

## Thyroid Malignancy in Clinically Benign Cystic Thyroid Nodule Presentation

William Stevenson<sup>1\*</sup>, Nico Lumintang<sup>2</sup>, Sherly Tandililing<sup>2</sup>

<sup>1</sup>Department of Surgery, Faculty of Medicine, Universitas Sam Ratulangi, Manado, Indonesia

<sup>2</sup>Department of Head Neck Surgery, Department of Surgery, Faculty of Medicine, Universitas Sam Ratulangi, Manado, Indonesia

\*Corresponding author: doc.stevensons@gmail.com.

### ABSTRACT

**Aim:** Cystic thyroid nodule (CTN) is almost always considered benign (noncancerous). Approximately 1% of people with cystic nodules will develop cancer, but less than 3% of those with partly cystic nodules who do not exhibit any suspicious symptoms will do so. In contemporary clinical practice, the most dependable diagnostic method for choosing patients for surgery is fine-needle aspiration biopsy (FNAC). However, because to the high frequency of insufficient smears and false-negative findings, FNAC has significant limits in instances with CTN. Two patients with cystic thyroid nodules were presented in this case report; however, further anatomical pathology reports following total thyroidectomy surgery revealed that the nodules were malignant. **Case Presentation:** This case report describes two cases of thyroid nodule patients who presented to Prof. Dr. RD Kandou Hospital. These patients had cystic thyroid nodules and subsequently underwent thyroidectomy due to large masses. Pathological examination was conducted and confirmed thyroid malignancy in both cases, specifically follicular variant papillary thyroid carcinoma. **Conclusion:** Ultrasound and FNAC examinations have limitations in detecting thyroid malignancies especially for large cystic thyroid nodule. Large nodule sizes and the inability to sample the whole lesion may potentially contribute to false negative results in FNAC. The experience of the operator also will determine the occurrence of false negatives in the ultrasound. Therefore, as clinician we should be aware there were potency of malignancy even in cystic thyroid nodule cases.

**Keywords:** cystic thyroid nodules, thyroid malignancy, FNAC, ultrasonography.

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### INTRODUCTION

Thyroid nodules are a prevalent endocrine issue observed globally. Thyroid cancer among people under 40 years old was expected to have caused 239,362 cases and 2409 deaths worldwide in 2022. The most prevalent endocrine system cancer and the sixth most frequent cancer globally in women between the ages of 20 and 84 is thyroid cancer.<sup>1</sup>

Thyroid cysts are enlarged areas of the thyroid that are filled with fluid. They can be minor (less than 1 cm) or large and they can occasionally appear very unexpectedly. It is possible for thyroid nodules to be completely cystic, in which case the fluid contains no solid

substances. On the other hand, the nodule could be complicated, including both solid and liquid components.<sup>2</sup>

Cystic thyroid nodule (CTN) is almost always considered benign (noncancerous). Approximately 1% of people with cystic nodules will develop cancer, but less than 3% of those with partly cystic nodules who do not exhibit any suspicious symptoms will do so. In contemporary clinical practice, fine-needle aspiration biopsy (FNAC) is the most dependable diagnostic technique for choosing patients for surgery. The high frequency of insufficient smears and false-negative findings, however, means that FNAC has significant limits in patients of CTN.<sup>2</sup> This

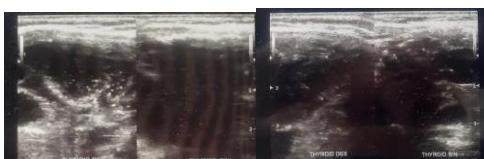
study aims to present two patients with cystic thyroid nodules.

## CASE REPORT

### Case 1. LM/female/56 years old

The patient initially admitted to the hospital because of enlarging lump on anterior neck for 8 years. The lump is slowly growing, not accompanied by pain, no fever, no hoarseness, no shortness of breath, no swallowing difficulties. She did not lose weight in spite of her increased hunger, erratic or fast heartbeat, anxiety, irritability, sleep difficulties, exhaustion, shaky hands, muscular weakness, sweating, difficulty with heat tolerance, or frequent bowel movements. There is no history of severe neck radiation exposure. absence of thyroidal disease in the family.

During the physical examination, blood pressure was within normal limits, pulse was not tachycardic, no tachypnea, there was a mass in the neck at anterior cervical triangle measuring 9x8x6 cm, well-defined borders, cystic consistency, and movement with swallowing. Thyroid function test within the normal range.



**Figure 1.** Ultrasound of thyroid showed right and left enlargement, wider – than – tall, visibly border of anechoic masses 9x8x6 cm, regular margin, TIRADS 1.

There were no indications of cancer in the fine needle aspiration biopsy investigation, which revealed cyst cell cells, macrophages, lymphocytes, erythrocytes, and colloidal aggregates.

