Superficial	<i>H. pylori</i> <sup>†</sup> eradication	30	CR	21 Months	NED
3	34	F	IE	Superficial	<i>H. pylori</i> eradication	30.6	CR	8 Months	NED
4	75	F	IE	Beyond submucosa	<i>H. pylori</i> eradication	39	CR	6 Months	NED
5	37	F	IE	Ulcerative lesion	<i>H. pylori</i> eradication	36	CR	5 Months	NED
6	55	M	IE	Superficial	RSTG <sup>‡</sup>	30.6	CR	16 Months	NED

\*FU, Follow-up; <sup>†</sup>*H. pylori*, *Helicobacter pylori*; <sup>‡</sup>RSTG, Radical subtotal gastrectomy; <sup>§</sup>CR, Complete remission; <sup>¶</sup>NED, No evidence of disease.



**Fig. 1.** Radiation field in conventional simulation. The target volume comprised of the stomach and draining lymph node groups with a 2 cm surrounding margin. The lower margin was selected between (A) the L4-5 junction and (B) the L2-3 junction.



**Fig. 2.** Radiation field in the virtual simulation using a CT simulator. The radiation portal consisted of a combination of (A) the anterior-posterior direction and (B) the lateral direction.

on an empty stomach. Verification of the contour and position of the stomach on portal film was carried out weekly. Metoclopramide was prescribed at a dose of 10-mg, three times per day, to facilitate the emptying of the stomach, as well as to reduce the symptom of nausea. The median radiation dose was 30.6 Gy (range; 30-39 Gy) in daily fractions of 1.5-1.8 Gy. A total dose of 39 Gy of radiation was given to one patient (case 4), whose tumor had extended beyond the submucosa, and 36 Gy of radiation was delivered to another patient (case 5), with an ulcerative lesion.

#### Response evaluation

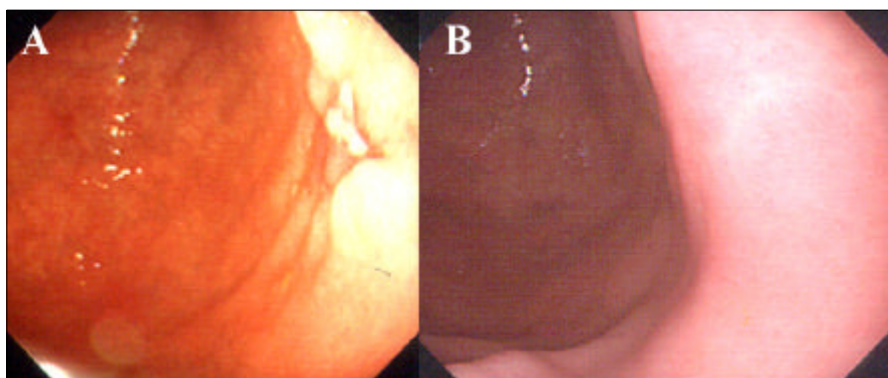
The endoscopic esophago-gastro-duodenoscopy, with biopsy tissue examination, was per-

formed 4 weeks after the completion of radiotherapy, and every 6 months thereafter. Blood work, including complete blood cells count and routine chemistry, were performed biannually for the evaluation of renal and hepatic toxicities.

## RESULTS

### Tumor response

The responses to treatment were assessable in all patients, and the treatment results are presented (Table 1). A complete response was obtained in all the patients, including the one with the submucosal infiltration (case 4) and the other with the deep ulcerative lesion (case 5) (Fig. 3). All



**Fig. 3.** Endoscopic response of a mucosa-associated lymphoid tissue lymphoma of the stomach. Pre-treatment endoscopic finding showing (A) an ulcerative lesion coated with whitish exudates surrounded by reddish mucosa. After 30 Gy of radiation therapy, there is (B) white scarring at the posterior wall.

patients have been followed-up, with no evidence of the disease. No patient suffered a relapse upto the time of the evaluation for this publication. The median follow-up period was 12 months.

