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ENDOCRINE SURGERY

The spectrum of thyroid disease requiring surgery: a single centre experience in South Africa

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Background: Thyroid disease is a frequently encountered condition for the general surgeon. Limited literature on surgery for thyroid disease is available from the study area in KwaZulu-Natal which has a largely rural Black population of over three million people. The aim of the study is to audit the spectrum of surgically managed thyroid disease in a tertiary hospital.
Methods: Descriptive analysis of six-years of prospectively collected thyroid surgery data from a tertiary hospital. Demographics, surgical indications, procedures, and histologies were studied and comparative analysis performed.
Results: 346 patients with a female:male ratio of 22:1; age: 19–91 years, mean 51. The majority (77%) were Black ethnicity. 377 operations were performed. 346 patients had either a lobectomy (64.7%), subtotal thyroidectomy (13.6), or total thyroidectomy (21.7%) at the initial surgery. Re-do surgery was performed in 31 patients. The majority of surgery was for therapeutic indications, 65% for symptomatic multinodular goitre (MNG). Thyroid carcinoma (TC) was more frequently diagnosed in older female patients and 91.8% were well-differentiated TC. Two-thirds of diagnostic thyroid procedures found an adenoma.
Conclusion: Thyroid pathology is prevalent in the study region. Most thyroid surgery was for middle-aged women with MNG which harboured TC in 11.2% of cases. A larger thyroid nodule did not correlate with the increased likelihood of TC. Follicular carcinoma was higher than international studies as was follicular variant of papillary thyroid cancer which may be explained by the study population. A national database is needed to audit the spectrum of thyroid disease requiring surgery across South Africa.
Keywords: multinodular goitre, thyroid adenoma, thyroid cancer, follicular carcinoma, KwaZulu-Natal province

Introduction

Thyroid disorders represent a significant global health burden, with surgical intervention being a cornerstone of management for various benign and malignant conditions. The epidemiology, clinical presentation, and pathology exhibit considerable variation across different geological regions and healthcare settings, influenced by factors such as iodine availability, socioeconomic status and access to surgical care. Thyroid surgery is commonly undertaken in South Africa (SA). However, the spectrum of surgically managed disease is not widely documented, and neither are the clinicopathological indications, operations, or the histological findings. With a unique population of mainly Black rural patients, we undertook this study to evaluate what our clinical practice involved and how it compared to other provinces in SA, Africa, and higher-income countries. It was our impression that a benign goitre is still the main indication for thyroid surgery despite compulsory table salt iodisation which became legislation in SA in 1995 and the knowledge that iodine is the most important environmental factor for goitre development.[1] In our setting, lobectomy was considered for multinodular goitre (MNG) if the disease was predominantly unilateral with no or minimal contralateral involvement so as to preserve thyroid function and avoid thyroid hormone replacement in a low resourced environment where patients have challenges accessing long term thyroid medication and monitoring. Otherwise, a total thyroidectomy was performed.

Other indications for surgery included thyroid malignancy, hyperthyroidism, and diagnostic procedures for suspicious or indeterminate nodules.

The incidence of thyroid cancer (TC) in the study area is unknown, and a high rate of thyroid follicular carcinoma (FC) was queried, which may reflect iodine deficiency. A recent multi-institutional study described the landscape of TC in SA and revealed considerable differences compared to international studies and variation in regional patterns.[2]

There is a paucity of research on thyroid surgery from KwaZulu-Natal province, and none from the study catchment area of over three million people. Our findings document the spectrum of thyroid surgery done at a single institution and provide specific data relevant to a largely rural South African setting which is compared with existing literature to highlight variations.

Methods

A descriptive retrospective study was undertaken of all thyroid surgeries performed at a tertiary hospital in Pietermaritzburg, KwaZulu-Natal, SA, over a six-year period from January 2013 to December 2018. Patients were identified from a surgeon's logbook and the Hybrid Electronic Medical Registry (HEMR) surgical database. Demographic data, clinical presentation, indication for surgery, operative intervention, and pathology were recorded from medical files and the HEMR reports. Self-reported ethnicity was recorded on the HEMR database.

