Diagnostic Accuracy of Lymph Nodes Fine Needle Aspiration Biopsy Based on The Sydney System for Reporting Lymph Node Cytology

by Indah Puspasari

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Running title:

Diagnostic Accuracy of Lymph Nodes FNAB Based on The Sydney System Reporting

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Abstract

Objective: To evaluate the diagnostic accuracy and malignancy risk of The Sydney System Reporting for Lymph Nodes Cytology.

Material and methods: This study utilized secondary data from 156 cases to conduct a retrospective analysis of a diagnostic test method. During 2019–2021, data were collected at Dr. Wahidin Sudirohusodo's Anatomical Pathology Laboratory in Makassar, Indonesia. The cytology slides of each case were split into five diagnostic groups using the Sydney method, which were then compared with the results of the histopathological diagnosis.

Results: There were six cases in the L1 category, thirty-two cases in the L2 category, thirteen patients in the L3 category, seventeen cases in the L4 category, and ninety-one cases in the L5 class. The malignant probability (MP) is computed for each diagnostic classification. L1 MP value is 66.7%, L2 MP value is 15.6%, L3 MP value is 76.9%, L4 MP value is 94.0%, and L5 MP value is 98.9%. The diagnostic value of the FNAB examination is as follows: 89.9% sensitivity, 92.9% specificity, 98.2% positive predictive value, 68.4% negative predictive value, and 90.47% diagnostic accuracy.

Conclusion: The FNAB examination provides high sensitivity, specificity, and accuracy in diagnosing lymph node tumors. Using a classification based on the Sydney system promotes communication between laboratories and clinicians.

Keywords: Lymph Node, Cytology, FNAB, Malignant Probability, Sydney System Reporting

Introduction

Lymph nodes are collections of lymphoreticular tissue found throughout the body. They are a component of the lymphatic system and play a role in the body's immunological mechanism. Lymphadenopathy is the medical term for lymph node enlargement, which can develop in infectious and neoplastic illnesses (Bazemore & Smucker, 2002). Hence, lymphadenopathy is a frequent clinical symptom that demands careful examination in medical practice.

Histopathological evaluation of a tissue biopsy is still the gold standard for diagnosing lymphadenopathy. Malignant lymphadenopathy is still diagnosed with excisional biopsy and histological examination (Kroft et al., 2021). Due to limited equipment, infrastructure, and medical professionals, not all health services can perform this operation. Furthermore, a biopsy or surgery is more invasive and costly. Therefore, a second examination that is simpler and less invasive is required. Examining a fine needle aspiration biopsy (FNAB) is one method (Orell et al., 2012).

The FNAB examination can be used for early diagnosis and has several benefits, which provide quick results. It also has a lower cost since it only requires a thin needle and does not require anesthesia. The side effects are virtually nonexistent because it does not create injuries like surgery does. Even though lymph node cytology does not always yield a definitive diagnosis, this procedure is believed to provide basic information for subsequent treatment (David et al., 2017; Zeppa & Cozzolino, 2017). Based on data from 42 studies, (Frederiksen et al., 2015) determined that the efficiency of FNAB in identifying the subtype of malignant lymphoma remains poor.

In 2019, at the 20th International Congress of Cytology held in Sydney, supported by The International Academy of Cytology and The European Federation of Cytology Societies, a panel of seasoned cytopathologists worldwide recommended a category-based reporting system for lymph node cytology. It categorically classified aspirates into five distinct groups based on particular cytological characteristics. In addition, it includes a management category for each class. The types are as follows: Category I/L1: inadequate or non-diagnostic; Category II/L2: benign; and Category III/L3: atypical cells of undetermined significance or atypical lymphoid cells of uncertain significance; Category IV/L4: suspicious for malignancy; and category V/L5: malignant (Al-Abbadi et al., 2020; Zeppa et al., 2020).

This research aims to examine and classify lymph node samples according to the recently proposed Sydney system and determine the malignant probability in each group by correlating histopathology reports wherever available.

Materials and methods

This study included 159 lymph node FNAB reports between January 2019 and December 2021. Cases of all ages and genders were considered. From the obtained test request forms, the pertinent clinical and demographic information about the patients was compiled.

