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The indolent extranodal lymphomas: What is the role of radiation therapy?

A B S T R A C T

The indolent lymphomas include follicular lymphoma (grade 1-2), marginal zone lymphoma, mycosis fungoides, primary cutaneous follicle center lymphoma, and solitary plasmacytoma. Although the follicular lymphomas rarely present with extranodal involvement only, the other indolent lymphomas occur frequently or exclusively with extranodal localizations. Radiation therapy plays a meaningful role in the management of all of these diseases. For patients who present with stage I-IIE disease, that treatment may be with curative intent and expectation. But even patients with stage IIIE-IV disease may achieve meaningful palliation with radiation therapy. This review will consider the role of radiation therapy in the management of extranodal lymphoma in the overall context of treatments available for these diseases.

The follicular lymphomas (Grade 1-2)

Most patients with follicular lymphoma present with extranodal disease, since the bone marrow, spleen and other extranodal sites such as the liver are often involved at presentation.[1] However, primary extranodal follicular lymphoma (stage IE-IIE) is relatively uncommon, accounting for only about 10-20% of patients with stage I-II disease and therefore only about 1-2% of patients with follicular lymphoma. Table 1 details the sites of extranodal involvement reported in the Stanford experience.[2] Other series report a similar distribution.[3,4] The principles for management of patients with stage IE-IIE primary extranodal follicular lymphoma are the same as those that are well-established for stage I-II nodal presentations. Involved field irradiation, in a dose range of 25-35 Gy, achieves very high response rates and local control rates, and about 50% of patients enjoy long-term relapse-free survival.[5] Comparison of patients with or without extranodal involvement reveals a similar outcome.[2] Few trials have looked at the value of combined modality therapy utilizing conventional chemo-therapy compared to irradiation alone, and these have not shown a significant benefit to the combination approach.[5] More provocative would be the use of rituximab, an anti-CD 20 antibody, in combination with irradiation. The addition of rituximab to conventional combination chemotherapy has been shown to improve the outcome of patients with advanced stage follicular lymphoma.[6] It is possible that ritux-

imab may also decrease the 50% relapse risk for patients with stage I-II disease. In addition, since laboratory studies have shown that exposure to radiation doses as low as 4 Gy may significantly enhance CD20 expression in B-cells, it is possible that even lower doses than the conventional 25-35 Gy may be considered for primary therapy.[7] This should be tested in a clinical trial.

The marginal zone lymphomas (excluding skin)

The marginal zone lymphomas commonly present with extranodal localizations and are often managed with radiation therapy alone. The most common sites of presentation for extranodal marginal zone lymphoma, based on the experience at the Princess Margaret Hospital in Toronto, are displayed in Table 1.[8] The most common are gastric (13 of the 14 gastrointestinal cases were gastric) and ocular adnexal sites. Gastric marginal zone lymphomas (or mucosa-associated lymphoid tumor [MALT] lymphomas) that are associated with *Helicobacter pylori* infection are treated initially with histamine H_2 receptor blockers and antibiotic therapy. However, stage IE gastric MALT lymphomas that are not associated with H. pylori or that persist after an adequate trial of antibiotic therapy may be treated quite effectively with local radiation therapy. This commonly occurs in gastric MALT lymphomas that are associated with the t(11;18) translocation, where the association with *H. pylori* is low and the response to antibiotic therapy unlikely. The appropriate treatment for these patients is involved field irradiation, which includes the entire stomach and the perigastric lymph nodes. A dose of 30 Gy has been associated with an event-free survival of 100%,[9] although interpretation of gastric biopsies after completion of irradiation is challenging.

Table 1. Distribution of extranodal sites for stage IE-IIE indolent lymphoma.

