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# Radiation Therapy for gastric MALT lymphomas. A Retrospective Study

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***Abstract***

***Background and Purpose:*** *Although rare, gastric mucosa associated lymphoid tissue (MALT) lymphomas have an exceptionally high cure rate with Helicobacter pylori (H. pylori) eradication treatment. Nevertheless, there is a proportion of cases that show antibiotic resistance or larger tumor burden that require radiation therapy (RT). The purpose of this study is to describe our 10-year experience in treating gastric MALT lymphomas with RT and a review of pertinent literature.*

***Materials and Methods:*** *A retrospective study was carried out at the National Cancer Institute, Mexico from January of 2008 to December 2018. Patients included were diagnosed with gastric MALT lymphomas after endoscopic biopsy.*

***Results**: We found 7 patients treated with RT. Prior to RT all patients received chemotherapy and two of them failed to antibiotic eradication. Radiation therapy with four-field 3D-CRT technique included whole stomach as primary site. Average dose prescribed was 30 Gy ranging from 20-40 Gy. After RT, an overall survival (OS) at 5 and 10 years were 100% and 43% respectively. Relapse free survival (RFS) at 5 and 10 years were 86% and 57% respectively. Overall toxicity was sporadic, (gastrointestinal and hematologic) presenting mild to moderate severity and exceptional tolerance.*

***Conclusions**: Our experience achieved a great rate of cure with more than acceptable posttreatment toxicity. Radiation therapy is remarkably effective even after chemotherapy and H. pylori eradication failure.*

## Introduction

Extranodal lymphomas of the mucosa-associated lymphoid tissue (MALT) is a rare entity complying for 8% of all B cell Non-Hodgkin lymphomas (1,2,3). Specifically, gastric MALT lymphomas represent 5% of all gastric malignancies and around 50% of all gastric lymphomas (4,5,6). According to national data, they constitute less than 2.4% of all malignancies in Mexico (6).

Despite its low frequency and good treatment response, some gastric MALT lymphomas required complementary treatment. Usually they have an intrinsic potential for local control and overall survival with non-invasive therapies. After antibiotic treatment failure, radiation therapy is an excellent option for achieving great outcomes with mild to moderate post-treatment consequences (7,8,9,10,11,12). Efforts must not be undermined for treating this disease.

Here we present our 10-year experience in treating gastric MALT lymphomas with radiotherapy through an observational and retrospective analysis and a review of pertinent literature to evaluate overall survival, relapse free survival and shown toxicities.

## Materials & Methods

### Study Design

This was an observational retrospective study, developed at the National Cancer Institute in Mexico. All patients included in this study had gastric MALT lymphomas confirmed with pathology under endoscopic biopsy. They also had undergone radiation therapy to the local site with or without any type of prior treatment, whether it had been antibiotic, chemotherapy or a combination of both. These

patients were considered from January 2008 to December 2018. Patients excluded from the study were those with any kind of response (partial or complete) upon completion of antibiotic and/or chemotherapy treatment. Given that this study was retrospective and without any kind of clinical or comparative intervention it didn`t need approval by the bioethics committee of the National Cancer Institute.

**Data Collection and Outcomes**

Data collection was obtained from electronic clinical records and patients` charts (age, sex, Karnofsky Score, ECOG score, Helicobacter pylori infection, Lugano-Ann Arbor staging and IPI criteria. Analysis of radiation therapy treatment was taken from the ECLIPSE (Varian Medical Systems, Palo Alto, CA) planning system.

**Statistical Methods**

All statistics were analyzed using IBM SPSS Statistics 25.0. Our observational study analyzed two primary outcomes: Overall Survival (OS) was defined as the time patients remained alive since the start of radiotherapy through the length of the study; and Relapse Free Survival (RFS) defined as the time patients were free of any kind of relapse, local or at distance. Both OS and RFS were calculated with the Kaplan-Meier method. A confidence interval of 95% was used for conclusions. As secondary outcomes we evaluated patient toxicity. We also recorded pertinent restriction doses. The study follow-up was 87 months.

**Radiation Therapy Treatment**

All patients were planned and treated in the supine position with arms raised towards the head. They were prepared with an empty stomach for at least 2 hours before the simulation and every given fraction. Image acquisition was performed with computed tomography with a minimum of 5 mm per slice. According to the International Commission on Radiation Units and Measures (ICRU 50), nomenclature, gross, clinical, and planning target volumes were considered.

