Thyroid cancer pathology: Insights from a developing region

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Background. The South African (SA) health sector and laboratories comprise a dual system that includes public and private providers. SA studies illustrate diverse thyroid cancer incidence across provinces, with papillary thyroid cancer (PTC) more prevalent in urban provinces than follicular thyroid cancer (FTC) and anaplastic thyroid carcinoma.
Objectives. To provide a deeper insight into the geographic intricacies of thyroid cancer types from public and private provider perspectives.
Methods. This study investigated thyroid cancer pathology in SA between 2015 and 2019, overall and by province and facility type (private, public). Laboratories provided data in different formats, requiring manual processing. The data extracted included date of birth, sex, province, specimen type and final histology results.
Results. A total of 14 157 reports were included, of which 3 235 were thyroid cancers. Multiple challenges were experienced in terms of data processing. The public sector contributed 53.6% of thyroid cancer cases. Preoperative cytology was performed in 19.8% of thyroid cancers, and was diagnostic in 23.6%. There was significantly more FTC in the public sector (20.8% v. 5.6%), and more PTC in the private sector (87.1% v. 55.2%). T3 tumours were most prevalent in the public sector (52.3%), and T1 tumours in the private (38.8%).
Conclusion. The dual SA health system and the geographical distribution of the population appear to influence the pathological landscape of thyroid cancer. Standardised thyroid cancer reporting across all public and private laboratories in the form of a prospective national thyroid registry would allow for a more accurate evaluation of thyroid disease, ultimately improving thyroid cancer care in SA.

Keywords: cancer, healthcare, private, public, South Africa, thyroid

S Afr Med J 2025;115(9):e2997. https://doi.org/10.7196/SAMJ.2025.v115i9.2997

South Africa (SA) is diverse, with a population of 62 million people across nine provinces, and varying urban-rural distribution in each province.[1] The dual health sector comprises a public and a private sector, each with unique characteristics, challenges and strengths. The public sector is funded by the government, has limited resources and faces a higher disease burden, yet serves 84% of the population. The private sector, servicing 16% of the population, is well resourced but expensive, and only accessible to those who can afford it or have medical insurance.[1] The National Health Laboratory Service (NHLS) is utilised by the public sector, while multiple laboratories are available in the private sector, but no uniform system for accessing results exists. Although there are specialised hospitals and subspecialist surgeons nationwide, most surgical procedures in SA are performed by general surgeons. The fragmentation of representative data information systems across provinces and health sectors remains a challenge, limiting our knowledge of thyroid cancer in SA.

Thyroid cancer is the most common endocrine malignancy, representing 3% of all global cancer cases.[2,3] The incidence is rising worldwide, with variations in occurrence and subtypes across different populations and regions.[4-6] Thyroid cancers are classified based on their cell of origin. Follicular cell-derived thyroid cancers include well-differentiated thyroid cancers (WDTC), such as papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and oncocytic carcinoma.[7,8] Poorly differentiated thyroid carcinoma (PDTC) and anaplastic thyroid carcinoma (ATC) result from the de-differentiation of WDTC. Medullary thyroid carcinoma (MTC) is a neuroendocrine tumour that arises from parafollicular cells and is often linked to RET (rearranged during transfection) proto-oncogene mutations.[9,10] Thyroid cancer diagnosis is typically made through cytology or diagnostic surgery. Treatment for WDTC includes surgery, radioactive iodine therapy and thyroid-stimulating hormone suppression, guided by cancer subtype and aggressive markers.[11-14] The prognosis is generally favourable, with a 10-year survival rate >90%.[13,15,16]

Published thyroid cancer rates in low- to middle-income countries (LMICs) are primarily from single institutions.[17-20] The only multi-institutional national study performed by the Thyroid Cancer Group of South Africa (TCGSA) describes the clinicopathological landscape of thyroid cancer in a cohort from the public sector.[21] PTC remains the most prevalent subtype of

thyroid cancer in SA, consistent with global trends.[5,22-24] However, the relative proportion of FTC, MTC and ATC varies across the provinces and geographical areas of SA.[18-21,25] The provinces with greater urbanisation have a higher incidence of PTC, whereas advanced and more aggressive thyroid cancer types such as ATC are diagnosed in the more rural provinces.[4,20,21,25,26] This nationwide study aimed to provide insight into the pathological variation of thyroid cancer in the public and private sectors and across the provinces of SA.

