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Research Letter

Ultra–Low-Dose Radiation for Extranodal Marginal Zone Lymphoma of the Lung

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Abstract

Purpose: Definitive intent radiation therapy (RT) for early-stage mucosa-associated lymphoid tissue (MALT) lymphoma typically includes a dose of 24 to 30 Gy. While modest, these doses may have associated toxicity. For patients with indolent B-cell lymphoma, there is increasing support for the use of ultra–low-dose RT (ULDRT) using 4 Gy in 2 fractions as part of a response-adapted approach, as high rates of complete response have been documented. This paradigm has been prospectively evaluated in the management of orbital and gastric indolent B-cell lymphomas; however, there is limited data guiding the use of ULDRT for lung MALT.

Methods: We conducted a retrospective review of 20 patients at our institution with lung MALT treated with ULDRT as part of a response-adapted approach. Clinical variables including prior systemic therapy and symptoms were abstracted from the electronic health record. Responses were assessed using the revised Lugano criteria.

Results: At a median follow up of 17 months following 4 Gy (IQR, 8-37 months), we observed 100% local control. Nineteen patients (95%) experienced a complete response. No patients with stage IE disease at RT (17/20; 85%) experienced distant progression. Nine patients (45%) were symptomatic prior to RT, with improvement or resolution of symptoms in 7 (7/9; 78%). One patient developed grade 2 pleuritic pain following RT, which resolved with a brief course of steroids. No other toxicities were noted.

Conclusions: ULDRT, given in a response-adapted approach, is effective and well tolerated by patients with lung MALT.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Introduction

Extranodal marginal zone lymphomas (ENMZLs) of mucosa-associated lymphoid tissue (MALT) are rare lymphomas that can present in virtually any site, often as a result of chronic antigen stimulation.[1] In patients with

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stage I marginal zone lymphoma (MZL), the incidence of lung involvement is as high as 8%.[2] Approximately half of patients with lung MALT are asymptomatic at diagnosis.[3] Treatment for lung MALT may include radiation therapy, surgery, or systemic therapy with chemotherapy and/or immunotherapy, depending on stage, performance status, and patient preference.

For early-stage indolent B-cell lymphomas such as MALT lymphoma, definitive-intent radiation therapy (RT) with doses of 24 to 30 Gy has been the standard of care.[4,5] Ultra–low-dose RT (ULDRT, 4 Gy in 2 fractions) for MALT lymphoma is gaining acceptance, with complete response (CR) rates of 70% to 88% reported.[6-8] Response-adapted (RA) ULDRT has been prospectively evaluated in indolent B-cell orbital and gastric MALT lymphoma, where patients are initially treated using 4 Gy in 2 fractions, with an additional 20 Gy in 10 fractions given only for patients with an incomplete response.[9,10] Local control (LC) rates of >90% have been reported with this staged approach, and few patients required the full RT dose.

Herein, we assessed outcomes of patients with lung MALT following treatment with RA-ULDRT, an approach that may better align treatment intensity with the indolent nature of MALT lymphoma.

Methods and Materials

We performed an institutional review board-approved retrospective review of patients with pathologically confirmed MALT lymphoma of the lung(s) treated at our institution with RA-ULDRT of 4 Gy between July 2015 and December 2022. Patients were typically simulated with deep inspiratory breath hold (DIBH), though 4-dimensional (4D) computed tomography (CT) was used for patients who did not tolerate DIBH. For DIBH, the gross target volume was contoured and expanded into an internal target volume if there was any significant variation on multiple DIBH scans. Typically, a 5 to 10 mm expansion for the planning target volume (PTV) was used, although PTV margins were chosen at the discretion of the treating radiation oncologist. For patients who were planned using a 4DCT, the gross target volume was contoured and expanded into an internal target volume using the maximum intensity projection with consideration of all phases of the 4DCT, typically with a 5 to 10 mm PTV expansion.

