Utility of Fine-Needle Aspiration Cytology as a Low-cost Tool to Diagnose Cervical Lymphadenopathy

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KEYWORDS	ABSTRACT
	Background and Objective: The current study aimed at observing the cytomorphological patterns in patients presenting with enlarged cervical lymphnodes, diagnosed by fine needle aspiration cytology (FNAC), their distribution with respect to age and gender, and determining the accuracy of FNAC as a diagnostic procedure in cases with cervical lymphadenopathy.
Article Info	**Methods:** Out of all patients presenting with cervical lymphadenopathy from September 2015 to September 2016, in the Department of Pathology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India 100 consecutive-cases were enrolled into the current study, following the exclusion of all cases where FNAC smears were inadequate or suboptimal for diagnostic interpretation. Histopathological examination was conducted on small excision biopsy specimens/radical neck dissection, where ever possible and diagnostic efficacy of FNAC was evaluated.
	Results: The overall age range of the enrolled patients, presenting with enlarged cervical lymph nodes, was 1-72 years with the mean age of 35.7 years and male-femaleratio of 1.6:1.Out of the 100 cases, benign and malignant lesions comprised 77 and 23 cases, respectively. The most common observed benign lesion was reactive hyperplasia (29%), while squamous cell carcinoma was the most common malignant lesion.The overall sensitivity, specificity, positive predictive value, negative predictive value, and the diagnostic accuracy was 100%, 91.67%, 92%, 100%, and 95.7%, respectively.
	Conclusion: FNAC in the diagnoses of inflammatory and neoplastic diseases serves as a reliable,low-cost, rapid diagnostic tool with reasonably good accuracy that can influence patient management in terms of early diagnoses, treatment, and prevention of unnecessary surgery in patients.
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Introduction

Lymph nodes are discrete ovoid structures and part of the peripheral immune system located along the course of lymphatics. They act as mirror of underlying disease proceses (1). Lymphadenopathy refers to nodes that are abnormal in size, consistency, or number. Cervical lymphadenopathy is one of the most common Presentation in inflammatory and neoplastic disorders. In general, lymph nodes greater than 1 cm in diameter are considered abnormal (2). Lymph node fine-needle aspiration cytology (FNAC) was first used by Greig and Gray in 1904 to diagnose trypanosomiasis, and Guthrie in 1921 systemically performed fine-needle aspirationon lymph nodes for diagnostic purpose,and was further used as a diagnostic tool by Martin and Ellis in 1930 (3). FNAC is a simple, safe, and cost-effective procedure that enables clinicians to reach the diagnosis in short time (4). The fine-needle

aspiration can be conducted in the Outpatient Department without anesthesia and causes no disfigurement or scar on the skin (3). The biopsy of the cervical lymph node is always the gold standard; however, it is more resource-intensive than FNAC, requires anesthesia, strict asepsis, theatre time, and often leaves a scar. In contrast, FNAC of the cervical node is relatively simpler and offers quick reliable results (5). The current study aimed at observing the cytomorphological patterns, their distribution among various age groups and genders, and evaluating FNAC as a diagnostic tool in the patients with cervical lymphadenopathy, admitted, as well as the ones attending the Outpatient Department, at Shri Ram Murti Smarak Institute of Medical Sciences Bareilly, Uttar Pradesh, India.

