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RESEARCHARTICLE

DIAGNOSTIC TEST EVALUATION PARAMETERS FOR FINE-NEEDLE ASPIRATION CYTOLOGY AMONG VISIBLE THYROID SWELLINGS

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ABSTRACT

FNAC has outgrown as a diagnostic tool in thyroid swellings. However, the routine parameters are influenced by the prevalence of the disease which is high among hospital based studies. Diagnostic Parameters not influenced by the disease prevalence need to be analysed among local population

Aim: To Assess the Diagnostic Parameters of FNAC among visible thyroid swellings

Settings and Design: Hospital Based cross sectional study

Methods and Materials: Two hundred and thirty specimens from visible thyroid swelling of patients consulting the Medicine, Surgery and ENT departments from January 2012 to July 2014 were analysed. The study was undertaken during the period from January 2012 to July 2014. Clinical grading of thyroid swelling was confirmed and data analysed with EPIINFO version 7.

Statistical analysis used: Sensitivity, Specificity, Likelihood Ratio, weighted Likelihood Ratio, Pre and Post Test Probability, Kappa statistics.

Results: Of the 230 cases of thyroid lesions, 194 were cases of non-neoplastic lesions and 36 cases of neoplastic lesions on FNAC. The concordance of the diagnosis for neoplastic and non-neoplastic lesions comparing histopathology as gold standard was 65.71% and 89.23% respectively. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and diagnostic accuracy for FNAC with respect to neoplastic & non-neoplastic lesions in thyroid in the present study are 40-74.38%, 94.87%, 58.33-72.22%, 10.1943.81%, 0.77-14.28, 0.27-0.63 and 86.50-91.74% respectively.

For neoplastic lesions, the weighted likelihood ratio Positive is 2.5689 and weighted likelihood ratio Negative is 0.11. For non-neoplastic lesions, the weighted likelihood ratio Positive is 1.4 and weighted likelihood ratio Negative is 0.11.

Conclusions: The weighted LR+ indicates there is 2.6 times more possibility of a neoplastic lesion compared to 0.11 times possibility of a negative result. FNAC being an excellent, rapid diagnostic procedure with high degree of accuracy, and high likelihood ratios, would be of immense benefit among cases with thyroid swelling

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INTRODUCTION

Thyroid lesions are one of the common conditions (Maharashtra (11.9%) and West Bengal (9%) 0 encountered in clinical practice. (WHO, 2003) Often thyroid swelling is difficult to accurately diagnose by clinical evaluation with inherent limitations. Nevertheless, it is difficult to distinguish the early malignant lesions from the more prevalent benign goitres. Thus, the distinction between benign and malignant nodule of the thyroid remains relatively unclear, despite the sophisticated tools with which the clinician is equipped today. A simple alternative approach of Fine needle aspiration cytology (FNAC) is in vogue but not explored extensively.

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FNAC claimed to bridge the gap between clinical evaluation and final surgical pathological diagnosis and would eliminate unwarranted radical surgeries.

It was reported that the cost effective, safe, rapid method of FNAC has a high degree of accuracy in the diagnosis of thyroid cancer. (Brian Haynes *et al*., 2006) The sensitivity ranged from 50-100% and specificity 73- 92% and accuracy of 67-87% among benign and malignant lesions. (WHO, 2003; Mitra and Abbas, 2010; Brunicardi *et al*., 2010) Sensitivity, specificity, likelihood ratios (LRs), receiver operating characteristic (ROC) curvesmis-represent a test's real value. These descriptors of diagnostic tests can misrepresent a test's real value (or uselessness). (Brian Haynes *et al*., 2006) Unless proper weight age is allotted to prevalence, the diagnostic accuracy studies might send erroneous signals. (Marc *et al*., 2007) Hence it is necessary to adopt prevalence free indicator to find out the

utility of the FNAC. In the present study, Likelihood Ratios independent of Prevalence of the disease, were utilised to assess the diagnostic utility of FNAC.

MATERIALS AND METHODS

Patients who are presenting with thyroid swelling to the Out Patient Department for the first time were included in this study. All the patients consulting (from January 2012 to July 2014) were clinically examined in detail and were subjected to FNAC examination. All the FNAC procedures were conducted by single investigator who is well trained in the technique. Standard Operating Procedures laid down were meticulously followed. The surgical interventions carried out on these patients were noted and the biopsy specimens were examined for histopathological study. FNAC results were reported by a trained Pathologist in the department and the Histopathological examinations were carried out in a blind manner by another pathologist having long standing experience with thyroid histopathology reporting. FNAC cytological diagnosis was correlated with the histopathology.

