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ARTICLE

Clinical and ultrasound characteristics distinguishing benign and malignant thyroid nodules in Johannesburg, South Africa

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Background: The detection of thyroid nodules is increasingly common in clinical practice owing to the widespread use of ultrasonography.
Objectives: The aims of this study were to describe the clinical and biochemical characteristics of patients undergoing fine-needle aspiration (FNA) of thyroid nodules and to assess the ultrasound, cytologic and, where relevant, histologic features of thyroid nodules in this cohort.
Methods: A retrospective study was conducted of 313 patients undergoing FNA at a private hospital in Johannesburg from October 2015 to July 2019. Demographic, clinical and biochemical data were recorded. Ultrasound features were graded according to the American Thyroid Association (ATA) guidelines and cytology was reported according to the Bethesda System for Reporting Thyroid Cytopathology.
Results: The mean (SD) age of patients in this study was 48.0 (12.7) years and 250 (80.1%) were female. White and Asian/Indian patients made up 79% of the cohort. Cytology results showed the following (*n* [%]): benign, 272 (86.9); indeterminate, 15 (4.79); suspicious/malignant, 25 (7.99). Sonographic characteristics associated with malignancy were microcalcifications and hypoechogenicity (OR [95% CI], *p*-value: 3.93 (1.62, 9.53), $p = 0.001$and 2.34 (1.01, 5.41), $p = 0.04$, respectively). There was an association with the composite ATA score and malignancy (3.59 [2.06, 6.25], $p < 0.0005$).
Conclusion: Thyroid ultrasound and FNA are important diagnostic modalities in identifying clinically relevant thyroid nodules. Concordance was shown with the ATA guidelines, Bethesda System for Reporting Thyroid Cytopathology and malignant histology, which validates their accuracy in the local population.

Keywords: thyroid nodule, ultrasound, fine needle aspiration, biopsy, malignancy

Introduction

A thyroid nodule on ultrasound is defined as a lesion that is distinct from the surrounding thyroid parenchyma. The prevalence of thyroid nodules has increased dramatically in recent years largely due to increased detection, related to the incidental finding of thyroid nodules during imaging for non-thyroid related disorders using imaging modalities such as ultrasound, computed tomography, magnetic resonance imaging, and ^{18}fluorodeoxyglucose positron emission tomography (^{18}FDG PET). The term 'thyroid incidentaloma' has been used for these nodules.[1]

Thyroid nodules have a prevalence of up to 65% in the general population.[2] Approximately 90–95% of these nodules are benign and asymptomatic at diagnosis and during follow-up,[3] therefore, most can be monitored without intervention. The need to evaluate further is based on excluding thyroid cancer, which is present in 5–15% of cases. Only a minority of thyroid nodules are malignant (10%),[4] symptomatic (5%) and cause thyroid dysfunction (5%). Symptoms of thyroid nodules include dysphagia, odynophagia, hoarse voice, dysphonia, dyspnoea and pain.[5] Thyroid nodules that are firm on palpation, fixed to surrounding tissues and exhibit rapid growth are concerning and need to be evaluated as soon as possible.[6] Increased focal uptake of thyroid nodules on ^{18}FDG PET scanning is associated with an estimated fivefold increased risk of malignancy.[7]

Routine screening for thyroid nodules in asymptomatic people is not recommended.[8] There is also insufficient evidence that screening of high-risk patients with a history of previous neck irradiation and familial non-medullary thyroid cancer reduces morbidity and mortality.[9]

The initial biochemical test in the evaluation of thyroid nodules is the serum thyroid-stimulating hormone (TSH) level.[9] A low or undetectable TSH will identify functional thyroid nodules, which can be visualised with radionuclide scanning.[9,10] Serum thyroglobulin is elevated in a variety of benign thyroid conditions and is not recommended in the routine evaluation of benign thyroid nodules.[9]

