Section 2: Disorders of the Head and Neck

Part 7: The Neck

Chapter 46: Lymphomas of the Head and Neck

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Lymphomas are the most common nonepithelial tumors of the head and neck. It is important for the head and neck surgeon to be familiar with these diagnoses, since they frequently present as enlarged neck nodes. Moreover, the examination techniques of the head and neck specialist are important to help determine extent of disease, treatment planning, and response to therapy.

Lymphomas are separated into two histopathologic groups: Hodgkin's disease and non-Hodgkin's lymphomas. The diagnosis of Hodgkin's disease depends upon the identification of the typical Reed-Sternberg cell or its variant, the lacunar cell. The Reed-Sternberg cell is a giant cell with abundant cytoplasm and a large multilobulated nucleus. It is believed that this cell is derived from the malignant cell in Hodgkin's disease, which is believed to be histiocytic in origin. Hodgkin's disease is a very unusual malignancy in that it is frequently accompanied by marked host inflammatory responses. These responses include the background of eosinophils, lymphocytes, and histiocytes that are typically present in involved lymph nodes; the occasional presence of nonspecific granulomas in the spleen, liver, or bone marrow; the presence of fever in some patients; and the defects in delayed hypersensitivity that frequently occur. These findings have led to suspicions that Hodgkin's disease may have an infectious cause. However, this has never been proved, and the cause of Hodgkin's disease remains unknown. A discussion of these and other fascinating aspects of Hodgkin's disease is beyond the scope of this chapter, and a detailed account is provided by DeVita and colleagues.

Non-Hodgkin's lymphomas include different diseases characterized by different natural histories, responses to treatment, and prognoses. The vast majority are malignancies of lymphocytes. A rare group is derived from histiocytes. The cause of most of the non-Hodgkin's lymphomas is unknown. However, some occur with increased frequency in patients with certain viral infections, immunoproliferative states, and immunosuppressed states. These conditions are listed in Table 1. Distinctive chromosomal abnormalities and immunoglobulin gene rearrangements are subjects of intense study in the non-Hodgkin's lymphomas; they are frequently demonstrable and promise to help elucidate the nature of these diseases.

**Table 1. Etiologic Factors in Non-Hodgkin's Lymphomas**

| Factor | Type of Lymphoma |
|---|---|
| Epstein-Barr virus | African Burkitt's lymphoma |
| | Posttransplant lymphoma |
| Human T-cell leukemia virus type I | Adult T-cell leukemia |
| Immunoproliferative small bowel disease | Immunoblastic lymphoma |
| Allograft transplants | Immunoblastic lymphoma |
| Congenital immune defects | Immunoblastic lymphoma |
| Systemic lupus erythematosus | Immunoblastic lymphoma |
| Sjögren's syndrome | Immunoblastic lymphoma |
| Diphenylhydantoin | Immunoblastic lymphoma |
| Angioimmunoblastic lymphadenopathy | Immunoblastic lymphoma |
| AIDS | Various lymphomas. |

## Classification

### Hodgkin's Disease

Hodgkin's disease is classified histopathologically according to the scheme proposed by Lukes and associates, which consists of four subgroups: (1) lymphocyte-predominant, (2) nodular sclerosis, (3) mixed cellularity, and (4) lymphocyte depletion (Table 2). These classifications are roughly related to prognosis, with lymphocyte predominance possessing a more favorable prognosis than lymphocyte depletion. Nodular sclerosis and mixed cellularity are intermediate in prognosis. The prognosis also depends on the stage, and patients with lymphocyte predominance are more likely to have stage I or stage II disease, whereas those with lymphocyte depletion are more likely to have stage IV disease.

### Non-Hodgkin's Lymphoma

The classification of non-Hodgkin's lymphoma has evolved from a situation in which at least six systems were used. Within the United States, the system put forth by Rappaport has been the most popular among clinicians. This system is based on the pattern of architecture of the abnormal lymph nodes, along with the cytologic features of the malignant cells. More favorable outcomes are predicted for patients whose lymph nodes possess a nodular appearance and small lymphoid cells. Less favorable outcomes are seen in those cases with a diffuse nodal pattern and large cells.

