



Morphological Assessment of Lymph Nodes Draining Carcinoma

Prema Saldanha

ABSTRACT

Lymph nodes draining tumors are considered anatomic barriers to tumor spread. The involvement of lymph nodes by metastatic spread of tumors signifies the start of a new phase in the progress of a cancer. It indicates that through a succession of molecular changes, the cancer cells have acquired phenotypes that enable them to invade, colonize, and disseminate. Lymph node status is one of the most important indicators of clinical outcome. Lymph nodes are also the site where specific immune interactions between tumor antigens and lymphoid cells take place. Enlargement of nodes may be caused by spread of cancer cells or due to reactive hyperplasia of lymph nodes in response to tumor-associated antigens (TAA). The various lymphoid cell populations react in various ways, giving rise to different morphologic patterns. Only a few studies have investigated possible correlations between the patterns of lymph node reactivity and prognosis in malignant tumors.

Histological analysis of the patterns in the regional lymph nodes draining the tumor could elucidate the immunological host-tumor relationship and provide additional information on patient survival. Increasing size of the tumor, higher grade, and stage are likely to show decreased number of reactive lymph nodes. More extensive studies on lymph node immune response patterns will be helpful in providing information on patient prognosis.

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INTRODUCTION

Carcinomas spread predominantly by the lymphatic route. Lymph nodes draining a primary tumor are considered anatomic barriers to the spread of the malignancy. The involvement of lymph nodes by metastatic spread of tumors signifies the beginning of tumor metastasis. This process indicates that through a succession of molecular changes, these cancer cells have acquired phenotypes

that enable them to invade, colonize, and disseminate. Lymph node status is a very important predictor of clinical outcome. Lymph nodes are also the site where specific immune interactions between the tumor antigens and the lymphoid cells take place. Enlargement of nodes may be caused by spread of cancer cells to the lymph nodes or due to reactive hyperplasia of lymph nodes in response to tumor-associated antigens (TAAs). The various lymphoid cell populations react in various ways, giving rise to different morphologic patterns. Only a few studies have investigated possible correlations between the patterns of lymph node reactivity and prognosis in malignant tumors.

The lymph nodes form a major part of the lymphatic system and are located in small groups or chains at locations where they drain the lymphatics from various anatomic regions. This process involves not only mechanical filtration of the foreign substances present in the lymph but also the recognition and processing of foreign antigens. The lymph nodes exhibit a complex architecture in which the various cell populations are arranged in distinct compartments. This provides a favorable environment suitable to process antigens, and generate the immune response.^{1,2}

Normal lymph nodes are not palpable. They become detectable as a result of intense immunological reactions or tumor metastasis. The characteristics of each group of lymph nodes vary in relation to location in the body; mesenteric nodes have wider medullary cords and sinuses, whereas peripheral nodes, particularly those draining areas of active antigenic stimulation, like the neck and abdomen, have larger and more numerous germinal centres.^{1,3} The lymphatic sinuses carry the lymph from the afferent lymphatics on the surface of the lymph node through the lymphoid parenchyma into the efferent lymphatics in the lymph node hilus. The phagocytic apparatus of the sinuses filters the lymph, retaining foreign bodies, and plays an important role in antigen binding. The passage of lymph and cells from one chain of lymph nodes to the next is a means by which the immune response is conveyed from the peripheral to the more central lymph nodes.¹ Regional lymph nodes draining tumor-bearing organs are considered anatomic barriers to tumor spread. They are also the site where specific immunological interactions between tumor antigens and reacting lymphoid cells take place. The primary

Professor

Department of Pathology, Yenepoya Medical College, Mangaluru
Karnataka, India

Corresponding Author: Prema Saldanha, Professor, Department of Pathology, Yenepoya Medical College, Mangaluru, Karnataka India, Phone: +91-8242411422, e-mail: premasaldanha@yahoo.co.in

antitumor function of lymph nodes is not only filtration but also immunologic tumor surveillance.^{1,4}

LYMPH NODE METASTASIS

Tumor spread to regional and distant lymph nodes occurs via lymphatic vessels whose proliferation is promoted by growth factors. Tumor lymphangiogenesis, which contributes actively to tumor dissemination, is stimulated by vascular endothelial growth factors (VEGF) like VEGF-C and VEGF-D, which are essential for lymph node metastases. Tumors that metastasize are characterized by increased lymphangiogenesis, which could serve as a predictor of tumor dissemination.^{5,6}