Thyroid sonography is an inexpensive, non-invasive, accurate and quick technique that forms the basis of thyroid nodule evaluation. There are various population-specific guidelines from endocrine and radiology societies describing sonographic features and patterns that are associated with thyroid malignancy.[9–13] Endocrine societies base their risk stratification on sonographic pattern recognition of high-risk features whereas the radiology societies focus on a scoring or points-based system. All guidelines share many similarities and their diagnostic accuracy is comparable.[3] High-risk ultrasound features include: the presence of microcalcifications, hypoechogenicity (i.e. darker than surrounding thyroid parenchyma), irregular or infiltrative borders and extra-thyroidal extension. Low-risk features include cystic, partially cystic or spongiform appearances (i.e. more than 50% cystic areas).

The American Thyroid Association (ATA) thyroid nodule guidelines use sonographic pattern recognition to risk stratify nodules into benign, very low suspicion, low suspicion, intermediate suspicion and high suspicion categories.[9] Each category has a different size cut-off for FNA and the risk of malignancy. FNA reporting was stratified internationally by the Bethesda System for Reporting Thyroid Cytopathology Edition 2, which divides samples into six categories (Bethesda I–VI), each corresponding to a risk of malignancy.[14] Various international studies have validated the predictive accuracy of the ATA and Bethesda guidelines for the risk of malignancy.[15–22]

In Southern Africa, endemic goitre is usually associated with iodine deficiency. This was initially described in 1954 in a goitre belt extending from Limpopo province through Swaziland and Lesotho into the Eastern Cape.[23] Prevalence rates of endemic goitre in Africa range between 1% and 90% depending on the study region.[24] Mandatory iodinisation of table salt in South Africa was introduced on 1 December 1995 and the Iodine Global Network now classifies South Africa's iodine intake as adequate.[25] A retrospective review at the endocrine unit of Chris Hani Baragwanath Academic Hospital compared thyroid ultrasound features with FNA and histology results. There was good correlation between the ATA ultrasound classification and cytopathology and histopathology results.[26] Non-diagnostic thyroid FNA rates in South African studies range between 9% and 10%.[26,27]

Given the increasing prevalence of thyroid nodules, a diagnostic algorithm that is simple, efficient and cost-effective is essential in order to avoid unnecessary fine-needle aspiration (FNA) and thyroid surgery. The aim of this study was to describe the clinical and biochemical characteristics of patients undergoing FNA of thyroid nodules and to assess the ultrasound, cytologic and, where relevant, histologic features of thyroid nodules in this cohort.

Methods

This was a retrospective study of thyroid ultrasound, thyroid FNA and thyroid histology results from a single private practice in Johannesburg, South Africa. Patients were referred for the evaluation of palpable nodules and incidental nodules that were discovered using other imaging modalities. Inclusion criteria were adult patients who underwent a thyroid FNA between October 2015 and July 2019. Exclusions included ultrasound reports that were incomplete or missing, FNAs of lymph nodes and FNAs done with no distinct nodules but other abnormal sonographic features (e.g. microcalcifications etc.). Patients attended the practice for the investigation of abnormal thyroid function tests, or palpable or incidentally discovered thyroid nodules. Ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee (Ethics approval number: M200144).

A total of 349 patient electronic medical records were reviewed and 377 thyroid FNAs were performed. Sixty-four FNA results were excluded from the study, resulting in a sample size of 313 patients ($n = 313$). Demographic, clinical and biochemical data were recorded. Ultrasound features were graded according to the ATA guidelines[9] and cytology was reported according to the Bethesda Classification.[14] FNA was performed as part of a routine diagnostic evaluation of thyroid nodules or abnormal lymph nodes. All analyses were performed using Statistica version 13.5 (Statsoft, Tulsa, OK, USA).