The multiplicity of classification schemes resulted in a vast amount of confusion within the field, with subsequent difficulties in communication of results among investigators. Recently, the National Cancer Institute (NCI) sponsored a study that attempted to develop a classification scheme combining the strong points of each of the previous proposals. Review of 1.175 cases by a series of experts resulted in a document entitled *A Working Formulation of Non-Hodgkin's Lymphomas for Clinical Usage.*

### Table 2. Classification and Histologic Features of Hodgkin's Disease

| Classification | Histologic Features | Prognosis |
|---|---|---|
| Lymphocyte predominance | Many lymphocytes or a mixture of lymphocytes and histiocytes<br>Few typical Reed-Sternberg cells<br>Lack of necrosis and fibrosis | Most favorable |
| Nodular sclerosis | Nodules of lymphoreticular cells partially or completely separated by bands of collagen<br>Many lacunar cell variants of Reed-Sternberg cells<br>Foci of necrosis and fibrosis | Favorable |
| Mixed cellularity | Mixture of cells, including lymphocytes, eosinophils, plasma cells, and histiocytes<br>Reed-Sternberg cells | Less favorable |
| Lymphocyte depletion | Many Reed-Sternberg cells and malignant histiocytes or abundant fibrosis and hypocellularity<br>Few lymphocytes. | Least favorable |

The working formulation divides non-Hodgkin's lymphomas into three major subgroups according to their clinical courses (Table 3). A subsequent retrospective study by Ersboll and colleagues of 658 cases of non-Hodgkin's lymphomas demonstrated that the working formulation can be substituted for any of the established classification schemes without loss of prognostic value. Other studies have confirmed this.

The new working classification of the non-Hodgkin's lymphomas is shown in Table 3. It is based on (1) the general clinical course, (2) the presence or lack of a follicular pattern in the lymph node, and (3) the Lukes-Collins cytologic categories of lymphocytes. The general clinical course is designed low-grade, intermediate-grade and high-grade, with median survival times of 7.5 years, 2.5 years, and 1 year, respectively. These median survival times are derived from the 1175 patients in the NCI-sponsored study, which were accrued between 1971 and 1975. It should be emphasized that the median survival times of the intermediate- and high-grade groups are now longer with the use of modern chemotherapy.

The term *follicular* replaces the term *nodular* in the Rappaport classification and refers to the preservation of a follicular pattern within the lymph node. It is also recognized that *histiocytic* in the Rappaport classification was a misnomer - these cells are actually large lymphocytes.

## Table 3. Classification of Non-Hodgkin's Lymphomas

| | Rappaport Equivalent | B- or T-cell | Usual Stage | Median Survival Time |
|---|---|---|---|---|
| *Low Grade* | | B-cell | III-IV | 7.5 yrs |
| Diffuse, small lymph | DLWD | | | |
| Follicular, small cleaved FCC | NLPD | | | |
| Follicular, small cleaved/large FCC | NM | | | |
| *Intermediate Grade* | | B-cell | I-IV | 2.5 yrs |
| Follicular, large FCC | NH | | | |
| Diffuse, small cleaved FCC | DLPD | | | |
| Diffuse, small cleaved/large FCC | DM | | | |
| Diffuse, large FCC | DH | | | |
| *High Grade* | | | III-IV | 1 yr |
| Immunoblastic | DH | B- or T-cell | | |
| Lymphoblastic | LB | Usually T-cell | | |
| Undifferentiated (small, noncleaved) | DU | B-cell | | |
| *Miscellaneous* | | | | |
| Mycosis fungoides | - | T-cell | IV | Variable |
| True histiocytic | - | - | IV | 1 yr |

FCC, follicle-center cell; DLWD, diffuse lymphocytic, well differentiated; NLPD, nodular lymphocytic, poorly differentiated; NM, nodular mixed; NH, nodular histiocytic; DLPD, diffuse lymphocytic, poorly differentiated; DM, diffuse mixed; DH, diffuse histiocytic; LB, lymphoblastic; DU, diffuse undifferentiated.