The recently refined techniques of sentinel detection of micrometastases have shown that changes in the lymph node microenvironment involving lymphatics, dendritic cells, and particularly the responding T cells may begin even before the metastatic cancer cells have arrived in the lymph node.^{5,7} Consequently, the regional lymph nodes are commonly enlarged as a result of reactive lymphadenopathy, tumor metastasis, or both.⁵

The involvement of lymph nodes by metastatic spread of tumors signifies the start of a new phase in the progress of a cancer. It indicates that through a succession of molecular changes, the cancer cells have acquired phenotypes that enable them to invade, colonize, and disseminate. Establishing the presence of metastatic tumor in lymph nodes is essential for the management and prognosis of cancer. Lymph node status is the most important indicator of clinical outcome.⁸

The anatomic location and the number of lymph nodes involved are also important indicators of the process, and new methods, such as sentinel lymph node biopsies, have been devised to answer questions of staging. Not infrequently, a lymph node metastasis is discovered before an occult primary tumor is detected.⁸ The presence of metastases in reactive lymph nodes is sometimes difficult to establish. The introduction of sentinel lymph node biopsy as an effective method of sampling potentially metastatic lymph nodes has had the additional benefit. The use of more sensitive assays for the detection of micrometastases is currently practiced. Despite the development of many advanced and sophisticated diagnostic techniques, histopathologic examination of the neck dissection material remains the most valid method for detecting occult metastasis. The true incidence of micrometastases is difficult to determine because no technique is capable of detecting all the foci of micrometastases. Moreover, even in experienced hands, micrometastases or the extent of metastases may be overlooked. Immunohistochemistry and polymerase chain reaction for pankeratin (AE1/AE3) as well as CK19/20 are very helpful in detecting occult micrometastasis.^{1,9-14} Detection of mutated *KRAS* has

been found to be useful in carcinoma of the breast.^{1,15} The technique of triple-leveling^{16,17} has been used for various tumors. The blocks containing lymph nodes showing no evidence of metastatic tumor are further cut at two extra levels separated by 1 mm. The original section obtained is counted as the first level, and the extra two sections cut become the second and third levels. As a result, patients are upstaged when micrometastases are found in sentinel lymph nodes that were not detected by the regular histologic approach. However, the prognostic significance of micrometastases in the setting of various tumors has not yet been established.⁸

The sentinel node concept implies that the lymphatic drainage from a primary tumor first drains to a certain locoregional lymph node specific for each individual and that its tumor status is representative for the entire lymphatic field. The concept is established in staging for various cancers. A sentinel node derived from a primary tumor contains specific tumor-reactive lymphocytes that have immunological reactivity toward the tumor. The first lymph nodes draining various types of metastases by lymphatics named "sentinel nodes" show both the analogy and difference to the well-known term sentinel node, which is the first node to receive lymphatic drainage from a primary tumor.^{18,19}

The major cause of the morbidity and mortality associated with tumors is metastasis. Although substantial progress has been achieved in the early diagnosis and treatment of malignant tumors, mechanisms of dissemination remain largely unknown. The elucidation of such mechanisms is essential to prevent metastases and cure cancer. Tumor metastasis is a complex phenomenon based on a cascade of interdependent events: Detachment of cells from the primary tumor, advancement through the tumor matrix, penetration through the basement membranes of lymphatics and blood vessels, circulation through the vascular flow, arrival in remote organs, and formation of independent colonies with their own growth factors and vascular supply.²⁰ Primary tumors are largely heterogeneous and so may include cells endowed with a capacity for growth autonomy and metastasis.⁷ It is also possible that the potential for metastasis arises through mutations, with new variants generated and selected during tumor development.²¹ Tumor cells and tumor-infiltrating lymphocytes (TIL), both in the primary tumor and in its metastases are engaged in reciprocal death-inducing activities. The interactions of tumor cells and TIL may result in the apoptosis of either cell. Tumor cells progressively acquire the characteristics necessary for invasion and metastasis, which characterize the metastatic phenotype. Consequently, the success or failure of a tumor to invade and metastasize depends on the interaction of gene products released by stimulatory and inhibitory metastasis genes.²²

