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R. Nassanga, MBChB, MMed, Makerere University, Kampala, Uganda, H. Kisembo, MBChB, MMed, MPH, Radiologist, Mulago National Referral and University Teaching Hospital, Kampala, Uganda, E. Othieno, MBChB, MMed, Pathologist, Makerere University, Kampala, Uganda, S. Bugeza, MBChB, MMed, Radiology Lecturer, Makerere University, Kampala, Uganda and J. Fualal, MBChB, MMed Surgery, Surgeon, Mulago National Referral and University Teaching Hospital, Kampala, Uganda

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R. NASSANGA, H. KISEMBO, E. OTHIENO, S. BUGEZA and J. FUALAL

ABSTRACT

***Objectives*: To describe the sonographic patterns of thyroid nodules in patients undergoing thyroid ultrasound, to correlate sonographic characteristics of thyroid nodules to ultrasound aided fine needle non aspiration(US-FNNA) cytology and to determine the sensitivity and specificity of Ultrasound in characterising thyroid nodules.**
***Design*: Cross sectional study.**
***Setting*: The department of Radiology at Mulago Teaching and National Referral Hospital in Kampala Uganda. The Hospital is a 1,500-bed unit providing tertiary diagnostic, curative, rehabilitative, preventive and teaching services. Patients were recruited from both Medical and Surgical outpatient thyroid clinics.**
***Subjects*: All patients with thyroid nodules > 5 mm and who consented to have US aided-FNNA were enrolled consecutively.**
***Results*: One hundred and eighty one (181) participants were enrolled and final diagnoses were concluded in 177 of the participants (analysed) while four participants were excluded due to inadequate samples. The participants' age range was 19 to 83 years (mean age - 42 years) and 93% were females. Five percent (n=9) were malignant, 18% suspiscious (n=34) and benign (n=134). The sonographic characteristics that were significantly correlated with final cytology diagnosis were a taller than wide AP diameter, micro-calcifications, heterogeneous and hypoechoic echo-patterns. Heterogeneous, hypoechoic and central vascularity had the highest sensitivity while wider than tall, anteroposterior diameter, no lymphadenopathy, and macro/no calcifications had the highest specificity.**
***Conclusion*: Sonographic features of micro-calcifications, taller than wide AP diameter, central vascularity and hypoechogenicity warrant US-FNNA. A bigger study correlating thyroid sonography with histological diagnosis is recommended.**

INTRODUCTION

An estimated 200 million individuals worldwide have a thyroid disorder. Thyroid nodules are very common, and are found in 4 to 8% of adults by palpation, 41% by ultrasound, and 50% by pathologic examination at autopsy. The risk of malignancy in thyroid nodules is about 10% (3,4,5). Thyroid cancer is the most common endocrine malignancy with more deaths annually than all other endocrine cancers combined. The annual incidence rates range from 1 to 10 cases per 100,000 population. Nodular thyroid disease is more common than diffuse thyroid disease in Mulago hospital accounting for 82.2% of all the patients referred with thyroid symptoms. In Uganda the reported relative survival of patients with thyroid cancer after five years of diagnosis is 12.5%. compared to 96.6% worldwide. Ultrasound (US) is a standard imaging modality for nodules. Ultrasound guided Fine Needle Aspiration Biopsy (US-FNAB) is a standard diagnostic test for evaluating thyroid nodules however, in comparison to Fine Needle Aspiration Technique (FNAT), the Fine Needle Non- Aspiration Technique (FNNAT) has a better diagnostic yield and causes less bleeding. In Mulago Hospital US-FNAB of thyroid nodules is usually done without ultrasound guidance yet it is estimated that palpation alone fails to detect up to two thirds of sonographically identifiable nodules . Currently there is no protocol for Fine Needle Non-Aspiration (FNNA) of thyroid nodules at Mulago

hospital. It is important to become familiar with the morphologic features associated with benign or malignant nodules. Results of this study may help in the predictability of malignancy basing on the thyroid morphology at Ultrasound. Our results may still be of use in the formulation of a standardised protocol for FNNA and this will eventually result in early diagnosis and may improve the survival.

