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UTILITY OF THE SYDNEY SYSTEM FOR REPORTING OF LYMPH NODE CYTOLOGY IN A TERTIARY HEALTH CARE SET UP OF NORTH-EASTERN INDIA

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Abstract – *Objective:* *Fine Needle Aspiration Cytology (FNAC) is a popular method for diagnosing lymphadenopathy. The Sydney system for lymph node cytology classification and reporting has been developed for unified reporting language among cytopathologists and clinicians. The purpose of this study was to determine the system's applicability and accuracy in the diagnosis of lymph node cytology.*

Patients and Methods: *This was a retrospective cross sectional study of lymph node cytology conducted from January 2018 to July 2021, and the results were reported using the Sydney System into 5 groups from L1 to L5. To measure diagnostic accuracy and the risk of malignancy for each diagnostic category, the diagnoses were compared with the corresponding histological diagnoses. The statistical tools used were calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and risk of malignancy (ROM).*

Results: *A total of 220 cases were chosen for the study from a total of 600 FNACs performed for lymphadenopathy since they had histological correlation. The L1, L2, L3, L4, and L5 categories were assigned to 7 (3.18%), 141 (64.09%), 44 (20%), 8 (3.63%), and 20 (9.09%) cases, respectively. Malignancy risk was determined to be 33.33%, 8.8%, 56.4%, 83.33%, and 94.74% for the various groups.*

Conclusions: *The proposed Sydney system of reporting and classification of lymph node cytology can help in achieving uniformity and reproducibility. This appears to be the first time, the Sydney system has been introduced in this region in routine patient care, and this has improved the clinicians' understanding of the risk of malignancy and subsequent care.*

KEYWORDS: *Fine Needle Aspiration, Positive predictive value, Negative predictive value.*

INTRODUCTION

Fine needle aspiration cytology (FNAC) is widely accepted as the first line approach in the evaluation of lymphadenopathy of unknown aetiology. Minimum invasiveness, rapidity, cost effectiveness, and the capability to provide material for several ancillary techniques contribute to its wide applicability in evaluation of lymphadenopathy [1-4]. In pediatric cases as well, FNAC in evaluation of lymphadenopathy is found to have high diagnostic accuracy [5]. Clinical, morphological, and ancillary data that are required for specific diagnoses of lymphoproliferative disorders are incorporated in the current World Health Organization (WHO) classification [6]. Lymph node-Fine Needle Aspiration Cytology (LN-FNAC) can thus play a key role in the evaluation of lymphadenopathies as it can provide cytomorphological information and material for ancillary testing that is diagnostic.

However, the conventional system of reporting lymph node smears lacks standardized diagnostic classification, a common language of reporting among cytopathologists and clear communication

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to clinicians about risk of malignancy and further management [7,8]. To address this problem, the Sydney system of lymph node cytology reporting and classification was proposed in 2020 by an expert panel where the use of five diagnostic categories was introduced [9] (Table 1).

Underutilization and limited literature are the causes of the knowledge gap in the applicability of the Sydney system of classification and reporting lymph node pathologies [11]. The present study thus aims to assess the applicability and accuracy of the system in the diagnosis of lymph node cytology. Only a few studies have been done regarding the Sydney system of reporting lymph node cytology. This study was carried out in a tertiary care center situated in the north-eastern part of India, and this system was introduced in routine patient care as a pilot project in this region. Moreover, this appears to be the first research article to give the perspective of the experience of using this system in patients from this region.

PATIENTS AND METHODS

Study Design

The study was cross-sectional and retrospective in design, and information regarding pathological records and demographic and clinical details were retrieved from the electronic databases in the Department of Pathology at our institution. A prior ethical clearance was taken from the Institutional Ethical Committee.

Study Period

Patients who underwent lymph node FNAC in the period from January 2018 to July 2021 were studied.

Inclusion Criteria

All patients with lymphadenopathy undergoing FNAC during the study period for which subsequent histopathological examination reports or clinical follow-up data were available, were included in the study.

Exclusion Criteria

Cases without corresponding histopathological correlation and loss to follow-up cases for subsequent clinical data were excluded from the study. FNAC samples yielding inadequate or nondiagnostic material (L1) were excluded from the calculation of sensitivity, specificity, PPV, NPV, and accuracy.