Calculation of Sensitivity, Specificity and Predictive Values are commonly used to describe the diagnostic evaluation of the test. The other less common indices are as follows.

(1) Youden Index= The Youden's index (J), is the difference between the true positive rate and the false positive rate.
(2) Diagnostic Odds Ratio= (TP/FN)/(FP/TN).
(3) Post Test Probability Positive Test (PoTPP)(Probability that test +ve will have target disease) =Post Test Odds/ (1+ Post Test Odds)
(4) Post Test Probability Negative Test (PoTPN)(Probability that a test –ve will have target Disease)= Post Test Odds / 1+ Post Test Odds)

Pre-test Probability = Prevalence
Pre-test Odds = Pre-test Prob / (1 - Pre-test Prob)
Post-test Odds = Pre-test Odds x Likelihood Ratio
Post-test Probability = Post-test Odds / (1 + Post-test Odds)

All these test evaluating indices are influenced by the prevalence/ stage of the condition under investigation. (Brenner and Gefeller, 1997; Willis, 2012) Hence, it is always suggested to consider the Likelihood Ratios in particular the weighted Likelihood Ratios. The calculation of the Likelihood Ratios (Weighted) is as follows. (Claudio Agostinelli and Marianthi Markatou, 2001; John Attia, 2003; AsliMuratli *et al*., 2014; http://vassarstats.net/clin1.html)

Positive (weighted for prevalence) =

$$\frac{Probabilitythatapostivetestresultisatrue Positive}{probabilitythatapositivetestresultisafalsepositive} = \frac{(Prevalence)(Sensitivity)}{(1-Prevalence)(1-Specificity)}$$

Negative (weighted for prevalence) =

$$\frac{ProbabilityofFalseNegativeResult}{probabilityofTrueNegativeResult} = \frac{(Prevalence)(1-Sensitivity)}{(1-Prevalence)(Specificity)}$$

The study protocol was approved by the institutional ethics committee. All the data collected was fed into the spreadsheet and was analysed with EpiInfo version7.

RESULTS AND DISCUSSION

Out of the total number of patients consulting the OPD, during the study period, 1587 patients presented with visible thyroid swelling were subjected to FNAC. Only 230 cases (14.5%) were subjected to surgery and the biopsy specimens were made available for histopathological examination. The gender wise age distribution of the patients is shown in Table 1.

Table 1. Age and gender Distribution of Patients

Age in Years	Gender		Total
	Female	Male	
0-9	1(25.00%)	3(75.00%)	4(1.73%)
10-19	8(66.67%)	4(33.33%)	12(5.21%)
20-29	26(89.65%)	3(10.34%)	29(12.60%)
30-39	65(86.66%)	10(13.34%)	75(32.60%)
40-49	50(83.34%)	10(16.66%)	60(26.08%)
50-59	18(62.07%)	11(37.93%)	29(12.60%)
≥60	15(71.42%)	6(28.57%)	21(9.13%)
TOTAL	183(79.56%)	47(20.44%)	230(100.00)

Out of 230 patients, majority of patients were in the age group between 30 – 49 years with total 135 cases accounting for 58.69% (Table 1). There were 183 females (79.56%) and 47 males (20.44%). The age distribution showed minimum age of 4 years and a maximum age of 89 years among the individuals presented with visible thyroid swelling. This clearly indicates the inclusion of the cases belonging to the entire spectrum of the thyroid lesions, thus eliminating the bias arising out of the hospital cases (Brian Haynes *et al*., 2006).

Table 2 depicts that out of the total 230 individuals with thyroid swelling and subjected to FNAC, 194 (84.34%) were found to have non-neoplastic lesions (Goitre, Hashimotos thyroiditis, Lymphocytic thyroiditis, Benign Cystic Lesion and Keratinous Cyst). Two thirds of non-neoplastic lesions (73.68%) were found be of goitre type.