Materials and methods

The present study was conducted in the Department of Pathology at Shri Ram Murti Smarak-Institute of Medical Sciences, Bareilly, Uttar Pradesh, India, from September 2015 to September 2016. A total of 100 consecutive cases were enrolled in the study for cytological evaluation, following exclusion of all cases where lymph node size was inappropriate for the procedure, or smears were inadequate/ suboptimal for diagnostic interpretation. Further, 47 cases were enrolled for histopathological evaluation. All cases of cervical lymphadenopathy irrespective of gender and age referred from various inpatient and outpatient clinical departments were evaluated for clinical features, physical examination, and local examination. The procedure of aspiration was explained to the patients including limitations and complications and consent was taken.Under strict aseptic conditions lymph node was aspirated with a 22-gauge needle attached to a 10-mLsyringe without local anesthesia. Smears were prepared from each patient, the alcohol fixed smears were stained with Papanicolaou (PAP) stain and air-dried smears were stained with May-Grunwald-Giemsa (MGG) stain. Smears of all suspected cases of tuberculosis were also stained with Ziehl-Neelsen stain. Lymphnode excision bi-opsies and radical neck dissection specimens were obtained wherever possible. Formalin-fixed samples of lymphnodes were processed in an automatic tissue processor for paraffin block preparation. From each block, 2-3-μm thick sections were prepared using rotatory microtome and all sections were stained with routine Hematoxylin and Eosin (H&E) staining methods. Slides were evaluated for cytomorphological and histomorphological features by three independent observers. Various cytomorphological patterns were compiled into corresponding to frequency tables and data were analyzed for the distribution of cases with respect to age and gender. The diagnostic efficacy of FNAC in cervical lymphadenopathy was evaluated in terms of sensitivity, specificity, positive predictive value, negative predictive value, and accuracy by comparing cytological diagnoses with histopathological diagnoses.

Results

Table 1 represents the frequency distribution of benign and malignant lesions diagnosed by FNAC, which comprised 77 benign and 23 malignant cases. Among benign lesions, reactive lymphadenitis (Figure1) was most common comprising 37.66% (n=29), followed by tubercular lymphadenitis (Figure 2), and granulomatous lymphadenitis (18.18%, n=14, each), Necrotizing lymphadenitis (15.58%, n=12), acute suppurative lymphadenitis (9.09%, n=7), and a single case of sinus histiocytosis (1.29%, n=1).Out of 23 malignant lesions, metastatic carcinomas and lymphomas contributed 69.57% (n=16) and 30.43% (n=7), respectively. Among the metastatic carcinomas, squamous cell carcinoma (Figure 3) was the most common morphological type observed in the current study comprising 87.5% (n=14) followed by one case each of poorly differentiated carcinoma and adenocarcinoma (6.25%, n=1). The Hodgkin's lymphoma (Figure 4) was more common (17.39%, n=4) than non-Hodgkin's lymphoma comprising 13.04% (n=3) of the total malignant cases.
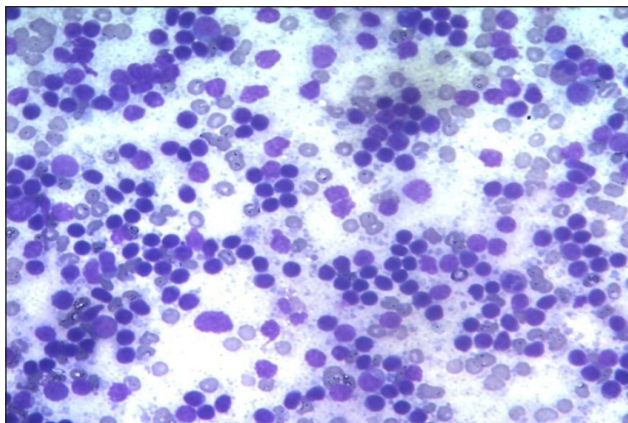
Figure 1. Photomicrograph of Reactive lymphadenitis showing a heterogenous population of lymphoid cells. (MGG stain, 40X)
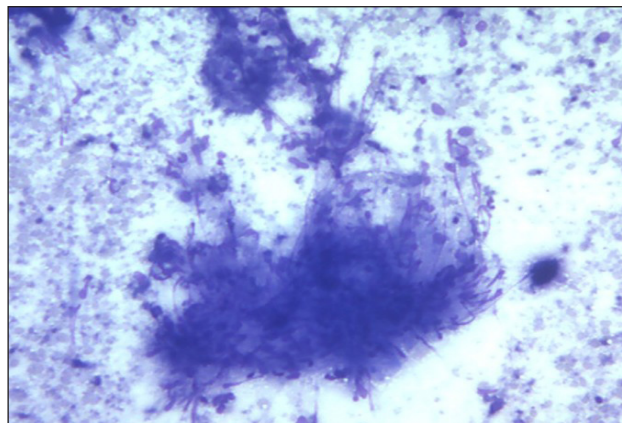

