Recurrence patterns of mucose-associated lymphoid tissue lymphoma after definitive radiation treatment: A single center experience

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Objectives: To evaluate the treatment outcomes in non-gastric and non-nodal mucose-associated lymphoid tissue (MALT) lymphoma patients treated by definitive radiation therapy (RT).

Methods: A total of 134 patients were analyzed. The RT dose was 30.6 or 36 Gy.

Results: The median follow-up duration for all patients was 51.1 months (range, 3.0–132.4 months). Among the 88 orbital MALT lymphoma patients, 12 had disease recurrence. There were 23 head and neck tumor patients. Two patients experienced relapse, all at out-of-field locations. Gastrointestinal MALT lymphoma was diagnosed in 13 patients, and three showed local (n = 1), distant (n = 1), or local/distant (n = 1) relapse.

Conclusion: RT alone is highly effective in achieving local control and long-term survival in localized MALT lymphoma. In orbital MALT, excellent local control is achieved, and relapse is predominantly observed in the contralateral eye. Other head and neck lymphomas are also well controlled.

Keywords: MALT, Radiotherapy, Recurrences, Lymphoma

Introduction

Mucose-associated lymphoid tissue (MALT) consists of small concentrations of lymphoid tissue found in certain epithelia, in particular the naso- and oropharynx, gastrointestinal tract, and lung. MALT is characterized by reactive follicles with germinal centers and prominent marginal zones, as well as numerous plasma cells and is thought to play a role in mucosal immunity. Lymphoma arising from MALT was first described in 1983 by Isaacson and Wright,¹ was later recognized as a subtype of marginal zone B-lymphomas in the revised European-American lymphoma (REAL) classification,² and is now considered a separate entity in the World Health Organization (WHO) classification.³ Gastric MALT lymphoma is the most common subtype of MALT lymphoma.⁴ Several etiologic factors for MALT including infectious microorganisms have been identified,⁵-⁷ and Helicobacter pylori (H. pylori) appears to be a particularly important antigenic stimulus for promoting and sustaining gastric MALT lymphoma.⁴,⁸-¹¹

As MALT lymphoma is a radiosensitive disease, studies have demonstrated that involved-field, modest-dose radiation therapy (RT) may be effective for these patients.¹²-¹⁴ However, no consensus has been established on the RT field and dose, as there have been no prospective trials except for gastric disease.¹² Therefore, an analysis of the pattern of recurrence depending on the primary site is needed. To the best of our knowledge, few studies have analyzed the outcomes after definitive RT for extragastrointestinal MALT lymphoma in a large number of patients.¹⁴,¹⁵ Here, we report our retrospective analysis on a large number of extragastrointestinal and non-nodal MALT lymphoma patients who were treated with involved-field RT with long-term serial follow-up.

Materials and methods

We reviewed the charts of 177 consecutive patients who had biopsy-proven extranodal MALT lymphoma between 1999 and 2013 at our hospital. Patients who had a transformed lymphoma component at diagnosis were excluded. We concluded that gastric MALT lymphoma...
patients because most were treated with RT with the aim of salvage after a failure of *H. pylori* eradication. To report our experience with the use of definitive RT for localized MALT lymphoma, only stage I and II patients presenting with disease infiltration of extra- lymphatic organs were included. A total of 134 patients were thus analyzed with a median age of 49 years and a male/female ratio of 1:1.2. Patient characteristics are detailed in Table 1. Staging assessments included complete blood counts; lactate dehydrogenase (in 91% of patients) levels; CT scans of the neck, chest, abdomen, and pelvis; bone marrow biopsy (in 92% of patients); and PET-CT (in 86% of patients). The Ki-67 proliferation index was measured in 79% of patients. For orbital adnexal MALT lymphoma patients, routine *Chlamydia psittaci* examination has been performed since 2009.

