Management of PET-avid thyroid nodules in cancer patients

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Abstract:

Background and aims:
FDG-avid thyroid incidentalomas (TI) are common findings (2.5%) in patients imaged for staging or treatment response and represent thyroid cancer in approximately 35% of cases. Consequently, the 2015 ATA guidelines strongly recommend investigation of such nodules ≥1cm without considering the prognosis of underlying malignancy. In addition, the utility of SUV-max which observes maximum uptake of FDG also has been the described as a potential surrogate marker of thyroid cancer. This study aims to assess the overall and thyroid cancer specific survival in a large cohort of FDG-avid TI; assess the role of SUV-max in predicting thyroid cancer in this cohort; and observe potential confounders of highly avid thyroid nodules – notably benign Hürthle cell adenomas.

Methods:
A retrospective review was performed on all patients at Peter MacCallum Cancer Centre between 2007 and 2015. 45,680 consecutive PET/CT scan reports were reviewed, identifying 2588 reports referring to the thyroid. Scan duplicates and normal thyroid reports were excluded. Other exclusions included physiological uptake to the thyroid gland, thyroiditis, patients known thyroid cancer, multi-nodular goitre, focal uptake less than 1mm and nodules identified with non-FDG radiotracers. FDG-avidity parameter data was gathered using MIM imaging software. Variables including age, gender, follow-up time >12 months, primary malignancy, overall survival, thyroid cancer-specific survival, cytology and histopathology were collected until January 2016. Multivariate logistic regression, survival analysis and receiver operator curve (ROC) analysis was performed.
Results:

The study included 362 patients who met the inclusion criteria with median age 65 years (range 19-96), and median follow-up of 24 months (range 1-103). Lymphoid, lung and colorectal malignancy were the most common indications for staging. The median overall survival was 20 months (IQR 9.5-39). The majority of deaths was due to the primary malignancy (92.2%). One patient (0.6%) died from incidental medullary thyroid cancer. FDG-avidity in primary malignancy, advanced stage and clinician decision to not investigate FDG-avid TI were all predictors of mortality with hazard ratios of 8.5 (95%CI 4.6-15.8), 3.0 (95%CI 2.3-3.9) and 3.3 (95%CI 2.0-5.0) respectively (P<0.001). Receiver operator curve (ROC) analysis demonstrated on optimal SUV-max threshold of 5.33. Sensitivity and specificity of thyroid cancer detected incidentally on PET/CT on ROC analysis was 73.47 and 46.94 respectively, with a broad area under the ROC curve of 0.66 (p = 0.005). Five nodules (20%) necessitated revision of diagnosis on correlative histopathologic-imaging review. Two presumed malignant FDG-avid TI found on imaging were correlated to non-malignant Hürthle cell adenomas on pathology, indicating misclassification by location.

Conclusion:

The overall survival with FDG-avid TI was poor due to the prognosis associated with underlying malignancy which must be considered prior to investigation of FDG-avid TI. Active surveillance should be considered in this group of patients. SUV-max is not a safe tool to discriminate benign from malignant TI and should remain a theoretical adjunctive tool for predicting thyroid cancer. Benign and malignant oncocytic lesions are a common cause of FDG-avid TI. The incidence of FDG-avid malignancy may be overestimated without careful imaging and histopathologic correlation.
Declaration:

This is to certify that

1. The thesis comprises only my original work towards the Masters of Surgery degree

2. Due acknowledgement has been made in the text to all other material used

3. The thesis is fewer than the maximum word limit, exclusive of tables, maps, bibliographies and appendices.

Signed,

Michael Bozin
April 2017
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First and foremost, I would like to acknowledge and thank my supervisor and mentor, Miss. Anita Skandarajah. Without her inspiration, guidance, and support, I would not be in the fortunate position of submitting my thesis and completing my Masters of Surgery degree.

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2017:


Presentations:

2016:

Incidental 18F- fluorodeoxyglucose (FDG) avid thyroid malignancy has no impact on overall survival in a large cohort of cancer patients. 86th Annual Meeting of the American Thyroid Association, Denver, Colorado, USA. 22/09/2016.

2015:


Predicting Malignancy in FDG- avid thyroid nodules based on standardised uptake value in oncology patients. Peter MacCallum Cancer Centre Cancer Surgery Divisional Research Meeting. Melbourne, VIC.18/12/2015.
Contents:

CHAPTER 1: BACKGROUND

Thyroid Nodules and Cancer

Introduction
Incidence and prevalence of thyroid cancer
Incidental thyroid nodules
Investigation of thyroid nodules
Diagnosis and classification of thyroid tumours
Cellular origins and histological subtypes of thyroid cancer

Papillary Thyroid Cancer

Follicular Thyroid Cancer

Follicular Variant or ‘Hürthle Cell’ Carcinoma

Anaplastic Thyroid Cancer

Treatment goals of differentiated thyroid cancer
Surgical considerations in the management of differentiated thyroid cancer

Pre-operative patient assessment

Risks of thyroid surgery

Active Surveillance
Assessing treatment response after thyroid surgery
Positron Emission Tomography / Computed Tomography (PET/CT)
Thyroid ‘Incidentalomas’ identified on PET/CT imaging
Standardised Uptake Value (SUV)
Best available evidence regarding FDG-avid TI
Impact of thyroid incidentalomas in cancer patients

Hypothesis

Aims and Objectives

Ethics approval
Patient selection
Patient Variables
Data collection and storage

Methodology 1. Assessing whether PET/CT behaviour (FDG-avidity) influences the pattern of investigation and management of thyroid nodules in the setting of a primary cancer diagnosis
1a) Determining the incidence of thyroid malignancy amongst FDG-avid TI in patients who are already being staged and treated for a primary cancer..............37

1b) Assessing thyroid cancer treatment response, determining which patients may have a structurally incomplete response .................................................................37

1c) Assessing thyroid cancer specific survival ..................................................................................37

Statistical analysis ..................................................................................................................38

Methodology 2. Assessing the role of SUV-max as a predictor of thyroid cancer.... 39
Methodology 3. Assessing oncocytic thyroid nodules as a common cause of FDG-avid thyroid incidentalomas ..............................................................39

PET/CT behaviour, investigation and management of FDG-avid TI ..............................42

Introduction ..........................................................................................................................42
Incidence of thyroid malignancy amongst FDG-avid TI ..................................................43
Assessing thyroid cancer treatment response – structurally incomplete .................44
Overall and thyroid cancer specific survival .................................................................45
Conclusion ..........................................................................................................................46