Response was assessed using the revised Lugano criteria.[11] CR was defined as a Deauville score of 1, 2, or 3 on positron emission tomography (PET)/CT or no measurable extranodal disease on CT for patients who did not undergo follow-up PET/CT. Patients were considered for additional RT in the setting of residual PET-avid disease or stable/progressive CT-based disease.[11] LC was defined as the absence of recurrence or progression within the PTV. Follow-up was defined from the start of RT. χ^2 and Mann-Whitney U tests were performed for categorical and continuous variables, respectively, using SPSS (v26, IBM) with a P value $< .05$ considered statistically significant.

Results

Twenty patients were included, with a median age at diagnosis of 69 years (IQR, 60-77) (Table 1). Twelve patients (60%) were female. Lung MALT was incidentally identified on imaging in 13 patients (65%), 5 of whom were undergoing surveillance for prior malignancy and 6 of whom (30%) were prior smokers. Seventeen patients (85%) had stage IE disease at the time of diagnosis. The 3 remaining patients had multifocal lung disease; 2 received comprehensive RT to all lung sites, the third had impaired pulmonary function, and only the largest biopsy-proven site was treated. All patients underwent pretreatment PET/CT, with a median pre-RT lesion standardized uptake value of 5.2 (IQR, 3.4-7.9). The median PTV was 76 cm^3 (IQR, 55-128).

Two patients received systemic therapy prior to RT. One patient received rituximab for 3 months with no significant change in disease. The other patient, who had undergone left upper lobectomy for pathologic diagnosis at an outside facility with residual MALT lymphoma in the left lower lung, received rituximab and then zanubrutinib with a partial response. However, therapy was discontinued due to hemoptysis. This patient had biopsy-confirmed residual disease prior to RT. Two patients received rituximab concurrent with RT. All 20 patients received 4 Gy in 1 (1/20; 5%) or 2 (19/20; 95%) fractions at a median of 2 months following diagnosis (IQR, 1-3).

The median follow-up for all patients was 17 months following RT (IQR, 8-37). All 17 patients who underwent post-RT PET/CT experienced a metabolic CR at a median of 3 months post-RT (IQR, 3-4) (Fig. 1). Three patients who were restaged with CT scans only experienced CR (2 patients) and partial response (PR) (1 patient, right upper lobe nodule decreased from 17 × 10 mm to 8 × 4 mm after RT). Therefore, 19 total patients (95%) experienced a CR. No patients were recommended additional RT following 4 Gy. On a per-lesion analysis, the CR rate was 96% (22/23 treated lesions), and the PR rate was 4% (1/23 lesions). LC in the treated lesions was 100% at 17 months. One patient experienced progression in the contralateral lung at a site of prior suspected involvement and was not treated due to impaired pulmonary function; he remains on surveillance. No other distant failures were noted.

At the last follow-up, 18 patients (90%) were alive. One patient died of complications from Alzheimer's disease, and 1 patient died from metastatic cutaneous squamous cell carcinoma of the scalp. This patient experienced a PR following RT for his lung MALT; however, additional lymphoma-directed therapy was not pursued following his diagnosis of squamous cell carcinoma.

Table 1 Patient and treatment characteristics

Characteristic	N = 20 n (%) or median (IQR)
Age (y)	69 (60-77)
Sex	-
Male	8 (40)
Female	12 (60)
Race	-
White	17 (85)
African American	2 (10)
Asian	1 (5)
Ethnicity	-
Hispanic	1 (5)
Stage	-
I	17 (85)
IV	3 (15)
SUV max prior to RT	5.2 (3.4-7.9)
Pulmonary symptoms at diagnosis	7 (35)
Prior therapy	-
Rituximab	1 (5)
Rituximab with zanubrutinib	1 (5)
RT dose, Gy	4 (4-4)
Fractions	-
1	1 (5)
2	19 (95)
Best response	-
PR	1 (5)
CR (CT) or CMR (PET/CT)	19 (95)
Distant progression	1 (5)

Abbreviations: CR = complete response; CMR = complete metabolic response; CT = computed tomography; PET/CT: positron emission tomography/computed tomography; PR = partial response; RT = radiation therapy; SUV: standardized uptake value.

Nine patients (45%) were symptomatic at the time of RT (5 with chronic cough; 4 with shortness of breath and/or dyspnea). Following radiation, 4 patients experienced resolution of symptoms, and 3 patients experienced improvement in symptoms. Larger lesions, as measured by PTV size, were not associated with increased symptoms prior to RT ($P = .18$) or with improvement in symptoms following RT ($P = .83$). One patient reported grade 2 pleuritic pain after RT, which resolved with steroids. No other treatment-related toxicities were noted.

