Malignancy Risk Analysis in Patients with Inadequate Fine Needle Aspiration Cytology (FNAC) of the Thyroid

Talib Al Maqbali1,*, Miroslav Tedla1, Martin O. Weickert2,3, Hisham Mehanna4

1 Institute of Head & Neck and Education Studies, University Hospital Coventry and Warwickshire, Coventry, United Kingdom, 2 Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism, University Hospitals, Coventry, United Kingdom, 3 Clinical Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry, United Kingdom, 4 Institute of Head and Neck Studies and Education (InHANSE), Divisional Offices, University Hospital, Coventry, United Kingdom

Abstract

Background: Thyroid fine needle aspiration cytology (FNAC) is the standard diagnostic modality for thyroid nodules. However, it has limitations among which is the incidence of non-diagnostic results (Thy1). Management of cases with repeatedly non-diagnostic FNAC ranges from simple observation to surgical intervention. We aim to evaluate the incidence of malignancy in non-diagnostic FNAC, and the success rate of repeated FNAC. We also aim to evaluate risk factors for malignancy in patients with non-diagnostic FNAC.

Materials and Methods: Retrospective analyses of consecutive cases with thyroid non diagnostic FNAC results were included.

Results: Out of total 1657 thyroid FNAC done during the study period, there were 264 (15.9%) non-diagnostic FNAC on the first attempt. On repeating those, the rate of a non-diagnostic result on second FNAC was 61.8% and on third FNAC was 47.2%. The overall malignancy rate in Thy1 FNAC was 4.5% (42% papillary, 42% follicular and 8% anaplastic), and the yield of malignancy decreased considerably with successive non-diagnostic FNAC. Ultrasound guidance by an experienced head neck radiologist produced the lowest non-diagnostic rate (38%) on repetition compared to US guidance by a generalist radiologist (65%) and by non US guidance (90%).

Conclusions: There is a low risk of malignancy in patients with a non-diagnostic FNAC result, commensurate to the risk of any nodule. The yield of malignancy decreased considerably with successive non-diagnostic FNAC.

Introduction

Thyroid nodules are common in clinical practice. Using ultrasound scanning, the prevalence of thyroid nodules can reach up to 50% of the population [1]. Approximately 5% of these nodules have been shown to be malignant [2]. Fine needle aspiration cytology (FNAC) is the accepted standard tool for the evaluation of thyroid nodules [3–12]. It is safe and accurate with reported high sensitivity and specificity for malignancy [13,14]. It is also reported to reduce the need for thyroid surgery by half [15] and to reduce the overall financial costs of medical care by 25% [2].

However, FNAC does have limitations, which include a significant rate of non-diagnostic results. This ranges from 0.6% [16] to 43.1% [17]. Nomenclature for inadequate FNAC varies in the literature causing unnecessary confusion [18]. It includes “inadequate”, “unsatisfactory”, “non diagnostic” and/or ‘Thy1’ (Thy1 category according to British Thyroid Association classification system). In this manuscript, we use the term non-diagnostic. The management strategies for these patients range in the literature from simple observation, to ultrasound surveillance to surgical intervention [19]. The recommended approach by both the British Thyroid Association and the American Thyroid Association is to repeat the biopsy [20–23]. However, repeating the biopsy may not always result in a definitive diagnosis, even if the procedure is done under ultrasound guidance. In addition, repeating the biopsy carries financial implications [24] and may not be acceptable to patients [25].

In this study, we aimed to determine the malignancy rate in cases where the FNAC result was non-diagnostic (Thy1), and to determine the success rates of successive FNAC in achieving a definitive cytology diagnosis in the setting of an initial non-diagnostic result. In addition, we aimed to identify risk factors that are associated with malignancy in nodules with a non-diagnostic (Thy1) presentation.

Materials and Methods

This was retrospective clinical audit from patient’s medical records. The research was limited to secondary use of information previously collected in the course of normal care and data were anonymised before the conduction of statistical analyses. Therefore, this research did not fulfil the requirements for Research Ethics Committee (REC) review. This is in accordance with the...
Malignancy rate in non-diagnostic cases

Data extraction and analysis

Slides processing, reading and labelling

After the samples were taken, a preservative medium was added and the mixture was centrifuged. Samples were then analysed using liquid based cytology techniques. This was followed by the staining process, where two slides are prepared with Papanicolaou’s (Pap) and May-Grunwald Giemsa (MGG) stains. Results are reported using the British Thyroid Association guidelines [1]. Specimens are considered adequate if they contain six or more groups of over 10 thyroid follicular cells, but the balance between cellularity and colloid is more important [1]. The FNAC was categorised as non-diagnostic Thy1 when samples do not meet the aforementioned criteria or where technical artefact precludes interpretation. The final histopathology diagnosis of the surgical specimen was based on WHO criteria.

