# ULTRASOUND THYROID NODULE SIZE AND HISTOLOGICAL FINDINGS

**BY**

**ELDRIDGE FABIAN COETZEE**

**Submitted in partial fulfilment of the requirements in respect of the Master's Degree Mmed in the Department of Surgery in the Faculty of Health Sciences at the University of the Free State.**

**Supervisor: Dr. E Arko-Cobbah**

**Department of surgery**

**University of the Free State**

**30 July 2020**

**DECLARATION OF AUTHORSHIP**

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I, Eldridge Fabian Coetzee, declare that the coursework Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree Qualification MMed (Surgery) at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education.

Dr. EF Coetzee Date: 13 July 2020

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## ABSTRACT

Introduction: Thyroid nodules occur in 4-7% of adults with a malignancy risk of 5-15%. Ultrasound plays an important role in the clinical workup of patients with solitary thyroid nodules to differentiate malignant from benign disease.

Objectives: To determine if ultrasound single thyroid nodule size can predict the probability of thyroid malignancy.

Method: Retrospective cross-sectional study of all thyroidectomies done (benign and malignant) from 2010 to 2016. Ethical clearance was obtained from University of the Free State (**HSREC 0664/2017**). Data was analyzed by means of descriptive statistics, namely frequencies and percentages for categorical data, medians, and percentiles for numerical data, were calculated. Associations regarding cancer were done for numerical data by means of Kruskal-Wallis test and contingency tables by means of Chi-square or Fischer's exact test. A p-value of $< 0.05$ was considered statistically significant. Diagnostic test statistics were calculated, namely sensitivity, specificity, positive and negative predictive values, and likelihood ratios.

Results: The overall incidence of thyroid cancer was 24.6%. The median age of thyroid cancer patients was 52.9 years and for benign disease 54 years. Female patients with thyroid cancer were 78.7% and for benign disease 90.1%. Male patients with cancer were 21.2%, for benign disease 9.9%. Papillary thyroid cancer remains the most common type of cancer at 87.8 % and follicular thyroid cancer 12.1%. The average size of thyroid cancer on histology was 2.1 cm and 3.2 cm for the non-cancer group, statistically significant with p-value of 0.0015. Ultrasound nodular size for cancer was 1.7 cm; and 1.9 cm for non-cancer group with p-value 0.209. The association between ultrasound size and histology size for cancer group were not significant with p-value 0.99. Size difference for non-cancer group between histology and ultrasound was significant with p-value 0.02.

Conclusions: The study did not prove our hypothesis that ultrasound single nodule size alone, can predict the risk of thyroid cancer. Diagnostic test results with 95% CI reveals a sensitivity of 96%, but a low specificity of 22% to predict the risk of thyroid cancer.

**KEYWORDS**

Ultrasound, thyroid, nodule, histology, cancer, benign, non-cancer, malignant, thyroidectomy

## LIST OF ABBREVIATIONS

| | |
|---|---|
| CI: | Confidence interval |
| HSREC: | Health Sciences Research Ethics Committee |
| Meditech: | Medical technology system data storage |
| FNAB | Fine needle aspiration biopsy |
| Snomed | Systematized Nomenclature of medicine |
| Mm | millimeter |
| Cm | centimeter |
| Patient’s | pts |
| UFS | University of the Free State |
| EFC | Eldridge Fabian Coetzee |
| EAC | Emmanuel Arko-Cobbah |
| SEER | Surveillance epidemiology and end results |

## LIST OF APPENDICES

A. HSREC ethics letter of approval
B. FS Department of Health letter of approval
C. Head of Department of Surgery letter of approval
D. Supervisor letter of approval
E. HSREC approved protocol
F. HSREC approved Data Sheet
G. Instructions to authors of the SAMJ
H. TURNITIN Plagiarism summary report

**CHAPTER 1:**

1.1 INTRODUCTION

Thyroid nodules are common. A thyroid nodule is called a nodule on ultrasound when a lesion within the thyroid gland is distinguishable from the adjacent parenchyma or tissue. For the nodule to be solid on ultrasound, it must appear purely solid or predominantly solid, with a cystic component of less than 10 % of the total volume of the nodule.

The American Thyroid Journal of the United States, Vol 19, 2009 [1,20] updated guidelines show that 4-7% of adults in North America have palpable nodules, and the prevalence increases to 30% with imaging studies. The American Thyroid Journal of the United States, Vol 19, 2009 [1] also found a 5-15 % probability of malignancy in any given thyroid nodule.

Thyroid cancers represent approximately 3.4 % of new cancers diagnosed in the US yearly. Number of new thyroid cancer cases was 14.2 per 100 000 men and women per year. Deaths were 0.5 per 100 000. Lifetime risk of developing thyroid cancer is 1.2% of men and women during their lifetime. These data are based on the 2010-2014 database from the National Cancer Institute of the United States [2].

Thyroid cancers are divided into 4 main types. The Journal of Clinical Endocrinology and Metabolism of 2014; 99(4) [4] included 31 studies between 1985 and 2012, with 18288 nodules evaluated. The results found Papillary cancer in (84%), Follicular (13%), Medullary (5-10%) and Anaplastic cancers (1-2%). The overall frequency of thyroid cancer was 20 %.

Clinically, thyroid cancer most commonly presents as a painless, palpable solitary nodule. High risk patients are those older than 60 and younger than 30 years, male patients, a family history of thyroid cancer, previous radiation to head and neck region, and MEN Type 2A and 2B syndromes. Prognostic factors include age at diagnosis of cancer: death is most likely to occur if the patient is >40 years old; and sex: males are twice as likely as women to die from thyroid cancer. Size >4 cm has a higher mortality rate, histology type like papillary cancer has a 6% 30-year mortality rate. [1]

Clinical workup of a solitary thyroid nodule is to differentiate a malignant disease from a benign disease. This will determine which patients require intervention and which patients may be monitored serially.

History taking, physical examination, laboratory tests, ultrasound, and fine needle aspiration biopsy (FNAB) are the mainstays in the evaluation of thyroid nodules. [1,7,8,9]. FNAB result can be benign, malignant, indeterminate, or non-diagnostic. Up to 10 to 30% of FNABs will be non-diagnostic.

**The American Thyroid Association Guidelines of 2009 [1]: Recommendations for FNABs:**

1. Sub centimeter nodule size biopsy should be done only if the nodule has a suspicious ultrasound finding or the patient has a history of radiation exposure or familial thyroid cancer.
2. Not to biopsy nodules less than 5 mm, due to high rate of inadequacy.
3. A nodule with indeterminate findings on ultrasound, but is larger than 1 cm, FNAB is recommended because malignancy cannot be excluded.
4. If the nodule has indeterminate finding on ultrasound and is 1 cm or less, then FNAB is not necessary.

**The American Thyroid Association Updated Guidelines of 2015 [20]: Recommendations for FNAB:**

1. Nodules >1cm in greatest dimension with high risk ultrasound features.
2. Nodules >1 cm with intermediate risk ultrasound features.
3. Nodules >1.5 cm with low risk ultrasound features.
4. Nodules >2 cm with very low risk ultrasound features may be considered.