Cytological Samples

In all cases, FNAC was conducted by experienced cytopathologists and under ultrasonography guidance as and when needed, such as in cases of deep-seated or suspected malignant lymph nodes. An explanation of the procedure to the patient along with its possible risks and benefits

TABLE 1. Cytomorphological features of each category of Sydney System for reporting of lymph node cytology.

Category	*Features*
L1: Inadequate/Insufficient	Scant cellularity; Extensive necrosis; Technical limitations that cannot be overcome
L2: Benign	Suppurative and granulomatous inflammation; Heterogeneous lymphoid population with small lymphocytes predominating, and often germinal centers with dendritic cells and tingible body macrophages
L3: Atypical (Cells) Undetermined Significance/Atypical Lymphoid (Cells) of Uncertain Significance (ALUS/AUS)	Heterogeneous lymphoid population, features suggest a reactive process, follicular lymphoma cannot be excluded; Excess of large cells (centroblasts or immunoblasts) or immature small lymphoid cells or cases where the atypical cells are not lymphoid cells.
L4: Suspicious.	Small and/or medium-sized, monomorphic atypical lymphoid cells suspicious of lymphoma, but the cytomorphology alone is not sufficient; Polymorphous lymphoid smears, few Hodgkin- or Reed-Sternberg-like cells are detected; Large cell or Burkitt lymphomas scantly cellular; Smears in which atypical cells suspicious for metastasis are detected, but are too scant to be diagnostic
L5: Malignant	NHL; HL: Appropriate cellular background and diagnostic Hodgkin and Reed-Sternberg cells; Metastatic neoplasms.

was given. A 23G needle was used to conduct the procedure, and direct smears were prepared from the first pass. Some of the smears were subjected to rapid on-site evaluation (ROSE) by using Diff-Quik stain to evaluate for adequacy. In case of smears that yielded scant material, a second pass was performed. The smears were stained by using both May Grünwald and Giemsa, and Papanicolaou stains. Immunophenotyping and cell block preparation were carried out for selected cases as recommended.

Diagnostic Categories

With the application of adequate blinding, the cytological slides were re-evaluated and classified into one of the following categories by consensus between two cytopathologists: L1, inadequate/nondiagnostic; L2, benign; L3, atypical cells of undetermined significance/atypical lymphoid cells of uncertain significance (AUS/ALUS); L4, suspicious; L5, malignant.

Histopathological Correlation and/or clinical follow up

To assess the risk of malignancy and diagnostic accuracy for each diagnostic category, histopathological diagnosis data were retrieved and correlated wherever it was available. In cases where no biopsies were performed, clinical follow-up data was correlated.

While making specific diagnoses, the neoplastic lesions were classified using the latest World Health Organization Classification of Haemato-lymphoid tumours, 4th edition, 2016.

Immunohistochemistry

Immunohistochemistry (IHC) was performed as per protocol for confirmation and categorisation of all suspected cases of lymphoma. The IHC panel included kappa and lambda antibodies to differentiate between reactive lymphadenopathy and lymphoma cases. The panel also included B-cell markers (CD20, CD79a), T-cell markers (CD3, CD5) and other markers like Leucocyte common antigen (LCA), CD 10, bcl-2, bcl-6, CD15, CD30, etc. to further subclassify the cases. In cases of metastatic deposits from carcinomatous lesions, the histological diagnosis was made according to the morphological features.

Statistical Analysis

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated for the diagnostic classification system, and also the risk of malignancy for each category was assessed.

A true positive was defined as any histologically or clinically confirmed malignant lesion with a malignant (L5), suspicious (L4) or atypical cytological diagnosis (L3); a true negative was defined as any histologically or clinically confirmed benign lesion with a benign (L2) diagnosis; a false positive was defined as any histologically benign lesion with an L5, L4, or L3 cytological diagnosis; a false negative was defined as any histologically malignant lesion with an L2 cytological diagnosis. Risk of Malignancy (ROM) was calculated by dividing the number of cases with a confirmed malignant lesion by the total number of cases with a histological or clinical follow-up within each diagnostic category [12]. All statistical analysis was done using SPSS version 26 (SPSS Inc., Chicago, IL, USA).