The Lukes-Collins cytologic classification is based on the malignant counterparts of different kinds of normal lymphocytes. The term *small lymphocyte* refers to the well-differentiated cell often present around the margins of follicles in the cortex of lymph nodes and in the blood and bone marrow. These are the same cells that are malignant in chronic lymphatic leukemia. The majority of lymphomas are derived from follicle-center cells, some of which are small, with a cleaved nucleus (small, cleaved follicle-center cells), whereas others are large and resemble histiocytes (large follicle-center cells). The immunoblastic lymphomas are derived from cells normally present within the paracortical regions of the lymph node.

It is evident from Table 3 that nearly all of the non-Hodgkin's lymphomas, and all of those derived from follicle-center cells, are B-lymphocytes. The proliferation of monoclonal antibodies directed against lymphoid cells has gone hand in hand with clarification of the normal routes of lymphoid cell differentiation and has contributed to the scheme outlined. This scheme has, in turn, contributed to a better understanding of the various subclasses of the non-Hodgkin's lymphomas and their positions within the lymphoid cell differentiation sequence. For instance, it is now apparent that virtually all lymphoid cells can be categorized as either B- or T-cells. As noted in Table 3, the majority of the non-Hodgkin's lymphomas are derived from follicle-centered cells; they fall within the range of early B-cell, nodal B-cell, and intermediate memory cells. The immunoblastic B-cell lymphomas span the intermediate, mature, and plasmacytoid range, whereas lymphoblastic B-cell and undifferentiated lymphomas are of pre-B-cell and early B-cell origin. Lymphoblastic T-cell lymphomas are frequently of thymic lymphocyte origin, whereas mycosis fungoides is composed of T-cells of the mature (blood and node) category.

## Clinical Presentation

A majority of patients with lymphomas first present with lymphadenopathy, and a majority of them have cervical lymphadenopathy. In addition, the head and neck specialist may encounter patients with lymphoma who have dysphagia, serous otitis media, odynophagia, respiratory obstruction, or superior vena cava syndrome.

## Hodgkin's Disease

Abnormal lymph nodes tend to be localized or to involve contiguous nodal groups in Hodgkin's disease. The most frequent palpable lymph nodes at presentation are the lower cervical and supraclavicular ones, and they are typically nontender, mobile and rubbery. Mediastinal or hilar nodes are a frequent occurrence at presentation. Abdominal involvement is unusual but is more likely to be present in patients with systemic (B-cell) symptoms or with a lymphocyte-depleted histological picture. It is rare for Hodgkin's disease to present as a primary extranodal lymphoma.

Overall, about half of the patients have localized disease in the sense that it is sufficiently limited to the area above the diaphragm that radiotherapy can be given with curative intent. When Hodgkin's disease progresses, or relapses after response to therapy, it frequently changes to a histologic picture or stage that one associates with a poor prognosis.

## Non-Hodgkin's Lymphoma

The incidence of non-Hodgkin's lymphoma rises with increasing age, so it is typically a disease of the fifth, sixth, and seventh decades of life. It also has a slight male predominance. Patients with nodal non-Hodgkin's lymphomas often present with cervical adenopathy, with equal instances of high and low cervical node enlargement. Unlike Hodgkin's disease, a substantial fraction of patients with non-Hodgkin's lymphomas, especially those with diffuse large-cell types, will present with both nodal and extranodal involvement. The majority of the extranodal lesions in the head are located in Waldeyer's ring, with the tonsils being the most common site. Nasal fossa and paranasal sinuses are the most common areas of involvement outside Waldeyer's ring.

The non-Hodgkin's lymphomas differ from Hodgkin's disease in that the involved sites are less likely to be contiguous, the mediastinum is less likely to be involved, the abdomen is more likely to be involved, and many fewer patients (less than 10 per cent) have truly localized disease. Extranodal involvement is common, and primary extranodal lymphoma (eg bone, brain, stomach, intestine, kidney) occurs (especially with diffuse large-cell and immunoblastic types). Systemic (B-cell) symptoms occur occasionally, especially in higher grade lymphomas.

