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# Cervical Lymph Node Excision – A Retrospective Analysis of Differential Diagnoses and Prognostic Variables

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## Abstract

**Background:** Lymphadenopathy often poses problems in terms of differential diagnosis. Lymph node excision is therefore frequently a necessary component in diagnostic work-up and confirmation. Current data are scarce concerning diagnostic frequency distributions and prognostic variables for this routine procedure in otorhinolaryngology.

**Methods:** All lymph node excisions conducted here between 01/2007 and 12/2011 were analyzed retrospectively. Exclusion criteria were previously known lymphomas or carcinomas in the head and neck region and peripheral malignomas if patients had not been recurrence-free for 5 years.

**Results:** The analysis included 175 patients (mean age: 40.0 years; 1-94), of whom 46.3% were female. Histology revealed reactive changes in 45.7% and specific changes in 11.4%, lymphomas in 29.7%, metastases in 5.1%, and other tumors in 8.0%. Malignant findings were recorded in 82.4% of cases of supraclavicular lymphadenopathy. Abnormal laboratory variables ($p<0.01$) were encountered significantly less frequently in reactive lymph node changes, B symptoms significantly more frequently in lymphomas ($p<0.01$) and nicotine and alcohol abuse in metastases ($p<0.01$). No significant differences were found for gender. The complication rate was 2.3%.

**Conclusion:** In just over 46% of cases lymph node histology revealed findings that required treatment, and in 75% of these the findings were malignant. Given the minimal surgical risk, lymph node excision should be performed at an early stage where the diagnosis is uncertain so that specific therapy can be initiated early. Location, laboratory variables and B symptoms may provide pointers to specific or malignant pathology.

**Keywords: Cervical lymph nodes; Excision; Specific lymphadenitis; Lymphoma; Malignoma**

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## Introduction

The human body has 600 to 800 lymph nodes, of which some 300 are located in the head and neck region [1-3]. Lymph nodes are categorized as belonging to the secondary lymphatic organs. They play a key role in the specific immune defence system [3,4]. Changes in terms of lymph node size and consistency are often the first signs of illness [3,5,6]. Lymphadenopathy is subcategorized as being localized or generalized. In generalized lymphadenopathy two or more non-contiguous areas are involved [2,4]. In adults palpable lymph nodes are considered to be abnormal if they are greater than 1 cm in diameter [4].

Cervical lymphadenopathy is a common problem in the outpatient setting in patients from all age groups [7-10]. Palpable lymphadenopathy is detected in 38% to 45% of children [6,11]. Among adults the annual incidence of lymphadenopathy is approximately 0.6% to 0.7% [6,9]. Half of cases are characterized exclusively by cervical lymph node involvement, while in a quarter of cases there is generalized lymphadenopathy [4]. Infectious, immunological, neoplastic or metabolic pathologies are etiologically involved in most cases [4,12]. This broad spectrum of possible causes presents the attending clinician with a diagnostic challenge in terms of identifying patients with diseases that require treatment and - in the worst-case scenario - that may be malignant and of establishing further appropriate diagnostic work-up. In the literature there is a discrepancy in the reported incidence of malignant pathology, ranging widely from just 1.1% to as much as 40% [6,13]. In order to exclude malignant processes of this type, invasive diagnostic procedures are recommended in any patient where lymphadenopathy has persisted for longer than 1 month or where there is a clinically

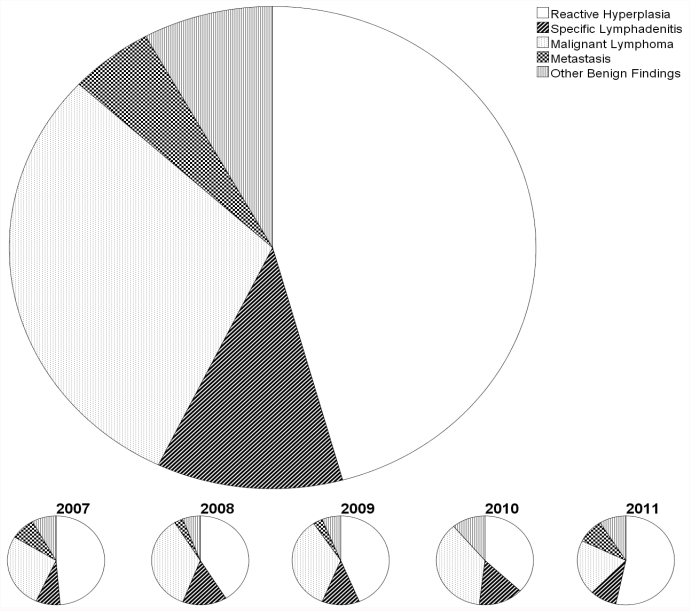


**Figure 1:** Frequency distribution of diagnoses.
Distribution over the entire study period (large graphic) and for each individual year (small graphics). Over the course of time there were no significant differences between the years.

