IF : 4.547 | IC Value 80.26 Volume-6, Issue-4, April - 2017 • ISSN No 2277 - 8160

Original Research Paper Medical Science

Fine Needle Aspiration Cytology of Thyroid Nodule and its Correlation with Histopathology Diagnosis of Cancer

Amani Alhozali Department of Medicine, King Abdulaziz University Hospital, Jeddah, Saudi Arabia

ABSTRACT The objective of this study is to do a retrospective review of fine needle aspiration cytology of thyroid nodules and its correlation with histopathology diagnosis of cancer. Ninety-five thyroid cancer patients at King Abdulaziz University Hospital, Saudi Arabia were the subjects for this study. FNAC of 95 patients were classified based on Bethesda system and histopathological evaluations obtained from the group were evaluated. Demographic information of the patients was analysed using frequency distribution. The sensitivity in the study was 92. 63%. As there was 100 % prevalence. Positive predictive value (PPV) was 100 %, and false negative rate was 7.37%. Accuracy rate was 92.63%. FNAC is a highly consistent and precise screening aid for differentiating malignant lesions from the benign ones. Thus, it is very helpful to clinicians in the diagnosis of cancer, especially in avoiding surgical procedures for benign lesions.

KEYWORDS : fine needle aspiration cytology, thyroid nodules, Histopathology Diagnosis

Introduction

Thyroid Nodule is a major problem in the general population, but, however, majority of them are non-neoplastic and do not require surgical intervention. When it comes to severity of the problem, less than 5 % of thyroid nodules are malignant (Sclabas et al., 2003). In the iodine-deficient regions, it has been found that the prevalence of thyroid nodules as high as 25 % or more. But, in non-iodine deficient regions only 4-7 % of the population have been found to have thyroid nodules (Tseng et al., 2008). In the recent years, incidence of thyroid nodules and thyroid malignancy has gone up significantly especially in high income countries of North America, Europe and Asia. The incidence of thyroid cancer has increased in the United States three times between 1975 and 2009. However, since thyroid carcinoma is also the least aggressive, the surge has not resulted in increase in death rate(Tedla, 2016).

Latest reports from the US state that there are close to 63,000 new cases of thyroid cancer in a year. 70-80 per cent of thyroid cancers are due to over-diagnosis of small benign tumours. Considerable increase in the number has been attributed to early detection using high resolution ultrasound and discovery of sub-clinical thyroid nodules (Wiltshire, Drake, Uttley, & Balasubramanian, 2016). This is a major concern as over-diagnosis leads to over-treatment. Identification of small thyroid nodules which would have otherwise been dormant poses a management hurdle for physicians besides increasing the anxiety for patients. This results in surgical procedures. Studies report that many people opt for aggressive management of benign lesions that could have been treated using conservative procedures. When it comes to the management of thyroid nodules, a rational approach would depend on the clinician's competency to distinguish between the more common benign thyroid nodules from malignant ones in a dependable and economic manner(Dankle, 2016).

The importance given to total thyroidectomy for benign nodular thyroid disease has always been a subject of debate in cases clear evidence is not present (Holzheimer & Mannick, 2001). In a study conducted in Japan it was found that surgery did not have any significant effect on small papillary thyroid cancers. Careful surveillance had almost the same effect in such cases. With an accurate preoperative diagnosis, surgeries can be avoided in benign conditions.

Ultrasonography, radionuclide scan, and fine needle aspiration cytology (FNAC) are the preliminary preoperative screening procedures. Ultrasonography is one of the most commonly used methods to image the thyroid gland. In addition to facilitating the diagnosis of clinically apparent nodules, the widespread use of ultrasonography has resulted in uncovering a multitude of clinically imperceptible thyroid nodules, the overwhelming majority of which are benign. The high sensitivity for nodules but inadequate specificity for cancer has posed a management and economic problem. Although ultrasonography is highly sensitive in deducting nodules, it lacks the specificity required to deduct malignancy (Manfred Blum, 2015).

Radionuclide thyroid scan or scintigraphy is helpful to determine if the thyroid nodule present in the patient is functioning autonomously. It estimates the timed radioisotope uptake by the thyroid gland on the premise that the uptake of radioisotope will be higher in hyper-functioning nodule and will be lower in most benign and virtually all malignant thyroid nodules than the nearby thyroid tissues (Blum & Goldman, 1975; Reschini et al., 2006; Shambaugh, Quinn, Oyasu, & Freinkel, 1974). Depending on whether the tracker uptake is greater, equal to less than the surrounding normal thyroid tissue, nodules appear 'hot', 'warm' or 'cold' (Tamhane & Gharib, 2016).