Examination of the environment in the immediate vicinity of neoplastic tissue has clearly indicated that lymphoid cells infiltrate the tumor in large numbers. It has been found that T cells predominate in the infiltrates in primary tumors and this pattern was evident regardless of anatomic site or the presence or absence of metastatic spread. In contrast, B cells predominate at the margins of tumor metastases. Thus, examination of local factors in and around such neoplastic tissues may eventually explain how an apparently effective immune response is subverted.^{4,23} Tumor cells spread by lymphatics to lymph nodes and disseminate the disease. Metastatic tumor cells first appear in the marginal (subcapsular) sinus, from which they penetrate the medullary sinuses, medulla, and cortex; the eventual result may be total parenchymal replacement. Even before metastatic tumor cells are present in the lymph node, reactive changes take place which reorganize favorably the microenvironment. The importance of tumor lymphangiogenesis has lately been proven in studies where high levels in colorectal cancer specimens of lymphangiogenic peptides, and vascular endothelial growth factor (VEGF)-C and/or VEGF-D promote tumor lymphangiogenesis which increase the proliferation of endothelial cells in high endothelial venules, resulting in blood- and lymph-enriched lymph nodes.^{8,18,19,24}

Cancer management and prognosis depend to a great extent on the presence and degree of tumor metastasis. These are evaluated by staging tumors according to the internationally accepted tumor-node metastasis (TNM) system. Of all the various criteria used as prognostic factors, the most powerful remains the description of anatomic spread according to the TNM staging. This classification by stage is as follows: Stage 0, preinvasive neoplasia; stage I, tumor confined to the organ of origin; stage II, direct tumor spread outside the organ of origin; stage III, metastasis to regional lymph nodes; and stage IV, metastasis to distant sites. Each successive stage in the TNM system indicates a significant decrement in the prognosis. The diagnosis of lymph node tumor metastasis is therefore essentially important for cancer therapy. This consists not only of establishing the presence of lymph node metastasis but also of evaluating the site of the primary tumor and its degree of histologic differentiation and determining the tumor cell phenotype and prognostic indicators of tumor cell behavior.⁸

At present, only the number of metastatic lymph nodes (positive lymph nodes) is used for the pN category of TNM system. This has been criticized as an oversimplification because the number of metastatic lymph nodes is influenced by the total number of examined lymph nodes (eLNs) and may increase the probability of stage migration. The eLNs have been demonstrated to affect both staging accuracy and oncological outcomes

in node-positive patients. The optimal eLNs for reliable prognostic stratification is less clear until now. If the surgeons and pathologists do not succeed in meeting minimal nodal staging, the pN category may be not accurate enough.²⁵ The number of nodes involved is more significant prognostically than the actual nodal stage. It is therefore important that a maximum number of lymph nodes be examined microscopically. There is some evidence that the presence of immunohistochemically detected micrometastases may also carry some prognostic significance.²⁶ Several methods have been tried to increase the yield of lymph nodes during grossing, including techniques like dye-injection and fat clearance.^{27,28}

Over the past few years, the ratio of metastatic to examined lymph node has been studied widely. Nearly all researchers demonstrated that the metastatic lymph node ratio (MLNR) is an independent prognostic factor i.e., highly related to the survival of patients with colon cancer and it has been recommended that the MLNR should be applied in prognostic assessment.^{25,29,30} Lymph nodes play an essential role in the control of tumor progression. In response to the antigenicity of tumor cells, regional lymph nodes may initiate and develop complex immune reactions. At the same time, they may entrap circulating tumor cells that have originated in their tributary territories; acting as efficient barriers, the lymph nodes may be able to destroy invading tumor cells completely, or at least stop their dissemination temporarily. Lymph node metastasis, in contrast to the vascular spread of tumors, presents an opportunity, even if temporary, for surgical intervention. In addition, because of their accessibility, lymph nodes with metastatic tumor present the best opportunity for primary tumor diagnosis through biopsy and histologic evaluation.⁸

LYMPH NODE REACTION TO TUMOR

In response to TAAs, the various cell populations of regional lymph nodes react in different ways, giving rise to a multitude of morphologic patterns. The term tumor-reactive lymphadenopathy is used which is defined as reactive, enlarged, regional lymph nodes draining tumors.⁵ The tumor cells may induce various tissue reactions, such as reactive follicular hyperplasia, sinus histiocytosis, angiogenesis, and foreign-body granuloma formation. Some metastatic tumors elicit intense desmoplastic reactions, which contribute to the partial or total replacement of lymphoid tissues. Finally, radiotherapy or chemotherapy may wipe out lymphoid tissue with the tumor and create an unusual histologic appearance of the lymph nodes affected.^{8,31}