SUV as a predictor of thyroid cancer .................................................................................48

Oncocytic thyroid nodules .................................................................................................50

Oncocytic nodules as a potential cause of varying rates of malignancy .................50
Oncocytic nodules and pathological misclassification ..............................................50
Cross-sectional analysis of histological and PET/CT findings ..................................51

PET/CT behaviour, investigation and management of FDG-avid TI ..........................54

SUV as a predictor of thyroid cancer .................................................................................59

Oncocytic thyroid nodules .................................................................................................64

Conclusion ..........................................................................................................................66

References .............................................................................................................................68
List of tables:

Table 1. Causes of thyroid nodules in patients who have normal (euthyroid) and elevated (thyrotoxic) hormone levels

Table 2. Risk stratification of thyroid nodules by ultrasound (1)

Table 3. Estimated risk of thyroid cancer according to Bethesda classification of thyroid cytopathology

Table 4. WHO classification of tumours related to the thyroid gland

Table 5. American Thyroid Association guidelines for assessing response to treatment during follow-up after thyroid surgery

Table 6. Systematic reviews of patients with thyroid incidentalomas identified on PET/CT

Table 7. Single-centre studies of patients with thyroid incidentalomas identified on PET/CT

Table 8. Baseline demographic and clinical data of study population

Table 9. Pathologic characteristics of malignant FDG avid thyroid incidentalomas

Table 10. Summary of patient follow-up & clinical outcome data

Table 11. FDG-avid thyroid nodule characteristics based on SUV-max and size

Table 12. Sensitivity and specificity of SUV-max at given cut offs

Table 13. Correlation of 18-F-fluorodeoxyglucose (FDG) avid lesions with pathological review, including percentage oncocytic density (POD)
List of figures:

Figure 1. Increasing incidence of thyroid cancer attributable to screening (3) ............ 12
Figure 2. Increasing trend of thyroid cancer incidence within Victoria (2) ................. 13
Figure 3. American Thyroid Association guidelines on management of thyroid nodules and treatment pathways (1) ................................................................. 16
Figure 4. Cellular origins of differentiated and undifferentiated (anaplastic) thyroid cancer ............................................................................................................. 18
Figure 5. Literature search of FDG-avid thyroid incidentalomas using PRISMA guidelines ............................................................................................................. 28
Figure 6. Review of PET/CT scan methodology to identify FDG-avid thyroid incidentalomas ......................................................................................................... 34
Figure 7. Methodology that reflects the results of each arm of study ......................... 36
Figure 8. Identification process of FDG-avid and investigated TI ............................. 38
Figure 9. Identification of TI available for PET/CT and pathological correlation ........ 41
Figure 10. FDG PET/CT performed in a 61 year old woman with metastatic duodenal carcinoid tumour (blue arrow; Grade 2, Ki,67 15%) showed mildly avid right thyroid nodule and intensely avid left thyroid nodule ........................................ 44
Figure 11. Kaplan Meyer survival distribution based on FDG-avidity, stage and type of malignancy ......................................................................................... 47
Figure 12. Diagnostic performance of SUV-max determined by receiver operator curve (ROC) analysis ...................................................................................... 50
Chapter 1: Background

Thyroid Nodules and Cancer

Introduction

A thyroid nodule is defined as an abnormal growths of cells that forms a lump within the thyroid gland. Thyroid nodules are a common clinical problem encountered by general practitioners, radiologists, physicians and surgeons. They occur in 5% of women and 1% of men in iodine-sufficient parts of the world (1). Thyroid nodules can be caused by degenerative cysts, nodular thyroiditis, follicular adenomas or toxic adenomas (1). However, the primary concern with thyroid nodules is the development of thyroid cancer, which is the most common endocrine malignancy. Important risk factors in the development of thyroid cancer include sex (female to male ratio of 3:1), a previous history radiation exposure (especially to the head and neck and prior to the age of 11), a family history of differentiated thyroid cancer and hereditary mutations such as RET proto-oncogene in Multiple Endocrine Neoplasia Type 2 (MEN2) (1).

Table 1. Causes of thyroid nodules in patients who have normal (euthyroid) and elevated (thyrotoxic) hormone levels

<table>
<thead>
<tr>
<th>Euthyroid Nodules</th>
<th>Thyrotoxic Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
<td></td>
</tr>
<tr>
<td>Degenerative cysts</td>
<td>Graves’ disease</td>
</tr>
<tr>
<td>Nodular thyroiditis</td>
<td>MNG</td>
</tr>
<tr>
<td>Follicular adenoma</td>
<td>Toxic adenoma</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
</tr>
<tr>
<td>Differentiated thyroid Ca</td>
<td></td>
</tr>
<tr>
<td>Anaplastic thyroid Ca</td>
<td>–</td>
</tr>
<tr>
<td>Metastasis</td>
<td></td>
</tr>
</tbody>
</table>

Incidence and prevalence of thyroid cancer

Thyroid cancer incidence is rising at a faster rate than any other solid tumour in the United States of America (USA). Between 1975 and 2009, the annual incidence of thyroid cancer has increased from 4.9 to 14.3 per 100,000 (1). This rise in thyroid cancer has also occurred within Australia. The Cancer Council Victoria’s 2015 Statistics and
Trends report demonstrates an increasing incidence annual incidence of thyroid cancer from approximately 1 to 4.2 per 100,000 men and 2.2 to 12 per 100,000 women (2). This is primarily attributable to increased detection via screening and improvements in resolution of imaging modalities such as ultrasound (US), computed tomography (CT) and positron emission tomography/computed tomography (PET/CT). In South Korea, the incidence of thyroid cancer increased dramatically from 6.3 per 100,000 in 1999 to 47.5 per 100,000 in 2009 as a result of thyroid cancer screening initiatives (Figure 1). This resulted in an economic burden of thyroid cancer sevenfold, from $257 million to $1724 million, with no change in survival (3).

High-resolution US has the ability detect thyroid nodules in 19-68% of randomly selected individuals, in which 7-15% of cases are found to be thyroid cancer (1). Subsequently, the detection of small sub-centimetre thyroid cancers has also increased over the five years.