The specific objectives of this study were to describe the sonographic patterns of thyroid nodules in patients undergoing thyroid US, to correlate sonographic characteristics of thyroid nodules to US aided-FNNA cytology and finally to determine the sensitivity and specificity of Ultrasound in characterising thyroid nodules.

MATERIALS AND METHODS

Design: This was a cross sectional study.

Setting: The study was carried out in the department of Radiology at Mulago Teaching and National Referral Hospital in Kampala Uganda between the period of June 2012 to December 2013. The Hospital is a 1,500-bed unit providing tertiary diagnostic, curative, rehabilitative, preventive and teaching services. Patients were recruited from both Medical outpatient (MOTC) and Surgical outpatient thyroid clinics (SOTC). Approximately 28 and 25 patients attend the SOTC and MOTC clinics which run every Wednesday and Monday from 9:00 am to 2:00 pm.

Ethics, consent and inclusion criteria: The study was approved by the Radiology Department at Mulago Hospital and Makerere University institutional review boards.

Five to eight FNNA biopsies were performed weekly. All patients from the SOTC and MOTC clinics with thyroid nodules > 5mm and who consented to have US guided-FNNA were enrolled consecutively.

Nodule sampling procedure: All patients referred for thyroid scan were screened for nodules using US. Those with nodules and who consented were enrolled into the study. The author carried out all the US-aided FNNA procedures under the supervision of a radiologist and pathologist who were conversant with the FNNA technique. With the patient in supine and a pillow under the shoulders and Using the HD7 US equipment with a high frequency linear probe of 7.5MHz, US of the thyroid was done; for obese patients or for very big thyroid glands, a 5MHz transducer was used for penetration. Scanning was done in both transverse and longitudinal planes and colour Doppler imaging was utilised. For nodules, the size, site, shape, margins, echogenicity, AP diameter, vascularity, associated calcifications and lymphadenopathy were recorded. The final diagnosis was arrived at with the help of two radiologists. Under aseptic conditions and using the US guided-FNNA technique under the supervision of a both a radiologist and a pathologist, a maximum of two nodules, >5 mm were sampled in a patient and all nodules were sampled at two opposite sides at the periphery for adequate cell harvesting. A 23 gauge needle with clear hub and clear syringe (5-10 mls) was used to obtain an aspirate from the nodules. The aspirate was gently expelled onto the surface of a labelled microscope slide from the aspiration needle tip. A smearing slide would then be slid over the specimen ensuring that both slides are smeared. One slide would undergo wet-fixation with alcohol and this was stained using the Papanicolaou method while the other slide was air-dried at room temperature and this was stained with the Diff quick method. The smears together with accompanying request forms were then taken to the department of Pathology, Makerere University College of Health sciences for analysis using the Papanicolaou and Diff quick techniques.

Statistical analysis: All exposure variables were analyzed alongside the Cytology results. Categorical variables were summarised using numbers and percentages, while continuous data were summarised using median and inter-quartile range (IQR). We assessed for existence of statistical significance using the chi-square test and Wilcoxon runksum test for categorical and continuous variables respectively. To assess for accuracy of characterisation of the nodules to predict cytological findings, we checked for sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV), and Likelihood Ratios (both positive (LR+)and negative (LR-) together with their respective 95% confidence intervals. Only benign, suspicious for malignancy and malignant cytological results were included in these analyses; in-adequate and indeterminate cases were excluded. Statistically significant differences were defined as those with p-values of less than 0.05, and analyses were per¬formed using the Statistical Package for the Social Sciences (SPSS, version 18; SPSS, Chicago, IL, USA).

RESULTS

A total of 181 participants were enrolled into the study between March to December 2013. Three hundred and fourteen nodules of these patients underwent FNNA plus cytology; final diagnoses were concluded in all. Four patients were excluded from the analysis because their cytology results were indeterminate and thus cytology results for 177 study participants were available for statistical analysis. The sonographic characteristics including AP diameter, margins, echo-pattern, calcifications, vascularity and cervical lymphadenopathy were correlated with

cytology. The echo-patterns that were considered negative were hyperechoic and isoechoic whereas the hypoechoic, heterogeneous and echocomplex were analysed as positive. During analysis, benign cytology results were described as negative whereas suspicious and malignant cytology findings were described as positive.

