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ORIGINAL ARTICLE

# Correlation between thyroid ultrasound and histology in patients with indeterminate cytology results: a local experience

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**Background:** Thyroid nodules are common. Most patients with indeterminate fine needle aspiration cytology (FNAC) results are subjected to thyroidectomy for fear of malignancy. However, only 20–30% of these cases are found to be malignant. The aim was to determine the value of thyroid ultrasound in diagnosing malignancy in patients with indeterminate fine needle aspiration cytology results in our practice. Fine needle aspiration was performed after ultrasound, thereby preventing architectural distortion of the nodule and to ensure that the most suspicious nodule was biopsied.
**Methods:** A retrospective review of records of patients who presented to two University of Pretoria academic hospitals, in South Africa, from 2001 to 2015 with nodular thyroid goitre was undertaken. Patients had a thyroid ultrasound scan, FNAC and had undergone thyroid surgery.
**Results:** Records of 104 patients were retrospectively evaluated. Patients were predominantly female (93.3%). Histology report was available for 101 of the 104 patient records. Malignancy was identified in 23 (22.8%). The overall sensitivity and specificity of thyroid image reporting and data system (TIRADS) score in this study were 69.5% and 61.5% respectively. The TIRADS classification had high sensitivity amongst the 26 patients with indeterminate cytology, with sensitivity and specificity of 85.7% and 52.6% respectively, however it was not statistically significant ($p = 0.28$).
**Conclusion:** There was poor identification of malignancy with the use of ultrasound TIRADS classification in cases of indeterminate FNAC results, Bethesda III or IV, in our study. This is probably related to the diversity of ultrasonographers in our practice. It is recommended that there should be a dedicated thyroid ultrasonographer for a better and consistent TIRADS classification that surgeons can rely on for guiding surgical intervention.
**Keywords:** thyroid, nodule, ultrasound, indeterminate, cytology, histology, cancer

## Introduction

Thyroid nodules are common and estimated to occur in 4–8% of an adult population.[1,2] Patients may present with associated thyroid symptoms such as hoarseness of voice, hyper- or hypothyroidism and pressure symptoms. The variation of thyroid nodule incidence is partly due to different methods used to detect thyroid nodules.[3] The majority of thyroid nodules are benign (> 80%), euthyroid and part of a colloid goitre (50–60%).[4] The main concern in the evaluation of thyroid nodules is to exclude thyroid malignancy. Certain clinical signs may predict the presence of malignancy, these include immobile vocal cords, firm nodules, a nodule fixed to the surrounding anatomical structures and cervical lymphadenopathy.[2] Diagnostic investigations include serum thyroid stimulating hormone (s-TSH), neck ultrasound and fine needle aspiration cytology (FNAC). Ultrasound and FNAC have reduced the rate of diagnostic thyroid operations.[4,5]

Thyroid cancers, although uncommon with an incidence of 13%,[6] are the most common endocrine malignancy. They predominately present as solitary euthyroid nodules. Although FNAC improves management of patients with thyroid nodules and has reduced the number of unnecessary thyroidectomies, it has to be preceded by neck ultrasonography.[4,7] The thyroid ultrasound findings guide the biopsy to the suspicious nodule. Various ultrasonography parameters are used individually and in combination to predict the likelihood of malignancy. A number of risk scoring systems for malignancy, which rely on combinations of ultrasound features, have been developed to predict the likelihood of malignancy in a thyroid nodule. One of these risk scoring systems is the thyroid imaging and reporting data system (TIRADS) which was first described by Horvath in 2009.[8] The classification was modified by Russ and colleagues in 2011,[9] and then updated in 2013.[10] The possibility of malignancy increases with increasing TIRADS score from 1 to 5.