All FNAB procedures were performed using aseptic precautions after obtaining written consent and discussing the procedure. A 22-gauge needle was employed for the treatment of superficial swellings. The Giemsa (MGG) and Papanicolaou stains were applied to all aspirate smears. Before the histopathological correlation was conducted, the cytology slides were reexamined by two pathologists using predefined cytological criteria.

We gathered histopathology reports for all included patients, and the diagnosis was verified whenever possible. The malignant probability (MP) for a category was determined by dividing the number of malignant cases validated by histology by the total number of patients with available histopathology. In the study, histopathology was deemed the gold standard for diagnosis. All cytologically and histopathologically malignant instances were regarded as positive (TP). True negative (TN) instances were malignancy-free based on cytology and histology. False-positive (FP) cases were diagnosed as malignant on cytology but benign on histopathology. False-negative instances were those identified as benign lesions on cytology but were malignant on histology (FN). Also calculated were the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy.

Results

Sample and Characteristics

This study revealed that 65.4% of the lymphadenopathy sample, or 104 individuals, were over forty years old, with the youngest being ten and the most senior 82. The number of female patients was 80, or 50.3%, somewhat higher than that of males, 79, or 49.7%. The distribution of age and gender are presented in Table 1.

The majority of lymphadenopathy cases, 131 (82.4%), were located in the cervical region, followed by axillary 9 (5.7%), submandibular 8 (5.0%), supra/infraclavicular 7 (4.4%), and inguinal 4 (2.5%). Based on the Sydney System approach, the cytology samples in this investigation were divided into five categories. Category L1: non-diagnostic in 6 (3.8%) cases, category L2: benign in 32 (20.1%) cases, category L3: AUS/FLUS in 13 (8.2%) cases, category L4: suspected of malignancy in 17 (10.7%) cases, and category L5: malignant in 91 (57.2%) cases.

Figure 1 depicts the microscopic appearance of FNAB smears from various Sydney System diagnostic categories. Identifying the pattern, evaluating the cells' cellularity and morphology, and assessing the smear's background are essential in classifying this lesion. Table 2 provides the MP data calculated for each diagnostic group. The L5 category had the highest MP value with 98.9%, followed by the L4 sort at 94.0%, L3 at 76.9%, L1 at 66.7%, and L2 at 15.6%.

Table 3 presents a 2x2 contingency table that displays the data required for calculating sensitivity, specificity, and positive and negative predictive values. Cytology and histopathology diagnoses are separated into benign and malignant groups to obtain diagnostic value by cross-tabulated the cytological and histological diagnoses of 147 patients provided in Table 3 with 107 true-positive diagnoses, 26 true-negative diagnoses, two false-positive diagnoses, and 12 false-negative diagnoses. After calculating the formula, the following diagnostic values were determined: a sensitivity of 89.9%, a specificity of 92.9%, a positive predictive value of 98.2%, a negative predictive value of 68.4%, and an accuracy of 90.47 percent. Moreover, Graph 1 yielded an Area Under Curve (ROC) value of 0.914.

Discussion

A common presenting symptom in the general outpatient department is lymph node enlargement. It is one of the initial and most common presenting symptoms of infectious, benign, and malignant disorders. FNA is excellent for evaluating lymph node enlargements because it is a speedy and relatively swift technique (Vigliar et al., 2021). The cytology results can aid in the early differentiation of benign and malignant tumors. The IAC has developed a standardized, classified lymph node cytology reporting system with diagnostic criteria and treatment recommendations for each group. Its purpose is to improve clinical integration and disease management in general (Al-Abbadi et al., 2020; Zeppa et al., 2020).

As the recommended reporting method is a relative discovery in cytopathology, only a few similar articles are accessible. This study comprised 159 FNAB instances of superficial lymphadenopathy over three years. These were all unguided FNAB techniques. Regarding the number of patients, our study is smaller than the retrospective analyses by (Joshee et al., 2022) and (Gupta et al., 2021), which comprised 1409 cases and 6983 cases, respectively. The 2021 retrospective studies by (Torres Rivas et al., 2021) and (Vigliar et al., 2021) investigated 363 and 300 cases using ultrasound-guided FNA for lymphadenopathy.

