THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Radiation Therapy alone for stage 1 and 2 MALT (mucosa-associated lymphoid tissue) lymphoma
ID99-384

Core Protocol Information

Short Title	MALT
Study Chair:	Bouthaina Dabaja
Additional Contact:	Aileen Mapps Brittany D. Spinelli Victoria Cox
Additional Memo Recipients:	**Recipients List** **OPR Recipients** (for OPR use only) None **Study Staff Recipients** None
Department:	Radiation Oncology
Phone:	713-563-2300
Unit:	97
Study Manager:	Bouthaina Dabaja
Full Title:	Radiation Therapy alone for stage 1 and 2 MALT (mucosa-associated lymphoid tissue) lymphoma
Public Description:	n/a
Protocol Type:	Standard Protocol
Protocol Phase:	N/A
Version Status:	Activated -- Closed to new patient entry as of 08/11/2019
Version:	07
Document Status:	Saved as "Final"
Submitted by:	Aileen Mapps--8/7/2019 7:18:06 AM
OPR Action:	Accepted by: Elaine Kramer -- 8/8/2019 4:45:22 PM

Which Committee will review this protocol?

◉ The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 To determine the efficacy and toxicity of radiation therapy alone in treating stage 1 and 2 MALT lymphoma for newly diagnosed patients and for the patients who failed other treatment modalities.

2.0 Background

2.1 Rationale- MALT lymphoma is a relatively recently described entity which is also known as extranodal marginal zone lymphoma (1)(2)(3)(4). It was initially recognized in gastrointestinal tract with the majority arising from the stomach. Nowadays, however, about 30 to 40% of the MALT lymphomas are thought to be of non-gastrointestinal origin according to the M.D. Anderson Cancer Center lymphoma data base and others (5). Though MALT lymphoma constitute about 7 to 8%(6) of non-Hodgkin's lymphoma, prospective clinical trials are scarce and optimal treatments still remain to be defined. It is generally considered to be a low grade lymphoma at early state (7)(8) having a very favorable prognosis even after localized treatments such as radiation therapy of surgical resection alone (9)(10). Most of the data on the treatments of MALT lymphoma come from experiences in gastric MALT lymphoma (11)(12)(13). There have been multiple retrospective series suggestive of favorable outcome for these patients. However, the first report on a prospective clinical trial in managing Ann Arbor stage 1 and 2 gastric MALT lymphoma with radiation therapy alone was published in 1998 and has been recently updated (14)(15). Twenty nine patients were treated with a median dose of 30 Gy (range 22.5 to 43.5) delivered at 1.5 Gy per fraction to the stomach and adjacent lymph nodes. At a median follow-up of 30 months, 94 % remain disease free. Non-gastric MALT lymphomas (16) (3)(5) have been reported in sites such as bowel (17) lung (18), breast (19)(20), skin (21), thyroid gland (22), bladder (23)(24), liver (25) dura (26)(27), esophagus (28) ocular adnexa (29)(30) along with other head and neck series limited by a small number of patients treated in a variety of different ways including any combination of chemotherapy, radiation therapy and surgery, thus yielding no significant insights into the optimal treatment except for the impression that most of them are very localized disease with favorable prognosis probably comparable to that of gastric MALT lymphoma (7). Therefore, we propose to prospectively study the efficacy and toxicity of radiation treatment for patients with stage 1 and 2 non-gastric MALT lymphoma as well as to verify the Memorial Sloan-Kettering Cancer Center data on gastric MALT lymphoma. Of note, a recent publication from the Non-Hodgkin's Lymphoma Classification Project reported an overall failure free survival of about 70% or higher if the International Prognostic Index is less than 4 in their retrospective analysis of 72 patients with stage 1 to 4 MALT lymphoma (33). Zinzani et al reported 5 year treatment failure rate of 70% for their review of 47 patients with stage 1 and 2 non-gastric MALT lymphoma(16). Based on the failure free survival curves presented in these studies, we believe it is a very reasonable hypothesis to test 75% or higher relapse free survival at 5 years with the majority of the relapses occurring within the first 5 years in our group of patients.

The data on the outcomes of the patients who relapse after initial treatment are lacking. The same statistical analysis and stopping rule will apply to the patients who are enrolled in this protocol after failure to initial treatment, though this may be very stringent criteria for this patient population.