Figure 2. Photomicrograph of Tubercular lymphadenitis showing epithelioid cell granuloma (MGG stain, 10X)
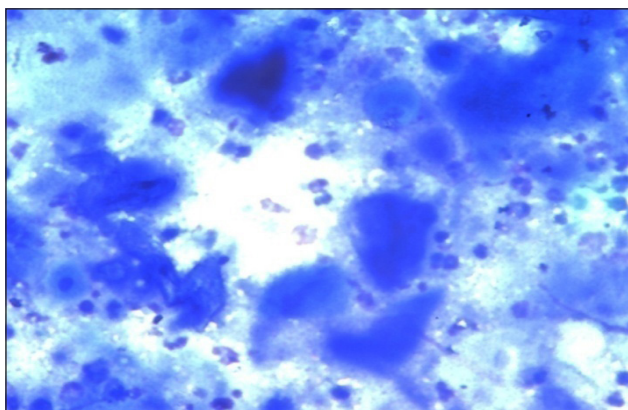

Figure 3. Photomicrograph of Squamous cell carcinoma showing polygonal cells with abundant glassy blue cytoplasm and enlarged hyperchromatic nucleus (MGG stain, 40X)
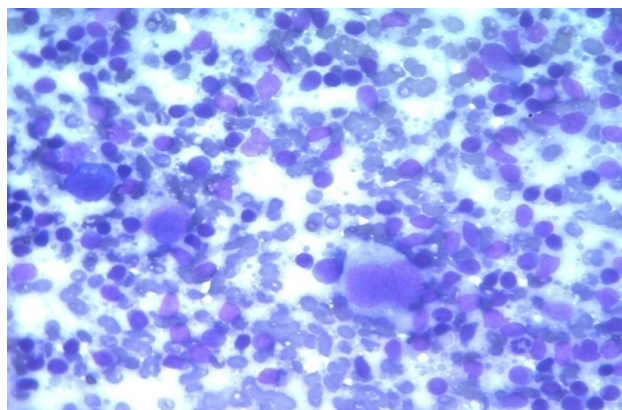

Figure 4. Photomicrograph of Hodgkin's lymphoma showing Reed-Sternberg cell (MGG stain,40X)

Table 1. Frequency Distribution of Various Cervical Lymph Node Lesions

Cytomorphological Pattern	Type	No. of Cases (N)
Benign (n=77)	ASL	7
	TL	14
	GL	14
	NL	12
	RL	29
	SH	1
Malignant (n=23)	SCC	14
	PDC	1
	Adenocarcinoma	1
	HL	4
	NHL	3

ASL: acute suppurative lymphadenitis, TL: tubercular lymphadenitis, GL: granulomatous lymphadenitis, NL: necrotizing lymphadenitis, RL: reactive lymphadenitis, SH: sinus histiocytosis;SCC, squamous cell carcinoma; PDC, poorly differentiated carcinoma; HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma

Figures 5 and 6 represent the frequency distribution of benign lesions with respect to age and gender, respectively. Overall, benign lesions were more common in the age group 11-20 years (27.27%, n=21). Males were slightly more affected than females, male-female ratio was 1.8:1; however, granulomatous lymphadenitis affected both equally. Acute suppurative lymphadenitis was the most common benign lesion in the age group of 1-10 years (5.19%, n=4), tubercular lymphadenitis (Figure 2) and reactive hyperplasia (Figure 1) in 11-20 years (9.09%, n=7 and 11.69%, n=9, respectively), granulomatous lymphadenitis in 31-40 years (6.49%, n=5) and necrotizing lymphadenitis in 41-50 years (6.49%, n=5).