Although FNAB examination of lymph nodes is performed routinely in hospitals, the samples in this study from 2019 to 2021 were relatively small, especially in lesions with a benign cytology diagnosis, which typically does not require excisional biopsy or surgery, so only 159 cases met the inclusion criteria. In this investigation, most lymph nodes were located in the cervical region. This distribution is consistent with (Vigliar et al., 2021) and (Gupta et al., 2021) 's findings that most lymph nodes are located in the cervical region.

Based on the Sydney categorization system, lymph node cytology is subdivided into five types. In this study, the L5 group had the most significant number of cytology cases, 91. Since the hospital where the sample was obtained is a referral hospital, the patients that visit are typically in the advanced stages of their illness.

In the L1 category, the probability of malignancy is relatively high, at 66.7%. Another study by (Vigliar et al., 2021) and colleagues yielded the same results: a 50 percent L1 category. This high finding may be attributable to the short sample size, consisting of only 6 cases, of which four were malignant based on histopathology. Doing FNAB operations under ultrasound supervision is recommended to limit the number of instances with non-diagnostic results. Resampling of LN-FNAC samples is recommended in cases of inadequacy due to a considerable risk of lymphoma (Makarenko et al., 2022).

The L2 classification has the lowest MP, at 15.6%. There were 31 cases of L2, of which five were histopathologically classified as malignant and four as metastatic carcinoma in the lymph nodes; consequently, partial lymph node involvement must be considered a potential misinterpretation cause in metastatic cases. This discrepancy was suspected because small lymphocytic malignant lymphoma

resembled chronic lymphadenitis in the appearance of 1 point of non-small Hodgkin's lymphocytic lymphoma.

The MP for the L3 category is relatively high, at 76.9%. Most of the histological diagnoses (10 out of 13 cases) were malignant in this group. AUS/ALUS is diagnosed if a cellular smear reveals heterogeneous lymphoid cells or large atypical cells scattered, making it difficult to establish whether the condition is benign or cancerous. The MP values for categories L4 and L5 are 94.1% and 98.8%, respectively. These findings are consistent with the results of (Gupta et al., 2021), namely L4 of 88% and L5 of 99.6%, but (Joshee et al., 2022) reported L4 of 78.5% and L5 of 96.6%.

In some instances, nevertheless, the FNAB cytology results may be non-diagnostic or equivocal, whereas subsequent histopathology findings disclose malignancy (Gaddey & Riegel, 2016). Several investigations have shown situations where FNAB cytology and histopathology diagnoses diverged. In a retrospective study of 635 FNAB and core-needle biopsy (CNB) subjects conducted to exclude lymphoma, 18.1% of cases had non-diagnostic cytology but were confirmed as malignant on histopathology (Jelloul et al., 2019). A separate investigation found that FNAB had shortcomings in subclassifying non-Hodgkin malignant lymphoma (NHML) based on morphology alone and frequently required supplementary studies, such as immunohistochemistry, for reliable diagnosis (Wakely, 2000). Notably, FNAB is a minimally invasive procedure. The quality of the obtained sample can vary based on several factors, including the technique employed, the operator's qualifications, and the type of lesion being collected. Insufficient sampling, poor collection of samples, or the inability to interpret the cytological findings can lead to non-diagnostic cytology results. In such instances, additional diagnostic evaluation, such as histopathology and further ancillary investigations, may be required for an accurate diagnosis.

Histopathology, which involves the examination of tissue sections under a microscope, provides a more comprehensive assessment of the cellular architecture and cellular characteristics than cytology, which consists of the analysis of single cells or small cell clusters. Histopathology can also provide additional information, such as immunohistochemistry and molecular studies, which can aid in determining the presence of malignant cells or specific lymphoma subtypes.

Therefore, while FNAB is a valuable diagnostic instrument for assessing lymph nodes, there are instances in which the cytology results are non-diagnostic or inconclusive, but histopathology reveals malignancy. The limitations of FNAB cytology can contribute to the discrepancy, such as insufficient sampling or difficulty interpreting cytological findings. In cases where FNAB cytology and histopathology diagnoses are distinct, a detailed review of clinical and pathological results and consideration of additional diagnostic tests may be essential (Jelloul et al., 2019).