Data extraction and analysis

Patient’s demographics, biochemistry, cytology, histopathology results and patient’s letters were available on computerised patient records system. Lesion characteristics such as number, size, consistency and suspicious features on U/S were extracted from electronic ultrasound reports. SPSS software (version 18.0, Chicago Illinois) was used to perform the statistical analysis. Patient characteristics are presented as mean +/- SE. Univariate analysis of lesions characteristics were used to calculate the risk and odds ratio with confidence intervals. Statistical significance was defined as p<0.05.

Results

1657 FNAC were performed during the period of the study. A total of 452 were reported as non-diagnostic (27.3%). 264 out of 452 samples were non-diagnostic on first FNAC and constitute the population of our study. The age of patients ranged from 16 to 90 years with mean age of 54.02±1.03 years and median age of 54 years. There were 212 females (80.3%), and 52 males (19.7%). Please refer to Figure 1 for further details.

Malignancy rate in non-diagnostic cases

In total, 16 (6%) of thy1 cases were diagnosed as having thyroid cancer on histology. Four patients had incidental papillary thyroid microcarcinoma in addition to a benign thyroid lesion (see table 1). These four cases were not included in the analysis for risk of malignancy as they were incidental findings and were not found in the sampled nodule. Therefore, the overall malignancy rate was 4.5% (12/264). The malignancy rate among operated cases was 18% (12/68).

Of the 264 patients with non diagnostic (Thy1) results on first FNAC, only 7% (19 patients) were operated on without a repeat FNAC. Most of these patients were operated on due to clinical suspicion and a high malignancy rate 37% (6/19) was found in this group. Malignancy rates after having successive non-diagnostic FNAC was much lower: 14% (5/21) after second non-diagnostic FNAC and 0% after fourth FNAC. In total, out of the 264 cases with Thy1 result in initial FNAC, only 10% (27/264) had more than three FNAC during their spell of care.

Effect of ultrasound guidance on repetition of non-diagnostic FNAC

79% of the first 264 FNAC were done using ultrasound guidance. This increased to 93% and 96% on second and the third FNAC respectively. Overall, repeating the FNAC on these lesions using palpation resulted in 90% non-diagnostic rate compared to 65% and 38% non-diagnostic rates when FNAC were repeated by

Table 1. Showing details of final histopathology results for the 68 operated cases.

| Benign final histology                  | n  | Malignant final histology | n  |
|----------------------------------------|----|--------------------------|----|
| Hyperplastic/regenerative nodule       | 21 | Papillary thyroid carcinoma | 5  |
| Adenoma                                | 15 | Minimally invasive follicular cancer | 3  |
| Multinodular goiter                    | 15 | Hurthle cell carcinoma | 2  |
| Thyroiditis and others                 | 5  | Anaplastic carcinoma | 1  |
|                                        |    | Non Hodgkin's Lymphoma | 1  |
| Total                                  | 56 |                          | 12 |

NB: 4 cases with incidental papillary thyroid microcarcinoma are listed in the benign category in this table.

Figure 1. Flow chart showing details of the thyroid non diagnostic FNAC and their cytolological and histological correlation.
doi:10.1371/journal.pone.0049078.g001
Discussion

Our study demonstrates several important findings. First, the yield of malignancy decreased considerably with successive non-diagnostic FNAC, whilst the proportion of operated patients increased. We found that if the result was non-diagnostic for the second time, the risk of malignancy decrease by two thirds, and after three inadequate FNAC the risk was nil in our cohort. This conform findings by other reports for example, Renshow [26] found that patients with at least two non diagnostic FNAC had significantly lower risk of malignancy (0%) compared to those who had only one non diagnostic FNAC (20%). On the other hand, Jo et al [27] found that there is no relation between the malignancy rate and the number of non diagnostic aspirations. We believe that incidental papillary thyroid microcarcinoma detected on post operative histology should be excluded as these lesions are not detected or sampled pre operatively [34]. The inclusion of these tumours may introduce bias to the results. For example, Oertel et al [32] reported a 3.4% overall rate of malignancy in non-diagnostic FNAC. This rate increased to 11% if incidental papillary thyroid microcarcinomas were included. Therefore, it is important that authors document this when reporting and calculating the overall rate of malignancy.