Figures 7 and 8 represent the frequency distribution of malignant lesions with respect to age and gender, respectively. Overall, malignant lesions were more common in the age group of 51-60 years (30.43%, n=7). Both males and females were almost equally affected (1.09:1). Metastatic carcinomas were more common (69.57%, n=16) followed by lymphomas (30.43%, n=7). Among metastatic carcinomas, squamous cellcarcinoma (Figure 3) was the most common (21.74%, n=5) morphological type in the age group of 51-60 years affecting females slightly more than males. A single case of adenocarcinoma and poorly differentiated carcinoma was observed in the age group of31-40 years (4.35%, n=1) and 41-50 years (4.35%, n=1), respectively. Cases of Hodgkin lymphomas (Figure 4) were observed between the age groups of 11-30 years (8.70%, n=2) and 51-60 years (8.70%, n=2), affecting males more than females (M:F-3:1). The most common age group for non-Hodgkin lymphoma was 41-50 years (8.70%, n=2) with male-female ratio 2:1.
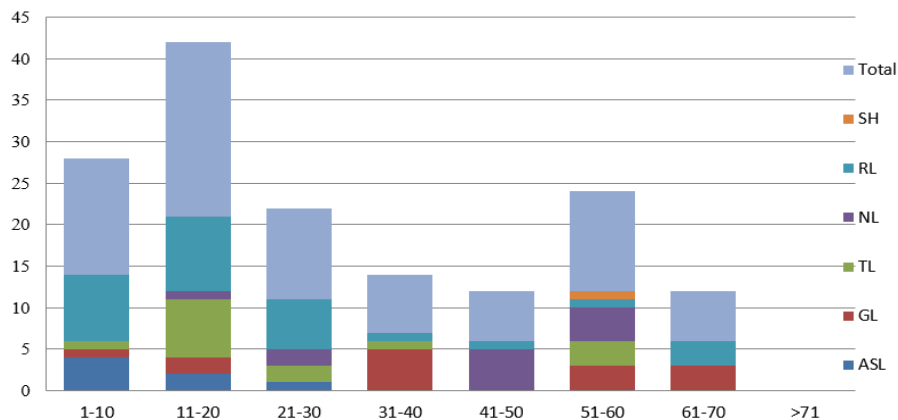

Figure 5. Frequency Distribution of Benign Cervical Lymphadenopathy With Respect to Age.
ASL: acute suppurative lymphadenitis, GL: granulomatous lymphadenitis, TL: tubercular lymphadenitis, NL: necrotizing lymphadenitis, RL: reactive lymphadenitis, SH: sinus histiocytosis

Figure 6. Frequency Distribution of Benign Cervical Lymphadenopathy With Respect to Gender.

