Review Article

Radiation therapy of extranodal marginal zone lymphomas

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Abstract: This review discusses the use of radiation therapy (RT) in the management of extranodal marginal zone lymphomas of mucosa-associated lymphoid tissues, also known as MALT lymphomas. Most patients with MALT lymphoma (~70%) present with stage I or II disease. The use of definitive moderate-dose RT (24–30 Gy) for these patients with localized disease results in a high rate of durable local control and often cure. Effective use of RT is frequently possible, with minimal short- and long-term toxicity, for both common and rare presentations of the disease. Emerging evidence also suggest an ultra-low dose regimen of 4 Gy in 2 fractions is useful as an initial approach for some sensitive anatomic sites. For patients with relapses of MALT lymphoma, the biologic behavior is often indolent, with slow growth and a tendency to relapse in other extranodal issues. Palliative RT is often the treatment of choice, as MALT lymphomas are exquisitely radiation sensitive. Similarly, for patients with stage III or IV disease and localized symptoms, ultra-low dose RT is often a good alternative to systemic therapy as it is very well tolerated in virtually any anatomic site in the body and has no significant toxicity.

Keywords: Extranodal marginal zone lymphoma; radiotherapy; moderate dose radiotherapy; ultra-low dose radiotherapy

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Introduction

Extranodal marginal zone lymphoma represents 70% of all MZL. The concept of MALT lymphoma was first proposed by Isaacson and Wright in 1983 (1) and is now a well-defined clinical-pathologic entity. The diverse anatomic locations where MALT lymphoma present are often associated with certain etiologic factors such as bacterial infections, or autoimmune diseases, and some have characteristic molecular pathologic features. Even in the same site, taking the stomach as an example, etiology may vary as in *H. pylori* induced MALT lymphoma, versus non-*H. pylori* dependent disease which is often characterized by t(11; 18) translocation. The natural history of MALT lymphoma is generally indolent, with frequent relapses. The site of involvement, stage, and related symptoms drive the optimal treatment approach.

Localized MALT lymphomas tend to remain confined to one region for an extended time. Symptoms are often mild and progress slowly. Local treatment such as radiation therapy (RT) is often useful either initially, or later depending on the course of the disease. The most compelling long-term RT data for the successful control of MALT lymphomas are in orbital and gastric sites. The use of moderate dose RT with 24–30 Gy provides excellent local control, approaching 100%, with most patients remaining disease-free for 10 or more years for orbital adnexa MALT lymphoma (2), and gastric MALT lymphoma (3-5). The

moderate doses of radiation used for definitive therapy are associated with a limited risk of serious long-term toxicity. However, special considerations are required for some sites including the orbit, salivary glands, lung, and stomach.

When MALT lymphoma presents as advanced (stage III/IV) disease, it is considered incurable (6). However, the progression of disease is often gradual with prolonged survival. In this setting palliative RT can have a significant role in providing local control and symptom relief. The use of RT for locoregional control of disease should be carefully considered, balancing the benefit of RT against the risk of treatment complications, which varies depending on the site being treated and the RT dose administered. We will discuss this aspect of therapeutic benefit of ultra-low dose (i.e., 2×2 Gy) or moderate dose (24–30 Gy) RT for each of the MALT sites, so that the reader can individualize the decision to use RT in a particular situation.

Principles and goals of radiation therapy in MALT lymphoma

Although preferred first line therapy for limited stage disease is often RT, no treatment consensus guidelines have been specifically developed for MZL. Consequently, the management of stage I/II MALT lymphoma often mirrors that of follicular lymphoma. In this context, RT aims to achieve durable local control with a minimal risk of acute and late effects. Taking advantage of the radiosensitivity of indolent lymphomas requiring lower doses than solid tumors, the ongoing strategy is to decrease RT intensity while maintaining high response rates (7,8).

The recommended RT dose was traditionally 30 Gy or higher. However, this has changed as a result of Lowry's milestone phase III study which compared 40 Gy to 24 Gy for patients with early stage indolent lymphomas (mostly follicular and extranodal marginal zone lymphomas) (7). This prospective trial showed that a dose of 24 Gy in 12 fractions was as effective as 40 Gy in 20 fractions for patients with indolent lymphomas in terms of overall response (92% *vs.* 93%) and complete response (82% *vs.* 79%) rates, as well as progression-free survival (7). Moreover, there was a trend for reduced toxicities in the low-dose arms, but only erythema was significantly reduced (P=0.004). This trial established 24 Gy as the standard of care for the definitive management of MZL, although it is recognized that many single institutional series have previously used 30 Gy with a slightly higher long term local control rate (approximately 90–95%) than was reported by the study conducted by Lowry *et al.* (7).

Over the past two decades, the effectiveness of lower doses has been widely reported. The so-called "boom boom" radiotherapy was firstly reported by Gamen *et al.* (9). Low-dose radiation, 4 Gy in 2 fractions, in the palliative treatment of indolent NHL has shown satisfying results with impressive response rates [overall response rate (ORR) 88%], and mild/rare toxicity (10). This schedule was studied by Hoskin *et al.* (8) in a multicenter randomized trial comparing 24 Gy in 12 fractions *vs.* 4 Gy in 2 fractions for both curative and palliative treatment of follicular and marginal zone lymphoma patients. While the 2×2 Gy schedule was statistically inferior in terms of time to local progression, remarkable activity was demonstrated in almost 75% of patients treated to 4 Gy in 2 fractions, with roughly half of patients (49%) achieving complete remission. Moreover, several retrospective clinical series have demonstrated efficacy of ultra-low dose radiotherapy for palliation of relapsed or refractory disease or in situations when the patient is not a candidate for systemic therapy (11-14). Taken together these data provide the basis for the use of the 2× 2 Gy regimen as the standard schedule in case of palliative-symptomatic lesions because of the high local response rate and the extremely rare and mild acute/late effects. Interest has emerged in utilizing this regimen in the initial management of limited stage MZL with a response adapted approach. Patients are initially treated to 4 Gy in 2 fractions with an additional RT dose of 20 Gy reserved for patients that do not achieve a complete response (ClinicalTrials.gov Identifier: NCT03680586, ClinicalTrials.gov Identifier: NCT02494700). If successful, response adapted therapeutic approaches should be evaluated in randomized trials for patients with early stage extranodal MZL.

Modern RT planning is no longer field based, rather target focused with treatment volumes delineated on volumetric radiographic (CT/MRI/PET) images. Presently the terminology is involved site RT (ISRT) and not involved field radiation therapy (IFRT) as recommended by the International Lymphoma Radiation Oncology Group (ILROG) (15). Delineation of target volumes follow the terminology of the gross tumor volume (GTV), clinical target volume (CTV) and the planning target volume (PTV). The GTV is the gross demonstrable lymphoma, while the CTV includes the GTV and/or subclinical extent of the lymphoma which must be eliminated. The PTV is defined as a RT planning volume which includes the CTV with an adequate margin to account for tumor motion (physiological such as breathing, organ filling such as it

happens in the stomach), and uncertainties in geometry and day to day patient positioning and movements. The PTV is a geometric concept applied in RT planning to ensure that adequate RT dose is actually delivered to the CTV with a high level of probability. Often, RT techniques utilize immobilization devices, motion management strategies (such as deep inspiration breath-hold, DIBH), and image guided RT to minimize the CTV to PTV margin and also the exposure to surrounding organs at risk.