### Toxicity

All patients tolerated the treatment well and completed the treatment course with no significant acute toxicity. Some patients experienced mild nausea, but this subsided with the use of anti-emetic medications. There were no perforations or hemorrhaging of the stomach, no renal or hepatic toxicities, and no development of secondary malignancies.

### DISCUSSION

As low-grade MLS have a tendency to be localized in the stomach, and rarely spread beyond regional lymph nodes, the treatment of choice has previously been a total or subtotal gastrectomy. Surgery can effectively control lymphomas with rare incidences of recurrence, however, morbidity following gastrectomies are troublesome, and can decrease a patient's quality of life.<sup>9</sup> In the last decade, with the accumulated knowledge on the pathogenesis of low-grade MLS, and their relationship with *H. pylori* infections, the policy for their treatment has been changing.<sup>10,11</sup> Superficially infiltrating lesions of *H. pylori* infection can be successfully treated with *H. pylori* eradication. However, a total gastrectomy is still a common practice, in our country, for the treatment of low-grade MLS without *H. pylori*

infection, in cases resistant to antibiotics therapy, or for more advanced deep infiltrating or ulcerating tumors.

The incidences of MALT lymphomas in Korea are high, comprising 6.5 - 17.3% of all non-Hodgkin's lymphomas, and more than half of these involve the stomach. In our hospital, of the 112 primary gastric lymphoma patients who received a gastrectomy in the last 10 years, 51 (46%) had a low-grade MALT type. Possible causes for the rising incidences would be from an increase of *H. pylori* infections, a higher diagnostic rate due to endoscopic evaluation, and the inclusion of MALT lymphomas in the newly developed REAL classification.<sup>9</sup> Many newly diagnosed gastric lymphomas were, at an early stage, low-grade lesions. Therefore, total gastrectomy is too radical for this indolent early stage disease.

As low-grade MALT lymphomas are very sensitive to radiation, and respond well to low-dose radiation, radiotherapy is often used in order to preserve the stomach. A recent series from the Memorial Sloan-Kettering Cancer Center has reported a 100% complete response rate, with radiation alone, in 17 consecutive patients following a median dose of 30 Gy.<sup>5</sup> All patients were in remission at a median follow-up duration of 27 months (range: 11 - 68 months). Another study from Japan, reported that the lesions, which showed enlargement of regional lymph nodes, and diffuse thickening of the second and third mural layers on the EUS, were treated successfully with radiotherapy.<sup>6</sup> In the current study, a complete response was obtained in all patients, including a patient with a large tumor mass (case

4), and another with a deep ulcerative lesion (case 5), following low-dose involved field radiotherapy.

The main argument against irradiation of gastric lymphomas has been the risk of perforation and bleeding.<sup>1</sup> Bleeding or perforation can occur in the first few days of chemotherapy, or radiotherapy, due to rapid tumorlysis. However, from the literature, the actual risk appeared to be minimal and often developed in the more advanced cases of MLS with large bulky masses. In a collective review, the incidences of gastric perforation or hemorrhage in non-surgically treated localized gastric lymphomas were only 3.5%.<sup>12</sup> In our opinion; the incidences might be much lower if the assessment were limited to patients with low-grade MLS. In fact, the risk might be negligible, especially in patients with superficially infiltrating lesions.

The other argument against irradiation is the potential for renal toxicity.<sup>1</sup> Only the upper portion of the left kidney is included in the radiotherapy field, so the risk of symptomatic renal dysfunction is rare.<sup>13</sup> Radiation in a fasting state, as in our treatment protocol allowed, a substantial reduction in the treatment volume enables the kidney to escape from the high-dose region. The DVH analysis in our patient who underwent a CT simulation showed that more than 20 Gy of radiation is delivered to 15% and 30% of the right and left kidney, respectively (Fig. 4).