**Figure 1.** Increasing incidence of thyroid cancer attributable to screening (3)
Incidental thyroid nodules

Incidental thyroid nodules or 'thyroid incidentalomas' (TI) found on imaging techniques are also attributed to the increasing incidence of thyroid nodules and cancer (1,4). Consequently the 2015 American Thyroid Association (ATA) guidelines\(^1\) strongly recommend investigation of such nodules ≥1cm with thyroid US and fine needle aspiration cytology (FNAC) albeit without consideration of the prognosis of the underlying malignancy (1).

Investigation of thyroid nodules

Ultrasound and biopsy using fine needle aspiration cytology (FNAC) are the gold standard investigation techniques for determining malignancy amongst all thyroid nodules. Ultrasound has the ability to determine a nodule's size, position, internal consistency/characteristics, relationship to adjacent structures and the presence of surrounding suspicious lymph nodes. Overall, ‘risk’ stratifies thyroid nodules in respect to predicting thyroid cancer, improves the accuracy of FNAC and locally stages cancerous appearing nodules to guide treatment decision-making (Table 2) (5,6).
<table>
<thead>
<tr>
<th>Ultrasound grade</th>
<th>Cancer risk</th>
<th>Sonographic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>High suspicion</td>
<td>70 – 90%</td>
<td>Extra-thyroidal extension, Taller greater than wider, Hypoechoic, calcification, Irregular margins</td>
</tr>
<tr>
<td>Intermediate suspicion</td>
<td>10 – 20%</td>
<td>Hypoechoic with regular margin</td>
</tr>
<tr>
<td>Low suspicion</td>
<td>5 – 10%</td>
<td>Isoechoic or hyperechoic with a regular margin</td>
</tr>
<tr>
<td>Very low suspicion</td>
<td>&lt; 3%</td>
<td>Cystic or spongiform appearance</td>
</tr>
<tr>
<td>Benign</td>
<td>&lt; 1%</td>
<td></td>
</tr>
</tbody>
</table>
Fine needle aspiration cytology (FNAC)

Biopsy results of FNAC are categorised according to the Bethesda classification: non-diagnostic or unsatisfactory; benign; atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); follicular neoplasm (FN); suspicious for malignancy; and malignant (Table 3).

FNAC is a reliable test to differentiate between benign and malignant nodules but has lower concordance rates with indeterminate nodules. The inter and intra-observer rate of FNAC concordance is 64 and 77% respectively (7).

Table 3. Estimated risk of thyroid cancer according to Bethesda classification of thyroid cytopathology (7)

<table>
<thead>
<tr>
<th>Bethesda Category</th>
<th>Estimated risk of malignancy (%)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diagnostic or unsatisfactory</td>
<td>1 - 4</td>
<td>Repeat FNAC</td>
</tr>
<tr>
<td>Benign</td>
<td>0 - 3</td>
<td>No Surgery</td>
</tr>
<tr>
<td>AUS* or FLUS**</td>
<td>5 - 15</td>
<td>See Figure 3</td>
</tr>
<tr>
<td>Follicular neoplasm (FN)</td>
<td>15 - 30</td>
<td>Surgery</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>60 - 75</td>
<td>Surgery</td>
</tr>
<tr>
<td>Malignant</td>
<td>97 - 99</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

*Atyopia of undetermined significance.
**Follicular lesion of undetermined significance
Figure 3. American Thyroid Association guidelines on management of thyroid nodules and treatment pathways (1)
Diagnosis and classification of thyroid tumours

Once the diagnosis of thyroid cancer is suspected by FNAC, a diagnosis is made based on macroscopic and microscopic description of surgically removed thyroid gland tissue. Molecular testing of thyroid cells is an emerging diagnostic modality used to stratify malignancy risk by detecting RNA expression profiles and gene rearrangements. The current role of molecular testing is only to complement clinical judgement, ultrasound and FNAC assessment (1). As thyroid cancer can develop from thyroid follicular, para-follicular cells or different cell lineages, it is classified into subtypes according to the World Health Organisation Classification of Tumours (Table 4) (8).

Table 4. WHO classification of tumours related to the thyroid gland (8)

<table>
<thead>
<tr>
<th>Epithelial</th>
<th>Non-epithelial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follicular cell origin</strong></td>
<td><strong>Secondary (metastatic)</strong></td>
</tr>
<tr>
<td>a) <strong>Benign</strong></td>
<td></td>
</tr>
<tr>
<td>▪ Follicular adenoma</td>
<td>▪ Primary lymphoma</td>
</tr>
<tr>
<td>▪ Hürthle cell adenoma</td>
<td>▪ Angiosarcoma</td>
</tr>
<tr>
<td>b) <strong>Malignant</strong></td>
<td>▪ Teratoma</td>
</tr>
<tr>
<td>▪ Papillary carcinoma</td>
<td>▪ Smooth muscle tumours</td>
</tr>
<tr>
<td>▪ Follicular carcinoma</td>
<td>▪ Nerve sheath tumours</td>
</tr>
<tr>
<td>▪ Follicular variant / Hürthle cell carcinoma</td>
<td>▪ Paraganglioma</td>
</tr>
<tr>
<td>▪ Poorly differentiated carcinoma</td>
<td>▪ Solitary fibrous tumour</td>
</tr>
<tr>
<td>▪ Anaplastic carcinoma</td>
<td>▪ Follicular dendritic cell tumour</td>
</tr>
<tr>
<td></td>
<td>▪ Langerhan's cell histiocytosis</td>
</tr>
<tr>
<td></td>
<td>▪ Rosai-Dorfman disease</td>
</tr>
<tr>
<td></td>
<td>▪ Granular cell tumour</td>
</tr>
<tr>
<td><strong>Para-follicular C-cell origin</strong></td>
<td></td>
</tr>
<tr>
<td>▪ Medullary carcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>Mixed</strong></td>
<td></td>
</tr>
<tr>
<td>▪ Mixed medullary and follicular carcinoma</td>
<td></td>
</tr>
<tr>
<td>▪ Mixed medullary and papillary carcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>Tumours of different cell origin</strong></td>
<td></td>
</tr>
<tr>
<td>▪ Muco-epidermoid carcinoma</td>
<td></td>
</tr>
<tr>
<td>▪ Squamous cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>▪ Mucinous carcinoma</td>
<td></td>
</tr>
<tr>
<td>▪ Spindle cell tumour with thymus-like differentiation (SETTLE)</td>
<td></td>
</tr>
<tr>
<td>▪ Carcinoma showing thymus-like differentiation (CASTLE)</td>
<td></td>
</tr>
<tr>
<td>▪ Ectopic thymoma</td>
<td></td>
</tr>
</tbody>
</table>
Cellular origins and histological subtypes of thyroid cancer

Thyroid cancer from follicular cell origin includes papillary, follicular – conventional, follicular – variant (also known as Hürthle cell carcinoma), poorly differentiated and anaplastic (Figure 3). To reflect the differences in cancer behaviour, thyroid cancer of epithelial cell origin can also be classified differentiated and anaplastic thyroid cancer. Thyroid cancer from para-follicular C-cell origin (cells that produce calcitonin) is known as medullary thyroid cancer. Rarer forms of thyroid cancer include epithelial tumours of uncertain cell origin and non-epithelial tumours such as lymphoma or angiosarcoma (8).