Generally elective nodal radiation is unnecessary for limited stage MALT lymphomas (15-19). Modern technology is utilized to achieve target coverage while minimizing doses to neighboring organs at risk (OAR) based on the ALARA (as low as reasonably achievable) principle. The definition of OAR and their uncertainties follow the same principles as defining target volumes as outline above. The choice of the set-up immobilization and radiotherapy technique will vary according to the region being targeted and the neighboring normal tissues that need to be avoided. Advanced techniques with multi-beams (IMRT) and arcs (VMAT) are standard methods to achieve a high of dose conformity with CTV/PTV coverage, while minimizing dose exposure to OARs. Given that the doses prescribed for MALT lymphoma are considered low to moderate, normal tissue constraints that are utilized for solid cancer high dose treatments are not appropriate. It is essential to reduce unnecessary radiation dose to normal tissues in order to minimize long term side effects such as secondary cancers in this patient population with highly curable disease, and prolonged survival.

Radiation therapy for specific anatomic sites

Gastric

Lymphoid tissue is scarce in normal gastric tissue. Gastric MALT lymphoma originates from the post-germinal center B-cells that reside in the marginal zone of mucosal lymphoid tissue that is often acquired in the stomach in response to infection [typically *Helicobacter pylori* (*H. pylori*)] or chronic immune stimulation (in the case of patients with auto-immune disease) (20). In 1991, Wotherspoon and colleagues reported the presence of *H. pylori* infection in over 90% of the 100 gastric MALT cases examined (21). In a follow up publication, the authors demonstrated gastric MALT regression after *H. pylori* eradication in 5 of 6 patients (22). Almost 3 decades later, anti-microbial therapy directed at *H. pylori* eradication remains frontline therapy for patients with localized gastric MALT lymphoma (23,24).

Gastric MALT lymphoma patients can present with various gastrointestinal symptoms including nausea, vomiting, weight loss, epigastric pain and even gastrointestinal bleeding. The gold standard for diagnosis is endoscopy with several biopsies for histological confirmation of disease as well as for the evaluation for the presence of *H. pylori* organisms. Patients should be advised to discontinue proton pump inhibitor (PPI) therapies as false negative *H. pylori* tests are common with PPI treatment within 2 weeks of endoscopy or urea breath tests (25,26).

Approximately 75–80% of patients treated with anti-microbial therapy will experience lymphoma regression. The current recommended regimen is a PPI and clarithromycin with either amoxicillin or metronidazole (27-29). In a large systematic review of over 1400 patients from 32 studies treated with up front *H. pylori* eradication for early stage gastric MALT lymphoma, the remission rate was 78%. For 994 patients with follow up data available, relapse occurred in 7% of patients (30). In an additional large study of 420 patients treated with initial *H. pylori* eradication, 77% of patients responded to therapy and long-term outcomes were excellent with 10-year overall survival rates of 95% (31). Despite the indolent nature of gastric MALT lymphoma and the excellent responses to primary antimicrobial therapy, several factors are associated with increased risk for lack of response including the presence of the API2-MALT fusion product of translocation t(11;18), regional lymph node involvement, *H. pylori* negativity and submucosal invasion appreciated on endoscopic ultrasonography (30-33).

For patients with localized disease that is unresponsive to *H. pylori* therapy, RT appears to be the most promising treatment strategy. In a pooled data analysis of 315 patients with persistent disease after *H. pylori* therapy, those treated with RT had a higher remission rate compared to chemotherapy (97% versus 85%, P=0.007) (34). Several series have demonstrated excellent disease outcomes after RT, regardless of *H. pylori* infection status and prior therapy (5,35,36). Current recommendations suggest RT for localized gastric MALT lymphoma that persists despite *H. pylori* eradication (23,24). While in the past RT was offered as upfront therapy to all *H. pylori* negative patients, increasing evidence suggests lymphoma regression can occur with anti-microbial therapy in the absence of known *H. pylori* infection (37-39). Therefore, even in cases where *H. pylori* infection is not detected, a trial of antibiotic therapy may be attempted. However, for symptomatic patients or those with risk factors that are associated with a

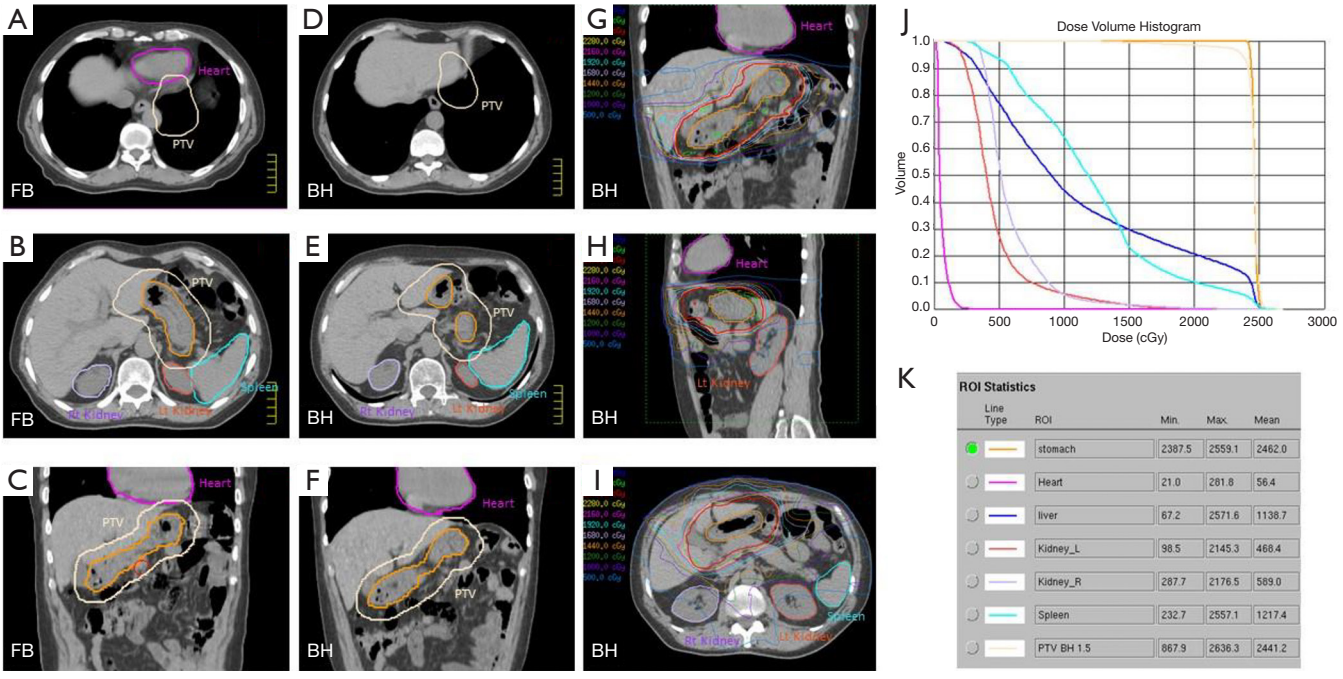

Figure 1 Treatment of Gastric MALT lymphoma with Deep Inspiration Breath-hold (DIBH) and Intensity Modulated Radiation Therapy (IMRT). A 44-year-old woman with gastric MALT lymphoma received definitive IMRT. Axial (A,B) and coronal (C) free-breath CT simulation images demonstrate the stomach clinical target volume with a 1.5 cm planning target volume (PTV) expansion). The PTV volume abuts and slightly overlaps with the heart, left kidney and spleen on the free-breathing images. The same patient underwent CT simulation with DIBH for the purpose of treatment planning and delivery. Corresponding axial (D,E) and coronal (F) images illustrate increased physical distance between the heart and the PTV. The patient was treated with IMRT and DIBH (G,H,I) with daily CT imaging for image guidance. The prescription dose was 24 Gy in 12 fractions of 2 Gy per fraction. The dose volume histogram (J) for the plan demonstrated excellent target coverage with low doses to organs at risk (K). The mean heart dose was <1 Gy and the mean kidney doses were both less than 6 Gy.

lower chance of response to antibiotic therapy (as described above), definitive RT is contemplated (23).