Among the three, FNAC is considered as the most accurate diagnostic modality. In the diagnosis of thyroid nodules, FNAC is considered the golden tool (Feldkamp et al., 2016). This procedure was first introduced in Scandinavian countries in 1950s. It became well known in the United States in 1970s. In 1980s, it became popular worldwide. The significance FNCA has today is such that it is a vital component of diagnosis for thyroid pathologies because it is a safe and relatively simple test. It is widely recognised as a very important primary diagnostic procedure for the assessment of patients having thyroid nodules. Further, the test can be performed as an out-patient procedure(Sharma, 2015).

Fine needle biopsy of a thyroid nodule can be employed in the followed cases (Cooper et al., 2009; Hossein Gharib et al., 2016; Perros et al., 2014).

(a) If the nodules are larger than 1 cm with minimum two ultrasound conditions for malignancy
(b) Irrespective of the size, nodules with extra capsular extension or indeterminate cervical lymph nodes
(c) Patients who have history of neck radiation. In this case also, the size of the nodule is not taken into account.
(d) If there is history of clearly differentiated thyroid cancer in more than two first degree relatives.
(e) In the case of medullary thyroid carcinoma or multiple endocrine neoplasia (MEN) type 2

FNAC should be avoided in cases where the nodule is a region of focal autonomy on thyroid radionuclide scan and or/ shows no ultrasound features indicating malignancy. In addition, needle biopsy should not be performed for simple cysts.

Wherever the situation warrants, the technique of FNAC should be performed under ultrasound guidance. This will help the clinicians to document that the needle was placed correctly in the target region.With regard to the complications of FNAC, it is not a matter of significant concern. There is little data available on pain associated with FNAC. Around 9 per cent of the patients who went for FNA biopsy reported mild pain (Frates et al., 2006).

Thyroid surgeries can be avoided with the help of benign FNAC results. Since FNAC is the accurate diagnostic application, In the event of the test (FNAC) showing the presence of malignant cells, it will be the decisive factor for determining the surgical strategy in terms of hemithyroidectomy vs. total thyroidectomy, extent of lymph node dissection. In the study conducted by Prasad (2016) it was found that while ultrasonography showed overlapping of benign thyroid nodules and malignant thyroid nodules, FNAC was effective in both diagnosing benign conditions and supplementing ultrasonography features in determining malignancy.

In the research conducted by Babu, Raju and Radhakrishnan (2010) it was found that the use of FNAC has brought down the number of patients with solitary thyroid nodules undergoing unwarranted surgeries, which in turn has led to effective planning of surgeries for malignant cases. The study conducted by Ayub, Sajid and Shahid (2016) concluded that sensitivity, diagnostic accuracy and specificity of FNAC were high indicating the significant role of fine needle aspiration cytology as the preliminary diagnostic utility in the management of thyroid nodules.

Thus, from the findings all the research studies mentioned in this section it is evident that FNAC is highly useful to clinicians to distinguish benign thyroid nodules from thyroid cancer. Further retrospective studies have reported lower rate non diagnostic and false negative cytology from FNA procedures used with ultrasonography guidance.

In the present study, FNA of thyroid cancer patients were reviewed retrospectively with the aim to correlate FNA result with final histopathology.

Methodology

The study was a retrospective review of the FNA of 95 thyroid cancer patients at King Abdulaziz University Hospital, Saudi Arabia with the objective to correlate the FNA result with the final histopathology. In the study, 95 FNAC of 95 patients were classified according to the Bethesda system and histopathological evaluations obtained from this group were evaluated. Statistical analysis was done using SPSS 20.0 software. Statistical analysis that was enumerated in the data included frequency distribution and sensitivity analysis. Frequency distribution was used to analyse the demographic information of the patients. Bethesda system was not used for all the 95 cases as in some cases, the patient history was before the implementation of the system, and, in the rest, the pathologist had not used it. The study sought ethical approval from the ethical committee at King Abdulaziz University Hospital.

Results

FNA of 95 case of thyroid cancer reviewed retrospectively at King Abdulaziz university Hospital to correlate FNA result with final histopathology. Data was analyzed using percentage analysis, descriptive statistics and sensitivity analysis.

Table 1 Sex distribution of the patients (n=95)

Sex	Number	Percentage
Male	21	22
Female	74	78
Total	95	100

Table 1 reveals the sex distribution of the patients. Out of these 95 cases, 74 (78%) cases were female and 21 (22%) cases were male.