Several linear accelerators were used for treating our patients, all with 6 MV of energy and with 3D CRT four-field technique. Conventional fractionation (between 1.8 and 2 Gy per fraction) was the standard. Patients were scheduled to receive five fractions per week (from Monday to Friday).

The organs at risk restrictions were evaluated with the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) initiative (13,14,15). Final dose and conformality (16) were reviewed in the ECLIPSE planning system.

### Toxicity

Upon every follow-up consults, potential toxicity symptoms were asked to the patient like dyspepsia or acid reflux. Renal, hepatic injuries, as bone marrow depletion was also taken into account (17). Every toxicity was evaluated with the Radiation Therapy Oncology Group (RTOG) criteria (18).

## Results

### Patient characteristics

Between January of 2008 to December of 2018, 7 patients diagnosed with gastric MALT lymphoma were found to be treated with radiation therapy, mostly after chemotherapy or antibiotic failure. Just one female patient (14.28%) was included in our group. This finding differs from normal gender distribution in gastric MALT lymphomas. The median age of diagnosis was 55 years old, with an age span between 26 and 83 years old. About 57% of patients were less than 60 years old with a favorable performance status (Karnofsky from 80 to 90%, ECOG score from 0-1).

Clinical stage was classified with the Lugano modification of the Ann Arbor staging system (7,19). Early stages were the most common. The IIE stage represented more than a half (56.5%). Our patients had a good prognosis overall. More than half of them had a low or low-intermediate International Prognostic Index (IPI) score (20).

Detection of H. pylori was only found in 28.57% of all patients. This concurs with the indolent evolution in which this disease behaves after antibiotic resistance is demonstrated (21). All characteristics are described in table 1.

| Characteristics | Total (%) |
|---|---|
| Gender | |
| Male | 6 (85%) |
| Female | 1 (15%) |
| Age | |
| Median (Range) | 55 years (26 - 83 years) |
| ≤ 60 years | 4 (57%) |
| > 60 years | 3 (43%) |
| Karnofsky Score | |
| 90 | 2 (28.5%) |
| 80 | 5 (71.5%) |
| ≤ 70 | 0 |
| ECOG score | |

| | |
|---|---|
| 0 | 4 (57%) |
| 1 | 2 (28.5%) |
| 2 | 1 (14.5%) |
| 3 or higher | 0 |
| *Helicobacter pylori* | |
| Positive | 2 (28.5%) |
| Negative | 5 (71.5%) |
| Lugano-Ann Arbor staging | |
| $I_E$ | 1 (14.5%) |
| $II_E$ | 4 (56.5%) |
| IV | 1 (14.5%) |
| $IV_b$ | 1 (14.5%) |
| IPI criteria | |
| Low (0-1) | 4 (56.5%) |
| Low-Intermediate (2-3) | 1 (14.5%) |
| High-Intermediate (4-5) | 2 (29%) |
| High (≥ 6) | 0 |

**Table 1.** Patient baseline characteristics.

**Treatment characteristics and follow-up**

The majority of patients (85.71%) received chemotherapy prior to radiotherapy. Regimes were heterogeneous (CHOP, COP, R-CHOP, and ICE). Antibiotic treatment for H. pylori eradication was given to 28.57% of patients. Only one patient received both treatments before radiotherapy.

Consolidation radiotherapy was the most common indication related to the treatment. Only one patient had local bulky disease that needed radiotherapy, and another one had disease progression. All patients received radiotherapy only to the primary site (22,23,24,25,26,27).

The total RT dose was diverse. Prescribed doses ranged from 20 Gy and 40 Gy, choosing a lesser dose for a 26-year-old patient with a low IPI score. On the other hand, the total dose of 40 Gy was prescribed when bulky disease was found. The median dose among the group was 30 Gy. Figure 1 describes the doses employed and time to finish radiation therapy.