The main indications for thyroid surgery were recorded as either therapeutic (goitre with compressive and/or cosmetic concern, laboratory confirmed hyperthyroidism, or cytologically proven malignancy) and/or diagnostic (solitary or suspicious nodule(s) requiring definitive diagnosis).

The operative interventions were documented as total thyroidectomy (TT), lobectomy, subtotal thyroidectomy, or re-do/completion thyroidectomy. Primary and any secondary pathologies, gland size and weight, and tumour size (if applicable) were noted.

De-identified data was entered into an Excel spreadsheet and saved on a password encrypted computer. Inclusion criteria were patients over 18 years who underwent thyroid surgery with available histological reporting.

Patients who only had a thyroid biopsy (core needle histology or fine needle aspiration cytology (FNAC)) without an operation, patients whose thyroid surgery was done as part of another operative intervention, and patients who had redo thyroid surgery with initial operation done before the study time period were excluded from the analysis.

Ethical approval was granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (KZN), South Africa (reference number BCA207/09 and BCA221/13).

Statistical analysis

Statistical analysis was performed using the R language for statistical computing (R version 4.1.1). Summary statistics for numerical variables were expressed as mean, standard deviation, median, range, and interquartile range values as appropriate. Continuous data were compared using a *t*-test or a Mann–Whitney-U test, comparing the mean or median of two groups. A χ^2 test for independence was used to evaluate the association between categorical variables. The chosen level of significance was $p < 0.05$.

Results

Of the total of 353 patients who underwent thyroid surgery during the study period, histology was available for 346 who formed the study cohort. Table I summarises demographics, indications for surgery, and surgical procedures. There was a female:male ratio of 22:1. Patient age ranged from 19 to 91 years with a mean of 50.9 years (SD 14.0) and median of 51 years. The average age for males was 47.5 years and 51.1 years for females. Most patients, 266 (76.9%) self-reported as Black.

The indications for thyroid surgery were therapeutic in 79.8% and diagnostic in 20.2%.

A total of 377 thyroid surgeries were performed on 346 patients. Of the 346 initial surgeries, a lobectomy was most often performed, 224 (64.7%). Completion thyroidectomies, for malignancy, were done for 31/271 (11.4%) patients. Overall, 30.6% had all thyroid tissue removed.

A total of 224 patients had either a lobectomy or a TT for non-toxic MNG. The average lobectomy weight was 101.8 grams (g) and 212.6 g for TT. The heaviest goitre weighed 1320 g. Incidental carcinomas were found in 25 (11.2%) of surgeries for MNG. No surgeries were performed for recurrence or progression of MNG following lobectomy during the study period.

Seventy patients had diagnostic surgery for solitary or concerning thyroid nodule(s) which demonstrated indeterminate or atypical cells or a follicular neoplasm or two inadequate smears on FNAC. Six (8.6%) of the diagnostic surgery patients had TT as initial surgery for a high index of suspicion for thyroid malignancy (all confirmed malignant on histology), and the remaining 64 (91.4%) patients had lobectomies. The pathology of the diagnostic surgeries was benign adenoma in 47 (67%) patients and TC in 23 (33%) of patients. There was no difference in the average size of TC and adenomas ($p > 0.05$) (Figure 1).

Thyroid malignancy was identified in 61 (17.6%) of all surgeries: 2/15 (13.3%) men and 59/335 (17.6%) women. The average age of TC patients was 55.6 years (SD 15.38) compared to 49.9 years (SD 13.55) for those with benign pathology; this was statistically significant ($p = 0.02$). The majority (91.8%) were well differentiated thyroid cancer (WDTC): papillary thyroid carcinoma (PTC) in 44.2%, FC also in 44.2%, and oncocytic carcinoma (OC) in 2.3% (Table II).

The incidental TC in operations for MNG were: 12 (48%) PTC, eight (32%) FC, two (8%) anaplastic carcinoma, two (8%) OC, and one (5%) medullary thyroid carcinoma (MTC). Two of the PTCs were in solitary cysts (Table II).

Analysis of ethnicity and TC showed that White patients had more PTC (80%) compared to Black patients (35.4%) ($p = 0.049$). Fifty-two per cent of the TC in Black patients was FC. Black patients had a PTC:FC ratio of 0.7:1 compared with a ratio in White patients of 4:1 and in Indian patients of 3:1 (Table II).