A few studies have been devoted to the analysis of such reactions, in an effort to understand the mechanisms

of lymph node metastases. Some studies have correlated various histologic patterns of reactive lymph nodes with the dissemination of tumors in cancers of various organs.⁵ Tumor-associated antigens, shed by tumor cells or released by cell death, in addition to viable tumor cells, are carried by lymph to the draining lymph nodes, providing constant nonspecific and specific stimulation. Thus, various defense reactions may be triggered, including phagocytosis, production of antibodies, and sensitization of lymphocytes. Such reactions were investigated in various studies by determining the amounts and types of immunoglobulins in pericancerous lymph nodes and by immunohistochemically detecting epitopes of tumor-associated glycoproteins in the draining lymph nodes. However, the nature of the molecules capable of stimulating immune responses in cancer patients is still unknown: In particular, possible relationships between expression of TAAs and *in vivo* immunogenicity of the tumor still need to be clarified.³²

Various defense mechanisms are variably activated to withstand the progress of tumors. Cytotoxic T lymphocytes and natural killer cells are mediators of immune responses against tumor cells and, as TIL, they are constant companions. In the interaction between tumor cells and TILs resulting in reciprocal apoptosis, an important effective system is represented by Fas and its ligand Fas-L, expressed by both the tumor cells whether primary or metastatic and the TIL.⁵

Sinus macrophages, lymphatic endothelial cells, and follicular dendritic cells in the unaffected lymph nodes show immune reactions with monoclonal antibodies against epitopes of some tumor- or colon-associated glycoproteins that are similar to their reaction to the carcinoma cells of the colonic tumor. In a study of primary and metastatic melanoma, identical T-cell responsive sequences, representing clonal expanded T-cells, were detected both in the tumor and in the draining lymph nodes, sometimes even in the absence of tumor cells.⁵

It has been found that as the tumor mass increases in the lymph nodes, the density of S100 + dendritic cells and of cytotoxic T lymphocytes decreases, indicating that the immune response of the tumor-bearing host was getting progressively inhibited. A relationship between immune deficiency and tumor occurrence and aggressiveness is generally well documented. Not infrequently, markedly enlarged and firm lymph nodes removed as part of radical tumor excision reveal no tumor metastasis on microscopic examination. The morphologic changes of lymph nodes draining tumor-bearing organs provide evidence for antitumor immune reactivity. Recognition of the histologic patterns of lymph node reactivity to the presence of tumors is an important objective in the study of biopsy and surgical specimens.⁵ A number of studies

have investigated possible correlations between patterns of lymph node reactivity and prognosis, so far without firm, conclusive results including colon,³³⁻³⁷ stomach,³⁸ oral,^{39,40} breast,^{41,42} lung,^{43,44} and the uterine cervix.⁴⁵ Reactive lymph node hyperplasia is the enlargement of lymph nodes or other lymphoid tissue as a result of stimulation of the lymphoid cells by various antigens. It is a benign, reversible process. The immune responses in lymph nodes may be predominantly of B-cell type, characterized morphologically by either follicular hyperplasia or plasmacytosis, or predominantly of T-cell type, with a characteristic pattern of T-cell hyperplasia.^{46,47}

Lymphadenopathies tend to exhibit one of the four characteristic histologic patterns, including follicular, sinusoidal, diffuse, or mixed. These patterns represent expansions of the normal follicular, paracortical, medullary, and sinusoidal lymph node compartments. The histologic patterns vary with the etiologic agent, the age of the lesion, as well as with the immune competence status of the host. Therefore, combined or mixed overlapping architectural features are a more common finding than clearly defined histologic patterns on biopsy specimens of lymph nodes without metastasis.⁴⁸ A proposal for a standardized system of reporting human lymph node morphology in relation to immune reaction was published in 1973 by the World Health Organization. The authors recommended a topographic examination of the lymph node sections with separate descriptions of the functional areas: Cortex with follicles and germinal centers, paracortex, sinuses, and medullary cords. Studies of regional lymph nodes in tumors of various organs show histologic patterns of reactions, possibly with prognostic implications. One of four major histologic patterns may be seen, and more often combinations thereof.⁴⁹ The four major patterns include lymphocyte predominance, germinal center predominance, sinus histiocytosis, and lymphocyte depletion. A granulomatous reaction has been described rarely.

