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**Pre-Operative Diagnosis of Thyroid Cancer:
Clinical, Radiological and Pathological Correlation**

by

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Declaration

I, Dr Lydia Leone Cairncross, hereby declare that the work on which this dissertation is based is my original work and that neither the whole work or any part of it has been, is being, or is to be submitted for another degree in this or any other university.

Signature:

Date: 31 August 2011

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Part A: Protocol

**Title: Pre-operative Diagnosis of Thyroid Cancer:
Clinical, Radiological and Pathological correlation**

Research Protocol towards MMed (Surg)

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Background:

Nodular disease of the thyroid is extremely common. As many as 3 – 7% of asymptomatic individuals may have clinically palpable nodules, and up to 50% will have nodularity detected on ultrasound. Thyroid cancer is relatively rare, with an incidence of 1 – 2 /100 000. Unfortunately, differentiating benign from malignant thyroid disease remains a challenge.

Ultrasound and cytological assessment are essential parts of the investigation of thyroid nodules, yet in most cases both have insufficient accuracy to allow a definitive diagnosis.

As nodular disease of the thyroid is very common, cancer rare and the diagnosis difficult to confirm, clinical decision making can be difficult. Yet having a confident pre operative diagnosis of thyroid cancer greatly facilitates surgical intervention and is cost effective. Identifying the potential areas for improvement in the various parts of our diagnostic algorithm may streamline investigation, surgery and follow up, providing a more efficient, safe and accurate service for our patients.

Aims:

Primary Aim:

- assess the accuracy of pre operative diagnosis of thyroid cancer in a single centre

Secondary Aims:

- evaluate the impact of preoperative diagnosis on surgical interventions for thyroid carcinoma
- develop locally applicable guidelines for patients with nodular disease of the thyroid

Methods

This is a retrospective review of all patients diagnosed with thyroid carcinoma evaluated or managed at Groote Schuur from 2004 to 2010. Oncology, pathology and surgical records will be used to identify all patients treated during this time.

Data will be captured against an anonymous code and entered on a standardized proforma.

Each component of the preoperative diagnostic process will be evaluated against the final histological report for its positive and negative predictive value. The diagnostic accuracy for different histological subtypes of thyroid cancer will also be evaluated.

Anticipated Outcomes

This study will provide an audit of the diagnostic accuracy of thyroid carcinoma in our unit and guide the development of appropriate, workable guidelines for management of nodular disease of the thyroid in our region. This may have beneficial clinical impact and allow for better use of hospital resources.

Part B: Literature Review: Contents

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Literature Review

Pre-Operative Diagnosis of Thyroid Cancer: Clinical, Radiological and Pathological Correlation

Introduction

The pre-operative diagnosis of thyroid cancer remains a complex problem for general surgeons and endocrinologists. The high prevalence of thyroid nodules in the general population and the relative rarity of thyroid carcinoma make the pre-operative diagnosis of malignancy critical to preventing hundreds of unnecessary diagnostic procedures. Unfortunately no single diagnostic modality can confidently rule out thyroid malignancy. The increased use of high resolution imaging in modern medicine and the consequent flood of the incidental thyroid nodules make the development of accurate thyroid diagnostics an urgent public health concern.

This literature review will examine the current status of the predictive accuracy of clinical assessment, ultrasound and fine-needle biopsy in making the diagnosis of thyroid cancer.

Section 1: Background

1.1. Histopathology of thyroid nodules

A thyroid nodule is a discrete lesion within the parenchyma which can be detected either by palpation or ultrasound¹. Thyroid nodules may be neoplastic or non-neoplastic with neoplastic nodules either benign or malignant (Table 1).

Non neoplastic lesions include simple cysts, haemorrhagic cysts, colloid nodules, hyperplastic nodules and palpable abnormalities related to underlying glandular pathology such as Hashimoto's thyroiditis. Colloid nodules are areas of hyperplasia within the gland which contain enlarged macrofollicles filled with colloid and lined by flattened thyroid epithelial cells².

Benign neoplasms are most commonly follicular adenomas or Hurtle cell adenomas. Adenomas are characterised by a thick, fibrous capsule, have uniform cells of ordered architecture with few mitoses and no lymphovascular invasion. Hurtle cell adenomas differ by being extremely

eosinophilic due to the abundance of cytoplasmic mitochondria. Adenomas differ from hyperplastic nodules in that they are of monoclonal cellular origin and have a thick, well defined capsule. Differentiating follicular adenomas from carcinomas is impossible on cytology and can be difficult on the final histopathological specimen³.

Well differentiated carcinomas (>90%) are papillary, follicular carcinomas and Hurtle cell carcinomas. Anaplastic and medullary carcinomas have a completely different clinical course and treatment. Lymphoma and distant metastases may present as a primary tumour in the thyroid.

Table 1: Differential Diagnosis of Thyroid Nodules

Benign – Non Neoplastic (80%)	Malignant – Neoplastic (5 – 10%)
- Simple cyst	- Papillary carcinoma
- Colloid Nodule	- Follicular carcinoma
- Hyperplastic nodule in MNG	- Medullary carcinoma
- Hashimoto’s Thyroiditis	- Anaplastic carcinoma
Benign – Neoplastic (10 -15%)	Rare Tumours
- Follicular adenoma	- Primary lymphoma
- Hurtle cell adenoma	- Sarcoma
- Embryonal adenoma	- Metastases

1.2. Aetiology – Thyroid Nodules

The aetiology of thyroid nodules is believed to be multifactorial: age, iodine deficiency, sex and irradiation play varying roles⁴.

Iodine deficiency has long been established as a causative factor in the development of multinodular goitre⁵. Iodine deficiency is caused by naturally occurring deficiencies within the soil in endemic areas typically in mountainous regions of the world or areas which have lost top soil cover. Endemic goitre areas occur on every continent. African countries affected are Morocco, Chad, Tunisia, Mozambique, Lesotho and in Europe parts of Italy, Spain, Germany, Poland, Romania, Austria and Hungary have a history of iodine deficiency. Global attempts to iodise salt

has decreased endemic goitre with relative success. South Africa is currently defined by the WHO as an iodine sufficient area ⁶.

Female preponderance is consistently noted in all studies on thyroid nodular disease with a female-male ratio of between 5:1 and 10:1 ⁷. The reason for this is not clear but the presence of oestrogen receptors in both normal and neoplastic thyroid tissue suggests a role for this hormone ⁸.

Irradiation of the head and neck for cancer or even for benign disease was relatively common in the first part of the 20th century. There is clear association between irradiation and the development of benign and malignant thyroid nodules ⁹. The development of nodules may also be affected by the levels of background radiation in a given geographic area ⁹.

1.3. Prevalence of Thyroid nodules – Scale of the Problem

Thyroid nodules are extremely common. The first population based report on the incidence of thyroid nodules in the normal population comes from the small town of Framingham, 21 km from Boston, Massachusetts in 1948 ¹¹. This town was selected for an epidemiology study on CVS disease and included 6600 participants. Palpation of the thyroid gland was part of the clinical examination and results showed that 4.2% of the normal, asymptomatic population had palpable thyroid nodules (6.4% in females, 1.5% in males). The next population study commonly quoted was in Whickham, UK where the prevalence of all types of thyroid disease was assessed. Closely reproducing the results of the Massachusetts study, 5.3% women and 0.8% men in the normal population had palpable thyroid nodules ¹². Later studies have confirmed the rate of palpable nodules to range from 3 – 7% ¹³ with an average of 5% depending on the iodine deficiency history of the region.

