RESEARCH ARTICLE
DOI: 10.26650/Tr-ENT.2023.1227477
The Turkish Journal of Ear Nose and Throat 2023;33(1):11-15

Predictive Value of Fine Needle Aspiration Biopsy and Ultrasonography in The Diagnosis of Cervical Lymphadenopathy*

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Citation: Sahin A, Koday MZ, Aktan B, Sakat MS, Kilic K. Predictive value of fine needle aspiration biopsy and ultrasonography in the diagnosis of cervical lymphadenopathy. Tr-ENT 2023;33(1):11-15. https://doi.org/10.26650/Tr-ENT.2023.1227477

ABSTRACT

Objective: Cervical lymphadenopathy (LAP) is one of the most common pathologies in adults and children. While ultrasonography (USG) and fine needle aspiration biopsy (FNAB) are the two methods used as diagnostic tests, excisional biopsy is the gold standard method for diagnosis. In this study, we aimed to show the relationship between USG findings and FNAB results with malignancy in patients with LAP.
Materials and methods: Patients who visited our clinic with the complaint of cervical LAP between March 2020 and September 2022 and underwent excisional biopsy were included in this retrospective study. The number, distribution, side, size, cortical thickness, conglomeration, and necrosis characteristics of LAP were evaluated on USG. The sensitivity and specificity of the FNAB were calculated in patients in accordance with the histopathological results.
Results: Of the patients included in the study, 45 were female and 42 were male. The overall mean age was 32.72 ± 20.02. The sensitivity of the FNAB was 43.5% and the specificity was 90.0%. Advanced age, presence of conglomeration, unilateral LAP, and generalized LAP were found to be statistically significant in terms of malignancy, while cortical thickness, the number and size of LAPs, and necrosis were not statistically significant.
Conclusion: FNAB was not found to be a reliable test to rule out malignancy due to low sensitivity for determining malignancy and but was found to be a highly selective test, and the malignancy-suspected result detected the real patients quite successfully. The advanced age, unilateral LAP, generalized distribution, and conglomeration were the parameters supporting malignancy.

Keywords: Cervical lymphadenopathy; excisional biopsy; fine needle aspiration biopsy; ultrasonography

INTRODUCTION

Lymphadenopathy (LAP) is defined as abnormal changes in a lymph node's size and/or character because of the migration of inflammatory or neoplastic cells to the lymph nodes (1, 2). Cervical LAPs arise from various causes, mainly infectious and neoplastic processes, and they need to be assessed with a detailed and multidisciplinary approach. Patients presenting with cervical LAP should be examined comprehensively in terms of features such as patient's age, onset and duration of LAP, changes in size and growth rate, pain, presence of B symptoms, and presence of accompanying systemic findings that may support malignancy (dyspnea, dysphagia, otalgia, etc.). If necessary, advanced laboratory tests, imaging methods (USG, Computed Tomography, Magnetic Resonance Imaging), and biopsy (fine needle aspiration biopsy, core needle biopsy, excisional biopsy) are performed (3).

While inflammatory pathologies are more frequent in children and young adults, neoplastic causes are more common with

* This study was presented as an oral presentation at the 43th Turkish National Congress of Otorhinolaryngology and Head and Neck Surgery, 16-20 November 2022, Antalya, Turkiye.

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Submitted: 01.01.2023 • **Accepted:** 17.03.2023 • **Published Online:** 29.03.2023

increasing age (2, 3). USG is a cheap, rapidly accessible, and non-invasive method in the evaluation of cervical LAP in terms of malignancy (4). In USG, parameters such as the number, distribution, size, shape, cortex, hilus of lymph nodes, and presence of necrosis are evaluated. An increase in the number of LAPs, generalized distribution, irregular borders, thick cortex, non-echogenic hilum, and necrosis are among the USG findings that can be interpreted in favor of malignancy (4-7).

