

Age Related Cytoarchitectural Comparison of Histopathological Changes in Thyroid Nodule

Tanweer Fatima, Sanum Ali, Ghansham Rawtani, Surrendar Dawani, Sehrish Hussain, Sarah Zahid, Aillah Baluch, Shahid Rasul

ABSTRACT

Objective: To compare age related histomorphological changes through cytology (Bethesda category) and histopathology in thyroid nodules.

Study design and setting: This cross sectional study was conducted at the Department of Anatomy, BMSI, JPMC Karachi from 31-March-2021 to 31-August-2021.

Methodology: Total n=120 patients of all ages, genders and ethnicities that underwent surgery for thyroid nodules were included after taking duly signed consent. On the basis of cytological reports (FNAC) patients were grouped according to age and gender. Processed paraffin blocks were sectioned at a thickness of 5µm and then were stained with Haematoxylin and Eosin (H&E) for histological evaluation. Masson trichrome stain was used to observe fibrosis, that was measured through Image J Fiji software.

Results: We evaluated that out of 120 patients, male to female ratio was 1:5.67. Among various ethnic groups; Urdu speaking (40.8%) with mean age of 40.3% were commonly affected. Histopathological examination revealed that most common benign lesion was colloid nodular hyperplasia and papillary carcinoma was the most common malignant lesion. Highest percentage of fibrosis (36%) was seen in middle aged participants (p=0.045). Basement membrane thickness with lowest percentage (12%) was observed in younger age participants while highest (31%) was measured in older aged participants (p=0.001). Accuracy score of FNAC showed sensitivity 59%, specificity 96.6%, accuracy 86%, positive predictive value (PPV) 86% and negative predictive value (NPV) 87%.

Conclusion: With progression in age thyroid gland undergo histomorphological changes, early diagnosis will help in categorical nomenclature and its implications for subsequent management of patients with thyroid lesions.

Key words: Bethesda category, Cytoarchitecture, Thyroid gland, Thyroid lesion, Thyroid nodule.

How to cite this Article:

Fatima T, Ali S, Rawtani G, Dawani S, Hussain S, Zahid S, Baluch A, Rasul S. Age Related Cytoarchitectural Comparison of Histopathological Changes in Thyroid Nodule. J Bahria Uni Med Dental Coll. 2023;13(2):135-9 DOI: <https://doi.org/10.51985/JBUMDC2022107>

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non commercial use, distribution and reproduction in any medium, provided the original work is properly cited.

Tanweer Fatima (*Corresponding Author*)
M.Phil. Anatomy Scholar, Department of Anatomy
Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate
Medical Centre (JPMC)
Email: dr.tanweerfatima@gmail.com

Sanum Ali
Assistant Professor, Department of Anatomy
Basic Medical Sciences Institute (BMSI),
Jinnah Postgraduate Medical Centre (JPMC)
Email: drdahri@gmail.com

Ghansham Rawtani
Assistant Professor, Department of Surgery
Jinnah Postgraduate Medical Centre (JPMC)
Email: drsham84@hotmail.com

Surrendar Dawani
Assistant Professor, Department of Surgery
Jinnah Postgraduate Medical Centre (JPMC)
Email: Surru82@hotmail.com

Sehrish Hussain
M.Phil. Anatomy Scholar, Department of Anatomy
Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate
Medical Centre (JPMC)
Email: drsehrishhussain@gmail.com

Sarah Zahid
M.Phil. Anatomy Scholar, Department of Anatomy
Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate
Medical Centre (JPMC)
Email: drsarahzahid@gmail.com

Aillah Baluch
Research Associate, Department of Anatomy
Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate
Medical Centre (JPMC)
Email: aillah357@yahoo.com

Shahid Rasul
Professor of Surgery, Department of Surgery
Jinnah Postgraduate Medical Centre (JPMC)
Email: drrasul@gmail.com

Received: 17-07-2022
Accepted: 07-03-2023

INTRODUCTION:

Thyroid nodules are one of the frequently presented endocrine disorders with prevalence range of 4% to 10%.¹ It remains a challenging task for clinicians to reach a clear diagnosis regarding the nature of the nodule and thereby, advocating precise and passable management. Various studies showed that 8% of population has palpable masses, most of them are benign and less than 5% are malicious.² Thyroid is a butterfly shaped bilobular gland joined by isthmus at center. It is situated in the neck anterior and inferior to the larynx at the level of C5-T1 vertebrae, surrounded by a thin capsule and pre-tracheal layer of deep fascia.³ Microscopically, the

gland consists of thyroid follicles that are lined by follicular cells secreting thyroid hormone and parafollicular cells are interspersed between them producing calcitonin. Lymph from thyroid gland drains into pre-tracheal, para-tracheal, pre-laryngeal, retro-esophageal and retropharyngeal lymph nodes.⁴ With increase in age the thyroid gland undergoes cytoarchitectural as well as functional characteristic changes. These variations vary from mild atrophy, decrease in weight, increase in basement membrane thickness and fibrosis to decreased peripheral formation of thyroid hormones.⁵

In Pakistan, due to different geographical distribution of population, the prevalence of thyroid nodule is quite common, increasing overall economic burden on the healthcare system.² With the introduction of iodine, prevalence of detectable goiter has been dropped in endemic areas of Pakistan¹. Many clinicians and researchers have categorized thyroid nodules as benign and malignant through various clinical, biochemical and imaging techniques, however, minimally invasive fine-needle aspiration cytology (FNAC) is usually used for pre-operative analysis.⁶ Yet FNAC is not without limitations; its accuracy is low in doubtful cytology and in specimen adequacy. About 20% of nodules with indeterminate cytological findings are found malignant, when excised surgically, therefore, histopathological assessment of surgically excised nodules has an utmost importance as it is gold standard method for diagnosis.⁷ Studies have shown that FNAC yields both false positive and false negative results. In order to make definite diagnosis of thyroid nodule that whether it is benign or malignant by comparing it with findings of the excisional biopsy.⁸

In our region most of the studies have focused on malignant thyroid lesions.⁹ In our work we tried to include both, benign and malignant thyroid nodules belonging to different age groups and genders to figure out prevalence of thyroid masses in our population. Previous studies have reported differences in incidence of thyroid nodules in relation to age and gender. Age has been said to have a crucial effect on patient's response to treatment. This study is proposed to compare histological differences in thyroid nodule based on FNAC and excisional biopsy in young and old subjects. Knowledge of age-related cytoarchitectural changes will help in categorical nomenclature and its implication on treatment and subsequent management of patients with thyroid lesions.

METHODOLOGY:

This cross sectional study was conducted at the Department of Anatomy in collaboration with Department of Histopathology, Basic Medical Sciences Institute (BMSI) and Surgical Units Jinnah Postgraduate Medical Centre (JPMC), Karachi, from 31-March-2021 to 31-August-2021 after getting ethical approval from Institutional Review Board (IRB) of JPMC (NO. F.2-81/2022-GENL/199/JPMC). During the study period of five months, 120 patients of all

ages, genders and ethnicities undergoing surgery for thyroid nodule were recruited after taking their consent on a duly signed consent form. Demographic and clinical data was also recorded. Patients with history of previous thyroid surgery for thyroid lesions were excluded from the study to avoid bias due to post-surgery structural changes.¹⁰

Sample size was calculated through OpenEpi, based on a prevalence rate of 8% mentioned by a recent study that studied incidence of thyroid lesions among different Asian ethnic populations, with confidence interval of 95%.¹¹ Non probability convenience sampling was used for the study.

On the basis of FNAC findings patients were stratified into different age groups and genders. Thyroidectomy specimen of same patients were collected and fixed in 10% formalin for 24 hours. After gross morphological examination specimens were dissected in midsagittal plane and three specimens from each thyroid gland were collected dehydrated, cleared and embedded in paraffin. The processed blocks sectioned at a thickness of 5µm were stained with Haematoxylin and Eosin (H&E) and masson trichrome stain for histological examination (basement membrane thickness and fibrosis respectively). These parameters were measured using image J Fiji software. Three slides per specimen and three areas per slide were studied thoroughly under light microscope (Nikon Eclipse 50i; Japan) connected to video link digitalizing board system (DS Camera control unit- DS-L2). Results were obtained by comparing microscopic features in different age groups of FNAC findings based on Bethesda scoring with histopathological outcomes of Thyroid lesions. Statistical analysis was carried out through SPSS version 21 by applying chi square test. A p value of < 0.05 was considered statistically significant.

