

## Characteristics of follicular adenoma patients at H. Adam Malik General Hospital, Medan, during the 2017-2020 period



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### ABSTRACT

**Background:** Follicular adenoma is a benign tumor enclosed by a capsule with follicular differentiation, more common in women and usually occurs in adulthood, and is more common in iodine deficiency. The average tumor size is 1-3 cm. Follicular neoplasms do not have features of papillary thyroid carcinoma and no capsule and/or vascular invasion were found. This study aims to evaluate the characteristics of follicular adenoma patients at H. Adam Malik General Hospital, Medan, during the 2017-2020 period.

**Methods:** This study is a descriptive study with a cross-sectional approach on 31 samples based on medical record data diagnosed as follicular adenoma. After reviewing the slides, 23 samples were obtained that met the inclusion and exclusion criteria. Samples were assessed according to age, sex, tumor size, number of nodules, growth patterns, and histopathological variants. Data were analyzed using SPSS version 26 for Windows.

**Results:** Cases of follicular adenoma at H. Adam Malik Hospital Medan during 2017-2020 with an average age of 46.7 years. The youngest age was 20 years and the oldest age was 71 years, with the highest age group being 50-59 years (26.1%). Most gender was female (87.0%) than male (13.0%). The most common tumor size was above 4 cm (69.6%). The highest number of nodules was found in 1 nodule (solitary or unilateral) (52.2%). The most common growth pattern in microscopic preparations was macrofollicular adenoma (65.2%), with the most histopathological variant being conventional follicular (91.3%).

**Conclusion:** Benign lesions such as adenomas are often misdiagnosed due to the lack of further studies on the histopathological criteria. Follicular adenomas can be treated with lobectomy and have a good prognosis if diagnosed early and with proper treatment.

**Keywords:** Follicular Adenoma, Benign Nodule, Thyroid.

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### INTRODUCTION

Thyroid follicular neoplasms are solitary nodules that appear as masses, benign or malignant.<sup>1</sup> Patients with solitary nodules on thyroid imaging examination produce cold nodules have a 20% chance of thyroid carcinoma, whereas, in multinodular lesions, the probability of thyroid carcinoma is 1%.<sup>1</sup> Thyroid nodules are enlargements of the thyroid gland, which can be inflammation, hyperplasia, or neoplasm, which is sometimes difficult to distinguish clinically. It is often found that the thyroid is enlarged and does not give significant complaints. It is rarely treated immediately and is found during physical examination, namely when palpation in the neck area and during Ultrasonography (USG) examination of the neck.<sup>2</sup> Approximately 5-10% of thyroid nodules are neoplasms, whether benign

or malignant, where this situation also depends on the age of the patient and the size of the thyroid nodule.<sup>2,3</sup>

A follicular adenoma is a benign tumor enclosed by a capsule with follicular differentiation, is more common in women and usually occurs in adulthood, and is more common in areas of iodine deficiency. The size of the follicular adenoma averages 1-3 cm and is generally smaller than follicular carcinoma, although in some studies, the tumor size is still overlapping. Follicular neoplasms do not have the cytologic features of papillary thyroid carcinoma (PTC).<sup>3,4</sup> Malignancy in follicular neoplasms should suggest capsular or vascular invasion. The capsule in follicular carcinoma is often thicker and more irregular than in follicular adenoma. Various histologic patterns, including microfollicular, macrofollicular,

normofollicular, and trabecular growths, can be seen in follicular neoplasms. Areas of papillary architecture may also be visible. Follicular neoplasms may have different cytomorphology, including mucinous, signet-ring cells, and clear cells, and may also feature intratumoral fat.<sup>3-6</sup>

Follicular adenomas showed increased expression of p27 protein for cell cycle inhibitors and decreased proliferative index Ki67 compared to follicular carcinomas, and carcinomas with metastases had higher Ki67 indexes than non-metastatic ones. However, in some lesions, immunohistochemical or other molecular markers cannot separate benign follicular neoplasms from malignant follicular neoplasms. Cytological specimens also cannot distinguish benign from malignant neoplasms because the diagnosis of malignancy requires invasive

growth.<sup>7</sup> Adenomas are classified based on the degree of follicular formation and the colloid content of the follicle. Follicular epithelial cells are the origin of the majority of thyroid cancers. Thyroid nodules (adenoma), thyroid enlargement (colloid goiter), and inflammation of the thyroid (thyroiditis) are the most important risk factors for thyroid cancer. One in five cases of thyroid cancer (20%) has a history of a non-cancerous thyroid. A history of existing adenomas, especially at a young age, is a risk factor leading to cancer. The need for early detection, diagnosis, and appropriate treatment and follow-up of non-cancerous lesions of the thyroid. Follicular adenomas can be treated with lobectomy and have an excellent prognosis if diagnosed early and with proper management.<sup>4,7-9</sup>