The rate of malignancy found in operated cases with non-diagnostic FNAC varies widely between studies, ranging from 2.2% to 51% [17,19,23,28,29,32–35] (see table 4). A high rate of malignancy among operated cases for non diagnostic FNAC may be due to patient selection bias i.e. those patients with a non-diagnostic (Thy 1) result who are suspected of having malignancy are more likely to undergo surgery [19,36]. Therefore, consideration of the overall rate of malignancy is probably more important in determining our treatment strategy towards non-diagnostic FNAC patients.

Our study also demonstrates that the risk of malignancy declines with each successive repetition of non-diagnostic FNA. Patients who had more than 3 non-diagnostic FNA's in our series had no malignancies detected. This would suggest a possible role for observation in patients who have had three or more non-diagnostic FNAC results and there is no clinical suspicion of malignancy. However, this finding would need to be indepen-

Table 2. Portions of FNAC done under ultrasound guidance and results of repeating FNAC.

| Number of FNAC | US guided | Non-diagnostic Thy1 |
|----------------|-----------|---------------------|
| 1st FNAC       | 264       | 79% 264             |
| 2nd FNAC       | 175       | 93% 108 (62%)       |
| 3rd FNAC       | 72        | 96% 34 (47%)        |
| 4th FNAC       | 24        | 87% 12 (50%)        |
| 5th FNAC       | 2         | 50% 2 (100%)        |
| 6th FNAC       | 1         | 0                   |

Table 3. Risk factor analysis for malignancy in inadequate FNAC.

| Risk factor                                | Odds ratio | 95% CI for odds ratio | P value |
|--------------------------------------------|------------|-----------------------|---------|
| HPE size (>4 cm VS <4 cm)                  | 3.4        | 0.865–13.492          | 0.080   |
| Gender (male VS female)                    | 3.28       | 0.864–12.497          | 0.081   |
| Consistency (solid VS cystic)              | 2.75       | 0.458–16.525          | 0.269   |
| Age (>50 years VS <50 years)               | 2          | 0.540–7.409           | 0.300   |
| US size (>4 cm VS <4 cm)                   | 1.64       | 0.457–5.94           | 0.45    |
| TSH (<0.36 VS 0.36–6.0)                    | 1.02       | 0.191–5.473          | 0.98    |
| No of nodules (multiple vs single)          |            | 0.006                |         |
Table 4. Non diagnostic and malignancy rate for thyroid FNAC in the literature.

| Author and Year | Total FNAC done | ND Rate | Patients with ND FNAC | Number Operated Cases | Malignancy among ND | Malignancy among Operated Cases |
|-----------------|-----------------|---------|-----------------------|-----------------------|---------------------|---------------------------------|
| Yoon et al [37] | 22754           | 16.3%   | NA                    | 230                   | 2.7%                | 43.9%                           |
| Gharib and Goellner [38] | 18183 | 15% | NA | NA | NA | NA |
| Piana et al [28] | 18000 | 12.5% | 1342 | 96 | 1.7% | 24% |
| Chow et al [19] | 17887 | 21% | 150 | 27 | 7% | 37% |
| Oertel et al [32] | 9397 | 1% | 117 | 38 | 3.4% | 11.3% |
| Caruso and Mazzaferrì [5] | 9119 | 22% | NA | NA | NA | NA |
| Slowinaka et al [25] | 4601 | 8.9% | 408 | NA | 6.6% | NA |
| Baloch et al [29] | 3007 | 8% | 237 | 53 | 11.3% | 51% |
| Baier et al [39] | 944 | 11.8% | NA | NA | NA | NA |
| Deandrea et al [35] | 927 | NA | NA | 51 | NA | 5.8% |
| Redman et al [40] | 693 | 4% | NA | NA | NA | NA |
| Baloch et al [33] | 662 | 11% | 72 | 8 | 2.7% | 25% |
| Bellantone et al [41] | 575 | 9.2% | NA | NA | NA | NA |
| Ceresini et al [16] | 465 | 0.6% | 307 | NA | NA | NA |
| Cai et al [42] | 434 | 7.3% | NA | NA | NA | NA |
| Singh et al [43] | 423 | 25% | NA | NA | NA | NA |
| Schmidt et al [30] | 345 | 17.1% | 59 | 21 | 2% | NA |
| Tabaqchali et al [17] | 239 | 43.1% | 77 | NA | 3.9% | 5.2 |
| Bakshi et al [34] | 128 | 35% | 45 | 45 | NA | 2.2% |
| Macdonald and Yazdi [31] | NA | NA | 91 | NA | 2% | NA |
| McHenry et al [23] | NA | NA | 92 | NA | NA | 9% |

ND: non diagnostic FNAC.

doi:10.1371/journal.pone.0049078.t004
The rate of non diagnostic FNAC has a very wide range in literature (table 4). The reasons for this are variable and beyond the scope of this paper, however, we reported the results of FNAC prepared using liquid base cytology which is reported to have less non diagnostic rate compared to conventional cytology results [47,48].