Figure 1 shows the schematic flow of this study and final diagnoses.

Figure 1
The schematic flow of this study and final diagnoses

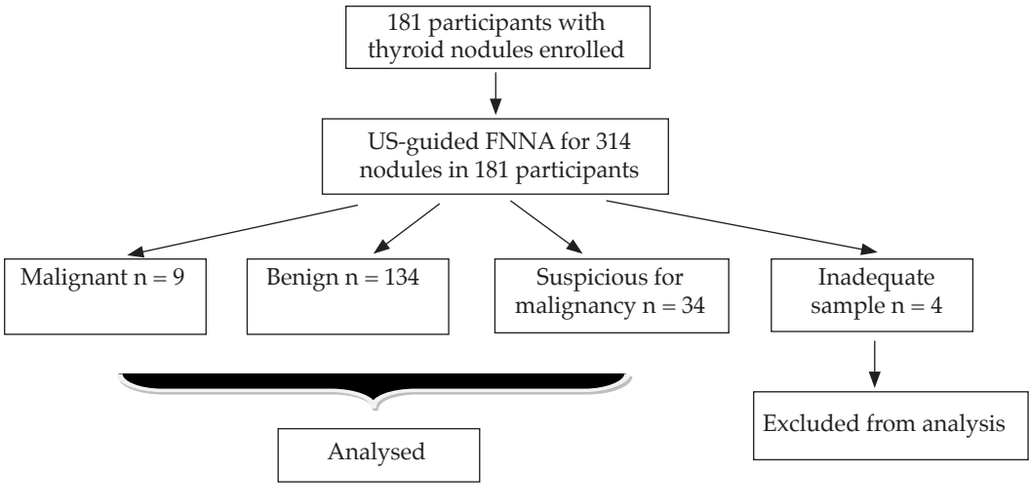

Figure 2 shows the cytology outcomes among study participants; Of the 181 participants, 5%(n=9) had malignant nodules, 19%(n=34) were suspicious for malignancy, 76%(n=138) were benign while 2.2%(n=4) were inadequate. For all the malignant nodules, the cytology result was papillary thyroid carcinoma.

Figure 2
Cytology outcomes among study participants

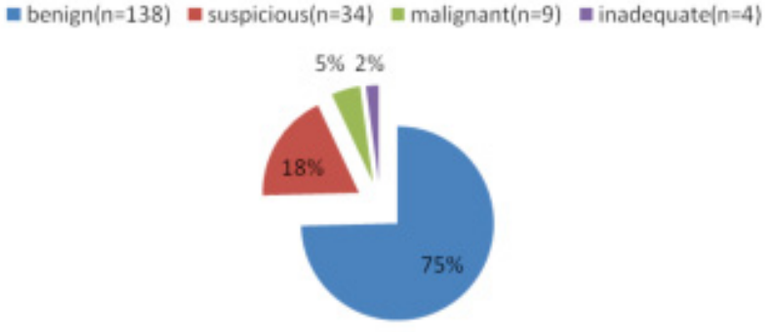

Figure 3 is a sagittal scan of a typical benign nodule showing an isoechoic nodule in a 39 year old female that was benign on cytology

Figure 3

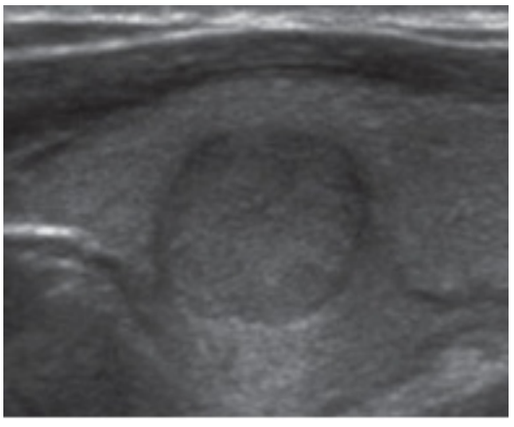

Figure 4 is a typical malignant nodule in 68-year-old male who had a solitary nodule. The nodule is irregular with microcalcifications Cytology results were malignant(papillary carcinoma).