Misdiagnosis is common with thyroid nodular lesions. Benign lesions such as hyperplastic nodules and adenomas are also often misdiagnosed due to the lack of further studies on the histopathological criteria of both. Without biomolecular examination, it is also said that it will be difficult to distinguish hyperplastic nodules and adenomas. Several studies have also investigated the expression of several immunohistochemical markers to differentiate benign neoplasms (follicular adenoma) and malignant neoplasms (follicular thyroid carcinoma).<sup>6,10</sup> There are many misdiagnoses of these two neoplasms. It was found that cases of malignant neoplasms were higher than benign neoplasms. Based on the literature, the proportion of cases of follicular adenoma is 1%-10% and follicular thyroid carcinoma (FTC) is 5%-15%.<sup>6,10</sup>

## METHODS

In this study, based on medical record data recorded in 2017-2020 for cases of follicular adenoma patients diagnosed histopathologically with Hematoxylin-Eosin (HE) staining at H. Adam Malik Hospital, Medan, 31 cases were found with total sampling technique. Of the 31 cases obtained in the medical record data, 23 cases were included in the inclusion criteria after being re-evaluated by researchers and supervisors. This study was a descriptive cross-sectional study in which each sample in this study

was observed once and only at one time. This study displays the characteristics of the sample in the form of age, gender, tumor size, number of nodules, growth pattern, and histopathological variants. The sample used is a sample that had the inclusion and exclusion criteria. Inclusion criteria were medical records of patients with follicular adenoma diagnosed histopathologically at the Anatomic Pathology unit of H. Adam Malik General Hospital Medan, which has data on age, sex, tumor size, and the number of nodules. In contrast, the exclusion criteria in this study were patients with follicular adenoma who did not have data on age, sex, tumor size and the number of nodules as well as damaged or unrepresentative slides for re-evaluation.

The data obtained in this study will be processed using a computer with SPSS analysis software version 26. The results of data analysis are then distributed descriptively using a frequency distribution table. The limitation of this study is that not all samples on macroscopic and microscopic examination explain whether an intact capsule is found or not.

## RESULTS

Of the 23 cases of follicular adenoma in 2017-2020 diagnosed histopathologically at H. Adam Malik Hospital Medan, an assessment of the variables of age, sex, tumor size, number of nodules, growth patterns, and histopathological variants was carried out. The assessment results are presented in the form of a table as follows. (Table 1)

Based on the age distribution in this study, most cases were found in the 50-59 years age group with a total of 6 cases (26.1%) with a mean age of 47.57 years, where the youngest age was 20 years and the oldest was 71 years (Table 1). The second most common age group was found at the age of 40-49 years with 5 cases (21.7%), followed by the age group 20-29 years and 60-69 years with the same number of cases, namely 4 cases (17.4%), and age group 30-39 years as many as 3 cases (13.1%) and the least found in the age group above is the same as 70 years, namely 1 case (4.3%). According to gender data, it was found that the incidence of cases was higher in women than men. The

number of cases in females was 20 cases (86.9%), while in the male, there were 3 cases (13.0%) (Table 1).

Based on data obtained in medical records regarding tumor size, the largest tumor size was found above 4 cm, with a total of 16 cases (69.6%). For tumors measuring 2-4 cm, data were obtained for 7 cases (30.4%), while tumor sizes below 2 cm were not found. Based on the number of nodules, it was found that there was a slight difference between the number of solitary and multiple nodules, where the number of solitary or unilateral nodules, which amounted to 1, was found in 12 cases (52.2%). In comparison, cases with multiple or bilateral nodules were obtained as many as 11 cases (47.8%) (Table 1).

On histopathological examination of 23 cases of follicular adenoma, by looking at the growth pattern found the most in each case, the highest growth pattern was macrofollicular in 15 cases (65.2%), followed by normofollicular in 5 cases (21.7%) and microfollicular as many as 3 cases (13.0%), while the pattern of trabecular and solid growth was not found as the most common growth pattern in each case (Table 1 and Figure 1). The most histopathological variants in follicular adenoma cases were conventional follicular adenoma with a total of 21 cases (91.3%), then found 1 case each (4.3%) with signet-ring cell follicular adenoma and clear variants. follicular cell adenoma. Other variants were not found in this study.