### Treatment

RT was delivered as a first curative treatment in all 134 patients. In some cases, combined chemotherapy was used at the discretion of the treating physician, usually due to bulky tumor or tumor aggressiveness. No cases were treated with chemotherapy concurrently with RT but chemotherapy was given before RT (*n* = 3) or after completion of RT (*n* = 1) in some patients. The detailed RT doses are described in Table 2. The most commonly prescribed doses were 30.6 and 36 Gy regardless of the anatomical site. The target field was individualized but generally included the whole extranodal organ (or whole intestinal segment) in which the tumor arose. If a regional lymph node was involved (stage IIE), the lymphatic drainage area was also included. For orbital lesions, electron beams were used most frequently as a single anterior field, with lens shielding. Intensity-modulated RT was used after 2013 in cases of posterior orbital mass-forming lesions. Two to six months after completing RT, the tumor response was evaluated in each patient by physical examination, CT or MRI, or endoscopy.

### Statistical analysis

The endpoints of our present study were overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), and local RFS (LRFS). Time was calculated from the date of RT commencement to the event. For OS, death from any cause was considered as the event. For RFS, time to first recurrence was considered, whereas for DFS, both time to first failure or death were considered as events. Survival rates were analyzed using the Kaplan–Meier method. The survival distribution was compared between the two groups using the log-rank test. Multivariate analysis was performed using Cox proportional hazard model. All statistical analyses were performed using SPSS ver. 21 software (IBM, Armonk, NY).

### Results

#### Overall treatment outcome

The tumor characteristics of our study patients are presented in Table I. The median follow-up duration for the whole patient cohort was 51.1 months (range, 3.0–132.4 months). A total of 71 patients (53%) had >50 months of follow-up duration. Complete response (CR/CRu) was observed in 129 (97%) of the 134 patients. A total of 18 patients had recurrences at last follow-up. The pattern of recurrence was local in three (17%), contralateral paired organ in seven (35%), distant in four (20%), both local and contralateral paired organ in one (5%), local and distant in two (11%), and contralateral paired organ and distant in one patient (5%) (Fig. 1). Overall, there was one death reported at last follow-up due to an unrelated cause (esophageal cancer). There were no deaths.
related to MALT lymphoma recurrence or treatment complication. The 5-year OS, RFS, DFS, and LRFS rates were 100, 82, 82, and 95%, respectively. The corresponding 10-year estimates were 97, 68, 66, and 92%, respectively. Survival plots are illustrated in Fig. 2. The majority of recurrences (15 of 20 patients, 75%) occurred within 5 years. The pattern of recurrence and salvage treatments are reported by treatment site below.

**Figure 1** The pattern of recurrence for total patients

**Treatment outcome by sites**

**Orbit**

Among the 88 orbital lesions, 59 were located in the conjunctiva, 17 in the retrobulbar area, six in the lacrimal gland, five in the eyelids, and one in the eyeball. Bilateral orbital involvement was diagnosed in 10 patients. Of the 38 patients examined, four were *Chlamydia psittaci*-positive, two of whom were treated with doxycycline for 2 weeks, and subsequent RT was performed on the persistent tumors. First response evaluation was performed at 2–6 months. At that time, CR/CRu was diagnosed in 46 (52%), and partial response (PR) and stable disease (SD) was diagnosed in 36 (41%) and six (7%) patients, respectively. However, CR/CRu was achieved in 86 (98%) patients sometime during the follow-up period. The remaining two patients showed persistent disease at biopsy and were treated with chemotherapy and doxycycline, respectively; both were successfully cured. Among the 86 patients who obtained CR/CRu, 12 had disease recurrence at a total of 14 sites. The sites of recurrence were local (n = 2), opposite eye (n = 5), distant (n = 3), local/opposite eye (n = 1),