The most common subtype of thyroid cancer is papillary thyroid cancer (PTC). It comprises 75 to 85% of all thyroid cancers, followed by follicular thyroid cancer (FTC) being 12%, with poorly differentiated and other thyroid cancers compromising 3% (1).

Figure 4. Cellular origins of differentiated and undifferentiated (anaplastic) thyroid cancer
**Papillary Thyroid Cancer**

PTC can occur at any age, but most commonly occurs in patients aged 20 to 40 years. It accounts for the majority of thyroid cancers that are associated with previous ionising radiation exposure to the head and neck (9). PTC arises from mutations in multiple non-overlapping molecular pathways that encode tyrosine and protein kinases – enzymes involved in cell signalling. These proto-oncogenes (genes that regulate cell growth) including RET, BRAF and RAS mutations, with BRAFV600E (valine to glutamine substitution) being the most common (9,10).

PTC arises in the thyroid as solitary or multi-focal lesions. Macroscopically, it displays a granular or papillary cut surface. The microscopic appearance is of branching papillae arising from a fibro-vascular stalk, lined by cuboidal cells. The nuclei appear empty due to finely dispersed chromatin, giving a pathognomonic designation of ‘Orphan Annie eye’ nuclei (9,11).

PTC has a tendency to spread via the lymphatic system to ipsilateral lymph nodes of the neck. Concentrically calcified microscopic structures within the papillae, termed ‘Psammoma bodies’ are exclusively found in PTC and if found in distant lymph nodes alone, is highly suggestive of an undiagnosed PTC (9,12).

**Follicular Thyroid Cancer**

In contrast to PTC, conventional follicular thyroid cancer (FTC), predominantly occurs in women aged 40 to 50 years. The incidence of FTC is increased in areas of iodine deficiency, which suggests that multinodular goitre may predispose to its development (9). FTC presents as slow growing thyroid nodules and if metastasises, has the propensity to spread haematogenously (via the blood stream) rather than via lymphatics (9). FTC tumours harbour mutation in either RAS proto-oncogenes or a translocation of genes between the PAX8 and the peroxisome proliferator-activated receptor y1 (PPARy1) – the PAX8-PPARy1 fusion – not present in follicular adenomas (13,14).
Macroscopically FTC occurs as a single nodule that is either well circumscribed or diffusely invasive. Microscopically, it has uniform small cells forming small follicles containing colloid, with similar appearance to a benign follicular adenoma. Capsular or vascular invasion is the hallmark of malignancy (9,15).

**Follicular Variant or ‘Hürthle Cell’ Carcinoma**

Follicular variant or ‘Hürthle cell’ carcinoma (HCC) is a counterpart of FTC, which is characterised by the predominant presence of Hürthle cells (aka oncocytic or oxyphillic cells). Hürthle cells themselves are characterised by the cytoplasmic accumulation of abundant mitochondria that frequently display abnormal morphology (16). This results in high FDG uptake on PET/CT owing to impairment of respiratory chain complexes and consequent upregulation of oxidative phosphorylation and high mitochondrial density (17).

The WHO defines Hürthle cell tumours as those consisting of at least 75% Hürthle cells (18). Thirty percent of Hürthle cell tumours are malignant, and represent 3-7% of all thyroid cancer (1,18). The HCC phenotype is caused by genetic alterations in both mitochondrial and nuclear DNA. Similarly to FTC, capsular or vascular invasion is the hallmark of malignancy as compared to its benign counterpart (19). HCC is more aggressive tumour than other forms of DTC, with a reduced disease-specific survival rate (8,18). A population level analysis of 3,311 patients with HCC demonstrated a reduced overall survival and disease-specific mortality of 82.1 and 5.9% respectively, as compared to patients with other forms of DTC (89.2 and 2.7%) (19).

**Anaplastic Thyroid Cancer**

Anaplastic thyroid cancer (ATC) is an undifferentiated tumour and in contrast to DTC, has an extremely poor outcome - with mortality reaching close to 100% and median survival of 6 months (9,20). Patients with ATC are generally older (mean age of 65 years), and present with a rapidly growing neck lump (9,15). Approximately 50% have a
history of multi-nodular goitre, 20% have a history of DTC and the remaining 20-30% have concurrent DTC with ATC. This suggests that ATC develops from de-differentiation of DTC, via the loss of the p56 tumour suppressor gene (9). A combination of chemotherapy and external beam radiotherapy is required for local control of the tumour, and unfortunately due to the aggressiveness and metastatic nature of ATC, treatment is predominantly palliative (20).

Treatment goals of differentiated thyroid cancer

When a patient is diagnosed with a localised DTC without a concomitant cancer, the goals of treatment include to improve cancer related patient survival; reduce the risk of local recurrence and metastatic spread; minimise the morbidity related to treatment and ensure accurate long term surveillance and follow-up for recurrent disease (1). Surgery is the mainstay treatment for localised DTC with or without removal of the central or lateral draining lymph nodes in the neck (cervical) and radioactive iodine treatment. The American Thyroid Association recommends the following surgical approach for DTC (1):

1. For small tumours less than four centimetres not invading beyond the thyroid gland substance (T1/T2) and without spread to regional cervical lymph nodes (N0) – removal of a single lobe of the thyroid (lobectomy) is recommended.

2. For larger tumours greater or equal to four centimetres or any tumour of any size invading beyond the thyroid gland substance (T3/T4) with or without spread to regional cervical lymph nodes (N0/N1) – Complete removal of thyroid tissue (total thyroidectomy) is recommended.

3. For tumours that have spread to the central group of cervical lymph nodes, central lymph node dissection (CLND) is recommended.