Although it has been argued there is a pos-

sibility of the development of a secondary adenocarcinoma after irradiation, it was considered that the patients with low-grade MLS tend to be at an increased risk due to a common pathogenesis of a gastric lymphoma or gastric adenocarcinoma, rather than the from the effect of the radiation.<sup>1</sup> In our series, all the patients were followed-up, and had no evidence of disease, or developed any complications.

There are several issues that require further clarification. Firstly, a clear-cut definition is required to identify the time when *H. pylori* eradication treatment has failed. Considering the indolent nature of low-grade MLS, room exists for controversy in the interval needed to determine the refractoriness to antibiotic *H. pylori* eradication; but further investigations are required on this subject. Secondly, the exact indication for surgical resection, rather than stomach-conserving treatment, should also be determined. A total gastrectomy is currently recommended for tumors that infiltrate beyond the submucosa or ulcerating lesion. However, from the treatment results in our patients, radiotherapy can be applied carefully for the more advanced tumors, but can still be localized to the stomach. In contrast to surgical treatment of the more advanced disease, the main drawback of radiotherapy is an inability to rule out the hidden high-grade components that require systemic management with chemotherapy. We need to know more about the clinico-pathological behavior of MALT lymphomas of the stomach. It is encouraging that the patterns of

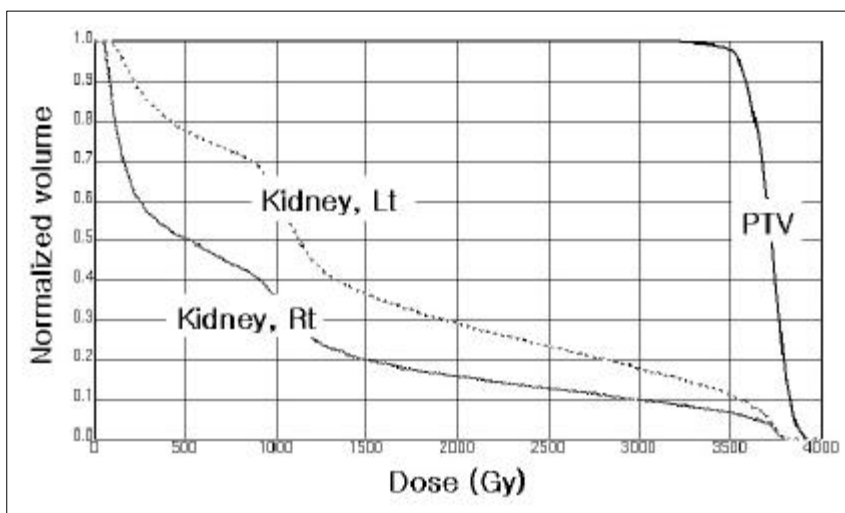


Fig. 4. The dose-volume histogram of the patient who underwent the computed tomography (CT) simulation.

relapse after conservative treatment have a tendency to be localized.<sup>9</sup> Surgical resection can be reserved for salvage treatment of radiotherapy failure or for the situation of bleeding or hemorrhage after radiotherapy. Thirdly, the proper extent of radiation volume needs to be determined to find if the low paraaortic lymph node area, below the level of renal hilum, should be included, or whether whole abdominal irradiation should be performed. Our policy is to treat the stomach and perigastric lymph nodes only. In our unpublished surgical series, lymph nodes were involved in 12 out of 51 cases of low-grade MLS, and only 2 of these cases had involvement beyond the radiation portal utilized in our study. Although these findings support the radiation volume used in our study; it needs to be defined further using a larger number of patients and long-term follow-up.

In conclusion, radiotherapy should be considered as the preferred treatment method for low-grade MLS, in patients with no evidence of *H. pylori* infection, or who do not respond to antibiotic therapy, due to the significant advantages of gastric preservation and the low morbidity.

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