justified suspicion of malignoma [4,14]. Lymph node excision in this context is one of the routine procedures in otorhinolaryngology. According to the literature, lymph node excision or biopsy is subsequently performed in 3% of patients in whom lymphadenopathy is detected in primary care practices [4,6]. Recent years have witnessed an increasing incidence of certain hematological diseases (e.g. non-Hodgkin's lymphoma) and a changing incidence of specific inflammatory conditions (e.g. tuberculosis) in westernized countries [15,16]. Despite this trend, current data from Western Europe are sparse concerning the distribution of diagnoses in cervical lymph node excision. The present study was conducted to investigate this aspect, as well as to identify possible prognostic variables with regard to the benign or malignant status of lymphadenopathy.

## Materials and Methods

The study was approved by the local Ethics Committee (no. 11-101-0148).

### Patient population and data collection

Data were collected retrospectively for all patients who had undergone lymph node excision or partial excision in the cervical region (level I - VI) in our Department of Otorhinolaryngology between January 2007 and December 2011. The following were excluded from the analysis: patients with previously known malignant lymphoma or previously known solid malignoma in the head and neck region, patients with suspected lymph node metastases with an already confirmed primary or one detected during laryngoscopy, and patients who had undergone a neck dissection involving more than one level. Patients with malignomas away from the head and neck region were included if they had been recurrence-free for a minimum of 5 years. Patient records yielded details of age, sex, clinical appearance of the lymph nodes (mobility, painfulness, consistency), duration of swelling, B symptoms, alcohol and nicotine abuse, laboratory variables (C-Reactive Protein [CRP; normal range <3.0 mg/l]), leukocytes (normal range 4.63/nl to 6.08/nl), platelets (normal range 163/nl to 337/nl), Lactate Dehydrogenase [LDH; normal range <250 U/l]), pre-operative imaging (ultrasound, Computed Tomography [CT], Magnetic Resonance Imaging [MRI]) where performed, type of anesthesia, postoperative complications and histology results.

For further analysis the study patients were categorized into five groups on the basis of histological diagnosis: lymph nodes showing non-specific/reactive changes, specific lymphadenitis, malignant lymphomas, metastases and other benign tumors. The latter were included only in the frequency analyses; they were excluded from the analyses of between-group differences.

### Statistical analysis

Statistical analysis and graphic presentation of results were performed using the SPSS Statistics 19.0 software (IBM Corporation, Armonk/USA). The primary study objective was to establish the distribution of diagnoses in cervical lymphadenopathy of uncertain etiology. Additional analyses were performed to elucidate possible associations between histological findings and age, noxious agent abuse, B symptoms and a number of laboratory variables. Between-group differences were studied using Fisher's exact test. P-values less than 0.05 were regarded as statistically significant, and those less than 0.01 as highly statistically significant.

## Results

In total, 175 patients with a mean age of 40.0 years (± 20.6; 1-94) were included in the analysis. Of this number 81 patients (46.3%) were female and 94 (53.7%) were male. The most frequent histological diagnosis in a total of 45.7% of cases was non-specific lymph node change (Table 1). Malignant lymphomas ranked second (29.7%), followed by specific lymphadenitis (11.4%) such as toxoplasmosis or sarcoidosis, other benign tumors (8.0%), and finally solid metastases (5.1%). The percentage distribution of diagnoses is shown in Figure 1 for the entire study period and for each year separately.