4. For tumours that have spread to lateral groups of cervical lymph nodes, lateral neck dissection is recommended.
Surgical considerations in the management of differentiated thyroid cancer

Pre-operative patient assessment

There are important considerations associated with surgery that are evaluated pre-operatively to maximise the goals of treatment. This includes accurate assessment of a patient’s fitness to safely tolerate a general anaesthetic and the stress response associated with surgery and the oncological factors that ensure complete removal of thyroid cancer. The latter is based on accurate local staging of disease with either ultrasound, CT and/or voice assessment (with or without naso-laryngoscopy). This is to determine the amount of thyroidal tissue to be removed; if suspicious cervical lymph nodes require removal; if adjacent aero-digestive structures are invaded by cancer; and to document vocal cord function which are supplied by the recurrent laryngeal nerves – which are at risk during surgery.

Risks of thyroid surgery

Additional risks of thyroid surgery include bleeding (given that the thyroid gland is a highly vascular organ) and haematoma formation – which can obstruct the airway and be a life-threatening event; wound infection; hypothyroidism – an inevitable consequence of thyroid surgery that requires exogenous thyroid hormone replacement; and hypocalcaemia due to potential removal of the adjacent parathyroid glands that are essential in regulation of plasma calcium levels (21). Recurrent laryngeal nerve (RLN) palsy is a specific risk of thyroid surgery that may result in significant patient morbidity. Amongst high volume thyroid surgeons, the incidence is as low as 1% to 2%, however may be as high as 23% (22,23). Factors that increase the risk of RLN palsy are the extent of thyroid surgery (more radical operations), bilateral thyroid surgery (total thyroidectomy), thyroidectomy for retrosternal multi-nodular goitres, re-operative surgery (for recurrent disease) and failure to visualise the RLN intra-operatively (24,25).
Active Surveillance

In cases where tumours that have a very low potential of spread (micro-papillary carcinoma with no aggressive features on imaging), patients are high risk surgical candidates, have a short life span or concurrent medical co-morbidities that require attention before surgery, active surveillance (AS) is a treatment option (1). This treatment consists of active observation of a known cancer where it is safe to do so – the risk of spread outside the thyroid is low and the risk of surgery outweighs the benefit. Patients may remain in an AS program indefinitely, unless their disease demonstrates signs of progression – in which they progress to surgical treatment. Progression rates in patients undergoing AS are low in the older population, with 1.6% of patients over 60 years progressing to surgery. However, rates of progression are worse in the younger population – 8.9% of patients under 40 years of age (26).
Assessing treatment response after thyroid surgery

Long term follow-up of patients after treatment for thyroid cancer is essential to monitor for disease recurrence and progression. To standardise the assessment and response to treatment, the ATA has developed guidelines to aid clinician decision making in respect to investigation and future treatment (Table 5) (1).

Table 5. American Thyroid Association guidelines for assessing response to treatment during follow-up after thyroid surgery (1)

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Clinical Outcome</th>
</tr>
</thead>
</table>
| **Excellent response**        | Negative imaging AND EITHER Suppressed Tg <0.2ng/ml OR TSH-stimulated Tg <1ng/ml | Ongoing surveillance  
   § 1-4% risk of recurrence  
   § <1% disease specific mortality |
| **Biochemical incomplete response** | Negative imaging AND Suppressed Tg ≥1ng/ml OR Stimulated Tg ≥10ng/ml OR Rising anti-Tg antibody levels | Additional imaging required to detect structural disease and potentially additional therapy  
   § 20% develop structurally incomplete disease  
   § <1% disease specific mortality |
| **Structural incomplete response** | Clinical or imaging findings demonstrating evidence of disease | Additional therapy  
   § Mortality 11% with loco-regional and 50% with distant metastasis |
| **Indeterminate response**    | Non-specific imaging findings OR Stimulated Tg < 10ng/ml OR Anti-Tg antibodies stable | Ongoing surveillance with serial imaging +/- biopsy  
   § 15-20% will develop structurally incomplete disease  
   § <1% disease specific mortality |
Petit Emission Tomography / Computed Tomography (PET/CT)

PET/CT is one particular imaging modality in which TI are being identified and increasingly studied. Fluorine-18 fluorodeoxyglucose (FDG) PET/CT is an accurate functional imaging technique increasingly used for the diagnosis, staging and therapeutic monitoring of many common cancers. The enhanced uptake of glucose (or its analogue FDG) by cancer cells due to inefficient aerobic glycolysis – termed the Warburg effect (27) – is the hallmark of in vivo cancer imaging with FDG PET/CT utilising a radiotracer (FDG being the most common). Being a measure of the rate of intracellular glycolysis, concomitant benign and malignant tumours unbeknown to the patient and treating physician may be detected. PET detected or ‘avid’ ‘incidentalomas’ have been reported to occur in up to 5% of scans.

Thyroid ‘Incidentalomas’ identified on PET/CT imaging

FDG-avid TI have been reported to occur in up to 2.5% of scans (28). The incidence of these incidentalomas varies widely within the literature, with a range from 0.02 to 8.9% from studies ranging from 689 to 15,711 patients (28–30). Rates of malignancy varying also widely between 13 to 59% of TI (29). A large systematic review of the literature conducted by Nayan et al. totalling 197,296 PET studies was pooled from 31 studies, identified 3659 (1.9%) focal thyroid incidentalomas (30). In addition, a cross-sectional analysis conducted by Uppal et al. who reviewed 97,908 imaging studies including CT, PET and MRI demonstrated an incidence of benign and malignant TI to be 358/100,000 PET scans (31). Incidental foci of FDG uptake unrelated to the primary malignancy therefore pose a significant problem for the reporting nuclear medicine specialist, treating physician and surgeon.
Standardised Uptake Value (SUV)

Cancer risk stratification of thyroid nodules and incidentalomas utilising the maximum standardised uptake value (SUV-max) of 18-FDG as a surrogate marker of malignancy has also been proposed within the literature (32,33). Currently, SUV-max may not be an adequate tool alone to determine the likelihood of metastatic versus primary disease. Generally, cancerous lesions will have a higher SUV-max than their benign counterparts due to their inherent abnormalities in aerobic glycolysis, however benign nodules such as Hürthle cell and follicular adenomas also have high SUV-max, which act as confounders (34). Therefore, controversy remains surrounding the utility of SUV-max as there can be considerable overlap between benign and malignant lesions (35,36). SUV-max itself is usually not reported by nuclear medicine physicians at many institutions, and in our institution, it is the wording of the report itself that guides a cancer clinician to whether the patient should be further investigated with ultrasound and FNAC. The key questions that arise following reporting is which patients should be further investigated with biopsy and if they are biopsied, is surgical resection if a cancer is found appropriate in the context of the primary malignancy. The excellent 5-year survival of PTC (greater than 90%) needs to be balanced with the patient’s stage of primary malignancy, their response to treatment and co-morbidities prior to proceeding to biopsy (37).