RESULTS:

Total one hundred and twenty (120) patients with thyroid nodules were enrolled during study period out of them most of patients (30%) were age ranged between 31 to 40 years. There were 15% males and 85% females representing male to female ratio 1: 5.67. In our study we found 40.83% patients were from Urdu speaking ethnicity. Neck swelling was the major presenting complaint as 85.83% patients were admitted with swelling; most commonly right side of lobe was affected (35.8%). Lobectomy was done in 70% of patients and 63.3% swelling had firm consistency (Table 1).

According to patient's FNAC reports there were 74.17% benign Bethesda category ? patients. Bethesda category ? includes 4.17% patients and 8.3% belonged to category ?. Bethesda category ? had 5.8% patients and 7.5% were included in malignant category ?. On histopathology of surgically removed thyroid gland we found 81.6 % were benign and 18.4% were malignant lesions (Table 2). It was observed that on FNAC out 74.17% benign lesions, there were 36% true positive colloid nodular hyperplasia, 31% were true positive benign lesion with cystic change lesions,

while 4.2% were false negative for follicular adenoma and 3.33%) were false negative for papillary carcinoma. Out of 10% follicular neoplasm there was 4.2% true positive follicular adenoma while 2.5% Colloid nodular hyperplasia and 3.33% were false negative for follicular carcinoma. The percentage of fibrosis was compared between age groups, lowest percentage of fibrosis (19%) was observed in age group ranged between 41 to 50 years and highest (36%) was seen in age group ranged between 31 to 40 years (p=0.045). out of 98 benign lesions, basement membrane with lowest percentage of thickness (12%) was perceived in age group ranged between 20 to 30 years while highest (31%) was measured in age group ranged between 51 to 60 years (p=0.001) (Table 3). Statistical analysis of thyroid nodules showed sensitivity 59%, specificity 97%, accuracy 86% positive predictive value (PPV) 86% and negative predictive value (NPV) 87%.

DISCUSSION

Thyroid gland is the most important endocrine gland of the body that controls metabolism, serum calcium levels, development and growth in mammals. Thyroid nodules are commonly presented lesions in outpatient departments; palpable lumps are observed in 4-7% of individuals and have chances to remain undetected in about 10 percent of subjects.¹² FNAC is performed to decrease the unnecessary load of surgical interventions for benign thyroid lesions.

In present study, the thyroid lesions were categorized according to Bethesda system and histopathological evaluation was performed to determine the diagnostic accuracy of FNAC with age related histomorphological changes. We found that females are most commonly affected by thyroid nodules with male to female ratio of 1:5.67, which is also reported by various other studies¹³ this could be due to fluctuations in female hormones; like estrogen, that predispose females to develop thyroid diseases.¹⁴

It is believed that with increase in age, accumulated free oxidative radicals can damage thyroid cells and predispose to thyroid diseases, our results showed that most prevalent age group was from years 31-40, followed by 20-30, these findings were in accord to many other studies.¹⁵ In terms of ethnicity majority of participants were from Urdu speaking ethnic population, similar results were observed in Pakistani study, this might be due to fact that the Urdu speaking residents being pioneers of Karachi constitutes main bulk of Urban population.¹⁶ However, another local study found equal incidence of thyroid lesions in various ethnicities.¹⁷ Majority of patient's complaint (85.8%) was neck swelling which is comparable to study done by Rout and coworkers.¹⁸ According to Kumar and associates the consistency is subject dependent, but it doesn't exclude the presence of malignancy, in our study we found majority of nodules had firm consistency which is in accordance with above study.¹⁰ In Rawalpindi a 20 years retrospective study done by Mehmood