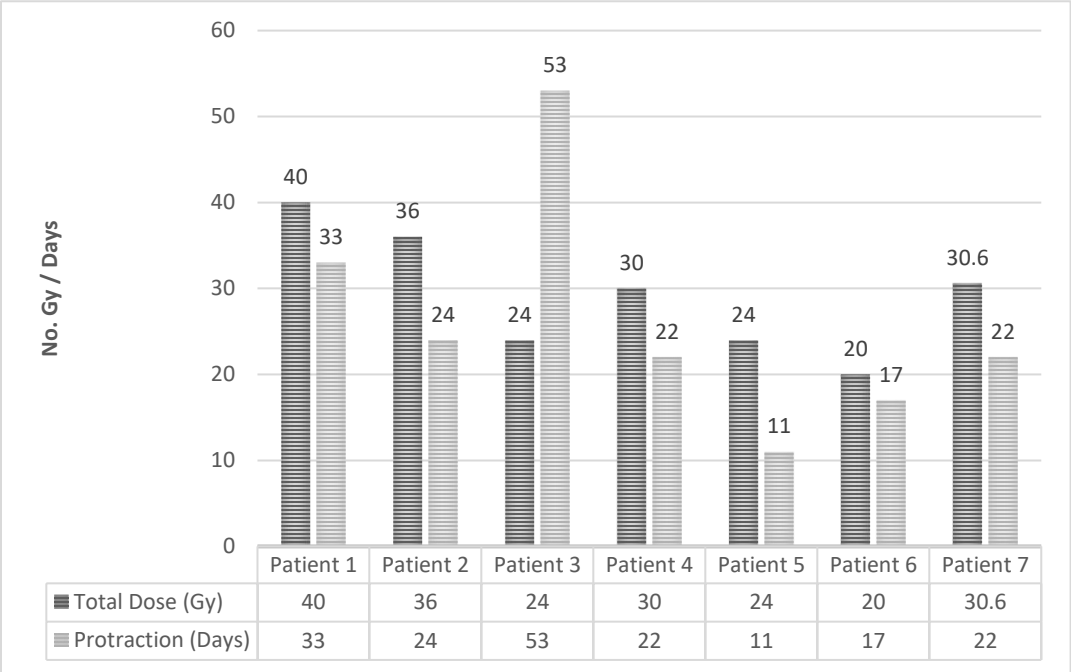


**Figure 1**. Total dose / Protraction

The maximum time of follow-up was 87 months and a median of 30 months. Average follow up time was reduced due to one patient who achieved complete response. Median treatment protraction was 22 days, spanning from 11 to 53 days. The greater protraction was again due to the same patient with poor adherence to follow-up.

We evaluated dose restrictions with the QUANTEC initiative for the relevant organs at risk. Kidney restrictions were analyzed individually and with a combined volume. Mean doses considered for preventing renal injury in less than 5% and 50% of the population were less than 15 Gy and less than 28 Gy, respectively. For the combined volume these restrictions were evaluated: V12 <55%, V20 < 32%, V23 <30% and V28 <20%. For preventing hepatic injury in 5% and 50% of the patients, a mean dose of 30 Gy and 42 Gy were chosen, respectively. Spinal cord restrictions were < 50 Gy, < 60 Gy and < 69 Gy to prevent myelopathy in less than 0.2%, 6% and 50% of all patients respectively. Heart and esophagus doses were minuscule and omitted for analysis. In table 3, we present an example of achieved restrictions.

| Organs at risk | Dose restrictions | Clinical outcome | Actual dose received | |
|---|---|---|---|---|
| **Kidney** | Mean dose <15 Gy | Renal injury in less than 5% of treated patients | Right Kidney 5.4 Gy | Left Kidney 6.9 Gy |
| | Mean dose < 28 Gy | Renal injury in less than 50% of treated patients | Right Kidney (N/A) | Left Kidney (N/A) |
| **Kidneys (Combined volume)** | V12 <55% | Renal injury in less than 5% of treated patients | 15.17% | |
| | V20 <32% | | 2.68% | |
| | V23 <30% | | N/A | |
| | V28 <20% | | N/A | |
| **Liver** | Mean Dose <30 Gy | Radio-induced hepatic injury (Classic) in less than 5% of treated patients | 15.45 Gy | |
| | Mean Dose < 42 Gy | Radio-induced hepatic injury (Classic) in less than 50% of treated patients | N/A | |
| **Spinal cord** | Max Dose <50 Gy | Myelopathy in less than 0.2% of treated patients | 11.82 Gy | |
| | Max Dose <60 Gy | Myelopathy in less than 6% of treated patients | N/A | |
| | Max Dose <69 Gy | Myelopathy in less than 50% of treated patients | N/A | |

**Table 2**. Restriction dose analysis.

**Outcomes**

Outcomes were calculated with the Kaplan-Meier method and represented in figures 2 and 3. Overall survival (OS) was defined as the time patients remained alive since the start of radiotherapy through the length of the study. Percentages at 5 and 10 years obtained were 100% and 43% respectively (95% CI 0.95-0.58). Relapse free survival (RFS) was described as the time patients were free of any kind of relapse, local or at distance. Of all patients, RFS was found to be 86% at 5 years and 57% (95% CI 0.91-0.65) at ten years of follow up. Only one patient presented relapse and was found outside the disposition of radiation treatment fields. The patient's RFS was of 49 months.