As can be seen in Table 3, the majority of the non-Hodgkin's lymphomas are derived from follicle-center cells. Their manifestations, and the differences between those with follicular and diffuse patterns, are summarized in Table 4. About half of these lymphomas are follicular and half are diffuse. The remaining non-Hodgkin's lymphomas have different and distinctive features.

**Table 4. Some Clinical Features of Adult Non-Hodgkin's Lymphomas of Follicle-Center Cell Origin (Fraction of Cases)**

| Involved Sites | Follicular (%) | Diffuse (%) |
|---|---|---|
| Palpable lymphadenopathy | > 80 | 80 |
| Splenomegaly or hepatomegaly | 50 | 30 |
| Para-aortic nodes | > 90 | 60 |
| Mesenteric nodes | 50 | 30 |
| Mediastinal nodes | 20 | 25 |
| Bone marrow | 45 | 30 |
| Other (Waldeyer's ring) | Unusual | Occasional |
| Primary extranodal | Unusual | 20 |
| B symptoms | 15 | 25 |
| Stage I-II | < 10 | 30 |
| Stage III-IV | > 90 | 70. |

Finally, like Hodgkin's disease, non-Hodgkin's lymphomas tend to evolve into poorer prognostic histologic categories (eg from follicular to diffuse and from small, cleaved cell to large-cell lymphomas).

### Diagnosis

The establishment of both the diagnosis and the histologic classification is critical for the proper evaluation and management of patients with lymphomas, as will become evident further on.

If at all possible, excisional biopsy of a large lymph node is preferred. The pathologist should be alerted ahead of time so that he or she will be prepared to (1) quickly process fresh rather than fixed tissue, (2) apply cell-marker techniques such as T- and B-cell markers and monoclonal antibodies, and (3) perform electron microscopy if poorly differentiated carcinoma is part of the differential diagnosis. The reasons for preferring an intact lymph node include (1) the possibility that only part of the node is involved and (2) the need to determine the histologic subclassification (eg follicular versus diffuse in the non-Hodgkin's lymphomas).

Frozen sections are not felt to be helpful in arriving at the diagnosis of lymphoma. They should be used primarily to inform the surgeon of the adequacy of the material submitted. In a similar vein, fine needle aspiration biopsy probably does not have a useful role to play in the evaluation of this disease except to assist in ruling out the possibility of metastatic carcinoma.

The lymphomas are sufficiently uncommon, the subclassifications sufficiently complex, and the impact of the correct subclassification on management sufficiently great that the opinion of an expert hematopathologist should always be sought.

## Staging

Both Hodgkin's disease and the non-Hodgkin's lymphomas are staged by the Ann Arbor scheme shown in Table 5. The precise stage is of greater importance in the management of Hodgkin's disease than in non-Hodgkin's lymphomas and reflects the extent of nodal involvement, the presence or lack of splenic or other tissue involvement, and the presence or lack of systemic ("B") symptoms.

### Table 5. Ann Arbor Staging System for Lymphoma

### Stage I

Involvement of a single lymph node region (I) or single extralymphatic organ or site (E).

### Stage II

Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of the extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE).

### Stage III

Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by localized involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE).

### Stage IV

Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. The reason for classifying the patient as stage IV should be identified further by defining site by symbols: H+, liver involvement; L++, lung involvement; M+, marrow involvement; P+, pleural involvement; O+, bone involvement; D+, skin involvement.

### A Symptoms

No significant fever, night sweats, or weight loss.

## B Symptoms

Unexplained weight loss of more than 10% of the body weight in the 6 months preceding diagnosis, or unexplained fever with temperature greater than 38°C, or night sweats.

## Hodgkin's Disease

Correct staging is crucial in the management of Hodgkin's disease because the choice of initial therapy may determine whether or not a patient is cured. In essence, one must answer the question, "Is this patient's disease sufficiently limited that it has an excellent chance of being cured by radiotherapy?" If not, chemotherapy should be the initial primary therapy.