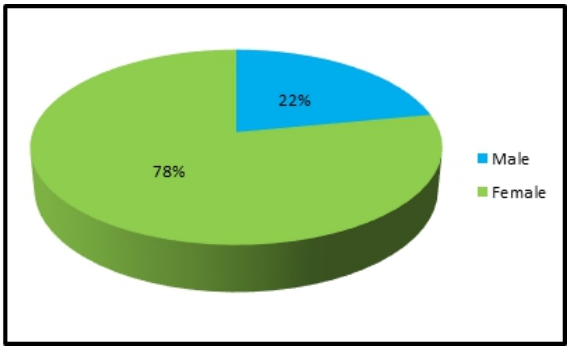

Figure 1 : Sex distribution of the patients

Table 2 Descriptive statistics for age (n=95)

	Mean	SD	Range (Max – Min)
Age	42.38	15.25	69 (84-15)

The average age of the patient is 42 years with SD 15.25. The age ranged from 15 to 84 years.

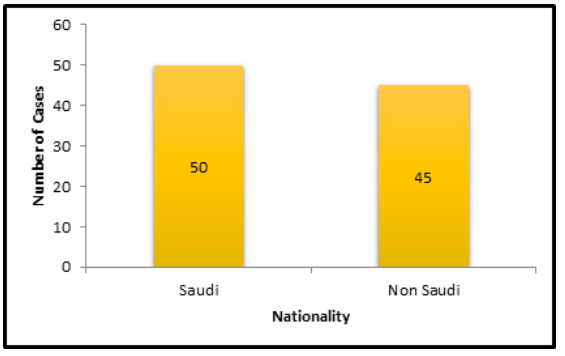

Figure 2: Distribution of nationality in patients

Table 3 Distribution of patients in FNA diagnosis (n=95)

FNA diagnosis	Number	Percentage
No malignant cell/Benign	7	7.4
Suspicious of malignancy	16	16.8
Malignant cell	44	46.3
Follicular neoplasm	9	9.5
Follicular lesion	14	14.7
Hurthel cell lesion/Neoplasia	4	4.2
Atypia of undetermined significant	1	1.1

Table 3 reveals the distribution of the patients in FNA diagnosis. Out of these 95 cases, 44 cases (46.3%) were malignant cell, 16 cases (16.8%) were Suspicious of malignancy, 14 cases (14.7%) were Follicular lesion, 9 cases (9.5%) were Follicular neoplasm, 7 (7.4%) were No malignant cell/Benign, 4 (4.2%) were Hurthel cell lesion/Neoplasia and 1 (1.1%) were Atypia of undetermined significant.

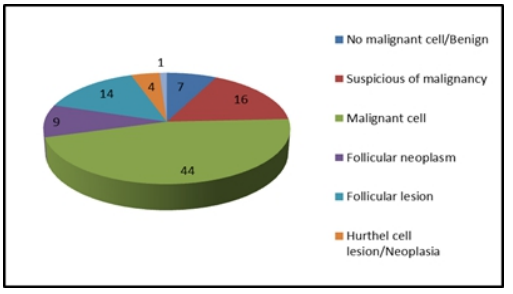

Figure 4 : Distribution of patients in FNA diagnosis

Table 4 Distribution of patients with Histopathology findings (n=95)

Histopathology	Number	Percentage
Papillary Thyroid Carcinoma (PTC)	79	83.2
Follicular Thyroid Carcinoma (FTC)	12	12.6
Medullary Thyroid Carcinoma (MTC)	2	2.1
Anaplastic Thyroid Carcinoma (ATC)	2	2.1
Total	**95**	**100**

Table 4 reveals the distribution of the patients with histopathology. Out of 95 cases, 79 cases were (83.2%) Papillary Thyroid Carcinoma (PTC), 12 cases (12.6%) were Follicular Thyroid Carcinoma (FTC), 2 (2.1%) were Medullary Thyroid Carcinoma (MTC) and Anaplastic Thyroid Carcinoma (ATC) in each.