Methods

We conducted a descriptive retrospective study investigating thyroid cancer pathology across SA between January 2015 and December 2019. All accessible thyroid pathology reports from the NHLS and three private pathology laboratories in SA were included, and data cleaning of PDFs, text files and large Excel (Microsoft, USA) sheets was done using manual and computer sorting. Exclusion criteria were patients <18 years of age; non-thyroid-directed surgery, such as laryngeal carcinoma or parathyroid disease; duplications; non-human thyroid tissue; and non-SA patients. Variables recorded included date of birth, sex, type of laboratory (public/private), province, specimen type and final histology results. The year trend for thyroid malignancy was calculated using the date of diagnosis and the cytology or operation date. Cases were excluded from the year trend analysis if dates were missing. When the subtype of PTC was not specified, it was regarded as the classic subtype.

Descriptive statistics are presented as means (standard deviations (SD)) or medians (interquartile ranges (IQRs)) for continuous variables, and counts and percentages for categorical variables. The χ^2 test was used to compare categorical variables. A p-value <0.05 was considered statistically significant.

Ethical approval

This study was approved by the Health Research Ethics Committee of Stellenbosch University (ref. no. S23/05/115). As this is a retrospective study, a waiver of consent was obtained.

Results

Sorting and filtering the diverse data sources and creating a master data sheet took >15 months. Due to the lack of robust data-collecting systems across the SA health system platforms, this process necessitated manual and computer sorting and data cleaning. A search for all specimens registered by the laboratories as thyroid tissue during the study period identified 23 321 cases, of which 9 164 were excluded due to non-thyroid-directed surgeries, including laryngectomy for squamous cell carcinoma, specimens of patients from neighbouring countries, autopsy reports and non-human thyroid specimens (Fig. 1). The public sector contributed 9 116 (64.4%) specimens, and 5 041 (35.6%) were from private laboratories. Thyroid cancer was diagnosed in 22.9% (3 235/14 157) of cases, and in these, pathological thyroid cancer type was reported in 95.3% (3 083/3 235) of cases.

Cytology specimen reports were identified in 17.3% (1 653/9 570) of all thyroid resections and 19.8% (609/3 083) of thyroid cancer cases. Thyroid cancer was diagnosed on cytology in 23.6% (144/609) of cases. Other cancer diagnoses were made through core biopsies in 2.2% (70/3 235), thyroid resections in 73.6% (2 381/3 235), and lymph node biopsies in 3.1% (99/3 235).

The age of the patients with thyroid cancer could only be calculated from 39.2% (1 207/3 083) of reports. The mean (SD) age was 49.5 (15.6) years. Sex was reported in 99.8% (3 228/3 235) of thyroid cancer cases. The majority, 77.3% (2 494/3 228) of patients, were female (F), and 22.7% (734/3 228) were male (M), with an F:M ratio of 3.4:1.

Surgery was performed in 67.6% (9 570/14 157) of thyroid specimen cases, and 17.3% (1 653/9 570) of surgical specimens had cytology reports. More than half (55.3%, 3 714/6 716) of the benign surgeries were thyroid lobectomies, and almost half (45.3%, 1 294/2 854) of all cancer surgeries were total thyroidectomies. The term 'thyroidectomy not specified' was used in 7.4% (708/9 570) of cases, which represented 14.4% (410/2 854) of the thyroid cancer operations. Parathyroid glands were present in resected specimens in 17.4% (334/1 919) of cancer surgeries, and resection margins were involved in 21.3% (344/1 617) of cancer histology specimens.