RESULTS

Cytological Samples

Out of a total of six hundred FNAC's done for lymphadenopathy, a total of 220 cases (36.67%), were selected in the study as they had subsequent histopathological correlation and/or clinical follow-up data. Out of these 600 cases, 325 (54.2%) patients were female, while 275 (45.8%) patients were male. Most of the cases (205, 34.2%) were below 20 years of age. Most of the cases (335, 55.8%) presented with cervical lymphadenopathy, followed by axillary lymphadenopathy in 155 cases (25.8%).

Diagnostic Categories

Out of the 220 cases which were included in the study, the number of cases categorized in the categories L1, inadequate/nondiagnostic; L2, benign; L3, atypical cells of undetermined significance/atypical lymphoid cells of uncertain significance (AUS/ALUS); L4, suspicious; L5, malignant, respectively, were 7 (3.18%), 141 (64.09%), 44 (20%), 8 (3.63%), and 20 (9.09%). Thus, L2 was the most frequently used category.

TABLE 2. Correlation of the cases categorized under each category with final diagnosis based on histopathological correlation and clinical follow up.

Categorization of smears based on Sydney System	*Final Diagnosis based on histopathological correlation and clinical follow up*	
	Non-Neoplastic	*Malignant*
L1 (n=6)	Reactive Lymphadenitis (n=3) Granulomatous Lymphadenitis (n=1)	Mets (n=2) • Papillary thyroid carcinoma with cystic change • Infiltrating ductal carcinoma with cystic change
L2 (n=125)	Reactive Lymphadenitis (n=79) Granulomatous Lymphadenitis (n=32) Sinus histiocytosis (n=1) Lipid lymphadenopathy (n=1) Castleman Disease (n=1)	Mets (n=10) • SCC (n=6) • AdenoCa (n=3) • Poorly Differentiated Ca (n=1) HL (n=1)
L3 (n=39)	Reactive Lymphadenitis (n=16) Granulomatous Lymphadenitis (n=1)	Mets (n=13) • SCC (n=7) • AdenoCa (n=4) • Poorly Differentiated Ca (n=1) • PTC Thyroid (n=1) NHL (n=8) HL (n=1)
L4 (n=6)	Reactive Lymphadenitis (n=1)	NHL (n=4) HL (n=1)
L5 (n=19)	Reactive Lymphadenitis (n=1)	NHL (n=15) HL (n=3)

Histopathological Correlation and/or clinical follow up

The correlation between the categorization of cytological smears and final diagnosis based on histopathological examination and/or clinical follow-up data is shown in Table 2. Out of the 7 cases (3.18%) categorized in the L1 Inadequate category, 2 (28.57%) turned out to be malignant in the final histopathological diagnosis. Both were cases of metastasis, one in a 37-year-old woman with infiltrating ductal carcinoma with cystic change (Figure 1), while the other was a case of papillary thyroid carcinoma with cystic change. A total of 141 cases (64.09%) was categorized under benign L2: Benign category. 130 of these turned out to be benign on histopathological follow up, of which 82 were reactive lymphadenitis (Figure 2). 11 (7.80%) of the 141 cases (64.09%) categorized under the L2: benign category proved to be malignant, i.e., false negative. These included 10 cases of metastasis, out of which 6 were cases of subcapsular deposits of squamous cell carcinoma (SCC), 3 cases of adenocarcinoma and 1 case of