**Thyroid nodule diagnostic FNAB not required:**

1. Nodules that do not meet above criteria.
2. Nodules that are purely cystic.

Treatment consists of surgical intervention plus adjuvant treatment. Surgical options include total or subtotal thyroidectomy, lobectomy plus/minus isthmusectomy. One study compared the overall survival of 23605 subjects with papillary and follicular thyroid cancer treated with local excision, lobectomy, subtotal, and total thyroidectomy using Surveillance, Epidemiology , and End-results (SEER) database. The SEER database concluded that the 10-

year overall survival after total thyroidectomy resulted in improved survival over other techniques [6]. A study by Jisheng HU *et al* (2016) published in the World Journal of Surgical Oncology [18] involving 5559 thyroidectomies concluded that total thyroidectomy dominates over lobectomy as being more cost effective and this approach maximizes the quality adjusted life expectancy in patients with thyroid cancer compared to lobectomy surgery.

Ultrasound was first used clinically in 1956 by obstetrician Ian Donald in Glasgow. The first thyroid ultrasound was done in 1965. Only 7 articles were published up to 1970. In 2015, a consensus statement from the American Thyroid Association [1,7,8,9] on preoperative imaging concluded that ultrasound remains the most important imaging modality in the evaluation of patients with suspected thyroid cancer nodule, and all should have an ultrasound done routinely.

Features of malignancy on ultrasound includes micro calcifications, central nodule hypervascularity, solid nodule, irregular borders, taller than wider, hypoechoic, and large size > 1 cm. [1,3,9,10,11,12,13,14]

Significant uncertainty remains surrounding the diagnostic accuracy of ultrasound features to predict the malignant potential of thyroid nodules that overlap with benign disease. In a meta-analysis published in **The Journal of Clinical Endocrinology 2014 Apr: 99(4):1253-1263 [4]** checking the accuracy of thyroid nodule on ultrasound to predict thyroid cancer, they included 31 studies from 1985 to 2012. This included 18288 nodules with an average size of 15mm; the frequency of thyroid cancer was 20%. The study used 14 sonographic features to evaluate the thyroid nodules. They concluded that low to moderate quality evidence suggests that individual ultrasound features are not accurate predictors of thyroid cancer. **[3,4].**

**Kamran SC et al (2013) [15]** evaluated 7348 nodules, with 13% overall being malignant. Size: 1-1.9 cm 10.5% , 2-2.9 cm 14%, 3-3.9 cm 16% and >4 cm 15% cancer rates. Their study concluded that increasing nodule size impacts cancer in a nonlinear fashion. The threshold was 2 cm; beyond that, cancer risk is unchanged

**Luciana Reck Remonti et al (2015) [19]** used 52 observational studies including 12786 nodules, looking at ultrasound features of malignancy. They concluded that ultrasound features in isolation can not reliably identify nodules with an increased risk for malignancy.

A Study by **Hammad Ay et al (2016) [16]** included 10817 thyroid nodules of which 20.4% were malignant. Nodule size of 3-5.9 cm had 26% greater malignancy risk. However, nodules

6 cm or larger had a 16% lower risk of malignancy compared to those < 3 cm. The conclusion was that size can predict risk, with sizes greater than 6 cm associated with benign disease.

.No South African data is available on this subject after searching EbscoHost.

Our study aim is to use preoperative ultrasound single solid nodule size of 1- 6 cm and compare it with histological type and size found post-operatively, to see if different ultrasound size can be used to predict thyroid cancer in our population. If it can be used it may impact on the surgical management of patients. A single operation, instead of two, may be possible. Biopsy may be omitted for indeterminate FNAB and also for nodules of 1 cm, and opt for thyroidectomy instead of biopsy/lobectomy and completion thyroidectomy (2 surgeries).

## 1.2 BACKGROUND

### A. Patient Factors

Age

The peak age of thyroid cancer is in the third and fourth decades of life. The patient's age at diagnosis is one of the most important prognostic features of well differentiated thyroid cancer. Recurrence rates increase in ages < 30 or > 60 years. National Cancer institute 2010-2014 [2,6] statistics shows the incidence of thyroid cancer as 18.9% for age group 35-44 and 23.4% for ages 45-54.

Gender

Thyroid cancer is 3 times more common in females than males, however males are more at risk of developing thyroid cancer if a nodule is found. [2,6]

### B. Tumor factors:

Size

As seen in previous literature, size can be an indicator measure of thyroid malignancy. Histological tumor size will be divided into ranges from 1 -1.9 cm, 2 - 2.9 cm, 3-3.9 cm and > 4 cm. [15]

The aim is to find the average thyroid cancer size on histology, and correlate it with ultrasound findings preoperatively, as was done by J Zheijang et al. (2012) [13] and Hammad AY et al June (2016). [16]

Histological type

Papillary carcinoma is the most common type (80%), followed by follicular cancer (10%). [1,6,16]. Mucinous and Anaplastic are very rare and will be classified as “Other”. Only nodules positive for malignancy will be used as data.

Another aim is to find the most common thyroid cancer in our population and compare to above study findings.

Type of lesion

Lesions will be divided into single solid lesions, and those with nodular appearance.
Single solid thyroid lesions > 1 cm is a clinical risk predictor of thyroid cancer. [1,2,6,7]

Ultrasound size

High resolution conventional ultrasound was used. Different operators were used for preoperative nodule evaluations. All patients with preoperative thyroid nodule size evaluation will be included. The measured sizes will be correlated with histological size and positivity for malignancy on histology. The above size measurements will also be used as for the histological size categories. Measurement from 1 cm to > 4 cm will be used and subdivided. Minimum size of 1 centimeter will be used, because the **American Thyroid Association** [1] regards a single solid nodule of 1 cm of having a higher risk of cancer. 6 cm will be the cut-off, as any size >6 cm is more likely benign (**Hammad et al (2016)** [16], **J Zheijang** et al (2012) [13]).

Type of operation

Surgical intervention remains the mainstay of thyroid cancer treatment. Surgical options include total or subtotal thyroidectomy, lobectomy plus minus isthmusectomy. Our study will be looking at the type of operation that was done for thyroid cancer. It will be divided into either lobectomy or total thyroidectomy.

The SEER database concludes that the 10-year overall survival after total thyroidectomy resulted in improved survival over other techniques [18]. A study by **Jisheng HU et al (2016)** concluded that total thyroidectomy dominates over lobectomy as being more cost effective and this approach maximizes the quality adjusted life expectancy.

## 1.3 LIMITATIONS OF STUDY

Incomplete and missing data was a definite limitation. Small sample size in the cancer group as well as a study population from a single institution could have contributed as limitations.

## 1.4 FUTURE RESEARCH

Further follow up of cancer patients who had lobectomies done to see what the rate of recurrence was and their survival outcome.

## 1.5 OBJECTIVE

Primary aim:

To determine if ultrasound single solid thyroid nodule size can be used to predict the probability of thyroid cancer.