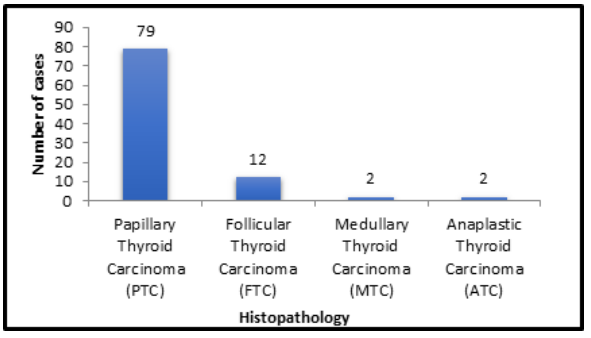

Figure4: Distribution of patients with Histopathology findings

Table 5 Correlation of FNA diagnosis and Histopathology

Cytological diagnosis	Histopathology diagnosis	Discordant cases
Benign (N=7)	(N=0) [TN]	Benign (N=7) [FN]
Malignant + Suspicious of Malignancy (N= 88)	Malignant (N=88) [TP]	(N=0) [FP]

Table 5 reveals the sensitivity analysis.
Prevalence = 100%
A=88; B=7; C=0; D=0
Sensitivity = A/ (A+B)*100
Sensitivity = 92.63%
Specificity = D/(C+D)*100
Specificity = NA

Sensitivity (probability that a test result will be positive when the disease is present – 'true positive rate') Sensitivity =True positive/ (True positive + False negative) = 88/ (88+7) = 92.63%.

Specificity (probability that a test result will be negative when the disease is not present – 'true negative rate') Specificity = True negative / (True negative + False positive) = 0/ (0+0) = NA

Positive predictive value (probability that the disease is present when the test is positive) Positive predictive value (PPV) =True positive/ (True positive+ False positive) = 88/ (88+0) = 100%.

Negative predictive value (probability that the disease is not present when the test is negative) Negative predictive value (NPV) = True negative/ (True negative + False negative) = 0/(0+7) = 0.

False positive rate = False positive / (False positive +True negative) = 0/ (0+0) = 0.

False negative rate= False negative / (False negative +True positive) = 7/ (7+88) =7.37%.

Accuracy: The accuracy of a test is its ability to differentiate the patient and healthy cases correctly. To estimate the accuracy of a test, we should calculate the proportion of true positive and true negative in all evaluated cases. Mathematically, this can be stated as:

Accuracy= TP+TN/ TP+TN+FP+FN = 88+0/88+0+0+7 = 88/95*100 = 92.63%

To summarize the results: False positive rate was 0 and false negative rate was 7.37%. The sensitivity was 92.63%. The positive predictive value was 100% and negative predictive value was 0.

Discussions

Thyroid swelling is a significant clinical problem. However, most of the cases are non-neoplastic and they can be treated without surgical intervention (Sukumaran et al., 2014). Screening tests that present accurate results are very helpful to clinicians in selecting the subcategory of patients who require surgery and eliminating the need for surgical intervention in patients with benign conditions who might otherwise undergo surgeries and be exposed to post-operation complications.

Fine needle aspiration cytology (FNAC) is considered a very high standard screening test in the preliminary diagnosis of thyroid nodules. FNAC is not only reliable and simple but also time saving and cost effective. Further, it is a minimally invasive procedure (Jayaram, 2006). The role of FNAC in identifying malignant lesions from benign ones has considerably brought down the surgery rates in thyroid pathologies (Sidawy, Del Vecchio, & Knoll, 1997). Although accuracy rates of diligently performed FNAC as high as 95-98 % have been reported, there have been reports of the tests presenting false positive and false negative results (Cramer, 2000).

The aim of this research is to study the correlation between fine needle aspiration cytology of thyroid nodule and histopathology diagnosis of cancer. In this study FNA of 95 thyroids cancer patients were studied retrospectively.

Out of 95 cases, 74 were women. This is indicative of prevalence of thyroid nodule could be much higher in women than men. A report by the University of California San Francisco states that thyroid nodules are common in 6 % Ladenson (Ladenson, 2008) of adult women and 2 % Ladenson (Ladenson, 2008) of adult men in the U.S. Similarly, in a study on 5234 individuals aged above 60 in Framingham it was found that 6.4 % Vanderpump (Vanderpump, 2011) women 1.5 % Vanderpump (Vanderpump, 2011) of men had thyroid nodules. Prevalence of thyroid nodules was more in women than men was further supported by the study conducted by Popoveniuc and Jonklaas (Popoveniuc & Jonklaas, 2012) They observed that thyroid nodules were four times more common in women than men.

The average age of a patient in this retrospective study was 42.38 years with the standard deviation of 15.25 years. This suggests that people develop thyroid nodules generally in the middle age. According to Kelley (Kelley, 2016) prevalence of thyroid nodules rises with age. It was found in 5 % of people with average age of 60. This was observed also in the study conducted by Ali M. Al-Amri. In this study 143 patients with thyroid tumours underwent thyroidectomy and the median age of the patients was 37.5 (Al-Amri, 2012). While thyroid nodule is seen to be more common in the middle age, it is observed in people below 20 and those above 80 as well. In our study, the range in ages was from 15 to 84 years. Similar pattern in the age of the patients was observed in the malignancy group, in the study conducted by Shokouh Taghipour Zahir et al. (Taghipour Zahir, Binesh, Mirouliaei, Khajeh, & Noshad, 2013) In their study they found that patients in the malignant group were be less than 30 years or more than 60 years.