The use of high resolution ultrasound has caused an explosion in the detection of thyroid nodules. The presence of incidental thyroid nodules on ultrasound varies from study to study, ranging from 17 – 48%. Improvements in imaging has revealed that up to 48% of patients who were thought to have solitary nodules on clinical examination, in fact have multiple nodules on ultrasound ¹⁴.

Autopsy studies are the gold standard for assessing the true prevalence of thyroid nodules. The first recorded autopsy study was conducted at the Mayo clinic in 1955 by Mortenssen and colleagues. A total of 821 thyroid glands in patients with no clinical thyroid disease were evaluated. 50.5% had thyroid nodules of which 4.2% were malignant ¹⁵. Subsequent autopsy studies showed a prevalence of between 37 – 57% ⁷.

Thus thyroid nodules are present in at least 50% of the adult population, approximately 5% of asymptomatic individuals will have a palpable nodule and the percentage detected with high resolution ultrasound continues to rise. Without rational criteria regarding fine-needle aspiration biopsy (FNA), ultrasound and surgery, there is a risk of being overwhelmed by this avalanche of thyroid nodules.

In sharp contrast to the prevalence of thyroid nodules, thyroid cancer is a rare disease. The annual incidence is 1-2/100 000 though this accounts for 90% of the total malignancies of the endocrine system¹⁶. Most thyroid cancers are well differentiated (90%) with a relatively good prognosis. In fact autopsy studies show that between 5 and 13% of thyroid glands harbour thyroid cancer clinically undetected during the patients' lifetime¹⁷.

The world-wide incidence of thyroid cancer is rising and has almost doubled in the last 30 years but mortality from thyroid cancer has remained unchanged. This may be because small papillary carcinomas of less than 2cm constitute 87% of this rise¹⁸. In fact the increase may only be due to improvements in the detection of sub clinical and probably insignificant small cancers. These increasing numbers of patients are being subjected to surgery, long term follow up and the psychological burden of a cancer diagnosis. Thus John Cronan in a recent editorial appeals for the research focus to move from the diagnosis of small, impalpable thyroid nodules and shift to identifying the small subset of thyroid cancers that behave aggressively and have a poor prognosis¹⁹.

Section 2: General Predictors of Risk:

2.1. History

History taking should include a history of head and neck irradiation and a family history of papillary or medullary cancer. Other rare familial syndromes such as MEN 2, FAP and Cowden's disease are also risk factors as is the presence of thyroid nodules in childhood¹⁹.

Male sex as a risk factor for thyroid malignancy is variably reported in the literature²⁰. The vast majority of thyroid nodules are in women and historically nodules in men were believed to have a higher risk of malignancy. Even though recent international guidelines still include this risk factor,

many recent studies do not support the finding^{21,22,23}. Some even demonstrate a higher incidence in women than men²⁴. Where a difference is noted in recent research it seems to be relatively small for example 11.5% vs 7%²⁵. The small number of men with thyroid nodules and therefore proportionally small number with thyroid cancer may be the cause of these discrepancies.

The duration of the presence of the thyroid nodule as well as its pattern of growth is important. Most thyroid malignancies will grow progressively over time. A sudden rapid increase in size associated with pain is usually related to haemorrhage into a cyst¹. Unfortunately, benign solid nodules also increase in size with 90% increasing by over 15% over 5 years²⁶. Critical questions on history also include asking about voice change and worsening compressive symptoms.

2.2. Clinical Examination

Clinical examination should include general examination, palpation of the nodule, the entire gland as well as the anterior and lateral nodal compartments for lymphadenopathy. Though palpation is not very sensitive, a hard fixed nodule with obvious adenopathy increases the suspicion of malignancy. Most patients with well differentiated thyroid carcinomas do not present with any significant risk factors on history or worrying signs on clinical examination.

2.3. Solitary Nodule vs Multinodular Goitre

Nodular goitres are clinically recognisable enlargements of the thyroid gland resulting from structural or functional changes. Until recently, it has been convention to view solitary nodules as having a significantly higher risk of malignancy than nodules in a multinodular goitre. Recent data, however, does not support this assessment. It is also important to note that palpation alone cannot accurately distinguish a solitary nodule from a multinodular goitre.

In 2006 Frates et al conducted a retrospective study 1985 patients to look at the prevalence of malignancy in multinodular goitres²⁷. The study included 1181 patients with a solitary nodule and 804 with multiple nodules. The rate of malignancy was 14.8% in patients who had a solitary nodule and 14.9% in patients with a multiple nodules. Solitary nodules had a higher likelihood of malignancy than each nodule in a multinodular goitre but the overall risk per patient was the same. In their study, up to four nodules greater than 10mm in size and with suspicious US findings were biopsied. It is interesting to note that only 72.5% of cancers occurred in the largest nodule.

Similar results were found in retrospective studies by Gandolphi et al ²⁸, and Tollin et al ²⁹. In a large prospective study done by Papinni et al in Italy, the rate of malignancy was 6.3% for solitary nodules and 9.2% of patients with multinodular goitre. This was not a statistically significant difference. This study also demonstrated that size criteria to determine which nodule to biopsy detected only 5.8% malignancies whereas using suspicious ultrasound criteria increased the diagnostic rate to 21.7% ³⁰. In the work done by Cappelli et al ²³, malignancy was slightly higher in the MNG group than in the solitary nodule group.

Multinodularity can therefore no longer be viewed as decreasing the risk of cancer. The practise of assessing the largest nodule or dominant nodule in a multinodular goitre is not only inaccurate but probably also increases the number of unnecessary procedures performed. Nodules in MNG should be assessed according to the ultrasound characteristics and identified for FNA on the basis of suspicious features and not size alone. More than one nodule may need to be biopsied if these criteria are applied.

2.4. Size

The size of thyroid nodules has long been perceived as an important factor in their risk of malignancy. However recent studies on small thyroid nodules show that the size of the nodule has no bearing on the rate of malignancy. In the large series published by Papini et al there was no difference in cancer rates within nodules 8 – 10mm and 11 – 15 mm ³⁰. Similarly, in a long term study from Boston, Yassa et al found no difference in cancer rates in nodules between 1cm and greater than 3cm ³¹. Similar results have been produced from other parts of the world ^{32,33}. A study from Seoul looking at sub cm nodules actually found a higher rate of malignancy in the smaller nodules ³⁴.

There seems to be little doubt that the malignancies within smaller nodules are at least as common as those in larger nodules. However the clinical significance of these small malignancies remains controversial. The majority of incidental thyroid cancers are papillary and are relatively benign with a 30 yr survival of over 95% ¹. In fact the very rare (1%) anaplastic carcinoma of the thyroid accounts for up to 50% of deaths from the disease ¹⁸. Thus there is little evidence that looking for sub cm thyroid cancers has a positive impact on the general health of the population ³⁵.

The question of malignant risk in larger nodules remains unanswered. This is a critical question in a clinical context where patients have larger, palpable nodules, often well over 4 cm. It is not clear

whether studies looking at predictive accuracy of FNA on small nodules can safely exclude cancer in larger nodules particularly since the clinical implications of missing a large thyroid cancer are significant. Historically, all nodules over 4cm were subjected to surgical intervention, though a literature search does not yield the original work in this area.