Figure 4

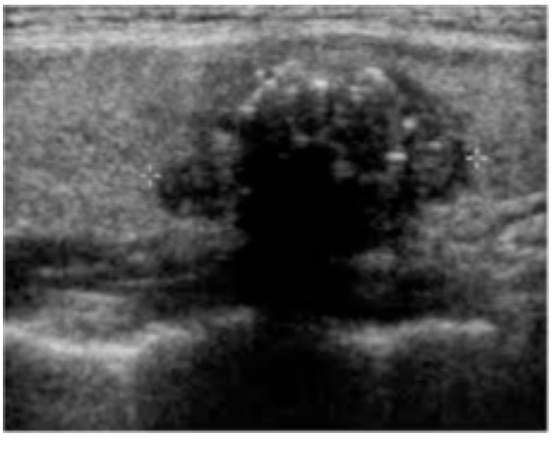

Figure 5 is a typical malignant nodule in 39-year-old male who had a solitary nodule. The nodule is irregular with bizarre margins and microcalcifications Cytology results were malignant (papillary carcinoma).

Figure 5

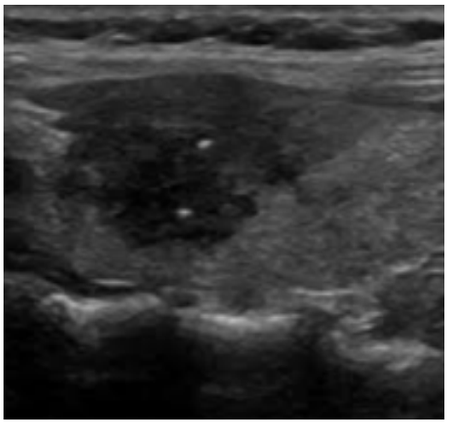

Table 1 shows the demographic and clinical characteristics stratified by cytology status. The patient population comprised of 93%(n = 164)female patients. Male to female sex ratio was 1: 13. The mean age of respondents was 42 years while the median age was 40 years. The interquartile range was 17 for those with positive cytology whereas it were 19 in those with negative cytology. The youngest participant was 19 years whereas the oldest participant was 83 years. The largest number of participants were from Uganda, 95.5% (n = 169) compared to 4.5% of non Ugandans. Of those with goitre 24% (n = 40) had positive cytology while 29% of those with no clinical goitre had positive cytology. The percentage of positive cytology in multinodular goitre was 22% whereas it were 31% in solitary nodular goitre.

Table 1

Variable	Cytology +ve	Cytology -ve	P-value
Female	126(71%)	38(21%)	0.535
Ugandans	41(23%)	128(72%)	0.445
Goitre	40(23%)	130(73%)	0.759
Solitary	12(7%)	27(15%)	0.291
Multinodular	30(17%)	107(60%)	

Table 2 shows the Bivariate analysis of US categories and the final diagnoses according to the cytological results; Intragroup comparison of sonographic features among benign and malignant nodules resulted in identification of a taller than wide AP diameter and intrinsic calcification as the only statistically significant predictors of malignancy respectively 16.7% and 23.8% sensitive and respectively 97.0% and 88.9% specific; $P < .005$. Margins, cervical lymphadenopathy and central vascularity did not show any significant difference between benign and malignant nodules in this study.

Table 2
Bivariate analysis of US categories and the final diagnoses according to the cytological results are summarised

Findings at US	cytology + (n)	Cytology - (n)	P-value
AP diameter			
Taller than wide	7(4.0%)	4(2.3%)	
Wider than tall	35(19.9%)	130(74%)	0.001
Margins			
Irregular/ill defined	9(5%)	14(7.9%)	
Smooth/well defined	33(18.8%)	120(68%)	0.065
Echo Pattern			
Positive	40(22.7%)	125(71%)	
Negative	2(1.1%)	9(5%)	0.648
Calcification			
Positive	10(5.7%)	15(8.7%)	
Negative	32(18.5%)	116(67%)	0.047
Lymphadenopathy			
Positive	4(2.3%)	6(3.4%)	
Negative	38(21.5%)	129(73%)	0.213
Vascularity			
Positive	40(22.5%)	113(63.8%)	
Negative	2(1.1%)	22(12%)	0.057

Table 3 shows the sonographic pattern and cytology diagnosis; The p-values of heterogeneous and hypoechoic nodules were statistically significant.(<0.05).

