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EDITORIAL – ENDOCRINE TUMORS

Disease-Specific Survival by Treatment Modality in Patients with Stage IE Primary Thyroid Lymphoma: Discussion of Risks and Benefits

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Approximately 788,781 people in the United States were living with non-Hodgkin lymphoma (NHL) in 2020. The incidence of NHL was 18.7 per 100,000 men and women per year, with a death rate of 5.1 per 100,000 men and women per year.[1] The 5th edition of the World Health Organization classification of hematolymphoid tumors uses a hierarchical system that organizes these diseases by the increasing levels of specification, such as cell lineage category (e.g. mature B cells), family/class (e.g. large B-cell lymphoma), entity/type (e.g. diffuse large B-cell lymphoma [DLBCL]), and subtype (e.g. DLBCL/high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangement).[2] The more detailed classification that incorporated pathogenic molecular alterations shifts the traditional grading to a biological grouping that can be targeted by small molecule inhibitors. The treatment modalities for NHL are systemic cytotoxic chemotherapy, biological (antibody-based or small molecule inhibitors) therapy, radiotherapy, and stem cell transplantation. The main roles of surgery in managing patients with NHL are to obtain tissue samples for diagnosis, to palliate symptoms, and to treat complications. The use of surgery as a primary treatment for NHL is generally limited to indolent disease in the early stage (Ann Arbor stage I (single lymph node region) and IE (single extralymphatic organ or site). For example, surgery with adjuvant chemo and/or radiotherapy is an adequate therapy for stage IE gastric mucosa-associated lymphoid tissue-type tumor (MALT) with a low complication rate and good survival. However, systemic chemotherapy should be a primary treatment in patients with more advanced gastric MALT.[3]

Primary thyroid lymphoma (PTL) is a rare malignancy of the thyroid gland, representing 1–5% of thyroid malignancies and 3% of NHLs.[4] Because of the lack of high-quality data in a large cohort, the management of indolent PTL such as MALT remains controversial. Patients with chronic lymphocytic thyroiditis have an increased risk of developing myeloproliferative and lymphoproliferative neoplasms, especially PTL, with an estimated relative risk of 67.[5] However, because chronic lymphocytic thyroiditis is a very common disorder, only 0.5% of patients (mostly female) with chronic lymphocytic thyroiditis develop PTL. Patients with PTL commonly present with a rapidly growing thyroid nodule causing compressive symptoms. The diagnosis is obtained by ultrasound-guided fine needle aspiration of a suspicious thyroid nodule in combination with flow cytometry and/or immunocytochemistry staining of the aspirates. Because the diagnostic sensitivity and reliability of the fine needle aspiration biopsy varied, core biopsy or surgical biopsy to obtain tissue diagnosis is not uncommonly required. Similar to NHL at other sites, pathologic subtypes and molecular alterations influence patient prognosis. It is critically important to distinguish between DLBCL, MALT, and mixed subtypes. Because DLBCL is more aggressive, the combination of radiotherapy, cytotoxic chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone), and monoclonal antibody (rituximab) treatment results in the highest survival. Although surgery is infrequently used as a primary

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treatment modality in patients with PTL, it can be considered in selected patients.

Tang et al. conducted a retrospective study to assess disease-specific survival by treatment modality in patients with stage IE PTL in the Surveillance, Epidemiology, and End Results (SEER) cohort. In addition, the authors reported the rate of disease recurrence and treatment-related complications in patients with PTL treated at their institution. Although there were several studies reporting overall and lymphoma-specific survival and clinical variables related to these outcomes, including treatment modalities in unmatched cohorts, the study conducted by Tang et al. compared the disease-specific survival by treatment modality to assess the efficacy of surgery alone versus surgery with radiotherapy and/or chemotherapy versus chemotherapy and/or radiotherapy in propensity-score matched cohorts to reduce selection bias. The matching process optimized the discrepancy in age and histology of PTL, as surgery cohorts had a higher rate of MALT and a lower rate of DLBCL. The estimated disease-specific survival of patients with stage IE PTL did not differ by the treatment modalities above. In addition, the authors reported the lack of statistically significant difference in estimated disease-specific survival in a subgroup analysis in patients with stage IE DLBCL by treatment modality. However, it is possible that there was a Type II error in the comparison of estimated disease-specific survival of patients with DLBCL treated with surgery vs. radiotherapy and/or chemotherapy due to a small sample size given a clear separation of the survival curves. In addition, the SEER cohort lacks data on recurrent disease. In their institutional cohort ($n = 38$), the authors showed that the surgical group had fewer complications and the cost of treatments was less than that of those who received radiotherapy and/or chemotherapy. The number of patients with recurrent disease was too few to compare the difference.

In the absence of level I data in this rare disease, treatment options should be individualized and thoroughly discussed in a tumor board, based on risks and benefits as well as patient preference. Accurate clinical staging is critically important to identify those who have stage IE PTL, as the data from this study suggest that surgery is a viable option in *stage IE PTL*, including those with DLBCL. Perhaps chemotherapy and/or radiotherapy may be reserved for patients who recur after thyroidectomy. A long-term follow-up is mandatory as locoregional recurrence or distant metastasis can occur following initial treatments, even many years after.[6]

The prognosis of PTL has improved and the prognosis is excellent for early-stage PTL (stage IE and IIE) after proper management, which traditionally includes radiotherapy and chemotherapy (and rituximab), especially in a more aggressive histology such as DLBCL.[7] The knowledge gap that should be addressed in a multi-institutional cohort, based on the study by Tang et al.[8] is the efficacy of surgery alone in stage IE PTL, with a focus on survival and disease recurrence. It is also important to assess whether the use of systemic therapy with or without radiotherapy in patients with recurrent disease following thyroidectomy would result in long-term survival.

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