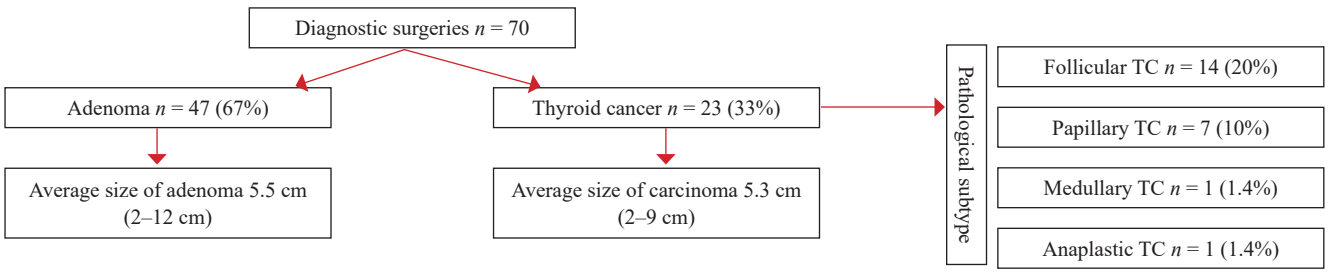

Figure 1: Pathology of diagnostic surgeries
TC – Thyroid cancer

Table I: Patient demographics, indications for surgery and thyroid procedures

Demographics		*n*	%
Sex	Female	331	95.7
	Male	15	4.3
Ethnicity	Black	266	76.9
	Indian	54	15.6
	White	23	6.6
	Coloured	3	0.9
Indication for surgery			
Therapeutic 79.8%	Compressive / cosmetic	224	64.7
	Carcinoma	13	3.8
	Hyperthyroid	39	11.3
Diagnostic 20.2%	Suspicious/indeterminate nodule(s)	70	20.2
Thyroid procedure			
Initial thyroid procedure *n* = 346	Lobectomy	224	64.7
	Total Thyroidectomy	75	21.7
	Subtotal thyroidectomy	47	13.6
Completion thyroidectomy (post lobectomy or subtotal)		31	
Total operations performed		377	

The average age of the patients with anaplastic carcinoma was 68 years (SD 18.2 y), not significantly older than all other TC types, mean 54.9 y (SD 15.1) ($p = 0.12$).

A TT either as the initial procedure or as staged/completion surgery was done for 54 (88.5%) of the 61 cases of TC: 23 (37.8%) patients had an initial TT, 37 (60.6%) had a lobectomy, and a single patient (1.6%) had a subtotal surgery. Completion thyroidectomy was done in 31 (50.8%) patients with TC, and seven (11.5%) patients had no further surgical intervention.

Malignant glands were heavier on average than benign ones with an average weight of 150 g (maximum 820 g) compared to benign gland weight of 135.4 g (maximum 1320 g); however, this was not significant ($p = 0.22$). The maximum diameter of glands did not differ between the malignant and benign pathologies. Cases with malignant disease had a mean diameter 8.1 cm (range 2–15 cm) and cases with benign disease had a mean diameter of 8.3 cm (range 3.5–27 cm) ($p = 0.53$).

Thirty-nine (11.3%) patients had surgery for hyperthyroidism: Graves' disease in 14 (35.9%) cases, toxic multinodular goitre (TMNG) in 15 (38.5%) cases, toxic nodule in seven (17.9%) cases, Hashimoto's thyroiditis in two (5.1%) cases, and a single patient had thyroiditis not specified. One (2.6%) of the patients with hyperthyroidism (Graves' disease) had an incidental carcinoma. Graves' patients were significantly younger with a mean 38 years compared to patients with TMNG with a mean age of 53 years ($p < 0.01$).

Discussion

Thyroid disease is a frequently encountered condition for the general surgeon. In this study, thyroid surgery was predominantly performed on middle-aged women to treat MNG with compressive or cosmetic concerns. Thyroid malignancy was diagnosed in almost one-fifth of patients undergoing thyroid surgery with an equal number of PTC and FC.

