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원 저

촉지 림프절의 세침흡인 세포검사
- 단일 기관의 1,346예 경험-

부산대학교 의학전문대학원 병리학교실

신 동 훈 · 최 경 운 · 김 지 연 · 강 현 정 · 김 익 두 · 설 미 영

Fine Needle Aspiration Cytology of Palpable Lymph Nodes
-A Single Institutional Experience of 1,346 Cases-

Dong Hoon Shin, M.D., Kyung Un Choi, M.D., Jee Yeon Kim, M.D., Hyun Jeong Kang, M.D., Ick Doo Kim, M.D., and Mee Young Sol, M.D.

Department of Pathology, Medical Graduate School, Pusan National University, Busan, Korea.

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책임저자 : 최 경 운
주 소 : (602-739) 부산광역시 서구 아미동 1가 10 부산대학교 의학전문대학원 병리학교실
전 화 : 051-240-7422
팩 스 : 051-242-7422
E-mail address : kuchoi@pusan.ac.kr

The aim of this study was to evaluate the diagnostic value of fine needle aspiration cytology (FNAC) for the assessment of palpable enlarged lymph nodes. The authors reviewed the results of 1,346 FNACs of palpable enlarged lymph nodes performed at Pusan National University Hospital from 1998 to 2004. Of the 1,346 cases, 1,265 (94.0%) were satisfactory and 81 (6.0%) unsatisfactory. Cytologic diagnoses were judged in 488 cases, based on subsequent histologic diagnoses, clinical follow up, or both. Global results for all malignancies (lymphoid and non-lymphoid neoplasms) based on cases with final diagnoses, showed a sensitivity of 87.4% and a specificity of 98.7%. The overall diagnostic accuracy was 93.2%, and the false negative rate reduced from 12.6% to 7.3% when lymphomatous cases were excluded. The annual data for this period showed that the number of diagnostic lymph node biopsies and the rate of inadequately sampled material markedly decreased. Gene rearrangement studies for IgH and TCR γ were helful in 30 cases. FNAC is a useful initial diagnostic procedure for the evaluation of palpable enlarged lymph nodes. However, the technique should be assisted by the appropriate ancillary studies and by proper interpretation by a cytopathologist.

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Key words : Fine needle aspiration cytology, Lymph node, Palpable

INTRODUCTION

Fine needle aspiration cytology (FNAC) is safe, simple, cost effective, well tolerated by patients, and repeatable and can be performed on an outpatient basis. FNAC has contributed greatly to reducing the rate of unnecessary surgery[1,2] and in cases of enlarged palpable lymph nodes, FNAC is used extensively as an initial diagnostic tool.[3-6] It is often possible to decide if a lymphadenopathy is the result of reactive lymphadenitis, metastatic malignancy, or lymphoma by cytomorphology alone.[2,3] However, the role of FNAC in the first time diagnosis of malignant lymphoma is less well established,[5-9] although on-site microscopic evaluation and the application of ancillary techniques such as immunohistochemistry (IHC), flow cytometry (FCM),

and polymerase chain reaction (PCR) have greatly improved diagnostic accuracy.[9-13] The aim of this study was to evaluate the global diagnostic value of FNAC for the assessment of enlarged palpable lymph nodes, to analyze its usefulness and the limitations, and to determine how it can be further promoted.

MATERIALS AND METHODS

During the seven-year period from 1998 to 2004, 1,346 FNACs were performed on enlarged palpable lymph nodes at the Pusan National University Hospital. FNAC results were classified as nonspecific, reactive disorder, granulomatous/necrotizing inflammation, lymphoma (suspected or diagnosed), metastatic non-lymphoid neoplasm, and inadequate material. The results were also simply categorized as benign/reactive, malignant, or inadequate. Aspirates were considered inadequate for a diagnosis when the smears showed too scant a cellularity, poor preservation, or too bloody a background. Outcome of treatment in cases of benign/reactive lymphadenopathy was observed. If the lymph nodes persisted, a biopsy was performed. In this manner, confirmation of final diagnosis by subsequent histologic diagnosis through biopsy or surgical operation was available in 347 cases and by a clinical follow up period for 12 months on an average in 141 cases. Diagnostic effectiveness was analyzed in these 488 FNAC cases. In order to assess each usefulness of non-lymphoid neoplasm and lymphoid neoplasm, we classified our cases into two groups: group A, cases, of which final diagnosis was a non-lymphoid neoplasm and FNA were performed as the initial approach or for staging a non-lymphoid neoplasm (n=204); group B, cases, of which final diagnosis was non-neoplastic disease (reactive, granulomatous, or necrotizing lesion) or lymphoproliferative disease (n=265).