In 2009, Madison et al from Wisconsin, designed a study to address the diagnostic accuracy of FNA in nodules greater than 4cm³⁶. A total of 155 patients were included and all patients had a pre-operative FNA and then surgery regardless of the result. The rate of malignancy was 14.8%. Correlation between benign cytology and histopathology was poor. There were four false negatives for malignancy and 22 benign reports with follicular adenomas diagnosed on final histology. While these follicular lesions were not malignant in this series, a follicular neoplasm on cytology would usually prompt surgical excision. The overall inaccuracy for cytology was 50%. The conclusion of the authors was to support current the norm of excising nodules greater than 4cm regardless of FNA findings. As this is only one article, and benign nodules often reach a substantial size, it is clearly an area that requires further research.

Section 3: Suspicious Features on Ultrasound

High resolution ultrasound is a critical step in the evaluation of thyroid nodules. Over the last 15 years, ultrasound features to stratify nodules into low or high malignant risk have been identified but the sensitivity and specificity for each feature varies widely from study to study. To get an accurate picture of the current information available, each ultrasound risk feature will be evaluated separately and, where available, sensitivities and specificities for each suspicious feature is extracted from a set of studies analysed in this review.

3.1.Solid/Cystic

The hypothesis that solid nodules are more likely to be malignant than cystic lesions is confirmed in recent ultrasound studies. In fact, many authors looking at newer ultrasound features only review solid nodules and exclude cystic lesions altogether^{32,33}. In an older paper from 2001, Koike et al from Japan showed that 81.8% of all malignant nodules were completely solid³⁷ and in 2007, a Korean study of 1036 patients demonstrated that 98.4% of papillary cancers and 82.6% of follicular cancers were solid³⁸. In a large and more detailed study from Boston, it was found that completely cystic lesions were never malignant and the malignancy rate decreased as the nodule

became more cystic with 14.3% malignancy in solid lesions, 10.3% in mainly solid lesions, 5.7% in mixed lesions and 2.3% cystic nodules ²⁷.

Thus simple cysts are almost always benign and most malignancies occur in solid or mainly solid lesions. However in light of the fact that at least 85% of even solid nodules are benign, more sophisticated ultrasound evaluation is necessary.

3.2. Calcification

Calcification within thyroid nodules is extremely common. There are three patterns of calcification: coarse calcification, egg shell calcification and microcalcification ³⁹. Coarse calcification usually results from dystrophic calcification of necrotic areas in multinodular goitre or occasionally solitary nodules ⁴⁰. Peripheral, rim or egg shell calcification surrounds the nodule and is usually associated with benign disease. Microcalcifications are less than 2 – 3 mm and represent psammoma bodies on histology and are therefore seen primarily in papillary carcinoma ⁴¹. On ultrasound these have the appearance of small punctate hyperechoic foci.

Studies assessing calcification on ultrasound as a risk for malignancy have focused on micro calcifications. Table 2 is a summary of the predictive value of microcalcifications in a series of recent studies examined for this literature review:

Table 2: Predictive Value of Microcalcifications on Ultrasound

Author	Year	Place	Sensitivity	Specificity
Rago ⁴²	1998	Pisa	54.0	76.6
Kim ⁴³	2002	Seoul	59.2	85.8
Papini ³⁰	2002	Rome	29.0	95.0
Cappelli ²³	2006	Brescia	72.0	72.0
Gulcelik ³³	2008	Ankara	65.4	94.4
Hong ³²	2010	Seoul	40.2	85.7

From this table, it appears that while the presence of microcalcifications is generally not a very sensitive predictor of malignancy it is relatively specific (75 – 95%) for identifying a malignant nodule.

3.3. Echogenicity

Many malignancies such as breast and prostate cancer are hypoechoic on ultrasound. In 2002 Kim et al found that while most solid thyroid nodules were hypoechoic compared to the rest of the thyroid gland, malignant nodules tended to be *markedly hypoechoic*. They used the strap muscle echogenicity to define marked hypoechoicity. In this study, a markedly hypoechoic solid lesion was a very specific marker of malignancy. The observation that malignant features in the thyroid are remarkably similar to those in the breast is also made: taller rather than wide, hypoechoic, irregular margin and microcalcifications. Using any of these criteria to indicate a suspicious lesion produced a high sensitivity of 93.8%.

Table 3 Predictive Value of Hypoechoicity on Ultrasound

Author	Year	Place	Sensitivity	Specificity
Rago ⁴²	1998	Pisa	66.6	48.6
Kim ⁴³	2002	Seoul	26.5	94.3
Papini ³⁰	2002	Rome	87.1	43.4
Cappelli ²³	2006	Brescia	81.0	47.0
Gulcelik ³³	2008	Ankara	84.6	61.5
Hong ³²	2010	Seoul	39.2	90.9

There is a wide range of sensitivity and specificity for hypoechoicity as a predictor of malignancy. This may in part be due to the fact that there is no uniform definition for “hypoechoic”. Some authors use the background thyroid as comparison and others the strap muscles.

3.4. Shape Taller than Wide

It has been hypothesised that nodules that are larger in the antero-posterior dimension than in the transverse dimension (i.e. tall) have a higher risk of being malignant. This may be due to the centrifugal growth of the tumour against tissue planes as occurs in the breast³⁹. In one of the earliest studies to look at this feature in 2002, Kim et al found it had a low sensitivity (32.7%) but high specificity 92.5% for predicting malignancy²⁴. In a more recent study, the sensitivity and specificity was reported as 50.5% and 92.4%²³. Not all studies looking at malignant features on

ultrasound report this sign hence the data remains scanty and further work is needed before its clinical usefulness can be defined.

3.5. Irregular margin/Absence of Halo

A nodule is ill defined when more than 50% of its border is not clear on ultrasound ³⁹. Pathologically this is due to malignant infiltration of surrounding thyroid tissue by carcinoma. Benign lesions often have a rim or halo which is a hypoechoic area of compressed thyroid tissue surrounding the nodule. This sign is often absent in benign lesions and may be present in some malignant lesions. An irregular margin is thus considered to be a better predictor of malignancy than the absence of a halo. The sensitivity is variable but generally low with a higher specificity (72 – 85%).

Table 4 Predictive Value of Irregular Margin on Ultrasound

Author	Year	Place	Sensitivity	Specificity
Papini ³⁰	2002	Rome	77.5	85
Kim ⁴³	2002	Seoul	55.1	83.0
Cappelli ²³	2006	Brescia	53	81
Hong ³²	2010	Seoul	58.9	72.2

3.6. Vascularity

Three patterns of vascularity in thyroid lesions have been identified: peripheral, intranodular and no flow. It is hypothesised that intranodular flow is associated with malignant lesions and peripheral or no flow with benign lesions ⁴¹. Of all the ultrasound signs for predicting malignancy, vascularity remains the most contested. Low sensitivities and specificities are reported in most studies and many studies do not report on this feature at all. In a number of centres vascularity has only recently been part of the routine assessment of thyroid nodules. Sensitivities range from 62 – 74% and specificities from 48 – 70% ^{23,30,42,44}. In 2010 Moon et al designed a large study to look specifically at the predictive value of vascularity and found it did not add any information to grey scale ultrasound ⁴⁵.

Thus for vascularity, there is still lack of consensus that it is a useful sign at all and there is certainly no accurate data on its predictive value.

3.7. Features of Benign Lesions

It is interesting to note that a number of benign features on ultrasound have also been identified though not extensively studied. These include: a spongiform appearance, a cyst with a colloid clot, “giraffe pattern” created by linear areas of hyper and hypoechogenicity and diffuse hyperechogenicity or “white knight” appearance⁴⁶. While seeing these features in addition to the absence of malignant signs may be reassuring, their predictive value remains untested.