2.2 Preliminary Data- We have recently reported our experience with 39 consecutive patients with MALT lymphoma with supradiaphragmatic presentation seen at M.D. Anderson Cancer Center between 1991 and 1997 (34). Ten of them were treated with radiation therapy alone. Two of them had stage 2 disease. The median dose was 39.6 Gy at 1.5 to 2.0 Gy per fraction. Everyone achieved a clinical complete response. At a median follow-up of 26 months, everyone is alive. Two patients experienced recurrence. Both of the recurrences were in the stomach. They were successfully salvaged, rendering every patient free of disease at the last follow-up. Of note is six of these 10 patients had primary conjunctiva lymphoma making the scope of this experience quite limited. We now propose to extend radiation treatment as the only modality to stage 1 and 2 non-gastric MALT lymphomas in general.

3.0 Background Drug Information

Cytotoxic drugs are not a planned part of treatment in this protocol.

4.0 Patient Eligibility

4.1 Inclusion Criteria

4.1.1 Patients with newly diagnosed stage 1 and 2 MALT lymphoma are eligible for this study.

4.1.2 Patients with H. pylori positive gastric MALT lymphoma are recommended to have treatments with antibiotics prior to enrollment to this protocol.

4.1.3 Patients who failed other treatment modalities (e.g. chemotherapy, antibiotics therapy etc) are also eligible as far as they never had stage 3 or 4 disease during the course of the disease or disease progression to the opposite side of the diaphragm. (As the time course of the response to antibiotic therapy can be very variable among patients, sometimes requiring more than one year for complete response, failure to antibiotic therapy can be very variable among patients, sometimes requiring more than one year for complete response, failure to antibiotic treatment will be defined as no response or progression of the disease documented by endoscopy and biopsy.)

4.1.4 Patients who have had stage 4 diseases due to bilateral parotid gland or ocular/ocular adnexal involvement or due to multiple sites within Waldeyer's ring will still be eligible.

4.2 Exclusion Criteria

4.2.1 Patients who had previous radiation dose to the site of the current primary disease which would lead to violation of known radiation tolerance limit of that particular site if treated again.

4.2.2 Patients with MALT lymphoma of the skin whose lesions are separated by more than 5 cm will be ineligible.

4.2.3 Previous or concurrent malignancy in any form would not be an exclusion criterion. However, patients who receive chemotherapy for concurrent malignancy will be excluded from statistical analysis.

4.2.4 Low blood cell counts would not be exclusion criteria as far as the patient is willing to accept supportive measures such as transfusions, filgrastim and epoetin.

5.0 Treatment Plan

5.1 Radiation treatment will consist of involved field radiation therapy to primary site and adjacent lymphatics (if indicated). Initial fields to encompass the tumor site and the suspected microscopic disease will be taken to 30 to 30.6 Gy. Boost to the gross disease to 36 is indicated in some patients when tumor is larger than 5 cm. The only exception would be orbital or ocular adnexal lymphoma which may be treated to the final dose of 30 Gy or 30.6 Gy.

a) CT Planning is required for every patient unless it is technically not feasible. The only exception would be MALT lymphoma of the skin which may be treated with electron beams.
b) Though involved field radiation therapy to stomach only is recommended for stage 1 gastric MALT lymphoma, generous fields to encompass the peri-gastric and celiac lymph nodes are recommended if the patient presents with recurrent or refractory disease after chemotherapy. Every attempt needs to be made to preserve the function of the left kidney by using oblique fields after the initial AP-PA fields are taken to the kidney tolerance. The gastric fields need to be simulated and treated with empty stomach for optimum reproducibility.

6.0 Pretreatment evaluation

See Appendix A

6.1 A complete history and physical examination including performance status (Appendix B)

6.2 Laboratory studies will include a CBC with differential, platelet count, electrolytes, biochemical survey, TSH (if indicated due to the site of the disease), and beta-2 microglobulin. Imaging studies will include PA and lateral chest roentgenograms, CT of the neck, chest, abdomen, and pelvis. Esophogogastroduodenoscopy (EGD) needs to be done for every patient. If EGD is positive, colonoscopy along with small bowel series will be performed. Unilateral bone marrow biopsies will be obtained prior to initiation of therapy.

6.3 Location, type and size of all measurable lesions must be recorded prior to treatment.

7.0 Evaluation During and After Treatment

(See Appendix A)

7.1 Patients will be followed while on treatment with CBC with differential and platelet count only as clinically indicated. These will be also obtained at the follow-up visits.

7.2 A biochemical survey will be performed before radiation therapy and at the follow-up visits.

7.3 All initially abnormal imaging studies and endoscopies will be performed 3 months after completion of radiation therapy and yearly thereafter. Additional studies will be obtained only if indicated by the interval history and physical examination.

7.4 The follow-up visits will be done between 6 weeks to two months, and then every 3-4 months for the first year, every 4-6 months for the second year, every 6 months for the third & fourth year, and once a year thereafter or as per physician's discretion.