## DISCUSSION

Based on the age distribution in this study, most cases were found in the 50-59 years age group with a total of 6 cases (26.1%) with a mean age of 47.6 years, where the youngest age was 20 years and the oldest was 71 years. According to WHO Endocrine Organs 2017, the incidence of follicular cases of adenomas can occur at any age but are more common in adults with a percentage of 3-5%, or the fifth or sixth decade of life.<sup>4</sup> Based on research by Anggraini T et al., in the case of thyroid nodules, the most follicular adenoma patients were found in the age range of 36-45 years as many as 2 cases, while those over 65 years old were found in 1 case.<sup>11</sup> Some found that the prevalence of thyroid

nodules was highest in the age range of 40-49 years, with a percentage of 31.9% cases with an average age of 45 years.<sup>12</sup> The percentage of follicular adenoma cases is more common in patients with iodine deficiency and radiation exposure. These neoplasms can develop 10-15 years after exposure, increasing the risk of surviving >50 years. This is due to a person's resistance and immunity, which decreases with age and increases in iodine.<sup>4,13</sup>

Based on gender data, it was found that the incidence in females was higher than the male with a ratio of 20 cases (87.0%)

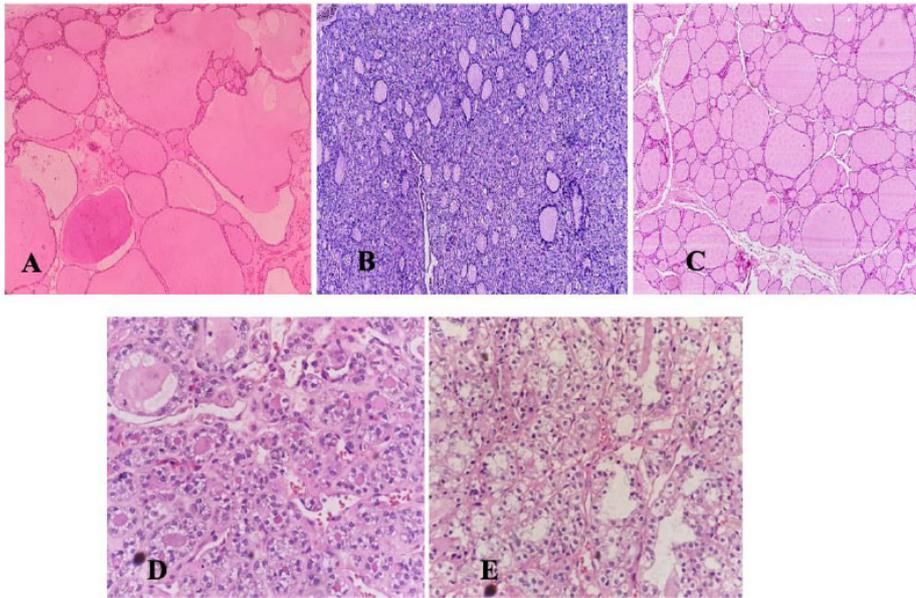
in females and 3 cases (13.0%) in males. This is in line with several studies and literature, one of which is the book WHO Endocrine Organs 2017.<sup>4</sup> According to research in general on thyroid nodules, the incidence ratio of cases in female is 78% and in male as much as 22%.<sup>12</sup> In line with a previous study, who gave the same result that the incidence of cases was higher in women than in men.<sup>14</sup> This is presumably because the thyroid gland contains estrogen receptors, as it is known that estrogen has carcinogenic properties to stimulate excessive cell growth.<sup>14</sup> The

influence of hormones in women is one of the predisposing factors for the increasing number of female patients compared to men. Estrogen can increase the level of thyroid-binding globulin (TBG), which acts as a transporter of T4 and T3 in the blood, resulting in a decrease in the levels of free T4 and free T3. This stimulates TSH so that glandular hyperplasia occurs as a compensatory mechanism to form more thyroid hormone so that serum T4 and T3 levels can return to normal.<sup>15</sup>

