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Performance of Thyroid Fine-Needle Aspiration Biopsy in a Low- and Middle-Income Country

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Keywords
Thyroid · Fine needle aspiration · Africa · South Africa · Risk of malignancy

Abstract

Introduction: The 6 categories of the Bethesda System for Reporting Thyroid Cytology (TBSRTC) with associated risk of malignancy (ROM) provide evidence-based clinical management guidelines. This study aimed to determine the ROM and accuracy of FNAB in South Africa (SA). ***Methods:*** Thyroid specimens from 3 pathology laboratories registered between January 2015 and December 2019 were considered for inclusion. ROM was obtained per TBSRTC category by cytohistological correlation and dividing the total number of specimens with malignant histology by the total number of cases operated. Accuracy was calculated based on the Bethesda category and eventual malignant histology. ***Results:*** Seventeen thousand seven hundred and seventy-three histology and 4,791 cytology cases were identified. Of the 4,791 cytology cases, 931 (19%) underwent surgery. More than a third (333, 35.8%) of cases were confirmed as malignant following histological assessment, with the majority being benign (584, 62.7%). The ROM for the nondiagnostic and benign categories was 24.3% and 20.5%. The highest ROM was for category VI (91.5%), followed by categories V (69.5%), IV (51.9%), and III (38.8%). Thyroid FNAB had a sensitivity of 73%, specificity of 74%, and overall accuracy of 74%. ***Conclusion:*** Bethesda categories II and IV have a relatively higher ROM in SA compared to findings from other developed countries. The diagnostic accuracy of thyroid FNAB in SA and the high rate of nondiagnostic diagnoses (38%) require further investigation. A national thyroid registry could provide location-specific data to aid the implementation of appropriate local policies and national guidelines for practicing thyroid surgeons.

Introduction

Palpable thyroid nodules are common, detected in 33–68% of the population on high-resolution ultrasound (US) [1–3]. The risk of malignancy (ROM) of thyroid

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Table 1. Distribution and ROM of Bethesda categories according to the 1st, 2nd, and 3rd editions

Bethesda category	Distribution of Bethesda categories meta-analysis 2012 [12] (%)	ROM % 1st edition 2009 [13]	ROM % 2nd edition 2017 [10]	ROM % 3rd edition 2023 [14]	Recommended management 2023 [14]
I Nondiagnostic	12.9	1–4	5–10	5–20	Repeat FNAB with US guidance
II Benign	59.3	0–3	0–3	2–7	Clinical and US follow-up
III AUS/FLUS	9.6	5–15	10–30	13–30	Repeat FNAB, molecular testing, diagnostic lobectomy or surveillance
IV FN/SFN	10.1	15–30	25–40	23–34	Molecular testing, diagnostic lobectomy
V Suspicious for malignancy	2.7	60–75	50–75	67–83	Molecular testing, lobectomy or total thyroidectomy
VI Malignant	5.4	97–99	97–99	97–100	Lobectomy or total thyroidectomy

ROM, risk of malignancy; AUS, atypia of undetermined significance; FLUS, follicular lesion of undetermined significance; FN, follicular neoplasm; SFN, suspicious for follicular neoplasm.

nodules is determined by clinical, US, and cytology assessment and ranges between 5% and 10% [4–7]. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was introduced in 2007, resulting in less ambiguous diagnoses and lower rates of unnecessary surgery while maintaining the accuracy of fine-needle aspiration biopsy (FNAB) results [8, 9]. The 6-tiered TBSRTC system provides evidence-based clinical management recommendations [7, 10, 11]. The distribution of Bethesda categories is reported in a meta-analysis conducted by Bongiovanni (n = 25,445) and presented in Table 1 [12], with ROM for each diagnostic category varying as diagnostic criteria evolved over time.