Table 2.Frequency of Cytological diagnosis of Thyroid Aspirate with FNAC

Cytological Diagnosis	Frequency
Goiter	169 (73.68%)
Benign cystic lesion	9 (3.95%)
Hashimotos thyroiditis	8 (3.51%)
Lymphocytic thyroiditis	7 (3.07%)
Keratinous cyst	1 (0.44%)
Follicular neoplasm	24 (10.09%)
Papillary carcinoma	6 (2.63%)
Hurthle cell neoplasm	4 (1.75%)
Medullary carcinoma	1 (0.44%)
Lymphoma	1 (0.44%)
Total	230 (100%)

The broad diagnosis of Goitre includes Colloid Goitre with/ withoutadenomatous Change and Multi-nodular Goitre. Out of

230 samples, 36 (15.65%) were diagnosed neoplastic (Follicular Neoplasm, Papillary Carcinoma, Hurthle Cell Neoplasm, Medullary Carcinoma and Lymphoma) on FNAC. Follicular neoplasms constitute 66.6% (24 out of 66) of the total neoplasms.

Table 3. Frequency of Histopathological diagnosis of Thyroid Specimen

Diagnosis	Frequency
Goiter	172(74.78%)
Benign cystic lesion	6 (2.61%)
Hashimotos thyroiditis	7 (3.04%)
Lymphocytic thyroiditis	9 (3.91%)
Keratinous cyst	1 (0.43%)
Follicular neoplasm	18 (7.83%)
Papillary carcinoma	11 (4.78%)
Hurthle cell neoplasm	4 (1.74%)
Medullary carcinoma	1(0.43%)
Lymphoma	1(0.43%)
Total	230(100.0%)

Table 3 points out that out of the total 230 specimens subjected to histopathological examination, 195(84.78%) were non-neoplastic (Goitre, Hashimotos Thyroiditis, Lymphocytic Thyroiditis, Benign cystic lesion and Keratinous cyst). Goitre constituted two thirds (74.78%) of the total. Goitre included Colloid Goitre with/ without secondary changes, Multi-nodular Goitre, Nodular Goitre, and AdenomatoidGoitre.

Thirty five (15.22%) specimens out of the examined 230, were diagnosed as neoplastic on histopathology. These include Follicular Neoplasm, Papillary Carcinoma, Hurthle Cell Neoplasm, Medullary Carcinoma and Lymphoma. Nearly half (51.42%) of these neoplasm belong to the Follicular Carcinoma category. Table 4 elaborates the diagnosis concordance of FNAC with that by the "Gold Standard" of Histopathology. The agreement varied from 42.8% for Lymphocytic Thyroiditis to the complete agreement of 100.0% to the Keratinous Cyst. The number of observed agreements (Concordance) is 200. i.e. 86.96% of the observations. The calculated number of agreements expected by chance: 132.6i.e57.66% of the observations. The calculated Kappa= 0.692 (CI 0.595 – 0.789) is significant and shows that the strength of agreement is considered to be 'good'.

The agreement details of neoplastic lesions between FNAC and histopathology are shown in Table 5. It is observed that in majority of the neoplastic conditions, there is absolute agreement. Number of observed agreements (concordance): 23 (88.46% of the observations); Number of agreements expected by chance: 9.3 (35.80% of the observations); Kappa= 0.820 (CI 0.624 – 1.000). The strength of agreement is considered to be 'very good'. However, there were 4 cases of Papillary Carcinoma initially diagnosed as non-malignant condition by the FNAC but, later on proved to be neoplastic by the histopathology.

Table 4. Correlation of Non-neoplastic Lesions Diagnosis with FNAC and Histopathology Studies

	Histopathology Diagnosis of Thyroid Specimen*						
Diagnosis-FNAC	Benign cystic lesion	Goiter	Hashimotos thyroiditis	Keratinous cyst	Lymphocytic thyroiditis	Neoplasms	Total
Benign cystic lesion	6 (66.67%)	2 (22.22%)	0	0	0	1 (11.11%)	9 (3.91%)
Goiter	0	159 (94.08%)	0	0	5 (2.96%)	5 (2.96%)	169 (73.47%)
Hashimotos thyroiditis	0	2 (25%)	5 (62.50%)	0	1 (12.5%)	0	8 (3.47%)
Keratinous cyst	0	0	0	1 (100%)	0	0	1 (0.43%)
Lymphocytic thyroiditis	0	0	1 (14.28%)	0	3 (42.85%)	3 (42.85%)	7 (3.04%)
Neoplastic	0	9(25%)	1 (2.77%)	0	0	26 (72.22%)	36 (15.65%)
Total	6 (2.60%)	172 (74.78%)	7 (3.04%)	1(0.43%)	9 (3.91%)	35 (15.21%)	230 (100%)