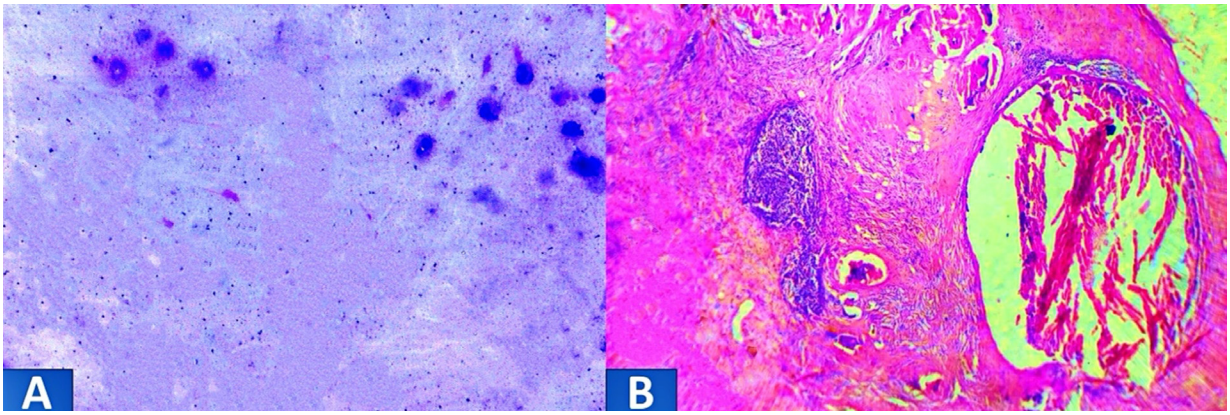

Fig. 1. *A*, Smear showing proteinaceous background with a few macrophages and scant necrotic material only. Categorized under Category L1: Non-diagnostic/Insufficient (MGG, 10X). *B*, Biopsy section from the case shows metastatic breast carcinoma with cystic change. (H&E, 10X).

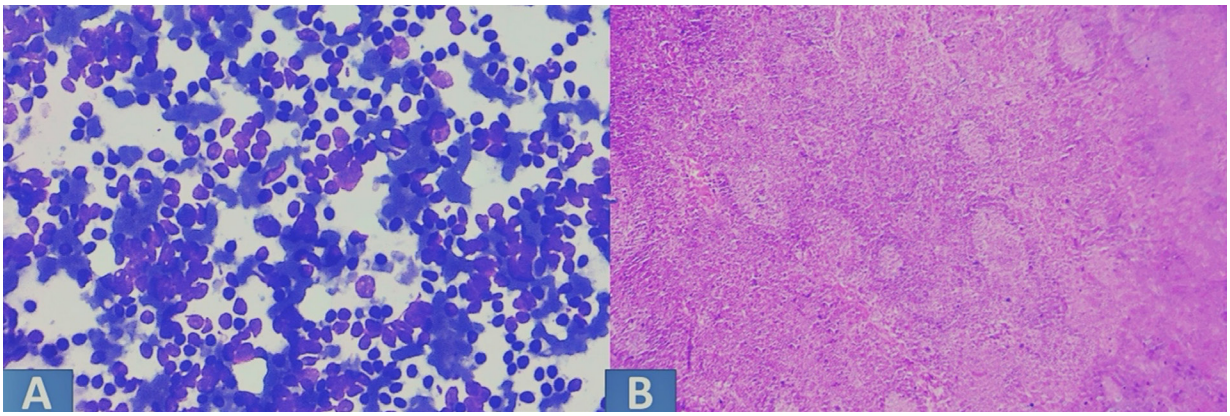

Fig. 2. *A*, Smear showing heterogenous population of lymphoid cells in logical proportions with predominantly small lymphocytes. Categorized under Category L2: Benign. (MGG, 10X). *B*, Section from the lymph node shows features of follicular hyperplasia (H&E, 10X).

poorly differentiated carcinoma. The remaining 1 case was a case of nodular lymphocyte predominant Hodgkin's lymphoma. 44 cases (20%) were categorized under the L3: Atypia of undetermined significance category, out of which 24 cases (54.54%) proved to be malignant. The cases that were placed under this category were those showing: a) heterogeneous lymphoid population, b) features suggesting a reactive process where follicular lymphoma cannot be excluded, c) an excess of large cells (centroblasts or immunoblasts) or immature small lymphoid cells, or d) cases where the atypical cells were not lymphoid cells. Out of the malignant cases, 15 were metastatic deposits of carcinoma, 8 were cases of non-Hodgkin's lymphoma (NHL), and 1 was a case of Hodgkin's lymphoma (HL). In one case where the smear showed a monotonous population of lymphoid cells with very few small lymphocytes. The corresponding histological picture showed features of follicular lymphoma which was positive for CD-20, bcl-2, and bcl-6. Hence, this case turned out to be a true positive.