Figure 2 presents the frequency of diagnoses with reference to the age of the patients. Whereas benign and reactive lymph node changes

**Table 1:** Frequency distribution of diagnoses.

| Diagnoses | Frequencies, absolute (percentage) |
|---|---|
| **Non-specific changes** | **80 (45.7)** |
| **Specific infections** | **20 (11.4)** |
| Toxoplasmosis (Piringer-Kuchinka lymphadenitis) | 5 |
| Sarcoidosis | 4 |
| Epitheloid cell granulomas without pathogen detected | 4 |
| Kikuchi-Fujimoto lymphadenitis | 3 |
| Cat scratch disease (*Bartonella henselae*) | 2 |
| *Mycobacterium avium* | 1 |
| Lymph node tuberculosis | 1 |
| **Malignant lymphomas** | **52 (29.7)** |
| Hodgkin's lymphomas | 26 |
| Mature B-cell neoplasias | 22 |
| Mature T-cell neoplasias | 2 |
| Precursor neoplasias | 1 |
| Composite lymphoma (T-cell and Hodgkin's) | 1 |
| **Metastases** | **9 (5.1)** |
| Squamous cell carcinomas | 3 |
| Adenocarcinomas (2x breast CA,1x bronchial CA) | 3 |
| Malignant melanoma | 1 |
| Lymphoepithelial carcinoma | 1 |
| Carcinoma, classification not possible | 1 |
| **Other tumors** | **14 (8.0)** |
| Salivary gland tumors | 5 |
| Tissue altered by inflammation | 3 |
| Lateral cervical cyst | 1 |
| Neurinoma | 1 |
| Atheroma | 1 |
| Lipoma | 1 |
| Pilomatrixoma | 1 |
| Inflammatory pseudotumor | 1 |

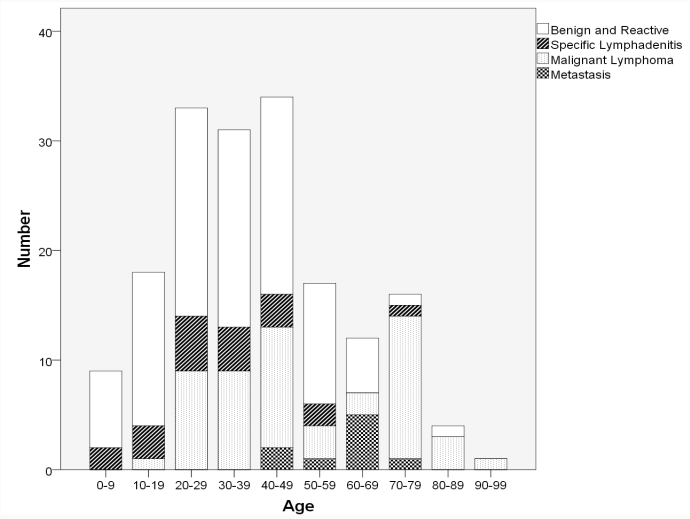


**Figure 2:** Age distribution of diagnoses.
The bars show the absolute numbers with the respective diagnoses for each age decade.

predominated up to and including the fifth decade, with increasing patient age there was a marked increase in metastases (7th decade of life) and malignant lymphomas (8th decade of life). Lymphomas also displayed a second peak in the 3rd to 5th decades of life. At the time when lymph node excision was performed, lymphadenopathy had been present on average for 5.8 months (± 10.0; 10 days - 5 years); there was no significant association with diagnosis. 61.7% of the procedures were performed under local anesthesia, and the rest under endotracheal anesthesia. Partial excision only was performed in 12% of cases; one lymph node was excised in 62.9% of cases, two lymph nodes in 20.0%, and up to four lymph nodes in 5.1%. Postoperative complications were encountered in four patients altogether and involved one case each of hematoma, seroma, abscess and secondary bleeding. Lymph node excision was performed for the first time in 92.6% of the patients (n=162), for the second time in 6.9% (n=12), and for the third time in one patient. Where first-time findings had been unremarkable, repeat biopsy revealed a malignant lymphoma in 7 out of 12 cases. The patient undergoing a third biopsy showed a non-specific result on that occasion too.