Surgery is indicated for Bethesda VI (malignant) and follow-up for Bethesda II (benign) nodules, with the management of indeterminate nodules being less precise. Management recommendations for indeterminate categories (Bethesda III, IV, and V) include, amongst others, molecular testing [7], which further defines the ROM, limiting unnecessary surgery, and tailoring surgical approaches [15, 16]. Molecular tests are costly and currently not available in South Africa (SA). Reported thyroid FNAB surgical rates in low- and middle-income countries (LMICs) are similar to those determined in high-income countries (HICs) (13.5–41.8% and 18.5–61%, respectively) [17–21].

The diagnostic accuracy of thyroid FNAB ranges between 69% and 78% [12, 22]. Substantial interobserver variability between cytopathologists exists and can be minimized by standardizing FNAB procedures, reducing unnecessary biopsies in benign nodules, and implementing rapid onsite cytology evaluation (ROSE) to ensure the adequacy of specimens [23–25]. Reporting improves when cytopathologists are onsite, as clinical and US parameters are also considered [23].

There is limited evidence about the ROM and diagnostic accuracy of thyroid FNAB in Sub-Saharan Africa [24, 26]. In 2013, researchers from Groote Schuur Hospital (GSH) in Cape Town, SA, determined a thyroid FNAB sensitivity of 44.7% in 109 patients [26]. In 2022, researchers at Tygerberg Hospital (TBH) in Cape Town, SA, determined the ROM for the Bethesda categories, with findings showing improved inadequacy rates (34.3–16.2%) after establishing a multidisciplinary thyroid clinic [24].

This knowledge gap is echoed by Ogbera et al. [27] in their review of thyroid disease epidemiology in Africa, emphasizing the need for thyroid registries in Africa. In 2022, Sajisevi et al. analyzed the mode of detection of thyroid cancer in 16 centers (USA, Canada, Denmark, and SA) across 4 countries. Extensive variation in practice was noted between the countries, with patients presenting more commonly with symptoms in SA and Denmark, compared to incidental detection with no thyroid symptoms in the USA and Canada [28]. The findings emphasize the need for national data collection, not only extrapolating evidence from developed countries. This study aimed to determine the ROM and diagnostic accuracy of thyroid FNAB in a large SA population.