Twenty of these cases proved to be benign on biopsy, out of which 19 were reactive lymphadenitis (Figure 3) and one was a case of granulomatous lymphadenitis. L4: Suspicious for malignancy category included cases which showed a) small and/or medium-sized, monomorphic atypical lymphoid cells suspicious of lymphoma, but the cytomorphology alone is not sufficient for diagnosis as malignant, b) polymorphous lymphoid smears where a few Hodgkin- or Reed-Sternberg-like cells were detected, or c) smears in which atypical cells suspicious for metastasis were detected but were too scant to be diagnostic. Eight cases (3.27%) were categorized in this category out of which 7 showed concordant results on histopathological follow up (Figure 4); however, 1 case (12.5%) turned out to be benign reactive hyperplasia in histopathological examination which was categorised as category 4 due to presence of Reed Sternberg like giant cells

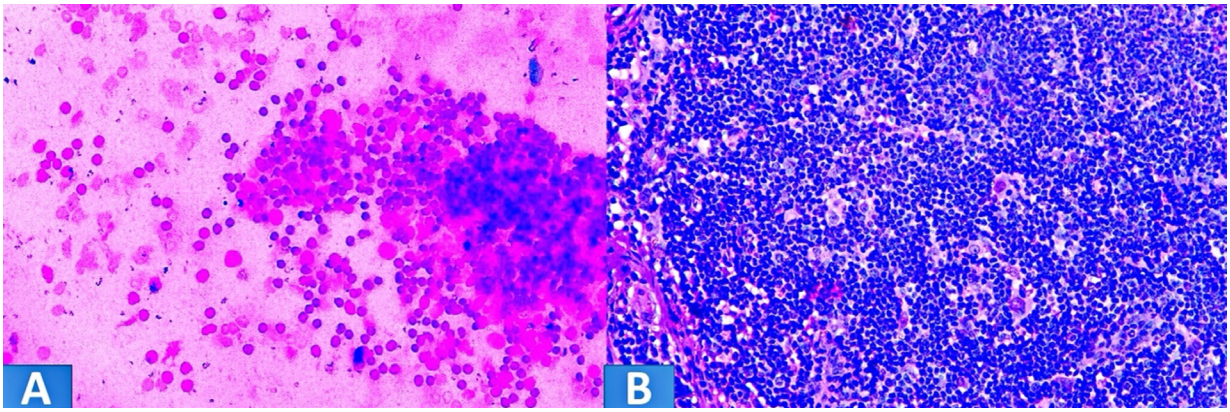

Fig. 3. *A*, Smear showing large cells with irregular nuclei, prominent nucleoli, and scant cytoplasm. Categorized under Category L3: Atypia of undetermined significance. (MGG, 10X). *B*, Histopathological section of the biopsy shows features of parafollicular hyperplasia with numerous macrophages along with immunoblasts. (H&E, 10X).

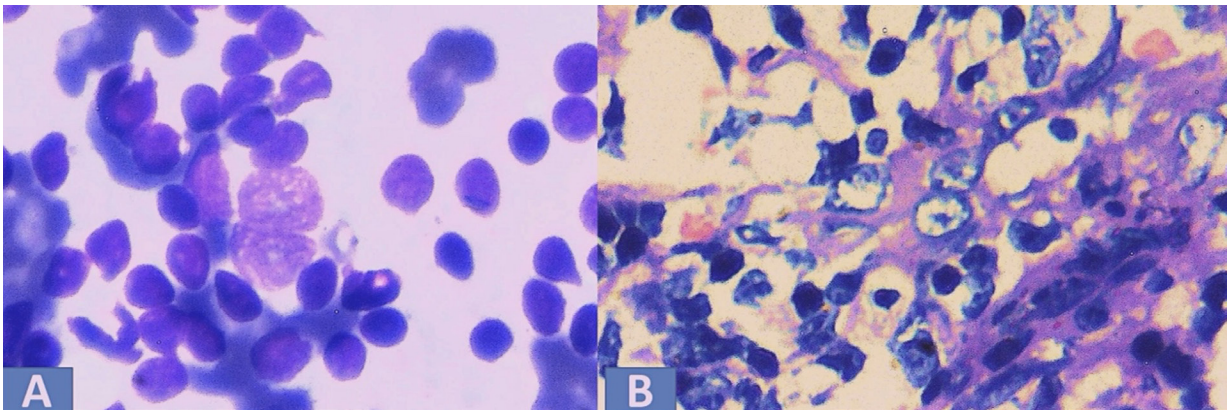

Fig. 4. *A*, Smear shows Reed Sternberg like giant cells dispersed among predominantly small lymphocytes. Categorized under L4: Suspicious for malignancy (MGG, 40X). *B*, Section from biopsy shows histomorphological picture of Hodgkin lymphoma with Reed Sternberg cells (H&E, 10X).