A careful history should be obtained regarding the presence of any systemic symptoms, such as night sweats or weight loss, that might be related to the disease. Physical examination should focus upon other lymph node-bearing areas of the body, as well as the spleen, liver, and Waldeyer's ring. A chest x-ray study is usually sufficient to determine mediastinal or hilar involvement, but in some cases tomograms or computed tomography (CT) scans are needed. A complete blood count (CBC) and liver function tests may point toward marrow or liver involvement. A CT scan of the abdomen and pelvis is emerging as a standard procedure. Lymphangiography is being used less often today than in the past with the continued improvement in CT scanning technology. Lymphangiography cannot visualize mesenteric nodes and nodes around the celiac axis and splenic hilum. In addition, the yield of the test can vary considerably, depending upon the technique and expertise of the radiologist performing the examination. It would have to be anticipated that as more dependence is placed upon the CT scan, the number of people skilled in lymphangiography will become fewer and its usage less frequent.

Bilateral iliac crest bone marrow biopsies complete the initial staging. If at this point it is evident that the patient has stage III or stage IV disease, it is likely that chemotherapy will be the primary choice of therapy, and no further staging is required. If, conversely, the clinical stage appears to be stage I or stage II (most of which are located above the diaphragm), a staging laparotomy is usually performed. The major benefit of the laparotomy is that it is the only way to ascertain whether or not the spleen is involved. Up to 25 per cent of patients with nonpalpable spleens are found to have Hodgkin's disease in them. Ironically, about 50 per cent of patients with enlarged spleens do not have Hodgkin's disease in them.

The staging laparotomy must be performed meticulously. It includes splenectomy, wedge biopsy of the liver, needle biopsies of the liver, and examination and sampling of para-aortic, portal, celiac, splenic, mesenteric, and iliac lymph nodes. Wedge biopsies of the iliac bone marrow can be performed, especially if prior marrow biopsies were insufficient or nondiagnostic. Finally, if there is any plan to consider pelvic radiotherapy in young women, oophoropexy is done to move ovaries away from the field.

Liver involvement is uncommon and usually occurs only in patients with poor prognoses based on histopathological features (eg mixed cellular or lymphocyte-depleted), those with enlarged spleens, or those with evident stage IV disease. The liver function tests can be abnormal without actual liver involvement. Nevertheless, in selected patients, closed

or peritoneoscopy-directed liver biopsies may be done prior to considering laparotomy.

Finally, there may be patients with localized disease in whom laparotomy is not required. Thus, in patients with high neck nodes (clinically stage I) and a good histologic prognosis, there is little chance that laparotomy results will be positive; therefore it may be avoided, and the patient treated with appropriate radiotherapy.

### Non-Hodgkin's Lymphomas

The staging of non-Hodgkin's lymphomas is in most cases less critical than it is for Hodgkin's disease. The prognosis and management of patients with stages II, III, and IV are not significantly different, and more than 90 per cent of all cases are found on clinical evaluation to be one of these stages. Moreover, even patients who appear to have stage I disease and who are irradiated with curative intent have a rate of relapse of about 50 per cent over 10 years. Nevertheless, it is worthwhile to define those subjects who truly have stage I disease, and if they are in the low-grade clinical course category (Table 3) to treat them with local irradiation.

The goals of staging the non-Hodgkin's lymphomas are to (1) identify the occasional patient who truly has stage I disease, (2) obtain sufficient information to establish a baseline for evaluation of response to therapy, and (3) document potentially harmful or life-threatening complications.

The staging of a patient with non-Hodgkin's lymphoma who presents with peripheral adenopathy includes a CBC; routine laboratory determinations, including lactase dehydrogenase (LDH), creatinine, uric acid, and calcium concentrations; a chest x-ray; a CT scan of the retroperitoneum and pelvis; and bilateral bone marrow biopsies. The CBC, with careful examination of the peripheral smear, may show a leukemic manifestation in some lymphomas and may reveal the presence of secondary autoimmune phenomena such as hemolytic anemia or thrombocytopenia. A high serum LDH level correlates with bulky disease in the abdomen. These procedures are usually sufficient for staging. Procedures such as liver biopsy, pleural tap, and so on are occasionally used when the clinical evaluation warrants them.