The diagnostic test in this investigation exhibited a sensitivity value of 89.9%, a specificity value of 92.9%, a positive predictive value of 98.2%, a negative predictive value of 68.4%, and a diagnostic accuracy of 90.47% (Table 3 and Graph 1). The sensitivity value represents the diagnostic test's capacity to detect the presence of disease or the likelihood that the diagnostic test findings will be true positives when performed on a group of diseased individuals. This investigation determined a sensitivity value of 89.9%, indicating that the FNAB test can diagnose lymph node malignancies. A positive predictive value of 98.2% means that if the FNAB results suggest a malignant lesion in the lymph nodes, there is a 98.2% likelihood that the patient has a malignant tumor.

Specificity is the capacity of a diagnostic test to demonstrate that a subject is not ill or the likelihood that a diagnostic test performed on a population of healthy individuals will yield negative results. This study determined a sensitivity value of 92.9%, indicating that the FNAB examination can diagnose benign lymph node abnormalities. In contrast, the negative predictive value in this study was only 68.4%, meaning that if the cytological diagnosis is a benign lesion, there is still a significant chance of a false-negative result on this test. In some cases, the diagnosis of FNAB does not correspond. Clinical circumstances or other supporting investigations should be provided before performing an FNAB biopsy and histological study to reach a definitive diagnosis. Due to the tiny tumor mass, the numerous necrotic masses, and misunderstandings, false negative results were typical in this investigation.

This study found that the diagnostic accuracy of FNAB lymph nodes ranged from 89.3% to 97.0%, consistent with the results of several other studies that found values between 89.3% and 97.0%. (Vigliar et al., 2021) reported FNAB lymph node sensitivity of 98.47%, specificity of 95.33%, positive predictive value of 96.27%, negative predictive value of 98.08%, and diagnostic accuracy of 97.06%. Ton Eryilmaz et al. (2021) found comparable outcomes in their research, with sensitivity and specificity

values of 87.9% and 89.7%, respectively, and diagnostic accuracy of 94.1%. In contrast, (Gupta et al., 2021) reported FNAB lymph node sensitivity of 79.9%, specificity of 98.7%, positive predictive value of 96.27%, negative predictive value of 98.08%, and diagnostic accuracy of 97.0%. Furthermore, The ROC curve, which exhibits an AUC value of 0.914, suggests that the FNAB report using The Sydney System Category can differentiate between true positive and false positive of malignant potential in lymph node lesions. The Area Under the Curve (AUC) metric is a numerical measure that ranges between 0 and 1, where a higher value signifies superior discriminatory ability. Typically, an AUC score falling from 0.7 to 0.9 is deemed satisfactory, whereas a score surpassing 0.9 is considered excellent.

On this basis, we conclude that the FNAB examination of the lymph nodes has relatively good diagnostic value and accuracy, allowing it to be utilized for the first diagnosis of lymph node lesions based on the findings of this study and other prior investigations. It is advisable to repeat FNAB with ultrasound guidance if the results of a benign cytology diagnosis require more attention than the clinic and radiology can provide to avoid false-negative consequences. It is envisaged that the classification based on the Sydney approach for reporting lymph node cytopathology will improve communication with physicians so that FNAB examinations can be recognized and implemented as a less invasive diagnostic tool.

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Study Approval

The health research ethics committee of the faculty of medicine at Hasanuddin University - Hasanuddin University Hospital - Dr. Wahidin Sudirohusodo Hospital authorized this study.

Conflict of Interest

Each author affirms that they have no competing interests.

Ethical approval

The health research ethics committee of the Faculty of Medicine at Hasanuddin University - Hasanuddin University Hospital - Dr. Wahidin Sudirohusodo Hospital waived informed consent for this study

Authors Contribution

JN, DI, and UM contributed to the idea and design of the approach; JN, DI, NKS, IPP, AL, and AFN were responsible for data curation, analysis, and interpretation. JN, DI, NKS, and UM conducted a comprehensive conceptual and editorial review; all writers revised and approved the final version of the essay.

Availability of Data

The data sets utilized in this study are available from the corresponding investigator upon reasonable request.