Risk factors for malignancy in non-diagnostic FNAC

In the literature, few studies have addressed possible risk factors specific for malignancy in non-diagnostic FNAC. For example, McHenry et al [23] identified male gender as a possible predictor of malignancy (P<0.05) in nodules with non-diagnostic FNAC. In contrast, Mendelson et al [49] found that male gender is not associated with high risk of malignancy and they did not find any statistically significant risk associated with radiation exposure, family history of malignancy, solitary nodule or nodule more than 5 cm. Similarly, Chow et al [19] reported no significant correlation between pre-operative findings and risk of malignancy including the number of nodules and ultrasound characteristics as well as physical findings. Our study identified multiple nodules on ultrasound as a significant risk factor for malignancy. In addition, it also demonstrated a possible trend for males to have a higher malignancy risk compared to females. Similarly, lesions sized ≥4 cm were more likely to be malignant compared to those less than 4 cm as were solid lesions compared to cystic lesions but again these associations did not reach statistical significance, table 3.

Conclusions

Thyroid FNAC is the preferred diagnostic modality for the investigation of thyroid nodules. However, this method has limitations among which is the inadequacy rate. Our study showed that yield of malignancy in persistently non-diagnostic FNAC is low, and decreases with successive inadequate FNAC. Furthermore, ultrasound guidance, especially by an experienced head and neck specialist radiologist, improves the non-diagnostic rate.

Author Contributions

Conceived and designed the experiments: TAM HM. Performed the experiments: TAM MT. Analyzed the data: TAM MT MIOW HM. Contributed reagents/materials/analysis tools: TAM MT. Wrote the paper: TAM MT MIOW HM.