*Number of observed agreements (Concordance): 200 (86.96% of the observations); Number of agreements expected by chance: 132.6 (57.66% of the observations); Kappa= 0.692 (CI 0.595 – 0.789); Weighted Kappa= 0.697:

Table 5. Correlation of Neoplastic Lesions Diagnosis with FNAC and Histopathology Studies

Diagnosis on FNAC	Diagnosis on histopathology*						Total
	Follicular neoplasm	Hurthle cell neoplasm	Lymphoma	Medullary carcinoma	Non neoplastic	Papillary carcinoma	
Follicular neoplasm	12 (50%)	0	0	0	10 (41.67%)	2 (8.33%)	24 (10.43%)
Hurthle cell neoplasm	0	4 (100%)	0	0	0	0	4 (1.73%)
Lymphoma	0	0	1 (100%)	0	0	0	1 (0.43%)
Medullary carcinoma	0	0	0	1 (100%)	0	0	1 (0.43%)
Non neo.	5 (2.57%)	0	0	0	185 (95.36%)	4 (2.06%)	194 (84.34%)
Papillary carcinoma	1 (16.67%)	0	0	0	0	5 (83.33%)	6 (2.60%)
Total	18 (7.82%)	4 (1.73%)	1 (0.43%)	1 (0.43%)	195 (84.78%)	11 (4.78%)	230 (100%)

*Number of observed agreements (concordance): 23 (88.46% of the observations); Number of agreements expected by chance: 9.3 (35.80% of the observations); Kappa= 0.820 (CI 0.624 – 1.000)

The diagnostic value of FNAC with respect to neoplastic conditions of thyroid lesions is detailed in Table 6. The sensitivity of FNAC to diagnose the neoplastic conditions among the visible thyroid swellings is 74.38% (CI 56.43 – 86.89) and Specificity is 94.87%(CI 90.49 – 97.37). The Positive Likelihood Ratio is 14.48 (CI 7.68 – 27.31). The weighted Likelihood Ratio indicated to be 2.6(CI 1.47 – 4.57). The diagnostic accuracy was 91.74. It can be concluded that the FNAC has high diagnostic value as SpPini.e in the inclusion of the neoplastic lesions of the visible thyroid swellings. The high Diagnostic Odds Ratio of 53.44 (CI 19.86 – 143.78) suggests that FNAC is an invaluable simple and rapid test to confirm the diagnosis of thyroid neoplasms. The farther the LR-(away from 1, the smaller it is), the more accurate FNAC.

Table 6.Diagnostic Value of FNAC with respect to Neoplastic Conditions of Thyroid Lesions

FNAC	Histopathology Diagnosis		Total
	Neoplastic condition	Non-neoplastic conditions	
Neoplastic conditions	26	10	36
Non-neoplastic conditions	9	185	194
Total	35	195	230
Sensitivity Sn		74.38%(CI 56.43 – 86.89)	
Specificity Sp		94.87%(CI 90.49 – 97.37)	
Positive Predictive Value PPV		72.22%(CI 54.56 – 85.20)	
Negative Predictive Value NPV		95.36%(CI 91.09 – 97.71)	
Likelihood Ratio (+) LR+		14.48 (CI 7.68 – 27.31)	
Likelihood Ratio (-) LR-		0.27 (CI 0.15 – 0.47)	
Likelihood Ratio (+) Weighted		2.6 (CI 1.47 – 4.57)	
Likelihood Ratio (-)Weighted		0.04 (CI 0.02 – 0.09)	
Diagnostic Odds Ratio		53.44 (CI 19.86 – 143.78)	
Youden Index		69.16%	
Post Test Probability Positive Test		0.71934	
Post Test Probability Negative Test		0.0462	
Diagnostic Accuracy		91.74	

The Pre and Post Test Probability of FNAC with respect to Neoplastic Conditions of Thyroid Lesions is depicted in Fig 1. The blue line indicates the post-test probability. The line nearing the top left corner of the graph indicates post-test probability of positive value having high diagnostic value and accuracy.