Total thyroidectomy was performed due to the large size of the tumor and the specimens were sent for histopathological examinations.



**Figure 2.** Thyroid tissue 2 nodules size 9x8x6 cm, brown color

The histopathological examination found some cystic dilated follicles, at other focus visible follicles coated by cells with a ground glass core. The conclusion is carcinoma papillary thyroid variant follicular.

Post-surgery, patient complained no hoarseness, no difficulty swallowing, no cramps, or numbness. The patient was discharged on third day. In the next follow-up, the patient was seen at the head and neck surgery outpatient clinic, and the patient's condition was good without postoperative complications.

### Case 2. AA/female/56 years old

The patient admitted to the hospital because enlarging lump on the anterior neck for 2 years. The lump is slowly growing, not accompanied by pain, no fever, no hoarseness, no shortness of breath, no swallowing difficulties. Despite having a heightened hunger, an erratic or fast heartbeat, anxiety, irritability, problems sleeping, exhaustion, shaking hands, muscular weakness, sweating, difficulty with heat tolerance, and frequent bowel movements, she did not lose weight. no history of serious neck radiation exposure. no thyroid problems in the family.

During the physical examination, blood pressure was within normal limits, pulse was not tachycardic, no tachypnea, there was a mass in the neck at anterior cervical triangle measuring 8.6 x 6.9 x 8.9 cm, well-defined borders, cystic consistency, and movement with swallowing. Thyroid function test within the normal range.

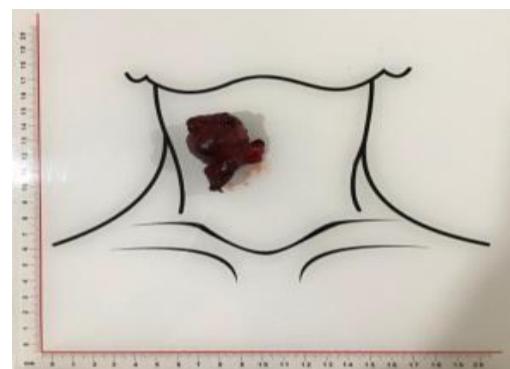


**Figure 3.** Ultrasound of thyroid showed isoechoic lesions with hypoechoic component, firm boundaries, regular margins without calcification measuring 8.6 x 6.9 x 8.9 cm. On doppler examination does not appear intralesional vascularization (TIRADS III).

An MSCT Scan examination has been carried out with and without contrast with the following results: visible on the right thyroid lobe lesions of iso-dense, heterogeneous with mixed cystic and solid lesions inside, firmly bounded, regular edges. On the post contrast scan, it appears that the enhanced inhomogeneous in the solid component pushing the trachea to the left, the lesion size is 8.6 x 6.9 x 8.9 cm. There were also lesions on the left thyroid with the same characteristics as the mass in the right lobe, measuring 2.3 x 2.6 x 3.3 cm and 2.8 x 3.3 x 3.3 cm. no visible lymph node enlargement. The conclusion is multiple bilateral thyroid lesions DD/ follicular thyroid adenoma.

One or two clusters of follicular epithelial cells were seen in the fine needle aspiration biopsy test findings, relatively homogeneous, few inflammatory cells and macrophage cysts. The conclusion is Benign Follicular Lesion (Bethesda Category II).

Total thyroidectomy was performed due to the large size of the tumor and the specimens were sent for histopathological examination. The histopathological examination of the tissue was papillary thyroid carcinoma variant follicular.



**Figure 4.** Specimen of nodule thyroid

Post-surgery, patient complained no hoarseness, no difficulty swallowing, no cramps, or numbness. The patient was discharged on third day. In the next follow-up, the patient was seen at the head and neck surgery outpatient clinic, and the patient's condition was good without postoperative complications.

## DISCUSSION

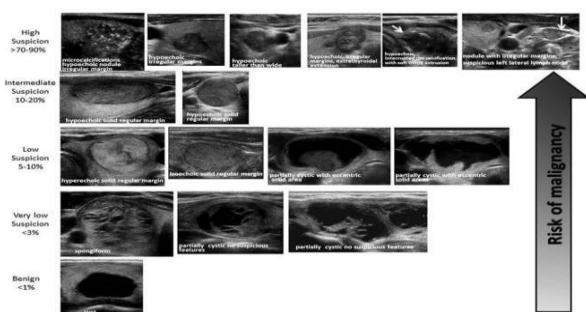
Solid nodules that have undergone cystic degeneration make up the majority of thyroid cysts that are clinically palpable; genuine thyroid cysts with a liquid core bordered by cells are uncommon. Usually, these cysts are benign thyroid adenomas. Additionally, it was mentioned that cystic lesions had the same chance of being malignant as solid lesions, and that neither the clinical features of the cysts nor the patient's demographic information can reliably predict this difference. It is advised that the majority of cysts that cannot be removed by aspiration be removed. A fully cystic nodule is thought to be less than 1% malignant, but a partly cystic nodule with no worrisome characteristics is thought to be less than 3%. Yet, since thyroid tumors can sometimes manifest as cystic nodules, their malignant potential should not be disregarded.<sup>2</sup>