Site	*Follicular lymphoma*	*Marginal zone lymphoma*
Gastrointestinal	6	14 (13 gastric)
Orbital Adnexa	5	30
Salivary Gland	3	21
Thyroid	1	13
Other Head/Neck	4	5
Lung		3
Genitourinary	2	3
Skin		2
Breast		2
Other	3	

Adapted from MacManus and Hoppe [2] and Tsang et al.,[8]

There is limited experience utilizing chemotherapy in the management of these patients. Hammel *et al.*[10] reported on 17 patients (*H. Pylori* status not defined) with stage IE disease treated with single agent chlorambucil. A complete response was achieved in 14/17 after a median duration of treatment of 9 months. Two of the 14 patients in CR relapsed one year after the cessation of therapy. A large randomized trial of *H. pylori* positive patients who had their disease eradicated by antibiotics failed to show any value from the administration of adjuvant chlorambucil.[11]

Rituximab has also shown activity in the management of gastric MALT lymphoma. Martinelli and associates treated 26 patients who were resistant, refractory, or not suitable for antibiotic therapy.[12] A compete response was achieved in 12 patients (46%) and two of these 12 subsequently relapsed.

Another common site of MALT lymphoma is the ocular adnexal tissues, including the conjunctiva, lacrimal glands, and retro-orbital tissues. These lymphomas almost always present as stage IE disease. Local (involved field) irradiation is the treatment of choice. Doses of only 25-30 Gy are associated with excellent long-term local control. Doses in this range are

below the threshold for damage to most parts of the visual apparatus (conjunctiva, retina and optic nerves), but radiation-related cataracts may develop at these dose levels and relatively complex configurations of treatment fields, often including combinations of photons and electrons, may be necessary in order to spare the lens.[13] In addition, lacrimal gland function may be affected by doses in excess of 30 Gy. Although local control for these patients is close to 100%, as many as 30-40% of patients will relapse. These relapses tend to occur in other MALT lymphoma sites, including the contralateral orbit.[8,14] The frequency of relapse in remote sites again would make adjuvant rituximab an attractive approach to study in a clinical trial. Rituximab as a single agent has been associated with CR rates of only ~50% in patients with MALT lymphomas of the ocular adnexae.[15,16] A small proportion of cases of orbital MALT have been associated with infection by *Chlamydia psitacci*. In a situation analogous to the use of antibiotics for patients with *H. pylori* associated gastric MALT, these patients may be treated with doxycycline. However, the complete response rate for these patients is less than 25%.[17] Other common primary sites of MALT lymphoma include the salivary glands and thyroid. Again, local control is generally achieved with a dose of 30 Gy. Distant failure is unusual for thyroid MALT, but occurs in as many as 20% of patients with salivary gland presentations.[8] Although the radiation dose recommended for patients with extranodal marginal one lymphoma is 25-35 Gy, there are provocative experiences utilizing a much lower dose, i.e., 4 Gy (2 Gy x 2). Experience with this very low dose has been reported in the palliative management of patients with advanced stage indolent lymphoma.[18] Given the high response rates and minimal toxicity to be expected with this dose, it affords an especially attractive option for treatment of orbital or salivary gland MALTs, where even doses of 25-30 Gy may be associated with some risk of toxicity.

The primary cutaneous lymphomas

Primary cutaneous lymphomas are lymphomas that arise in the skin and upon careful staging evaluation no extracutaneous disease is detected, the exception being mycosis fungoides, which may have an extracutaneous component. Mycosis fungoides (MF) is a T cell lymphoma and the most common cutaneous lymphoma. Radiation therapy is a very effective agent in managing this disease.[19] Patients with MF commonly present with generalized skin involvement, consisting of patches and plaques. Topical therapies such as nitrogen mustard or corticosteroids, phototherapy such as narrow band UVB, and radiation therapy may all be used for patients with generalized skin disease. Radiation therapy achieves the highest complete response rates. When cutaneous tumors are present, radiation has a far greater ability to eradicate disease than any other modality. For patients with generalized skin involvement, a special technique of irradiation has been developed, total skin electron beam therapy (TSEBT) that permits treatment to the entire skin. Patients are treated in the standing position and must assume several different 'poses' in order to expose the entire skin surface to the treatment.[20] Electrons are chosen as the form of ionizing irradiation because they will penetrate to only a finite depth. Therefore, despite the entire skin surface being treated, there is no effect of the irradiation beyond a centimeter or so of depth. The total dose delivered is generally 30-36 Gy. The results of TSEBT are excellent. For stage IB-IIA disease (generalized patch/plaque disease), the overall response rate is nearly 100% and the complete response rate is 56-81% in large series. For patients with stage IIB (cutaneous tumors), the

