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The term "malignant lymphoma" refers to cancer of the lymphatic/reticuloendothelial system and comprises two major categories of malignant disease—Hodgkin's disease and non-Hodgkin's lymphoma. Both Hodgkin's disease and non-Hodgkin's lymphoma share the commonalities of frequent presentation with lymphadenopathy; a common symptomatology of fever, night sweats, and weight loss; a common staging classification; and a therapeutic approach using radiation and/or chemotherapy. They also have important distinguishing features in terms of age spectrum, histologic and cytologic appearances, prognosis, and the frequency with which non-Hodgkin's lymphomas present as primary extranodal tumors—a circumstance of extreme rarity in Hodgkin's disease.

"Primary extranodal lymphoma" refers to a localized presentation of lymphoma arising within an extranodal tissue and deemed to be the site of origin of the lymphoma even though regional lymphadenopathy may be present. The term implies that disseminated disease is not clinically evident, thus distinguishing extranodal presentation with or without lymphadenopathy (stages I to IIE) from disseminated or stage IV disease. The term also has more relevance when applied to the tissue of origin, for example, tonsil, paranasal sinus, or thyroid lymphoma, than to an anatomic region of the body, for example, head and neck lymphoma.

This chapter addresses primary extranodal lymphomas other than those arising in skin or the central nervous system (CNS). Although it is not known whether mediastinal large cell lymphoma arises from nodal or extranodal (thymic) tissue, it is included as a characteristic clinic entity distinguishable from nodal lymphoma of equivalent stage presenting in nonmediastinal sites.

Whereas Hodgkin's disease virtually always arises in nodal tissue and relatively less commonly involves extranodal tissues by extension from nodal tissue or by dissemination, non-Hodgkin's lymphomas have a much greater propensity to disseminate early through systemic circulation of lymphoma cells. In principle, therefore, it is not really surprising that extranodal lymphomas have been recorded in virtually every tissue of the body, as either primary or metastatic lesions. It is also clear, however, that certain tissues are much more commonly the site of primary extranodal lymphoma, for example, gastrointestinal (GI) tract and tonsil, and that there are factors that determine preferential patterns of spread of lymphoma and the receptiveness of c or organs to accommodate metastatic growth.

The following three principal issues are con respect to primary extranodal lymphoma:

- *Does the presentation of localized dis extranodal site confer a different progr presentation of similar stage in a nodal si* presented in Figure 25–1 suggest that wh by stage alone, there is no difference in patients presenting with nodal or extr phoma. This is somewhat surprising given extranodal lymphomas are much more c diffuse large cell type (or more aggressiv types) than nodal lymphomas, despite oth parable prognostic attributes. Thus, the between nodal versus extranodal lympho constitute a prognostically relevant distinc further analysis of the subcategories o disease.
- *Do all primary extranodal lymphomas ha natural history and prognosis?* A more de of the natural history and prognosis o lymphoma reveals a wide diversity that la the frequency with which low-grade, indo constitute a substantial proportion of p conferring a "favorable" prognosis (≥60% vival rate)—for example, GI tract, Wald orbit, salivary gland, and lungs—as oppose tissues where intermediate- and high-grad types constitute the dominant proporti ample, testis or ovary, bone, breast, or pr Even with certain sites or tissues, th spectrum and prognosis can be extreme neous, for example, primary cutaneous lym T-cell and B-cell representation through high-grade malignancies (see Chapter 27) tant concept in primary extranodal ly mucosa-associated lymphoid tissue (MA subsequent relationship to low-grade mali possible etiologic association with antige tion and favorable natural history with lo potential are features of MALT lymphoma trasts with the more fulminant presentati

Time in years

Figure 25–1. Cause-specific survival rates from the date of diagnosis for extranodal and nodal presentations of stages I and II non-Hodgkin's lymphoma. (From Sutcliffe SB, Gospodarowicz MK: Localized extranodal lymphomas. *In* Keating A, Armitage J, Burnett A, Newland A [eds]: Haematological Oncology. Cambridge, Cambridge Medical Reviews, 1992, pp 189–222.)

and widespread dissemination of disease in sites or tissues characterized by intermediate- or high-grade tumors, for example, bone or testis. Primary CNS lymphomas also present characteristic features related to the histologic type, the growth pattern (largely confined to the nervous system), the probability of local recurrence (high), and the etiologic role of immunodeficiency, particularly acquired immunodeficiency syndrome (AIDS) and post–organ transplantation (see Chapter 27).

- Do the same management principles apply to localized nodal and extranodal lymphoma? Both nodal and extranodal non-Hodgkin's lymphomas share a number of common prognostic determinants, for example, stage, symptoms, tumor bulk, and histologic type. These attributes define the survival probability, largely as a measure of the likelihood of primary tumor control with therapy, either as a function of recurrence after radiation or complete response after chemotherapy or combined-modality therapy. The site of extranodal disease provides the additional dimensions of histologic characteristics, preferential organ localization, and patterns of relapse or dissemination that may be factored into the initial management plan.