Secondary aim:

- To describe the different histological types of thyroid cancer, as well as their population demographics
- Association between ultrasound size and histology

## 1.6 HYPOTHESIS

The study hypothesis was that ultrasound single nodule size can be used as an independent predictor of thyroid cancer risk to be used as a predictive tool to guide further surgical management.

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# CHAPTER 2

# ULTRASOUND THYROID NODULE SIZE AND HISTOLOGICAL FINDINGS

Coetzee EF, Arko-Cobbah E

Department of Surgery, School of Clinical Medicine, Faculty of Health Sciences, University of the Free State, Bloemfontein

Contact details:

Coetzee EF

eldridgecoetzee@yahoo.com

072 635 2498

Arko-Cobbah E

docemmanuel@gmail.com

082 512 2177

## 2.1 ABSTRACT

Introduction: Thyroid nodules occur in 4-7% of adults with a malignancy risk of 5-15%. Ultrasound plays an important role in the clinical workup of patients with solitary thyroid nodules to differentiate malignant from benign disease.

Objectives: To determine if ultrasound single thyroid nodule size can predict the probability of thyroid malignancy.

Method: Retrospective cross-sectional study of all thyroidectomies done (benign and malignant) from 2010 to 2016. Ethical clearance obtained from University of the Free State (**HSREC 0664/2017**). Data analyzed by means of descriptive statistics, namely frequencies and percentages for categorical data, medians, and percentiles for numerical data, were calculated. Associations regarding cancer were done for numerical data by means of Kruskal-Wallis test and for contingency tables by means of Chi-square or Fischer's exact test. A p-value of < 0.05 was considered statistically significant. Diagnostic test statistics were calculated, namely sensitivity, specificity, positive and negative predictive values, and likelihood ratios.

Results: The overall incidence of thyroid cancer was 24.6%. The median age of thyroid cancer patients was 52.9 years and for benign disease 54 years. Female patients with thyroid cancer were 78.7% and for benign disease 90.1%. Male patients with cancer were 21.2%, for benign disease 9.9%. Papillary thyroid cancer remains the most common type of cancer at 87.8% and follicular thyroid cancer 12.1%. The average size of thyroid cancer on histology was 2.1 cm and 3.2 cm for the non-cancer group, respectively: statistically significant with p-value of 0.0015. Ultrasound nodular size for cancer was 1.7 cm, and 1.9 cm for the non-cancer group, with p-value 0.209. The association between ultrasound size and histology size for cancer group were not significant with p-value 0.99. Size difference for non-cancer group between histology and ultrasound was significant with p-value 0.02.

Conclusions: The study did not prove our hypothesis that ultrasound size alone, can predict the risk of thyroid cancer. Diagnostic test results with 95% CI reveals a sensitivity of 96% but low specificity of 22% to predict the risk of thyroid cancer.

## 2.2 INTRODUCTION

Significant uncertainty remains surrounding the diagnostic accuracy of ultrasound features to predict the malignant potential of thyroid nodules that overlap with benign disease. Our study aim was to determine if ultrasound size of a solid thyroid nodule of at least 1 cm can be used to predict thyroid cancer in a solid thyroid nodule.

Thyroid nodules are a common occurrence in clinical practice.

A thyroid nodule is called a nodule on ultrasound when a lesion within the thyroid gland is distinguishable from the adjacent parenchyma or tissue. For the nodule to be solid on ultrasound it must appear purely solid or predominantly solid with a cystic component of less than 10 % of the total volume of the nodule.

Clinical workup of a solitary thyroid nodule is to differentiate malignant from benign disease. That will determine which patients require intervention and which patients may be monitored serially. History taking, physical examination, laboratory tests, ultrasound, and fine needle aspiration biopsy (FNAB) are the mainstays in the evaluation of thyroid nodules. [1,7,8,9]. FNAB can be benign, malignant, indeterminate, or non-diagnostic. Up to 10 to 30% of FNABs will be non-diagnostic.

The American Thyroid Journal of the United States, Vol 19 (2009,2015) [1,20] updated guidelines shown that 4-7% of adults in North America have palpable nodules, and the prevalence increase to 30% with imaging studies. The American Thyroid Journal of the United States, Vol 19, 2009 [1] also found a 5 -15 % probability of malignancy in any given thyroid nodule.

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2. Nodules >1 cm with intermediate risk ultrasound features.
3. Nodules >1.5 cm with low risk ultrasound features.
4. Nodules >2 cm with very low risk ultrasound features may be considered.

**Thyroid nodule diagnostic FNAB not required:**

1. Nodules that do not meet above criteria.
2. Nodules that are purely cystic.

Treatment consists of surgical intervention plus adjuvant treatment. Surgical options include total or lobectomy plus minus isthmusectomy. One study compared the overall survival of 23605 subjects with papillary and follicular thyroid cancer treated with local excision, lobectomy, subtotal, and total thyroidectomy using Surveillance, Epidemiology, and End Results (SEER) database. The SEER database concluded that the 10-year overall survival after total thyroidectomy resulted in improved survival over other techniques [18]. A study by **Jisheng HU et al (2016)** published in the World Journal of Surgical Oncology [18] after 5559 thyroidectomies concluded that total thyroidectomy dominates over lobectomy as being more cost effective, and this approach maximizes the quality adjusted life expectancy in patients with thyroid cancer compared to lobectomy surgery.

In 2015, a consensus statement from the American Thyroid Association [1,7,8,9,20] on preoperative imaging concluded that ultrasound remain the most important imaging modality in the evaluation of patients with suspected thyroid cancer nodules and all should have an ultrasound routinely.

Ultrasound features of malignancy include micro calcifications, central nodule hypervascularity, solid nodule, irregular borders, taller than wider, hypoechoic, and large size > 1 cm. [1,3,9,10,11,12,13,14]

In a meta-analysis published in **The Journal of Clinical Endocrinology (2014) [4]** analysing the accuracy of thyroid nodule on ultrasound to predict thyroid cancer, they included 31 studies from 1985 to 2012. This included 18288 nodules with average size of 15 mm; the frequency of thyroid cancer was 20%. This study used 14 sonographic features to evaluate the thyroid nodules. They concluded that low to moderate quality evidence suggest that individual ultrasound features are not accurate predictors of thyroid cancer. **[3,4].**

**Luciana Reck Remonti et al (2015) [19]** used 52 observational studies including 12786 nodules looking at ultrasound features of malignancy. They concluded that ultrasound features in isolation can not reliably identify nodules with an increased risk for malignancy.

A Study by **Hammad Ay et al (2016) [16]** included 10817 thyroid nodules of which 20.4% were malignant. Nodule size 3-5.9 cm had 26% greater malignancy risk. However, nodules 6 cm or larger had a 16% lower risk of malignancy compared to those < 3 cm. The conclusion was that size can predict risk, sizes greater than 6 cm being associated with benign disease.

**Kamran SC et al (2013) [15]** evaluated 7348 nodules, 13% overall malignant. Size: 1-1.9 cm 10.5% , 2-2.9 cm 14%, 3-3.9 cm 16% and >4 cm 15% cancer rates. Their study concluded that increasing nodule size impacts cancer in a nonlinear fashion. The threshold was 2 cm; beyond that, cancer risk is unchanged.