FNAC was performed as the conventional method of needle aspiration using a 23 gauge needle. Aspirated material was smeared onto glass slides, for Diff-Quick, Papanicolaou and Hematoxylin-eosin staining. At our institution, all FNACs were performed by clinicians before September, 2001. When performed by cytopathologists, on-site cytomorphologic evaluation was performed to determine cellular adequacy and cases were selected for ancillary studies. If possible, remaining aspirates were sent to the cytologic laboratory for cell block analysis. Depending on the cytomorphologic results by on-site evaluation, and based on clinical suspicion by a physician, ancillary studies were also performed. PCR for immunoglobulin heavy chain (IgH) and T cell receptor gamma-receptor (TCRγ) have been used as diagnostic tools in our department since Sep. 2001.[14,15] The cytologic diagnoses of all FNACs was determined by cytopathologists.

A false negative (FN) was defined as a benign cytologic diagnosis and a malignant final diagnosis. A false positive (FP) was defined as malignant cytologic diagnosis and benign final diagnosis. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of FNAC relative to final diagnoses were calculated.

RESULTS

A total of 1,346 cases were examined at the Pusan National University Hospital between 1998 and 2004. Their ages ranged from 3 to 80 years and the male to female ratio was 1:1.4. Of these, 1,265 (94.0%) were satisfactory and 81 (6.0%) unsatisfactory. Of the 1,265 cases, 728 (54.1%) were classified as a nonspecific-reactive disorder, 237 (17.6%) as granulomatous/necrotizing lymphadenitis, 36 (2.7%) as lymphoma, 264 (19.6%) as metastatic non-lymphoid neoplasm. 347 cases underwent subsequent biopsy or operation and 141 had an average 12 months of follow up data. The follow up study group ranged in age from 1 month to 66 months. The results were founded on these 488 cases with final diagnoses based on the histological diagnoses and clinical follow up. Table 1 shows the anatomic distribution

Table 1. Frequency of malignancy in lymph node FNAC by anatomic sites

Site	No. of total cases	No. of lymphoid neoplasm	No. of non-lymphoid neoplasm	No. of total neoplasm
Cervical	362 (74.2%)*	35	120	155 (42.8%)†
Axilla	57 (11.7%)	0	46	46 (80.7%)
Supraclavicular	36 (7.4%)	1	23	24 (66.7%)
Inguinal	5 (1.0%)	0	4	4 (80%)
Others	28 (5.7%)	3	7	10 (35.7%)
Total	488	39	200	239

* Percentage of involving area in total cases

† Percentage of neoplasm in the given area

Table 2. Correlation between the cytological diagnoses and the final diagnoses

Cytologic Diagnosis	Final Diagnosis		Total
	Negative for malignancy	Positive for malignancy (lymphoid neoplasm/non-lymphoid neoplasm)	
Reactive/non-specific	174	19 (13/14)	193(39.5%)*
Granulomatous/necrotizing lymphadenitis	70	2 (2/0)	72(14.8%)
Non-Hodgkin's lymphoma	3	20 (20/0)	23(4.7%)
Hodgkin's lymphoma	0	2 (2/0)	2(0.4%)
Nonlymphoid neoplasm	0	179 (0/179)	179(36.7%)
Inadequate	10	9 (2/7)	19(3.9%)
Total	249(51.0%)†	239(49.0%)	488

* Percentage of a cytologic diagnostic entity in total cases

† Percentage of cytologic diagenosis in total cases

of lesions of 488 cases. Correlation between the cytological diagnoses and the final diagnoses for 488 cases is summarized in Table 2. 249 cases (51.0%) were negative for malignancy and 239 (49.0%) were positive at final diagnoses.