Thyroid sonography was performed by a single operator using a GE Logiq VQ (GE Healthcare, Chicago, IL, USA) with a 12Mhz probe (L6-12 RS). Thyroid FNA was performed with sonographic guidance using a 27G BD (Becton Dickinson, Franklin Lakes, NJ, USA) PrecisionGlide needle (0.4 × 30 mm) attached to a 10 ml syringe. A trans-isthmic approach was used. Two to three passes were performed for each nodule and negative suction on the syringe was not applied during the procedure. Topical anaesthetic (5% EMLA cream: 1 g contains 25 mg lidocaine and 25 mg prilocaine) was applied to the skin approximately 30 minutes prior to the procedure.

Two to six slides were prepared by the operator who performed the FNA using the 'classic' smear technique. One slide was air dried, and the remainder of the slides were fixed with Fencott cytological fixative (Sangene Products, Cape Town, South Africa). The cytology slides were stained with a Papanicolaou stain (Merck, Darmstadt, Germany) and were screened by a cytotechnologist using Olympus (CX31) microscopes (Olympus Corp, Shinjuku City, Tokyo, Japan). Adequate specimens contained ≥ 6 groups of well-visualised follicular cells (≥ 10 per cluster), which is consistent with the Bethesda System for Reporting Thyroid Cytopathology.[14]

Cytological evaluation was done by a single cytopathologist using Olympus (BX41) microscopes. Cytology was reviewed using the following cytopathological criteria: the slides were assessed for cellularity, ratio of colloid to cells, number and variation of groups of cells (variable, in microfollicular, papillary arrangements or single lying) and types of cells (i.e. follicular cells, Hurthle cells, neuroendocrine cells etc.). Abnormal cytological features include nuclear grooves, inclusions, neuroendocrine chromatin and microfollicular or papillary arrangements. The presence of calcifications, psammoma bodies, background lymphocytes, multinucleate giant cells and granulomas and other abnormal cytopathology features were reported. The slides were then reported with a conclusion according to the Bethesda System for Reporting Thyroid Cytopathology Edition 2.[14] The cytopathologist is based at Lancet Laboratories (Kampala, Uganda); therefore, a data-use agreement was approved by Lancet Laboratories for the use of thyroid cytology results, because thyroid histology results were evaluated in patients who were referred for surgery.

All statistical analyses were performed using Statistica version 13.5 (Statsoft, Tulsa, OK, USA). The demographic and clinical characteristics of the patients were presented using means ± standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables with normal or skewed distribution, respectively, and as proportions (%) for categorical variables. Data that were not normally distributed were log transformed to normality before being analysed using parametric statistical tests. Categorical variables were compared across groups using the chi-square test. Continuous variables were compared between groups using Student's unpaired *t*-test. Multivariable logistic regression analysis was used to determine the relationship of thyroid malignancy with sonographic characteristics of the nodules.

Results

Demographic, clinical, laboratory and sonographic characteristics of patients who underwent FNA are described in Table 1. The number of patients included in the study was 313 ($n = 313$). The mean (SD) age of patients in this study was 48.0 (12.7) years and 250 (80.1%) were female. White and Asian/Indian patients made up 79% of the cohort. Pre-existing thyroid disease was noted in 67 patients (21.4%), a family history of thyroid disease was documented in 27 patients

Table 1: Demographic, clinical, laboratory and sonographic characteristics of patients who underwent FNA

Factor	*n* = 313
Age	48.0 (12.7) years
Female	250 (80.1)
Race	
Black	57 (18.3)
White	125 (39.9)
Indian/Asian	123 (39.2)
Mixed	8 (2.55)
Smoker	30 (9.58)
Family history of thyroid disease	27 (8.63)
Pre-existing thyroid disease	67 (21.4)
Thyroid stimulating hormone (mIU/l)	1.43 (0.74, 2.49)
Thyroid antibody positivity:	
Anti-thyroid peroxidase	48 (15.3)
Anti-thyroglobulin	50 (15.9)
Nodule characteristics:	
Intra-nodal vascularity	99 (31.6)
Hypoechoic	68 (21.7)
Irregular shape	49 (15.7)
Microcalcifications	42 (13.4)
Irregular contour	24 (7.68)
Taller > wide	21 (6.71)
Extra-thyroidal extension	2 (0.63)
Nodule volume (ml)	1.12 (0.31,4.40)

Data reported as mean (SD), median (IQR) or *n* (%).