3.8 Summary of Ultrasound Results

Six ultrasound predictors for malignancy have been presented here. Unfortunately no ultrasound sign is both sensitive and specific for the prediction of malignancy. From the evidence reviewed here solidity and hypoechogenicity are *sensitive* signs and microcalcifications, irregular margins and taller shape are more *specific* signs. The presence of any one suspicious ultrasound feature is a highly sensitive predictor for a malignant nodule ranging from 83 – 93%^{30,43,45}. This fact may help increase the number of nodules for which a benign diagnosis can confidently be assigned.

However a cautionary note regarding follicular carcinoma is raised by Jeh et al³⁸. In their series follicular carcinomas had no microcalcifications, often had regular margins and were not hypoechoic or tall. These possible differences between the appearance of papillary and follicular carcinoma on ultrasound scan still need to be carefully assessed.

The current evidence demonstrates that meticulous ultrasound examination and clear reporting of suspicious findings is invaluable in helping clinicians make decisions about FNA and surgery. This is an active area of research interest and hopefully more consistent sensitivities and specificities will soon be demonstrated.

Section 4: Fine-Needle Aspiration Biopsy

Fine-needle aspiration (FNA) biopsy of thyroid nodules is a critical step in distinguishing benign from malignant and has improved the surgical yield of diagnostic thyroid surgery from 15 to 50%¹³. FNA of the thyroid is difficult for a number of reasons. It is a very vascular gland making blood only and inadequate sampling common; sampling error can occur because of deep seated lesions or difficult to identify suspicious nodules in a multinodular goitre; interpretation of cytology is

complex and requires an experienced pathologist; reporting has been fraught with inconsistency and unhelpful terminology and finally some thyroid carcinomas such as follicular and Hurtle cell simply cannot be diagnosed by FNA alone²⁵.

Strategies to improve the predictive value of thyroid FNA includes the creation of a uniform classification system, attempts to standardise biopsy technique and the increasing use of ultrasound guided FNA (US-FNA). These aspects will be discussed below.

4.1. Universal Classification System - Bethesda Categories⁴⁷

The prior lack of standardised reporting for thyroid cytology specimens made communication between pathologists, endocrinologists and surgeons difficult. Similar problems had been encountered with cervical cytology leading to the Bethesda system for cervical Pap smear results in 1988. Inspired by this, the National Cancer Institute hosted a multidisciplinary meeting including endocrinologists, pathologists, surgeons and radiologists in Bethesda October 2007. This meeting produced the Bethesda System for Reporting Thyroid Cytopathology.

Table 5 The Bethesda System divides thyroid cytopathology into six general categories: NCI Consensus Meeting¹³

Diagnostic Category	Implied Risk of Malignancy	Usual Management
1. Non diagnostic		Repeat Bx
2. Benign	0 – 3 %	Observe
3. Atypia of undetermined significance	5 – 15%	Repeat Bx/ Surgery
4. Follicular Lesion	15 – 30%	Diagnostic lobectomy
5. Suspicious for Malignancy	60 – 75%	Definitive Surgery
6. Malignant	97 – 99%	Definitive Surgery

Bethesda Category 1: Non Diagnostic

An adequate specimen is defined as six groups of follicular cells with at least ten cells per group. Specimens are also inadequate if improperly fixed, obscured by blood or too thick. Exceptions to the necessary cell count are the presence of abundant colloid with sparse benign follicular cells which implies a colloid macrofollicle or abundant macrophages representing a pure cyst. The diagnosis of a cyst must be interpreted in the context of ultrasound features. A definitive diagnosis such as thyroiditis or clear atypia over rides the cell count criteria and places the specimen in that category. This category should not include more than 10% specimens.

Bethesda Category 2: Benign

An FNA is benign if there are sufficient benign follicular cells with colloid arranged in macrofollicles or macrofollicular fragments. Macrofollicles are intact spheres surrounded by flat evenly spaced follicular cells. Thyroiditis in the correct clinical context is also considered benign. It is estimated that between 60 – 70% of thyroid biopsies should be benign.

Bethesda Category 3: Atypia of Undetermined Significance

This category was created for lesions which did not fall clearly into the other five categories. It is meant to be used sparingly (<7% samples). Samples falling into this category have some features of a follicular lesion but in a predominantly benign background. Examples would be predominance of microfollicles in an otherwise scanty cellular sample with colloid or Hurtle cells with otherwise scanty cells and colloid or a few cells with papillary changes in a background of macrofollicles.

Bethesda Category 4: Follicular Neoplasm

This category is for nodules that may be a follicular carcinoma to be marked for lobectomy. These are very cellular smears with minimal colloid. The follicular cells are arranged in a microfollicular or trabecular pattern with cellular overlapping. Hurtle cell adenoma/carcinoma are oncocytic variants of follicular adenoma/carcinoma characterised by very eosinophilic cytoplasm caused by an abundance of mitochondria. The aspirate may be sub categorised as Hurtle cell adenoma if the sample is almost exclusively made up of Hurtle cells.

Bethesda Category 5: Suspicious for Malignancy

This category is for specimens which have some but not all the diagnostic features for papillary carcinomas. It may also include reports suspicious for medullary carcinoma or lymphoma.

Bethesda Category 6: Malignant

This category is for samples that are conclusive for malignancy, usually 3 – 7 % of samples with the majority being papillary carcinoma. The malignant cytological features of papillary carcinoma include papillary cellular formations, large nuclei with grooves and prominent nucleoli, cellular inclusions resulting in an “Orphan Annie” appearance and calcified psammoma bodies.

4.2. Recommended Technique of FNA

Technical aspects are important in improving the diagnostic accuracy of thyroid FNA and a standardised technique is advisable. A review article from Radiographics Continuing Education outlines the advised technique ⁴⁸:

Pre procedure planning: Informed consent should be taken. There are very few complications associated with this procedure and bleeding is exceptionally rare. Routine coagulation checks are not necessary but warfarin should be stopped 4 – 7 days prior to the procedure. Stopping aspirin remains controversial. **Procedure:** Patient is in supine position with the neck slightly extended. A 22 – 27 gauge needle should be used. Ultrasound guidance is preferable to manual palpation. At least two passes into the nodule using either non aspiration or aspiration technique. Non aspiration technique relies on capillary action as the needle is passed to and fro in the nodule and rotated on its axis. Aspiration may be with a 2 – 10 ml syringe but is not suitable for very vascular lesions. Slides should be fixed immediately and the syringe rinsed with saline and sent for cell blocks.

Post procedure: Simple dressing and local pressure is advised.

4.3. Ultrasound guided FNA vs Palpation:

Ultrasound guided FNA (US-FNA) is gaining popularity over FNA by palpation alone. US-FNA makes sense in the context of our awareness that malignancy is as likely to be in a multinodular goitre as in a solitary nodule, that many patients with only a solitary nodule on palpation have multiple nodules on ultrasound and that impalpable lesions may be large yet difficult to palpate due to position in the gland or in patients where the neck is difficult to examine ⁴⁹. Ultrasound also

allows the biopsy of the most suspicious area in complex solid or cystic nodules and ensures that the most suspicious nodule in a multinodular goitre is sampled. Ultrasound may also be used to avoid vessels in very vascular lesions leading to a higher diagnostic rate.

The hypothesis that US-FNA is superior to FNA by palpation alone is supported by a study from a single unit where the inadequate FNA rate decreased from 12.8 – 5.2% after the introduction of US-FNA⁵⁰. A prospective trial from Istanbul compared the accuracy of palpation vs US-FNA and found the inadequate rate was 27% vs 13% for the US-FNA group⁵¹. The usefulness of US-FNA has reached such acceptance that most published trials in the last few years use US-FNA exclusively regardless of whether nodules are solitary, multiple, palpable or impalpable.