Important preoperative techniques used to evaluate suspicious adenomas are ultrasonography and fine-needle aspiration biopsy. Therefore, it is necessary to check the integrity of the capsule. A definitive diagnosis of thyroid adenoma can only be made after careful histological examination of the resection specimen. The typical thyroid adenoma is a spherical, solitary lesion that compresses the surrounding non-neoplastic thyroid tissue. The neoplastic cells are separated from the surrounding parenchyma by a thin and intact capsule (capsule).<sup>4,6</sup> This feature is important in distinguishing it from a multinodular goiter, which contains multiple nodules in cross-section (although the patient may present clinically with a solitary dominant nodule), but does not show compression of the surrounding thyroid parenchyma, and lacks a well-formed hoop.<sup>4,6,16</sup> Tumors are usually 1-3 cm in size but can be larger. On cutting, it appears a homogeneous mass of grayish-white, brownish, or brown mass like meat. In general, tumors are grayish-white, more cellular, and have solid or trabecular growths, whereas the brownish tumor mass is an area with a follicular component containing a colloid mass. Secondary changes such as a hemorrhagic mass and cystic degeneration may also be seen. According to the tumor size data listed in the medical record data, it was found that the most tumor size in follicular adenoma cases was above 4 cm in 16 cases (69.6%). According to WHO Endocrine Organs, the nodule size in cases of follicular adenoma is on average 1-3 cm, but it can be larger than the usual size.<sup>4</sup> Determination of this size is taken from the results of radiological examinations, namely ultrasound (USG) contained in the medical records of each patient.

**Table 1. Frequency distribution of study samples based on age, sex, tumor size, number of nodules, growth pattern, and histopathological variants.**

Variable	Amount (n=23)	Percentage (%)
Age (Years)		
<20	0	0.0
20-29	4	17.4
30-39	3	13.0
40-49	5	21.7
50-59	6	26.1
60-69	4	17.4
≥70	1	4.3
Gender		
Male	3	13.0
Female	20	87.0
Tumor size (cm)		
<2	0	0.0
2-4	7	30.4
>4	16	69.6
Number of Nodules		
1 (solitary or unilateral)	12	52.2
>1 (multiple or bilateral)	11	47.8
Growth pattern		
Normofollicular	5	21.7
Macrofollicular	15	65.2
Microfollicular	3	13.0
Trabecular	0	0.0
Solid	0	0.0
Histopathology variant		
Conventional follicular adenoma	21	91.3
Hyperfunctioning (toxic adenoma)	0	0.0
Follicular adenoma with papillary hyperplasia	0	0.0
Lipoadenoma	0	0.0
Follicular adenoma with bizzare nuclei	0	0.0
Signet-ring cell follicular adenoma	1	4.3
Clear cell follicular adenoma	1	4.3
Spindel cell follicular adenoma	0	0.0
Black adenoma	0	0.0



**Figure 1.** Microscopic examination. Growth pattern (A, B, and C); A) Macrofollicular; B) Microfollicular; and C) Normofollicular. Histopathological variant (D and E); D) Signet-ring cell follicular adenoma and E) Clear cell follicular adenoma.

However, in some patients, the ultrasound examination results were not found in their medical records; therefore, the size data was taken from a macroscopic examination of tumor size. In Iskandar's 2017 study, of 37 cases of thyroid nodules >4 cm in size, 18 of them were benign nodules. The study also found malignant nodules with tumor size <4 cm.<sup>3</sup> Based on research by Kamran SC et al., the relationship between nodule size and risk of malignancy is not always linear.<sup>17</sup> The larger the nodule size increases the risk of malignancy but only up to 2.0 cm in size. If the size of the nodule is more than 2.0 cm, the risk of cancer does not change. However, the risk of follicular thyroid carcinoma and other rare malignancies increases as the size of the nodule increases.<sup>17</sup>

From the results of the assessment of the number of nodules in this study, it was found that there was an almost equal comparison between solitary or unilateral nodules and multiple or bilateral nodules, with a slightly higher number of cases with solitary nodules, namely 12 cases (52.2%) while multiple or bilateral nodules as many as 11 cases (47.8%). According to Norris JJ and Farci F, the clinical appearance of follicular adenoma generally shows a solitary nodule.<sup>18</sup> In line with the research

by Iskandar, thyroid neoplasms were more common in cases with solitary nodules, as many as 60% of cases. Through this study, it can also be seen that of the patients with unilateral nodules, 51% of them were malignancy. Meanwhile, only 25% of patients with bilateral nodules are malignancy.<sup>3</sup> According to the theory that 20% of solitary nodules are malignant while multiple nodules are rarely malignant, multiple nodules can be found in 40% of thyroid malignancies.<sup>2</sup>