(8.63%) and 30 patients (9.58%) had a history of smoking. The median (IQR) TSH level was 1.43 mIU (0.74, 2.49). Anti-thyroid peroxidase and anti-thyroglobulin antibodies were positive in 48 (50%) and 50 (51.5%) patients, respectively.

Intra-nodal vascularity and hypoechogenicity were noted in 99 (31.6%) and 68 (21.7%) nodules respectively. Microcalcifications were present in 42 nodules (13.4%) and 21 nodules (6.71%) had nodules with a taller-than-wide shape. Forty-nine nodules (15.7%) had an irregular shape and 24 nodules (7.68%) had an irregular border/contour. Extra-thyroidal extension was seen sonographically in 2 patients (0.63%). The median (IQR) nodule volume was 1.12 ml (0.31, 4.40).

Thyroid nodules were classified according to the ATA guidelines (Figure 1). Fifty-eight nodules (18.5%) were classified as high suspicion and 99 nodules (31.6%) were intermediate suspicion. There were 139 (44.5%) low suspicion nodules and 17 (5.4%) very low suspicion nodules. None of the nodules were classified as benign.

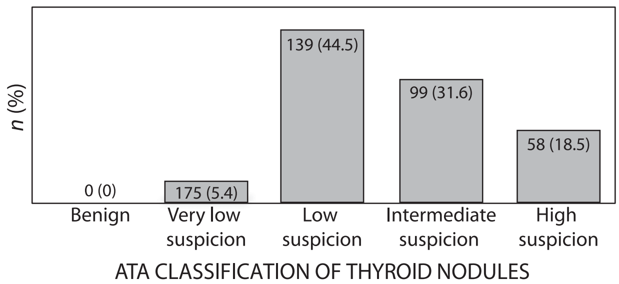

Figure 1: ATA classification of thyroid nodules (%)

Cytologically benign nodules (Bethesda II) accounted for 86.9% (272) of the fine-needle aspirate samples (Figure 2). Malignant (Bethesda VI) and suspicious for malignancy (Bethesda V) cytology was present in 16 (5.1%) and 9 (2.9%) samples, respectively. There were 15 (4.85%) cytologically indeterminate nodules (Bethesda III and IV), of which 5 (33.3%) returned malignant histology. One aspirate (0.3%) was reported as non-diagnostic (Bethesda I).

Thyroid cancer was diagnosed histologically in 24 patients (8%), with 80% of these being papillary thyroid carcinoma (PTC) (Figure 3). Hurthle cell carcinoma, medullary thyroid carcinoma and thyroid paraganglioma comprised 8%, 8% and 4% of the total histology specimens.

Multivariable logistic regression analysis showed that sonographic characteristics that were significantly associated with malignancy were microcalcifications and hypoechogenicity (OR [95% CI], *p*-value: 3.93 (1.62, 9.53), $p = 0.001$ and 2.34 (1.01, 5.41), $p = 0.04$, respectively) (Table 2). Other individual sonographic characteristics, such as taller-than-wider shape, irregular shape, irregular margin/contour and intra-nodal vascularity, were not associated with malignancy. However, there was a significant association with the composite ATA score and malignancy (OR [95% CI], *p*-value) at 4.61 (2.47, 8.61), $p < 0.0001$. There was no association between malignancy and nodule volume.

Discussion

In this retrospective study of 313 predominantly female patients who underwent FNA of thyroid nodules, we found that 18.5% of patients had nodules that were sonographically highly suspicious for malignancy. Overall, 8% of patients had a histologically proven thyroid malignancy. We also showed that the ATA score as well as the two sonographic characteristics, namely microcalcifications and hypoechogenicity, were associated with malignant histology.