Figures and Tables

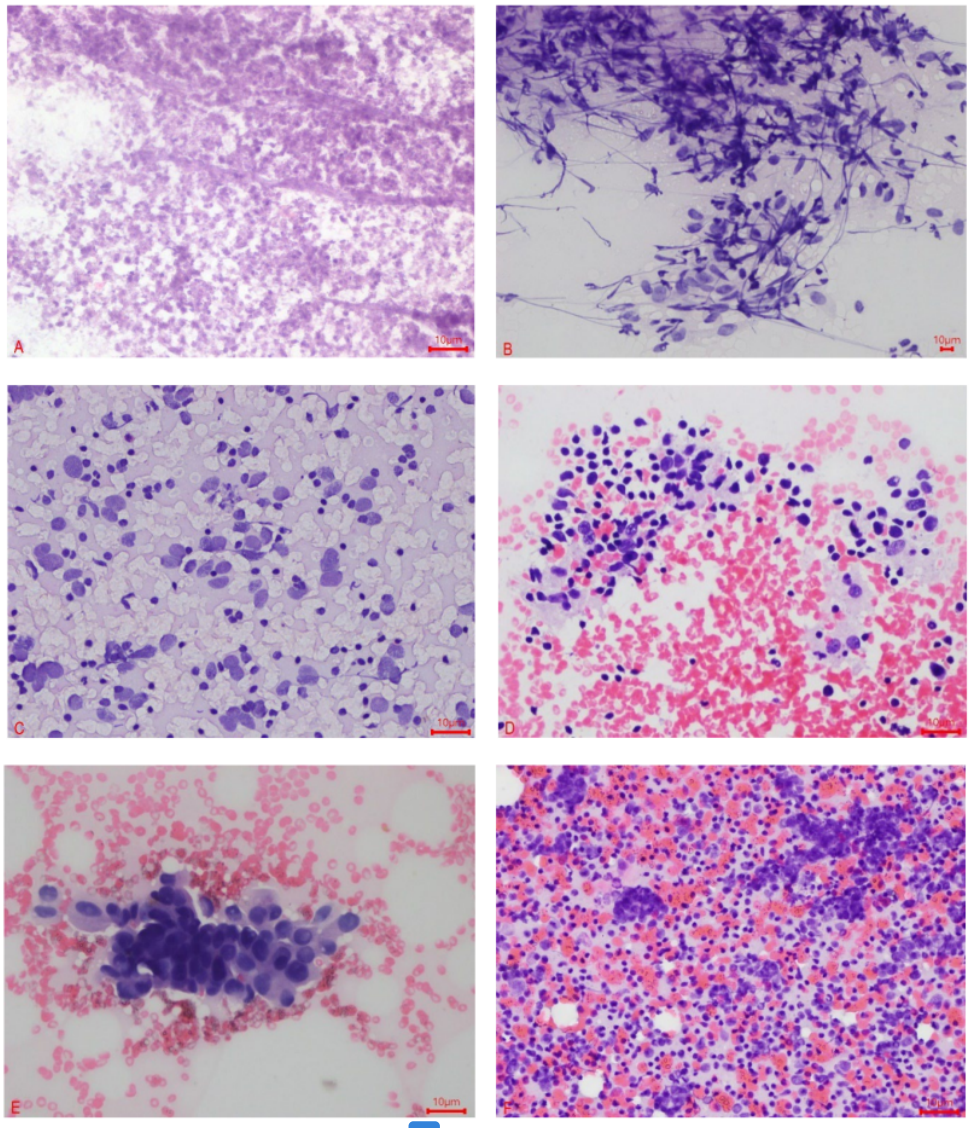


Figure 1: A representative depiction of lymph node cytology according to the Sydney System Category. A. Only contains necrosis material (L1: Non-diagnostic), Obj.40x; B. Granulomatous lymphadenitis (L2: Benign), Obj.10x; C. Large cells scattered among the lymphocyte cells (L3: AUS), Obj.40x; C. Large cells scattered among the lymphocyte cells (L3: AUS), Obj.40x; D. There are cells resembling datia cells Reed-Sternberg-like cells (L4: Suspicious for malignancy), Obj.40x; Lymph node metastases from adenocarcinoma and Non-Hodgkin lymphoma, respectively (L5: Malignant), obj.40x. (Papanicolauo Stain, Olympus CX-43, Scale bar 10 µm).