As gastric MALT lymphoma is often a multifocal disease, the radiation target volume should include the entire stomach, even in cases where the disease may appear to be confined to one region of the stomach. Lymph nodes are only included if they are suspected to be involved with the disease. In older RT series, patients were treated with extensive RT fields to the entire abdomen (5,40,41). Long term outcomes reported by Wirth *et al.* on behalf of the International Extranodal Lymphoma Study Group (IELSG) revealed that radiation field size and RT dose was not associated with increased treatment failure among 102 gastric MALT lymphoma patients in which 41 received RT to the whole abdomen and 61 were treated to the stomach and involved nodes (5). The German Study Group on Gastrointestinal Lymphoma performed stage adaptive RT field reductions over the course of 3 prospective trials for gastric MALT lymphoma patients without loss of local control but with lesser frequency of treatment related toxicities (42). Current recommendations from ILROG suggest that the CTV should encompass the stomach from the gastroesophageal junction to beyond the duodenal bulb as well as any pathologically involved nodes (15). Modern technology should be used to reduce doses to neighboring normal structures, including the heart, kidneys and spleen (*Figure 1*). As the stomach is subject to significant motion due to peristalsis, respiratory motion and variations in stomach filling, techniques and procedures directed at accounting for organ motion are essential. Patients should have NPO status at least 6 hours prior to therapy, four dimensional (4D) CT simulation or DIBH techniques should be used for treatment and PTV margins should be adjusted according to the image guidance technique utilized

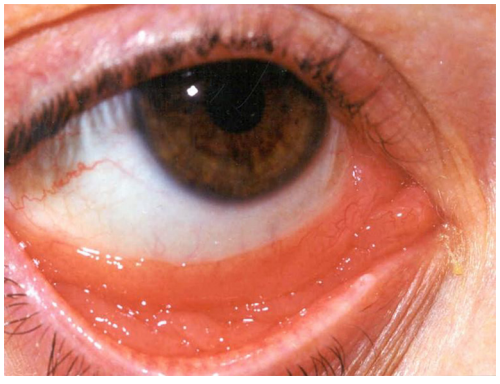

Figure 2 Conjunctival MALT lymphoma, with typical "salmon-pink" infiltration.

(*Figure 1*). With DIBH and daily CT image guidance, 1.0–1.5 cm margins are often used (43). With free breathing treatment and 2D imaging alignment to bony anatomy however, margins of 2.2 cm or greater have been shown to be necessary to achieve adequate PTV coverage (44). DIBH technique has been shown to be a promising strategy to reduce unintended radiation to the heart when treating gastric MALT lymphoma patients (45,46).

While older series have reported median RT doses of 40–50 Gy for the treatment of gastric MALT, many oncologists have treated to 30 Gy in 1.5 Gy fractions delivered over 4 weeks based on excellent outcomes of 17 patients treated with this approach at Memorial Sloan Kettering Cancer Center (MSKCC) in the late 1990's (47). Since that time, the exquisitely radiosensitive nature of MALT lymphoma has been appreciated and lower RT doses have been utilized. In a prospective, multicenter study of refractory or *H. pylori* negative gastric MALT patients, 29 patients were randomized to definitive RT to a dose of 25.2 Gy (n=14) or 36 Gy (n=15; both in 1.8 Gy fractions). All patients experienced a complete response (CR) to RT, regardless of dose, with excellent long-term control in both arms of the study (48). In a series of 32 patients treated at MDACC with definitive RT and doses of 30–36 Gy in 1.5–2.0 Gy fractions (n=21) or 24 Gy (administered mostly in 2 Gy fractions, n=11), CR was achieved among all patients regardless of dose. Two-year treatment outcomes were not impacted by RT dose (49). Given these excellent outcomes with doses of 24–25 Gy administered in 1.8–2.0 Gy fractions, coupled with the known high response rate of other extranodal MALT lymphomas to low RT doses, an ongoing prospective study is evaluating response to 4 Gy in 2 fractions as definitive therapy for *H. pylori* negative or *H. pylori* positive refractory gastric MALT lymphoma (ClinicalTrials.gov Identifier: NCT03680586).

Orbit

Prior to the 1990's, much of the experience with RT for orbital adnexa MALT lymphomas are inferred from reports of patients treated for "low grade" lymphoma and "pseudolymphoma". Many of these cases are now recognized as MALT lymphomas (50,51). The disease affects older individuals, with a median age in the sixth to seventh decade. The conjunctiva is the most commonly involved site, with characteristic "salmon-pink" infiltration (*Figure 2*). Another frequent orbital presentation is involvement of the lacrimal gland (*Figure 3*), followed by periorbital soft tissues and the retro-orbital space. Sometimes multiple lesions are found within the orbit. For conjunctival presentations, there is a tendency for bilateral involvement either at diagnosis, or later (52). Typical symptoms are irritation, pain, and epiphora. For retro-orbital presentations the patient may have proptosis and diplopia. Cervical lymph nodes are rarely involved, but distant sites of disease may be detected on detailed staging with CT, PET scan or bone marrow biopsy (53). For the patients with stage IE disease (localized to one or both orbits), treatment is directed at cure and preservation of both vision and integrity of the orbit. Therefore, extensive surgery is not indicated and should be avoided. RT is the standard treatment and achieves local control in over 95% of cases (2,3,54,55). Detailed ophthalmologic assessment prior to RT to document the vision and the presence of any ophthalmologic co-morbidity is recommended.

The radiation target volume need not include the whole orbit for conjunctival lesions. For other adnexal infiltrations and retro-orbital disease, the target volume includes the whole orbit. It is not necessary to cover regional lymph nodes or the contralateral orbit. For patients with conjunctival involvement and no retro-orbital extension, a single direct anterior field with either high energy electrons or photon energies ranging from 4mV to 6mV from a linear accelerator is sufficient. This technique is simple, reproducible and it also allows the option to provide shielding to the lens, anterior chamber, and the macula by suspending a 1 cm diameter cylindrical eye bar directly over the cornea ("pencil" eye shield) (*Figure 4A*). For electron beams, a similar eye shield of lesser thickness (1–1.5 cm, lead) can be used (51,56,57). Shielding should only be considered if there is assurance on the clinical setup that the disease will not be shielded. When photons