dispersed among predominantly small lymphocytes. Out of 20 cases (9.09%) categorized under the L5 out of which 19 cases were concordant on biopsy (Figure 5): Malignant category. In 1 (5%) case, smear showed presence of medium sized centroblast like lymphoid cells with a few small lymphocytes and classified as category 5; however, turned out to be false positive, i.e., benign (reactive lymphadenitis).

Assessment of risk of malignancy (ROM)

The L4 and L5 categories had higher risk of malignancies, that is 87.5% and 95%, respectively, while the L2 category had the lowest ROM, 7.80%. The L1 category also had a low ROM of 28.57%, while the L3 category showed an intermediate ROM of 54.54% (Table 3). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated to be 81.97%, 85.53%, 69.44%, 92.20%, and 84.51%, respectively (Table 4). The limitations in this study were to have a small sample size, a single-centre study, and limited use of ancillary techniques. The small sample size and single centre of the study may not be reflective of the real scenario in the population. The study was conducted in a centre where there is a greater percentage of reporting benign cases, so the results of the study may not hint about the applicability of the Sydney system in centres where more malignant cases are reported. Only immunohistochemistry was used as an ancillary technique to confirm histopathological diagnosis. The use of flow cytometry and immunocytochemistry on cell blocks as a second line of cytological diagnosis would have decreased the false positivity of L4 and L5 categories as evidenced by other studies and increased the overall specificity and accuracy of the reporting system [12].

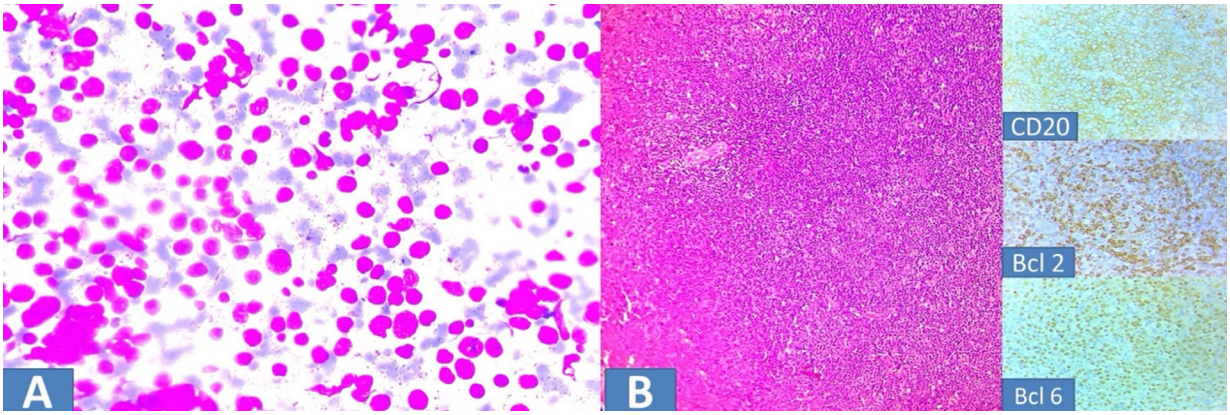

Fig. 5. *A*, Smear showing predominantly a monotonous population of medium sized centroblast like lymphoid cells with a few small lymphocytes. Categorized under L5: Malignant (MGG, 10X). *B*, Section from biopsy shows histomorphological picture of follicular lymphoma. Inset shows positive immunostaining for CD20, bcl-2 and bcl-6 (H&E, 10X).

TABLE 3. Risk of Malignancy calculated for each category.