Ultrasound findings, however suggestive, cannot confirm malignancy. FNAC is the preoperative diagnostic modality of choice for diagnosing thyroid malignancy. FNAC results may range from non-representative to malignancy. A commonly used FNAC classification system is the Bethesda system of reporting thyroid FNAC result (I = nondiagnostic/unsatisfactory; II = benign; III = atypia/follicular lesion of undetermined significance; IV = follicular neoplasm or suspicious for a follicular neoplasm; V = suspicious

for malignancy; and VI = malignant).[11] Treatment options range from regular follow-up for a Bethesda II nodule to lobectomy or thyroidectomy for a Bethesda VI nodule. However, FNAC of thyroid nodules has significant false positive and false negative rates due to sampling error or difficulty in pathological diagnosis. Some thyroid tumours are challenging for the cytopathologist to diagnose, such as follicular carcinoma and the recently classified indolent tumour "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP).[12] The above limitations still exist despite guidelines used to aid analysis and interpretation of thyroid FNAC.[11] A malignant thyroid FNAC diagnosis can be confidently made for papillary, medullary, poorly differentiated or anaplastic carcinoma, but not for follicular carcinoma. The diagnosis of follicular carcinoma or Hurthle's cell carcinoma requires demonstration of capsular and/or vascular invasion, which can only be demonstrated on histology. The FNAC report in such cases would be classified as indeterminate, i.e. Bethesda III or IV. Repeat FNAC or molecular testing should be considered.[13] Molecular testing is not universally available, including South Africa. If repeat FNAC is still inconclusive, then diagnostic thyroid lobectomy or total thyroidectomy for histology is undertaken.[13] The risk of malignancy in patients with an indeterminate thyroid nodule is between 20–30%.[4] If the indication for surgery is solely for malignancy risk, the indeterminate FNAC results would therefore be exposing 70–80% of patients with such results to unnecessary surgery and its complications.[14,15] If the ultrasound TIRADS classification proves to be highly accurate in a given setting, then the decision to operate on a patient with indeterminate FNAC results may be considered. However, for follicular carcinoma, FNAC is always indeterminate. Until recently, follicular carcinoma was more prevalent than papillary carcinoma in South Africa.[16-18]

## Aim

To determine the value of thyroid ultrasound TIRADS classification in the diagnosis of malignancy in patients presenting with nodular thyroid goitre and an indeterminate (Bethesda III or IV) FNAC result in our practice.

The objectives were to compare TIRADS classification, FNAC and histology findings in patients who had thyroid surgery for nodular goitre, and to determine if there was correlation between TIRADS classification and histology findings in patients with indeterminate FNAC result.

## Methods

A retrospective cross-sectional study of patients with thyroid nodular goitre was undertaken. Data were collected from Steve Biko Academic Hospital and Kalafong Provincial Tertiary Hospital in Pretoria, South Africa. All patients 18 years or older who presented with single or multinodular thyroid goitre at these 2 hospitals and had a thyroid ultrasound scan, a FNAC and a diagnostic or therapeutic thyroid surgery performed during January 2001 to December 2015 were included in the study. Associated thyroid symptoms were also recorded. The updated modified TIRADS classification by Russ was used.[10] TIRADS 1 is considered as normal thyroid, TIRADS 2 as benign, TIRADS 3 as probably benign, TIRADS 4A as low suspicion for malignancy, TIRADS 4B as high suspicion for malignancy with 1 or 2 suspicious signs, and TIRADS 5 as malignant with 3 or more suspicious signs. Histology results were considered the reference standard. Pathologists were aware of the clinical information.

## Statistical analysis

Descriptive statistics were determined for the data, including mean and standard deviation for continuous data, and proportions for categorical data. Spearman's rank correlation coefficients were calculated in order to identify linear relationships between the ordinal variable TIRADS classification and histology, and malignancy. The value of ultrasound in determining malignancy was evaluated by comparing TIRADS classification and true malignancy on histology. Sensitivity and specificity of TIRADS classification for determining malignancy were calculated. All analyses were conducted with STATA v.12 and a $p < 0.05$ was deemed significant.

## Results

Records of 104 patients were retrospectively evaluated. Ninety-seven patients were female (93.3%) and the mean age was 48.3 (SD = 13.6) with a range of 18–85 years ($n$ = 102). All patients included in the study had nodular thyroid goitre. Other thyroid related findings were 9 (8.6%) hyperthyroidism, 7 (6.7%) hoarseness, 6 (5.7%) dysphagia, 5 (4.8%) rapid growth and 3 (2.8%) pain. The age distribution demonstrated that thyroid malignancy occurred more commonly in patients in two peak age groups of 21–30 years and 51–60 years (Figure 1). A majority of thyroid cancers in the 21–30 age group were papillary cancer (4/7) and follicular were more common in the 51–60 age group (6/7).