Global results for all malignancies (lymphoid and non-lymphoid neoplasms), excluding 19 cases with inadequate smears, revealed 87.4% sensitivity, 98.7% specificity, 98.5% positive predictive value and 89.1% negative predictive value. False positive diagnoses were made in 3 cases (1.3%) and false negative diagnoses in 29 cases (12.6%). Diagnostic accuracy was 93.2%. Table 3 presents this data. The results for non-lymphoid neoplasm were sensitivity 92.7%, specificity 100.0%, accuracy 93.1%, and there were 0 FPs and 14 FNs (7.3%). In cases of lymphoid neoplasm, sensitivity was 59.5%, specificity 98.7%, and accuracy 93.2%, and there were 3 FPs (12%) and 15 FNs (40.5%). These data are shown in tables 4 and 5. An analysis of discordant cases is included in the Discussion. PCR for IgH and TCR γ gene rearrangement as an ancillary study was performed on

Table 3. Global results for all malignancy in lymph node FNAC

Cytologic Diagnosis	Final Diagnosis		Total
	Negative	Positve	
Negative	236	29	265
Positive	3	201	204
Total	239	230	469

Sensitivity, specificity, positive predictive value(PPV), and negative predictive value(NPV) were 87.4%, 98.7%, 98.5% and 89.1%.

False positive diagnosis(PF) and false negative diagnosis(FN) were 1.3% and 12.6%.

Dignostic accuracy was 93.2%

Table 4. Results for non-lymphoid neoplasm (group A) in lymph node FNAC

Cytologic Diagnosis	Final Diagnosis		
	Negative	Positve	Total
Negative	11	14	25
Positive	0	179	179
Total	11	193	204

Sensitivity, specificity, dignostic accuracy, FP and FN were 92.7%, 100%, 93.1%, 0 and 7.3%

Table 5. Results for lymphoid neoplasm (group B) in lymph node FNAC

Cytologic Diagnosis	Final Diagnosis		
	Negative	Positve	Total
Negative	225	15	240
Positive	3	22	25
Total	228	37	265

Sensitivity, specificity, dignostic accuracy, FP and FN were 59.5%, 98.7%, 93.2%, 12% and 40.5%

Table 6. Results of PCR for gene rearrangement

Cytologic Diagnosis	No.	Gene Rearrangement Study	
		IgH	TCR
Reactive hyperplasia	18	-	-
Small cell carcinoma, metastatic	4	-	-
Malignant lymphoma	8	+	-

Both IgH and TCR rearrangement studies were performed in all cases.

Table 8. Annual results of lymph node FNAC

Year	No. of cases with final diagnosis	No. of FP cases	No. of FN cases	diagnostic accuracy
1998	60	0	2	96.4%
1999	46	0	1	97.6%
2000	34	0	2	93.5%
2001	100	0	1	99.0%
2002	93	0	6	90.1%
2003	84	3	5	93.8%
2004	71	0	4	94.3%
Total	488	3	21	93.2%

the aspirate material obtained in 42 cases of the 488 cases. The results of 30 cases are shown in Table 4. Amplification was unsuccessful in the remaining 12 cases. In some cases, cytologic diagnoses were made after considering these results.

Table 7 and 8 highlight changes in the absolute numbers of FNACs for diagnosis performed for the diagnosis of lymphadenopathy, diagnostic accuracy, FP and FN rates, inadequate material rates, and the numbers of lymph node biopsies performed for diagnosis performed at our institution. The inadequate material rate markedly decreased. We found an increase of more than twofold in absolute number of FNACs performed over the study period, and a marked reduction in the number of lymph node biopsies performed from 14.8% out of total FNACs during the first 4 years to 7.5% during the final 3 years.