Pathological types and subtypes were reported in 3 083 (95.3%) of the 3 235 thyroid cancer cases, of which 70.0% were PTC and 13.7% FTC (Table 1). Micropapillary thyroid cancer (mPTC) was found in 6.8% of thyroid cancer resections.

An increase in the diagnosis of thyroid cancer was noted between 2015 and 2019. The trend was primarily due to an increase in the diagnosis of PTC, with the diagnosis of other types of thyroid cancer largely static (Fig. 2).

Pathological T staging was reported in 1 326 (43.0%) thyroid cancer cases. Most cases were T3 tumours (35.2%), while 31.1% (412) were T1, 28.6% (379) T2 and 5.1% (68)T4 (Table 2). More than half (51.9%) of the patients with T1 tumours and 48.0% with T2 tumours underwent total thyroidectomies.

When comparing the incidence of PTC and FTC based on a province's rural population percentage, FTC appeared to be more common in provinces with a higher rural population (Fig. 3),[28] such as Limpopo and Mpumalanga provinces.

Of the 3 083 cancers, 1 653 (53.6%) were from the public sector (Table 3). FTC was more common in the public than the private sector (20.8% v. 5.6%), and PTC was more common in the private sector (87.1% v. 55.2%). In the public sector, T3 tumours were the most common (52.3%), and in the private sector, T1 tumours formed the majority (38.8%).

Discussion

This first nationwide report on thyroid cancer pathology in SA represents an audit of both public and private sector cases across nine SA provinces, which is, to our knowledge, the largest to date. It highlights challenges encountered due to a lack of standardised pathology reporting and uniform data capturing in thyroid cancer patients. Furthermore, it draws attention to the limited utilisation of thyroid cytology in patients diagnosed with thyroid cancer. Lastly, it emphasises geographical differences in thyroid cancer pathology in SA, likely due to economic and access disparity.

Numerous challenges were encountered during data acquisition. These included obtaining approval for and release of the data, the format in which they were received, such as PDFs and text files, and the conversion into an appropriate format before analysis. In addition to these obstacles, multiple data points, such as date of birth, were still missing, only captured in 39.2% of cases. A collaborative data collection process embedded into a national system would facilitate quality control, streamline research and optimise patient care.

Only 19.8% of thyroid cancer operations had preoperative cytology, with most diagnosed following thyroidectomy or biopsy techniques. This contrasts with the TCGSA study in the public sector in SA, where 83.8% of thyroid cancer surgery patients had preoperative cytology.[21] Reasons may include non-adherence to recommendations, but also allude to coding discrepancies at the laboratory level, and the database search methodology.