Fine needle aspiration biopsy (FNAB) in suspicious lymph nodes is one of the minimally invasive methods that can be used in the diagnosis. Although FNAB is not a diagnostic method alone in the diagnosis of hematological malignancies, the diagnostic success rate of FNAB varies between 75-98% (8, 9). Non-diagnostic samples, high false-negative rates in Hodgkin lymphoma, and incomplete classification in Non-Hodgkin lymphoma are among the disadvantages of FNAB (8-10).

In this study, we aimed to present the role of FNAB and USG in diagnosis in patients with cervical LAP with the literature by comparing the preoperative USG features and FNAB reports with postoperative histopathological results of patients admitted to our clinic with a complaint of LAP.

MATERIALS AND METHODS

A total of 87 patients who underwent lymph node excision between March 2020 and September 2022 at the Otorhinolaryngology Clinic of Atatürk University Medical Faculty Hospital were included in this retrospective study. The study was carried out with the approval of Atatürk University Faculty of Medicine Clinical Research Ethics Committee dated September 29, 2022, numbered 590. Informed consent was obtained from the patients. Patients with a known diagnosis of a disease that can cause LAP (hematological malignancy, epithelial tumor history, thyroid cancer history, etc.) were excluded from the study.

The systemic examinations in terms of lymphadenopathy and neck ultrasonography reports of all patients participating in the study were investigated by scanning the medical files. In USG results, the number, distribution, side, size (long axis of LAP), cortical thickness, conglomeration, and necrosis characteristics of LAP were recorded. Patients were divided into groups according to the number of LAPs (single or multiple), distribution of LAP (localized: having only cervical LAP and generalized: inguinal and/or axillary LAP in addition to cervical LAP), side of the LAP (unilateral and bilateral), and size of LAP (between 1.5 and 2 cm, between 2 and 3 cm, and greater than or equal to 3 cm).

The histopathological results of patients who underwent FNAB before excisional biopsy were categorized as malignant and reactive. The concordance and differences between the FNAB and excisional biopsy histopathological results of the patients were investigated.

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) program was used for data analysis. In the statistical analysis of the study, mean ± standard deviation was used for continuous variables, whereas frequency and percentage values were defined for categorical variables. General characteristics and demographic features of the groups were determined by Frequency (Descriptive analysis: frequency analysis for a single variable) analysis. Since the findings in the data did not follow normal distribution according to the Kolmogorov-Smirnov (K-S) test, nonparametric tests were applied. In pairwise comparisons, the Mann-Whitney U Test was used to compare the mean of two independent groups. The Kruskal-Wallis Test was applied for the mean comparison of multiple independent groups. Post-Hoc Tamhane's T2 analysis was used for multiple comparisons. Chi-square test was used to define the relationship between categorical variables. A $p \leq 0.05$ value was considered statistically significant throughout the entire study.

RESULTS

Patients aged between 2 and 80 (32.72±20.02) were included in the study. 45 (51.7%) of the patients were female and 42 (48.3%) were male. FNAB was studied in 43 (49.4%) patients preoperatively. The histopathological results were reactive LAP in 31 (72.1%) of the patients who underwent FNAB, and the results were suspicious for malignancy in 12 (27.9%) of them. When the excisional biopsy pathology results of all patients were analyzed, the result was reactive in 48 (55.2%) patients, compatible with hematological malignancy in 29 (33.3%) patients, and compatible with other malignancies in 10 (11.5%) patients (Table 1).

FNAB and excisional biopsy results of 43 patients who previously underwent FNAB were compared. The positive predictive value of FNAB was 83.3% and the negative predictive value was 58.1%. The sensitivity value of FNAB was 43.5% and the specificity value was 90.0% (Table 2).