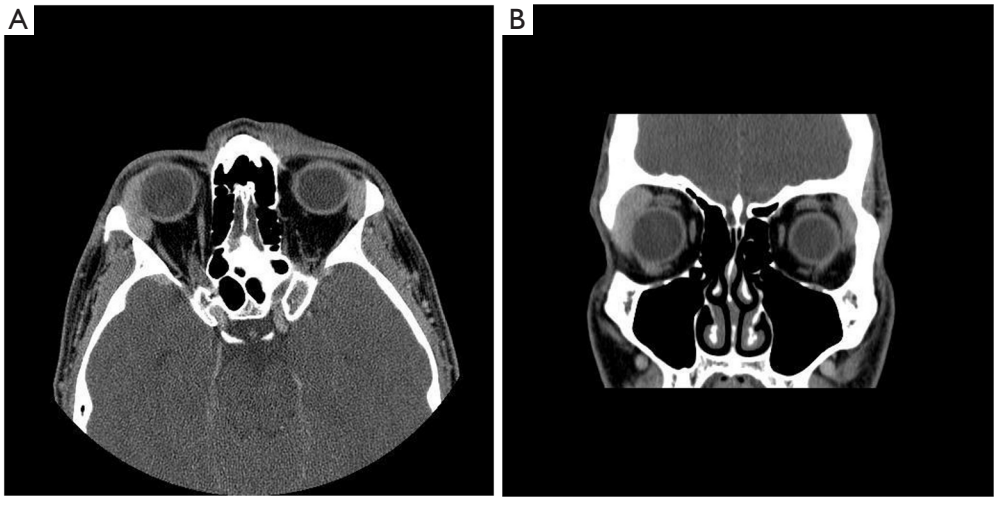

Figure 3 MALT lymphoma of the right lacrimal gland. CT images: axial (A) and coronal (B) images.

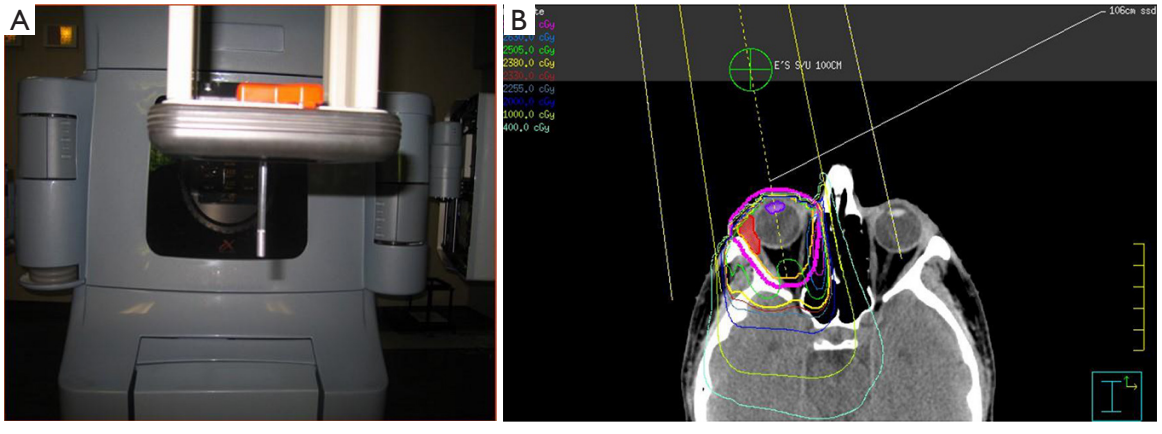

Figure 4 Radiation treatment for lacrimal MALT lymphoma. (A) Pencil eye shield to protect the cornea and lens suitable for high energy electron beams. (B) 20 MeV electrons beam with full coverage of the right orbital tissues, prescribed dose 2380 cGy (yellow isodose line) in 15 fractions.

are utilized to target the conjunctiva, bolus should be used to provide adequate surface dose. A prescribed dose of 24–25 Gy delivered in 1.5–2.0 Gy fractions specified at D_{norm} will result in a dose of 20–24 Gy to most of the retro-orbital tissues (*Figure 4B*). For patients with retro-orbital disease, IMRT or VMAT will achieve a homogeneous dose to the CTV. In this scenario, lens shielding is omitted to avoid shielding the retro-orbital disease. Care is taken to minimize dose to the brain. For patients requiring bilateral orbital radiation, lateral opposed fields are often preferred, or a 3-field technique with addition of an anterior field with shielding of the midline structures between the orbits. For situations with bilateral involvement of the conjunctiva, bolus is used with opposed lateral photon fields to provide buildup of the prescription dose at the conjunctival surface.

The moderate doses of radiation of 24–25 Gy required to achieve a high rate of local control will result in acute side effects of skin erythema, epilation of eye lashes, and conjunctival irritation lasting a few weeks. These effects are temporary and can be managed with conservative measures. Specialized ophthalmologic care should be readily available if required. In the long term, the RT dose of 25–30 Gy without lens shielding will result in cataract formation in over 90% of patients (2,58). If the lens was shielded, cataract formation occurs in about 15% of cases (2). Apart from the cataract risk, the RT described herein is

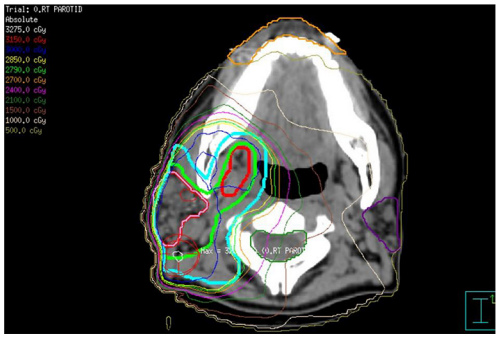

Figure 5 MALT lymphoma of the parotid gland. Radiation treatment for a right parotid MALT lymphoma. Because of deep lobe involvement, the whole parotid gland is covered with an IMRT technique, note sparing of the contralateral parotid gland.

within the tolerance of the eye and deterioration of vision due to RT is rarely observed. The higher risks reported in the literature has been due to higher doses of 35–40 Gy (54) which are unnecessary for MALT lymphoma. A mild degree of permanent dryness of the eye may be observed if the lacrimal gland was treated to full dose. Therefore, ophthalmologic follow up is important.

Emerging evidence indicate that a much lower dose, e.g., 2×2 Gy regimen, can result in a high rate of local control, and can be adopted as an initial treatment strategy to minimize the orbital toxicity of higher dose treatment (12,14, ClinicalTrials.gov Identifier: NCT02494700). It is uncertain at this time if the local control is as durable compared with higher dose standard regimen, although if the patient has a local recurrence the standard 24–25 Gy regimen can still be successfully applied at that time.

Salivary gland and other head and neck locations

MALT lymphoma of the salivary gland is often seen in patients with Sjögren's syndrome (59) which may not have been recognized at the time when lymphoma is diagnosed. Clinical features and serologic studies should be sought to confirm a diagnosis of Sjögren's syndrome, as treatment selection with use of RT for the MALT lymphoma can be affected. Middle aged adults are often affected, with a median age of 62 years (60). The parotid gland is the most commonly involved, sometimes bilaterally. Patients usually present with a painless mass. Non-malignant changes of myoepithelial sialadenitis may be present. Cervical lymph node involvement is occasionally seen, either located in the parotid area or in the upper cervical chain (levels 2 and 3). Surgical biopsy should be pursued with caution and may involve a superficial parotidectomy, since a lesser procedure in the parotid area would not allow adequate exposure to reliably identify and preserve the facial nerve or its branches.