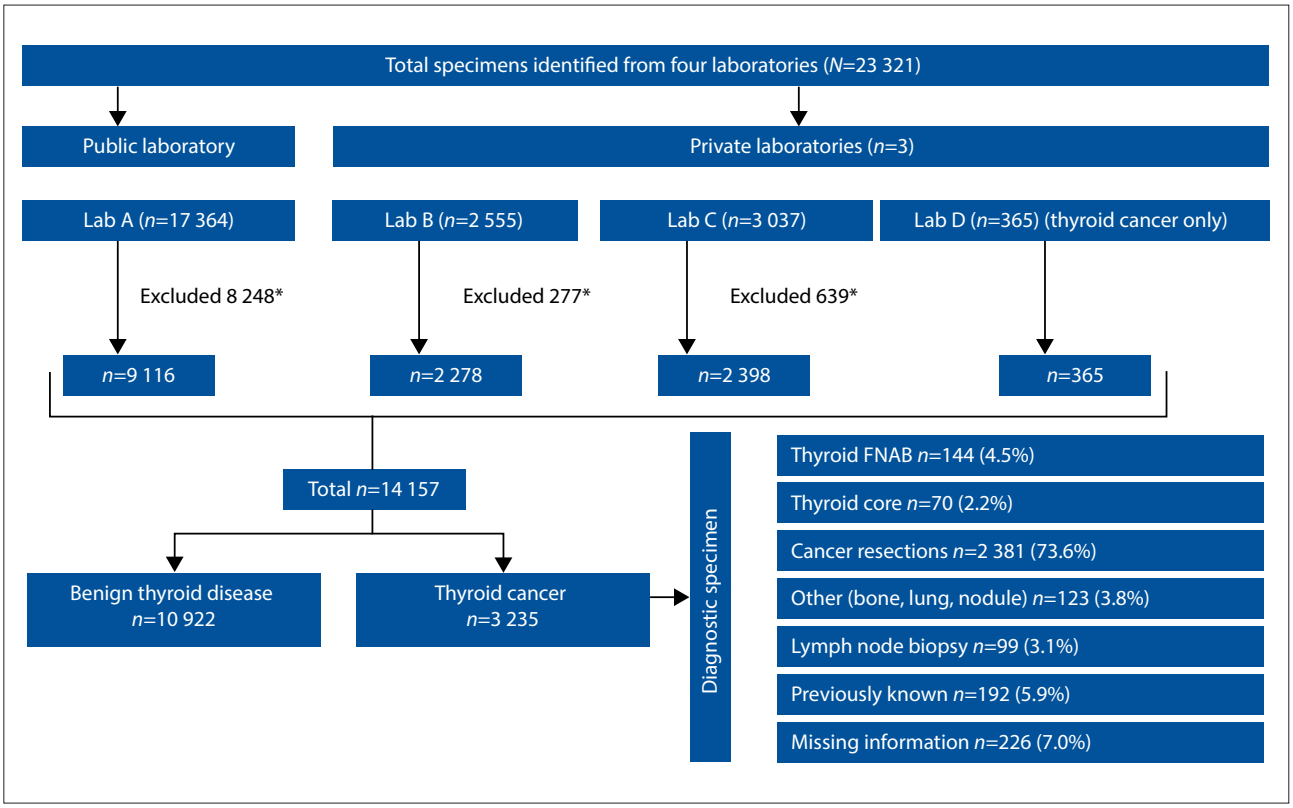

*Fig. 1. Flow diagram indicating specimen inclusion and exclusion, public and private sector specimen contribution and pathological thyroid cancer figures. *Exclusions for non-thyroid directed surgery, e.g. laryngectomy; parathyroid operations; duplicates; age <18 years; autopsy reports. (FNAB = fine needle aspiration biopsy.)*

Table 1. Pathological subtype of thyroid cancer in 3 083 cases (missing data for those where subtype not specified)

Pathological subtype	*n*	Percentage of total cancers	Percentage of PTC
Papillary	2 158	70.0	
Classic subtype	1 200		55.6
Follicular subtype	557		25.8
Micropapillary thyroid cancer (<1 cm)	210		9.7
Tall cell subtype	64		3.0
Encapsulated subtype	40		1.9
Oncocytic subtype	32		1.5
Solid/trabecular subtype	24		1.1
Columnar cell subtype	12		0.6
Hobnail subtype	5		0.2
Cribriform-morular subtype*	5		0.2
Clear cell subtype	4		0.2
Spindle cell subtype	3		0.1
Diffuse sclerosing subtype	1		0.0
Warthin-like subtype	1		0.0
Follicular	423	13.7	
Medullary	132	4.3	
Oncocytic	112	3.6	
Poorly differentiated	91	3.0	
Undifferentiated/anaplastic	50	1.6	
Lymphoma	30	1.0	
Other (metastatic, squamous, etc.)	87	2.8	

*According to the 2022 World Health Organization thyroid pathology classification, the cribriform-morular subtype is no longer classified as a PTC subtype – now categorised as a tumour of uncertain histogenesis.[27]
PTC = papillary thyroid cancer.