Please note: The post-treatment lab test and follow-up visits can be done less often (than previously stated) depending on the clinical judgment of the physicians.

8.0 Criteria for Response and Toxicity

(See Appendices C and E)

8.1 Tumor Measurements

a. Lesions will be measured in centimeters prior to the course of therapy.

b. The longest diameter and its perpendicular will be measured for bi-dimensionally measured lesion. Size will be reported as the product of the diameters.

c. Measurements should be made and recorded by the physician.

d. An estimate of overall objective and subjective response will be made and recorded at each visit.

e. Endoscopy findings will be mapped out.

8.2 Response Definitions

a) Clinical responses- The guidelines from the 'Report of an International Workshop to Standardized Response Criteria for Non-Hodgkin's Lymphoma' will be followed (35). (See Appendix E for Summary of Response Criteria for Non-Hodgkin's Lymphoma)

CR – 1) Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of the biochemical abnormalities (eg, lactate dehydrogenase [LDH] definitely assignable to lymphoma).
2) All lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy.) Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
3) Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present.
4) Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time.
CR/unconfirmed (Cru) – 1) Those patients who fulfill criteria 1 and 3 above, but with one or more of the following features:
A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
PR – 1) ≥ 50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimension, (b) they should be from as disparate regions of the body as possible, and (c) they should be included mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2) No increase in the size of the nodes, liver, or spleen.
3) No new sites of disease.
Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

Relapsed disease (CR, Cru) – 1) Appearance of any new lesion or increase by ≥50% in the size of previously involved sites. **2)** ≥50% increase in greatest diameter of any previously identified node greater than 1 cm its short axis or in the SPD of more than one node.
Progressive disease (PR, nonresponders) – 1 ≥50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders. 2) Appearance of any new lesion during or at the end of therapy.

b. Response Assessment
Response is assessed on the basis of clinical radiologic, and pathologic (i.e, bone marrow) criteria. CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence.

A bone marrow aspirate and biopsy should only be performed to confirm a CR if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

c. Response durations are measured from the time of response (not the beginning of treatment) until there is evidence of progressive disease. Progression free survival will be measured from protocol entry.

8.3 Frequency of Response Determination: All lesions must be measured at baseline and then as per section 7.4

8.4 Survival Durations: The survival of patients will be measured from entry into protocol.

8.5 All toxicities encountered during the study will be evaluated according to the grading system (0-4) in Appendix C. Duration and treatment will be recorded. Life-threatening toxicities should be reported immediately to the study chairman who in turn must notify the IRB. Should this occur, it will mandate closure of the protocol to patient entry for investigation as to the reasons for this and a decision can be taken as to whether the protocol can remain open or should be closed.

9.0 Criteria for Removal from the Study

9.1 Progressive disease during radiation therapy which encompasses all known tumors.

9.2 The development of unacceptable toxicity defined as unpredictable, irreversible, or Grade 4.

9.3 Non-compliance by patient with protocol requirements.

9.4 Patient refusal.

10.0 Data and Protocol Management

10.1 Protocol Compliance: The attending physician must see each patient prior to the start of irradiation and at each follow-up visit post-treatment. All required interim and pretreatment data should be available and the physician must make a designation as to tumor response and toxicity grade.

10.2 Data Entry: Data must be entered into the Protocol Data Management system before therapy can be given. A brief explanation for required but missing data should be recorded as a comment.

10.3 Accuracy of Data Collection: The study chairman will be the final arbiter of response or toxicity should be a difference of opinion exist.

11.0 Statistical Considerations and Stopping Rules

This is a trial to estimate the relapse-free survival rate (RFS) of patients with gastric and non-gastric MALT lymphoma treated with radiation therapy alone. Patient accrual is expected to be 10 – 15 per year for gastric and 5 – 10 per year for non-gastric MALT lymphoma at initial presentation. Accrual of less than 5 patients per year for either gastric or non-gastric MALT lymphoma is expected for presentation upon failure of other treatment modalities. The patient accrual and outcome analyses will be done separately in the following 4 groups: Gastric vs non-gastric MALT at initial presentation vs upon failure to toher treatment(s).

Accrual goals

The accrual goals for the patients at initial presentation are 40 for gastric and 35 for non-gastric MALT lymphoma. Based on the expectation that the relapse rate after radiation therapy alone will be 25% and that 70% of the relapsing patients will fail within 5 years, these numbers will provide a 95% confidence bound of +/- 5.9% for estimating the 2-year RFS. This calculation assumes that RFS follows an exponential distribution and we will follow all patients for at least 2 years.