Both of these features have been shown to be individually associated with malignancy in numerous studies.[9,11,15–22,28,29] A study conducted at Chris Hani Baragwanath Hospital, Soweto reported similar findings.[26] Microcalcifications have a sensitivity, specificity and positive likelihood ratio of 39.5%, 87.8% and 3.26 respectively.[29] Two other large studies also found that microcalcifications had low sensitivity and high specificity.[30,31] Hypoechogenicity has a higher sensitivity and lower specificity in comparison with microcalcifications. Sensitivity, specificity, positive likelihood ratio and post-test probability (i.e. probability of malignancy after having a positive test result) are 62.7%, 62.3%, 1.66% and 15.4%, respectively.[29] Both of these sonographic features lack the appropriate sensitivity to be used individually as a screening test.

Other individual sonographic characteristics, such as taller-than-wider shape, irregular shape, irregular margin/contour and intra-nodal vascularity, were not associated with malignancy in this study. A possible explanation of these findings is due to the smaller sample size, as these sonographic features have a low sensitivity and high specificity. A large meta-analysis including 52 studies and 12 786 thyroid nodules concluded that no individual sonographic feature had a positive likelihood ratio and post-test probability that was significantly associated with malignancy.[29] In the same study, central/intranodal vascularity had the best specificity for malignancy (96%). Moon *et al.*