**Figure 2** Overall survival (A); disease-free survival (B); recurrence-free survival (C); and local recurrence-free survival (D) for total patients
and opposite eye/distant (n = 1). Among the two patients with local relapses, one underwent biopsy and neither showed disease transformation. While they did relapse, both patients remained under close observation for 60 and 68 months, respectively. The local control rates at 5 and 10 years were 94% and 89%, respectively. Recurrence in the opposite eye was diagnosed in five patients, with a median recurrence-free duration of 47.9 months (range, 18.0–55.1 months). These five patients were treated with RT (n = 3) or observation (n = 2). There were three patients with distant failures, resulting in a projected 5- and 10-year distant failure-free survival rate of 97 and 86%, respectively. One patient had relapse at the cervical/pelvic lymph node, and a biopsy specimen indicated disease transformation to follicular lymphoma. At relapse, this patient was treated successfully with cyclophosphamide, vincristine, doxorubicine, and prednisone (CHOP) regimen and rituximab, and is now under observation with no evidence of disease. The other patient, who initially had extensive maxillary sinus and nasal cavity extension, was treated with induction chemotherapy and RT. After 81 months, she had relapsed at the intra-abdominal and mediastinal lymph nodes. She was treated with salvage chemotherapy with CHOP regimen and remained free of disease at 34 months. The remaining patient had relapse at the pelvic lymph node and is currently under observation. One patient relapsed at both the opposite eye and distant sites (perirenal mass and sacral spinal canal lesion). He was treated with salvage RT to the opposite eye and with salvage chemotherapy by cyclophosphamide, vincristine, and prednisone (CVP) regimen. After salvage treatment, he remained free of disease for 45 months. One patient with both local and opposite eye relapses is currently under follow-up without treatment. The 5 and 10-year RFS rates for orbital lesions were 80 and 68%, respectively. None of the patients with orbital MALT lymphoma died during follow-up.

**Head and neck**

Excluding the orbit, there were 23 head and neck MALT lymphoma patients treated with RT. Sites included the salivary gland (n = 6), Waldeyer’s ring (n = 5), nasal cavity/nasolacrimal duct (n = 3), and thyroid (n = 2). Multiple head and neck organ involvement was diagnosed in seven patients. The Ann Arbor stage was IE in 15 patients, and IIE in eight patients. Twenty-one cases were treated with primary RT alone, one with induction chemotherapy plus RT, and one with surgical excision plus adjuvant RT. CR was achieved in all 23 patients. Two of the 23 patients experienced relapse. Overall, RFS was 93% at 5 years and 77% at 10 years. All salivary gland tumors were located in the parotid gland (n = 6). Four patients had stage IE disease, and two patients had stage IIE disease. Treatment was RT alone in five patients, and combined RT after surgery in one patient. Among patients with salivary gland tumors, there were no cases of disease recurrence or death for a median follow-up duration of 44.4 months (range, 37.4–107.0 months).

There were five Waldeyer’s ring MALT lymphomas in our current study cohort, which were located in the nasopharynx in two patients and in the palatine tonsil in three patients. One patient had stage IIE disease. Four patients were treated with RT alone, and one with induction chemotherapy (CVP regimen) followed by RT. For Waldeyer’s ring MALT lymphoma patients, there were no cases of disease recurrence or death during a median follow-up of 58.7 months (range, 5.4–88.5 months). There were three cases of nasal cavity/nasolacrimal duct MALT lymphoma, all of which were stage IE and treated by definitive RT alone. One patient with nasolacrimal duct lymphoma had recurrence at the ipsilateral conjunctiva, contralateral nasolacrimal duct (both out-of-RT field), and in the bone marrow after 85 months; he was treated by salvage RT. At presentation, seven patients had multiple head and neck mucosal organ involvements, and all of these patients had non-contiguous mucosal lesions. The involved sites were orbit + nasopharynx (n = 4), orbit + parotid gland (n = 2), and nasopharynx + trachea (n = 1). Among the multi-mucosal lymphoma patients, three had cervical node involvement and were treated by primary RT alone; one of these three patients relapsed. Initially, this patient had left eyelid and right parotid gland disease and after 50 months of treatment he relapsed at the untreated left eye. Doxycycline was used as a salvage treatment in this individual.

**Gastrointestine**

Gastrointestinal MALT lymphomas other than gastric MALT lymphomas were diagnosed in 13 patients with the following involved sites: esophagus in one, duodenum in two, ileum in four, colon in two, and rectum in four patients. All of these patients were treated using primary RT alone, and CR was achieved in nine and PR in four patients. Three patients experienced relapse at local (rectum), distant (esophagus), and both local and distant sites (duodenum and lung). One patient died of esophageal cancer (out-of radiation field). Overall, local control rate and RFS rate at 5 years was 75 and 60%, respectively.

**Prognostic factors**

The sites of recurrences in our study patients are detailed in Table 3. For prognostic factor analysis, the following variables were examined; age (≥50 years vs. <50 years), sex, stage (IE vs. IIE), radiation...
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A brain MALT lymphoma patient relapsed at the opposite hemisphere, which was outside the radiation field.