Table 1: Clinicopathological characteristics of Patients

Characteristics	Number of patients (n=120)	Percentage (%)
Gender		
Male	18	15
Female	102	85
Age		
20-30	34	28.33
31-40	36	30
41-50	19	15.83
51-60	31	25.83
Ethnicity		
Sindhi	30	25
Pathan	10	8.33
Balochi	2	1.67
Urdu	49	40.83
Punjabi	26	21.67
Bengali	4	3.33
Presenting complain		
Neck Swelling	103	85.83
Neck discomfort	17	14.17
Side		
Left	41	34.17
Bilateral	36	30
Right	43	35.83
Type of surgery		
Lobectomy	84	70
Total thyroidectomy	36	30
Consistency		
Soft	35	29.17
Firm	76	63.33
Hard	9	7.5

and colleagues,¹⁹ showed that rate of total thyroidectomy was 27.37% and lobectomy was performed for 5.04% of all thyroid surgeries, whereas in our study lobectomy was done in 70% of thyroid nodules and total thyroidectomy was done in 30% of nodules these results are relatable to a five years study on thyroid malignancies done by Razzak *et al.*²⁰

In our study FNAC showed 39.17% Colloid nodular hyperplasia and 35% were benign lesion with cystic changes, similar findings were also found by Gupta *et al.*,²¹ but histopathology confirms that 4.17% cases of follicular adenoma and 3.33% cases of papillary carcinoma were misdiagnosed as benign by FNAC. Out of 10% follicular neoplasms diagnosed by FNAC, biopsy confirmed that there were only 4.2% follicular adenoma, 2.5% Colloid nodular hyperplasia and 3.33% were follicular carcinomas. There were 5.8% cases of suspicious for malignancy on FNAC but on histopathology 5% patients had papillary carcinoma and 1% found to have medullary carcinoma, such drawbacks

Table 2: Comparison of Bethesda categories with histopathology of Thyroid Nodules

Bethesda Category N=no (%)	FNAC	No. of Patients (%)	Histopathology	No. of patients (%)
Non- diagnostic/ inadequate (I)	-----	-----	-----	-----
Benign (II) 89 (74.17%)	Colloid nodular hyperplasia	47 (39.17%)	Colloid nodular hyperplasia	43 (36%)
			Benign lesion with cystic changes	37 (31%)
	Benign lesion with cystic changes	42 (35%)	Follicular Adenoma	5 (4.2%)
			Papillary Ca	4 (3.33%)
Atypia/ follicular lesion of Undetermined significance (III) 5 (4.17%)	Atypia of undetermined significance	5 (4.17%)	Benign nodular hyperplasia	5(4.1%)
Follicular neoplasm / suspicious for FN (IV) 12 (10%)	Follicular neoplasm	12 (10%)	Follicular Adenoma	5(4.1%)
			Colloid nodular hyperplasia	3(2.5%)
			Follicular Ca	4 (3.33)
Suspicious for malignancy (V) 7 (5.83%)	Suspicious of malignancy	7 (5.83%)	Papillary Ca	6 (5%)
			Medullary Ca	1 (1%)
Malignant (VI) 7 (5.8%)	Papillary Ca	7 (5.8%)	Papillary Ca	7 (5.83%)

Table 3: Histopathological variables

Variables	Age Distribution (years)				p-value
	20-30	31-40	41-50	51-60	
Fibrosis (%) n= 120	34	36	19	31	0.045
B/M thickness (%) n=98	12	29	26	31	0.001

of FNAC were also observed in earlier studie.²²

With the increase in age thyroid gland also undergo structural and functional changes, on microscopy increased basement membrane thickness and fibrosis was observed with increase in age by previous studies²³ that also effect the treatment of patients, such studies are in covenant to our study results. Literature review of FNAC findings showed that the study conducted by Agrawal and colleagues found sensitivity 88.8%, specificity 100%, PPV 100% and NPV 95.12%²⁴ while Jesrani *et al*, in their elastographic study of benign and malignant thyroid nodules perceived, sensitivity 100%, specificity 80.2%, PPV 61.7%, NPV 100% and accuracy 85%.²⁵ These results are in favour of our study findings for FNAC of thyroid nodules except for the sensitivity which is at a little lower side in our observations.