Table 7. Annual results of lymph node FNAC

Year	No. of total cases	No. of cases with the subsequent histologic diagnosis (%)	No. of cases of diagnostic biopsy (%)	No. of inadequate material (%)
1998	108	17(15.7)	15(13.9)	14(13.0)
1999	86	18(20.9)	17(19.8)	17(19.8)
2000	70	13(18.6)	11(15.7)	13(18.6)
2001	168	41(24.4)	21(12.5)	9(5.4)
2002	309	90(29.1)	23(7.4)	6(1.9)
2003	307	79(25.7)	24(7.8)	12(3.9)
2004	298	70(23.5)	22(7.4)	10(3.4)
Total	1,346	328(24.4)	123(10.5)	81(6.0)

DISCUSSION

FNAC as a first line of investigation is useful because it is a simple, cost-effective, minimally invasive procedure with low morbidity. Many studies have been done to evaluate the value of FNAC for evaluating the cause of lymph node enlargement.[1-6] This study was undertaken to evaluate the diagnostic value of FNAC for the assessment of palpable enlarged lymph nodes, to analyze its usefulness and limitations, and to make suggestions that improve its value, by reviewing global results in a variety of disorders, based on an single institutional experience.

On reviewing the 1,346 cases, 81 cases (6.0%) were unsatisfactory and the most common cytologic diagnosis was reactive, non-specific hyperplasia (728 cases, 54.1%). Granulomatous/necrotizing lymphadenitis was diagnosed in 237 cases (17.6%) based on cytologic findings. Thirty-six (2.7%) and 264 (19.6%) cases were lymphomas and non-lymphoid neoplasms, respectively. The final diagnosis of 488 cases was negative for malignancy in 249 (51.0%) and positive in 239 (49.0%). Almost all non-lymphoid neoplasm were metastatic carcinomas. The results in Table 1 reveal that axillary lymph nodes were more frequently malignant than other sites, and that inguinal lymph nodes were the second most common site of metastasis. The supraclavicular lymph nodes were also an important metastatic region.[3,6] The most frequent primary site was the breast,[5] which recently ranked as the cancer with greatest incidence in Korean women.

The overall accuracy of FNAC for these 469 cases was 93.2%. The sensitivity and specificity were 87.4% and 98.7%. They are comparable to them reported previously.[1-6,8,9] The overall low FP rate (1.3%) is significant because improper treatment can be avoided. The results for non-lymphoid neoplasm showed 93.1% accuracy with perfect specificity. All FN cases were due to sampling errors as the aspirates were non-representative. A review of cytologic smears failed to reveal any malignant cells. Based on these findings, the usefulness of FNAC for the evaluation of non-lymphoid neoplasm was judged to be excellent. The difficulty of diagnosis by FNAC in malignant lymphoma has repeatedly been acknowledged[5-9] as do we in this study, and this is highlighted by our FN rate of 12.6%, which reduced significantly to 7.3% when lymphoid neoplasms were excluded.

All three FP cases were due to mis-interpretation and were interpreted as malignant lymphoma on cytologic diagnosis, but their final diagnoses were reactive hyperplasia in 2 cases and necrotizing lymphadenitis in one. Florid lymphoproliferative lesions with a large population of enlarged lymphoid and histiocytic cells, and a marked necrotic background were overdiagnosed as findings supporting malignant lymphoma.[16-19] But large cell lymphoma should be diagnosed when they have a significant component of atypical large cells.[16,17] On considering that enlarged lymph nodes in these cases were multiple and more than 3 cm in greatest diameter, it should be mentioned that when a cytopathologist had an opportunity to assess the patients first hand, the FP rate could have been increased.

Thirteen of the 15 FN cases were originally misdiagnosed as benign/reactive lesion but subsequent histologic diagnoses revealed low grade non-Hodgkin's lymphoma (NHL) in 8 cases, high grade NHL in four, and Hodgkin's lymphoma (HL) in one. A review of cases diagnosed as low grade NHL on histologic diagnosis revealed mixed a population of lymphoid cells and even tingible body macrophages, especially in some partially replaced cases. Multiple passes from different parts of the lesions can help to obtain sufficient neoplastic cells. But recognition of low grade NHL by cytology remains problematic.[17,21] A FN case of high grade NHL involved the interpretation of some cell aggregation with elongated nuclei and necrotic background as a granuloma and caseating necrosis. If cytologically necrotic background is shown, tuberculosis can be considered.[2,20] The cytologic interpretation should be made with attention, particularly in endemic area like Korea. Three cases of high grade NHL and one of HL revealed

only a few atypical cells with a marked polymorphous lymphocytic background, which caused misinterpretation.[16-19] Although, the diagnosis of malignant lymphoma is uncertain by FNAC, the results presented in our study further support the initial use of FNAC for the evaluation of enlarged palpable lymph nodes for the diagnosis of benign or malignant lymphadenopathy. The remaining two FN cases were due to sampling errors as the aspirates were either non-representative or too scanty.