Histology results identified malignancy in 23 of the 101 patients (22.8%) on whom histology results were available. The histology showed papillary carcinoma in 14 (60.9%), follicular carcinoma in 8 (30.4%) and medullary carcinoma in 1 (4.3%) (Figure 2).

The number of patients per TIRADS classification is shown in Figure 3. The TIRADS classification showed moderate sensitivity and specificity overall in the patients with thyroid nodules. The sensitivity of TIRADS classification in identifying malignancy was 15/23 (65.2%) and

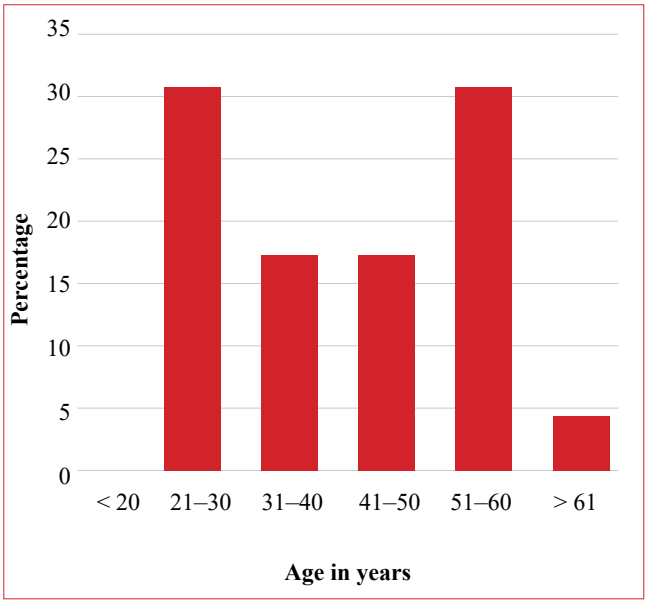


*Figure 1: Age distribution of thyroid malignancy histology*

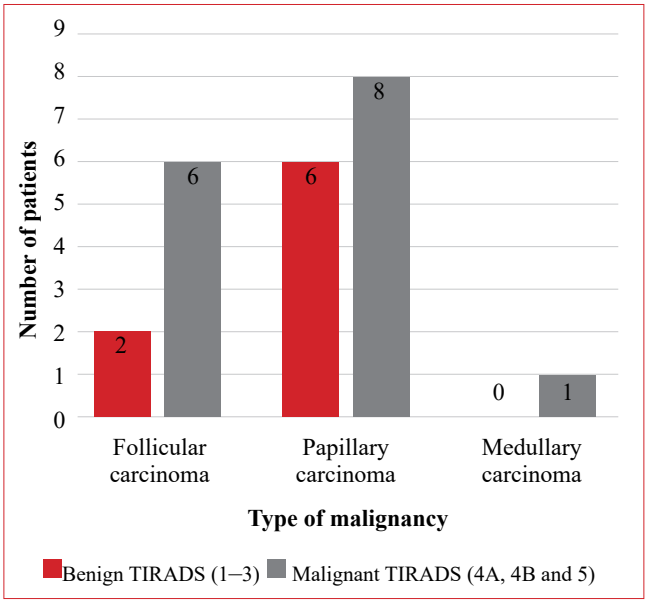


*Figure 2: Correlation of TIRADS classification with thyroid malignancy histology*