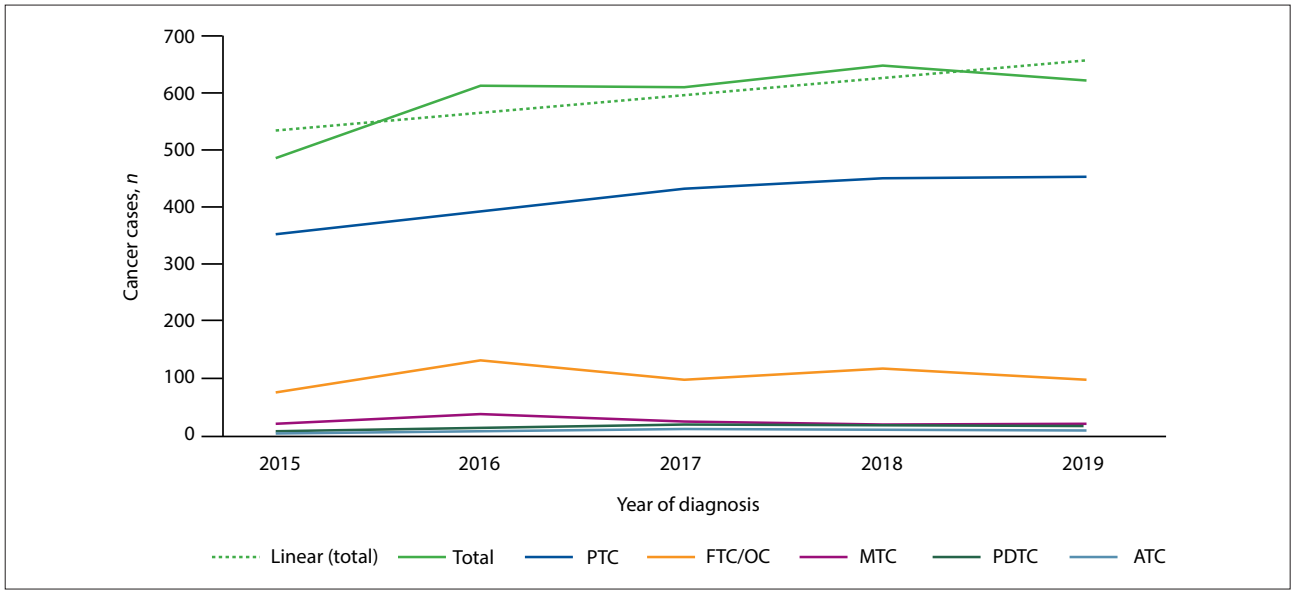

Fig. 2. Thyroid cancer incidence in South Africa over 5 years (n=2 985). (PTC = papillary thyroid carcinoma; FTC = follicular thyroid carcinoma; OC = oncocytic carcinoma; PDTC = poorly differentiated thyroid carcinoma; ATC = anaplastic thyroid carcinoma; MTC = medullary thyroid carcinoma.)

Table 2. Thyroid operations per pathological T stage in 1 326 thyroid cancer cases

Operation	T1, *n* (%)	T2, *n* (%)	T3, *n* (%)	T4, *n* (%)	Total, *n* (%)
Thyroid lobectomy	98 (23.8)	100 (26.4)	116 (24.8)	10 (14.7)	324 (24.4)
Total thyroidectomy	214 (51.9)	182 (48.0)	261 (55.9)	40 (58.9)	697 (52.6)
Thyroidectomy not specified	91 (22.1)	85 (22.4)	74 (15.8)	11 (16.2)	261 (20.0)
Other	9 (2.2)	12 (3.2)	16 (3.4)	7 (10.3)	44 (3.3)
Total	412 (31.1)	379 (28.6)	467 (35.2)	68 (5.1)	1 326 (100)

Table 3. Comparison between public and private sector thyroid specimens, operations, pathology and staging