Category	*Malignant Cases*	*Risk of Malignancy*
Non-diagnostic (L1)	2	33.33%
Benign (L2)	11	5.3%
Atypia of Undetermined Significance (L3)	22	56.41%
Suspicious for Malignancy (L4)	5	83.33%
Malignant (L5)	18	94.74%

DISCUSSION

It has been seen that the application of standardised reporting systems in cytopathology reduces intra-observer variability in reporting and helps in the communication of clinically relevant information in a reproducible manner [7,13,14]. Moreover, it enhances the interpretation of cytopathological reports by clinicians with regard to risk assessment.

The proposed system for reporting LN-FNAC cytopathology had the following seven aims:

1. Develop consensus guidelines and a framework of reference to facilitate communication among cytopathologists, hematopathologists, clinicians, surgeons, and other healthcare providers.
2. Define and identify LN-FNAC indications, preferred operators, recommended performance, analytical and preanalytical issues, technical and diagnostic limitations, as well as the basic diagnostic reporting categories and additional diagnostic information that can produce specific disease subtyping when possible.
3. Obtain the key diagnostic cytopathological features of lesions that occur commonly in the various categories.
4. Make recommendations on the components of standardized diagnostic reports with the aim to improve reporting and communication between cytopathologists and clinicians.
5. Provide management recommendations linked to the reporting categories with possible options that include the use of clinical and imaging follow-up, ancillary testing, and the possible need for LN excision.
6. Encourage cyto-histopathological correlations, cell storage, and research on neoplastic and non-neoplastic LN specimens.
7. Increase LN-FNAC reliability and clinician awareness of its diagnostic potential [9].

TABLE 4. Sensitivity, Specificity, PPV, NPV, Accuracy calculated for the Sydney system of lymph node cytology classification and reporting in this study.

Statistic	*Value*
Sensitivity	80.36%
Specificity	85.71%
Positive Predictive Value	70.31%
Negative Predictive Value	91.20%
Accuracy	84.13%

In the present study, the risk of malignancy was calculated for every diagnostic category in the Sydney system of classification and reporting of lymph node cytopathology. It was found that the risk of malignancy was 28.57% for the non-diagnostic category. This is comparable to 27.5% found by Gupta et al [11] and much less than the 50% found by Vigliar et al [13], and 66.7% found by Caputo et al [25] (Table 4). Repeat FNA's using ultrasound guidance and utilization of ROSE explains the lower rate of false negative results in this category in our study. However, the high risk of malignancy found in this category by Vigliar et al [13] is explained by them to be owing to the lower number of cases having histopathological follow-up data under this category. The two cases found to be malignant under this category in this study was metastatic papillary thyroid carcinoma with cystic change and metastatic infiltrating ductal carcinoma with cystic change. The lack of yield of cellular material in the cytological smears was owing to the fact that greater portions of the lymph nodes had cystic components in these cases and, so the smear was not representative of the site with clear pathology. This is a commonly encountered reason for false negative results in FNAC in case of metastasis in lymph nodes with cystic change [15-24].

Within expectations, the benign category (L2) had the lowest ROM of 7.80%. This is slightly higher compared to that found by Vigliar et al [13] (1.92%) but lower than that found by Gupta et al [11] (11.5%) and comparable with that of Caputo et al [25] (9.38%) (Table 4). Out of the 11 malignant cases classified in this category, 10 were of metastatic carcinoma in lymph nodes, and all of these cases in histopathological sections were found to have the metastatic deposits concentrated around the subcapsular area. This explains the lack of representation of the metastatic component in the cytopathological slide. This was a similar problem with that encountered by Vigliar et al [13] and Garg

et al [22] in their study where lymph nodes with partial involvement by metastatic carcinoma did not yield representative malignant cells on cytology [13, 22]. The single case of Hodgkins' lymphoma categorized under this category was found to be of the lymphocyte predominant type in histopathology and so predominantly small lymphocytes appeared on the cytopathological slide. The diagnosis of lymphocyte predominant type of Hodgkin lymphoma has been found to be extremely difficult by FNAC and similar sampling errors in case of FNAC of Hodgkin lymphoma has been seen in other studies [7,18,19].