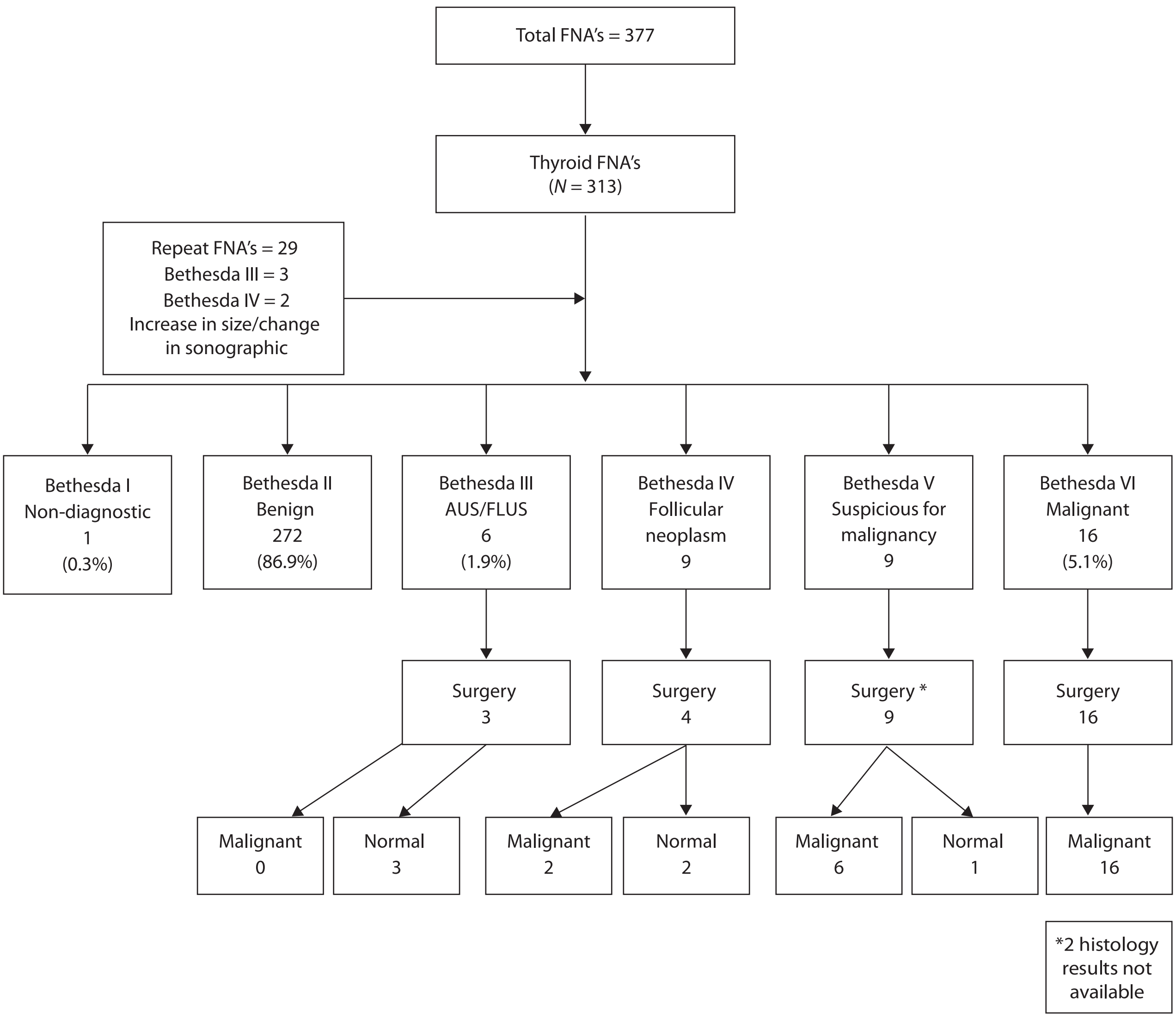

Figure 2: Flowchart showing summary of fine-needle aspiration cytology results

and Popowicz *et al*. found low sensitivity for most ultrasound features for thyroid malignancy.[30,31]

We found a significant association with the composite ATA score and malignancy (OR [95% CI], *p*-value) at 4.61 (2.47, 8.61), $p < 0.0001$, which is consistent with numerous international studies.[19–21,32,33] The 2015 ATA guidelines use pattern recognition with different risk categories and FNA size cut-offs. There is no evidence to suggest which of the endocrine and radiology societies guidelines is the best in the evaluation of thyroid nodules.[3]

The mean nodule volume in this study was 1.12 ml (0.31, 4.40), which was not associated with the risk of malignancy (OR [95% CI], *p*-value) at 0.98 (0.93, 1.03), $p = 0.52$.[34] A retrospective

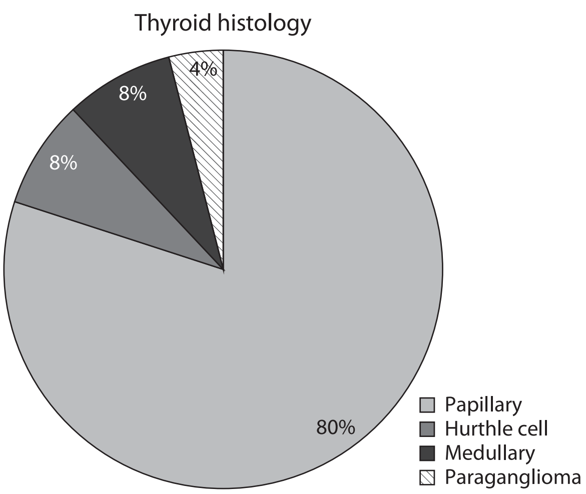

Figure 3: Thyroid histology of malignant nodules

Table 2: Association between sonographic features of thyroid nodules and malignancy

Factor	OR (95% CI)	*p*-value
ATA score	4.61 (2.47, 8.61)	<0.0001
Microcalcifications	3.93 (1.62, 9.53)	0.002
Hypoechoic	2.34 (1.01, 5.41)	0.045
Taller > wide	2.73 (0.84, 8.84)	0.092
Irregular shape	1.23 (0.44, 2.36)	0.681
Irregular contour	0.95 (0.21, 4.30)	0.95
Intra-nodal vascularity	0.74 (0.30, 1.82)	0.515
Nodule volume (ml)	0.98 (0.93, 1.03)	0.52

cohort analysis of 7 348 thyroid nodules concluded that nodule growth above 2 cm does not affect the risk of malignancy.[35] There was an inverse correlation with thyroid nodule size and the risk of malignancy, with lower risk nodules being larger in size.[21] Cavallo *et al*. reported that larger nodules have a lower rate of malignancy and concluded that size alone should not be regarded as an independent risk factor for malignancy.[36]