ASL: acute suppurative lymphadenitis, GL: granulomatous lymphadenitis, TL: tubercular lymphadenitis, NL: necrotizing lymphadenitis, RL: reactive lymphadenitis, SH: sinus histiocytosis
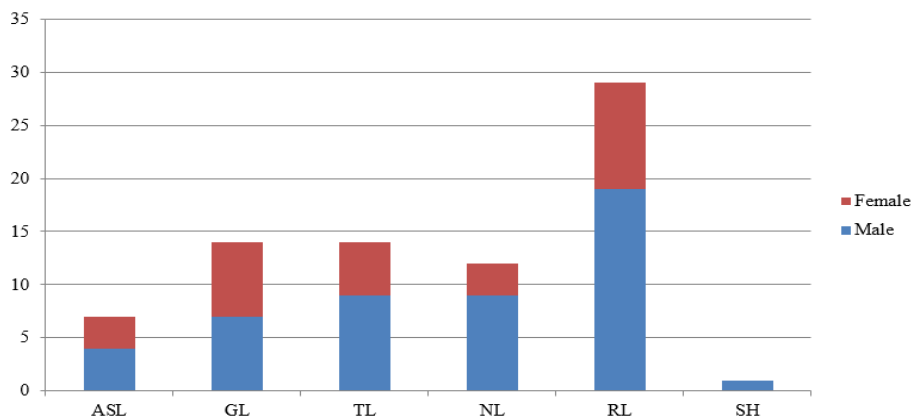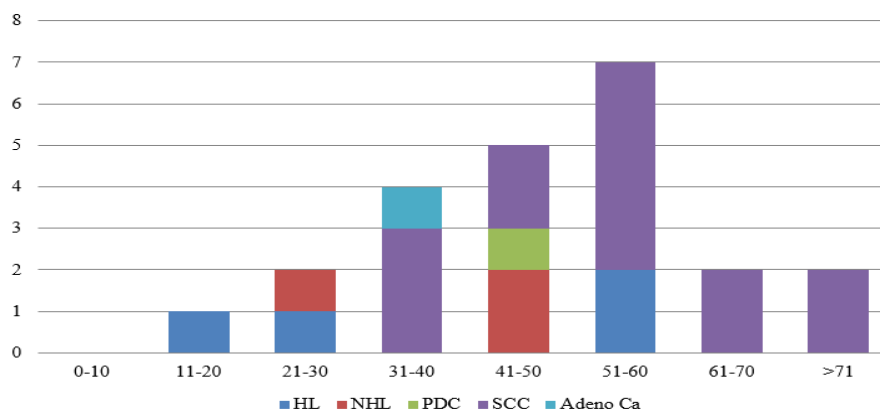
Figure 7. Frequency Distribution of Malignant Cervical Lymphadenopathy With Respect to Age

HL: Hodgkin's lymphoma, NHL: non-Hodgkin's lymphoma, PDC: poorly differentiated carcinoma, SCC: squamous cell carcinoma, Adenoca: adenocarcinoma
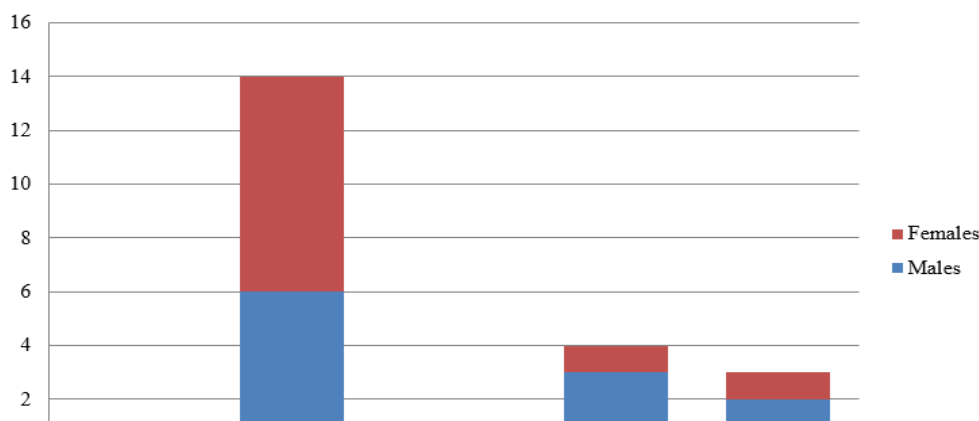

Figure 8. Frequency Distribution of Malignant Cervical Lymphadenopathy WithRespect to Gender

HL: Hodgkin's lymphoma, NHL: non-Hodgkin's lymphoma, PDC: poorly differentiated carcinoma, SCC: squamous cell carcinoma, Adenoca: adenocarcinoma

In the current study, out of 47 cases diagnosed by FNAC and histopathology both, 23 (true positive) were diagnosed malignant by both diagnostic methods while two cases (false positive) were diagnosed malignant by FNAC and benign by histopathology. Twenty-two cases (true negative) were diagnosed benign by both methods. No case was diagnosed as false positive (Table 2).