Thyroid nodules can be classified as benign or cancerous based on certain ultrasonography

features. A biopsy might not even be necessary if a purely cystic nodule is discovered because its likelihood of being malignant is less than 1%.<sup>2</sup>

If the operator has experience with thyroid ultrasonography, high-definition ultrasonography can yield important information regarding the nodule's features and the risk of cancer.<sup>3</sup>

Because a nodule less than 1 cm is just as likely to have neoplastic cells in the presence of suspicious US findings as a bigger nodule, neither the number of nodules nor their size can be used to predict malignancy.<sup>4</sup>



**Figure 5.** ATA nodule sonographic patterns and risk of malignancy.<sup>5</sup>

The diagnostic FNA results are categorized as follows, according the revised Bethesda System for Reporting Thyroid Cytopathology: follicular or Hurthle cell neoplasm, follicular lesions of uncertain significance or atypia, benign (70%), malignant (5%), and suspected for malignancy. Among the most prevalent benign lesions are lymphocytic thyroiditis, macrofollicular adenoma, and colloid nodules. Papillary thyroid cancer is by far the most common malignant lesion, with high-grade metastatic neoplasms, anaplastic carcinoma, follicular thyroid cancer (FTC), and MTC following.<sup>4, 5, 6</sup>

According to the ATA Recommendation, additional diagnostic testing or therapy is not necessary if the nodule is benign on cytology

(strong recommendation, high-quality evidence). However, we must also keep in mind that a number of elements, including as the operator's expertise, the FNA method, specimen preparation, and cytology interpretation, all play a role in an accurate FNAC diagnosis.<sup>6</sup>

The most crucial stage in treating thyroid nodules is fine needle aspiration cytology (FNAC). The sensitivity and specificity of FNAC range from 65% to 98% and 72% to 100%, respectively. False negative rates for cancer range from 1% to 11%, whereas false positive rates range from 0% to 7%. In the event that the lesion is perceptible, FNAC can be carried out free-hand or with ultrasound guidance to boost confidence. The use of ultrasound-guided FNAC is growing in popularity and has been shown to increase FNAC accuracy. With ultrasound-guided FNAC, the acellular or non-diagnostic aspirate is lowered from 14% in free-hand FNAC to 8%. Under ultrasound guidance, FNAC's sensitivity increased from 92% to 98% and its specificity increased from 69% to 71%. Furthermore, lesions smaller than 1 cm, impalpable lesions, or situations where the first free-hand FNAC was non-diagnostic can all be located with the use of ultrasound-guided FNAC.<sup>7</sup>

Clinical monitoring alone can be adequate for thyroid cysts that are benign on FNAC and do not return at follow-up. During follow-up, recurrent thyroid cysts should be aspirated again, and a sample should be sent for cytological analysis. A diagnostic lobectomy may be an option for patients with high risk characteristics identified by history and examination.<sup>7</sup>

Our patients' big nodules may potentially contribute to false-negative results because it is impossible to sample the whole lesion, even when guided by ultrasonography. The most significant cause of erroneous negative

findings is known to be large nodules. Although completely cystic tumors are uncommon, partially cystic lesions are not prevalent in the presentation of papillary thyroid cancer. Numerous factors, including large nodule size ( $>3-4$  cm), bloody cystic fluid, male sex, incomplete cyst resolution, recurrence after repeated aspirations, prior neck irradiation, or radiological findings of local invasion, are actually linked to malignancy and are therefore considered indications for surgery. Cystic thyroid nodules can be classified as benign or malignant based on no broad clinical characteristics.<sup>8</sup>

Aspirated cyst fluid might seem thick, hemorrhagic, or brownish, or it can be clear, watery, and yellow. Since a tumor may overrun its blood supply and experience infarction and cavitation, which implies that the fluid is created from follicular destruction, chocolate-colored aspirates and hemorrhagic are typically thought to be more predictive of neoplasm. The study by Rosen and colleagues found that bloody aspirates were more common in malignant lesions (74%), but they were also observed in 50% of colloid nodules and 38% of benign adenomas. There was no correlation between the aspirated fluid's color or volume and the incidence of cancer in the Cusick et al. trial.<sup>9</sup>