Abbreviations:
- L: Lung and airway
- S: Salivary glands
- N: Nasal cavity/nasolacrimal duct
- T: Thyroid
- M: Multiple mucosal organs
- I: Gastrointestinal tracts
- L: Lung and airway
- O: Others

Table 3 Relapse patterns in the MALT lymphoma study patients after definitive radiation treatment

| Site                              | No. of relapse patients (%) | L | C | D | L&C | L&D | C&D |
|-----------------------------------|-------------------------------|---|---|---|-----|-----|-----|
| Orbital adnexa                    | 16/86 (18)                   | 6 | 5 | 3 | 1   | 1   | –   |
| Salivary glands                   | 0/6 (0)                      |   |   |   |     |     |     |
| Waldeyer’s ring                   | 0/5 (0)                      |   |   |   | 1   |     |     |
| Nasal cavity/nasolacrimal duct    | 1/3 (33)                     |   |   |   |     |     |     |
| Thyroid                           | 0/2 (0)                      |   |   |   |     |     |     |
| Multiple mucosal organs           | 1/7 (14)                     |   | 1 |   |     |     |     |
| Gastrointestinal tracts           | 3/13 (23)                    |   | 1 | 1 | 1   |     |     |
| Lung and airway                   | 0/2 (0)                      |   |   |   |     |     |     |
| Others                            | 1/8 (13)                     | 1 |   |   |     |     |     |

Abbreviations: L = local; C = contralateral paired organ; D = distant.

*A brain MALT lymphoma patient relapsed at the opposite hemisphere, which was outside the radiation field.

dose (≥35 Gy vs. <35 Gy), site, LDH level, tumor bulk, and FDG uptake. None of these factors predicted relapse. However, given the small number of events, these results should be interpreted with caution.

Discussion
We report our experience of the outcomes of RT in stage I and II MALT lymphoma patients, emphasizing excellent local control and OS. RT is used as first line treatment for MALT lymphoma, except for H. pylori-positive gastric MALT lymphoma. This is because MALT lymphoma is less responsive to standard chemotherapy than other aggressive lymphomas and is radiosensitive. Over the last decades, a series of MALT lymphomas treated with RT have been reported, and radiosensitivity of this disease is also well established. However, to date, there are few well-documented reports of the efficacy of RT and patterns of relapse according to treatment site. National Comprehensive Cancer Network (NCCN) guideline suggests treatment option for the non-gastric MALT lymphoma. Involved site RT is recommended, but without site-specific RT prescription. There is only comment that lower dose can be used for eye involvement.16

Our current data showed that localized MALT lymphomas respond extremely well to moderate-dose RT. These findings demonstrated that RT-alone was highly effective in achieving local control and long-term survival. These favorable outcomes are consistent with the result of previous studies in large cohorts. Goda et al. treated 192 stage I and II MALT lymphoma patients with RT alone, and reported OS and RFS rates of 95% and 79%, respectively, at 5 years.14 In a Japanese prospective multicenter phase II trial, 37 extragastric MALT lymphoma patients were treated with RT and showed 3-year OS, progression-free survival, and local control rates of 100%, 92%, and 97%, respectively.15 Among our present study patients, isolated local recurrence was rare. A pattern of preferential recurrence in contralateral paired organs or in distant mucosal sites rather than local recurrence after definitive RT has also been documented by other investigators. Historically, the local control rate is consistently reported to be >95%, whereas distant recurrence occurs in 8–23% of patients, with a contralateral paired organ recurrence rate of about 5%.14,15,18,19 Recently, Teckie et al. analyzed a large number of MALT lymphoma patients treated by RT. The high OS (92%), RFS (74%) and local control rates were similar to that of our study.20 In the contralateral paired organ or other mucose-associated sites, the majority of relapsed MALT lymphomas show a localized, indolent pattern. We observed continued survival of all patients in our present cohort who experienced relapse. The median follow-up duration from first relapse was 25.2 months in our series, and additional observations will determine if these second remissions are maintained.