Table 1: Age, gender, FNAB, and excisional biopsy results of cervical LAP patients

			n=87
Age	**Mean ± SD (min-max)**		32.72±20.018 (2-80)
Gender	Female	n (%)	45 (51.7)
	Male	n (%)	42 (48.3)
FNAB	Absent	n (%)	44 (50.6)
	Present	n (%)	43 (49.4)
Result of FNAB	Absent	n (%)	44 (50.6)
	Reactive	n (%)	31 (35.6)
	Suspicious for malignancy	n (%)	12 (13.8)
Result of excisional biopsy	Reactive	n (%)	48 (55.2)
	Hematological malignancy	n (%)	29 (33.3)
	Other malignancies	n (%)	10 (11.5)

FNAB: Fine needle aspiration biopsy, SD: Standard deviation

Excisional biopsy results were divided into two groups as reactive and malignant. There were 48 (55.17%) patients in the reactive LAP group and 39 (44.83%) patients in the malignant LAP group. Reactive and malignant LAP groups were statistically analyzed based on age, gender, and USG features, and those data are presented in Table 3.

As summarized in Table 3, increased age (p=0.001), generalized LAP (p= 0.011), unilateral LAP (p=0.015), and LAP presenting with conglomeration (p=0.004) had statistically significant results in favor of malignancy throughout the comparison between reactive and malignant LAP groups. On the other hand, no statistically significant data was obtained from the comparison of groups by gender of patients (p=1.000), the number of LAPs (p=0.105), size of LAP (p=0.097) as well as displaying thick cortex (p=0.519) and necrosis (p=0.720).

Table 2: Comparison of FNAB and Excisional Biopsy Results

		Result of Excisional Biopsy			p
		Malignant	Reactive	Total	
Result of FNAB	Suspicious for Malignancy	10 (%83.3)	2 (%16.7)	***12***	***0.019****
	Reactive	13 (%41.9)	18 (%58.1)	31	
	Total	23	20	43	

FNAB: Fine needle aspiration biopsy

It was reported from the analysis that the risk of a malignancy-positive result was increased 3.15 times by a unilateral LAP, 4.88 times by generalized LAP, and 3.92 times by a LAP presenting with conglomeration.

DISCUSSION

Cervical LAP is a common pathology in both pediatric and adult populations. If the LAP grows rapidly within 2 weeks, if there is no reduction in LAP dimensions within 4-6 weeks, and if it does not disappear completely within 8-12 weeks, a biopsy should be performed (1). There are similarities and differences in cervical LAP characteristics between adult and pediatric patients. Generalized LAP and LAP in the supraclavicular region have an increased risk for malignancy in both children and adults, and biopsy should be considered without delay (2, 11). LAP size greater than 1.5 cm in the cervical region in adult patients raises suspicion for malignancy, while LAP greater than 2 cm in pediatric patients is more significant in terms of malignancy (2, 11).

While cervical LAP is more likely to be malignant in advanced age (>40), benign pathologies are more frequent in children and young adults (2, 3). In our study, the mean age of the patients was calculated as 32.72±20.02 (2-80). In the comparison between age and LAP between the reactive and malignant LAP groups, there was a statistically significant difference between advanced age and the possibility of LAP being malignant. The comparison for age was found to be compatible with the literature.

Table 3: Characteristics of Excisional Biopsy Results

			Reactive n=48	Malignant n=39	p	OR (Odds ratio)
Age	Mean ± SD		24.00±16.678	43.46±18.668	***0.001****	
Gender	Female	n (%)	25 (52.1)	20 (51.3)	1.000	
	Male	n (%)	23 (47.9)	19 (48.7)		
Increase in cortical thickness	Absent	n (%)	25 (52.1)	17 (43.6)	0.519	
	Present	n (%)	23 (47.9)	22 (56.4)		
Conglomeration	Absent	n (%)	37 (77.1)	18 (46.2)	***0.004****	***3.92***
	Present	n (%)	11 (22.9)	21 (53.8)		
Number of LAP	Multiple	n (%)	45 (93.8)	32 (82.1)	0.105	
	Single	n (%)	3 (6.2)	7 (17.9)		
Side of LAP	Unilateral	n (%)	12 (25.0)	20 (51.3)	***0.015****	***3.15***
	Bilateral	n (%)	36 (75.0)	19 (48.7)		
Size of LAP	1.5-2 Cm	n (%)	18 (37.5)	17 (43.6)		
	2-3 Cm	n (%)	21 (43.8)	9 (23.1)	0.097	
	≥3 Cm	n (%)	9 (18.8)	13 (33.3)		
Distribution of LAP	Localized	n (%)	44 (91.7)	27 (69.2)	***0.011****	***4.88***
	Generalized	n (%)	4 (8.3)	12 (30.8)		
Necrosis	Absent	n (%)	46 (95.8)	32 (82.1)	0.720	
	Present	n (%)	2 (4.2)	7 (17.9)		