In the current study, the distribution of patients in FNA diagnosis out of 95 patients, 44 patients had malignant cell and in 16 cases showed suspicious signs of malignancy. In the retrospective study

conducted by Teixeira et al. (Teixeira et al., 2012), out of 197 patients who underwent FNA for diagnostic evaluation of a thyroid nodule, incidence of thyroid cancer was found to be in 16.2 % of patients. In the diagnostic study for efficacy and importance of fine needle aspiration cytology of thyroid nodules conducted by Murali et al. (Muratli, Erdogan, Sevim, Unal, & Akyuz, 2014), out of 1333 patients, 283 patients showed malignancy and 45 patients presented suspicious signs of malignancy. In the study to determine the utility and diagnostic accuracy of FNAC of thyroid lesions, conducted by Bagga et al (Bagga & Mahajan, 2010), it was found that out of the total 252 patients, 228 (90.5%) patients had benign lesions and 17 (6.7%) had lesions that showed suspicious signs for malignancy. In the retrospective study by Lin et al. (Novaes, Ruben, & Kramer, 1979) on thyroid cancer in the thyroid nodules evaluated by ultrasonography and fine needle aspiration cytology found that 3.9 % (858 out of 21,748 patients) of patients with thyroid nodules showed histopathologically proven malignancy.

The current study presented 79 cases (out of 95) with papillary thyroid carcinoma (PTC). In the study to analyse the epidemiological trends and cytohistological correlation of PTC and review the conflicting cases and drawbacks of FNCA, conducted by Sharma (Sharma, 2016), it was found that out 72 cases reported as papillary thyroid carcinoma (PTC) on cytology, 53 cases were diagnosed for PTC and 10 cases showed suspicious signs of PTC. Yang et al (Yang, Stern, & Messina, 2010) examined the reliability of ultrasound-guided FNAC in excluding PTC in thyroid cysts containing mural nodules. Histological follow-up reports of 11 women and 6 men who had been reported to have cystic PTC on FNA over a period of 13 years, was reviewed. This was 4.4 % of 383 cases of PTC reported 0.25 % of all thyroid FNA performed. In all of the 17 cases, histopathology presented encapsulated PTC in different stages of cystic degeneration. In the diagnostic study for ascertaining the accuracy of fine needle aspiration cytology in thyroid lesions by Sinna and Ezzat (Sinna & Ezzat, 2012) it was reported that out of 296 patients, 72.4 % of the patients, with thyroid nodules, papillary carcinoma was found to be most frequent malignant lesion.

In this study the prevalence rate was 100 %. Out of 95 patients, 88 cases were malignant and suspicious of malignancy, where as seven cases were benign on FNA cytology. In retrospective study conducted by Doshi et al Doshi et al. (2016) to ascertain the distribution pattern of lesion on the basis of age and sex and to assess the FNAC efficacy in the diagnosis of clinically apparent and palpable solitary thyroid nodule. FNAC done on the total 75 cases of thyroid nodules, 6 cases showed malignancy, 6 cases showed suspicious malignancy and 63 cases were benign. Histopathological examination found 60 cases were benign and 15 cases were malignant. In the study conducted by Sukumaran et al (Sukumaran et al., 2014) 148 patients were identified for malignancy in FNAC and in the final histopathology, all the 149 were found to be malignant lesions.

Diagnostic accuracy of the results of this study is 92.63%, with Sensitivity of 92.63% and specificity of 0%, as there were no cases of true negative or false positive. Agarwal et al (Agrawal, Saxena, & Kumar, 2015) studied the cyto-histopathological correlation in 134 patients. Sensitivity of the test was 96.7 % and the diagnostic accuracy was 97.0%. Positive predictive value of this study test was 88 %, and the negative predictive value is 0. Positive predictive value in the research by Sharma (2015) was 84.6% and it was 85.7- 98.6 in the studies conducted by Sangalli et al.(Sangalli, Serio, Zampatti, Bellotti, & Lomuscio, 2006) Sinna and Ezzat (Sinna & Ezzat, 2012). Negative predictive value in the current study was 0. In this study, false positive rate was 0 and false negative rate was 7.37%. The false negative rate ranges from 1 % to 19 % in the research conducted by Sidawy et al.(Sidawy et al., 1997) Al-Shaikh et al. (Al-Shaikh, Ngan, Daneman, & Daneman, 2001). Determining the actual frequency of false-negative results is difficult as just a small proportion of patients having diagnosed with benign cytology opt for surgical intervention.

