Treatment Options for Extra-nodal Mucosa Associated Lymphoma Tissue (MALT) of the Stomach: Role of Radiation Therapy

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Introduction

Extra-nodal mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach is a rare among the non-Hodgkin's lymphoma's (NHL). Other histological variants of gastric NHL are diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and mantle cell lymphoma. Marginal zone B-cell lymphomas of MALT are indolent, low grade B-cell lymphomas arising from the marginal zone of the lymphoid follicles of the lymphoid tissue and also seen at other sites like lung, orbit, spleen, skin, and thyroid apart from stomach. Association with Helicobacter pylori is noted in majority of cases of gastric MALT lymphoma [1]. Eradication of H. pylori was known to be associated with very good pathological response rates [2] (80% complete histologic remission) after treatment with proton pump inhibitors (PPI), as part of triple antibiotic regimen (clarithromycin and amoxicillin, or metronidazole for patients allergic to penicillin). Translocation of t(11:18), thickening of the stomach wall (sub-mucosal involvement) and H. Pylori negative are associated with poor response rates to the triple antibiotic regimen and needs to be treated with either radiation therapy and/or systemic therapy, chemotherapy or single agent Rituximab [3]. MALT lymphomas rarely metastasize to lymph nodes (peri-gastric or celiac axis) unlike DLBCL or FL and the majority present in early stages. Stage I and II MALT of the stomach is usually treated with definitive radiation therapy (RT) alone with involved site RT (ISRT), and provides high local control rates (LCR) and overall survival (OS) [4]. RT doses of 24-30 Gy given in 13-20 fractions using 1.5-1.8 Gy per fraction over 3-4 weeks duration has been shown to provide LCR of 95-100% [5-10]. Observation is another treatment option include surgery (currently, limited to cases with life-threatening hemorrhage) and chemotherapy (single agent or combination regimens). Long-term survival rate for stage I and II gastric MALT lymphoma patients is 80-90% [5,6]. There is a concern for second malignancies for these patients treated after radiation therapy in the long-term follow-up [5,6]. There are limited published randomized studies or data to direct the therapy for gastric MALT lymphoma except for the ESMO (European Society for Medical Oncology) clinical practice guidelines.

Role of Radiation therapy: RT dose and techniques

Efficacy of low-dose involved-field radiation therapy (IFRT) was reviewed in several retrospective studies. Involved-site radiation therapy (ISRT) has been adopted into recent clinical practice by the International Lymphoma Radiation Oncology Group [7]. We reviewed the treatment results of radiation therapy (RT) for stage I and II gastric lymphoma patients treated between years 1999-2013 [8]. Intensity modulated radiation therapy (IMRT, VMAT) was adopted since 2010 and AP-PA, 3D-conformal radiation therapy (3D-CRT) techniques were used prior. All patients underwent for CT simulation on an empty stomach. Oral contrast was given at the discretion of the treating physician and a fixed measured amount of gastrografin (50 mL) was given and patients were informed to drink the same amount of water prior to daily treatment for reproducibility when treated with IMRT or VMAT. Daily image guidance with CBCT (cone beam CT) was done for these patients to verify the accuracy of treatment setups. Stomach and peri-gastric lymph nodes were included in the clinical target volume (CTV) with a margin of 0.5-1 cm around the internal target volume (ITV) to create the planning target volume (PTV). Image fusion with pre-chemotherapy PET/CT was adopted for the recent patients with DLBCL of the stomach to generate CTV. Logistic regression was used to correlate patient and treatment factors with LCR and OS. Kaplan-Meier method was used to estimate OS and LCR. Twenty five patients met the inclusion criteria. A total of 21 patients had MALT (84%), 18 (72%) had stage IE disease, 2 (8%) with IIE disease. None of the patients had B symptoms. Median age was 62 years (range: 33-85 years). Median follow up was 37 months (range: 1.08-158 months). Median RT dose was 30 Gy (range: 27-36). Helicobacter pylori (H. Pylori) was positive in 9 patients (39%) and a trial of antibiotics PET/CT was adopted for the patients with DLBCL of the stomach to generate CTV. Logistic regression was used to correlate patient and treatment factors with LCR and OS. Kaplan-Meier method was used to estimate OS and LCR. Twenty five patients met the inclusion criteria. A total of 21 patients had MALT (84%), 18 (72%) had stage IE disease, 2 (8%) with IIE disease. None of the patients had B symptoms. Median age was 62 years (range: 33-85 years). Median follow up was 37 months (range: 1.08-158 months). Median RT dose was 30 Gy (range: 27-36). Helicobacter pylori (H. Pylori) was positive in 9 patients (39%) and a trial of antibiotics was given to 12 patients (52%) prior to RT. IMRT was used for 7 patients (18%), 10 patients (40%) were treated with 3D-CRT, 6 (24%) with AP-PA fields. Use of IMRT resulted in optimizing the doses to the normal critical structures particularly to the left kidney. Median survival cannot be estimated as the survival curve did not reach 50% mortality rate. The 3- and 5-year actuarial rates of LCR for all patients were 95%, 79% and OS was 90%. For stage I and II MALT, the 3- and 5-year LCR and OS rates were 100% and 94% respectively with RT alone. None of the patients had local recurrence in the stage I and II at the time of last follow up. On univariate analysis, RT technique, performance status (PS), histology type, H. pylori status, RT dose, only PS was significant for OS (p<0.0001).