The overall sensitivity, specificity, PPV and NPV (positive and negative predictive values)and diagnostic accuracy was 100%, 91.67%, 92%, 100%, and 95.7%, respectively, when cytopathological and histopathological diagnoses were compared (Table 3).

Table 2. Cyto-histopathological correlation in patients with cervical lymphadenopathy

Cytopathological diagnosis	Histopathological diagnosis	
	Malignant	Benign
Malignant	23 (TP)	2 (FP)
Benign	0 (FN)	22(TN)

TN: true negative cases; FN: false negative cases; FP: false positive cases; TP: true positive cases.

Table 3. Diagnostic reliability of cytopathological diagnoses of cervical lymphnodes as compared with histopathological diagnoses

Statistical Parameter	Percentage	95%CI (%)
Sensitivity	100	85.18-100
Specificity	91.67	73.00-98.97
PPV	92.0	73.97-99.02
NPV	100	84.56-100
Diagnostic accuracy	95.7	76.54-100

PPV, positive predictive value; NPV, negative predictive value

Discussion

In the current study, cervical lymphadenopathy was the commonest presentation in the patients observed at FNAC clinics irrespective of their age and gender. The age of patients presenting with cervical lymphadenopathy ranged 1-72 years, which was almost in agreement with the observations of the studies by Patel et al (6). (2-82 years), Rahman et al (7). (2-85 years),and Rakshan et al (8) (1-87 years).The mean age of the study subjects was 35.7 years, which was closely similar to those of Patel et al (6)., and Singh et al (3).The most common age group for cervical lymphadenopathy in the current study was 11-20 years, which was slightly lower in comparison withthose of Hafez et al (9) and Patel et al (6).In the currentstudy, the observed male to female ratio was 1.8:1 similar to that of Patel et al (6). Almost similar results were reported by Rakhshan et al (3) Slightly higher ratio was observed by Qasmi et al (10). Reactive lymphadenitis was the most common lesion comprising 37.66% of total benign lesion and 29% of all the cases diagnosed with FNAC.Almost similar distribution of reactive lymphadenitis was reported by Patel et al (6).and Singh et al (3) out of the total cases in their studies.Next in order among benign lesions was tubercular lymphadenitis and granulomatous lymphadenitis each comprising 18.18% of the total benign lesion and 14% each of the total selected cases. Almost similar distribution of tubercular lymphadenitis was reported by Uwimama et al (11) (18.1%), while much higher numbers were reported by Kumar et al (5) and Aslam et al (12) of the total cases in their studies.Out of 23 malignant lesions metastatic carcinomas and lymphomas contributed 69.57% and 30.43%, respectively; however,

among all the 100 cases diagnosed with FNAC they comprised 16% and 7%, respectively. Almost similar distribution of metastatic carcinoma was reported by Hafez et al (9). while much lower numbers were reported by Patel et al (6) and Singh et al (3) of the total cases in their studies. Compared with the current study, Aslam et al (12). reported a much higher number of metastatic carcinomas (34.6%), while almost similar distribution of lymphomas was reported by them (7.7%). In the studies conducted by Aslam et al (12) and Singh et al (3) cases diagnosed with lymphoma were less than that of the current study comprising 5.5% and 5.45%, respectively. Among the metastatic carcinomas, squamous cell carcinoma was the most common morphological type observed in the current study as also reported by Singh et al (3). (75%), Pavithra et al (1) (56.25%), Hafez et al (3) (45.20%), Rahman et al.(7) (33%), and Qadri et al. (13) (32.20%), although in variousnumbers. In the current study, metastatic adenocarcinoma and poorly differentiated carcinomas,each comprising6.25% of metastatic lesions while 1% of the total cases,were diagnosed with FNAC. Qadri et al (13) and Hafez et al (9) reported adenocarcinoma as the second most common metastatic tumor comprising 21.9% and 25.8% of the metastatic lesions. Poorly differentiated carcinoma was reported in 14.6% and 22.6% of the metastatic lesions diagnosed by them. In contrast to the current study and other studies, Pavithra et al (1) reported poorly differentiated carcinoma (25%) as the second most common morphological type than adenocarcinoma (9.5%).Among lymphomas, the Hodgkin's lymphoma was more common in the current study; comprising 17.39% of the total malignant cases and