Almost all the patients (98.9%) had undergone preoperative ultrasonography of the affected lymph node; 22.3% of patients had also undergone CT and 8.6% had undergone MRI. Clinical examination revealed impaired lymph node mobility more frequently (but without statistical significance) in metastases and malignant lymphomas. Malignant lymphomas also often presented as being less

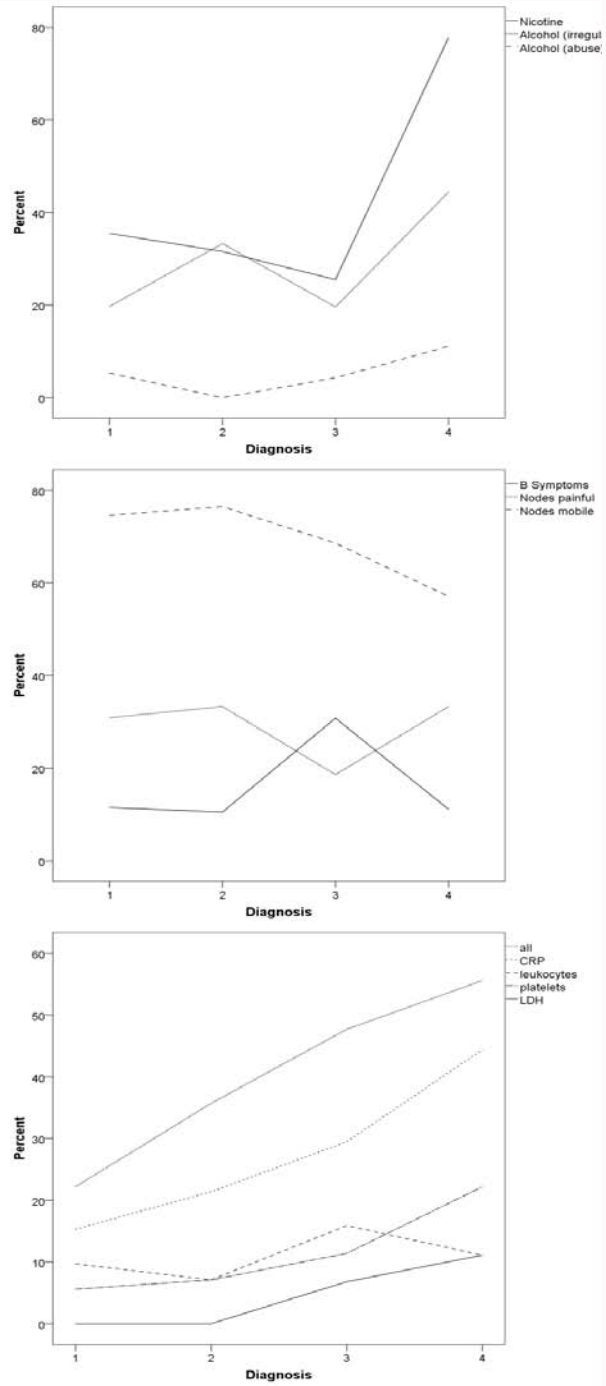


**Figure 3:** Possible prognostic parameters.
Percentage details for noxious agents, B symptoms, painfulness, mobility and abnormal laboratory variables.
Irregular alcohol consumption equates to occasional consumption, abuse equates to consumption in excess of 2 beers or the equivalent per day. For CRP and LDH only abnormal increases were counted, while for leukocytes and platelets abnormal reductions were also counted.
Diagnoses: 1= non-specific/reactive, 2= specific lymphadenitis, 3=malignant lymphomas, 4= metastases.

painful and they caused B symptoms significantly more commonly ($p<0.01$) (Figure 3). In this context, night sweats and weight loss were particularly important. Metastases were significantly more often associated with a history of noxious agent abuse ($p<0.01$) (Figure 3). Supraclavicular lymphadenopathy revealed malignant findings in 82.4% of cases. The analysis of laboratory variables focused particularly on the relevance of LDH, CRP and platelets. Overall, abnormal laboratory values occurred significantly more rarely in reactive lymph node changes ($p<0.01$ for all variables together; $p=0.044$ for CRP, $p=0.051$ for LDH) (Figure 3).