Currently no South African data is available on this subject after searching EbscoHost.

Our study aim is to use preoperative ultrasound single solid nodule size of 1 cm and bigger to compare with histological type and size found post-operatively, to determine if different ultrasound size can be used to predict thyroid cancer in our population. If it can be used it may impact on surgical management of patients: one operation instead of two operations may be possible. Biopsy may be omitted for indetermined FNAB and nodule of 1 cm, and opt for total thyroidectomy instead of biopsy/lobectomy and completion thyroidectomy (2 surgeries).

## 2.3 BACKGROUND

### A. Patient Factors

Age

The peak age of thyroid cancer peaks in the third and fourth decades of life**.** The patient's age at diagnosis is one of the most important prognostic features of well differentiated thyroid cancer. Recurrence rates increase in ages $< 30$ or $> 60$ years. National Cancer institute 2010-2014 [2,6] statistics reveal an incidence of thyroid cancer as 18.9% for age group 35-44 and 23.4% for ages 45-54.

Gender

Thyroid cancer is 3 times more common in females than males, however males are more at risk of developing thyroid cancer if a nodule is found. [2,6]

### B. Tumor factors:

Size

As seen in previous literature size can be an indicator measure of thyroid malignancy. Histological tumor size will be divided into ranges from 1 -1.9 cm, 2 - 2.9 cm, 3-3.9 cm and $> 4$ cm. [15]

The aim is to find the average thyroid cancer size on histology, and correlate with ultrasound findings preoperatively as was done by J Zheijang et al. (2012) [13] and Hammad AY et al June (2016). [16]

Histological type

Papillary carcinoma is the most common type (80%), followed by follicular cancer (10%). [1,6,16]. Mucinous and Anaplastic are very rare and will be classified as "Other". Only nodules positive for malignancy will be used as data.

The aim is to find the most common thyroid cancer in our population and compare to above study findings.

Type of lesion

Lesions will be divided into single solid lesions and those with nodular appearance. Single solid thyroid lesions > 1 cm is a clinical risk predictor of thyroid cancer. [1,2,6,7]

Ultrasound size

High resolution conventional ultrasound is used. Different operators were used for preoperative nodule evaluations. All patients with preoperative thyroid nodule size evaluation will be included. The measured sizes will be correlated with histological size and positivity for malignancy on histology. Above size measurements will also be used as for the histological size categories. Measurement from 1cm to > 4cm will be used and subdivided. Minimum size of 1cm will be used because the **American Thyroid Association** regards a single solid nodule of 1cm of having a higher risk of cancer. 6cm will be the cut-off, as any size >6cm is more likely benign **(Hammad et al) [16** J Zheijang et al (2012) [13]

Type of operation

Surgical intervention remains the mainstay of thyroid cancer treatment. Surgical options include total or subtotal thyroidectomy, lobectomy plus minus isthmusectomy. Our study will be looking at the type of operation that was done for thyroid cancer. It will be divided into either lobectomy or total thyroidectomy.

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## 2.4 AIMS AND OBJECTIVES

Primary aim:

To determine if ultrasound single solid thyroid nodule size can be used to predict the probability of thyroid cancer.

Secondary aim:

- To describe the different histological types of thyroid cancer, as well as their population demographics.

- Association between ultrasound size and histology

## 2.5 METHODS

A retrospective cross-sectional study was performed, by means of a file review. All files of adult patients seen from 1 January 2010 to 31 December 2016 were reviewed. Inclusion criteria were: All thyroidectomies (benign and malignant) done at Universitas Academic Hospital from 2010-2016, except those on exclusion criteria namely,

- Incomplete / untraceable notes
- No ultrasound size measurement preoperatively
- All cystic nodules
- Patients with recurrence of thyroid cancer

The study was approved by the Ethics committee of the University of Free State **(HSREC 0664/2017).**

Data was collected from files obtained through records department, theatre admission book, electronic filing system (Meditech©) and histology reports from department of anatomical pathology DISA lab and NHLS LABTRAK. Diagnostic ultrasound reports were obtained from PACS electronic radiology and Meditech.

Measurements:

The following was noted:

- Age and gender
- Tumor factors (size, type of lesion and type of cancer)
- Type of operation (total or lobectomy)
- Ultrasound measured size

Data captured was recorded on the approved data sheet by the researcher and onto an Excel sheet that serves as a second copy of all data. Histological and ultrasound size ranges from 1-1.9 cm, 2-2.9 cm, 3-3.9 cm and > 4 cm were used to calculate probability of thyroid cancer. Sizes were calculated using length, height and width divided by 3 to get average size in cm.

Data analyzed by means of descriptive statistics, namely frequencies and percentages for categorical data, means and standard deviations or medians and percentiles for continuous data. Associations regarding cancer were done for numerical data by means of Kruskal-Wallis test and for contingency tables by means of using Chi-square or Fischer's exact test.

Diagnostic test statistics were calculated, namely sensitivity, specificity, positive and negative predictive values, and likelihood ratios. Analysis was done by the Department of Biostatistics University of Free State. A p-value of $< 0.05$ was considered statistically significant. Graphs and tables were used to plot the results.

## 2.6 RESULTS

A pilot study, including the first 2 files per year for the study period 2010-2016, was retrieved and analyzed. Following the pilot study, modifications were made to the protocol and data sheet.

A total of 169 files, which fulfilled the inclusion criteria were retrospectively reviewed, 35 files were excluded due to incomplete data and 134 patient files were entered into the study, which included both benign and malignant thyroid disease. In total 33 files were confirmed thyroid cancer and 101 for non-cancer.

In our study the overall incidence of thyroid cancer was **24.6%**. Hammad AY et al 2016 [[16]] found overall thyroid cancer incidence of 20.4%, Kamran SC et al 13% [[15]] and 20% found after a meta-analysis of 31 studies published in the Journal of endocrinology 2014.[[4]]

**<u>Table 1</u>**

| Characteristics | Patients n =134 (%) |
|---|---|
| **Age** | |
| <45 | 40 (29.8) |
| >45 | 94 (70.1) |
| Mean Age ± SD | 53.5 |
| Range | 14 – 83 years |
| **Gender** | |
| Male | 17 (12.6) |
| Female | 117 (87.3) |
| **Nodules** | |
| Single/Solid | 66 (49.2) |
| Nodular | 68 (50.7) |
| **Histology** | |
| Benign | 101 (75.3) |
| Malignant | 33 (24.6) |
| **Histological type of cancer** | **N=33** |
| Papillary carcinoma | 29 (87.8) |
| Follicular carcinoma | 4 (12.1) |
| Medullary carcinoma | 0 |
| Anaplastic | 0 |
| **Size of nodules** | |
| 1-1.9 cm | 73 (54.4) |
| 2-2.9 cm | 34 (25.3) |
| 3-3.9 cm | 16 (11.9) |
| >4 cm | 11 (8.2) |
| **Type of operation** | |
| Thyroid Lobectomy | 89 (66.4) |
| Total thyroidectomy | 45 (33.5) |