4% of the total cases diagnosed with FNAC; the findings werein agreement with those of Sen et al (14) and Singh et al (3) although in various numbers that reported 8% and 4% of the cases of Hodgkin's lymphoma, respectively. In contrast to the current study and several other studies Pavithra et al (1) Hafez et al (9) and Qadri et al (13) reported non-Hodgkin's lymphoma as the common morphological type out of the total cases in their studies comprising 0.63%, 2.6%, and 2%, respectively. In the current study to diagnose malignant and benign lesions FNAC had an overall diagnostic sensitivity of 100% and specificity of 91.67%. The PPV was 92.0% and NPV was 100%. The overall diagnostic accuracy of FNAC in patients with cervical lymphadenopathy, for malignant and benign lesions, was 90%. These values were compared with those of the studies of different authors such as Rakshan et al (8), Hafez et al (9), Qasmi et al (10), Qadri et al (13). and Babu et al (4) (Table 4). In the current study, two false positive cases were reported diagnosed as NHL on cytopathology and reactive on histopathology due to non-representative sampling

from germinal center, which can lead to misdiagnosis of non-Hodgkin lymphoma, especially centrocytic and centroblastic types, since in both conditions cells with centroblasts and centrocyte-like features present as the predominant cell population. The study supports the view of Bhasker et al (15) that the most difficult area in the diagnosis of lymph node diseases by FNAC is non-Hodgkin lymphoma. Complete clinical work up, immunocytochemistry and flow cytometry can enhance the accuracy of the procedure to diagnose lymphoma. Rakhshan et al (8) also suggested that ancillary methods such as immunohistochemistry (IHC) in the evaluation in aspiration smear can optimize the accuracy of the method.Weiss et al (16) suggested that immunohistochemical and other special studies may be very helpful to distinguish reactive follicular hyperplasia and follicular lymphoma. Determination of bcl-2 is the single most useful ancillary study, which is consistently negative in reactive follicular hyperplasia, but positive in about 90% of cases of follicular lymphoma.

Table 4. Comparison of Different Statistical ParametersBetween thePresent Study andOtherStudies

Author/Year	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic Accuracy(%)
Present study	100	91.67	92	100	95.7
Babu et al., 2014	89.5	100	100	90.5	91
Qadri et al., 2012	94.5	90.5	96.6	85.2	92.4
Qasmi et al., 2012	79.5	47.6	78	50	70
Hafez et al., 2011	90.9	67.2	82.6	81.3	100
Rakshan et al., 2009	75.8	96.6	94	85.1	88

PPV, positive predictive value; NPV, negative predictive value

Conclusion

In the current study, reactive hyperplasia, tubercular and granulomatous lymphadenitis were observed as the common causes of benign cervical lymphadenopathy, while metastatic squamous cell carcinoma was the most common cause of malignant cervical lymphadenopathy. FNAC is a simple and easy diagnostic tool with good sensitivity and specificity to diagnose benign and malignant lesions of lymph nodes. The procedure has good diagnostic accuracy in differentiating benign and malignant lesions. However, for typing of the lesions with FNAC may be difficult in certain cases, especially lymphomas; therefore, it may be used as the initial investigation tool, which can be followed by histopathology and immunohistochemistry for confirmation. Negative results on FNAC does not rule out a neoplastic pathology, which may be due to non-representative sampling and should be followed with biopsy for definitive diagnosis by histopathological evaluation.

Acknowledgment

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Conflict of Interest

The authors declared no conflict of interest.

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