Stopping Rules for patient accrual at initial presentation

Based on the expectation that the relapse rate after radiation therapy alone will be 25% or less, RFS will be evaluated in each of the two subgroups of previously untreated patients and accrual stopped in RFS is < 70% after the first 15, 30, or 45 patients have been followed for a minimum of 2-years. Assuming that 70% of the relapsing patients will fail within 5 years, computer simulations indicate that this stopping rule will terminate patient accrual in both the gastric and non-gastric arms of the trial with a probability of 1% if the relapse rate is 25% with a 17% probability if the relapse rate is 50%, and with a probability of 60% if the relapse rate is 75%.

Stopping Rules for patient accrual upon failure to other treatments

When the accrual goals of both gastric and non-gastric MALT lymphoma patients at initial presentation are met, the data for the patients who presented upon failure to other treatments will be analyzed. Decision regarding continued accrual of the patients will be made on the RFS outcome and patient accrual rate at that time.

As toxicity of 3 or higher is not expected, we do not have a stopping rule based on toxicity. However, any toxicity of 4 or 5 will be immediately investigated (see 12.1)

12.0 Reporting Requirements

12.1 Any life-threatening and/or unexpected and serious (Grade 4 or 5) toxicity will be reported immediately to the study chair who in turn must notify the Surveillance Committee.

13.0 References

1. Isaacson P, Wright D. Malignant lymphoma of mucosa-associated lymphoid tissue: a distinctive type of B-cell lymphoma. Cancer 1983;52; 1410-1416
2. Harris NL, Jaffe ES, Stein H, et al. A Revised European-American Classification of Lymphoid Neoplasms: A Proposal From the International Lymphoma Study Group. Blood 1994;84(5); 1361-1392
3. Banks PM, Isaacson PG. MALT Lymphomas in 1997 Where Do We Stand? Am J Clin Pathol 1999;111:S75-S83
4. Harris NL, Isaacson PG. What Are the Criteria for Distinguishing MALT From Non-MALT Lymphoma at Extranodal Sites? Am J Clin Pathol 1999; 111 (Suppl. 1):S126-S132.
5. Thieblemont C, Bastion Y, Berger F, et al. Mucosa-Associated Lymphoid Tissue Gastrointestinal and Nongastrointestinal lymphoma Behavior: Anaysis of 108 Patients. Journal of Clinical Oncolgoy 1997;15 (4)(April):1624-1630
6. The Non-Hodgkin's Lymphoma Classification Project. A Clinical Evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin's Lymphoma. Blood 1997;89 (11); 3909-3918.
7. Burke JS. Are There Site-Specific Differences Among the MALT Lymphomas-Morphologic, Clinical? Am J Clin Pathol 1999;111 (Suppl. 1); S133-S143.
8. Isaacson P. Mucosa-Associated Lymphoid Tissue Lymphoma. Seminars in Hematology 1999; 36(2):139-147
9. Porcu P, Nichols CR. Evaluation and Management of the "New" Lymphoma Entities: Mantle Cell Lymphoma, Lymphoma of Mucosa-associated Lymphoid Tissue, Anaplastic Large-cell Lymphoma, and Primary Mediastinal B-cell Lymphoma. Current Problems Cancer 1998;22(5):283-368.
10. Thieblemont C, Berger F. Coiffier B, Sud L, Benite P. Mucosa-associated lymphoid tissue lymphomas. Current Opinion in Oncology 1995;7:415 – 420.
11. Fung CY, Grossbard ML Linggod RM, et al. Mucosa-Associated Lymphoid Tissue Lymphoma of the Stomach ; Long Term Outcome after Local Treatment. Cancer 1999;85(1):9-17.
12. Hammel P, Haioun C, Chaumette M-T, et al. Efficacy of Single-Agent Chemotherapy in Low-Grade B-Cell Mucosa-Associated Lymphoid Tissue Lymphoma With Prominent Gastric Expression. Journal of Clinical Oncology 1995; 13(10):2524-2529.
13. McLaughlin P, Seymour J, Fuller L, Cabanillas F. Letters to the Editor; Combined modality therapy for stage I-II MALT lymphoma and mantle cell lymphoma. Annals of Oncology 1996;7(2):211-212.
14. Schechter NR, Portlock CS, Yahalo J. Treatment of Mucosa-Associated Lymphoid Tissue Lymphoma of the Stomach with Radiation Alone. Journal of Clinical Oncolgoy 1998;16(5):1916-1921.
15. Yahalom J, Schecter NR, Gonzales M, C.S.P. Effective Treatment of MALT Lymphoma of the Stomach with Radiation Alone. Annals of Oncology 1999;10 Supplement 3:135.
16. Zinzani PL, Magagnoli M, Galieni P, et al. Nongastrointestinal Low-Grade Mucosa-associated Lymphoid Tissue Lymphoma: Analysis of 75 Patients. Journal of Clinical Oncology 1999; 17(4): 1254-1258.
17. Matsumoto T, Shimizu M, Lida M, Amano K, Nakamura S, Fujishima M. Primary low-grade, B-cell, mucosa-associated lymphoid tissue lymphoma of the colorectum: clinical and colonoscopic features in six cases. Gastrointestinal Endoscopy 1998; 48(5):501-508.
18. Elenitoba-Johnson K, Medeiros LJ, Khorsand J, King TC. Lymphoma of the Mucosa-Associated Lymphoid Tissue of the Lung; A Multifocal Case of Common Clonal Origin. Am J Clin Pathol 1995;103 (3):341-345.