For stage IE disease, the radiation target volume (CTV) should include the whole parotid gland, including the deep lobe. Elective nodal coverage is not required. For those with cervical lymph node involvement (stage IIE), the ipsilateral cervical nodal chain should be covered. The RT dose is 24–30 Gy given in 1.5–2.0 Gy fractions. Conformal techniques with IMRT and VMAT are desirable, as it is important to spare the midline structures, the orbits, and the contralateral salivary glands (*Figure 5*). The acute side effects of parotid radiation include change of taste, xerostomia, limited mucositis and skin erythema. A pre-RT dental assessment is important, as the RT treatment may exacerbate any pre-existing dental problems. As many patients have Sjögren's syndrome, a variable degree of permanent dryness will occur. Symptomatic management with meticulous oral and dental hygiene, consultation with dietician, avoidance of tobacco smoke and alcohol, use of salivary substitutes are all important elements of follow up care. Drugs to improve dryness such as pilocarpine can be tried but can give undesirable cholinergic side effect. Given the concern for increased risk of xerostomia in the population of patients with co-existing Sjögren's syndrome, ultra-low dose RT is often pursued to limit treatment related morbidity (61).

MALT lymphoma can present in the other major salivary glands (sublingual and submandibular), or other minor salivary gland locations in the upper aerodigestive tract, e.g., larynx, trachea, and rarely the maxillary sinus and soft tissue. MALT lymphomas arising from Waldeyer's ring lymphatic tissue (e.g., tonsil, nasopharynx) are exceedingly rare, accounting for only 3.6% of 329 cases of low-grade lymphomas in this site in the series from Kiel (62). RT for these head and neck locations follow the same principles as for the parotid gland, with coverage of the local organ/region. The RT dose is 24 Gy given in 1.5–2.0 Gy fractions.

Thyroid

Thyroid MALT lymphoma is typically seen in patients with Hashimoto's thyroiditis (i.e., lymphocytic thyroiditis) (63) which may not have been clinically obvious. Thyroid function is usually normal, although a long history of Hashimoto's thyroiditis can result in hypothyroidism. Middle-aged adults are often affected, the median age being

62 years (60). Patients commonly present with a painless mass. Regional lymph node involvement is infrequent, but if present, often affects the central neck (paratracheal, perithyroidal lymph nodes). Suspicious thyroid nodules are often investigated with a fine needle aspirate biopsy (FNAB), hence MALT lymphoma can be suspected on this basis, and additional conservative biopsy approaches can be conducted. A routine total thyroidectomy is not required as RT will generally be recommended for local control following surgery. The limited data published suggests that local therapy with surgery with or without RT results in a high likelihood of local control, and unlike MALT lymphoma presenting in other mucosal sites, a very low risk of distant dissemination (2,3,18).

For stage IE disease, the radiation target volume (CTV) should include the whole thyroid gland or in cases where biopsy was performed surgically, the entire thyroid bed. For those with cervical lymph node involvement (stage IIE), the affected cervical nodes should be included in the radiation target volume. The RT dose is 24–30 Gy given in 1.5–2.0 Gy fractions, with conformal techniques to minimize dose to neighboring salivary tissues and the spinal cord.

The main acute side effects of radiation to the thyroid and surrounding neck tissues are skin erythema, temporary laryngitis, tracheitis, and dysphagia to solid foods (secondary to esophagitis), all mild to moderate in degree. These effects resolve over a period of 2–3 weeks after completion of treatment. Hypothyroidism may exist prior to therapy either due to Hashimoto's thyroiditis or as a complication of surgical biopsy (18,63). For patients with normal thyroid function prior to RT, hypothyroidism is an expected complication. Management of treatment related hypothyroidism requires periodic monitoring and thyroxine replacement. Serious long-term toxicity is not observed for the moderate RT doses used for this disease.

Breast

MALT lymphoma of the breast is a rare disease entity (64). In the largest series of histologically low-grade primary breast lymphoma, 24 patients with MALT lymphoma of the breast from multiple centers were retrospectively evaluated by the IELSG (65). The median age at diagnosis was 62 and all patients except for one had unilateral breast disease with (n=25) or without (n=71) regional nodal involvement. The treatment approaches in this study were heterogeneous and included surgery (including breast conserving resection or mastectomy), RT and chemotherapy or some combination of these. The ORR regardless of initial treatment approach was excellent at 100%, however 37% of patients relapsed, typically at distant sites. The relapses were largely salvageable, as the cause specific survival at 10 years was 80%. Of note, no patients who received RT relapsed locally, highlighting a benefit of RT to prevent local recurrence. Moreover, there was a trend towards improved PFS for breast MALT patients who received RT (HR 4.6; 95% CI: 0.9–23.3; P=0.07). The study was limited however in that no patients received immunotherapy with rituximab as a component of therapy.

When RT is used for the definitive management of MALT lymphoma of the breast the entire breast is often targeted with inclusion of regional nodal basins only in cases of disease involvement. In a MDACC series of 11 patients, those treated with RT had local control of 100%, even with low doses of 4 Gy in 2 fractions (17). Distant relapse was not uncommon however with 55% of patients eventually having recurrent disease after initial therapy. Salvage therapy with single agent rituximab was effective and no deaths occurred at a median follow up of 8 years. These limited data suggest a role for initial definitive RT in the management of MALT lymphoma of the breast.

Skin

Among cutaneous B-cell lymphomas (CBCL), primary cutaneous marginal zone B cell lymphoma (PCMZL) is a relatively rare entity, representing 2-16% of all cutaneous lymphomas (66). PCMZL is clinically characterized by multifocal small plaques or nodules mostly on arms and trunk, and histologically by small B cells, monotypic plasma cells, reactive germinal centers, and numerous T cells. RT is a preferred treatment option along with surgical excision, topical/intralesional steroids, monotherapy or combination chemotherapy regimens. The PCMZL prognosis is excellent with 5-year survival rate over 95–98%, however, up to 50% of patients manifest a cutaneous relapse (67).

Comparative data on local excision and RT are still scarce, however locoregional RT is an important option because of the high risk of local recurrence after localexcision (68). Moreover, cosmetic outcomes may be superior with RT. With an RT approach there is also a consideration of the necessity to perform multiple sites of irradiation in some, and reirradiation in case of relapses which occurred mostly outside treatment fields. For stage IE disease, the standard CTV includes the macroscopic disease with 1–2 cm lateral margins (69,70), however Servitje

et al. in a retrospective series of 137 PCMZL applied 5 cm margins (19). Safety margins are needed in order to reduce the risk of local relapse. Depending on the depth of skin infiltration, radiation beam and energy selection can include electron beams (typically with energies 6–9 MeV) or low-energy orthovoltage x-rays (80–120 kV). Bolus material is required to achieve full skin dose for electron beams and higher energy x-rays from linear accelerators. Elective nodal coverage is not recommended. The standard recommended dose is 24 Gy in 1.8–2.0 Gy fractions (68,71,72).

Excellent local control and cosmetic outcomes are expected with a moderate dose of 24 Gy. Toxicity is limited and if it is observed is limited to grade 1 or 2 erythema. Late effects are rare with 24 Gy delivered with conventional fractionation and are typically characterized by skin hypo/hyperpigmentation or alopecia. For such reasons ultra-low dose RT (2×2 Gy) could be an attractive alternative that can also be applied to cutaneous disease (68,73,74), with complete response rates up to 86% and no reported late toxicity while offering excellent cosmetic outcomes. However, Oertel *et al*. (74) comparing standard doses to ultra-low doses showing significantly lower complete response rates (CRR 29%) for the latter group and did not recommend 2×2 Gy as standard treatment. Therefore, the standard of care is not well established because there are only retrospective and single center data with small number of patients. Clinical registry and multicenter studies may help in further explore the role of RT intensity and determine the minimal necessary dose to maintain high response rates.