The main limitation is that it was single centered study conducted on small group of population so results could not be generalized in relation to ethnicity. It is recommended that in future study should be done on different demographic

zones involving large scale of population.

CONCLUSION

The current study determines that, age related histomorphological assessment of thyroid nodules in relation to fibrosis and basement membrane thickness might be helpful for clinicians to classify and modulate the treatment plans for patients of different age group with suspected thyroid lesions.

Authors Contribution:

Tanweer Fatima: Conception & design, interpretation of data and analysis

Sanum Ali: Literature search, manuscript drafting, data analysis and interpretation and critical review

Ghansham: Surgical expertise and relevance in write up

Surrendar Dawani: Surgical expertise and relevance in write up

Sehrish Hussain: Data analysis and interpretation, follow-up of patients

Sarah Zahid: Literature review, data acquisition, follow-up of patients

Aillah Baluch: Data analysis and computational graphics

Shahid Rasul: Surgical relevance in write up and critical review

REFERENCES:

- Arul P, Masilamani S. A correlative study of solitary thyroid nodules using the Bethesda system for reporting thyroid cytopathology. *J Can Res Ther.* 2015; 11(3): 617-622. DOI: <https://doi.org/10.4103/0973-1482.157302>
- Uyar O, Cetin B, Aksel B, Dogan L, Beksac K, Akgul GG, et al. Malignancy in solitary thyroid nodules: evaluation of risk factors. *Oncol Res Treat.* 2017;40 (6):360-363. DOI: <https://doi.org/10.1159/000464409>