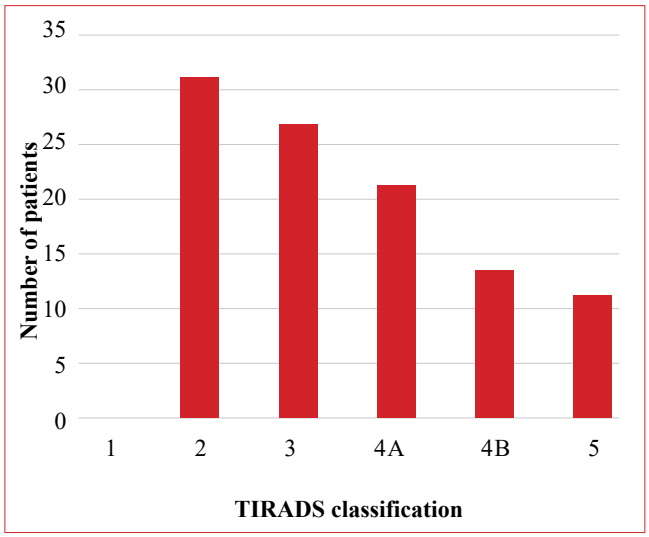


*Figure 3: Number of patients per TIRADS classification (n = 104)*

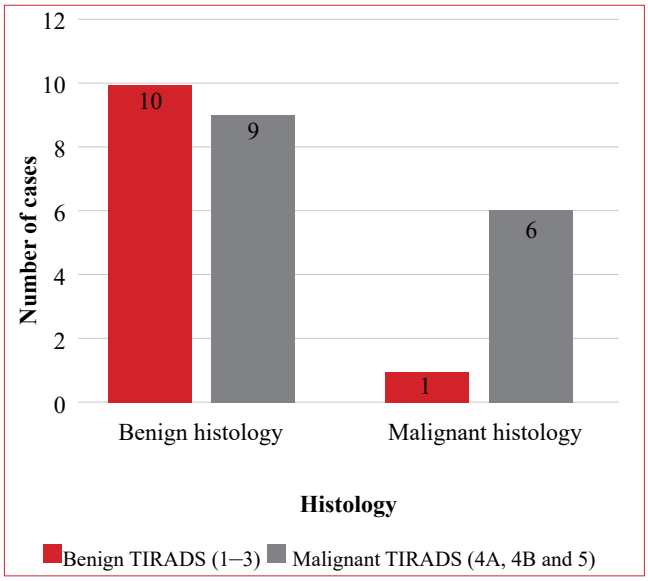


*Figure 4: Correlation of TIRADS classification with thyroid histology amongst indeterminate FNAC*

non-malignancy in patients with benign conditions (i.e. specificity) was 49/78 (62.5%). There was a correlation between TIRADS classification and histology in patients with follicular carcinoma where 6 out of 8 patients (75%) were appropriately classified as suspicious for malignancy (Figure 2). However, the correlation of TIRADS and histology for papillary carcinoma was poorer at 8/14 (57.1%).

The majority of cytology results were classified as Bethesda I (37.5%) or Bethesda II (29.8%) (Table I). The indeterminate FNAC result group consisted of 26 patients (25%), where 7 were classified as Bethesda III (6.7%) and 19 as Bethesda IV (18.3%). Half of the FNAC results for patients with papillary carcinoma were non-diagnostic, only 3/14 (21.4%) were correctly diagnosed as papillary carcinoma, therefore FNAC was unreliable overall in these patients.

From the 26 patients with indeterminate FNAC results, 19 (73%) had benign and 7 (26.9%) had malignant histology (Figure 4). TIRADS categories did not correlate consistently with histological results. Benign TIRADS classification correlated well with benign histology where 3 (75%) and 7 (100%) for TIRADS 2 and 3 classification were correctly assigned for a benign histology result respectively. However, the malignant TIRADS categories 4A, 4B and 5 only appropriately assigned 2 (50%), 3 (37.5%) and 1 (33%) patients with malignant histology respectively.

The TIRADS classification had high sensitivity amongst the indeterminate FNAC results patients, correctly diagnosing 85.7% of patients with malignancy. However, the specificity was lower at 52.6%.

Spearman's rank correlation coefficients showed no significant correlation between the TIRADS classification and malignancy in the indeterminate FNAC results patients ($r$ = 0.22, $p$ = 0.28) and also no significant correlation between the TIRADS classification and the histology results ($r$ = -0.02, $p$ = 0.92).