## Discussion

Cervical lymph nodes are the most commonly enlarged and most commonly biopsied of all the peripheral lymph nodes [17,18]. According to Pangalis et al. [19], cervical lymphadenopathy may be palpated in primary care as an incidental finding in 56% of patients. Textbooks state that non-specific changes are present in two-thirds of these cases [14]. In our study in an university hospital, such non-specific changes were found in a total of 45.7% of patients, and in 35.6% in a comparable study from India [5]. Other studies from tertiary referral centers confirm this high proportion of non-specific lymphadenopathy (43.3% to 62.3%) [8,11,19]. In our series specific lymphadenitis was present in 11.4% of cases, the leading diagnoses in this category being toxoplasmosis and sarcoidosis. As expected, marked regional differences are found in this respect. In India, for example, tuberculosis alone accounts for 31.3% of cases [5]. However, it is of interest to note that very marked differences are also to be found in centers within Europe: specific lymphadenitis was detected by Laffers et al. [8] in Germany in only 0.6% (one case each of tuberculosis and sarcoidosis), compared with 30.9% by Pangalis et al. [19] in Southern Europe. In the latter study toxoplasmosis was also the main cause, with tuberculosis in third place. Malignant conditions, such as metastases and especially Hodgkin's and non-Hodgkin's lymphomas or chronic lymphatic B-cell leukemia, also typically manifest themselves initially as lymphadenopathy [20]. Working in a primary care setting, Fijten et al. [21] reported a malignant cause in 1.1% of their patients with unexplained lymphadenopathy [21]. This is backed up by two further studies where malignancy was detected as the cause of lymphadenopathy in only 3 out of 238 patients [22] and in none out of 80 patients examined [23]. In our study malignancy was diagnosed in more than one-third (34.8%) of lymph node biopsy specimens. This clearly higher percentage can be accounted for by the highly selected patient population attending our university hospital. Studies by Laffers et al. [8] and Lee et al. [13], also conducted in tertiary referral centers, reported similarly high numbers, with malignancy being detected in 38% and even 40% of cases respectively.

In the malignant pathology category malignant lymphomas dominated in our study, accounting for 85.2% (altogether 29.7%). Numbers of Hodgkin's and non-Hodgkin's lymphomas were evenly balanced. In other studies too malignant lymphomas were represented clearly more often than metastases. For example, malignant lymphomas were detected by Chau et al. [9] in 11.3%, by Lee et al. in 12% [13], and by Laffers et al. [8] in 19% of patients studied. In routine clinical practice Non-Hodgkin's Lymphoma (NHL) in particular appears to be playing an ever-increasing role. Several studies have reported a seriously increased incidence by about 50% in westernized countries in recent years [15,24,25]. Aside from altered environmental factors, one reason appears to be the increased ageing of the general population, because the risk of developing NHL rises continuously with increasing age until a peak is reached in the 7th and 8th decades of life [4]. By contrast, the incidence curve for Hodgkin's lymphoma is characteristically bimodal, with an initial peak occurring between the ages of 20 and 25 and a second peak around the age of 65 [14]. This pattern was also reflected in our study.

In other respects too patient age was found to be an important predictive factor for the benign or malignant status of lymphadenopathy. In our study, with one single exception, only benign lymphadenopathy was detected in the first two decades of life. Metastases occurred from the age of 40, with a peak between the ages of 60 and 70 (41.7%). Above the age of 70 malignant lymphomas were the most common diagnosis, accounting for up to 81.3% of cases. Specific lymphadenitis showed no age-dependency. Comparable results were also reported by Lee et al. [13] who stated that patient age was in fact the most important criterion for estimating the probability of whether lymphadenopathy is due to a benign or malignant process. Pangalis et al. [19] also reported age-related factors: in their study, for patients aged over 40, the risk of malignant or granulomatous lymphadenopathy was already increased 20-fold.

Gender-specific differences were not detected by us or in other comparable studies [6,13,19]. However, Laffers et al. [8] and Chau et al. [9] have reported a marked preponderance of malignant pathologies in male patients. They attribute this finding to greater noxious agent abuse among men. In patients with metastases, but not in those with malignant lymphomas, we also noted alcohol abuse and especially nicotine abuse significantly more often. Some authors have concluded that lymphadenopathy that is present for two to four weeks or for longer than one year is generally benign [12,18]. We are unable to concur with this view for two reasons in particular. Firstly, as well as acute inflammatory diseases, tumors with a high proliferation rate may also display a rapid and only short-lived size increase [4]; and secondly, malignant diseases with a low proliferation rate (low malignant Hodgkin's and non-Hodgkin's lymphomas, chronic lymphatic leukemia) exhibit very slow growth [26].