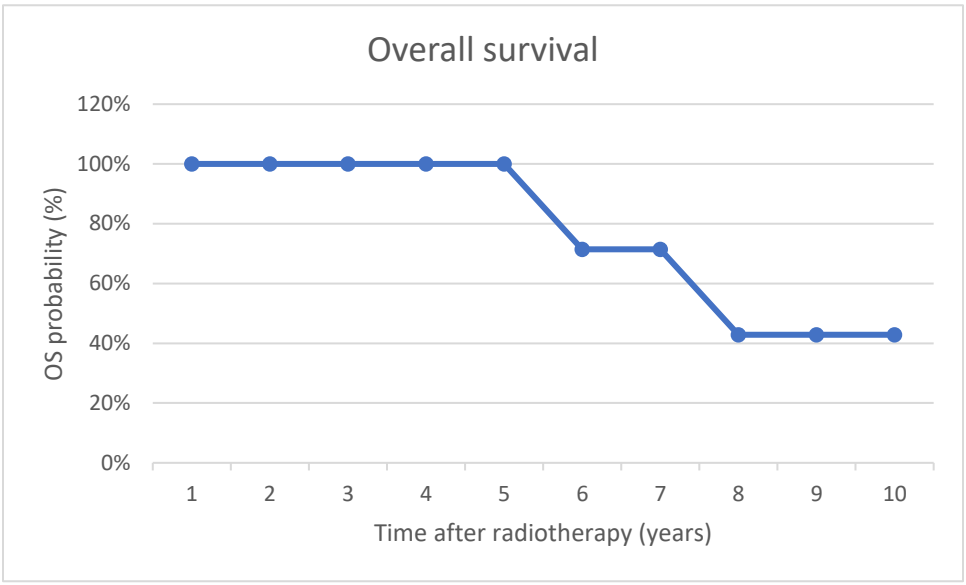


**Figure 2**. Kaplan-Meier method for Overall Survival.

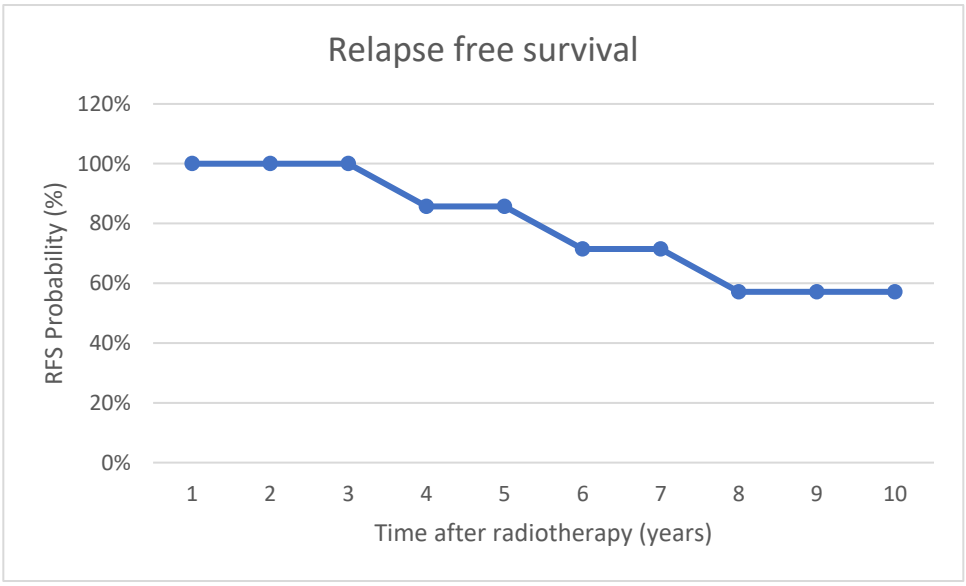


**Figure 3.** Kaplan-Meier method for Relapse Free Survival.

Complete response was observed in 57% of patients. Furthermore, 28.5% had partial response. There is growing evidence that defines the optimal time for evaluating response in gastric MALT lymphomas (28), although it is yet inconclusive. We established the best time to be from the start date of RT up to documentation of complete response. Our average time for CR was of 29 days and for any response of 30.3 days.