Lung

Primary lung lymphomas are rare, but approximately 70–80% are MALT lymphomas (75,76). The median age at presentation is 68 years (60), and up to 30% of patients may have an associated autoimmune disease such as Sjögren's syndrome (75,77). The etiologic factor is not known, although long-term exposure to smoking, infection and autoimmune disease may determine antigenic stimuli (76). Characteristic findings on CT imaging include the presence of a mass, consolidation, airway dilatation, air bronchograms, and surrounding ground-glass changes (78). Multifocal disease is common, occurring in 19 of 24 cases (79%) (78). Regional lymph node is frequently involved, occurring in 44% of cases according to Kurtin *et al.* (75).

For patients presenting with stage IE or stage IIE disease, RT is recommended if the volume of lung exposed to radiation is not excessively large. Pre-RT assessment of pulmonary and cardiac function is important, and should include clinical evaluation, spirometry and diffusion capacity, and cardiac ejection fraction. The target volume encompasses the gross disease with a margin taking account of organ motion due to the respiratory cycle (*Figure 6A*). Established methods of motion management (e.g., DIBH) should be used whenever feasible. A RT dose of 24–30 Gy given in 1.5–2.0 Gy fractions over 2 to 3 weeks is prescribed (*Figure 6B*, *C* and *D*). As the lung tissue has limited tolerance to radiation (79,80), large target volumes result in a high risk of radiation pneumonitis and later pulmonary fibrosis with functional impairment. Therefore, if the tumor is bulky, or has significant pleural extension or malignant effusion, or if multiple lung nodules are present, conventional RT fractionation should not be used. Low dose RT with 2×2 Gy regimen can be very effective for local control (11). Otherwise, for more extensive disease chemotherapy is recommended. Lung tissue exposed to a dose of 30 Gy given in 2 Gy fractions or less have an approximately 40–50% chance of manifesting visible changes of pneumonitis on a CT scan (80). Factors that affect this risk include the volume of lung tissue irradiated, and the dose/fraction (81). The presence of RT changes in the lung can make response assessment difficult if residual treatment related abnormalities persist. For patients with small MALT lymphomas treated with complete surgical excision confirmed pathologically, RT may be unnecessary. If resection margins are positive, postoperative RT can be considered.

The literature describing the clinical outcome of MALT lymphoma of the lung documents an indolent disease similar to MALT lymphoma of other sites (16,82,83). Kurtin *et al.* reported a 10-year cause-specific survival of 72% in a series of 50 patient with lung lymphoma (52% were of MALT histology) (75). A series of 35 patients predominately treated surgically had 5- and 10-year survival of 68% and 53% respectively (76).

Dura

Primary dural lymphoma is an infrequent subtype of primary CNS lymphoma that arises from the dura mater without direct involvement of the parenchyma of the brain (*Figure* 7). Dural lymphoma are often mistaken for meningiomas due to similarities in radiographic features and clinical presentation (84). While the majority of primary CNS lymphomas are aggressive DLBCL, dural lymphoma

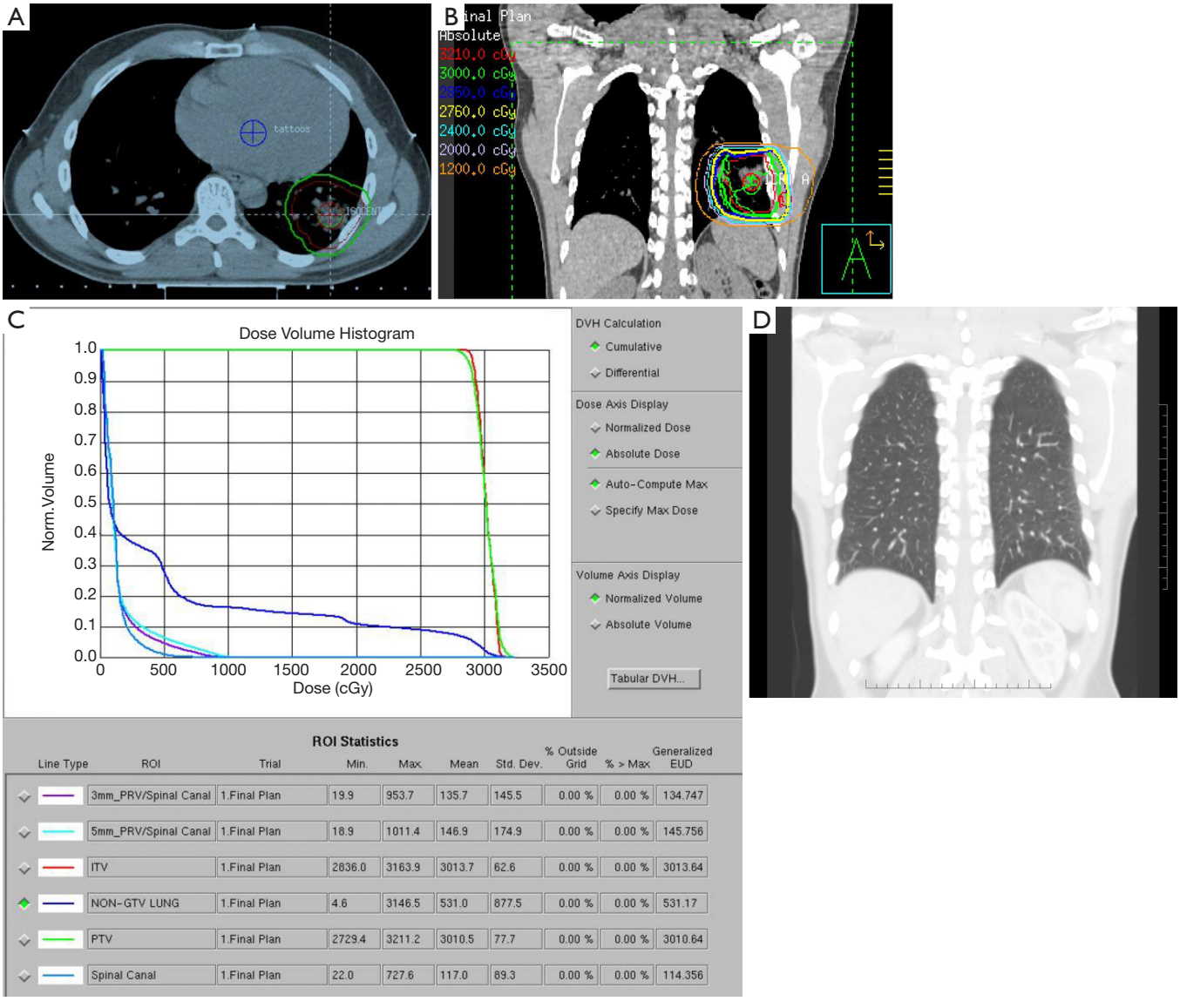

Figure 6 MALT lymphoma of the lung. A 40-year-old man with localized disease (stage IE) in the left lower lobe of the lung, a 2.5 cm lesion. (A) The internal target volume (ITV-red line) takes respiratory motion into account, and an added 5 mm safety margin gives the planning target volume (PTV-green line). (B) Isodose distribution in the coronal perspective, prescribed dose 3,000 cGy in 20 fractions. (C) Dose volume histogram. Note that the volume of non-target lung tissue receiving a dose of 20 Gy or more (V20) is less than 12%. (D) CT scan (coronal perspective) 6 months post RT showed complete response. The patient is alive and free of recurrent lymphoma 12 years after RT.

are typically marginal zone lymphomas (85). Dural MALT lymphoma patients can present with a range of clinical symptoms; however, headache and seizures are common (86). A female predominance has been reported. Treatment approaches are varied; however, RT has been utilized with good outcomes (86,87). In a large series of 26 marginal zone dural lymphoma patients treated at MSKCC and the University of Miami, 22 patients achieved CR, including 12 patients treated with focal RT and 7 patients that received WBRT with or without a boost (88). Most patient were treated to a dose of 30–36 Gy. At a median follow up of just over 5 years, the median PFS and OS were not reached. All patients were alive at last follow up indicating the indolent nature of the disease and success of local therapy.