In recent years, the use of aspirated material for ancillary studies such as immunocytochemistry,[7,9-11] flow cytometry,[1,10,11] and gene rearrangement studies by PCR7,[12,13] seems to aid the diagnosis of lymphoma, although the relative merits of these studies are debatable. We have only recently started to use gene rearrangement studies for IgH and TCR γ on FNAC samples in our department to determine whether this is of value in the diagnosis of difficult cases of lymphoma. In the study, these techniques were used in fourty-two cases and led to useful diagnostic information in 30 cases, as shown in Table 6. A negative finding for an IgH and TCR γ rearrangement supported the diagnosis of reactive hyperplasia in 18 cases, which lacked the classic cytomorphologic features of reactive hyperplasia, and helped to differentiate metastatic small cell carcinoma from lymphoma in 4 cases. A positive finding for an IgH rearrangement was valuable in diagnosing lymphoma in 8 cases. At our institution, ancillary studies are not routinely performed and samples for appropriate ancillary studies are selected by morphologic findings through on-site evaluation by a cytopathologist or because of clinical suspicion. We emphasize based on the present study that ancillary studies can reduce the FP rate and improve the general diagnostic accuracy of FNAC for lymphoid neoplasm. We cannot perform ancillary studies routinely on aspirated lymph node material in the absence of a suspicion of lymphoma by on-site evaluation because of the cost-burden and the relative low incidence of lymphoid neoplasm.[1-3,6]

Unsatisfactory specimens composed 6.0% (81 cases of 1,346) of the total lymph node FNAs in our study, which is a little lower than that obtained by other authors.[1-6] In 19 of the 81 cases, which had inadequate material, a biopsy of persistent and enlarging lymph nodes was done and in nine cases (11.1%), and malignant tumors were found. These cases emphasize the need for following up cases with inadequate material on FNAC.

The on-site evaluation of FNAC samples was found valuable, as it provided an 'on the spot' provisional diagnosis and an interpretation of sample adequacy, in addition it was useful for selecting samples for appropriate ancillary studies.[2,22] Table 7 highlights the marked reduction in the inadequate rate, after setting up the FNAC room in our Department of Pathology, a marked reduction from 15.5% to 3.0% in inadequate specimens occurred.

Tables 7 and 8 show additional results of interest. The observed increase in the absolute number of FNACs performed for lymphadenopathy diagnosis and the marked reduction in the number of lymph node biopsies required to reach a diagnosis exhibit confidence in FNAC as an initial diagnostic tool and its advantages versus surgical biopsy. However, the diagnostic accuracy of the modality has not improved greatly, though in the present study the introduction of an ancillary studies reduced the FP rate, but not the FN rate. Moreover, FP cases of overdiagnosis were due to a cytopathologist's immediate assessment.

We conclude that FNAC is a useful initial diagnostic tool in patients with enlarged palpable lymph nodes and provides information that is of direct value for patient management, although FNAC does not totally replace surgical biopsy. We make the following suggestions to increase its usefulness and overcome some of its limitations. Optimal results are obtained by experienced cytopathologists in combination with well-chosen ancillary studies. Cytopathology based FNAC has many advantages, however, overdiagnosis should also be borne in mind. Guidelines concerning the applica-

tion of ancillary studies are needed, that consider diagnostic accuracy, practicality, and cost-effectiveness.