Table 3
Sonographic pattern and cytology diagnosis

Findings at US	cytology + (n)	Cytology - (n)	P-value
Isoechoic			
Positive	1(0.6%)	1(0.6%)	
Negative	41(23.2%)	134(75.7%)	0.38
Hypoechoic			
Positive	16(9.0%)	14(7.9%)	
Negative	26(14.7%)	121(68.3%)	0
Hyperechoic			
Positive	2(1.1%)	9(5.1)	
Negative	40(22.5%)	126(71%)	0.655
Heterogeneous			
Positive	21(11.9%)	103(58.2%)	
Negative	21(11.9%)	32(18.1%)	0.001
Echo-complex			
Positive	4(2.3%)	14(7.9%)	
Negative	38(21.5%)	121(68.4%)	0.874

Table 4 Shows the Senstivity, Specificity, Positve and Negative Predictive Values, Positive and Negative Likelihood Ratios of US features used to detect malignancy among 177 study participants.

Table 4

Showing Senstivity,Specificity, Positve and Negative Predictive Values, Positive and Negative Likelihood Ratios of US features used to detect malignancy among 177 study participants

	APDiameter	Margins	Calcification	Lympadenopathy	Vascularity	Echo Pattern
Sensitivity	16.67(6.97.0-31.36)	21.43(63.19-89.70)	23.8 (12.1-39.5)	9.52(2.66-22.62)	95.24(83.84--99.42)	95.24(83.84-99.42)
Specificty	97.01(92.53-99.18)	89.55(5.83-16.91)	88.9(82.3-93.6)	95.56(90.58-98.35)	16.30(10.50-23.63	6.72(3.12-12.37)
PPV(CI)	63.64 (30.79-89.07)	69.23(15.34-28.94)	40.0(21.1-61.3)	40.0(12.16-73.76)	26.14(19.40-34.00)	24.24(17.92-31.52)
NPV(CI)	79.79(72.75-84.76)	78.43(38.54-80.30)	78.9(71.6-85.1)	77.25(70.13-83.37	91.67(73.00-99.00	81.82(48.22-97.72)
PLR(CI)	5.58(1.72-18.14)	0.88(0.74-1.04)	2.08 (1.01-4.28)	2.14(0.63-7.24)	1.14(1.03-1.26)	24.2(17.9-31.5)
NLR(CI)	0.86(0.75-0.99)	2.05 (0.96-4.40)	0.86(0.72-1.03)	0.95(0.85-1.05)	0.29(0.07-1.19)	81.8(48.2-97.7)

The most sensitive sonographic characteristic in the diagnosis of malignancy were a positive echo-pattern and central vascularity at 95%. This implies that 95% of patients with positive cytology were correctly identified as having positive echo-pattern and central vascularity. Thus of the total respondents with positive cytology, only 5% were fasely diagonised as having a negative echo-pattern and no vascularity. Positive echo-pattern and central vascularity were highly suggestive of malignancy. US signs of wider than tall anteroposterior diameter, macro/no calcifications and absence of lymphadenopathy had high specificity rates of 97%, 89% and 96% respectively in the diagonosis of malignancy. This means basing on the above US signs, 3%, 11%, and 4% respectively of study participants with negative cytology were falsely identified as having positive AP diameter, microcalcifications and lymphadenopathy tests,and thus falsely identified as having the malignancy. A wider than taller AP diameter, absence of calcifications and absence of lymphadenopathy were seen to be highly suggestive of a negative cytology. Nodules with sonographic microcalcifications and Lymphadenopathy had 40% chance of having the malignancy while those with taller than wide diameter, had a 64% chance of having the malignancy. Nodules with no vascularity, negative echo-pattern and wider than tall AP diameter respectively had a 92%, 82% and 80% chance of not having malignancy.

DISCUSSION

Ultrasound imaging gives valuable diagnostic information prior to biopsy. Ultrasound also confirms that the lesion arises from the thyroid. It quantifies its size as well the number of lesions present. In correlating sonography with cytology most patients with clinically significant cancers go on to appropriate further investigations, but, much more importantly, most of the patients who have benign lesions can thereby avoid a costly and potentially harmful, further workup.