4.4. Accuracy of FNA

Use of thyroid FNA has the potential to reduce the number of diagnostic thyroid operations by up to 50%, can double the diagnostic rate and reduce cost by 25%¹⁶. Recently published international guidelines report the average sensitivity and specificity for thyroid FNA as 83% and 92% respectively¹³.

However, there is inherent uncertainty in thyroid cytology because of the category of follicular neoplasm which triggers surgical excision but cannot reliably predict malignancy. Category 3, atypia of unknown significance and Category 1, inadequate cytology add to this uncertainty. The high reported overall sensitivity and specificity for FNA is due to the varied definition of “positive” and “negative” used in different studies. For example, some studies include Bethesda categories 3,4,5 and 6 in their “positive” group as these patients proceed to surgery. The predictive value is then calculated but not always defined as whether predictive of malignant or benign disease. Other authors exclude the “atypia of unknown significance group” but include “follicular neoplasm” as predictive of malignancy. In some cases, it is not stated how overall sensitivities and specificities were arrived at.

From a surgical point of view, overall prediction is not as useful as knowing the accuracy of FNA for diagnosing benign disease (Bethesda category 2) and malignant disease (Bethesda category 6). If we can reliably diagnose benign nodules, these patients can be followed up without surgery. If malignant nodules are reliably diagnosed, immediate definitive surgery can be performed. For categories atypia, follicular lesions and suspicious for malignancy, diagnostic procedures will still need to be done.

With this aim in mind, a number of study results are tabulated below looking at cytology and histopathology correlation for the benign and malignant categories and recording the percentage of FNA results in the other categories.

Table 6 Cytological and Histological Correlation for Bethesda Categories

Study	No. Pts	Category 2 Benign Cytology %	Predictive Accuracy* %	Category 6 Malignant Cytology %	Predictive Accuracy* %	Category 1 Inadequate Cytology %	Category 3,4,5 Suspicious %
Yassa et al ³¹ Boston 2007	2587	60	99.7	5	97	13	22
Yang et al ²⁵ New York 2007	3337	64.4	99.3	7.6	98.5	10.4	17.6
Rorive ²² Brussels 2010	5283	77.4	98.4	2.7	94.9	4.2	15.6
Zagorianakou ⁵² Ioannina 2005	900	69.7	99.5	3.6	90.9	19.9	6.8
Kim ⁵⁰ Seoul 2008	500	61.4	**	14.4	100	5.8	14.8
Gul ²¹ Ankara 2009	2082	88	97.4	4.8	96.6	3.3	6.4

*"Predictive Accuracy": where cytology results were benign or malignant, this was the percentage correlation on final diagnosis.

**Percentage not quoted in this study.

Correlation between malignant cytology and final malignant histology is very high. These patients can thus have definitive surgery. The final diagnosis of a benign lesion is based on clinical and ultrasound follow up of varying lengths of time. Patients with increasing nodule size were either re biopsied or subjected to diagnostic surgery hence the 1 – 2% later diagnosed with malignancies.

The lack of final histology in the benign category makes true assessment of the accuracy of FNA difficult. At least one study, Yassa et al ³¹ followed patients up for nine years and still found a very low rate of malignancy in nodules classified benign on initial FNA. It therefore seems a reasonable clinical strategy to watch these patients if ultrasound, FNA and clinical assessment are all in keeping with benign disease.

The correct management of patients with an inadequate FNA (5 – 20%) remains controversial. Many authors suggest diagnostic surgery as between 25 – 38% of second biopsies will remain inadequate and 24.5% of these nodules may be malignant ⁵³. Others point out that inadequate cytology is more common in cystic or mainly cystic nodules where the risk of cancer is lower and therefore suggest follow up ultrasound if no there are no other suspicious features ⁵⁴. The decision to re biopsy, observe or operate is currently up to the discretion of the treating clinician.

4.5. Overall Preoperative Diagnostic Accuracy

If recent FNA accuracy rates reported at high volume centres can be reproduced elsewhere, 60% patients should have a confident diagnosis of benign disease and 5% a diagnosis of malignancy. This leaves uncertainty for 35% who still need diagnostic surgery and 40 – 50% of these excisions should be positive for malignancy.

Of the literature reviewed, only one large study from Harvard, Boston was close to this with 56% malignant rate for diagnostic surgery ³¹. Other centres show an upward trend but still lower percentages: Maia et al in 2011 25% ⁵⁵, Tan et al 28% ⁵⁶, Gul et al 2009 32.7% ²⁷ and Cheung et al 2007 33% ⁵⁷. This is unsurprising as results from research in large volume centres are often difficult to match in local environments with unique clinical pressures and skills levels.

Section 5: Research Questions and Conclusion

A number of questions remain unanswered in the field of thyroid nodules.

- It is heartening to read that up to 60% thyroid nodules should have a benign diagnosis on FNA. However, this is usually not confirmed on histology. To confidently use this information in the clinical arena and simply follow these patients up, research looking at the long term outcome of nodules diagnosed as benign is still necessary.

- The large thyroid nodule and its management has recently received very little attention with a massive focus rather on impalpable and sub centimetre nodules. As differentiating benign from malignant in this context is unequivocally clinically relevant, more work is needed in this area.
- The answer to the question of how intensively to investigate sub centimetre nodules can only be answered once the clinical outcomes of micro carcinomas have been clarified. As the numbers of these small cancers increase, long term studies should shed some light onto whether or not we should be investigating small thyroid lesions at all.
- Lastly some promising work is being done on molecular, hormonal and biochemical markers to help predict malignancy and distinguish more aggressive cancers from those with a more indolent course. As these are perfected, they may add another arm to the diagnostic algorithm currently available to us in thyroid nodule decision making.

University of Cape Town

Part C: Research Article as for submission to the South African Journal of Surgery

Pre-Operative Diagnosis of Thyroid Cancer: Clinical, Radiological and Pathological Correlation

Abstract

Aim:

The aim of this study was to assess the accuracy of the diagnosis of thyroid cancer in our institution.

Methods:

Data for all patients diagnosed with thyroid carcinoma from 2004 -2010 at Groote Schuur Hospital was retrospectively collected. The patients were identified from the oncology, pathology and surgical records and a standardised confidential proforma was used to capture the information. The pre-operative clinical assessment, ultrasound and fine needle biopsy results were analysed and compared to the final histopathology results and the total number of diagnostic lobectomies were recorded

Results:

A total of 109 patients, 79 female and 30 male patients were identified. The majority, 99, were well differentiated thyroid cancers: 56 papillary 30 follicular, 10 mixed and 3 Hurtle cell carcinomas. There were 6 anaplastic and 4 medullary carcinomas. 38 patients had a definitive pre-operative diagnosis, 61 a suspicion of malignancy and 10 had surgery for benign disease. Fine needle aspiration biopsy (FNA) was inadequate in 11 patients, benign in 47, suspicious in 13 and malignant in 38 patients diagnosed with thyroid carcinoma. FNA diagnosed all patients with medullary and anaplastic carcinoma but less than half of patients with well differentiated thyroid carcinoma. Ultrasound detected at least one suspicious feature in 44 patients. Microcalcification was the most common sign. 229 diagnostic lobectomies were performed from 2004 – 2010 of which 56 had thyroid cancer and 46 required completion lobectomies. The overall diagnostic rate for malignancy was 24.4%.