We found no association of TSH, thyroid autoantibody status or body mass index (BMI) with risk of thyroid malignancy in this study, which is in agreement with other studies.[37–39]

Bethesda VI cytology was in concordance with the Bethesda System for Reporting Thyroid Cytopathology Edition 2,[14] as malignancy was confirmed histologically in 100% of samples. Approximately 67% of Bethesda V cytology were malignant histologically; however, these results may be skewed due to missing histology reports. Bethesda II, V and VI categories have high negative and positive predictive values that enable the clinician to accurately decide on further management.[40] Indeterminate cytology (Bethesda III/IV) was present in 15 FNA samples (4.85%) of which 5 (33.3%) returned malignant histology. These findings are similar to the estimated risk of malignancy outlined in the Bethesda System for Reporting Thyroid Cytopathology Edition 2.[14]

In keeping with reports in the international literature, PTC was the most prevalent malignancy. Follicular thyroid carcinoma is commoner in iodine-deficient populations, whereas the incidence of PTC is higher in iodine-sufficient populations.[41] Follicular carcinoma has been reported as more prevalent in the black South African population. A study conducted at Chris Hani Baragwanath Hospital, Soweto reported a prevalence of PTC of 67%[26] versus 86.9% in this study. Kalk *et al*. found follicular thyroid histology in 55% of patients who were predominantly black females from rural areas of the former Transvaal. PTC predominated in urban areas irrespective of race.[41] A predominance of follicular thyroid cancer was found at the Chris Hani Baragwanath Academic Hospital in Soweto,[42,43] Dr George Mukhari Academic Hospital in Ga-Rankuwa[44] and in other iodine-deficient regions in South Africa.[41] In KwaZulu-Natal, follicular thyroid cancer predominated in African patients (68%) whereas PTC was more frequently seen in Indian patients (57%).[45] It is possible that iodine deficiency could explain the predominant follicular histology in black South African populations. The effect of goitrogens, such as cassava, in this population has not been evaluated. The predominant racial groups in this study were white and Indian/Asian from urban areas, which could explain why PTC was the most prevalent malignancy.

The non-diagnostic rate in the literature varies widely with rates of 6–36% being reported.[46–50] We reported lower non-diagnostic rates (0.3%), which is probably related to a single experienced operator performing the thyroid ultrasounds and FNAs and a single cytopathologist evaluating the slides. In this study, the operator performing the sonar and FNA prepared the slides and there was no rapid on-site evaluation/immediate adequacy assessment by a cytopathologist. Rapid on-site evaluation/immediate adequacy assessment has been shown to reduce non-diagnostic rates in various studies.[51–53]

The limitations of this study are its retrospective design and the fact that black South African patients and those of mixed descent are under-represented in the cohort. The strengths of this study are that histopathological diagnoses were included; unlike other FNA studies, a single cytopathologist analysed the slides and a single operator performed the thyroid ultrasounds and FNAs.

Conclusion

Benign thyroid nodules are common in the general population and the majority can be followed without intervention. Classical PTC was the most prevalent malignancy in this study. Both the ATA score and the two sonographic characteristics, namely microcalcifications and hypoechogenicity, were associated with malignancy. We showed the concordance of the Bethesda System for Reporting Thyroid Cytopathology and malignant histology. This correlation validates the accuracy of the ATA guidelines and the Bethesda System in the local population.

This study confirms that a diagnostic approach using ultrasound and FNA provides a practical and economical way of identifying clinically relevant nodules that require surgical intervention.

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