Discussion

To our knowledge, this study represents the largest series to date describing outcomes of RA-ULDRT for lung MALT and demonstrates high response rates with limited toxicity. In our series, all patients experienced LC after ULDRT of 4 Gy, with no patient requiring the completion 20 Gy dose. None of the patients with stage IE disease experienced distant progression. Almost 80% of symptomatic patients experienced resolution or improvement. Given the expected excellent prognosis for patients with ENMZLs and the lack of symptoms in many patients, it is important to balance possible treatment-related toxicity with the benefit of therapy.

Long-term outcomes for MALT lymphoma patients are generally very favorable, regardless of treatment modality.[12,13] A retrospective study of 244 stage IE/IIE MALT lymphoma patients treated with radiation alone (median dose 30 Gy) demonstrated 5-year disease-specific mortality of 1.1% and relapse-free survival of 74%.[12] Though 24 Gy remains the standard of care for definitive-intent RT,[4] there is the suggestion that MZL may be more

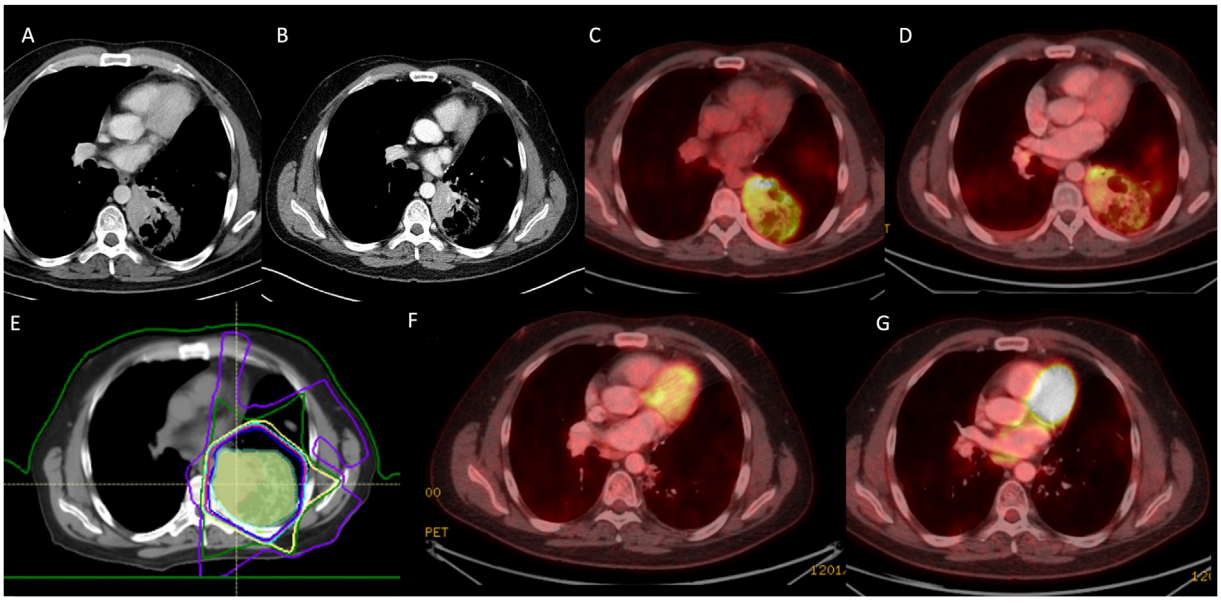

Figure 1 A 47-year-old man with a history of recurrent lung infections refractory to antibiotics and biopsy-proven lung mucosa-associated lymphoid tissue lymphoma (A) prior to therapy, (B) after weekly rituximab × 4 with improvement, (C) subsequent progression on positron emission tomography (PET)/computed tomography (CT), (D) with slight improvement following a 3-month trial of zanubrutinib, which was discontinued due to hemoptysis. He had a biopsy redemonstrating mucosa-associated lymphoid tissue lymphoma prior to (E) ultra—low-dose radiation therapy, 4 Gy in 2 fractions, with (F) a complete metabolic response on PET/CT 2 months later with a Deauville score of 2, and (G) ongoing response 26 months following radiation.