Conclusion:

The diagnosis of well differentiated thyroid carcinoma is difficult and requires accurate pre-operative ultrasound and cytopathology. Recent advances in thyroid diagnostics using high resolution ultrasound, ultrasound guided FNA and standardised cytology reporting may improve overall diagnostic rates.

Introduction:

The diagnosis or exclusion of thyroid cancer in the thyroid nodule remains a clinical dilemma for general surgeons and endocrinologists. The general prevalence of thyroid nodules is astounding. Thyroid nodules are detectable in 5% of the normal population on clinical examination ^{11,12}, in over 48% on high resolution ultrasound ¹⁴ and over 50% at autopsy ¹⁵. The widespread use of imaging in modern medicine is resulting in a flood of incidental thyroid nodules, many of them impalpable and asymptomatic.

In sharp contrast, thyroid cancer remains a rare disease with an incidence of only 1-2/100 000 of the population ¹³. Papillary carcinoma and follicular carcinoma remain the most common histological subtypes and, in general, have very good long term prognosis and survival ¹. Poor prognosis and decreased survival in thyroid cancer is associated with the rare and aggressive anaplastic and medullary histological subtypes ¹⁸ which are relatively easy to diagnose pre operatively.

As nodular disease of the thyroid is very common, cancer rare and the diagnosis difficult to confirm, clinical decision making is difficult. Yet having a confident pre-operative diagnosis of thyroid cancer greatly facilitates appropriate surgical intervention, decreases unnecessary surgery, and is safer for patients. Recent advances in the use of ultrasound and fine needle aspiration biopsy have resulted in improved pre-operative diagnosis of nodules in many centres. These advances include defining ultrasound features that predict malignancy, increased use of ultrasound guided fine needle aspiration biopsy (US-FNA), as well as standardised reporting of cytopathological specimens.

Aim:

The aim of this study was to assess the pre-operative accuracy of the diagnosis of thyroid cancer in our institution, evaluate the extent to which ultrasound and fine needle aspiration biopsy (FNA) was utilised and to identifying the potential areas for improvement. Comparing this to the most recent international experience will assist in streamlining our diagnostic algorithm and surgical intervention, thus providing a more efficient, safe and accurate service for our patients.

Methods:

A retrospective collection of data was conducted for all patients diagnosed with thyroid carcinoma from 2004 -2010 from a single institution. The patients were identified from the oncology, pathology and surgical records. In addition, all patients who had undergone a diagnostic lobectomy during this time period for features suspicious for thyroid carcinoma were identified. The pre-operative clinical assessment, ultrasound and fine needle biopsy results were compared to the final histology results. A standardised confidential proforma was used to capture the data from patients with confirmed thyroid carcinoma. The total number of diagnostic lobectomies for suspicious nodules during this time period was recorded separately as a simple total and compared to the final positive malignancy rate.

Ultrasound results were recorded as suspicious if any feature known to be predictive of malignancy was reported. This included: microcalcifications, hypoechoic echogenicity and increased vascularity. Irregular margin and shape were not recorded in any ultrasound results. Fine needle biopsy reports were recorded as benign if colloid, macrophages and follicular cells were reported, suspicious if any suspicious cytological features were reported and malignant if a definitive diagnosis was given. The final assessment of the thyroid nodule pre-operatively as documented by the surgical team was recorded as malignant, suspicious multinodular goitre /solitary nodule or benign. Patients with malignancies diagnosed on lobectomy underwent a completion thyroidectomy if the tumour size was >1cm.

Results:

A total of 109 patients, 79 female and 30 male patients were diagnosed with thyroid cancer on final histopathology reports. The majority, 99 were well differentiated thyroid cancers with 56 papillary carcinoma, 30 follicular carcinoma, 10 mixed follicular/papillary and 3 Hurtle cell carcinomas. There were 6 anaplastic and 4 medullary thyroid carcinomas. The majority, 65%, of patients had solitary nodules.

General Risk Factors

Most patients did not have any warning signs on history or physical examination. Only one had been exposed to radiation, two had a family history of MENII, 12 were under 25 and one patient had a family history of papillary carcinoma. Most patients were asymptomatic with only 14 presenting with symptoms of compression due to multinodular goitre, and 4 complained of significant voice changes. 14 patients had either metastatic disease or clinically detectable lymphadenopathy at presentation.

Definitive Diagnosis of Malignancy (38 patients)

In 38 patients there was a definitive pre-operative diagnosis of thyroid cancer. This included all 10 of the patients with anaplastic and medullary cancers, 22/56 papillary cancers and 6/30 follicular cancers. In the 22/56 patients with definitive papillary cytology results, nine were obtained from biopsy of metastatic cervical lymph nodes. All 6/30 patients with follicular carcinoma were diagnosed pre operatively on biopsy of metastases (2 lung, 3 bone and 1 lymph node.)

Suspicious for Malignancy (61 patients)

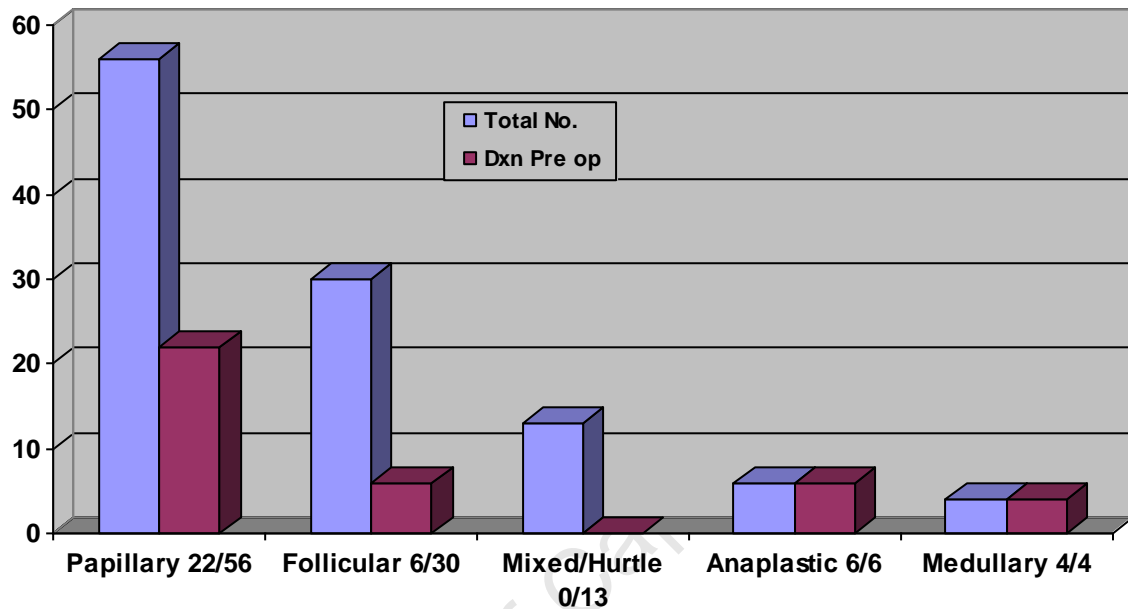
61 patients were operated on for the suspicion of malignancy, 39 solitary nodules and 22 suspicious nodules in a multinodular goitre. Of these 46 underwent a diagnostic lobectomy followed by a completion thyroidectomy at a later date. In 8 patients, the initial lobectomy was adequate surgical management, 5 patients had a primary total thyroidectomy and 2 had on table frozen section of the lobe and immediate total thyroidectomy.