References

1. British Thyroid Association (2007) Royal College of Physicians: British Thyroid Association Guidelines for the management of thyroid cancer. 2nd Edition. Internet: [http://www.british-thyroid-association.org/Guidelines/]. (cited 04/01/2011).
2. Lande H (2004) The Thyroid Nodule. The New England Journal of Medicine 35:1:1764–71.
3. Pu RT, Yang J, Wasserman PG, Bhatia T, Griffith KA, et al. (2006) Does Hurthle cell lesion neoplasm predict malignancy more than follicular lesion neoplasm on thyroid fine-needle aspiration. Diagn Cytopathol 34(5):330–334.
4. Gharib H, Goellner JR (1993) Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med 115;4(18):202–9.
5. Caruso D, Mazzafferri EL (1991) Fine needle aspiration biopsy in the management of thyroid nodules. Endocrinologist 1: 194–202.
6. Mauno N, Mustajoki S, Minzaffar M, Khan AH (1997) The use of fine needle aspiration biopsy in the management of thyroid disease. J Pak Med Assoc 47(10):253–258.
7. Castro MR, Gharib H (2003) Thyroid fine-needle aspiration biopsy: progress, practice, and pitfalls. Endocr Pract 9(7):128–36.
8. Caji J, Ryska A, Rehorkova P, Hovorkova E, Kerekes Z, et al. (1999) Sensitivity and specificity of the fine needle aspiration biopsy of the thyroid: clinical point of view. Clin Endocrinol (Oxf) 51(4):509–515.
9. Ko HM, Jhs BK, Yang SH, Lee JH, Nam JH, et al. (2003) Clinicopathological analysis of fine needle aspiration cytology of the thyroid. A review of 1,613 cases and correlation with histopathological diagnoses. Acta Cytol 47(5):737–732.
10. Al-Hureebi KA, Al-Hureebi AA, Abdulmughni YA, Aulaqi SM, Salman MS, et al. (2003) The diagnostic value of fine-needle aspiration cytology in thyroid swellings in a university hospital, Yemen. Saud J Med J 24(4):499–503.
11. Anrikachi M, Ramzi I, Rubenfield S, Wheeler TM (2001) Accuracy of fine-needle aspiration of thyroid. Arch Pathol Lab Med 125(4):484–488.
12. Schlinkert RT, Van Heerden JA, Schlinkert RT, Young WF Jr, Farley DR (1997) Factors that predict malignant thyroid lesions when fine-needle aspiration is "suspicious for follicular neoplasm." Mayo Clin Proc 72(10):913–916.
13. Gharib H, Goellner JR (1993) Fine-needle Aspiration Biopsy Of Thyroid Nodules. Endocrine practice 1(6): 410–417.
14. Corrias A, Einandi S, Chiobaru E, Weber G, Grino A, et al. (2001) Accuracy of Fine Needle Aspiration Biopsy of Thyroid Nodules in Detecting Malignancy in Childhood: Comparison with Conventional Clinical, Laboratory, and Imaging Approaches. The Journal of Clinical Endocrinology & Metabolism 86(10):4644–4648.
15. Mazzafferi EL, (1993) Management of a solitary thyroid nodule. New England Journal of Medicine 329(8):553–559.
16. Ceresini G, Cureccio L, Morganti S, Milli B, Bertone L, et al. (2004) Ultrasound-Guided Fine-Needle Cytology Biopsy of Thyroid Nodules, Coupled with On-Site Cytologic Review, Improves Results. Thyroid 14(3):385–389.
17. Tabaqchali MA, Hamon JM, Johnson SJ, Wadherat V, Lennard TJW, et al. (2000) Thyroid aspiration cytology in Newcastle: a six year cytology/histology correlation study. Ann R Coll Surg Engl 82:149–155.
18. Oerdt YC (2006) Unsatisfactory vs. non-diagnostic thyroid aspirates: a semantic issue? Diagn Cytolopatohy 34(2):87–88.
19. Chow LS, Gharib H, Goellner JR, Van Heerden JA (2001) Non-diagnostic thyroid fine-needle aspiration cytology: Management dilemmas. Thyroid 11(12):1147–1151.
20. Orja IB, Hamrahian AH, Reddy SS (2004) Management of nondiagnostic thyroid fine-needle aspiration biopsy: survey of endocrinologists. Endocrine practice 10(4):371–375.
21. Layfield LJ, Abrams J, Cochand-Priestt B, Evans D, Gharib H, et al. (2008) Post-thyroid FNA testing and treatment options. A synopsis of the National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. Diagn Cytopathol 36:442–448.
22. ACE/AME Task Force on Thyroid Nodules American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi (2006) Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 12(2):163–102. Accessed online. Cited 10.02.2011. Available: [http://www.scribd.com/doc/39025547/Thyroid-Guidelines].
23. McHenry CR, Wallish PG, Rosen IB (1993) Non-diagnostic fine needle aspiration biopsy: A dilemma in management of nodular thyroid disease. The American Surgeon 59(7):415–419. (abstract only).
24. Borget I, Vielh P, Leboeufouis S, Allyn M, Iacobelli S, et al. (2000) Assessment of the cost of fine-needle aspiration cytology as a diagnostic tool in patients with thyroid nodules. Am J Clin Pathol 129:763–771.