radiosensitive than other indolent B-cell lymphomas, evidenced by the 5-year local progression-free rate of 88% after 4 Gy in the Follicular Radiotherapy Trial.[7] A growing body of literature demonstrates excellent LC following 4 Gy.[6,14,15] A recently published phase 2 trial evaluating RA-ULDRT for indolent B-cell lymphomas of the ocular adnexa demonstrated that 45 of 50 patients (88%) experienced a CR to ULDRT (44 patients) or ULDRT with an additional 20 Gy (1 patient).[9] No local recurrences were observed after a CR, and no grade 3 or higher toxicity was observed.[9] A prospective trial of RA-ULDRT in 24 patients with gastric MALT lymphoma demonstrated a 3-year LC rate of 96% with this RA approach.[10] The CR rate to ULDRT alone was 83% at a median of 4 months (IQR, 3-5.5), and again, no grade 3 or higher toxicity was observed. In a previously published series of 10 lung MALT patients treated with ULDRT, patients experienced a CR rate of 60% at 2 months, which improved to 80% at a median follow-up of 56 months (2 PR converted to CR).[16] A recent series of 10 patients with ENMZLs of bronchus-associated lymphoid tissue demonstrated a CR in 6 of 10 patients treated with ULDRT with no local recurrences at a median follow-up of 36 months.[17]

Minimizing radiation-related toxicity is critical, given the excellent prognosis of this patient population. This is highlighted by a retrospective series of 123 patients with primary MZL involving the lung. This study demonstrated a 6-year event-free survival of 65% in patients initially managed with active surveillance (defined as a documented plan for observation and at least 3 months of observation prior to initiating treatment) compared with 74% with surgical resection, which suggests that expectant management may be reasonable for some patients.[18]

Additionally, MALT lymphoma often arises in the setting of chronic inflammation, possibly related to infection or autoimmune conditions; this places patients at increased risk for RT-related side effects.[19,20] Strong data demonstrate that dosimetric parameters, such as mean lung dose and the volume of lung receiving 20 Gy, are associated with rates of radiation pneumonitis.[21,22] Though treatment of 24 to 30 Gy for lung MALT is likely to meet conventional criteria for safety, data from Pinnix et al[22] suggests that even low-dose volumes (ie, 5 Gy) can be associated with radiation pneumonitis. Doses "as low as reasonably achievable" to organs at risk should be the goal in the management of indolent lymphomas. In our cohort, there were no grade 3 toxicities observed. Combined with the high response rates, this suggests that ULDRT with 4 Gy may be an excellent therapeutic option for lung MALT patients, particularly those who are symptomatic and require treatment.

Notably, 7 of 20 patients (35%) had at least 1 other malignancy, and 5 of 20 patients (25%) previously received radiation for another malignancy, most commonly prostate and breast cancer. The limited toxicity and short duration of ULDRT (1-2 days) are valuable for

patients with comorbidities or other malignancies requiring treatment and may help reduce overall treatment intensity.

Limitations of this study include its retrospective nature, the small and heterogeneous patient population, and relatively short follow-up post-RT for this indolent lymphoma patient population. Three patients did not undergo PET/CT imaging for metabolic response assessment at follow-up. Patient symptoms were obtained only through retrospective chart review. We did not encounter any patients with bulky disease, urgent symptoms, or reservations related to close follow-up with the RA approach. Whether this strategy is appropriate for such patients still warrants investigation. All patients were seen at a tertiary cancer hospital, which may limit the generalizability of our findings.

Conclusions

Patients with lung MALT experienced excellent outcomes following RA-ULDRT, with 100% LC after 4 Gy and no patients requiring additional RT. As expected, toxicity was minimal. None of the 17 patients with stage IE disease experienced distant progression, suggesting that this approach may be considered even for definitive treatment. As MALT lymphoma often presents in older patients and has an indolent clinical course, dose de-escalation could better align treatment intensity with the typically nonaggressive disease behavior. A prospective investigation with a longer follow-up is needed.

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