There is no standard approach for the management

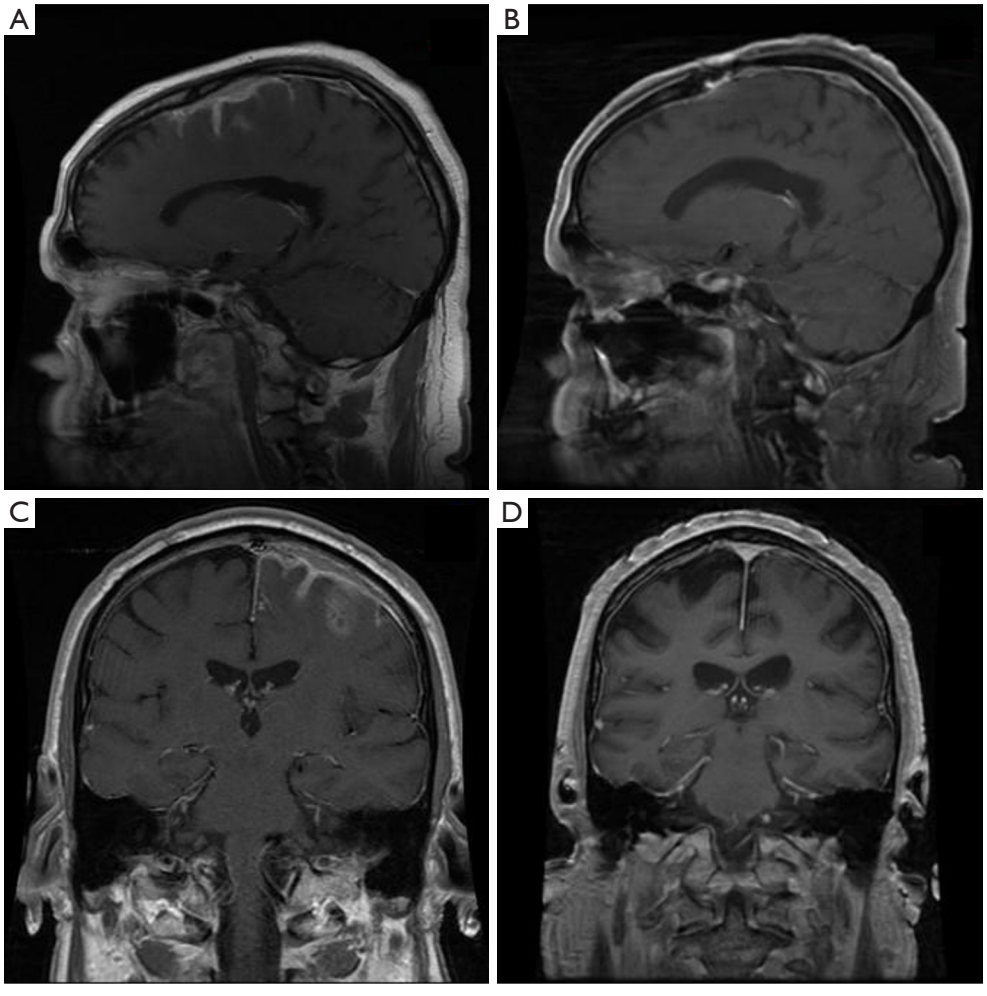

Figure 7 Dural marginal zone lymphoma. A 62-year-old male presented with a tonic clonic seizure. MRI revealed leptomeningeal enhancement in the left frontoparietal region apparent on T1 post contrast sagittal (A) and coronal (B) images. Biopsy revealed marginal zone lymphoma. Additional work up including PET-CT imaging, bone marrow biopsy and MRI imaging of the spine revealed no evidence of additional sites of disease. He received 4 cycles of Rituxan followed by focal RT to a dose of 36 Gy in 20 fractions. He achieved a complete response to therapy as evidenced on MRI performed 3 months after completion of therapy (C,D). He remains in remission 11 years later.

of MZL involving the dura, however aggressive systemic therapeutic approaches are often not warranted. In most cases the use of high dose methotrexate is discouraged, especially if RT is considered given the risk for neurotoxicity (88) and the excellent outcomes that can be achieved with single modality local therapy. Current guidelines from ILROG suggest focal therapy to the presurgical/biopsy MRI volume with margin to a dose of 30–36 Gy in cases of a single lesion (15). For multifocal disease WBRT to 24 Gy followed by a boost to involved sites with an additional 12 Gy is considered appropriate therapy. It is likely that lower RT doses such as 24 Gy would be effective, however existing published data indicates good outcomes of moderate RT doses of 30–36 Gy.

Summary/conclusions

We focused on the use of RT in the management of MALT lymphomas (*Table 1*). The evidence where the definitive use of RT has been successful in the management of the disease was presented. The outcome following moderate-dose RT for stage IE and IIE MALT lymphoma is that of long-term local control and possible cure. However, five to ten years of follow up is likely still insufficient to fully characterize