**Table 2**
**Comparison between non-cancer and cancer nodules**

| Characteristics | Non-cancer n=101 (%) | Cancer n=33 (%) | P-value |
|---|---|---|---|
| **Age** | | | 0.82 |
| <45 | 30 (29.7) | 10 (30.3) | |
| >45 | 71 (70.2) | 23 (69.6) | |
| **Gender** | | | 0.12 |
| Male | 10 (9.9) | 7 (21.2) | |
| Female | 91 (90.0) | 26 (78.7) | |
| **Nodules** | | | 0.48 |
| Solid | 38 (37.6) | 30 (90.9) | |
| Multiple/Nodular | 63 (62.3) | 3 (9.0) | |
| **Size of nodules by ultrasound** | | | 0.2 |
| 1-1.9 cm | 52 (51.4) | 21 (63.6) | |
| 2-2.9 cm | 26 (25.7) | 7 (21.2) | |
| 3-3.9 cm | 13 (12.8) | 3 (9.0) | |
| >4 cm | 10 (9.9) | 2 (6.0) | |
| **Size of nodules by histology** | | | 0.0015 |
| 1-1.9 cm | 23 (22.7) | 15 (45.4) | |
| 2-2.9 cm | 23 (22.7) | 6 (18.1) | |
| 3-3.9 cm | 20 (19.8) | 6 (18.1) | |
| >4 cm | 35 (34.6) | 6 (18.1) | |
| **Type of operation** | | | 0.13 |
| Thyroid Lobectomy | 63 (62.3) | 26 (78.7) | |
| Total thyroidectomy | 38 (37.6) | 7 (21.2) | |

**Table 3**

**Ultrasound as predictive tool (Cancer Patients n=33)**

| Size | Cancer by histology | Cancer by ultrasound |
|---|---|---|
| 1-1.9 cm | 15 (45.4) | 21 (63.6) |
| 2-2.9 cm | 6 (18.1) | 7 (21.2) |
| 3-3.9 cm | 6 (18.1) | 3 (9.0) |
| >4 cm | 6 (18.1) | 2 (6.0) |

**Table 4**

**Association between ultrasound size and histology**

**Average size**

| | Cancer | Non-cancer | P-value |
|---|---|---|---|
| Histology | 2.1 cm | 3.2 cm | 0.0015 |
| Ultrasound | 1.7 cm | 1.9 cm | 0.209 |

Ultrasound size vs cancer histology – not significant P-value 0.99
Ultrasound size vs non-cancer histology – showed significant P-value 0.02

**Table 5**

Diagnostic test results with 95% confidence intervals

Sensitivity = 96% (95% CI: 89% - 99)

Specificity = 22% (95% CI: 11% - 38%)

Predictive value of positive test = 74% (95% CI: 65% - 81%)

Predictive value of negative test = 69% (95% CI: 39% - 91%)

Likelihood ratio of positive test = 1.23 (95% CI: 1.04 – 1.45)

Likelihood ratio of negative = 0.20 (95% CI: 0.06 – 0.60)

False positive rate = 78% (95% CI: 62-89%)

False negative rate = 4% (95% CI: 1% - 11%)

Misclassification rate = 27% (95% CI: 20 % - 14%)

Prevalence (95% CI: 61% - 77%)

Efficiency (Correct classification rate) =73% (95% CI:65 % - 80%)

## 2.7 DISCUSSION

**Primary aim**

The question was asked if ultrasound single thyroid nodule size can be used to predict the probability of thyroid cancer. Diagnostic test results reveal ultrasound thyroid nodule size test has a sensitivity of 96%, specificity of 22%, a positive predictive value of 74%, and a negative predictive value of 69%. The likelihood ratio of a positive test was 1.23, for negative test it was 0.20. A likelihood ratio greater than 1 indicates the test result is associated with the presence of the disease, but a likelihood ratio less than 1, is associated with the absence of disease. A high likelihood ratio may show that the test is useful, but it does not necessarily prove to be a good indicator of the presence of disease.

Although 27 cancer patients fell into ultrasound size range 1-3.9 cm (81.8%), there was no statistical significance between cancer ultrasound size and confirmed histological cancer for the same size range (p-value 0.99). (See Tables 2 and 4). The false positive rate for ultrasound size test to predict malignancy was high at 78%. (Table 5)

Considering these results, our hypothesis that ultrasound thyroid single nodule size can predict malignancy was not proven.

**Secondary aim:**

- To describe the different histological types of thyroid cancer, as well as their population demographics.

- Association between ultrasound size and histology

### Patient factors

Age

The minimum age for the benign group was 14 years and maximum 82 years with a median of 54 years for benign disease. The minimum age for thyroid cancer group was 21 years and maximum 83 years with a median age of 53 yrs. No statistically significant difference was found between the groups, with p-value 0.82.

The peak age for thyroid cancer is in the third and fourth decades of life. [2,6]

In our study the age group <45 years the cancer incidence was 30.3% and 69.9% for age

group >45 years. (Table 2). The National Cancer Institute statistics reveal the incidence of thyroid cancer as 18.9% for age group <45 and 23.4% for age group >45[2,6]. In our study, the incidence of cancer was higher in both age groups, compared to the National Cancer Institute statistics.

Gender

The total female patients were 117 and males 17. There were 26 females with cancer (78.7%) and 7 males with cancer (21.2%). (Table 1, 2)

Thyroid cancer is 3 times more common in females than males [2,6]. Our study also confirms this finding. (Table 2)

**Tumor factors**

- Tumor size

The median size for the non-cancer group was 3.2 cm and cancer group median size were 2.1 cm. A statistically significant difference was found between size of the non-cancer group and cancer group histology size with p-value 0.0015 (Table 2, 4). In comparison, the average size for cancer was 1.5 cm; that included 31 studies from 1985 to 2012, published in The Journal of Endocrinology 2014.[4]

Our study concludes that benign histology is associated with a larger size than cancer histology. A study by Hammad AY *et al* 2016 found sizes greater than 6 cm is associated with benign disease [16]. Kamran SC *et al* 2013 concluded that increase in nodule size impacts cancer in a nonlinear fashion; beyond 2 cm, the cancer risk is unchanged [15]. In our study this was reproduced with cancer size beyond 2 cm the risk of cancer remained unchanged at 18.1% (Table 2).

- Ultrasound size

The average size in the non-cancer group was 1.9 cm and 1.7 cm for the cancer group.

A p-value of 0.2 showed no significant difference between ultrasound sizes in the cancer and non-cancer groups (Table 4).

In comparison, the average size for cancer was 1.5 cm, concluded from 31 studies from 1985 to 2012, published in The Journal of endocrinology (2014) [4].

- Ultrasound size as a predictive tool

The aim was to find the average size of thyroid cancer on histology and to correlate with pre-operative ultrasound size. The median histological cancer size was calculated at 2.1 cm and ultrasound size for cancer was 1.7 cm. No statistically significant difference was found, with a p-value 0.99 (Table 4).