25. Slowski-Klencka D, Sperny D, Klencki M, Lewinski A (2004) Non-Diagnostic Cytological Outcome of Thyroid Biopsy and the Risk of Thyroid Malignancy. Endocrine pathology 15(1): 65–75.
26. Renshaw AA (2011) Significance of repeatedly nondiagnostic thyroid fine-needle aspirations. Am J Clin Pathol 135(5):750–2.
27. Jo VY, Vanderlaan PA, Marqusee E, Krane JF (2011) Repeatedly nondiagnostic thyroid fine-needle aspirations do not modify malignancy risk. Acta Cytol 55(6):539–43.
28. Piana S, Fraisdadi A, Ferrari M, Vavucva R, Froio E, et al. (2010) Is a five-category reporting scheme for thyroid fine needle aspiration cytology accurate? Experience of over 18 000 FNAAs reported at the same institution during 1998–
29. Baloch Z, LiVolsi VA, Jain P, Jain R, Aljada I, et al. (2003) Role of repeat fine-needle aspiration biopsy (FNAB) in the management of thyroid nodules. Diagnostic Cytopathology 29(4):203–206.
30. Schmidt T, Riggs MW, Speights VO Jr (1997) Significance of nondiagnostic fine-needle aspiration of the thyroid. Southern Medical Journal 90:1183–1186.
31. MacDonald L, Yazdi HM (1996) Non diagnostic fine needle aspiration biopsy of the thyroid gland. Acta cytologica 40: 423–429.
32. Oertel Yolanda C, Miyahara-Felipe Leika, Mendoza Mayo G, Yu Kai (2007) Value of Repeated Fine Needle Aspirations of the Thyroid: An Analysis of Over Ten Thousand FNAs. Thyroid 17(1):1061–1066
33. Baloch W, Sack J, Yu H, Livolsi A, Gupta K (1998) Fine-Needle Aspiration of Thyroid: An Institutional Experience. Thyroid 8(7):565–569
34. Bakhsh A, Mansoor Ibrahim, Jones A (2003) Analysis of inconclusive fine needle aspiration of thyroid follicular lesions. Endocrin Pathol 14(2):167–175.
35. Deandrea M, Ragazzoni F, Motta M, Torchio B, Mormile A, et al. (2010) Diagnostic Value of a Cytomorphological Subclassification of Follicular Patterned Thyroid Lesions: A Study of 927 Consecutive Cases with Histological Correlation. Thyroid 20(10): 1077–1083
36. Kelm S, Rahm A, Leibowitz J, Burstein E, Haber S (2001) Thyroid cytology and the risk of malignancy in thyroid nodules: importance of nuclear atypia in indeterminate specimens. Thyroid 11(3): 271–277.
37. Yoon JH, Kwak JY, Kim EK, Moon HJ, Kim MJ, et al. (2010) How to Approach Thyroid Nodules with Indeterminate Cytology. Annals of Surgical Oncology 17(3): 2147–2155
38. Gharib H, Goldhar JR (1993) Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med 118(4):282–9.
39. Baier ND, Hahn PF, Gervais DA, Samir A, Halpern EF, et al. (2009) Fine-needle aspiration biopsy of thyroid nodules: experience in a cohort of 944 patients. Am J Roentgenol 193(4):1175–9.
40. Redman R, Zalaznick H, Mazzaferri EL, Massell NA (2006) The Impact of Assessing Specimen Adequacy and Number of Needle Passes for Fine-Needle Aspiration Biopsy of Thyroid Nodules. Thyroid 16(1):55–60
41. Bellantone R, Pio Lombardi C, Raffaelli M, Trianni E, De Crea C, et al. (2004) Management of Cystic or Predominantly Cystic Thyroid Nodules: The Role of Ultrasound-Guided Fine-Needle Aspiration Biopsy. Thyroid 14(1):43–47
42. Cai XJ, Vaiyaparambath N, Nixon P, Wagborn A, Giles T, et al. (2006) Ultrasound-guided fine needle aspiration cytology in the diagnosis and management of thyroid nodules. Cytopathology 17(3):251–256
43. Singh N, Ryan D, Berney D, Calamimini M, Sheaff MT, et al. (2003) Inadequate rates are lower when FNAC samples are taken by cytopathologists. Cytopathology 14(6): 327–331
44. Richards ML, Bohnenblust E, Sirinek K, Bingener J (2008) Nondiagnostic thyroid fine-needle aspiration biopsies are no longer a dilemma. American Journal of Surgery 196(3): 391–402.
45. Danese D, Sciacchitano S, Farinetti A, Andreoli M, Poncecorvi A (1998) Diagnostic accuracy of conventional versus sonography-guided fine-needle aspiration biopsy of thyroid nodules. Thyroid 8(1):15–21.
46. Carcheci C, Jeffrey RB, McDougall IR, Nowels KW, Weigel RJ (1998) Ultrasound-guided fine-needle aspiration biopsy of thyroid masses. Thyroid 8(4):201–9.
47. Saleh H, Bassil N, Hammoud MJ (2009) Utility of a liquid-based, monolayer, preparation in the evaluation of thyroid lesions by fine needle aspiration biopsy: comparison with the conventional smear method. Acta Cytol 53(2):130–6.
48. Rossi ED, Raffaelli M, Zannoni GF, Poncecorvi A, Mulè A et al. (2009). Diagnostic efficacy of conventional as compared to liquid-based cytology in thyroid lesions: evaluation of 10,360 fine needle aspiration cytology cases. Acta Cytol 53(6):659–66.
49. Mendelson AA, Tamalia M, Rivera J, Hier MP, Sherman M, et al. (2009) Predictors of malignancy in preoperative nondiagnostic biopsies of the thyroid. Journal of Otolaryngology - Head and Neck Surgery 38(3):395–400.