3. Dhingra PL. Diseases of Ear, Nose and Throat & Head and Neck surgery: Thyroid gland and its disorders: 6th Ed, Elsevier; 2014. p. 326.
4. Standring S, editor. Gray's Anatomy: the anatomical basis of clinical practice: Head and neck: 41st Ed, Elsevier; 2016. p. 470-471.
5. Abdullah SI, Al-Samarrae AJ, Mahood AK. The Effect of Aging on Human Thyroid Gland:(Anatomical and Histological Study). Iraqi J Comm Med. 2010; 23(3), 158-164.
6. Zhu Y, Song Y, Xu G, Fan Z, Ren W. Causes of misdiagnoses by thyroid fine-needle aspiration cytology (FNAC): our experience and a systematic review. Diagn Pathol. 2020;15(1): 1-8. DOI: <https://doi.org/10.1186/s13000-019-0924-z>
7. Jayaram J, Sandhya J, Garimella R, Ashfaq B. A clinical study of solitary nodule of thyroid. Indian J Appl Res. 2019; 9(12): 34-36. DOI: <https://doi.org/10.36106/ijar>
8. Karim MI, Nachev R, Fuklev N, Nargis N. A study on evaluation of solitary nodular thyroid lesions by FNAC and its histopathological correlation. BJMS. 2019; 30;18(4): 789-795. DOI: <https://doi.org/10.3329/bjms.v18i4.42906>
9. Jabeen S, Fatima S, Sheikh A, Islam N. Non Invasive Follicular Thyroid Neoplasm with Papillary like nuclear features (NIFTP), A time for change in Pakistan. Pak J Med Sci. 2020;36 (2):151-155. DOI: <https://doi.org/10.12669/pjms.36.2.1123>
10. Kumar RS. Evaluation and Management of Solitary Thyroid Nodules. J Cont Med A Dent. 2021; 9(2): 4-7
11. Lee AW, Mendoza RA, Aman S, Hsu R, Liu L. Thyroid cancer incidence disparities among ethnic Asian American populations, 1990–2014. Ann Epidemiol. 2022; 66: 28-36. DOI: <https://doi.org/10.1016/j.annepidem.2021.11.002>
12. Beynon ME, Pinneri K. An overview of the thyroid gland and thyroid-related deaths for the forensic pathologist. Acad Forensic Pathol. 2016; 6(2):217-236. DOI: <https://doi.org/10.23907/2016.024>
13. Mishra S, Sathe NU, Chavan K, Misal P. A Prospective Comparative Study Of Fine Needle Aspiration Cytology And Histopathology In Thyroid Disorders. Br J Bio Med Res. 2019; 03(05): 1121-1145. DOI: <https://doi.org/10.24942/bjbr.2019.581>
14. Khan F, Hilal K, Ali I, Samad M, Tariq R, Ahmad W, et al. Hospital-based ultra-sonographic prevalence and spectrum of thyroid incidentalomas in Pakistani population. Cureus. 2021; 13(8): e17087. DOI: <https://doi.org/10.7759/cureus.17087>
15. Xu L, Zeng F, Wang Y, Bai Y, Shan X, Kong L. Prevalence and associated metabolic factors for thyroid nodules: a cross-sectional study in Southwest of China with more than 120 thousand populations. BMC Endocr Disord. 2021; 21(1): 1-11. DOI: <https://doi.org/10.1186/s12902-021-00842-2>
16. Kamran M, Raza I, Mohiuddin M, Adnan N, Shaheen S, Rehan R. Quantitative assessment of thyroid gland volume among the ethnic groups of Karachi population. PJMD. 2019;8(1): 44-48. DOI: <http://ojs.zu.edu.pk/ojs/index.php/pjmd/article/view/123>
17. Kamran M, Hassan N, Ali M, Ahmad F, Shahzad S, Zehra N. Frequency of thyroid incidentalomas in Karachi population. Pak J Med Sci. 2014; 30(4): 793-797. DOI: <https://doi.org/10.12669/pjms.304.4808>
18. Rout K, Ray CS, Behera SK, Biswal R. A comparative study of FNAC and histopathology of thyroid swellings. Indian J Otolaryngol Head Neck Surg. 2011; 63(4):370-372. DOI: <https://doi.org/10.1007/s12070-011-0280-0>
19. Mehmood NM, Bhatti LA, Anwar MI, Chaudhry MA, Ahmed MI, Nadir M, et al. Comparing the Outcomes of Thyroid Surgical Procedures for Benign Diseases with Expertise of the Surgeon in a Tertiary Care Hospital in Rawalpindi, Pakistan. J Islamabad Med Dent Colleg. 2021;10(2): 68-75. DOI: <https://doi.org/10.35787/jimdc.v10i2.697>
20. Razzak SA, Baloch MN, Mehmood Z, Shafiqatullah S, Shahid H, Khalid F. Thyroid malignancy: 5 years' experience. J Surg Pakistan. 2019; 24(4): 186-190. Doi: <https://doi.org/10.21699/jsp.24.4.6>
21. Gupta M, Gupta S, Gupta VB. Correlation of fine needle aspiration cytology with histopathology in the diagnosis of solitary thyroid nodule. J Thyroid Res. 2010; 2010: 1-5. DOI: <https://doi.org/10.4061/2010/379051>
22. Attia R, Kotb F, Rabie OM. Role of fine-needle aspiration cytology in the diagnosis of thyroid diseases. The Egyptian Journal of Surgery. 2019; 38(3):439-450. DOI: https://doi.org/10.4103/ejs.ejs_32_19
23. Abdullah SI, Al-Samarrae AJ, Mahood AK. The Effect of Aging on Human Thyroid Gland:(Anatomical and Histological Study). Iraqi J Comm Med. 2010;23(3):158-164.
24. Agrawal D, Bhake AS, Rastogi N, Laishram S, Wankhade A, Agarwal A. Role of Bethesda system for reporting thyroid lesion and its correlation with histopathological diagnosis. J Datta Meghe Inst Med Sci Univ. 2019; 14(2): 74-81. Doi: https://doi.org/10.4103/jdmimsu.jdmimsu_76_18
25. Jesrani A, Hameed M, Ahmed N, Devi P, Baseer A. Diagnostic Accuracy of Elastography in Differentiating Benign from Malignant Thyroid Nodules Taking Fine Needle Aspiration Cytology as Gold Standard. J Bahria Uni Med Dental Coll. 2021; 11(2): 70-75. DOI: <https://doi.org/10.51985/OLBL1894>