Best available evidence regarding FDG-avid TI

To ascertain the best available evidence regarding the incidence, utility of SUV-max and potential confounders of FDG-avid TI, a systematic review of the literature was performed according to the PRISMA guidelines (Figure 5). Medical databases that were searched included MEDLINE, EMBASE and COCHRANE databases. Articles assessed were limited to English-language peer-reviewed publications that included original research, reviews and case reports published between 1980 and 2016. The medical subject heading (MeSH) “thyroid neoplasm(s)” was used in combination with
search terms “positron emission tomography”, “incidentaloma”, “fluorodeoxyglucose” and “Hürthle”. Acceptable articles were searched for further relevant references. In total, 356 studies were identified from an initial search of full text human studies in the English Language. 65 studies were excluded for duplicated reporting. 291 studies were screened and 195 studies were excluded by screening of titles and abstracts. The remaining 96 original studies were reviewed by careful screening of the full texts, after which 37 were eliminated due to lack of eligible data. Finally, 59 studies were included that related to thyroid incidentalomas identified on PET/CT, 15 studies observing the utility of SUV-max in thyroid incidentalomas and one study observing Hürthle cell neoplasms amongst FDG-avid thyroid nodules. This included 9 systematic reviews, 3 cross-sectional analyses 38 retrospective reviews, 5 case series, 1 case control study, 2 editorials and 1 case report.
Figure 5. Literature search of FDG-avid thyroid incidentalomas using PRISMA guidelines

Table 6. Systematic reviews of patients with thyroid incidentalomas identified on PET/CT

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Scans (N)</th>
<th>Patients with incidental TI (%)</th>
<th>TI Investigated</th>
<th>Cancer incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nayan 2014</td>
<td>Systematic review</td>
<td>197,296</td>
<td>3659 (1.9)</td>
<td>1340 (37)</td>
<td>479 (13)</td>
</tr>
<tr>
<td>(30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bertanga 2012</td>
<td>Systematic review</td>
<td>147505</td>
<td>3629 (2.5)</td>
<td>Not reported</td>
<td>34.6</td>
</tr>
<tr>
<td>(33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shie 2009</td>
<td>Systematic review</td>
<td>55160</td>
<td>571 (1.0)</td>
<td>322 (56)</td>
<td>107 (19)</td>
</tr>
<tr>
<td>(38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Single-centre studies of patients with thyroid incidentalomas identified on PET/CT

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Scans (N)</th>
<th>Patients with incidental TI (%)</th>
<th>TI undergoing Investigation (%)</th>
<th>Incidence of thyroid Ca (FNAC/Histo) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boeckmann 2012 (39)</td>
<td>Retrospective review</td>
<td>23384</td>
<td>690 (2.9)</td>
<td>103 (15)</td>
<td>28 (4)</td>
</tr>
<tr>
<td>Yerubandi 2016 (40)</td>
<td>Retrospective review</td>
<td>21402</td>
<td>31 (0.1)</td>
<td>31 (100)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>King 2007 (41)</td>
<td>Retrospective review</td>
<td>15711</td>
<td>22 (0.2)</td>
<td>22 (100)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Kwak 2008 (42)</td>
<td>Retrospective review</td>
<td>14436</td>
<td>88 (0.6)</td>
<td>85 (97)</td>
<td>42 (48)</td>
</tr>
<tr>
<td>Kang 2009 (43)</td>
<td>Retrospective review</td>
<td>12840</td>
<td>535 (4.2)</td>
<td>148 (28)</td>
<td>55 (10)</td>
</tr>
<tr>
<td>Kim BH 2010 (44)</td>
<td>Retrospective review</td>
<td>11623</td>
<td>159 (1.4)</td>
<td>140 (88)</td>
<td>37 (23)</td>
</tr>
<tr>
<td>Pagano 2011 (45)</td>
<td>Retrospective review</td>
<td>11040</td>
<td>191 (1.8)</td>
<td>37 (19)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Are 2007 (46)</td>
<td>Retrospective review</td>
<td>8800</td>
<td>263 (2.9)</td>
<td>84 (32)</td>
<td>44 (16)</td>
</tr>
<tr>
<td>Pampaloni 2012 (36)</td>
<td>Retrospective review</td>
<td>8464</td>
<td>156 (1.8)</td>
<td>40 (71)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Uppal A 2015 (31)</td>
<td>Cross-sectional analysis</td>
<td>7828</td>
<td>28 (100)</td>
<td>28 (100)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Bogsrud TV 2007 (47)</td>
<td>Retrospective review</td>
<td>7347</td>
<td>79 (1.1)</td>
<td>48 (61)</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Chu 2006 (48)</td>
<td>Retrospective review</td>
<td>6241</td>
<td>76 (1.2)</td>
<td>14 (18)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Ho 2011 (49)</td>
<td>Retrospective review</td>
<td>5877</td>
<td>220 (3.7)</td>
<td>55 (25)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Chen 2005 (50)</td>
<td>Retrospective review</td>
<td>4803</td>
<td>60 (1.2)</td>
<td>50 (83)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Nishimori 2011 (51)</td>
<td>Retrospective review</td>
<td>4726</td>
<td>160 (3.4)</td>
<td>50 (31)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Cohen 2001 (52)</td>
<td>Retrospective review</td>
<td>4525</td>
<td>102 (2.3)</td>
<td>15 (15)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Kim 2005 (53)</td>
<td>Retrospective review</td>
<td>4136</td>
<td>94 (2.2)</td>
<td>32 (34)</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Nilsson 2011 (54)</td>
<td>Retrospective review</td>
<td>3641</td>
<td>64 (1.8)</td>
<td>27 (42)</td>
<td>16 (25)</td>
</tr>
<tr>
<td>Zhai 2010 (55)</td>
<td>Retrospective review</td>
<td>3600</td>
<td>115 (3.2)</td>
<td>96 (83)</td>
<td>48 (42)</td>
</tr>
<tr>
<td>Bae 2009 (56)</td>
<td>Retrospective review</td>
<td>3379</td>
<td>285 (8.4)</td>
<td>99 (35)</td>
<td>22 (8)</td>
</tr>
<tr>
<td>Bonabi 2012 (57)</td>
<td>Retrospective review</td>
<td>3062</td>
<td>73 (2.4)</td>
<td>58 (79)</td>
<td>23%</td>
</tr>
<tr>
<td>Adas 2015 (58)</td>
<td>Cross-sectional analysis</td>
<td>2654</td>
<td>34 (1.2)</td>
<td>34 (100)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>Chen 2009 (59)</td>
<td>Retrospective review</td>
<td>2594</td>
<td>99 (3.8)</td>
<td>11 (11)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Even-Sapir 2006 (60)</td>
<td>Retrospective review</td>
<td>2360</td>
<td>59 (2.5)</td>
<td>41 (70)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Pritchard 2011 (61)</td>
<td>Retrospective review</td>
<td>2105</td>
<td>35 (1.6)</td>
<td>8 (23)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Ishimori 2005 (62)</td>
<td>Retrospective review</td>
<td>1912</td>
<td>29 (2.5)</td>
<td>11 (38)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Choi 2006 (63)</td>
<td>Retrospective review</td>
<td>1763</td>
<td>70 (4.0)</td>
<td>44 (62)</td>
<td>17 (24)</td>
</tr>
<tr>
<td>Ohba 2010 (64)</td>
<td>Retrospective review</td>
<td>1501</td>
<td>20 (1.3)</td>
<td>20 (100)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Kung 2010 (65)</td>
<td>Retrospective review</td>
<td>1407</td>
<td>45 (3.2)</td>
<td>30 (66)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Kang 2003 (66)</td>
<td>Cross-sectional analysis</td>
<td>1330</td>
<td>29 (2.2)</td>
<td>15 (52)</td>
<td>4 (14)</td>
</tr>
</tbody>
</table>
Impact of thyroid incidentalomas in cancer patients