It is hypothesised that true false-negative is less than 5 % in case all patients with thyroid FNA also present themselves for histologic examination (H Gharib & Goellner, 1993). In this study, false negative rate was 7.3 %. This is on the higher side in relation to the level in the previous research studies probably because of the same reason. Seven benign FNA cytology confirmed to be malignant on histopathology 3 cases proved to be follicular thyroid cancer and rest were PTC. Further, this is indicative of the limitation of FNAC in presenting an accurate diagnosis of cystic papillary thyroid carcinoma (PTC), papillary microcarcinoma, and follicular pattern lesions.

Conclusion

FNAC has been found to be a highly dependable and precise screening aid to distinguish malignant lesions from benign ones. Its accuracy level is estimated to be 97%. Nevertheless, clinicians should consider its shortcomings while reporting the findings. False negative diagnosis in the cases with follicular patterns is one of the major FNAC limitations. FNA cannot distinguish Carcinoma and follicular neoplasms and thus excision is a must for an accurate and definite diagnosis. As papillary microcarcinomas are small, there is a possibility of FNA missing them. It is necessary for patients with benign FNAC of thyroid to undergo close follow up with ultrasonography.

References

1. Agrawal, R., Saxena, M., & Kumar, P. (2015). A Study of Fine Needle Aspiration Cytology of Thyroid Lesions with Histopathological Correlation. Indian Journal of Pathology and Oncology, 2(4), 277–283. Retrieved from https://www.innovativepublication.com/admin/uploaded_files/IJPO_2(4)_277-283.pdf
2. Al-Amri, A. (2012). Pattern of Thyroid Cancer in the Eastern Province of Saudi Arabia: University Hospital Experience. Journal of Cancer Therapy, 3(3), 187–191. doi:10.4236/jct.2012.33027
3. Al-Shaikh, A., Ngan, B., Daneman, A., & Daneman, D. (2001). Fine-needle aspiration biopsy in the management of thyroid nodules in children and adolescents. The Journal of Pediatrics, 138(1), 140–142. doi:10.1067/mpd.2001.109609
4. Ayub, M., Sajid, M. A., & Shahid, Z. A. (2016). Diagnostic Accuracy of FNAC in cases of Thyroid Nodules while taking histopathology as Gold Standard. Pakistan Journal of Medical and Health Sciences, 10(3), 1016–1018.
5. Babu, S. B. K., Raju, R., & Radhakrishnan, S. (2010). Correlation of Fine Needle Aspiration Cytology with Histopathology in the Diagnosis of Solitary Thyroid Nodule. International Surgery Journal, 3(3), 1437–1441. doi:10.4061/2010/379051
6. Bagga, P. K., & Mahajan, N. C. (2010). Fine needle aspiration cytology of thyroid swellings: how useful and accurate is it? Indian Journal of Cancer, 47(4), 437–42. doi:10.4103/0019-509X.73564
7. Blum, M. (2015). Ultrasonography of the Thyroid. Retrieved March 14, 2017, from http://www.thyroidmanager.org/chapter/ultrasonography-of-the-thyroid/
8. Blum, M., & Goldman, A. B. (1975). Improved diagnosis of "nondelineated" thyroid nodules by oblique scintillation scanning and echography. Journal of Nuclear Medicine : Official Publication, Society of Nuclear Medicine, 16(8), 713–5. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1177047
9. Cappelli, C., Castellano, M., Pirola, I., Cumetti, D., Agosti, B., Gandossi, E., & Agabiti Rosei, E. (2007). The predictive value of ultrasound findings in the management of thyroid nodules. QJM : Monthly Journal of the Association of Physicians, 100(1), 29–35. doi:10.1093/qjmed/hcl121
10. Cooper, D. S., Doherty, G. M., Haugen, B. R., Kloos, R. T., Lee, S. L., Mandel, S. J., … Tuttle, R. M. (2009). Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid, 19(11), 1167–1214. doi:10.1089/thy.2009.0110
11. Cramer, H. (2000). Fine-needle aspiration cytology of the thyroid. Cancer, 90(6), 325–329. doi:10.1002/1097-0142(20001225)90:6<325::AID-CNCR1>3.0.CO;2-U
12. Dankle, S. K. (2016). Thyroid Nodule. Retrieved March 14, 2017, from http://emedicine.medscape.com/article/127491-overview
13. Doshi, H., Bathla, M., & Kansara., A. (2016). An Open, Retrospective Study Of Comparison Of Fine Needle Aspiration Cytology (FNAC) And Histopathology Findings In 75 Cases Of Solitary Thyroid Nodule. Natl J Integr Res Med, 7(5), 53–55. Retrieved from http://www.scopemed.org/?mno=251320
14. Feldkamp, J., Führer, D., Luster, M., Musholt, T. J., Spitzweg, C., & Schott, M. (2016). Fine Needle Aspiration in the Investigation of Thyroid Nodules: Indications, Procedures and Interpretation. Deutsches Ärzteblatt International, 113(20), 353–359. doi:10.3238/arztebl.2016.0353
15. Frates, M. C., Benson, C. B., Doubilet, P. M., Kunreuther, E., Contreras, M., Cibas, E. S., … Alexander, E. K. (2006). Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. The Journal of Clinical Endocrinology and Metabolism, 91(9), 3411–7. doi:10.1210/jc.2006-0690
16. Gharib, H., & Goellner, J. R. (1993). Fine-needle aspiration biopsy of the thyroid: an appraisal. Annals of Internal Medicine, 118(4), 282–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8420446
17. Gharib, H., Papini, E., Garber, J. R., Duick, D. S., Harrell, R. M., Hegedüs, L., … AACE/ACE/AME Task Force on Thyroid Nodules. (2016). AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS, AMERICAN COLLEGE OF ENDOCRINOLOGY, AND ASSOCIAZIONE MEDICI ENDOCRINOLOGI MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND MANAGEMENT OF THYROID NODULES--2016 UPDATE. Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, 22(5), 622–39. doi:10.4158/EP161208.GL