Table 1. Samples and Characteristics

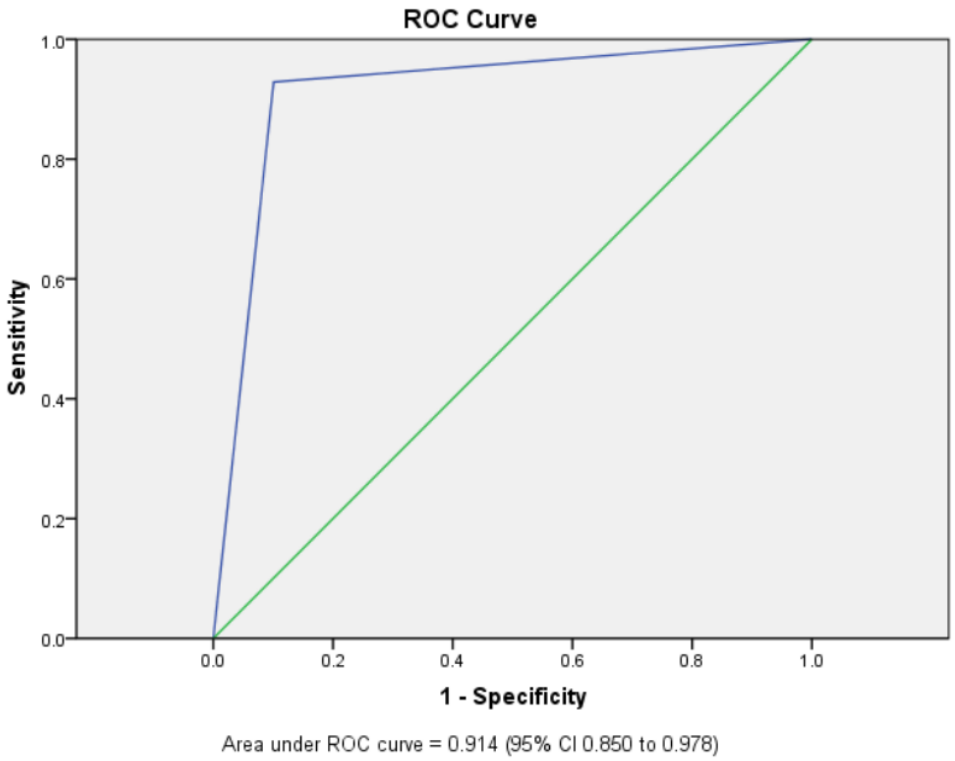
Variables	n	%
Age		
≤ 40 years	55	34,6
>40 years	104	65,4
Sex		
Male	79	49,7
Female	80	50,3
Site		
Submandible	8	5,0
Cervical	131	82,4
Axilla	9	5,7
Inguinal	4	2,5
Supra/infra clavicular	7	4,4
Sydney System Category		
L1: Non diagnostic	6	3,8
L2: Benign	32	20,1
L3: AUS / ALUS	13	8,2
L4: Suspicious for malignancy	17	10,7
L5: Malignant	91	57,2
Total	159	100

Table 2. Number of cytological diagnoses by category

Category	n	Confirmed by Histopathology		Malignant Probability (%)
		Benign	Malignant	
L1	6	2	4	66,7
L2	31	26	5	15,6
L3	13	3	10	76,9
L4	17	1	16	94,1
L5	90	1	89	98,9

Table 3. Comparison of cytological and histopathological findings

Cytology	Histopathology		Total
	Malignant	Benign	
Malignant	107	2	109
Benign	12	26	38
Total	119	28	147



Graph 1. Receiver Operating Curve (ROC) of sensitivity of cytological findings confirmed by histopathology. The research yielded the subsequent diagnostic measurements: a sensitivity rate of 89.9%, a specificity rate of 92.9%, a positive predictive value of 98.2%, a negative predictive value of 68.4%, and an accuracy rate of 90.47%.

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