Table 7.Diagnostic Value of FNAC with respect to Non-neoplastic Conditions of Thyroid Lesions

FNAC	Histopathology Diagnosis		Total
	Non-neoplastic condition	Neoplastic Conditions	
Non-neoplastic condition	14	10	24
Neoplastic Conditions	21	185	206
Total	35	195	230
Sensitivity Sn		40.0%(CI 24.35 – 57.79)	
Specificity Sp		94.87%(CI 90.49 – 97.37)	
Positive Predictive Value PPV		58.33%(CI 36.94 – 77.20)	
Negative Predictive Value NPV		89.80%(CI 84.63 – 93.43)	
Likelihood Ratio (+) LR+		7.80 (CI 3.76 – 16.14)	
Likelihood Ratio (-) LR-		0.63 (CI 0.48 – 0.82)	
Likelihood Ratio (+) Weighted		1.4 (CI 0.78 – 2.50)	
Likelihood Ratio (-)Weighted		0.11 (CI 0.75 – 0.17)	
Diagnostic Odds Ratio		12.33 (CI 4.87 – 31.21)	
Youden Index		34.87%	
Post Test Probability Positive Test		0.5833	
Post Test Probability Negative Test		0.10158	
Diagnostic Accuracy		86.5%	

The red line indicates the post-test probability of a negative value. This line reaching closer towards the extreme right lower corner indicates the good diagnostic value of the test.

Table 8. Diagnostic Value of FNAC with respect to Colloid Goitre Condition of Thyroid

FNAC	Histopathology Examination Finding		Total
	ColliodGoitre	Other Conditions	
Colloid Goitre	159	10	169
Other Conditions	13	48	61
TOTAL	172	58	230
Sensitivity Sn		92.44% (CI 87.15 – 95.74)	
Specificity Sp		82.75% (CI 70.11 – 90.98)	
Positive Predictive Value PPV		94.08% (CI 89.08 – 96.96)	
Negative Predictive Value NPV		78.68% (CI 65.97 – 87.73)	
Likelihood Ratio (+) LR+		5.36 (CI 3.04 – 9.43)	
Likelihood Ratio (-) LR-		0.091 (CI 0.05 – 0.15)	
Likelihood Ratio (+) Weighted		15.9 (CI 8.70 – 29.04)	
Likelihood Ratio (-) Weighted		0.27 (CI 0.16 – 0.44)	
Diagnostic Odds Ratio		58.71 (CI 24.22 – 142.30)	
Youden Index		84.88%	
Post Test Probability Positive Test		0.9410	
Post Test Probability Negative Test		0.2125	
Diagnostic Accuracy		89.56	

The diagnostic value of FNAC with respect to non-neoplastic conditions of thyroid lesions is shown in Table 7. The sensitivity of the FNAC to diagnose non-neoplastic thyroid lesions was found to be around 40.0% (CI 24.35 – 57.79) but with high specificity of 94.87% (CI 90.49 – 97.37). The Positive Predictive Value PPV is 58.33% (CI 36.94 – 77.20) and the Negative Predictive Value NPV is 89.80 % (CI 84.63 – 93.43). The Likelihood Ratio (+) LR+ is 7.80 (CI 3.76 – 16.14) and the Likelihood Ratio (-) LR- is 0.63 (CI 0.48 – 0.82). The Diagnostic Odds Ratio is 12.33 (CI 4.87 – 31.21). The diagnostic accuracy of FNAC in non-neoplastic thyroid lesions is 86.5%. The Pre and Post Test Probability of FNAC with respect to non-neoplastic conditions of thyroid lesions is depicted in Fig 2. The blue line indicating the post-test probability of a positive test is nearing the top left corner of the graph. Hence, it can be concluded that the positive post test probability of FNAC in cases on non-neoplastic lesions of thyroid is of immense diagnostic value as SnNout. However, the post-test probability of a negative test is of no diagnostic value as shown in Fig. 2.