The most important consideration of most oncology patients with FDG-avid TI is the patient's overall survival. This is likely to be determined by the underlying malignancy given the excellent prognosis associated with thyroid cancer. Consequently, the costs, anxiety and risks associated with investigation and surgical management of incidental FDG-avid thyroid cancer need to be carefully balanced with the bio-psycho-social impacts of their primary cancer. The relative clinical impact of an incidental, asymptomatic thyroid cancer in the context of active non-thyroidal malignancy is unknown within the literature. It is however critically important information to guide the interpretation and management of this finding.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Patients (N)</th>
<th>FDG Avid (%)</th>
<th>Thyroid Cancer (%)</th>
<th>Incidentaloma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kao 2012 (67)</td>
<td>Retrospective</td>
<td>942</td>
<td>21 (2.2)</td>
<td>6 (29)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Nam 2007 (68)</td>
<td>Retrospective</td>
<td>689</td>
<td>19 (2.8)</td>
<td>12 (63)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Eloy 2009 (69)</td>
<td>Retrospective</td>
<td>630</td>
<td>30 (4.8)</td>
<td>18 (60)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Hsieh 2003 (70)</td>
<td>Retrospective</td>
<td>477</td>
<td>12 (2.5)</td>
<td>10 (83)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Lee 2012 (71)</td>
<td>Retrospective</td>
<td>327</td>
<td>33 (10.1)</td>
<td>17 (51)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Sharma 2015 (72)</td>
<td>Retrospective</td>
<td>235</td>
<td>9 (3.8)</td>
<td>9 (100)</td>
<td>5 (55)</td>
</tr>
<tr>
<td>Yoon 2015 (73)</td>
<td>Retrospective</td>
<td>84</td>
<td>84 (100)</td>
<td>84 (100)</td>
<td>40 (46)</td>
</tr>
<tr>
<td>Beech 2016 (74)</td>
<td>Retrospective</td>
<td>48</td>
<td>48 (100)</td>
<td>48 (100)</td>
<td>4 (10.4)</td>
</tr>
<tr>
<td>Hsiao 2011 (75)</td>
<td>Retrospective</td>
<td>35</td>
<td>35 (100)</td>
<td>35 (100)</td>
<td>13 (49)</td>
</tr>
<tr>
<td>Bahl 2014 (76)</td>
<td>Cohort study</td>
<td>25</td>
<td>25 (100)</td>
<td>25 (100)</td>
<td>25 (100)</td>
</tr>
</tbody>
</table>
Hypothesis

The hypothesis for regarding FDG-avid thyroid incidentalomas is that:

1. PET/CT behavior (FDG-avidity) may influence the pattern of investigation and management thyroid nodules in the setting of a primary cancer diagnosis, and that:
   a. The cancer-specific survival of patients is based on the prognosis of the primary cancer, rather than due incidentally detected synchronous thyroid cancer (TI) on PET/CT
   b. Most malignant FDG-avid TI are as a result of papillary thyroid cancer (PTC), which has an excellent prognosis, rather than poorly differentiated or anaplastic thyroid cancer.

2. The maximum standardised uptake value (SUV-max), which represents the maximum FDG-uptake within a measured area on PET/CT is a poor predictor of thyroid cancer and diagnosis of thyroid cancer by US and fine needle aspiration cytology (FNAC) is still paramount

3. Benign and malignant oncocytic (Hürthle cell) thyroid nodules are a common cause for intensely FDG-avid TI. Pathologic misclassification by identification of microscopic incidental thyroid cancer in an area not attributing to the FDG-avidity of a benign thyroid nodule is a potential cause of error in respect to thyroid cancer malignancy rates.
Aims and Objectives

The main objectives are:

a) Determine the incidence of thyroid malignancy amongst FDG-avid TI in patients who are already being staged and treated for a primary cancer.

b) Assess the thyroid cancer treatment response, determining which patients may have a structurally incomplete response.

c) Assess the thyroid cancer specific survival.