Thyroid disease predominates in female patients with a female to male ratio 22:1 in this study. This is consistent with other studies showing women are affected 500% more than men.[3] This disparity in sex is thought to be due to the oestrogen environment and cyclical hormonal variations being promotors of thyroid dysfunction, and autoimmune diseases being more prevalent in females.[3]

The majority, 65%, of surgery was performed for MNG; this is similar to other African and Asian reviews which found MNG to be the commonest thyroid pathology: Nigeria[4] with 72%, Ghana[5] with 77.5%, and Pakistan[6] with 61.6%.

Goitre is defined as a thyroid gland of more than 30–35 g at autopsy,[7] the lobes each being larger than the patient's terminal phalanges of the thumb,[8] or the thyroid being two times that of normal.[9] A normal thyroid lobe is 4 to 4.8 by 1 to 1.8 by 0.8 to 1.6 cm in dimension, and 10 to 20 g in weight.[10] In our study, MNG were 10 to 20 times heavier than normal (heaviest 1320 g) and more than twice the length.

The prevalence of MNG in iodine sufficient countries is 4%[11] compared to countries with previous deficiency, before salt iodination, where about 10% of the elderly have goitres.[12] Despite iodisation of table salt in SA since 1995,[1] food manufacturers are exempt from mandatory use of iodised salt. Non-iodised salt used in food manufacturing, agriculture, and animal feed is cheaper and often sold in informal settlements.[13] In 2018, Charlton et al. showed South African adults whose salt intake was within the World Health Organization (WHO) recommended range had suboptimal iodine intakes and, therefore, sodium reduction

Table II: Thyroid cancer and ethnicity

Cancer Type	*n* (%)	Average age years	Ethnicity		
			Black	Indian	White
Follicular	27 (44.2)	58	24 (52%)	2 (22%)	1 (20%)
Papillary Classic PTC Follicular variant Columnar cell Micropapillary	27 (44.2) 8 15 1 3	52.6	17 (35.4%)	6 (66%)	4 (80%)
Oncocytic	2 (3.3)	49	1	1	
Medullary	2 (3.3)	53	2		
Anaplastic	3 (4.9)	68	3		
Total	61		47	9	5

strategies may impact adversely on iodine intakes[13] and result in thyroid disease. Iodine deficiency may explain the high incidence of FC noted in this study of largely rural patients.

In the past, thyroid nodules within a MNG were considered less likely to harbour malignancy with rates around 3%.[14] Higher percentages, up to 35%, have now been reported in numerous studies; Apostolou et al. showed 31.7% of 3233 patients with MNG and a benign preoperative FNAC result had an incidental TC, of which 44% were PTC.[15] Fewer nodules, smaller gland weight, younger age (< 50 years), smaller adenomas and hypothyroidism were identified as increasing the risk for thyroid malignancy in MNGs.[15] The higher rate of incidental TC may reflect the increasing incidence of PTC (both papillary thyroid microcarcinoma (PTMC) and PTC larger than 1cm in size), as well as an increase in the standard of examination of the surgical specimen.[16] We found TC in 11.2% of MNG, lower than studies outlined above but with a similar percentage of PTC. In a South African study, Bombil et al.[17] found a 5.7% incidence of incidental TC in MNG, and in Nigeria this was reported to be 15% of which 50% were PTC.[18] Eleven percent of surgery in this study was for hyperthyroidism: Graves' disease (4.1%), TMNG (4.3%), toxic nodule (2%), and Hashimoto's thyroiditis (0.6%). The practice patterns for the treatment of Graves' disease vary geographically, between disciplines, and over time. Surgery for Graves' disease, rather than radioactive iodine, is offered to those with significant Graves' ophthalmopathy, large goitres, concern for malignancy and those intolerant to medical management or have contraindications to radioactive iodine, as per the guidelines from the American Society of Endocrine Surgeons.[19]

Thyroid malignancy co-existing with hyperthyroidism is an uncommon occurrence, likely due to low thyroid-stimulating hormone levels suppressing the development and growth of differentiated thyroid carcinoma cells. This study identified one patient with a PTMC associated with Graves' disease. However, the literature reports an increasing number of TC being diagnosed in patients with the commoner causes of hyperthyroidism. A recent study showed TC in 22.6% of hyperthyroid patients having surgery, with PTMC the most common histologic type.[20]