The local control rate for orbital MALT lymphoma was excellent in the present study patients. A favorable outcome has also been shown in previous reports. In a study from Harada et al., of moderate-dose RT, only one of 88 orbital MALT lymphoma patients developed local recurrence whereas contralateral orbital relapse and distant relapse were more frequently seen.21 Similarly, Goda et al. reported a 3% local recurrence rate in 71 orbital MALT lymphoma patients treated with RT.14 A total dose of approximately 30 Gy in a conventional fractionation seems to be the most commonly prescribed regimen for orbital MALT lymphoma, consistently reporting local control rates >95%.17,19,21–23 Considering the indolent disease characteristics, it is crucial to determine the ‘lowest effective dose’ for the treatment of orbital MALT lymphoma. MALT lymphoma is thought to be a bridge between chronic inflammatory status and aggressive lymphoma. Few studies have reported dose reduction, with a dose of 25 Gy reported to have excellent local control probability.14 Tran et al. also reported that 24–25 Gy RT provided 2- and 5-year local control rates of 100% and 92%, respectively.24 However, data on the maximum safe dose reduction for curative treatment of orbital MALT lymphoma are limited. Therefore, future clinical trials are
warranted to determine effective and safe dose reduction for patients with this disease. Similarly to previous studies, our current data showed that contralateral orbital relapse was the most common pattern of relapse. Considering the high local control rate and low probability of progression to systemic disease, contralateral orbital relapse is thought to be a second primary MALT lymphoma rather than recurrent disease. Thus, a second course of primary RT should be performed on the contralateral eye, rather than chemotherapy, despite relapse. Goda et al. have also stated that an isolated contralateral relapse can be successfully managed with another course of RT and often does not result in further disease relapse in other sites. However, further studies are warranted to confirm these findings.

In our current study, for patients with head and neck MALT lymphoma except in the orbit, the actual local control rate was 100%, as there were no cases of isolated in-field recurrence. This excellent local control rate may reflect a sufficient radiation target volume. For example, in our nasal cavity or nasolacrimal duct cases, both the nasal cavity and part of nasopharynx were included in the CTV. For parotid gland lesions, the preauricular lymphatic area with or without the jugular chain was included in the CTV. Only one patient in our study population with nasolacrimal duct disease received treatment to the ipsilateral nasal cavity only, and she developed recurrence at the contralateral nasal cavity with distant metastasis. A tendency towards multifocality in MALT lymphoma has been reported in several previous studies. In our present study, seven patients had synchronous multi-mucosal lesions, which were closely related anatomically: orbit + nasopharynx, orbit + parotid gland, and nasopharynx + trachea. Thus, in the treatment of head and neck MALT lymphomas at such areas as the nasal cavity, nasolacrimal duct, or Waldeyers’ ring, we suggest irradiation of the contralateral areas and of part of the adjacent mucosa.

Among the 13 gastrointestinal MALT lymphoma patients in our current series, three developed recurrences. Unlike those of other sites, gastrointestinal lesions seemed to have a tendency towards local failure. While the time to progression was not short, the possibility of mucosal spreading relapse cannot be excluded. In a study by Ha et al., of the 27 small bowel lymphoma patients who were treated with RT, three developed local recurrence. As most patients had diffuse-large B-cell lymphomas or follicular lymphomas in that report, differences in RT dose and field may have contributed to the more favorable outcome compared to our present study. In that earlier study, the RT field included the whole abdomen in 67% and the upper two-thirds of the abdomen in 19% of patients. The RT dose was 30 Gy plus a 10 Gy tumor boost. As primary rectal MALT lymphoma is extremely rare, there are few published case reports, and treatment modalities are diverse. Our present results suggest that a reduction of the RT field and dose for gastrointestinal MALT lymphoma should be considered with caution. However, due to the lack of clinical data, further studies are needed to confirm our conclusion.

Conclusions

RT alone is highly effective in achieving local control and long-term survival in localized MALT lymphoma patients. In orbital MALT, excellent local control can be achieved, and relapse is predominantly observed in the contralateral eye. Contralateral relapse is successfully managed with a second RT. Head and neck MALT lymphomas except those of the orbit are also well controlled by RT; possibly due to sufficient adjacent mucosa irradiation. Further investigation is warranted on the treatment of gastrointestinal disease, with a focus on the RT field and dose.

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