Histological size in the non-cancer group was found to be bigger than the cancer group, proven by a p-value of 0.0015. This correlates with the preoperative ultrasound size which shows a statistically significant p-value of 0.02 (Table 4). This was also found by Kamran Sc (2013) [15] and Hammad AY (2016) [16], that bigger size > 4 cm is more likely to be benign disease.

Diagnostic test statistics were calculated, namely sensitivity, specificity, positive and negative predictive values, and likelihood ratios. We wanted to find out if the ultrasound size of a solid lesion can be used as an independent predictor of thyroid malignancy.

Sensitivity is the proportion of true positives that are correctly identified by the test. Specificity is the proportion of true negatives that are correctly identified by the test. The likelihood ratio indicates the value of the test for increasing certainty about a positive diagnosis. A likelihood ratio of more than 1 indicates that the test result is associated with the presence of the disease whereas a ratio of less than 1 the absence of disease. The likelihood ratio indicates the value of a test for a positive diagnosis [21,22,23,24].

Our study found a sensitivity of 96% and specificity of 22%, with a likelihood ratio of 1.23 (Table 5). Although our study found that ultrasound size as predictive tool has a high sensitivity, a likelihood ratio of more than 1; its specificity is 22%, and a false positive result of 74%.

- Histological type

The aim was to find the most common type of thyroid cancer in our population. 4 types were specified, Papillary, Follicular, Medullary and Anaplastic.

Papillary cancer was the most common type (87.8%), followed by follicular cancer (12.1%). No patients were found who had medullary or anaplastic cancer. Data from the National

cancer institute recorded papillary cancer as the most common (80%) and follicular cancer (10%) [2,4,6].

- Type of lesion

Data from the American Thyroid Association [1,2,6] regards any single solid thyroid lesion greater than 1 cm to have a 5-15% chance of malignancy and should be investigated.

Our study results found that 49.2% of all the lesions were solid, and 45.4% was found in the cancer group (Table 1,2).

- Type of operation

Lobectomy or total thyroidectomy was the 2 type of surgeries performed for benign and malignant disease. In our study, 26 cancer patients had lobectomies done and 7 had total thyroidectomies (Table 1). According to the SEER database [6], the 10-year overall survival results concluded that total thyroidectomy resulted in improved survival over lobectomy group. Jisheng HU et al (2016) concluded that total thyroidectomy is safe to perform as initial surgery for thyroid cancer with decreased recurrence rates [18]. Our study findings show that lobectomies were the majority operation done for cancer, different from the above studies.

## LIMITATIONS OF STUDY

Incomplete and missing data was a definite limitation. Small sample size in the cancer group as well as a study population from a single institution could have contributed as limitations.

## 2.8 CONCLUSION

The study revealed an incidence of 24.6% for thyroid cancer, more common in females. Histological size for non-cancers was larger in size than for cancer, which was statistically significant. Ultrasound size and histology size did not show any statistical significance in the cancer group. Papillary cancer was the most common type with 87.8%. Ultrasound remains an important imaging modality for thyroid nodules, but size alone cannot be used to accurately predict thyroid cancer due to the low specificity of 22% and false positive rate of 78%.

However, it may be used as a negative predictor – the larger the nodule, the less potential for malignancy.

## 2.9 AUTHOR CONTRIBUTION

EFC was the principal investigator. EAC was the supervisor for this research project. Both authors worked together on the protocol and analyzed the data. EFC collected the data.

## 2.10 ACKNOWLEDGEMENTS

The authors are grateful for contributions from Riette Nel (Department of Biostatistics, University of the Free State. Thank you to the secretary at the Department Anatomical Pathology, University of the Free State.

## 2.11 CONFLICT OF INTEREST

None

## 2.12 AUTHOR FUNDING SOURCES

Self-funded.

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# APPENDIX A: HSREC ETHICS LETTER OF APPROVAL

**Health Sciences Research Ethics Committee**

23-Apr-2018

Dear **Dr Eldridge Coetzee**

Ethics Clearance: **Ultrasound thyroid nodule size and histological findings** Principal Investigator: **Dr Eldridge Coetzee**

Department: **Surgery (Bloemfontein Campus)**

**APPLICATION APPROVED**

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2017/0664**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

**Health Sciences Research Ethics Committee**
**Office of the Dean: Health Sciences**
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784

Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa www.ufs.ac.za

APPENDIX B: FS DOH LETTER OF APPROVAL

health

Department of Health

FREE STATE PROVINCE

09 January 2018

Dr EF Coetzee
Dept. of Surgery
Faculty of Health Science
UFS

Dear Dr EF Coetzee

SuWect: Ultrasound th roid nodule size and histolo ical findin s.

- Please ensure that you read the whole document, Permission is hereby granted for the above — mentioned research on the following conditions:
- Serious adverse events to be reported and/or termination of the study.
- Ascertain that your data collection exercise neither interferes with the day to day running of Pelonomi and Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and no names will be used.
- Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to khusemj@)fshealth.gov.za or sebeelats@fshealth.gov.za before you commence with the study
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution managers/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future resea h will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.

Kind Regards

Dr D Motau HEAD: Date:

H 2018

Tel: (051) 408 1527 Fax: (051) 408 1556 e-mail:sebeelats@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

www.fs.gov.za

APPENDIX C: HEAD OF DEPARTMENT OF SURGERY LETTER OF APPROVAL

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS•UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

07 November 2017

TO WHOM IT MAY CONCERN

This is to certify that Dr E Coetzee (MP0500852) will have completed the requirements to write the Intermediary exams in January 2018. Including but not limited to:

1. General Surgery 1 year
2. Multi-ICU 3 months
3. Trauma 3 months
4. Research requirements

**DR N PEARCE**
**HEAD: DEPARTME**HEAD: DEPARTMENT OF SURGERY
FACULTY OF HEALTH SCIENCES
UNIVERSITY OF THE FREE STATE BLOEMFONTEIN

Department of Surgery/ Departement Chirurgie
Medical School/Mediese Skool
T: +27(0)51 405 3545 | F: +27(0)51 444 1023
205 Nelson Mandela Drive/Rylaan | Park West/Parkwes | Bloemfontein 9301 | South Africa/Suid-Afrika
P.O. Box/Posbus 339 | Bloemfontein 9300 | South Africa/Suid-Afrika | www.ufs.ac.za

APPENDIX D: SUPERVISOR LETTER OF APPROVAL

pelonomi hospital

Department of Health
Pelonomi Tertiary Hospital
FREE STATE PROVINCE

25 March 2020

TO WHOM IT MAY CONCERN

Re: Dr E Coetzee

I approve of his submission of his research, Ultrasound Thyroid Nodule Size and Histological Findings, for marking

Kind regards

Dr E Arko-Cobbah
Consultant: Trauma and General Surgery
Head of Unit: Pelonomi ICU