According to the World Health Organization (WHO) Classification of Tumors of Endocrine Organs in 2017, follicular adenoma is a benign neoplasm, with ICD-O code: 8330/0. It has a fibrous capsule with thin and medium characteristics on microscopic examination, and no invasion of tumor cells into the capsule and blood vessels was found. The architecture and appearance of tumor cells differ from the surrounding parenchyma tissue. Follicular adenoma has several growth patterns: normofollicular, macrofollicular, microfollicular, solid, and trabecular. More than one pattern can be found in a single nodule. Although rare, it can also show features of papillary or insular growth. Tumor cells are cuboidal or polygonal. In an adenoma with

hyperfunction of the thyroid, many cells can be found.

The cytoplasm is slightly abundant and slightly eosinophilic to amphophilic. The nucleus is located at the base and is spherical, with the chromatin being evenly distributed and smooth. Follicular adenoma with lipid-rich cells consists of abundant cytoplasm and vacuoles containing fat. Vacuoles are small or large and have a clear or finely granular appearance. The shape of the nucleus and the size of the nucleus and the texture of the chromatin may vary. Mitosis is rare and the stromal component is usually abundant. Some adenomas have edematous and abundant stroma, mucinous and hyaline, with hyalinized stroma more commonly seen in the central region of the nodule.<sup>4</sup> Secondary changes such as stromal fibrosis, hyalinization, hemorrhage, edema, cystic degeneration, calcification, and metaplasia of bone and cartilage can also be seen, especially in large tumor masses. Sometimes the blood vessels in the adenoma show a focal thickening of the wall, which is referred to as a muscular cushion.<sup>4</sup>

Based on the growth pattern of thyroid follicles obtained on microscopic examination, it was found that the highest growth pattern was macrofollicular in 15 cases (65.2%), followed by normofollicular growth pattern in 5 cases (21.7%). According to WHO Endocrine Organs 2017, several growth patterns found are normofollicular, macrofollicular, microfollicular, solid and trabecular, and sometimes papillary and insular growth patterns can be found. In one nodule, several growth patterns can be found.<sup>4</sup> According to Norris JJ and Farci F, the most common growth patterns are macrofollicular and microfollicular. For the pattern of microfollicular growth, after an adequate examination of the preparation, 5% of cases were reported as follicular carcinoma. Some literature recommends that tissue excision be performed with a minimum of 10 tissue blocks originating from the capsule and thyroid tissue.<sup>18</sup>

From the results of microscopic examination of follicular adenoma preparations, it was found that the most histopathological variants were

conventional follicular adenoma were 21 cases (91.3%) followed by signet-ring cell follicular adenoma variants and clear cell follicular adenoma with 1 case each (4.3%). The limited research and literature regarding the incidence, clinical utility, and prognostic of several histopathological variants of follicular adenoma, causes investigators to lack referrals.

## CONCLUSION

Adenomas are classified based on the degree of follicular formation and the colloid content of the follicle. Follicular epithelial cells are the origin of the majority of thyroid cancers. Thyroid nodules (adenoma), thyroid enlargement (colloid goiter), and inflammation of the thyroid (thyroiditis) are the most important risk factors for thyroid cancer. One in five cases of thyroid cancer (20%) has a history of a non-cancerous thyroid. Having a history of existing adenomas starting, especially at a young age, is a risk factor leading to cancer. The need for early detection, diagnosis, and appropriate treatment and follow-up of non-cancerous lesions of the thyroid. Misdiagnosis is common with thyroid nodular lesions. Benign lesions such as hyperplastic nodules and adenomas are also often misdiagnosed due to the lack of further studies on the histopathological criteria of both. It is also said that it will be difficult without biomolecular examination to distinguish hyperplastic nodules and adenomas. Follicular adenomas can be treated with lobectomy and have a good prognosis if diagnosed early and with proper treatment.

## CONFLICT OF INTEREST

We declare that there were no conflicts of interest in this study.

## ETHICS CONSIDERATION

The patient approved informed consent based on COPE and ICMJE protocols for publication ethics prior to the study being conducted.

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This research did not receive any funding.

## AUTHOR CONTRIBUTION

All authors contributed to the collection of patient data and the writing process of the manuscript.

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