19. Hugh J, Jackson F, Hanson J, Poppema S. Primary breast lymphoma. An immunohistologic study of 20 new cases. Cancer 1990;66:2602-2611
20. Mattia A, Ferry J, Harris N. Breast lymphoma. A B-Cell spectrum including the low grade B-cell lymphoma of associated lymphoid tissue. Am J Surg Pathol 1993;17(6):574-587
21. Bailey E, Ferry J, Harris N, Mihm MJ, Jacobson J, Duncan L. Marginal zone lymphoma subcutaneous tissue: a study of 15 patients. American Journal of Surgical Pathology 1996;20(8):1011-23
22. Anselll SM, Grant CS, Habermann TM. Primary Thyroid Lymphoma. Seminars in Oncology 1999;26(3):316-323
23. Yuille F, Angus B, Roberts J, Vadanan B. Low grade MALT lymphoma of the urinary bladder. Clinical Oncology (Royal College of Radiologists) 1998;10 (4):265-6.
24. Kempton C, Kurtin P, Inwards D, Wollan P, Bostwick D. Malignant lymphoma of the bladder: evidence from 36 cases that low-grade lymphoma of the MALT-type is the most common primary bladder lymphoma. AM J of Surg Path 1997;21(11):1324-33.
25. Isaacson PG, Banks PM, Best PV, McLure P, Muller-Hermelink HK, Wyatt JI. Primary Low-grade hepatic B-cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT)-Type. Am J Surg Pathol 1995;19(5):571-575.
26. Kambham N, Chang Y, Matsushima A. Primary low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) arising in dura. Clinical Neuropathology 1998;23(1):311-7.
27. Kumar S, Kumar D, Kaldijian E, Bauserman S, Raffeld M, Jaffe E. Primary low-grade B-cell lymphoma of the dura: a mucosa associated lymphoid tissue-type lymphoma. American Journal of Surgical Pathology 1997;21(1):81-7.
28. Soweid AM, Zachary J, Paul E. Mucosa-associated lymphoid tissue lymphoma of the esophagus (letter). The Lancet 1996;348(9022):268.
29. White W, Ferry J, Harris N, Grove AJ. A clinicopathologic study with identification of lymphomas of mucosa-associated lymphoid tissue type. Opthalmology 1995;102(12):1994-2006.
30. Hardman-Lea S, Kerr-Muir M, Wotherspoon AC, Green WT, Morell A, Isaacson PG. Mucosal-Associated Lymphoid Tissue Lymphoma of the Conjunctiva. Arch Opthalmol 1994;112(September):1207-1212.
31. Horny H-P, Ferlito A, Carbone A. Clinicopathological Consultation; Laryngeal Lymphoma Derived from Mucosa-Associated Lymphoid Tissue. Ann Otol Rhinol Laryngol 1996;105.
32. Bhattacharyya N, Frankenthaler RA, Gomolin HI, Kadin ME, Lauretano AM. Clinical and Pathologic Characterization of Mucosa-Associated Lymphoid Tissue Lymphoma of the Head and Neck. Ann Otol Rhinol Laryngol 1998;107:801-806.
33. Armitage JO, Wisenburger DD. New Approach to Classifying Non-Hodgkin's Lymphmas: Clinical Features of the Major Histologic Subtypes. Journal of Clinical Oncology 1998;16(8):2780-2795.
34. Liao Z, Ha CS, McLaughlin P, et al. MALT (mucosa associated lymphoid tissue) lymphoma with supradiaphragmatic presentation: natural history and patterns of failure. Int J Rad Oncol Biol Phy 1998;42(1 (supp)):343 Abst. #2232.
35. Cheson B, Horning S. Coiffier B, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma. Journal of Clinical Oncololgy 1999; 17: 1244-1253