## Discussion

The patients who presented with a nodular thyroid goitre during the 15-year period, 2001 to 2015, were predominantly female (93.3%), which is comparable to previous studies.[19] Twenty-three of 101 patients (22.8%) were diagnosed with malignancy on histology. Papillary thyroid carcinoma was the most common, followed by follicular carcinoma. Papillary carcinoma is more common in areas with adequate dietary iodine, whereas follicular carcinoma is predominant in iodine deficient areas.[18,20] The introduction of compulsory iodation of table salt in South Africa from 1995 may explain

**Table I: Overall FNAC Bethesda category in 104 patients**

| Bethesda Category | Number (%) | Cumulative percentage (%) |
|---|---|---|
| I | 39 (37.5) | 37.5 |
| II | 31 (29.8) | 67.3 |
| III | 7 (6.7) | 74 |
| IV | 19 (18.3) | 92.3 |
| V | 3 (2.9) | 95.2 |
| VI | 5 (4.8) | 100 |
| **Total** | **104 (100)** | **100** |

the predominance of papillary cancer in this study compared to previous reports in this population.[18,20]

The increased incidence of thyroid malignancy demonstrated a two age peak distribution at 21–30 years and 51–60 years. This finding contrasts with reported increase in the prevalence of thyroid cancer in the 30–49-year age group.[19,21] The predominant type of thyroid cancer differed in these two peak age groups with papillary cancer in the younger, and follicular cancer in the older age groups. It is known that papillary carcinoma starts in a younger age group,[22] whereas follicular cancer is more common with increasing age.[23]

From the 26 patients with indeterminate FNAC results, Bethesda III or IV, 7 (26.9%) were malignant with 1 classified as Bethesda III and 6 as Bethesda IV. A meta-analysis by Bongiovanni et al. found that 14% of patients classified as Bethesda III and 25% as Bethesda IV showed malignant histology results.[24] The diagnosis of malignancy in thyroid nodules should improve with the combination of ultrasound findings (TIRADS classification) and FNAC. The TIRADS classification had high sensitivity (85.7%) and low specificity (52.6%) amongst the indeterminate FNAC results patients, implying that patients with malignancy were correctly diagnosed by the TIRADS classification in 85.7%. This sensitivity was in a similar range as the reported 97.4%, but the specificity was higher than the reported 29.3%.[25] The higher the TIRADS classification, the higher the risk of malignancy and therefore the indication for surgery. A TIRADS 5 classification is usually a strong predictor of malignancy, approaching 100%, and therefore the proposed management of indeterminate FNAC classification has been definitive surgery in such patients.[26,27] Six of the seven patients with malignancy in the indeterminate FNAC results group were classified by TIRADS classification as 4A or higher. However, unexpectedly, the malignancy rate for TIRADS 4A, 4B and 5 in the indeterminate FNAC results group were 50%, 37.5% and 33% respectively in our study. The TIRADS 5 classification with an accuracy rate of 36% (or 33.3% for the indeterminate FNAC results group) for malignancy in this study is therefore of concern, and did not reliably assist the clinician in the preoperative diagnosis of thyroid malignancy in our setting. In addition, TIRADS 1–3 in this study missed malignancy in 34.8%.

The pattern based TIRADS classification described by Horvath[8] has recently been updated by the American College of Radiology into a point system.[28] The updated TIRADS classification may improve the correlation with histology. However, only limited studies have validated the updated guidelines[29,30] and the rate of malignancy has not been reported for each category.

There were limitations to this study. The study was performed retrospectively in a limited sample size and over a long period. There were different sonographers in the two academic hospitals who performed the investigation and reported on the thyroid findings. This introduced potential inter-observer variation. However, the relevance of the study is to serve as an audit of the reliance of the thyroid ultrasound and the FNAC results against histology in our clinical practice.

## Conclusion

There was poor identification of malignancy with the use of ultrasound TIRADS classification in cases of indeterminate FNAC results, Bethesda III or IV, in our study. This is probably related to the diversity of ultrasonographers in our practice. It is recommended that there should be a dedicated thyroid ultrasonographer for a better and consistent TIRADS classification that surgeons can rely on for guiding surgical intervention.


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### *Conflict of interest*

The authors declare no conflict of interest.

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### *Ethical approval*

Ethical approval for the study was granted by the Human Research Ethics Committee of the University of Pretoria (reference number 95/2016).



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