In patients with high-grade lymphomas, there is a high incidence of central nervous system (CNS) involvement, and spinal taps with cytologic examination are done even when there are no signs or symptoms. The cerebrospinal fluid is also examined in patients with lymphoma involving the paranasal sinuses. The association between disease in Waldeyer's ring and the gastrointestinal tract has been felt to be as high as 11 per cent. With this in mind, a gastrointestinal series has been recommended by several authors. Other authors have recommended investigation of the gastrointestinal tract only in symptomatic patients.

There are very few indications for laparotomy in staging non-Hodgkin's lymphomas; they include (1) clinical stage I disease if curative radiotherapy is contemplated; (2) if it is required for diagnosis (eg primary isolated splenic, gastrointestinal, renal lymphoma); and (3) for debulking of mesenteric or ovarian Burkitt's lymphoma. Otherwise, the laparotomy rarely changes the apparent clinical stage.

<center>**Treatment**</center>

<center>**Hodgkin's Disease**</center>

Patients with stages IA and IIA disease are treated with radiotherapy. Most of these patients have disease located above the diaphragm, and the radiation portal is referred to as *mantle* radiation. It includes all of the suboccipital, cervical, supraclavicular, mediastinal, and hilar nodes, and is usually extended to the celiac axis and splenic hilum (the spleen will have been removed at staging laparotomy). The dose is 40 to 45 gray (Gy) to involved areas and 30 to 35 Gy to apparently uninvolved areas. The apparent cure rate (relapse-free survival at 5 to 10 years) is about 90 per cent for stage IA and 80 per cent for stage IIA.

There are three groups of patients with stage I or stage II disease who have poor prognostic features and for whom treatment is modified. The first are patients with stage IIB disease; they usually receive either more extensive irradiation (eg total nodal irradiation, TNI), or combination chemotherapy. The second group consists of patients with a lymphocyte-depleted histologic picture; they also are treated either with TNI or combination chemotherapy. The third group is made up of patients with very large mediastinal masses. A frequent approach for these patients is to give combination chemotherapy and then irradiate the area of bulky disease. These patients usually do not have laparotomy for staging, since they are being treated with chemotherapy anyway and because they are at high risk for complication during intubation for anesthesia.

Patients with stage IIIA disease, in which abdominal involvement is limited to the spleen or to the upper para-aortic region (the latter is referred to as IIIA1), can be treated with TNI in such a manner as to achieve more than 50 per cent relapse-free survival.

The majority of patients with stage III Hodgkin's disease, and all of those with stage IV disease, are treated with combination chemotherapy. The standard, established by DeVita and colleagues in the 1960s, is MOPP. MOPP consists of nitrogen mustard, Oncovin (vincristine), procarbazine, and prednisone given in 4 week cycles for eight to nine cycles. Eighty per cent of patients have complete remission (documented by restaging short of laparotomy), and their relapse-free survival between 10 and 17 years is 64 per cent. Hence, 51 per cent of all patients treated with MOPP are cured. Those without B-cell symptoms have a higher rate of complete response (100 per cent) and a lower rate of relapse.

Another regimen for Hodgkin's disease is ABVD which includes four drugs that are entirely different from those used in MOPP. They are Adriamycin (doxorubicin), bleomycin, vinblastine, and DTIC (dacarbazine). ABVD is effective for patients who fail to respond to MOPP or who relapse after response to MOPP, and it may be used as initial chemotherapy or given in conjunction with MOPP.

<center>**Non-Hodgkin's Lymphomas**</center>

Management is different for the different grades of disease outlined in Table 3.

**Low-grade Disease.** Those few patients who truly have stage I or stage II disease with limited involvement of contiguous nodal groups are treated with localized radiotherapy.

Although nearly all of them have complete responses, 50 per cent relapse over the following 10 years. In all other patients with low-grade lymphomas, the median survival of 7.5 years is not affected by the nature or timing of therapy. If a diagnosis is made when there are no significant symptoms or manifestations, it may be appropriate not to treat at all. For focal palliation (eg a bulky node, ureteral compromise, and so on), radiation may be effective. When progression is evident, treatment with a single drug (eg chlorambucil) or a mild combination like cyclophosphamide and vincristine, and prednisone will have an excellent chance of inducing a complete or partial remission in 90 per cent of patients. If the lymphoma evolves to a higher grade, more aggressive regimens are tried.