Study population (% of total specimens)	Total, *n* (%)	Public, *n* (%)	Private, *n* (%)	
Specimens	14 157 (100.0)	9 116 (64.4)	5 041 (35.6)	
Operations	9 570 (100.0)	6 003 (62.7)	3 567 (37.3)	
Cancers	3 083 (100.0)	1 653 (53.6)	1 430 (46.4)	
Operation types for cancers (% of total operations in sector)	**Total (*n*=3 083), *n* (%)**	**Public (*n*=1 653), *n* (%)**	**Private (*n*=1 430), *n* (%)**	***p*-value**
Total thyroidectomy	1 294 (42.0)	770 (46.6)	524 (36.6)	<0.001
Thyroid lobectomy	935 (30.3)	620 (37.5)	315 (22.0)	<0.001
Thyroidectomy not specified	481 (15.6)	69 (4.2)	412 (28.8)	<0.001
Other	144 (4.7)	72 (4.4)	72 (5.0)	0.373
No operation	229 (7.4)	122 (7.4)	107 (7.5)	0.914
Pathological subtypes (% of total cancers in sector)	**Total (*n*=3 083), *n* (%)**	**Public (*n*=1 653), *n* (%)**	**Private (*n*=1 430), *n* (%)**	***p*-value**
PTC	2 158 (70.0)	913 (55.2)	1 245 (87.1)	<0.001
FTC	423 (13.7)	343 (20.8)	80 (5.6)	<0.001
OC	112 (3.6)	67 (4.1)	45 (3.1)	0.118
PDTC	91 (3.0)	83 (5.0)	8 (0.6)	<0.001
ATC	50 (0.2)	39 (2.4)	11 (0.8)	<0.001
MTC	132 (4.3)	107 (6.5)	25 (1.7)	<0.001
Other	117 (3.8)	101 (6.1)	16 (1.1)	-
T-staging (% of 1 326 cancers; 1 757 missing information)	**Total (*n*=1 326), *n* (%)**	**Public (*n*=564), *n* (%)**	**Private (*n*=762), *n* (%)**	***p*-value**
T1	412 (31.1)	116 (20.1)	296 (38.8)	<0.001
T2	379 (28.6)	116 (20.1)	263 (34.5)	<0.001
T3	467 (35.2)	295 (52.3)	172 (22.6)	<0.001
T4	68 (5.1)	37 (6.6)	31 (4.1)	0.894

PTC = papillary thyroid carcinoma; FTC = follicular thyroid carcinoma; OC = oncocytic carcinoma; PDTC = poorly differentiated thyroid carcinoma; ATC = anaplastic thyroid carcinoma; MTC = medullary thyroid carcinoma.