APPENDIX E: HSREC APPROVED PROTOCOL

# STUDY PROTOCOL

# Ultrasound Thyroid nodule size and histological findings

Dr EF Coetzee, MBCHB (Stell), Registrar: Department of Surgery, Universitas Academic Hospital

eldridgecoetzee@yahoo.com/ (0726352498)

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**Researchers:**

DR EF Coetzee
MBCHB (Stell)
Registrar: Department of Surgery, UFS, Universitas Academic Hospital
eldridgecoetzee@yahoo.com

DR E Arko-Cobbah
MBChB (UFS), MMED (SURG), Cert Trauma Surgery (SA)
Trauma surgeon
Department of Surgery, UFS, Universitas Academic Hospital
docemmanuel@gmail.com

**Introduction:**

Thyroid nodules are common. The American Thyroid Journal of the United States revealed that 4-7 % of adults in North America have palpable nodules, and the prevalence increase to 30% with imaging studies. There is a 5- 15% probability of malignancy in any given thyroid nodule. A thyroid nodule is called a nodule on ultrasound, when a lesion within the thyroid gland is distinguishable from the adjacent parenchyma or tissue. For the nodule to be solid on ultrasound it must appear purely solid or predominantly solid with a cystic component of less than 10 % of the total volume of the nodule.

Thyroid cancers represent approximately 1% of new cancers diagnosed in the US yearly. Number of new thyroid cancer cases was 14.2 per 100000 men and women per year. Deaths were 0.5 per 100000. These data were based on 2010-2014 data from the National Cancer Institute. Lifetime risk of developing thyroid cancer is 1.2 % of men and women during their life, based on 2012-2014 data. Thyroid cancers are divided into 4 types: Papillary (80%), Follicular (10%), Medullary (5-10%) and Anaplastic cancers (1-2%). Thyroid cancer most commonly present as a painless, palpable solitary nodule. High risk patients are those older than 60 and younger than 30 years, male patients, and family history of thyroid cancer, previous radiation to head and neck region and MEN type 2. Prognostic factors include age at diagnosis of cancer: death is most likely to occur if the patient is > 40 years old; males are twice as likely as women to die from thyroid cancer. Size >4cm has a higher mortality rate, histology type like papillary cancer has a 6% 30yr mortality rate.

Clinical workup of a solitary thyroid nodule is to differentiate malignant from benign disease. This will determine which patients require intervention and which patients may be monitored serially. History taking, physical examination, laboratory tests, ultrasound and fine needle aspiration biopsy (FNAB) are the mainstays in the evaluation of thyroid nodules. FNAB can be benign, malignant, indeterminate or non-diagnostic. Up to 10 to 30% of FNABs will be non-diagnostic.

**The American Thyroid Association guidelines of 2009 recommendations for FNAB's**

1. Sub centimeter nodule size biopsy should be done only if the nodule has a suspicious ultrasound finding or the patient has a history of radiation exposure or familial thyroid cancer.
2. Not to biopsy nodules less than 5mm, due to high rate of inadequacy.
3. A nodule with indeterminate findings on ultrasound, but is larger than 1cm, FNAB is recommended because malignancy cannot be excluded.
4. If the nodule has indeterminate finding on ultrasound and is 1 cm or less, then FNAB is not necessary

Treatment consists of surgical intervention plus adjuvant treatment. Surgical options include total or subtotal thyroidectomy, lobectomy plus minus isthmusectomy. One study compared the overall survival of 23605 subjects with papillary and follicular thyroid cancer treated with local excision, lobectomy, and subtotal and total thyroidectomy using Surveillance,

Epidemiology and End Results (SEER) database. The 10-year overall survival results concluded that total thyroidectomy resulted in improved survival over other techniques.

Ultrasound was first used clinically in 1956 by obstetrician Ian Donald in Glasgow. The first thyroid ultrasound was done in 1965. Only 7 articles were published up to 1970. Currently more than 1300 articles were published in the past 5 years. In 2015 a consensus statement from the American Thyroid Association on preoperative imaging concluded that ultrasound remain the most important imaging modality in the evaluation of patients with suspected thyroid cancer nodules, and all should have a ultrasound routinely. Ultrasound features of malignancy includes micro calcifications, central nodule hyper vascularity, solid nodule, irregular borders, taller than wider, hypoechoic and large size > 1cm. Significant uncertainty remains surrounding the diagnostic accuracy of ultrasound features to predict the malignant potential of thyroid nodules due to overlapping with benign disease. In a meta-analysis published in The Journal of Clinical Endocrinology 2014 Apr: 99 (4):1253-1263 checking the accuracy of thyroid nodule on ultrasound to predict thyroid cancer, they included 31 studies from 1985 to 2012. That included 18288 nodules with average size of 15 mm; the frequency of thyroid cancer was 20 %. The most common cancer was papillary thyroid cancer (84%). They used 14 sonographic features to evaluate the nodules.

They concluded that low to moderate quality evidence suggest that individual ultrasound features are not accurate predictors of thyroid cancer.

A 2015 study done showed nodule size <3cm was 41 % malignant, 38% for size 3-4 cm. Overall conclusion was that increase in size does not increase malignancy **(International Institute for Anticancer Research)**

**Study by Hammad Ay 2016** had 10817 thyroid nodules, of which 20.4% were malignant. Nodule size 3- 5.9 cm had 26% greater malignancy risk. Conclusion was that size can predict risk, sizes greater than 6cm associated with benign disease.

**Kamran Sc 2013, Endocrine Society** evaluated 7348 nodules, 13% overall malignant. Size: 1-1.9 cm 10.5% cancer rate, 2-2.9 cm 16% cancer rate. Their conclusion was that increasing nodule size impacts cancer in a nonlinear fashion. Threshold was 2 cm, beyond that cancer risk is unchanged.

No South African data is available on this subject after searching EbscoHost.

This study aims to use preoperative ultrasound single solid nodule size of 1- 6 cm and compare with histological type and size found postoperatively, to see if different ultrasound size can be used to predict thyroid cancer in our population. If it can be used it may impact on surgical management of patients: 1 operation instead of 2 may be possible. Biopsy may be omitted for indeterminate FNAB and nodule of 1cm, and opt for thyroidectomy instead of biopsy/lobectomy and completion thyroidectomy (2 surgeries).

**Background:**

**Patient factors**

Age
The peak age of thyroid cancer peaks in the third and fourth decades of life**.** The patient's age at diagnosis is one of the most important prognostic features of well differentiated thyroid cancer. Recurrence rates increase in ages < 30 or > 60 years. National Cancer institute statistics reveal incidence of thyroid cancer as 18.9% for age group 35-44 and 23.4% for ages 45-54.

Race
American data from cancer institute reported thyroid cancer in all ages for women as 21/100000 and men 7.1/100000 persons. White women as 22.4 vs black women as 13/100000. White men were 7.6 vs black men as 3.7/100000.2010-2014 statistics

Sex
Thyroid cancer is 3 times more common in females than males. Males are more at risk of developing thyroid cancer if a nodule is found.