In lymphocyte-predominant tumor-reactive lymphadenopathy, lymph nodes are enlarged particularly because of the increased number of lymphocytes in the paracortical areas (T-cell zone). The lymphoid follicles are effaced, and the nonreactive germinal centers are mostly inapparent, whereas the paracortex is markedly thickened. Such lymphoid hyperplasia may or may not be associated with sinus histiocytosis. The pattern is thought to reflect changes related to cellular immunity and to be associated with an earlier diagnosis and a better prognosis.^{33-37,41-45}

In germinal center-predominant tumor-reactive lymphadenopathy, the lymph nodes are enlarged, but the increase in volume is caused by hyperplasia of follicles, particularly the germinal centers, which is the

B-cell zone.⁶ Reactive follicular hyperplasia is the B-cell response to various antigens. A predominantly B-cell response is characterized by hyperplasia of germinal centers and therefore by a follicular pattern. Centroblasts, centrocytes, and mantle zone cells are all reactive with the pan-B-cell monoclonal antibodies CD19, CD2, CD22, and CD79a.^{5,48}

The germinal centers are prominent and the medullary cords are also enlarged and contain increased numbers of plasma cells. Sinus histiocytosis may coexist with these changes, which are considered to be associated with humoral immunity. Follicles and germinal centers reactive in a tumor-free lymph node may remain reactive in lymph nodes largely replaced by metastatic tumor.⁵ The lymph node follicles become numerous and enlarged, located not only in one row in the cortex but also in two or three rows in the paracortex, corticomedullary junction, and sometimes even the medulla.⁴⁹ They vary considerably in size and shape, occasionally coalesce, and display dumbbell, hourglass, or other bizarre configurations. The mantle zone and germinal center are sharply demarcated in a reactive follicle.⁴⁶

The germinal centers are prominent and hyperplastic and composed mostly of large, primitive cells with numerous mitoses. These comprise a mixture of small and large lymphoid cells, centrocytes, and centroblasts. The centroblasts accumulate at the medial pole of the germinal center, forming a darker zone in contrast to a lighter zone toward the peripheral pole occupied by centrocytes. Characteristic features of follicular hyperplasia are the persistence, at least in part, of a lymphocytic mantle around the germinal centers, and the presence of tingible-body macrophages (i.e., macrophages with engulfed nuclear debris) scattered throughout the germinal centers, and alternating with the cells in mitosis in the dark zone, creating the characteristic "starry-sky" pattern. Surrounding the activated germinal centers are concentric, thick, darkly staining layers of small inactivated lymphocytes forming the mantle zone of the secondary follicles. Large numbers of lymphocytes may infiltrate the capsule and perinodal fat or surround the lymphatics and blood vessels.⁴⁶

Sinus histiocytosis is associated with a more favorable prognosis. A predominance of sinuses characterizes the morphologic pattern of sinus histiocytosis, which can occur in isolation or together with one of the preceding patterns. The lymph node is enlarged by markedly distended sinuses and hyperplasia of the sinus histiocytes. The pale staining of histiocytes and endothelial cells that line the branching lumina contrasts strongly with the dark staining of lymphocytic areas and produces the characteristic appearance of sinus histiocytosis.⁶ Monocytoid B lymphocytes with abundant pale

cytoplasm, round to slightly indented nuclei, open chromatin, and inconspicuous nucleoli distend the subcapsular and medullary lymph node sinuses and resemble monocytes or histiocytes. They appear as patches or perivascular aggregates of cells. Histiocytes and macrophages are selectively immunostained with CD68, HAM56, and MAC 387 antibodies and sinus endothelial cells with CD31 and CD34 antibodies.⁴⁸

Sinus histiocytosis may be difficult to distinguish from some types of metastatic carcinoma including micrometastasis. Distention of sinuses and hyperplasia of histiocytes is commonly seen in lymph nodes draining malignant tumors before or in the process of being invaded by metastases. Immunohistochemical stainings with cytokeratin antibodies are very useful, not only in the detection of micrometastases but also in differential diagnosis. However, not all cytokeratin-positive cells in lymph nodes are carcinoma cells, as other normal cells like dendritic cells and endothelial cells are also stained. The use of a panel of B- and T-cell marker antibodies to identify the lymphoid cells and the use of histiocyte/monocyte marker antibodies to highlight the histiocytes is indicated for this particular problem. Immunostaining for carcinoembryonic antigen or other TAAs is indicated to detect them in tumor-draining lymph nodes.⁵