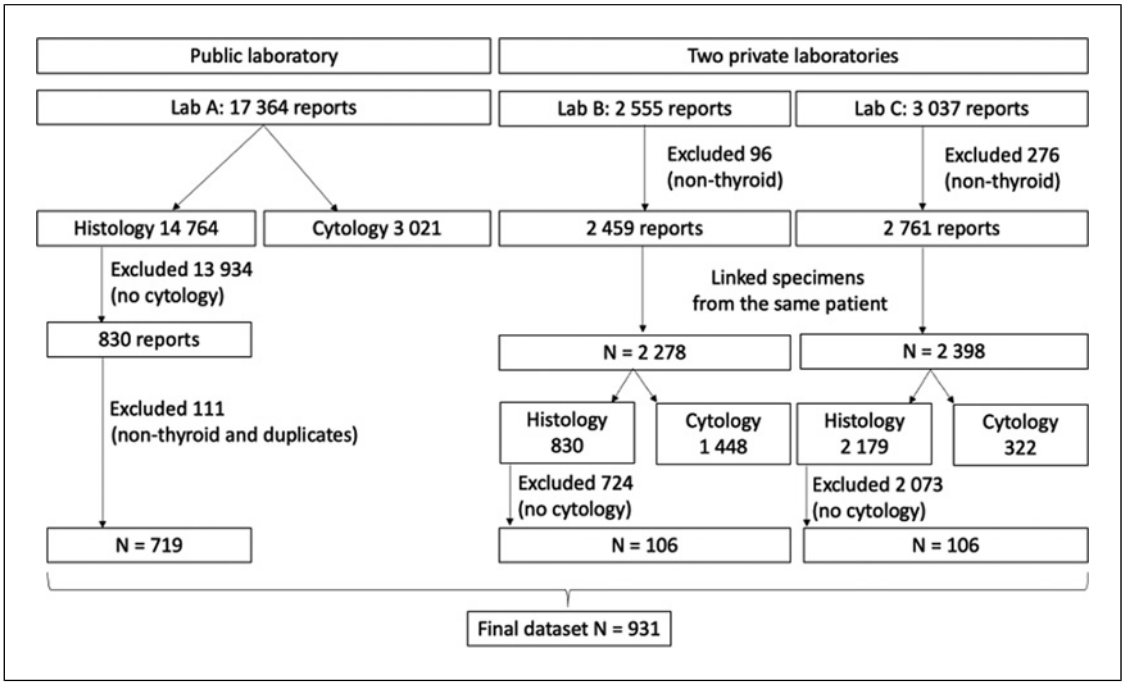


Fig. 1. Flow diagram indicating inclusion and exclusion.

Methods

Thyroid specimens from 3 SA laboratories (1 public, 2 private), registered between January 2015 and December 2019, were included. Histology results were categorized into benign or malignant according to the 2022 World Health Organization classification of thyroid tumors [29]. Cytology and histology reports from the same patient were matched, and only cases with both cytology and histology reports were included in the final dataset. Bethesda I and III were excluded in the calculation of diagnostic accuracy as these categories commonly require re-biopsy and not surgery [12, 19].

The 2009 TBSRTC was used as a model to create the statistical analysis plan [10]. The distribution of cases in the TBSRTC was determined by dividing the number of FNABs in each category by the total number of FNABs [19]. Cytohistological correlation assessing the ROM was obtained per category by dividing the total number of malignant histology results by the total number of cases operated. The diagnostic accuracy of FNAB was calculated based on all patients who had surgery and not on all cytology specimens [18, 21, 22, 30–32]. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated based on the two groups: TBSRTC category and malignancy (histology) [32].

Results

After removing duplicates, 17,773 histology cases and 4,791 cytology cases were identified (Fig. 1). Overall cytology results were reported as Bethesda I (non-diagnostic) in 38% (n = 1,810) and Bethesda II (benign) in 43% (n = 2,027) (Table 2). Of the 931 operated patients where correlating cytology was performed, 778 (83.6%) were female, and the median age was 50 (IQR 41–61).

Only 931 (0.5%) of 17,773 histology cases had correlating cytology, indicating a 19% surgery rate in all FNAB cases (Table 3). The final histological diagnosis for each TBSRTC category is presented in Table 4. Overall, 333 (35.8%) cases were malignant, and 14 were low-risk neoplasms (including NIFTP, follicular thyroid tumor of uncertain malignant potential, and hyalinizing trabecular tumor) [29]. Benign histology (Table 4) was reported in 589 (63%) cases, with thyroid follicular nodular disease being the most common. There were 216 papillary thyroid cancers compared to 44 follicular thyroid cancers. Of the 216 papillary thyroid cancers, 33 (15%) were smaller than 1 cm.

The ROM in nondiagnostic samples and benign FNAB was 24.3% and 20.5%, respectively (Fig. 2). The highest ROM was in category VI (91.5%), followed by categories V (69.5%), IV (51.9%), and III (38.8%). Nine low-risk neoplasms were excluded when calculating the ROM.

The diagnostic accuracy of FNAB was 74%, with a sensitivity of 73% and specificity of 74%. The positive predictive value was 67%, and the negative predictive value was 79%.

Table 2. Distribution of Bethesda categories and cytohistological correlation for operated patients

Bethesda category	All cytology, *n* = 4,791 (% of total)	Cytology cases with correlating histology, *n* = 931 (% operated)	Benign histology, *n* = 589 (% operated)	Malignant histology, *n* = 333 (% operated)	Low-risk neoplasms, *n* = 9 (% operated)
I	1,810 (38)	288 (16)	216 (75)	70 (24)	2 (0.7)
II	2,072 (43)	292 (14)	232 (79)	60 (21)	0 (0)
III	303 (6)	98 (32)	59 (60)	38 (39)	1 (0.1)
IV	314 (7)	135 (43)	60 (44)	70 (52)	5 (0.04)
V	125 (3)	59 (47)	17 (29)	41 (69)	1 (0.02)
VI	167 (3)	59 (35)	5 (8)	54 (92)	0 (0)
Total	4,791 (100)	931 (19)	589 (63)	333 (36)	9 (0.01)