LAP: Lymphadenopathy

In cervical LAPs, FNAB is an inexpensive, rapid diagnostic, and minimally invasive procedure compared to excisional biopsy. The most significant disadvantages of FNAB are the inability to subtype hematological malignancies, nondiagnostic sampling, and high false negative rates. Although FNAB is currently one of the most frequently used diagnostic methods in cervical masses, the gold standard method in the diagnosis of LAP is excisional biopsy (8).

In the literature, the sensitivity of FNAB in diagnosis varies between 62% and 100%. (12) In our study, the sensitivity was found to be 43.5% and the specificity was 90.0%. Our sensitivity value was found to be low when compared to the literature values, yet the specificity was coherent with the literature (8, 10, 12, 13). In our study, we also discovered that the positive predictive value of FNAB was 83.3% and the negative predictive value was 58.1%. When sensitivity and negative predictive value data were evaluated together, it was determined that FNAB was not a sensitive test for malignancy and was not reliable enough to rule out malignancy.

In our study, the specificity of FNAB in terms of malignancy was 90% and the positive predictive value was 83.3%. When the positive predictive value was evaluated together with the specificity, it was seen that FNAB is a highly selective test in our clinic and the suspicious for malignancy result indicated the real patients quite successfully.

The size, location, number, shape, cortex, echogenicity, and presence of necrosis of the LAP can be investigated by USG. Increased number of LAP, supraclavicular location of LAP, size greater than 2 cm in children and 1.5 cm in adults, the ratio of short to long axis (S:L) ≥0.5 cm, increased cortical thickness, absence of echogenic hilus, and presence of necrosis can be interpreted in favor of malignancy, although it is not specific (5, 6).

In the comparison between the reactive LAP group and the malignant LAP group in terms of the number of LAPs (single or multiple), no statistically significant difference was observed. In the comparison carried out in terms of LAP distribution (localized or generalized), the generalization of LAP was a statistically significant feature in terms of malignancy. It was observed that generalized LAP increased the probability of malignancy 4.88 times. In a study by Darnal et al., generalized LAP was found in 53% of 45 patients with primary malignancies (14). In the study of Kamat on 244 cases with generalized LAP, the most common cause was granulomatous disease (58.19%) followed by reactive LAP (30.73%), then hematological and other malignancies (11.04%) (15). The presence of generalized LAP in a patient does not necessarily signify that patient has a diagnosis of malignancy; however, they should be examined for granulomatous diseases and malignancies.

Side features (unilateral or bilateral) of malignant LAP have brought controversial results in studies. In a study by Çelenk et al. on the pediatric population, 31% of patients with benign pathology had unilateral LAP, and 69% had bilateral LAP; on the other hand, it was found that 30% of patients with malignant pathology had unilateral LAP and 70% had bilateral LAP (16). In another study conducted by Kartal et al. in patients younger than 20 years of age, the unilateral/bilateral ratio was 69.8%/30.2% in the benign group, and 93.2%/ 6.8% in the malignant group. It was determined that unilateral LAP gave significant results in terms of malignancy (17). In our study, 25% of the reactive LAP group had unilateral LAP and 75% had bilateral LAP; 51.3% of the malignant LAP group had unilateral LAP and 48.7% had bilateral LAP. We determined that unilateral LAP was a statistically significant characteristic in terms of malignancy and unilateral LAP increased the probability of malignancy 3.15 times.