In lymphocyte depletion, the lymph node is of normal or diminished size, and the lymphocytic population is depleted. The loosely packed lymphocytes are separated by deposits of amorphous substance and areas of fibrocollagen. The vessels have thick walls, with hyaline deposits. Diffuse fibrosis and patchy deposition of hyaline involve both the cortex and medulla. These changes are considered to reflect an exhausted ("burnt out") lymph node and to be associated with metastases and a poor prognosis.⁴¹⁻⁴⁵

Granulomatous reaction comprising clusters of epithelioid histiocytes sometimes resembling non-necrotizing granulomas may be seen in draining lymph nodes. Atypical cells singly or in small clusters may be seen occasionally, however they are not accompanied by a desmoplastic reaction, and their origin, usually histiocytic or dendritic, can be determined by immunohistochemical staining.⁵

Pattern of lymph node reaction has shown that patients with colorectal carcinoma in whom the regional lymph nodes show morphologic evidence of a cell-mediated immune response (manifested by an increased number of paracortical immunoblasts and/or sinus histiocytosis) survive longer than those patients whose nodes do not show these changes.³³⁻³⁷ Studies suggest that the immune response of the patient against antigens expressed on tumor cells may influence the behavior of colorectal carcinomas. In this study, particular epitopes

of TAG-72 and CAA were detected in antigen-presenting cells, such as peritumoral and sinus macrophages, in sinus endothelial cells, and in germinal centers of regional lymph nodes.¹⁵

Immunostaining of germinal centers tended to be localized at the periphery, assuming a circular or crescentic shape. This pattern of immunostaining parallels the distribution of antigen-presenting follicular dendritic cells, which entrap and process soluble antigens for presentation to B-lymphocytes.³² The best 5-year survivals were seen in patients whose lymph nodes demonstrated immunologic responses in the form of a lymphocyte predominance pattern and, to a lesser degree, the germinal center predominance pattern. Patients whose lymph nodes demonstrated no morphologic evidence of an active immunologic response, in the form of an unstimulated pattern, or patients whose lymph nodes showed the lymphocyte depletion pattern had the poorest 5-year survival rate. Further analysis of our results shows that the lymphocyte predominance pattern was found to be more common in nonmetastatic cases and in carcinomas of a high grade of differentiation. Also, it is interesting that the survival rate in cases with lymphocyte predominance pattern and in cases with metastases to the regional lymph nodes was higher.⁵⁰

Lymph nodes with combined B- and T-cell hyperplasia were significantly more common in cases of good tumor differentiation. The findings suggest that sinus histiocytosis and hyperplasia of both major lymphocyte populations are morphological expressions of *in vitro* antitumor immunoreactivity in the regional lymph node.³⁵

The clinical value of lymph node size in colon cancer has been investigated only in a few studies. Only in radiological diagnosis is lymph node size routinely recognized, and nodes >10 mm in diameter are considered pathologic. However, the few studies regarding this topic suggest that lymph node size is not a reliable indicator of metastatic disease. The prognostic relevance of lymph node size was investigated in a subset of cases. The occurrence of >7 lymph nodes that were 45 mm in diameter was significantly associated with better overall survival. Our data show that lymph node size is not a suitable factor for preoperative lymph node staging. Minute lymph nodes have virtually no role in correct histopathological lymph node staging. Finally, large lymph nodes in stage I/II disease might indicate a favorable outcome.²⁷ Histologic parameters which are thought to reflect either cell-mediated (T-cell) or humoral (B-cell) immune responses in lymph nodes have been studied in regional lymph nodes. Patients whose lymph nodes show morphological evidence of cell-mediated immunity, manifested either by an increased number of paracortical immunoblasts or sinus histiocytosis, survive significantly

longer than those whose lymph nodes show no such changes. Patients whose lymph nodes show simultaneous paracortical activity and sinus histiocytosis have the best survival of all. Histologic parameters which suggest an antibody-mediated immune response (germinal center activity) were not an important prognostic indicator.³³

CLINICAL IMPLICATIONS

Several parameters are used for predicting the prognosis in cancer patients. It is assumed that the histological analysis of the patterns in the regional lymph nodes draining the tumor could elucidate the immunological host-tumor relationship and provide additional information on patient survival. Increasing size of the cancer, higher grade, and stage of the malignancy are likely to show decreased number of reactive lymph nodes. It has been found that certain patterns like lymphocyte predominance have a lower risk of metastasis while in some studies germinal center predominance has a higher risk of metastasis. However, more extensive studies on lymph node immune response patterns will be helpful in providing information on patient prognosis.

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