Table 3. Surgical rate in the current study and other low- and middle-income countries

	Tepeoglu, Turkey (2014) [17]	Mahajan, India (2017) [18]	Reuters, Brazil (2018) [19]	Zhu, China (2020) [20]	Kamboj, India (2022) [21]	Current study, SA (2023)
Cytology number	1,021	4,532	585	2,781	431	4,791
Surgery number	220	335	245	1,122	142	931
Surgery rate (%)	21.5	13.5	41.8	40.3	33	19.0

Table 4. Final histopathology report for each Bethesda category [29]

Bethesda category	Follicular-derived neoplasms									Thyroid C-cell-derived carcinoma	Other		Total
	Benign lesions			Low-risk neoplasms, e.g., NIFTP	Malignant thyroid neoplasms						Benign[a]	Malignant[b]	
	T-FND	FA	OA		PTC	FTC	OCA	PDTC	ACA	MTC			
I	150	39	6	8	38	16	5	8	0	2	15	1	288
II	157	40	9	5	50	6	1	3	0	1	20	1	292
III	34	9	5	4	24	5	4	3	2	0	9	0	98
IV	36	12	8	5	29	15	9	10	0	5	4	2	135
V	9	4	1	2	35	0	0	0	0	2	3	4	59
VI	1	0	0	1	41	1	0	1	4	3	4	4	59
Total	381	104	4	25	217	43	19	25	6	13	55	12	931

T-FND, thyroid follicular nodular disease; FA, follicular adenoma; OA, oncocytic adenoma; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; OCA, oncocytic carcinoma of thyroid; PDTC, poorly differentiated thyroid carcinoma; ACA, anaplastic thyroid carcinoma; MTC, medullary thyroid carcinoma. [a]Other benign (thyroiditis 27, normal thyroid 14, thyroglossal duct cyst 2, other 12). [b]Other malignant (lymphoma 4, squamous cell carcinoma 5, metastases 2, non-medullary neuroendocrine tumor 1).