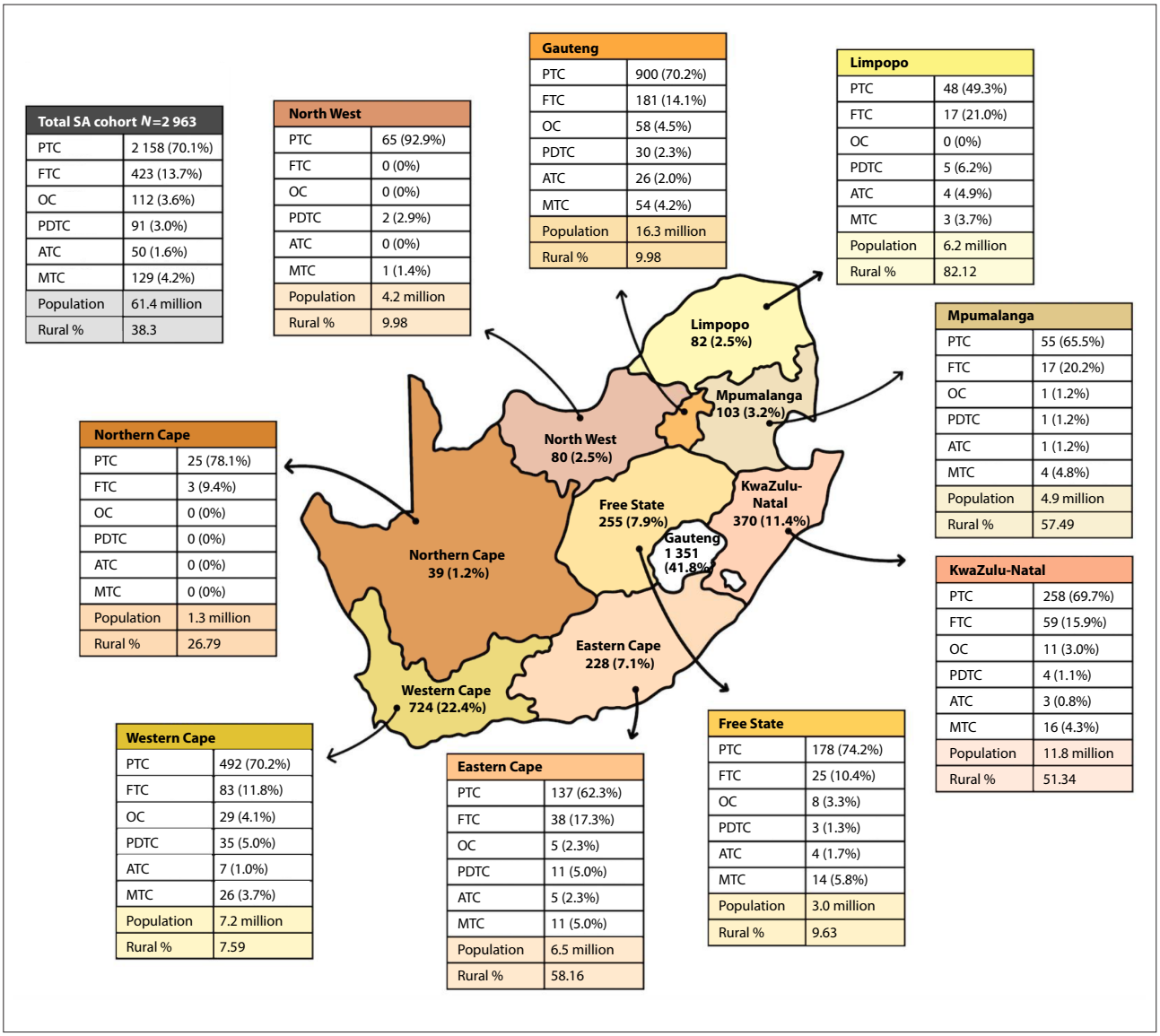

Fig. 3. Pathological subtypes of 2 963 thyroid cancer specimens across provinces, including the SA population in millions and the rural percentage per province (according to Census 2022).[28] Numbers within provinces describe the frequency of specimens and the percentage of total specimens across South Africa. 'Rural' was defined in the census based on municipal borders, the type of economic activity and land use.[28] (SA = South Africa; PTC = papillary thyroid carcinoma; FTC = follicular thyroid carcinoma; OC = oncocytic carcinoma; PDTC = poorly differentiated thyroid carcinoma; ATC = anaplastic thyroid carcinoma; MTC = medullary thyroid carcinoma.)

The International Collaboration on Cancer Reporting provides a benchmark to improve thyroid cancer outcomes.[29] The proposed thyroid cancer pro forma can be implemented uniformly across SA laboratories to promote standardisation, allowing for correct specimen coding, accurate interpretation of results and, therefore, clinical decision-making. This would also improve data acquisition for research or auditing purposes.

The increase in PTC over time, as seen in our study, might be explained by SA's high urbanisation rate. Better access to healthcare in urban areas can increase the likelihood of thyroid cancer diagnosis and, therefore, the risk of overdiagnosis. Although mPTC is usually associated with asymptomatic disease and overdiagnosis, it accounts for only 9.7% of PTCs in SA. It should therefore not be considered a reason for the increase in prevalence. FTC was found in the TCGSA to be more common in provinces with a high rural population, such as KwaZulu-Natal (41%) and Limpopo (36%).[21] However, in the current study, FTC was only found in 15.9% in KwaZulu-Natal and in 21.0% in Limpopo. FTC was found to be more common in public sector patients ($p<0.001$), also supported by the TCGSA study, where FTC occurred in 22.1% of thyroid cancers, compared with 13.7% in the current study. The incidence of FTC is probably lower in the current study because public and private data were pooled.