The occurrence of fever (>38°C), night sweats and weight loss (>10% in 6 months) has been reported in the literature for malignant lymphomas in particular [4,6]. These prognostically unfavorable features, known as B symptoms according to the Ann Arbor classification dating from 1966, were observed significantly more frequently in our study in 44.4% of malignant lymphomas [4,27]. A comparable frequency was also found in the study by Pangalis et al. [19] in 30% of Hodgkin's and 10% of non-Hodgkin's lymphoma patients. The presence of B symptoms in the history may therefore strengthen the suspicion of malignant lymphoma; however, it should be remembered that B symptoms also regularly occur in specific lymphadenitis, e.g. in tuberculosis or Kikuchi- Fujimoto disease [2,6,28]. On palpation, rock hard lymph nodes are considered to be typical for metastases, firm rubbery lymph nodes for malignant lymphomas, and soft tender lymph nodes for inflammatory or infectious processes. Painless and poorly mobile lymph nodes in particular are reported to be indicative of a malignant process [2,4,20]. Our results confirm this tendency only in part and to a non-significant degree, with the consequence that in our view palpatory findings should be categorized as having only vague prognostic utility. In addition, palpation is fraught with major inherent shortcomings in terms of size estimation: according to Gobbi et al. [29], actual lymph node size is clearly underestimated in most cases. Ultrasonography should therefore be performed routinely because as well as permitting precise measurement, it offers a good indication of benign or malignant status. According to the published literature, lymph node size greater than 2.25 $cm^2$ is viewed as particularly critical; secondly, a longitudinal-to-transverse axis ratio of less than 2.0 is suggestive of malignant lesions. Sensitivity and specificity of 95% have been reported for this latter aspect [14,19].

As well as size and consistency, location plays an important role. While the common distinction drawn between localized and generalized lymphadenopathy appears to be of only little differential diagnostic utility [14,19,20], the data for supraclavicular lymphadenopathy are unequivocal. This finding was reported to be malignant in 55% of 309 patients in a study by Ellison et al. [30], and in as many as 85% of 1103 patients in a study by Steel et al. [31]. In agreement with these authors, a malignant finding was made in our study in 82.4% of these lymph nodes. Thorough investigation in this location is therefore always advisable.

A study by Trichopoulos et al. [32] demonstrated an association between elevated CRP levels and certain cancers, including leukemia and malignant lymphomas. In addition, raised CRP levels in cancer have prognostic relevance in terms of survival. By also including abnormal leukocyte or platelet counts, prognostic utility can be enhanced even further [33]. LDH is an important independent prognostic factor, for example, in aggressive NHL or in certain metastasizing cancers [34,35]. Our results too indicate that unremarkable laboratory variables are readily consistent with non-specific lymphadenopathy, whereas raised CRP and/or raised LDH in particular point to a malignant etiology. Although the diagnostic yield from cervical lymph node biopsies is very high compared with other lymph node sites [13], unremarkable histological findings are repeatedly made despite the clear suspicion of malignoma. If this suspicion subsequently persists, further lymph node excision is strongly indicated; on repeat histology a malignant lymphoma was found in 7 out of 12 cases in the present study.

It should be mentioned that excision or biopsy appears to be clearly more useful than fine-needle aspiration, a procedure that is often cited as an alternative. Excision is a simple and effective method, it can be performed under local anesthetic in the vast majority of cases, and it is associated with an only minimal complication rate and no mortality [5]. By contrast, it is often not possible to make an unequivocal diagnosis using fine-needle aspiration cytology and so this investigation should be regarded as only second choice [4,36].

When evaluating our own study and comparable studies it must always be remembered that a special selection of patients has been made, depending on center (e.g. primary care or tertiary referral center) and country or continent. This leads to altered diagnosis frequencies. The relatively small patient population in our study may also be categorized as a flaw. However, since there were no significant differences in the distribution of diagnoses over the five years of the analysis, the study may nevertheless be regarded as being representative.

## Conclusion

Abnormal findings were recorded in just over 46% of cervical lymph node excisions performed in our university hospital. In one-ninth of these patients the findings related to metastases, in one-quarter to a specific lymphadenitis, and in just under two-thirds to a malignant lymphoma. As prognostic parameters, patient age, B symptoms, lymph node site, noxious agent abuse and abnormal laboratory values (e.g. CRP or LDH) may yield evidence to support a specific or malignant process. Lymph node excision is a low-risk procedure that can be performed in most cases under local anesthesia and permits a definitive diagnosis. It should be considered at an early stage in patients with unexplained, persistent cervical

lymphadenopathy.

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