A prospective comparison of different treatments including radiation therapy, surgery followed by chemotherapy and chemotherapy alone was done in a randomized trial for stage I and II MALT and DLBCL of the stomach in 49 patients by Fischbach [9]. Complete response rates for MALT were equal with either of the modalities, 88% with surgery and 89% with RT alone. Quality of life was measured using SF-36 health survey and the gastrointestinal life quality index (GLQI) and the post-treatment QOL was better in patients treated with conservative measures like RT compared with surgery. Another retrospective review of 48 patients with gastric MALT treated with combination of different treatments was done including RT alone (n=34), chemotherapy followed by RT (n=10), and one patient with surgery followed by RT [6]. The 5-year overall survival...
and cause-specific survival rates were 90.3% and 100%. Median dose of RT was 30.6 Gy and all patients treated with RT achieved pathological complete response. None of patients developed grade 3 or higher acute or late complications.

Relationship to RT dose response was not studied in any prospective study but several retrospective studies have shown improved LCR with RT doses of 24-30 Gy. Long-term outcomes (median follow-up of 7.4 years) of 25 patients with gastric MALT out of 192 extra-nodal MALT cases treated with involved field RT showed a 10-year recurrence-free rate of 92% for stage IE and IIE [10]. Outcomes were poor for patients with MALT from other locations, orbit 67%, 68% for salivary glands. RT doses were 30 Gy (range: 17.5-35) to the non-orbital sites and 25 Gy for the orbit (range: 25-35 Gy). Another review reported RT doses of 30-40 Gy in 15-20 fractions to the stomach and peri-gastric lymph nodes for patients with incomplete responses to H. pylori eradication and H. pylori negative cases [11].

Different RT techniques were compared in a prospective study with involved field RT (stomach and peri-gastric lymph nodes) in 61 patients and whole abdomen RT (20 Gy followed by boost to the stomach) in 41 patients with gastric MALT [12]. Recurrent/residual disease after prior treatment (H. pylori eradication in 35, chemotherapy in 9, surgery in 8 patients with more than one treatment in 7 patients) was noted in 44/102 patients. The median RT dose was 40 Gy given in 22 fractions (range: 26-46 Gy). The 10- and 15-year freedom from treatment failure (FFTF) was 88%. Exophytic pattern and presence of large-cell component contributed to higher treatment failures. There was no association with RT field size (whole versus partial abdominal), RT dose (<30.6 Gy or ≥ 40 Gy) and failure to prior therapy for FFTF.

Conclusions

RT alone should be the primary treatment modality for patients diagnosed with Stage I or IIE gastric MALT. Current practice is to treat with involved site radiation therapy to RT doses of 24-30 Gy to the stomach for patients with gastric MALT lymphoma. Patients after complete H. pylori eradication are followed with serial endoscopic evaluations with radiation therapy reserved for salvage treatment. Our results correlate with the outcomes from the published data. Treatment with modern RT techniques needs to be done by an experienced team of radiation oncologists at big volume centers.

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