Females(93%, n=164) contributed the highest number of population in this study with a female to male ratio of 13:1 and literature in a general population survey showed that up to 4 to 8% of adult women and 1% to 2% of adult men have thyroid nodules detectable by physical examination. Our ratio is higher possibly because this was a survey in a national referral hospital that has the only thyroid clinic in the country. In other studies clinically apparent thyroid nodules were present in 6.4% of women and 1.5% of men with a ratio of 4:1 . This ratio is lower than the one found in our study and this is possibly because women are better seekers of medical treatment, are more aware of health issues and are also more beauty conscious.

The participants' mean age was 42 years; age range was 19 to 83 years. This is comparable with previous studies that have found a mean age, 49.7 years; range, 18-79 years , and in another study, there were 3011 women with mean age of 41.5 +/- 13.9 years, and 618 men with a mean age of 45.7 +/- 14.9 years.

The most common sonographic characteristics in this study were wider than tall AP diameter (93%), smooth margins (87%), macro/no calcifications(86%) and central vascularity(86%). A few nodules were

associated with lymphadenopathy(5.6%). The most common echo-pattern was heterogeneous (70%), hypoechoic(17%) and echocomplex(10%). Previous studies show heterogeneous as the most common echo-pattern.

In recent studies, the accuracy of FNA cytology has been reported as 69-97%. Marian et al found specimen adequacy to be 93.7% with FNNA and 88.3% with FNA and this difference was statistically significant (37) while another study found an inadequacy rate of 7% with FNNA and of 18.5% with FNA (33). In this study only the FNNA technique was used and the adequacy rate was 98% (177/181) while inadequacy rate was 2.2%(n = 4).

Of the 181 participants, 5% had malignant nodules, 18% were suspicious for malignancy, 75% were benign and 2% were inadequate samples. The rate of malignancy in thyroid nodules is a range of 5-10% in previous studies (3,17). Papillary thyroid carcinoma is the most common thyroid malignancy and accounts for up to 90% of thyroid malignancies (21), worldwide. In our study only nine participants had malignant nodules and 100% of maliganancies were papillary thyroid carcinoma. In Makoba's study titled "The role of Ultrasound and Ultrasound guided FNAB in the management of thyroid disease at Mulago Hospital" (unpublished study) found that 85% of the nodules were benign, with a higher rate malignancy at 8.5% while 6.2% were inadequate however, in Makoba's study Follicular carcinoma accounted for 57.1% while papillary carcinoma accounted for 42.9% (5).

The average age of the participants with malignancy was 45 years while average age of males and females was with 49 and 44 years compared to previous studies that have shown peak incidence of thyroid cancer diagnosis at 65 to 69 years in men and 45 to 49 years in women (21).

Studies done in Uganda show an annual incidence of thyroid cancer in Kyadondo county of 1.6-1.9/100,000 in females and 0.8-5.0/100,000 males where as in this study incidence was not estimated but the prevalence of cancer was 15.4% in males and 4.3% in females. A previous study reports that about 0·5% of thyroid cancer is in men and while 1·5% is in women.

The percentage of positive cytology in multinodular goitre was 22% whereas it was 31% in solitary nodular goitre. Reported prevalence of thyroid carcinoma in an asymptomatic solitarynodule is 3.4-29%. Some studies show no difference in the rates of malignancy of either solitary or multiple nodules. In a meta-analysis of these studies, the risk of thyroid cancer was significantly lower in the multinodular group but there were some inconsistencies among the studies.