**Tumor factors:**

Size
As seen in previous literature, size can be an indicator measure of thyroid malignancy. Histological tumor size will be divided into ranges. 1-1.9 cm,2- 2.9 cm and 3 to 6cm. Aim is to find the average size of thyroid cancer on histology and correlate with ultrasound findings preoperatively.

Histological type
Papillary carcinoma is the most common type (80%), followed by follicular cancer (10%). Mucinous and Anaplastic are rare and will be classified as "Other". Only nodules positive for malignancy will be used as data. Aim is to find the most common thyroid cancer in our population.

Type of lesion
Determine if nodule was single and solid of consistency. Single solid thyroid nodule is a clinical risk predictor of thyroid cancer.

Ultrasound size
High resolution conventional ultrasound was used. Different operators were used for preoperative nodule evaluations. All patients with preoperative thyroid nodule size evaluation will be included. The measured sizes will be correlated with histological size and positivity for malignancy on histology. Above size measurements will also be used as for the histological size categories. Measurement from 1 cm to 6cm will be used and subdivided. Minimum size of 1 cm will be used, because the American Thyroid Association regards a single solid nodule of 1 centimeter as having a higher risk of cancer. 6 cm as cut off, because Hammad AY 2016 concluded sizes >6cm associated more with benign disease.

**Aim and Objective of the Study:**

**Primary aim:**

To determine if ultrasound single solid thyroid nodule size can be used to predict the probability of thyroid cancer.

**Secondary aim:**

To describe the different histological types of thyroid cancer, as well as their population demographics

Association between ultrasound size and histology

**Methodology**

Study design:

- Retrospective cross-sectional study
- The study will consist of retrospectively identified cases. Histology records, Meditech notes plus diagnostic sonar reports will be analyzed retrospectively.

Study location:

- Universitas Academic Hospital Endocrine Uunit and Pelonomi Hospital

Study population:

- All thyroidectomies including with or without cancer done from 2010 to 2016 at above 2 hospitals for thyroid cancer, except those on the exclusion criteria. An estimated number of cases are roughly 80 to 100.

**Exclusion criteria:**

- Incomplete / untraceable notes
- No ultrasound size measurement preoperatively
- All cystic nodules
- All benign histological types
- Patients with recurrence of thyroid cancer

SNOMED search on the DISA and Labtrek system will be used to identify the cases. Patient hospital numbers will be used to track on Meditech and files of patients for completion of the data sheet. Data collection will be done by the researcher.

**Measurements:**

The following will be noted:

- Age, gender and race
- Tumor factor like size
- Ultrasound measured size
- Anatomical pathology records of different thyroid cancers

All data recorded will be captured on a data sheet by the researcher (appendix A)

**Methodological and measurement errors:**

- Data –poor documentation of diagnosis, displaced files or no Meditech notes will affect data collection and number of study participants.
- Time – older records, retrospective study design might prove difficult to trace and can prolong data collection.

**Pilot study**:
The first two cases per year will be used for the pilot study. This will be done to test the data form and to amend it if needed. These 10 cases will also be included in the main study.

**Data capturing and analysis:**

Descriptive statistics namely frequencies and percentages for categorical data, means and standard deviations or medians and percentiles for continuous data will be calculated. Associations by means of contingency tables using Chi-square or Fischer's exact test will be used. Significant variables will be further analyzed in a multivariate regression analysis. Analysis will be done by the Department of Biostatistics University of Free State.

**Proposed Time Schedule:**

May 2017-Submit protocol to Ethics committee

August 2017 to March 2018- data collection

Pilot study April 2018

January 2019- submit data for analysis

Writing of article – April 2019

**Budget**

The budget will be funded by the researcher. The projected cost will be R500- R1000. Data analysis will be done at no additional cost. The study is not funded by any sponsors.

**Ethical considerations:**

The study protocol will be submitted to the Ethics Committee of the Faculty of Health Sciences at the University of the Free State for approval. A letter of approval with the protocol will be send to the Free State Department of Health requesting permission to conduct the study.

As this is a retrospective study, all data and information collected will be regarded as confidential. Only researchers will have access to patient records. Hospital numbers will be recorded on the data sheet, but will not be coded for. This will limit the association between patients and the information.

Every precaution will be undertaken to ensure privacy of the research participants and their personal information.

The data file will be stored at the Department of Surgery, University Free State for safe keeping, and only accessible to the researchers.

**Dissemination of Results**:

Results will be made available to the Department of Surgery, Anatomical pathology and Ethics when completed.

**Implementation of results:**

This study will be used for the MMED dissertation to be handed in and marked as part of the curriculum MMED. The study findings will try and determine if nodule size can predict thyroid cancer risk to be used as a predictive tool to guide further surgical management.

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**Appendices:** - Files attached, data sheet and curriculum vitae

APPENDIX F: HSREC APPROVED DATA SHEET

# Ultrasound Thyroid nodule size and histological findings

Hospital number [ ]

## Demographics

Age [ ] years

Gender2 [Male] 1 [Female]

## Tumour factors

Size(cm)

____________________

Histological type

- Papillary1 [ ]
- Follicular2 [ ]
- Medullary3 [ ]
- Anaplastic4 [ ]

Type of Lesion

- Single1 [ ]
- Nodular2 [ ]

Ultrasound size (cm)

____________________

Type of thyroidectomy done:

- Total [ ]
- Lobectomy [ ]

Cancer

| Yes | No |
|---|---|

APPENDIX G: INSTRUCTION TO AUTHORS OF THE SAMJ

## SAMJ Author Guidelines General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

*SAMJ* is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.' - Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

**Research**

*Guideline word limit: 4 000 words*

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text. Do not replicate data in tables and in text .

*Structured abstract*

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

*Main article*

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.

- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

*Results*

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

*Discussion*

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

*Conclusions*

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

## Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.

- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

## Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

**Do not:** Use [Enter] within a row to make 'new rows':

*Rather:*
Each row of data must have its own proper row:

**Do not:** use separate columns for *n* and %:

*Rather:*
Combine into one column, *n* (%):

**Do not:** have overlapping categories, e.g.:

*Rather:*
Use <> symbols or numbers that don't overlap:

## References

**NB:** *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g.

These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]

- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef: ○ On the Crossref homepage, paste the article title into the 'Metadata search' box.

○ Look for the correct, matching article in the list of results.

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**Some examples:**

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182 • *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations.

Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

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1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

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(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

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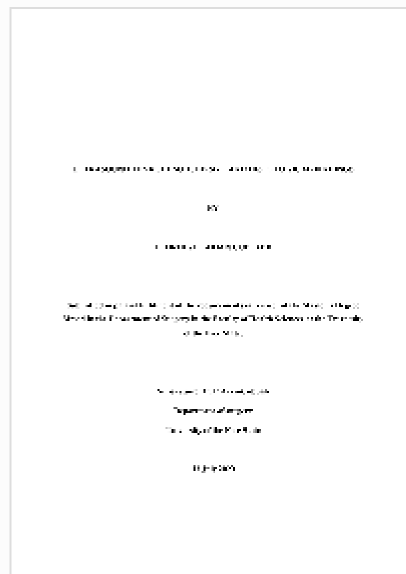

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