Benign Diagnosis (10 patients)

In 10 patients the diagnosis of thyroid cancer was unexpected. Their indication for surgery was multinodular goitre with compression or thyrotoxicosis. In 50% of these patients lobectomy was adequate surgical treatment as the cancers were under 1cm in size. Primary total thyroidectomy

was performed on 3 patients and 2 required completion thyroidectomy. Table 1 summarises these findings by histological sub type.

Figure 1: Final Histology Results and the Rate of Pre-Operative Diagnosis



Accuracy of Fine Needle Aspiration Biopsy (FNA)

All patients had fine needle biopsy performed pre operatively. Of the 109 patients, 58 had a cytology report which did not assist in the pre-operative diagnosis: 11 biopsies were inadequate and 47 consistent with a benign lesion. In 51 patients, the FNA was helpful. All anaplastic and medullary cancers were diagnosed confidently on FNA. In papillary cancer, 13 patients were positively diagnosed with FNA of the thyroid gland and the remaining 9 from lymph node biopsies. A further 6 results were suspicious. For follicular carcinoma, the only cancers diagnosed on FNA were from metastasis and 3 FNA from the thyroid were reported as suspicious. The accuracy of FNA for well differentiated thyroid carcinomas is summarised in Table 1.

Table 1: Accuracy of FNA for Well Differentiated Thyroid Carcinoma

	Definitive	Suspicious	Benign/Inadequate i.e. false negative
Papillary (56)	22	6	28 (50%)
Follicular (33)	6	5	22 (66%)
Mixed (10)	0	2	8 (80%)
Total 99	28	13	58 (53%)

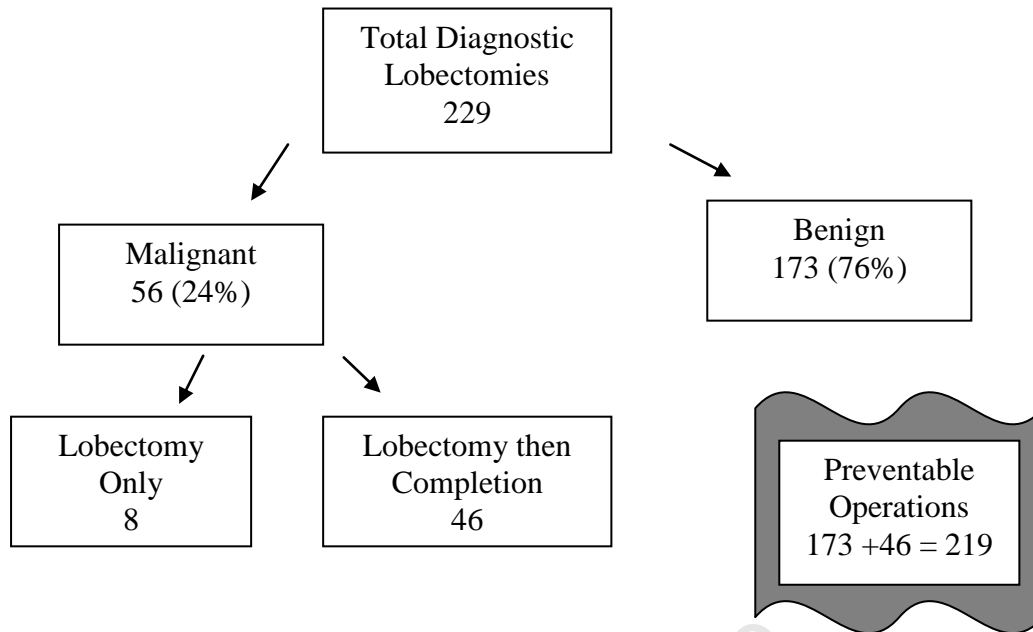
Accuracy of Ultrasound

Ultrasound reports mentioned at least one malignant feature in 44 patients (40.3%). The presence of micro calcifications was the most commonly reported suspicious feature on ultrasound. Where no suspicious features were reported, reports did not specifically mention the absence of these features.

Surgical interventions:

During the seven year period, a total of 229 diagnostic lobectomies for the suspicion of cancer were performed. There was a significant rise in the annual number of diagnostic lobectomies from 2004 to 2010 (13, 25, 27, 19, 36, 55, and 54). The overall diagnostic rate for malignancy was 24.4% (56 patients). In 8 patients, lobectomy was adequate surgical management but 46 patients required further surgery and completion thyroidectomy. Figure 2 summarises the surgical interventions for patients undergoing diagnostic thyroid surgery during the study period.

Figure 2: Diagnostic Surgical Interventions Groote Schuur Hospital 2004 - 2010



Discussion

The results of this study illustrate the difficulty of diagnosing well differentiated thyroid cancer. The lack of a single sensitive and specific pre-operative diagnostic tool results in a large number of diagnostic lobectomies. The general demographics of our group with women predominating, two thirds being solitary nodules and well differentiated cancer representing over 90% of malignancies, is consistent with the international experience ¹.

High resolution ultrasound is critical in the diagnosis of thyroid lesions. A number of ultrasound features have been identified over the last 10 – 15 years which assist in predicting the risk of malignancy in a nodule. These include: solid vs cystic consistency, echogenicity, microcalcifications, shape, irregular margin and central/nodular vascularity ³⁹. There is a wide range of sensitivities and specificities reported for each sign and intense research in this area is ongoing. The overall sensitivity reported for any one suspicious ultrasound feature is 83 – 93% ^{30,43,45}.

In our series, there was a lack of consistency in the quality of ultrasound reporting. This may be the result of the large number of consultants and trainees performing ultrasounds and the lack of a standardised reporting format. Of the six commonly reported ultrasound signs of malignancy,

shape and irregular margin were never reported. The reporting of other signs was variable and in only 40.4% of nodules which proved to be malignant, was a suspicious sign reported. The commonest suspicious feature reported was micro calcifications. The absence of suspicious features as an important negative was not specifically stated in reports.

Ultrasound reports of multinodular goitres usually reported on *dominant nodules* implying the largest nodule. However recent research suggests that size is not a factor in predicting malignancy^{31,32,33} and thus the most ultra-sonographically suspicious nodule and not the largest should be identified for biopsy. In the work done by Papini³⁰, the efficiency of using malignant ultrasound features to target biopsy in multinodular goitres resulted in the diagnosis of 21.7% of malignant nodules as opposed to only 5.8% when using size alone. The FNA of the largest nodule in a multinodular goitre would have represented a sampling error and contributed to the high benign false negative cytology results in this series.

According to international guidelines, FNA has improved the yield rate of malignancy from diagnostic thyroid surgery from 15% to 50%¹³ resulting in a significant reduction of unnecessary operations. FNA accuracy is reported to range between is 80 – 90%¹³ though the methodology for generating these predictive values vary from series to series. False negative benign results are reported to be between 1-3% in a number of research studies^{21,22,25,31}. In contrast to these high accuracy rates, FNA results in our series were unhelpful in 53% of patients. While cytology was 100% accurate in diagnosing anaplastic and medullary carcinoma, the performance for well differentiated cancers was poor.

In patients with well differentiated cancers on histology, the pre-operative cytology was reported as benign in for 43%. There was greater accuracy in diagnosing papillary carcinoma where cytology was positive or suspicious in 53% of patients. For follicular carcinoma, the FNA was only suggestive in 33% of patients. Although follicular carcinoma is impossible to diagnose on cytology, a report of a follicular neoplasm (Bethesda category 4)⁴⁷ with features of microfollicles and no colloid was only reported in a small group of patients. This would be regarded as a positive cytology result and prompt surgical excision of the lesion.