The L3, or atypia of undetermined significance category, was introduced in most reporting systems with the aim of maintaining high negative and positive predictive values in the benign and malignant categories respectively. The risk of malignancy calculated for the L3 category in this study was intermediate (54.54%). This was quite comparable with 58.3% and 66.7% in the studies conducted by Vigliar et al [13] and Gupta et al [11], respectively, but higher than that calculated by Caputo et al [25] (28.6%) (Table 4). Of the 20 cases diagnosed as benign in histopathological sections in this category, 19 were diagnosed as reactive lymphadenitis. Most of these cases had interfollicular expansion and thus the cytological smears showed large cells with irregular nuclei, prominent nucleoli, and scant cytoplasm, leading to their categorization as such. Vigliar et al [13] similarly encountered the highest number of discordant cases in this category due to large cells from interfollicular expansion of benign reactive lymph nodes being represented on cytology slides [13]. Other studies also encountered similar pitfalls in cytology smears of reactive lymph nodes due to viral etiology and interfollicular expansion [20, 21]. One case showed a greater number of medium to large cells, raising the suspicion for non-Hodgkin's lymphoma. However, subsequent biopsy showed follicular hyperplasia and sampling from the germinal center may explain the findings on cytology, as also seen in other studies [7, 22].

Each of the L4 (suspicious for malignancy) and L5 (malignant) categories in this study had a very high ROM of 87.5%, and 95%, respectively (Table 4). The ROM calculated for these categories by Gupta et al [11] was 88% and 99.6%, respectively. Vigliar et al [13] calculated it to be 100% for both the categories, which is owing to the extensive use of ancillary procedures and flow cytometry in their studies. The number of false negative results may be further diminished by use of 2nd diagnostic level based on ancillary techniques as suggested in the proposal for the classification system [4]. The benign case categorized under the L4 category in this study was a case of parafollicular hyperplasia containing large immunoblast like cells and histiocytes along with numerous tingible body macrophages, which revealed Reed-Sternberg like binucleate cells in the cytopathology smear. Immunoblasts mimicking Reed-Sternberg cells on cytology is a commonly encountered phenomenon [23,24]. The benign case categorized under the L5 category in this study revealed reactive hyperplasia with a predominance of centroblast like cells in the smear. Sampling from the germinal centre of the reactive follicles may explain the paucity of small lymphocytes in the smear and predominantly medium-large sized cells in the cytology smear as discussed before.

It was seen in this study that the maximum number of cases were categorized under the benign category (64.09%) and only 9.09% of cases were categorized under the malignant category. This was in contrast to the studies conducted by Vigliar et al [13] and Gupta et [11] which had a greater number of cases categorized under the malignant category. However, this is owing to the pattern of cases commonly encountered in the health care set up, being located in the region where there is a high predominance of tuberculosis and benign lymphadenopathies being routinely sent for FNA. The sensitivity, specificity, NPV, PPV and accuracy were found to be on par with other studies (Table 4).

CONCLUSIONS

The proposed Sydney system of reporting and classification of lymph node cytology can help in achieving uniformity and reproducibility of cytopathological diagnosis. It will lead to a fairly accurate risk assessment of malignancy for further clinical management. In our institute, which is a tertiary care centre in this region, there is extensive use of reporting systems for various organ systems using cytology specimens. We have now introduced the Sydney system for lymph node cytology as a pilot project in this region, and this has improved the clinicians' understanding of the risk of malignancy and subsequent care. Additionally, this appears to be the first research piece to present a perspective using this system in patients from the north-eastern part of India.

Ethics Approval:
This study protocol was reviewed and approved by Institutional Ethics Committee, IEC(H) Reg. No. EC/NEW/INST/2020/1221.

Consent to participate:

The study, being a retrospective study will collect all patient related data from the hospital medical records only. The study involves no more than minimal risk to the study subjects. Therefore, the institutional ethics committee, Jorhat medical college and hospital, has granted an exemption from requiring written informed consent for the study.

Data Availability Statement:

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Conflict of Interest:

The authors have no conflict of interest to declare.

Author Contributions:

Abir Kumar Baruah- Concept, design, literature search, Data acquisition, data analysis, manuscript editing and review. Geet Bhuyan- Concept, design, literature search, manuscript preparation, manuscript editing and review, guarantor.

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