Table 1 Main series of radiotherapy for extranodal marginal zone lymphoma

Anatomic site	Author	Type of study	N. pts	Histology	Dose, median (range)	Target volume	RT technique	Local control	Follow-up, median (range)	Survival rates	Toxicity
Gastric	Abe 2013 (36)	Retrospective	34, 100% failed HPE	100% MZL	30 Gy, 1.5–2 Gy/fr	CTV: stomach wall & perigastric lymph nodes	Opposed anterior and posterior fields or multiple field irradiation	97.1% CR	7.5 yr (1.2–13.0)	97%. 5-yr RFS 97% 5-yrOS 100% 5-yr DSS	No serious late events
	Wirth 2013 (4)	Retrospective	102, 34% failed HPE	100% MZL	40 Gy (26–46 Gy)	Whole abdomen 50%, IFRT (stomach wall)	Antero-posterior pair and multi-field technique	96% CR	7.9 yr (0.3–24)	70% 10-yr OS	11 second malignances: 4 in field
	Pinnix 2019 (49)	Retrospective	32	100% MZL	21 pts: 30 to 36 Gy, 11 pts: 24 Gy, 1.5–2 Gy/fr	CTV: stomach wall	IMRT with DIBH	100% CR; 100% 2-yr FFTF	55.2 months (32.4–78.1)	97% 2-yr OS	No cardiac renal late events
	Schmelz 2019 (48)	Prospective	29	100%	36 Gy versus 25.2 Gy	CTV: stomach and the local lymph nodes	3D CRT	100% CR	79 months (36.4-143.8)	NA	3 second malignances
Orbit	Le 2002 (51)	Retrospective	31	100%MZL	30–40 Gy, 1.8–2 Gy/fr	CTV Conjunctiva; CTV Retrobulbar	6–20 MeV electron anterior field; 4–6 MV photon multiple beam	100% CR; 71% 10-yrs FFR	5.9 yr (9 months – 20.3 yr)	73% 10-yr OS	No cataract; 1 retinopathy
	Fasola 2002 (12)	Retrospective	20	40% MZL	4 Gy 2Gy/fr	Entire conjunctiva:	6–12 MeV electron anterior field, 4-6MV photon beam	96% ORR; 100% 2-yrs FFLR	26 months (7–92)	96% 2-yr FFRR	No retinopathy or keratitis; No cataract RT-related
	Goda 2011 (2)	Retrospective	89	100%MZL	25 Gy 98%, 30 Gy 2%, 2.5 Gy/fr	Entire orbit	Electron anterior field, 4–6 MV photon multiple beam	99% CR; 7-year LC rate 97%; 64% 7-yrs RFS	5.9 yr (1–16)	91% 7-yr OS 96% 7-yr CSS	25% Grade 3 cataract at 7 yrs
	Pinnix 2017 (14)	Retrospective	22	64% MZL	4 Gy 2Gy/fr	CTV: entire palpebral and bulbar conjunctiva or entire orbit	Electron and photon	100% ORR	14.1 months (range, 3.7–29.9)	NA	1 dry eye syndrome
Breast	Martinelli 2009 (65)	Retrospective	60	40% MZL	Breast: median 38 Gy (range 25–50 Gy): median 36 Gy (range 30-46 Gy)	CTV: whole breast, if indicated axilla and supraclavicular node	NA	100% ORR	44 months (5–156 months)	64% 5&10-yr OS 72% 3-yr PFS 56% 5-yr PFS 34% 10-yr PFS	NA
	Ludmir 2019(17)	Retrospective	11	100%MZL	Median 30 Gy (range, 4–45 Gy) 1.5–2 Gy/fr	CTV: whole breast	Opposed tangent beams	100% LC	8 yr (4.8–10.2)	60% 5-yr PFS	1 pts: late grade 1 breast fibrosis
Skin	Neelis 2009 (73)	Retrospective	18	55% MZL	4 Gy, 2 Gy/fr	CTV: gross tumor plus 2 cm margins	Electron beam mostly 4 MeV	72% CRR	13 months (2.3–42)	NA	None
	Servitje 2013 (19)	Retrospective	137	100%	Range 30–40 Gy	CTV: gross tumor plus 5 cm margins	Single electron field	88% CRR	54 months (12–165)	46% 5-yr DFS 93% 5-yr OS	NA
	De Felice 2018 (72)	Retrospective	42	45% MZL	Median 36 Gy range 20–46 Gy	CTV: gross tumor plus 2 cm margins	Electron field	100% CRR	9.5 yr	79% 5-yr RFS 71% 10-yr RFS 87% 10-yr OS	
	Gauci 2018 (71)	Retrospective	46	46% MZL	Median 24 Gy (18–30 Gy) 3 Gy/fr	CTV: gross tumor plus 0.5–1 cm	Low-energy X-rays (80–120 KV)	96% CRR	43.5 months (0.6–100)	55% 3-yr DFS	78% moderate sequelae (pts reported)
	Oertel 2020 (74)	Retrospective	26	38.5% MZL	Median 40 Gy (4–50 Gy)	NA	Electron and photon	ORR: 92% *vs.* 86% CRR: 84% *vs.* 29% conventional RT *vs.* low dose RT	NA	55% 10-yr PFS	54% grade 1 late toxicity (conventional RT); None in low dose RT

Table 1 (*continued*)

Table 1 (*continued*)

Anatomic site	Author	Type of study	N. pts	Histology	Dose, median (range)	Target volume	RT technique	Local control	Follow-up, median (range)	Survival rates	Toxicity
Lung	Girinsky 2012 (11)	Retrospective	10	100% MZL	4 Gy 2 Gy/fr	PTV: gross tumor plus1 cm isotropic margin	3D CRT	80% CR	56 months (2–103 months)	86% 5-yr PFS 100% 5-yr OS	None
Central Nervous system Dura	de la Fuente 2017 (88)	Retrospective	26	100% MZL	16 to 36 Gy in 9 to 20 fr 36 to 39 Gy in 20 to 26 fr	13 pts focal RT 6 whole brain RT	IMRT	85% CR	64 months (2–209 months)	89% 3-yr PFS	NA
	Sunderland 2020 (87)	Retrospective	26, 27% Sugery+ RT	100% primary or secondary MZL	NA	NA	NA	77% CR in primary MZL 2% CR in secondary MZL	1.9 yr (0.1–11.4)	59% 2-yr PFS 80% 2-yr OS	NA
Mixed anatomic site	Tsang 2001 (9)	Retrospective	75	100% MZL	25 Gy for orbital lymphoma, 30–35 Gy fractions for other sites 1–2.5 Gy/fr	CTV: involved organ/lymph node, with or without the adjacent first echelon lymph node region	IFRT	96% CRR	4.2 yr (0.3–11.4)	76%5-yr DFS 96%5-yr OS	No serious toxicity observed
	Goda 2010 (2)	Retrospective	167, Salivary glands 28; Thyroid 21; Other head and neck sites 6	100% MZL	Median 30 Gy (range, 17.5–35 Gy)	CTV: whole organ plus locoregional lymph nodes for thyroid	Electron field/photon beam 2D, 3DCRT & IMRT	99% CRR 76% 10-yr RFR Salivary gland: 68% 10-yr RFR Thyroid: 95% 10-yr RFR	7.4 yr (0.67–16.20)	68% 10-yr DFS 87% 10-yr OS 98% 10-yr CSS	NA
	Teckie 2015 (3)	Retrospective	244	100% MZL	Median 30 Gy	NA	Electron fields 3-D CRT or IMRT	88% CR	5.2 yr (0.2–21.3)	92% 5-yr OS 74% 5-yr RFS	NA

N, number; Pts, patients; HPE, *Helicobacter Pilory* eradication; RT, radiation therapy; fr, fraction; LC, local control; CR, complete response; CRR, complete response rate; ORR, overall response rate; DFS, disease free survival; RFS, recurrence free survival; DSS, disease specific survival; FFLR, freedom from local relapse; OS, overall survival rate; FFR, freedom-from relapse; RFR, recurrence free rate; FFRR, freedom from regional relapse; CSS, cancer specific survival; RFS, relapse-free survival; CTV, clinical target volume; PTV, planning target volume; 3D CRT, 3 dimensional conformal radiotherapy; IMRT, intensity modulated radiation therapy; NA, not available.

the impact of treatment on MALT lymphomas since late recurrences can occur, and patients with recurrent disease often have prolonged survival. We are of the opinion that where local disease control can be achieved without significant toxicity, involved site RT should be offered (15).

The technical aspects of delivering effective and safe RT were illustrated for both common and rare presentations of the disease and expected side effects of therapy were discussed. The concern about late effects of radiation, mainly induction of second cancers should lead to the use of more restricted involved site RT volumes, lower RT doses, and techniques that optimize normal tissue protection (15). Given the unique biologic behavior of MALT lymphoma with a tendency to relapse in extranodal MALT sites and an indolent course, it is not surprising that RT is often the treatment of choice again for patients with localized relapses. We suggest clinicians must remain vigilant in weighing the relative benefit of radiotherapy and chemotherapy, and the toxicities of both modalities to optimize the management of patients with MALT lymphomas.

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Footnote

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