Higher rates of aggressive thyroid cancer types such as FTC and ATC are documented in the public sector. This may be due to differences in patient profile, specifically health-seeking behaviour, environmental and social exposures, rural location, variation in the availability of experienced pathologists and access to healthcare. In a limited-access setting, aggressive cancers may present symptomatically, whereas indolent PTC remains undetected, distorting the ratio of pathological subtypes. The public sector profile of pathological subtypes aligns with findings in LMICs, whereas the landscape of thyroid cancer in the private sector in SA mirrors that in high-income countries (HICs). This difference in disease profile should also influence diagnostic and therapeutic recommendations

and guidelines. Despite having more aggressive tumours, public sector patients have limited access to neo-adjuvant and adjuvant targeted therapies that are available in the private sector.

Patients in the public sector in SA are more likely to have a lower socioeconomic status, and the health system has fewer resources, prolonged referral times and long surgery waiting lists; therefore, public sector patients are more likely to present with advanced disease. In our study, T3 tumours were more common in the public sector (52.3%), while T1 tumours were more common in the private sector (38.8%). As mPTC is included in T1 tumour staging, one might consider overdiagnosis in the private sector, as is seen in HICs. However, the similar rate of mPTC in the two groups (6.9% in public, 6.7% in private) makes overdiagnosis less likely. Overall, there is significant variability in thyroid cancer pathology types across the public and private sectors as well as geographical regions. This information is crucial for developing targeted interventions and improving the management of thyroid cancer in SA.[35]

Limitations

Limitations of this study include selection bias, as not all private laboratories were represented in the cohort. In addition, reporting bias may exist owing to missing and incomplete coding and data. The lack of standardisation in reporting thyroid pathology and variation in data capturing across laboratories affected the comparability of results. Some patients might have moved between provinces and between public and private sectors. Confounding variables such as environmental and genetic factors could not be accounted for. Other confounders may include the centralisation of laboratories, where peripheral provinces might divert to more central laboratories. The public sector pathology service might sometimes outsource reporting to the private sector owing to staff shortages, and in the private sector, many thyroid fine needle aspiration biopsies (FNABs) are performed by radiologists, and not necessarily referred to the same laboratory as the thyroid surgeon's resected specimen.

Conclusion

Multiple challenges were experienced with the data process, potentially hampering research in developing regions. Limited cytology was identified for the surgically resected samples, implying a non-conformity to practice guidelines that recommend FNAB as part of the diagnostic work-up of thyroid nodules. The health system, as well as the geographical distribution of the population, may influence the pathological landscape of thyroid cancer. Standardised thyroid cancer reporting across all public and private laboratories in the form of a prospective national thyroid registry would allow for a more accurate evaluation of thyroid disease, ultimately improving thyroid cancer care in SA.

Data availability. Data used for this study are available from the authors on request.

Declaration. This study was carried out as part of WC's PhD degree at Stellenbosch University.

Acknowledgements. The authors would like to thank Maja van Aswegen for her contribution to the data collection and data cleaning.

Author contributions. WC: conceptualisation, data acquisition, analysis, writing original draft, reviewing and editing of final manuscript. JL: conceptualisation, reviewing and editing of final manuscript. LM: conceptualisation, analysis, reviewing and editing of final manuscript. TL: conceptualisation, reviewing and editing of final manuscript. RR: conceptualisation, reviewing and editing of final manuscript. AA: conceptualisation, data acquisition, reviewing and editing of final manuscript. FC: conceptualisation, data acquisition, reviewing and editing of final manuscript. SN: conceptualisation, data acquisition, reviewing and editing of final manuscript. JD: conceptualisation, data acquisition, reviewing and editing of final manuscript. KB: conceptualisation, writing original draft, reviewing and editing of final manuscript.

Funding. This work was supported by the HB & MJ Thom Award and Stellenbosch University Research Funding and Capacity Development Fund.

Conflicts of interest. None.

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Received 31 December 2024; accepted 12 May 2025.