Multiple factors contributed to the low diagnostic yield of fine needle aspiration biopsy. Sampling error probably played a major role. Contrary to the practice in many high volume centres, ultrasound guided FNA (US-FNA) is not standard practice in our unit and is only performed where

a particular nodule in a multinodular goitre is reported as suspicious. However US-FNA is often not done by the same radiologist who initially diagnosed the lesion. Hence often the largest or dominant and not the most ultrasonographically suspicious nodule was biopsied. Patients felt to have solitary nodules were biopsied on palpation alone which may also have resulted in sampling error, particularly in complex solid-cystic nodules. In addition, there was no standardised technique for thyroid FNA across radiology and surgical services.

The reporting of cytopathology added another area of potential inaccuracy. The study period begins before the international Bethesda guidelines on reporting thyroid cytopathology were published⁴⁷. However even cytopathology done after 2007 was not routinely reported according to the Bethesda category guidelines. Thus interpretation by treating surgeons remained difficult. Many centres have only a few dedicated cytopathologists who have a special interest in this area looking at thyroid cytology. The consultant staff to support this practice within our pathology department may not have allowed for this degree of sub-specialisation and partly resulted in the variable reporting of thyroid cytology.

Surgery for thyroid carcinoma or suspicion of carcinoma increased steeply over the seven year period of the study from only 13 diagnostic lobectomies in 2004 to 54 in 2010. This is probably due to changes in unit practice as well as increased referrals of incidental thyroid nodules. Our overall rate of cancer of 24.4% for diagnostic procedures is not completely out of keeping with units of similar size^{55, 56}. However in large centres where there is a focus on thyroid nodular disease, 56% of all diagnostic surgery is positive for malignancy³¹. While some uncertainty is inevitable with thyroid cytology, the correct application of Bethesda criteria should result in a benign diagnosis in approximately 60% of nodules and a confident malignant diagnosis in at least 5%. The combined cancer rate in the remaining categories should then approach 50%⁴⁷.

In this series, of the 229 patients who underwent a diagnostic lobectomy, only 56 had thyroid cancer and 46 required completion surgery. Thus theoretically 219 patients had an avoidable operation. If the correct use and interpretation of high resolution ultrasound and FNA can produce a cancer yield for diagnostic surgery of 50%, this number could theoretically have been reduced to 114. Clearly the translation of research results from high volume centres to a local context should be done with caution but these percentages are a target to aim for as we improve our diagnostic modalities.

Conclusion

The results of this study illustrate the complexity of thyroid nodule assessment specifically with regards to the diagnosis of well differentiated thyroid cancer. It also highlights the need for multidisciplinary co-ordination as thyroid nodular disease is a clinical problem which cuts across several disciplines including endocrinology, pathology, radiology and surgery. While the diagnostic accuracy for ultrasound and FNA was relatively low in this study, the overall diagnostic surgical yield was comparable to that in other smaller centres.

The reported results of preoperative diagnostic techniques from the international literature are a source of optimism for surgeons looking for rational, safe and efficient strategies to manage thyroid nodules. Achieving similar clinical outcomes locally will mean translating research results from high volume centres with experienced, committed multidisciplinary teams, to the practical reality of our pressurised clinical context. This requires both local research and protocols which include the standardisation of ultrasound reporting, implementation of Bethesda Category Classification for cytology results and improvements in biopsy techniques. Engagement with radiology, endocrine and pathology colleagues is thus critical if we are to rationalise our collective management of the ubiquitous thyroid nodule. This is a long term and energy intensive project but holds the promise of reducing the number of unnecessary operations done and allowing greater confidence in the management and counselling of patients with thyroid disease.

Part D: Appendices

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Appendix 2: Ethics Approval



UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

05 July 2010

HREC REF: 325/2010

Dr L Cairncross
Department of Surgery

Dear Dr Cairncross

PROJECT TITLE: PRE OPERATIVE DIAGNOSIS OF THYROID CANCER: CLINICAL, RADIOLOGICAL AND PATHOLOGICAL CORRELATION.

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 15th July 2011.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

S Thomas

Appendix 3: Standardised Proforma

Thyroid Cancer Data Sheet

Personal Details

Patient name Folder Number

Date of Birth Gender

Address

Contact Numbers

Symptoms:

1. Incidental
2. Airway
3. Dysphagia
4. Systemic/LOW
5. Voice Change
6. Nil

Risk Factors

1. Age<25
2. Radiation
3. Family History
4. MEN

Signs:

1. Solitary Nodule
2. MNG
3. Lymphadenopathy
4. Metastases
5. RLN paresis
6. Stridor/airway

Special Investigations

1. Euthyroid/Not
2. Ultrasound
3. Nuclear Medicine
4. Cytology
5. CT

Ultrasound Report:

1. MNG
2. Dom nod MNG (Susp)
3. Solitary Nodule (Not susp)
4. Solitary Nodule (Susp)
5. Size SN or DN in MNG

Cytology:

1. Inadequate
2. Colloid/macrophages
. Follicular cells/colloid
4. Atypical foll. cells/pap
5. Def ca a)pap b)fol c)ana d)med

Pre Operative Diagnosis:

1. MNG
2. Suspicious SN/MNG
3. Definitive ca
4. Lymphadenectomy (central/lateral)

Operation:

1. Lobectomy only
2. Total thyroidectomy
3. Lobectomy + completion

Time presentation to surgery

Complications:

1. Re-op bleeding
2. RLN injury
3. Hypoparathyroidism
4. Other
5. None

Adjuvant Treatment

1. I131
2. Other
3. None
4. TSH suppression

Final Histology:

1. Papillary ca
2. Follicular ca
3. Mixed
4. Hurtle cell
5. Anaplastic
6. Medullary

Outcome:

1. Well
2. Alive with recur/disease
3. Demised
4. Lost to follow up
5. Duration follow up (months)

Appendix 4:

South African Journal of Surgery Author Guidelines

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Work that is based on or contains reference to ethnic classification must indicate the rationale for this.

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Short items are more likely to appeal to our readers and therefore to be accepted for publication.

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Research articles should have a structured abstract not exceeding 250 words (50 for short reports) comprising: Objectives, Design, Setting, Subjects, Outcome measures, Results and Conclusions. Refer to articles in recent issues for guidance on the presentation of headings and subheadings. Abbreviations should be spelt out when first used in the text and thereafter used consistently. Scientific measurements should be expressed in SI units except: blood pressure should be given in mmHg and haemoglobin values in g/dl. If in doubt, refer to 'uniform requirements' above.

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Figures consist of all material that cannot be set in type, such as photographs and line drawings. If any tables or illustrations submitted have been published elsewhere, the author should obtain written consent to republication from the copyright holder and the author(s). All illustrations, figures etc. must be of high resolution/quality, preferably jpeg or equivalent but not powerpoint, and preferably attached as supplementary files.

REFERENCES

References should be inserted in the text as superior numbers and should be listed at the end of the

article in numerical and not in alphabetical order.

Authors are responsible for verification of references from the original sources.

References should be set out in the Vancouver style and approved abbreviations of journal titles used; consult the List of Journals in Index Medicus for these details.

Names and initials of all authors should be given unless there are more than six, in which case the first three names should be given followed by et al. First and last page numbers should be given.

Journal references should appear thus:

Price NC . Importance of asking about glaucoma. BMJ 1983; 286: 349-350.

Book references should be set out as follows:

Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975: 96-101.

Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974: 457-472.

Manuscripts accepted but not yet published can be included as references followed by (in press).

Unpublished observations and personal communications may be cited in the text, but not in the reference list

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