FNAC has a worse diagnosis accuracy for cystic changes of thyroid cancer than it does for solid nodules. Specifically, compared to cystic nodules, which have lower sensitivity and specificity rates (88 and 52%, respectively), solid nodules have significantly better sensitivity and specificity, reaching rates of 100 and 55%, respectively. In this case, additional surgical intervention is strongly advised.<sup>10</sup>

The Belantone research discovered that in 10 out of 119 individuals who had thyroidectomies, the final histology revealed a follicular form of papillary thyroid cancer,

even though preoperative cytology had not shown any malignancy. The sensitivity of FNAC in diagnosing this kind of papillary carcinoma is reported to be poor (less than 30%). The most dependable diagnostic method for choosing patients for surgery in modern clinical practice is fine-needle aspiration biopsy (FNAC). However, because to the high likelihood of false-negative results and insufficient smears, FNAC has significant limits when it comes to cystic thyroid nodules.

Up to 50% of smears have been found to be nondiagnostic. The paucity of follicular cells in the cyst fluid and the challenge of collecting a sufficient specimen from the solid section of the wall of CTN may be the causes of the high occurrence of unsatisfactory smears in this condition. In as many as 50% of CTN instances, false-negative findings have been seen, particularly when the nodule is big ( $>3$  cm). It has been found that malignancy rates in cytologically benign simple cysts that returned after aspiration are comparable to those in solid and mixed (solid/cystic) nodules. In the case of CTNs, this potential is especially concerning because a false-negative result suggests a missing malignant tumor. Even under UG, the high nodule size may make it impossible to sample the whole lesion, which might lead to a false-negative result. It has been established that the primary cause of false-negative findings is large nodules.<sup>11</sup>

According to a research by Cooperberg et al., 45% of cases were falsely negative for cystic papillary cancer. Instead of a cytologic misinterpretation, the false negative might be the result of a sample error. As a result, they suggested doing an aspiration biopsy and guiding the needle toward the lesion using sonography.<sup>12</sup>

In our cases, two patients with clinically presented as cystic thyroid nodule that was classified as a benign lesion. However, after

surgery and pathological examination, malignancy was confirmed. In the first case, the patient was identified with an ultrasound as TIRADS 1, which based on the literature is benign with a malignancy potential of < 1%, but upon histopathological examination post-thyroidectomy, follicular variant papillary thyroid carcinoma was found.

In the second case, the patient was identified with an ultrasound as TIRADS 3, which based on the literature is mildly suspicious with a malignancy potential of 13.3%. However, post-thyroidectomy histopathological examination revealed follicular variant of papillary thyroid carcinoma

US had an 81.8% sensitivity and a 91% specificity in detecting malignancy, according to a research by Eisuke Koike et al. Another research by Dhanadia et al. in Gujarat, India, found that ultrasonography had an 83.3% sensitivity and a 72.7% specificity in identifying a malignant lesion. In 2016, Tyagi et al. conducted a research in Uttar Pradesh, India, to identify cancer in the United States. The results showed that the sensitivity was 80%, the specificity was 100%, and the PPV was 100%. According to the Gagandeep Singh Sethi research, US has a 92.31% sensitivity, 97.30% specificity, and 92.31% PPV in detecting a malignant lesion.<sup>13</sup>

In a study by Vinay Raj Thattarakkal et al., that evaluate correlation of TIRADS and Clinicopathological. TIRADS 2, TIRADS 3, TIRADS 4, and TIRADS 5 had risks of malignancy of 4.2%, 13.3%, 57.9%, and 100%, respectively. With a 77.8% sensitivity, 89.6% specificity, 66.6% positive predictive value, and 93.8% negative predictive value, TIRADS categorization proved beneficial in predicting malignancy. The experience of the operator will determine the occurrence of false negatives in the ultrasound examination

because ultrasound is an operator-dependent examination.<sup>14</sup>

Large nodule sizes ( $\geq 3.0\text{--}4.0$  cm) have been linked to a higher risk of cancer, according to some research, which has supported surgical removal of these nodules. However, other studies have supported the idea that surgery shouldn't be done based only on the size of a big nodule because the incidence of malignancy does not significantly rise when comparing large and small nodules. According to a meta-analysis of 10,817 thyroid nodules by Hammad et al., there was a higher probability of malignancy for nodules between 3.0 and 5.9 cm in size than for those that were 3.0 cm or larger (OR 1.26).<sup>15</sup>

## CONCLUSION

Ultrasound and FNAC examinations have limitations in detecting thyroid malignancies especially for large cystic thyroid nodule. The size of the nodule and the inability to sample the whole lesion may potentially contribute to FNAC false negative results. The experience of the operator also will determine the occurrence of false negatives in the ultrasound. Therefore as clinician we should be aware there were potency of malignancy even in cystic thyroid nodule cases.

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## DISCLOSURE

The authors affirm no conflict of interest

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