Seventy patients had diagnostic surgery; one-third were found to be malignant and 66% were adenomas. Two-thirds of the malignancies were FC. Boonrod et al. reviewed solitary nodules with FC, OC and adenoma histology and showed preoperative imaging height of nodule more than 4 cm to be a predictor of malignancy (OR 4.5, 95%CI 1.021-1.074).[21] This differs from our study where there was no significant difference in tumour size of adenomas (average 5.5 cm, range 2–12 cm) and FC (5.3 cm, range 2–9cm). This may be explained by the late presentation of our patients with more advanced pathology and possibly the small number of patients. Thyroid lobectomy was done in 91% of cases of diagnostic uncertainty with benign histology in 73%, which justifies doing only a lobectomy in our setting regardless of the nodule size.

Thyroid malignancy was found in 17.6% of study patients, similar to other South African studies[22] and reports from other low-to-middle income countries including Kenya,[23] Nigeria,[18] and Pakistan[6] who noted TC rates of 11–14.35%. However, the true incidence of TC in SA remains unknown and behoves the need for a National South African TC Registry.

Globally, PTC accounts for 88% of TC.[16] However, on the African continent the histological subtype prevalence varies widely with PTC 6.7–72.1%, FC 4.9–68%, anaplastic 5–21.4%, and medullary 2.6–13.8%.[24]

Even within SA, a large variation in TC histological subtypes is documented.[2] Small numbered studies have shown Gauteng province (2019) had 65% PTC, 16.8% FC, 9.8% MTC and 2.8% anaplastic carcinoma,[25] whilst KZN (2001) had 25% PTC and 60% FC.[26] The Western Cape (2013) reported 51.4% PTC, 27.5% FC, 3.7% MTC and 5.5% anaplastic carcinoma.[27] All these studies showed WDTC made up the majority of TC.[25-27]

This study aligns with other literature with WDTC comprising the majority of TC (91.8%). However, we found equal numbers of PTC and FC at 44% each. This is a decrease from the 60% FC from an earlier KZN study,[26] performed some years earlier, and may reflect iodisation practices. The incidence of FC still is much higher than other South African provinces and higher-income countries studies.[2] Racial/ethnic differences have been identified in TC incidence, tumour size, and histological subtype in SEER reviews; PTC being the most widely variable compared to other histological subtypes and FC higher in Black races.[28,29] The high proportion of FC in our study may reflect our ethnic proportions where over three-quarters of patients were Black. This is representative of the area that the study hospital services, rural KZN with a largely Black population, 27 referring district levels hospitals, and a population of more than three million. At odds with this finding that Black patients have a high incidence of FC is a study from Nigeria (2018) that found PTC to be the most common (71.4%) TC although ethnicity was not specifically reported.[4]

Most PTC cases comprise two histologic subtypes – classic papillary (CPTC) and follicular variant of PTC (FvPTC) – which account for 55–65% and 23–41% of cases respectively.[30] The incidence of FvPTC has been increasingly diagnosed in recent years[29] but to lesser extent than seen in this study which showed FvPTC in 56% of PTC, which may reflect our ethnic groups.

The limitations of this study were small numbers and a single centre experience, as well as the lack of correlation with thyroid ultrasound using the TI-RADS score and inconsistent use of the Bethesda cytological classification. Fine needle aspiration cytology was not always performed under ultrasound guidance.

Further studies evaluating the clinicopathology of thyroid disease in SA as a whole, as well as comparisons between provinces and regions, should be undertaken to establish the spectrum of surgical thyroid disease.

Conclusion

This study reviews the profile of surgically managed thyroid disease at a tertiary hospital servicing a largely rural African population. Multinodular goitre constituted the largest proportion of cases with 11.2% harbouring TC. Surgery is still performed for the management of hyperthyroid conditions including TMNG, toxic nodules and a subgroup of Graves' disease. Solitary nodules were malignant in one third of patients with the majority being FC; however, larger nodule size did not correlate with an increased risk of malignancy. Thyroid malignancy was mostly WDTC

but with a higher incidence of FC and FvPTC, which may be related to ethnicity and insufficient salt intake despite iodisation.

There is a need for South African thyroid surgery studies as great variation exists between provinces, and this mandates the need for a national thyroid database.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethical approval was granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (KZN), South Africa (reference number BCA207/09 and BCA221/13).

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