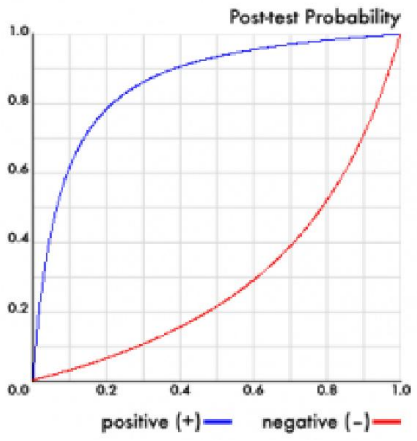

Fig. 1. Pre and Post Test Probability of FNAC with respect to Neoplastic Conditions of Thyroid Lesions

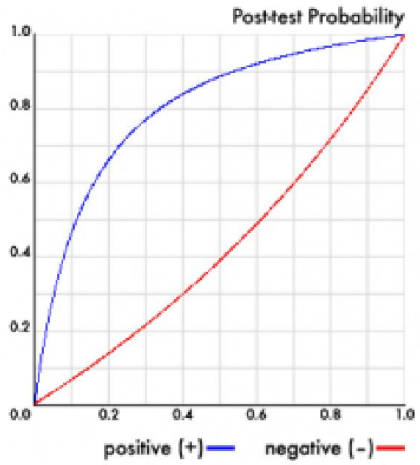

Fig. 2. Pre and Post Test Probability of FNAC with respect with respect to Non-neoplastic Conditions of Thyroid Lesions

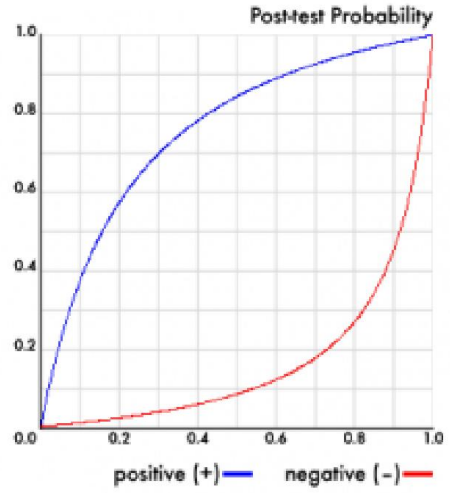

Fig. 3. Pre and Post Test Probability of FNAC with respect Colloid Goitre Condition of Thyroid

The Diagnostic Value of FNAC with respect to Colloid Goitre Conditions of Thyroid is shown in Table 8. The sensitivity of FNAC in diagnosis of Colloid Goitre was found to be 92.44% (CI 87.15 – 95.74) and the specificity was 82.75% (CI 70.11 – 90.98). A high Post-test probability of the positive test indicates the essential role of FNAC in the diagnosis. Though the sensitivity and specificity are comparatively high, the Post test probability of a negative result with FNAC is more of a value compared to the positive result. The redline proximity towards the extreme right lower corner compared to the blue line being away from the extreme left top corner (Fig. 3). The diagnostic accuracy of FNAC in colloid goitre was 89.56.

A likelihood ratio of greater than 1 indicates the test result is associated with the disease. A likelihood ratio less than 1 indicates that the result is associated with absence of the disease. FNAC with likelihood ratios more than 1 show practical significance as the post-test probability (odds) is different from the pre-test probability. (Jeffrey Sonis, 1999) The pre-test probability refers to the chance that an individual has a disorder or condition prior to the use of a diagnostic test. It allows the clinician to better interpret the results of the diagnostic test and helps to predict the likelihood of a true positive (T+) result through better post-test probability.As demonstrated in this study, the positive post-test probability is numerically equal to the positive predictive value; the negative post-test probability is numerically equal to (1 -negative predictive value) (http://ktclearinghouse.ca/cebm/practise/ca/calculators/statscalc). This hospital based study proved that FNAC has high sensitivity, specificity, PPV, and NPV, Hence more accurate. The large LR+ of FNAC indicates that it is a more accurate test in case of thyroid swellings. The smaller LR- confirms that FNAC is more accurate. When FNAC test result is negative, (High Sensitivity & High LR+), SnNout, *rules out* the target disorder. The FNAC with high specificity is very high and LR of a negative test is very low, then a positive test result pretty well rules in the target disorder. "SpPin," means, "When FNAC with high specificity, a positive test result rules in the target disorder". Finally based on the diagnostic criteria, in a resource crunch country like India, FNAC is an important diagnostic tool in the diagnosis of visible thyroid swellings

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