**Intermediate-grade Disease.** Patients with stage I or contiguous stage II nodal disease can be treated with radiation to doses of 45 to 50 Gy. However, most patients who have stage I primary extranodal disease, such as diffuse large-cell lymphoma of the stomach, intestine, spleen, and so on, are treated with combination chemotherapy in the same manner as for stage III and stage IV disease. The large-cell lymphomas have a high rate of complete response to aggressive combination chemotherapy, somewhere between 55 and 75 per cent, and about 50 per cent of complete responders appear to be cured. Active drugs that are combined together include cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin, etoposide, cytosine arabinoside, and high-dose methotrexate. Prognosis is worse and the relapse rate is high in patients with B symptoms, with involvement of marrow or liver, or with bulky (greater than 10 cm diameter) abdominal masses. There is a difference of opinion as to whether local radiotherapy to areas of bulky disease will improve survival in such patients. In addition, some patients have a higher risk of CNS disease upon relapse; the risk appears greater in elderly patients, in patients with sinus involvement, and in patients with marrow or testicular involvement. In such cases, it might be worthwhile to give prophylactic CNS treatment (as outlined further on), although there is no evidence that it prolongs survival.

**High-grade Disease.** These lymphomas are treated with aggressive combination chemotherapy in the same manner as are the diffuse large-cell lymphomas. In children and young adults with lymphoblastic and undifferentiated lymphomas, high response rates and long-term remissions are reported. The results for immunoblastic lymphomas are less clear, in part because they often occur in subjects who are already immunosuppressed or who have other underlying disorders. Patients with high-grade lymphomas have a high risk for having CNS disease, sometimes on presentation and often upon relapse. Consequently, they are usually treated prophylactically. A standard regimen would include cranial irradiation (25 Gy) and several courses of intrathecal methotrexate or cytosine arabinoside, or both. Finally, in many patients with "American" Burkitt's lymphoma, there is bulky involvement of the mesentery or ovary, and it appears that surgical resection helps pave the way for more effective results with chemotherapy.

## Conclusion

The major presenting feature of lymphomas is peripheral lymphadenopathy, and the majority of patients have cervical or supraclavicular lymphadenopathy. For this reason, the head and neck specialist is frequently the first physician to encounter these patients.

Hodgkin's disease is a unique malignancy of histiocytic origin with four distinct histologic features that appear to reflect the extent of host response to the disease and are

major factors in determining prognosis. The most frequent pattern of disease is contiguous nodal involvement, and it is typically above the diaphragm or predominantly so. The staging of this disease is critical and frequently requires laparotomy. Eighty to 90 per cent of patients with stage I or stage II Hodgkin's disease are cured by appropriate radiotherapy. Fifty per cent of patients with stage III and stage IV disease are cured by combination chemotherapy.

The non-Hodgkin's lymphomas are a group of unique different malignancies of lymphocytes. Many fewer are stage I or are curable by radiotherapy, unlike Hodgkin's disease. Recent advances in the understanding of lymphoid cell differentiation, using cytologic techniques, monoclonal antibodies, and chromosome analysis, combined with better understanding of the clinical course of these lymphomas, have led to a rational classification of them. They are divided into low-grade, intermediate-grade, and high-grade clinical groups. The majority of the non-Hodgkin's lymphomas, and virtually all of those in the low and intermediate grades, are derived from B-lymphocytes of lymphatic follicle-center origin. The low-grade lymphomas have an inherent median survival of 7.5 years, but in spite of a high response rate to chemotherapy, they do not have improved survival with aggressive therapy. The majority of the intermediate-grade lymphomas, of the large-cell type, have a 30 per cent cure rate with aggressive combination chemotherapy. The high-grade lymphomas have an inherent median survival of 1 year or less, but a significant fraction can now be cured with aggressive chemotherapy.