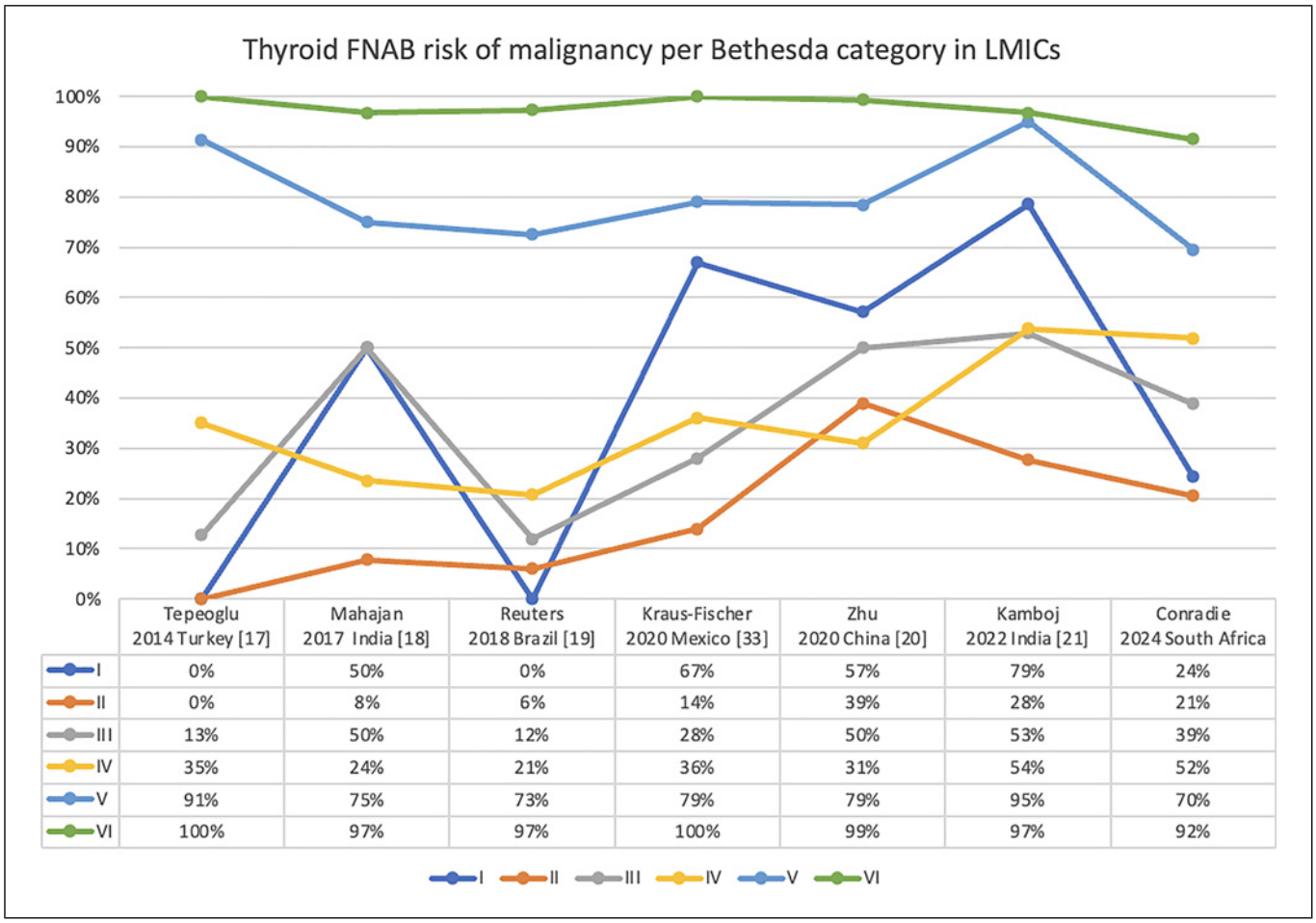
Discussion

This study calculated the ROM and diagnostic accuracy of FNAB in SA, with 77% of the data representing the single public health system laboratory utilized by 84% of the country's population [34]. The SA health system is divided into public and private healthcare sectors. The public health care system serves 84% of the population, with a maldistribution of doctors – only 30% of doctors working in the public sector. The public sector is in a chronic state of distress,

Table 5. Diagnostic accuracy of thyroid FNAB for the current study and other low- and middle-income countries

	Mahajan, India [18]	Reuters, Brazil [19] (%)	Kraus Fischer, Mexico [33] (%)	Zhu, China [20] (%)	Kamboj, India [21] (%)	Current study, SA
Sensitivity	80.5	92.1	92.5	98.1	94.4	73
Specificity	85.9	67.8	63.1	81.5	61.9	74
PPV	80.7	61.4	78.7	99.3	90.3	67
NPV	85.7	93.9	–	61.1	72.2	79
Accuracy	82.4	–	80.8	97.5	–	74

PPV, positive predictive value; NPV, negative predictive value.



	Tepeoglu 2014 Turkey [17]	Mahajan 2017 India [18]	Reuters 2018 Brazil [19]	Kraus-Fischer 2020 Mexico [33]	Zhu 2020 China [20]	Kamboj 2022 India [21]	Conradie 2024 South Africa
I	0%	50%	0%	67%	57%	79%	24%
II	0%	8%	6%	14%	39%	28%	21%
III	13%	50%	12%	28%	50%	53%	39%
IV	35%	24%	21%	36%	31%	54%	52%
V	91%	75%	73%	79%	79%	95%	70%
VI	100%	97%	97%	100%	99%	97%	92%

Fig. 2. ROM per Bethesda category compared to findings from other low- and middle-income countries [17–19, 21, 33].

with a high burden of traumatic injuries, violence, and chronic diseases, limited resources and access to care [34].