GENERAL ASPECTS OF EXTRANODAL LYMPHOMA

INCIDENCE AND DISTRIBUTION

Non-Hodgkin's lymphomas account for approximately 5% of human cancers, with an age-standardized incidence of around 17 per 100,000 persons. They occur more commonly with advancing age (Fig. 25–2) and do not show the bimodal adult age distribution characteristic of Hodgkin's disease.

The frequency of occurrence of primary extranodal lymphoma has been reported as

and in comparison with the series of Freeman[1] and Otter and colleagues in Tables 25–1 a

PATHOLOGY

Traditional classifications of non-Hodgkin's derive from morphologic observations stressing change in relation to normal tissue anatomy (u node) and cytologic appearances of infiltratin cells. Subsequently, concepts emphasizing linea and differentiation using phenotypic and mol niques have been introduced. Morphologic c are more suited to lymph node interpretatio classic classifications, which formed the basis studies, are as follows:

- Rappaport—nodular versus diffuse; varial tiation of lymphocytes; histiocytic cells; mi cytic and histiocytic populations[5]
- Lukes and Collins—B cell versus T cell; sm cyte, plasmacytoid lymphocyte, follicular c small and large, cleaved and noncle tumors—small lymphocytes, convoluted or cells, lymphoepithelial, immunoblastic les

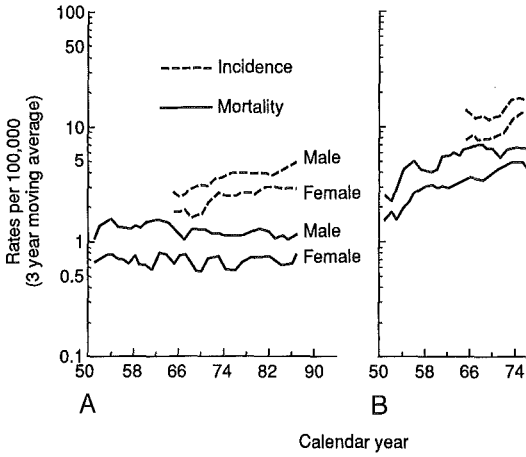
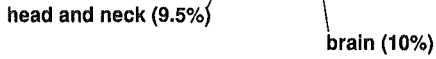


Figure 25–2. Incidence and mortality rates expressed per population for non-Hodgkin's lymphoma (ICD 9: 200,20 younger (A) or older (B) than 50 years of age for the Provi Age is adjusted to the world standard population. ICD Classification of Diseases. Data from the Division of Epi Statistics, Ontario Cancer Treatment and Research Found



- Kiel—lymphocytic, immunocytic, and centrocytic tumors; centroblastic/centrocytic tumors; centroblastic, immunoblastic, and lymphoblastic tumors[7]; subsequent additional distinction of B-cell and T-cell lineage[8]
- Working Formulation prognostic categories—low, intermediate, and high grade, characterized predominately by Rappaport groupings but applicable to other classifications[9]

When applied to the characterization of primary extranodal lymphoma, limitations of these classifications become apparent.

- The extranodal site architecture does not necessarily align itself with nodal architecture, displaying a clear distinction of nodular (follicular) and diffuse effacement of tissue.
- Extranodal tissue biopsies are frequently small and often crushed or distorted. Issues relating to sample size, adequacy of material for interpretation, and representativeness of tissue involved by lymphoma arise. There are also issues related to preservation and handling of small fragments or biopsy specimens and the adequacy of material for phenotypic and molecular analysis.
- Distinction of normal physiologic lymphoid aggregates from localized involvement of tissue by lymphoma, for example, Askanazy nodules in bone marrow biopsy specimens and periportal lymphocytic infiltrates in liver biopsy specimens can be difficult. In certai has historically been controversy as to th lymphoid pseudotumors, for example, orb nary, and GI pseudotumors, and their dist low-grade malignant lymphoma.
- Although these histologic classifications a factorily to nodal and B-cell lymphoma, th classification of T-cell disease in nodal an sites posed difficulties. Additionally, the cla a guide to prognostication is often limite categories of T-cell disease, for example, noblastic lymphadenopathy, lymphomatoid tosis, and peripheral T-cell lymphomas.

A recently proposed Revised European-Am phoma (REAL) classification for malignant addresses some of these issues by including all proliferative disorders.[10] The REAL classificati a number of distinct disease entities not rep previous classifications (Table 25–3). It is ba premise that B-cell malignancies are distinct malignancies and attempts to describe a numb entities, while treating the grade of disease a within a given disease rather than the basis for c as does the Working Formulation.

Several of the histopathologic and clinical en particular importance to the primary extranodal The most common is MALT lymphoma (discu following section).

Table 25–1. Distribution of Patients with Non-Hodgkin's Lymphoma*

Series	Period	Total Number	Stages I and II (No.)	Primary Extranodal (No.)
Freeman et al[1] (1972)	1950–1964	1467	—	1467†
Otter et al[2] (1989)	1981–1986	580	242	236
Sutcliffe and Gospodarowicz[4] (1992)	1967–1988	2254‡	1391	708§

*Number of patients
†Refers to nondisseminated lymphoma.
‡Excludes 79 patients with primary brain lymphoma.
§Clinical stages IE and IIE.

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