REFERENCES

1. Nasuti JF, Yu G, Boudousquie A, Gupta PK. Diagnostic value of lymph node fine needle aspiration cytology: an institutional experience of 387 cases observed over a 5-year period. *Cytopathology* 2000;11:18-31.
2. Thomas JO, Adeyi D, Amanguno H. Fine-needle aspiration in the management of peripheral lymphadenopathy in a developing country. *Diagn Cytopathol* 1999;21:159-62.
3. Serrano Egea A, Martinez Gonzalez MA, Perez Barrios A, Alberti Masgrau N, de Agustin de Agustin P. Usefulness of light microscopy in lymph node fine needle aspiration biopsy. *Acta Cytol* 2002;46:364-8.
4. van de Schoot L, Aronson DC, Behrendt H, Bras J. The role of fine-needle aspiration cytology in children with persistent or suspicious lymphadenopathy. *J Pediatr Surg* 2001; 36:7-11.
5. Lioe TF, Elliott H, Allen DC, Spence RA. The role of fine needle aspiration cytology (FNAC) in the investigation of superficial lymphadenopathy; uses and limitations of the technique. *Cytopathology* 1999;10:291-7.
6. Steel BL, Schwartz MR, Ramzy I. Fine needle aspiration biopsy in the diagnosis of lymphadenopathy in 1,103 patients. Role, limitations and analysis of diagnostic pitfalls. *Acta Cytol* 1995;39:76-81.
7. Stewart CJ, Duncan JA, Farquharson M, Richmond J. Fine needle aspiration cytology diagnosis of malignant lymphoma and reactive lymphoid hyperplasia. *J Clin Pathol* 1998;51:197-203.
8. Jaffer S, Zakowski M. Fine-needle aspiration biopsy of axillary lymph nodes. *Diagn Cytopathol* 2002;26:69-74.
9. Gupta RK, Naran S, Lallu S, Fauck R. Diagnostic value of needle aspiration cytology (NAC) in the assessment of palpable inguinal lymph nodes: a study of 210 cases. *Diagn Cytopathol* 2003;28:175-80.
10. Nasuti JF, Mehrotra R, Gupta PK. Diagnostic value of fine-needle aspiration in supraclavicular lymphadenopathy: a study of 106 patients and review of literature. *Diagn Cytopathol* 2001;25:351-5.
11. Saleh H, Masood S. Value of ancillary studies in fine-needle aspiration biopsy. *Diagn Cytopathol* 1995;13:310-5.
12. Grosso LE, Collins BT. DNA polymerase chain reaction using fine needle aspiration biopsy smears to evaluate non-Hodgkin's lymphoma. *Acta Cytol* 1999;43:837-41.
13. Safley AM, Buckley PJ, Creager AJ, et al. The value of fluorescence in situ hybridization and polymerase chain reaction in the diagnosis of B-cell non-Hodgkin lymphoma by fine-needle aspiration. *Arch Pathol Lab Med* 2004;128:1395-403.
14. Benhattar J, Delacretaz F, Martin P, Chaubert P, Costa J. Improved polymerase chain reaction detection of clonal T cell lymphoid neoplasms. *Diagn Mol Pathol* 1995;4:108-12.
15. Cho EY, Ko YH, Kim DS, Han JJ, Ree HJ. Diagnostic Utility of Polymerase Chain Reaction-Based Clonality Analysis for Immunoglobulin Heavy Chain Gene and T-cell Receptor Gamma Chain Gene Rearrangement in Lymphoid Neoplasms. *Korean J Pathol* 2001;35:461-9.
16. Young NA, Al-Saleem T. Diagnosis of lymphoma by fine-needle aspiration cytology using the revised European-American classification of lymphoid neoplasms. *Cancer* 1999;87:325-45.
17. Kim CH. Fine needle aspiration cytology of lymph node - reactive hyperplasia vs malignant lymphoma. *Korean J Cytopathol* 2006;17:75-8.
18. Saboorian MH, Ashfaq R. The use of fine needle aspiration biopsy in the evaluation of lymphadenopathy. *Semin Diagn Pathol* 2001;18:110-23.
19. Onciu M, Medeiros LJ: Kikuchi-Fujimoto lymphadenitis. *Adv Anat Pathol* 2003;10:204-11.
20. Han EM, Sone DE, Eom DU, Choi HJ, Cha HJ, Huh JR. Differential diagnosis of fine needle aspiration cytology of benign lymphadenopathy. *Korean J Cytopathol* 2006;17: 99-107.
21. Lee SS. Fine needle aspiration cytology of non-Hodgkin lymphomas predominating small lymphoid cells. *Korean J Cytopathol* 2006;17:87-98.
22. Padel AF, Coghill SB, Powis SJ. Evidence that the sensitivity is increased and the inadequacy rate decreased when pathologists take aspirates for cytodiagnosis. *Cytopathology* 1993;4:161-5.