complete response rate is 24-53%.[21] However, the complications may be significant and include hair loss, temporary effects on ability to sweat, occasional skin atrophy or telangiectasia, and an increased risk of squamoproliferative lesions. Because of those risks, the treatment is generally not used for patients with stage IA disease (limited patch/plaque). In addition, it is not often used in stage IIIA (erythroderma), since the atrophic skin of those patients does not tolerate irradiation very well. Although TSEBT has a high likelihood of clearing the skin, disease will often recur, and the major benefit of treatment is its important palliative effect and ability to decrease the disease 'burden'. Other therapies, such as topical nitrogen mustard or phototherapy, may then be used in an attempt to maintain the skin clearance. Occasional patients present with 'unilesional MF.' When this disease presents as a solitary patch or plaque, the likelihood of eradicating it completely and permanently with a single course of local electron beam therapy is excellent.[22] Doses of 25-35 Gy have been used in this setting, treating the primary lesion and including 2 cm margins of apparently normal skin. Local irradiation is also very useful as a palliative therapy for patients with cutaneous tumors or plaques that are refractory to other therapies. Doses of 15-35 Gy may be used, depending upon the site of involvement and rapidity of response. Patients with extracutaneous MF may also benefit from the use of irradiation. Lymph node involvement, especially when localized, can be treated with involved field irradiation in a fashion analogous to that used for other lymphomas. The most common types of primary cutaneous B-cell lymphoma include marginal zone lymphoma and follicle center cell lymphoma. Follicle center cell lymphoma includes many lymphomas classified previously as follicular lymphoma or diffuse large B cell lymphoma.[23] These B-cell lymphomas may present as solitary lesions. Local irradiation is usually successful in achieving long-term local control.[24] Doses of 25-36 Gy, depending upon location and size of disease, are usually employed. Margins of uninvolved skin should be 1.0-2 cm., depending on the site being treated. Although the local control rates are excellent, as many as 50% of patients will have a relapse of disease in a remote skin site. New sites of disease may again be treated with irradiation. When there are multiple lesions at presentation, they may still be irradiated; however, the risk of subsequent relapse is much greater. Recently, rituximab has been shown to be of value for these patients. At Stanford, we treated a series of 15 patients who had multiple cutaneous lesions.[25] The overall response rate was 13/15 (87%) and the complete response rate was 9/15 (60%). Although 4/9 patients in complete response eventually relapsed, the median time to progression was 24 months.

Solitary plasmacytoma

Solitary plasmacytoma is a "solid tumor" manifestation of multiple myeloma. Solitary plasmacytomas may occur in soft tissue (extramedullary) or bone (osseous) and, by definition, are not associated with bone marrow involvement, although M protein may be detected in the serum or urine in one-third to one-half of patients. Osseous plasmacytomas account for 70% of solitary plasmacytomas. They arise most commonly in the vertebrae, pelvis, ribs, sternum, scapula, and femurs. The treatment of choice is radiation therapy. The treatment volume includes the involved bone and any adjacent soft tissue extension, with margins of 2-2.5 cm. For example, when treating an involved vertebral body, at least one additional vertebra should be included above and below the involved vertebra. The prescribed dose is at least 40 Gy in 2 Gy fractions.

The local control rate after radiation therapy alone is ~85%.[26-27] The actuarial risk of progression to myeloma is greater than 60-70% at ten years. The risk of progression is greater if there is persistence of abnormal protein following radiotherapy. The overall median survival is about ten years following diagnosis. Extramedullary plasmacytomas are less common than plasmacytomas of bone. Most (~80%) occur in the upper aerodigestive tract, including the nasal cavity and maxillary sinus, and may be associated with secondary bony destruction. Again, radiation therapy is the treatment of choice, although the recommended dose is slightly higher, 50 Gy in 2 Gy fractions. The volume should include the entire tumor with reasonable margins. Regional nodes are sometimes included in treatment of plasmacytomas of non-sinus head and neck sites. Local control is reported in 85-95% of patients and the presence of bony erosion is not necessarily an adverse factor. In contrast to osseous plasmacytomas, the actuarial risk of progression to myeloma is only 20-30%.

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