In the study, LAPs were examined in 3 groups (between 1.5 to 2 cm, between 2 to 3 cm, and greater than or equal to 3 cm) according to their size, and in the analysis performed among the three groups, it was discovered that the size did not cause a significant difference in terms of malignancy. In the study by Kartal et al., LAP size was evaluated according to the short and long axis. In the malignant group, the mean of the short axis was 18.7±8.8 mm and in the benign group, the mean of the short axis was 13.7±7.3 mm; hence, there was a statistically significant difference between the malignant-benign groups (17). In our study, it can be assumed that a statistically significant difference could not be obtained since the short and long-axis values were not calculated separately when measuring the LAP size.

The increase in thickness of the LAP cortex is one of the features that arouse the suspicion of a pathological LAP. In a study by Kurt et al. on cervical LAP, the hilar:cortical thickness ratio was examined, and cortical thickness gave a statistically significant result in favor of malignancy (18). In this study, groups were separated according to the presence of an increase in cortical thickness, and no statistically significant difference was obtained between the reactive LAP group and the malignant LAP group.

Contradictory results have been concluded from the literature about the relationship between lymph node conglomeration and malignancy. In a study by Khanna et al. with 192 patients, it was determined that conglomeration did not create a statistically significant difference between malignant and benign lesions, while in the study by Kartal et al., conglomeration was detected as a significant variable between benign and malignant groups (17, 19). In our study, the conglomeration of LAP was determined to be statistically significant in terms of malignancy and it was observed that conglomeration increased the probability of malignancy by 3.92 times.

The presence of necrosis in LAP is another feature that supports malignancy. In our study, 4.2% of the reactive LAP group and 17.9% of the malignant LAP group had LAP with necrosis. Despite the fact that there were more patients with necrotic LAPs in the malignant LAP group, no statistically significant difference was defined between the groups. In the study conducted by Kartal et al., necrosis was observed in 4.7% of the reactive group and 18.2% of the malignant group, and a

statistically significant difference was found between the two groups. (17) In another study conducted by Vandana et al., necrosis was seen at a rate of 30% in patients with tuberculosis, and at a rate of 5% in patients with a malignant diagnosis, while necrosis was observed at a rate of 7.5% in the reactive group (4). Considering all these data, it is concluded that necrosis supports malignancy and granulomatous diseases such as tuberculosis.

There are several limitations of this study. First, the pediatric and adult patients were evaluated together. Examining these two populations separately would give more objective results. Secondly, carrying out such a study with larger patient groups will give more comprehensive and accurate results. Finally, not examining the lymph nodes with elastography is another limitation of this study.

CONCLUSION

Although cervical lymphadenopathy is mostly caused by benign pathologies, it is a pathology that should be investigated extensively in terms of malignancy, particularly in elderly patients. As a result of our study, it was observed that the specificity and positive predictive values of FNAB were quite high. However, its sensitivity and negative predictive values were lower. When we focus on the USG features, unilateral LAP, generalized distribution, and presence of conglomeration provide significant information for indicating malignancy. We believe that conducting studies with larger patient groups about this topic will provide more consequential results to the literature.

Ethics Committee Approval: This study was approved by Ataturk University Faculty of Medicine Clinical Research Ethics Committee (Date: 29.09.2022, No: 590).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- A.Ş., M.Z.K., B.A., M.S.S., K.K.; Data Acquisition- A.Ş., M.Z.K., B.A., M.S.S., K.K.; Data Analysis/Interpretation- A.Ş., M.Z.K., B.A., M.S.S., K.K.; Drafting Manuscript- A.Ş., M.Z.K., B.A., M.S.S., K.K.; Critical Revision of Manuscript- A.Ş., M.Z.K., B.A., M.S.S., K.K.; Final Approval and Accountability- A.Ş., M.Z.K., B.A., M.S.S., K.K.; Material or Technical Support- A.Ş., M.Z.K., B.A., M.S.S., K.K.; Supervision- A.Ş., M.Z.K., B.A., M.S.S., K.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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