**Toxicity**

The summary of all patient toxicity is shown in table 3. Overall toxicity after radiation treatment was well tolerated. Despite the primary site and high variability in doses prescribed, the only relevant reports were mild gastroenterological and hematological toxicities. Nausea was noted in 42.8% of patients, vomit in 28.5%, and diarrhea in 14.5%. On the other hand, leukopenia was described in 42.8% and lymphopenia in 28.5 of all patients. The most severe finding, according to RTOG toxicity criteria, was for lymphopenia grade 3.

| | Severity | | |
|---|---|---|---|
| **Toxicity** | Grade 1 | Grade 2 | Grade 3 |
| **Gastrointestinal** | | | |
| Nausea | 1 | 2 | 0 |
| Vomiting | 0 | 2 | 0 |
| Diarrhea | 1 | 0 | 0 |
| **Hepatic** | | | |
| Hepatic test alterations | 0 | 0 | 0 |
| **Renal** | | | |
| Renal test alterations | 0 | 0 | 0 |
| **Hematological** | | | |
| Leukopenia | 2 | 1 | 0 |
| Lymphopenia | 0 | 0 | 2 |
| **Neurological** | | | |
| Pain or weakness | 0 | 0 | 0 |

**Table 3.** Toxicity analysis.

## Discussion

According to the national statistics (6), the male to female proportion (1:1) concurs with what is observed internationally. But the proportion of MALT lymphomas with need of RT greatly favors presentation for males. Only 28.5% of patients had H. pylori infection. This correlates with the poor control they had after eradication treatment. Having said that, we must not neglect the important proportion of the Mexican population with H. pylori infection (5). Another factor to acknowledge is that all of our patients were t (11;18) negative. Whether this is relevant to the behavior of the disease in our population remains unknown (29,30).

The cardinal symptom found was dyspepsia. None of the patients referred gastrointestinal bleeding or 'B' symptoms. At diagnosis, the majority of patients had a low risk. More than half (57%) had less than 60 years of age All patients presented a good performance status (KPS 80-90% and ECOG 1-2). Early clinical stages were also the most frequent in 71%. Clinical stage IIE was the most common. IPI was also low in 56.5% and low-intermediate in 14.5%.

Treatment before RT was heterogeneous. Of all patients, 85.7% of them received a diversity of chemotherapy regimens with poor tumor response. Only patients with H. pylori detection received antibiotics as first-line treatment (31). We consider these findings to be explained because a great proportion of patients were treated when Rituximab was unavailable in our country.

Radiation therapy indication was mostly for consolidation (85.7%). Age, tumor size, and tumor burden were considered for determining total doses. They ranged from 20 to 40 Gy, and the most common dose was 30 Gy. Average number of fractions was 14 ranging from 10 to 20. All patients received conventional fractionation. Overall, protraction was satisfactory, with an average of 26 days. It is noteworthy that the patient who showed the longest protraction was due to health complications not related to RT.

Through all ten years, we obtained remarkable OS and RFS. Relapse was found in only one patient. This patient was the same one who needed radiation therapy for bulky disease and even had the group's worst prognosis. This relapse presented outside of the RT fields. A 4-year RFS was achieved despite poor baseline prognosis.

After RT treatment toxicity was well tolerated. No renal, hepatic or neurologic injury was presented. Most common toxicities were gastrointestinal and hematologic, being mild and moderate. Nausea was found in 42.8% of patients. Vomit was presented in 28.5%. Of hematological toxicities, leukopenia was the most common in 42.8%, followed by lymphopenia in 29%.

The present study has certain limitations inherent to an observational, single-center investigation. Our limited sample size and patients lost during follow-up can be explained by the prevalence of the disease and the long distances some of our patients have to travel (around 520 miles / 10 hours) to receive any kind of treatment or attending for follow ups. Other important factors such as the available technology through the timespan (2D-CRT to 3D-CRT evolution), and a lack of homogeneity in treatment algorithms in the early years were not controlled for in the present study.

## Conclusion

Our findings over 10 years suggest that rather than multiple chemotherapy regimens, radiotherapy is the next best option after antibiotic failure, H. pylori naïve, or bulky disease. We found a OS at 5 and 10 years of 100% and 43% respectively and a RFS at 5 and 10 years of 86% and 57% respectively. At least 57% of all patients treated with radiotherapy had CR.

Toxicity was very well tolerated showing only mild gastrointestinal symptoms. The only moderate toxicity found was lymphopenia. All toxicities were well controlled without complications.

Although our data has its limitations it contributes to the evidence (39) that RT obtains a high rate of OS and CR even at low doses < 30 Gy given with 3D-CRT. Further larger scaled studies are needed to clarify the optimal dose, safety profile, and the efficacy of this technique with other modalities.

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