The current study's 38% nondiagnostic rate is higher than the previously reported 15% [35]. This high rate may, in part, be due to staff shortages, lack of seniority at healthcare facilities, limited FNAB technique training, limitations in availability of senior staff, and access to US and ROSE. Implementing a multidisciplinary biopsy team may decrease the nondiagnostic rate to 16.2%, as in the previous study [24].

Similarly, the thyroid surgery rate of 19% determined in the current study may be due to various factors,

including limited access to surgery, loss to follow-up, patient preference, a difference in surgical threshold, or incomplete laboratory data. The data revealed mostly histology cases, with limited correlating thyroid cytology (0.5%), suggesting that many thyroid surgeries are being performed without FNAB, contrary to recommendations by the American Thyroid Association [7]. The limited number of cytological reports may be explained by clinical/sonographic concerns or cytology at a different laboratory. The low surgical rate (35%) for Bethesda VI nodules may be explained by unresectable disease, patients declining surgery, histology reported at a different laboratory, or poor follow-up of results.

Over the last 2 decades, the ROM diagnostic criteria have evolved. In the current study, ROM in most categories is higher than in other countries, particularly for follicular neoplasms (51.9%). This increased ROM raises questions about differences in thyroid disease management in SA. We hypothesize that the thyroid surgery threshold in SA is much higher, and therefore, only patients with highly suspicious nodules are offered surgery. As highlighted in the Sajisevi study, this may be explained by a rural population with limited access to specialized care [28].

Studies examining the accuracy of thyroid FNABs reveal a wide range of sensitivities (80.5–98.1%) [26, 36]. The sensitivity and specificity determined in this study is lower compared to some LMICs, suggesting more false positives. An FNAB reported as suspicious for malignancy will result in unnecessary interventions or surgeries, and overtreatment of thyroid nodules.

The accuracy rate of thyroid FNAB (74%) can be addressed by improving specimen retrieval and interpretation errors. To help increase the accuracy of FNABs, multiple passes of various parts of a large nodule can be performed to reduce the false-negative rate. To prevent interpretation errors, cytopathologists can revisit the criteria for identifying cystic lesions, thyroiditis, and adenomatous hyperplasia to minimize false-positive diagnoses. Careful patient selection for FNAB, skill and expertise development in FNAB, and the utilization of molecular testing may improve diagnostic accuracy in SA [37–39].

This study highlights several challenges encountered in investigating thyroid disease management in SA. Difficulties in terms of recruitment, participation, and time were encountered. Data capturing was labor and time-intensive as reports were received as single text files, PDFs, and Excel sheets containing thousands of text reports requiring extraction from every individual report. Selection bias for surgery served as a limitation. The ROM and diagnostic accuracy were calculated based on surgical cases with benign thyroid nodules not undergoing surgery. This may have skewed results, similar to other referenced studies [18, 21, 22, 30–32].

The challenges encountered with data acquisition and the variation in diagnostic accuracy and ROM compared to other publications support the implementation of a prospectively collected national thyroid registry that will inform decision-making and local guidelines, promote collaboration, and improve thyroid nodule management in SA.

Conclusion

In SA, thyroid FNAB reflects a higher ROM with a lower surgical rate compared to other international publications. The diagnostic accuracy of thyroid FNAB in SA and the high rate of nondiagnostic diagnoses (38%) is concerning and requires further investigation. Country and institution-based rates should be tracked by locally driven research, and a uniform national registry could allow for centralized data collection and contextual analysis, informing more appropriate interventions.

Statement of Ethics

This study was approved by the Health Research Ethics Committee of the University of Stellenbosch (S23/05/115). A waiver of written informed consent was granted by the Health Research Ethics Committee of the University of Stellenbosch (S23/05/115).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

W.C. and K.B. contributed to the design and implementation of the study. W.C., K.B., T.L., J.B., J.D., F.C., A.A., J.L., and R.R. contributed to the analysis, interpretation, and writing of the manuscript. All authors approved the final paper.

Data Availability Statement

Data will not be publicly accessible due to ethical reasons. The corresponding author may be contacted directly in this regard.

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