18. Holzheimer, R., & Mannick, J. (2001). Surgical Treatment: Evidence-Based and Problem-Oriented. Surgical Treatment: Evidence-Based and Problem-Oriented. Munich: Zuckschwerdt. doi:21028753
19. Ito, Y., Tomoda, C., Uruno, T., Takamura, Y., Miya, A., Kobayashi, K., … Miyauchi, A. (2005). Needle tract implantation of papillary thyroid carcinoma after fine-needle aspiration biopsy. World Journal of Surgery, 29(12), 1544–9. doi:10.1007/s00268-005-0086-x
20. Jayaram, G. (2006). Papillary carcinoma. Atlas and text of thyroid cytology. New Delhi: Arya publications.
21. Kelley, D. J. (2016). Evaluation of Solitary Thyroid Nodule. Retrieved April 12, 2017, from http://emedicine.medscape.com/article/850823-overview
22. Ladenson, P. W. (2008). Goiter & Thyroid Nodules. Retrieved April 12, 2017, from http://surgery.ucsf.edu/conditions--procedures/thyroid-nodules.aspx
23. Mandel, S. J. (2004). Diagnostic use of ultrasonography in patients with nodular thyroid disease. Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, 10(3), 246–52. doi:10.4158/EP.10.3.246
24. Muratli, A., Erdogan, N., Sevim, S., Unal, I., & Akyuz, S. (2014). Diagnostic efficacy and importance of fine-needle aspiration cytology of thyroid nodules. Journal of Cytology, 31(2), 73. doi:10.4103/0970-9371.138666
25. Novaes, A. B., Ruben, M. P., & Kramer, G. M. (1979). Proteins of the gingival exudate: a review and discussion of the literature. The Journal of the Western Society of Periodontology/Periodontal Abstracts, 27(1), 12–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/160533
26. Perros, P., Boelaert, K., Colley, S., Evans, C., Evans, R. M., Gerrard Ba, G., … British Thyroid Association. (2014). Guidelines for the management of thyroid cancer. Clinical Endocrinology, 81(1), 1–122. doi:10.1111/cen.12515
27. Popoveniuc, G., & Jonklaas, J. (2012). Thyroid Nodules. Medical Clinics of North America, 96(2), 329–349. doi:10.1016/j.mcna.2012.02.002
28. Prasad, C. V. (2016). Evaluation of correlation between ultrasonography and FNAC of thyroid nodules. IAIM, 3(2), 92–97.
29. Reschini, E., Ferrari, C., Castellani, M., Matheoud, R., Paracchi, A., Marotta, G., & Gerundini, P. (2006). The trapping-only nodules of the thyroid gland: prevalence study. Thyroid : Official Journal of the American Thyroid Association, 16(8), 757–62. doi:10.1089/thy.2006.16.757
30. Sangalli, G., Serio, G., Zampatti, C., Bellotti, M., & Lomuscio, G. (2006). Fine needle aspiration cytology of the thyroid: a comparison of 5469 cytological and final histological diagnoses. Cytopathology : Official Journal of the British Society for Clinical Cytology, 17(5), 245–50. doi:10.1111/j.1365-2303.2006.00335.x
31. Sclabas, G. M., Staerkel, G. A., Shapiro, S. E., Fornage, B. D., Sherman, S. I., Vassillopoulou-Sellin, R., … Evans, D. B. (2003). Fine-needle aspiration of the thyroid and correlation with histopathology in a contemporary series of 240 patients. The American Journal of Surgery, 186(6), 702–710. doi:10.1016/j.amjsurg.2003.08.015