Statistically significant predictors of malignancy in our study were identification of a taller than wide AP diameter and intrinsic microcalcification; respectively 16.7% and 23.8% sensitive , and respectively 97.0% and 88.9% specific; P<.005 while in another study by Jason D Iannuccilli *et al*, intragroup comparison of sonographic features among benign and malignant nodules resulted in identification of intrinsic calcification as the only statistically significant predictor of malignancy (35.3% sensitive and 94.4% specific; P < .005). In another study by Peccin S *et al*, microcalcifications had a sensitivity of 56%, specificity of 94% (31) while Kim EK found that microcalications were highly specific for malignancy with a specificity of 93 to 95% while the sensitivity was lower at 29 to 59% and the prospective positive predictive value was 70 to 71%. These findings are comparable to our study where the sensitivity, specificity and PPV of microcalcifications were 24%, 89% and 40% respectively. The microcalcifications seen in malignant tumours are dystrophic, the irregular margins are as a result of malignant tumours growing by infiltration of surrounding tissues while the central vascularity is explained by angiogenesis where tumours have their own blood supply. These findings reflect that malignant nodules grow across the normal tissue plane in a centrifugal way, while benign nodules grow along the tissue plane in a parallel fashion.

The most sensitive sonographic characteristics in the diagnosis of malignancy were a positive (hypoechoic, heterogeneous, echocomplex) echo-pattern(95%) and presence of central vascularity (95%). US signs of Anteroposterior diameter, lymphadenopathy and microcalcifications had the highest specificity rates of 97%, 96% and 89% respectively in the diagonosis of malignancy. The heterogeneous (0.001) and hypoechoic(0.00) echo-patterns were also significantly correlated with final cytology diagnosis (p< 0.005). Monn *et al* found a sensitivity and specificity of the hypoechogenicity to be 80 and 53% respectively while Peccin S *et al* found that hypoechogenicity had a sensitivity and specificity 44 and 83% respectively. In general, the sensitivity and specificity are higher in our study probably because we used the US-guided FNNA technique that has a higher cell yield compared to US-guided FNA. Previous studies reviewed used the FNA technique while in this study the FNNA technique was used in our study. Nyonyintono and Olwa compared FNNA with FNA in thyroid nodules and head-neck cancers and found that the FNNA technique had a better yield of cells for cytodiagnosis (9,10). This is the first study done in Uganda to correlate sonography with cytology using the US-guided FNNA method.

In this study intranodular colour flow on doppler was found in 95% with positive cytology and in 84% in those with negative cytology and it was not a statistically significant predictor of malignancy(P=0.057) compared to a study done by

T. Rago where an intranodular flow pattern was found in 50%(15/30) with cancer and in 10.8%(8/74) of the benign nodules ($P < 0.0001$; specificity 89.0%, sensitivity 50.0%). Emmanuel Varverakis found that color Doppler sonography contributes to the differential diagnosis of vascularised large nodules, although it is less helpful in non-vascularised small ones and that Peripheral vascularisation is a feature of benignancy with high specificity, although it can also be revealed by high resolution conventional sonography while central vascularisation is a feature of malignancy with medium specificity .

The highest PPVs were observed in taller than wide nodules(64%) and microcalcifications(40%) and this is comparable to a study by Peccin S *et al* where the PPVs for malignancy were taller than wide shape(59.8%) and microcalcifications(38.6%) The highest NPVs were in nodules with no vascularity, negative echo-pattern and wider than tall AP diameter at NPVs of 92% , 82% and 80% respectively. In another study by Kim EK *et al,* the overall PPV and NPV of sonography were 56.1 and 95.9% respectively. There is no study that has looked at individual NPVs for the sonographic characteristics.

STUDY LIMITATIONS

There may be a possibilty of having missed follicular carcinoma(FC) since on FNNA samples, marked cytological atypias are only observed in moderately to poorly differentiated FC while they may be completely lacking in well differentiated angio- or capsulo-invasive FC. In this study, thyroid nodules with benign and malignant cytologic results without surgery were included yet false-negative and false-positive cytologic results may exist. Histology gives the ultimate diagnosis for nodules especially for the suspicious nodules but this was not done in this study.

In conclusion, sonographic features of microcalcifications, taller than wide shape, central vascularity, hypoechoic, and heterogeneous echo-patterns warrant US-FNNA. The most sensitive sonographic characteristics in the diagnosis of malignancy were heterogeneous and hypoechoic echo-patterns and presence of central vascularity whereas a wider than tall anteroposterior diameter, macro/no calcifications and absence of cervical lymphadenopathy had the highest specificity rates in the diagnosis of malignancy. US-aided FNNA has a good diagnostic yield.

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