32. Shambaugh, G. E., Quinn, J. L., Oyasu, R., & Freinkel, N. (1974). Disparate thyroid imaging. Combined studies with sodium pertechnetate Tc 99m and radioactive iodine. JAMA, 228(7), 866–869. doi:4406304
33. Sharma, C. (2015). Diagnostic accuracy of fine needle aspiration cytology of thyroid and evaluation of discordant cases. Journal of the Egyptian National Cancer Institute, 27(3), 147–153. doi:10.1016/j.jnci.2015.06.001
34. Sharma, C. (2016). An analysis of trends of incidence and cytohistological correlation of papillary carcinoma of the thyroid gland with evaluation of discordant cases. Journal of Cytology, 33(4), 192. doi:10.4103/0970-9371.190455
35. Sidawy, M. K., Del Vecchio, D. M., & Knoll, S. M. (1997). Fine-needle aspiration of thyroid nodules: correlation between cytology and histology and evaluation of discrepant cases. Cancer, 81(4), 253–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9292740
36. Sinna, E. A., & Ezzat, N. (2012). Diagnostic accuracy of fine needle aspiration cytology in thyroid lesions. Journal of the Egyptian National Cancer Institute, 24(2), 63–70. doi:10.1016/j.jnci.2012.01.001
37. Sukumaran, R., Kattoor, J., Pillai, K. R., Ramadas, P. T., Nayak, N., Somanathan, T., … Sebastian, P. (2014). Fine Needle Aspiration Cytology of Thyroid Lesions and its Correlation with Histopathology in a Series of 248 Patients. Indian Journal of Surgical Oncology, 5(3), 237–241. doi:10.1007/s13193-014-0348-x
38. Taghipour Zahir, S., Binesh, F., Mirouliaei, M., Khajeh, E., & Noshad, S. (2013). Malignancy Risk Assessment in Patients with Thyroid Nodules Using Classification and Regression Trees. Journal of Thyroid Research, 2013, 1–9. doi:10.1155/2013/983953
39. Tamhane, S., & Gharib, H. (2016). Thyroid nodule update on diagnosis and management. Clinical Diabetes and Endocrinology, 2(1), 17. doi:10.1186/s40842-016-0035-7
40. Tedla, K. (2016). The Rise Of Thyroid Cancer By Overdiagnosis. Retrieved March 14, 2017, from http://acsh.org/news/2016/09/02/rise-thyroid-cancer-overdiagnosis-9971
41. Teixeira, G. V, Chikota, H., Teixeira, T., Manfro, G., Pai, S. I., & Tufano, R. P. (2012). Incidence of malignancy in thyroid nodules determined to be follicular lesions of undetermined significance on fine-needle aspiration. World Journal of Surgery, 36(1), 69–74. doi:10.1007/s00268-011-1336-8
42. Tseng, C.-E., Wei, C.-K., Kuo, C.-S., Yan, S.-T., Chen, P.-F., Lien, W.-C., … Tseng, Y.-H. (2008). Fine Needle Aspiration Cytology of Thyroid Nodules: Evaluation of Diagnostic Accuracy. Tzu Chi Medical Journal, 20(4), 296–303. doi:10.1016/S1016-3190(08)60054-3
43. Vanderpump, M. P. J. (2011). The epidemiology of thyroid disease. British Medical Bulletin, 99(1), 39–51. doi:10.1093/bmb/ldr030
44. Wiltshire, J. J., Drake, T. M., Uttley, L., & Balasubramanian, S. P. (2016). Systematic Review of Trends in the Incidence Rates of Thyroid Cancer. Thyroid, 26(11), 1541–1552. doi:10.1089/thy.2016.0100
45. Yang, G. C. H., Stern, C. M., & Messina, A. V. (2010). Cystic papillary thyroid carcinoma in fine needle aspiration may represent a subset of the encapsulated variant in WHO classification. Diagnostic Cytopathology, 38(10), 721–6. doi:10.1002/dc.21282