Secondary objectives are to:

a) Determine if the maximum standardised uptake value (SUV-max) can be used as a surrogate marker of malignancy in FDG-avid TI.

b) Determine if pathological misclassification (by location and histological diagnosis – particularly Hürthle cell tumours) of FDG-avid TI accounts for the varying rates of thyroid malignancy.
Chapter 2: Methods

Ethics approval

Ethics approval was obtained from the Department of Surgical Oncology ethics review board (number 17/17R). The study was conducted according to the NHMRC National Statement on Ethical Conduct in Human Research and the World Medical Association Declaration of Helsinki 2008. There was no contact with patients or patient primary care providers in a prospective manner for the purposes of this review (patients were not consented to provide data in this manner).

Patient selection

A retrospective review was performed of demographics, imaging (PET/CT scans and reports), pathology and outcomes (overall survival, primary cancer-specific survival, thyroid cancer specific survival as documented on patient electronic medical records) in patients with a primary cancer diagnosis and incidentally detected thyroid nodules on PET/CT. This was performed on patients underwent a PET/CT at Peter MacCallum Cancer Centre (PMCC) between January 2007 to January 2015 for the purpose of diagnosis, staging or treatment response in relation to a patient’s primary malignancy. All PET/CT scans were performed with Discovery 390, Biograph and Discovery STE PET/CT scanner systems (GE Medical Systems, Waukesha, WI, USA).

PET/CT scan reports of 45, 680 consecutive patients from the PMCC Nuclear Medicine Department PET/CT database were reviewed, identifying 2,588 FDG PET/CT reports referring to the thyroid, after using ‘thyroid’ as a search term. Patient duplicates and scans with normal thyroid reports were excluded. Other exclusions included diffuse or physiological uptake to the thyroid gland, thyroiditis, patients known thyroid cancer, reported multi-nodular goitre without FDG-avidity, focal uptake less than 1mm without association with nodule on CT and nodules identified with non-FDG radiotracers (GA-Tate, 1-Flurocholine, PSMA) (Figure 6).
**Patient Variables**

Data analysed by the statistician was de-identified by allocating case numbers to each patient to protect patient privacy and that any retrospective review of raw data can be examined in the future by the named investigators.

The PMCC Verdi electronic medical record (EMR) was utilised to conduct patient search and document:

i. Patient demographics

ii. Type and stage of primary malignancy

iii. Presence of FDG-avidity pertaining to the patient’s primary cancer (presence of active cancer)

iv. Thyroid lobe affected by incidental thyroid nodule, the presence of suspected PET/CT metastasis from a primary cancer to the thyroid

v. The level of investigation conducted amongst patients with TI (ultrasound, FNAC and surgery)

vi. Histological features (subtype, size and the presence of capsular invasion)

vii. FDG-avidity parameters pertaining to the incidental thyroid nodule (SUV-max, SUV-mean, dimensions of the thyroid nodule, SUV-mean of the liver as quality assurance, dose of FDG and uptake time).
viii. Overall mortality, cause of death, follow up period, and thyroid disease status (based on American Thyroid Association 2015 guidelines).

FDG-avidity parameter data was gathered using MIM imaging software (MIM, OH, USA), using nuclear medicine work stations within the Department of Cancer Imaging at Peter MacCallum Cancer Centre. This was conducted by identifying the thyroid nodule on a maximum projection image (MIP) and selecting PET EDGE tool to delineate the thyroid nodule. Dimensions of the selected area of avidity will be recorded using the RECIST tool. The process will be repeated using a homogenous area of the liver to gather quality assurance data related to uptake of FDG (aiming for a SUV-mean between 2 and 3).

Data collection and storage

Patient data (master list of patient unique identifier numbers, demographics, variables and outcomes) was captured using Microsoft Excel 2015, version 15.15 (MICROSOFT, USA) and stored electronically using password encryption only accessible to the investigators. The patient data was kept strictly confidential according to the National Statement on Ethical Conduct in Human Research 2007 and the Australian Code for Responsible Conduct of Research 2007. Following completion of the study, any paper information will be destroyed. An electronic copy of the data will be provided to the Department of Surgical Oncology. Patient and research data will be stored on hard disk for a period of at least 5 years. After 15 years these files will be destroyed by erasure unless further approval for retention is obtained.
Methodology 1. Assessing whether PET/CT behaviour (FDG-avidity) influences the pattern of investigation and management of thyroid nodules in the setting of a primary cancer diagnosis

Patients who were alive and received follow-up (by clinical or radiological assessment) > 12 months, or died after index PET/CT were further assessed for differences in overall survival. This was based on primary malignancy, American Joint Committee on Cancer (AJCC) stage, FDG-avidity within the primary malignancy on index PET/CT (first scan to identify an incidental thyroid nodule) and level of investigation (histological or cytological) patients received and overall survival and thyroid cancer-specific survival. These were assessed and followed up until January 2016. Secondary outcomes of FNAC based on the Bethesda classification, and histopathology (including risk stratifying features of size, capsular and vascular invasion) were also assessed.

Definitions and measures of primary study outcomes are defined below:
1a) Determining the incidence of thyroid malignancy amongst FDG-avid TI in patients who are already being staged and treated for a primary cancer

- Incidence of FDG-avid thyroid cancer was determined by calculating the number of malignant cases and dividing this by the number of TI identified between 2007 and 2015.
- Incidence of FDG-avid thyroid nodules was determined by calculating the number of TI and dividing this by the total number of PET/CT scans performed between 2007 and 2015.
- Fine needle aspirate results were documented in accordance with the Bethesda classification of reporting thyroid nodule cytopathology (7).
- Histopathology results / thyroid pathology were documented in accordance with the WHO classification of endocrine tumours (8).

1b) Assessing thyroid cancer treatment response, determining which patients may have a structurally incomplete response

- If a patient has thyroid cancer, their response to treatment was documented as per the 2015 American Thyroid Association guidelines for Thyroid nodules and differentiated thyroid cancer (1).
- Structural incomplete response was defined as recurrence of thyroid cancer on imaging in patients who are still alive and being actively treated for their incidental thyroid cancer (1).

1c) Assessing thyroid cancer specific survival

- Primary cancer, thyroid cancer and overall survival were determined from the time of the patient’s index PET/CT defined as the first scan that detects the thyroid nodule and occurs prior to investigation (start point) to the patients documented death.
- If the patient was alive at the completion of documented follow-up, they were documented as being alive.
- Completion of documented follow up of all patients was January 2016.

**Figure 8. Identification process of FDG-avid and investigated TI**

**Statistical analysis**

Multivariate logistic regression was used to determine true predictors of death, and survival analysis (using both graphical (Kaplan Meier curve) and analytical (Cox proportional hazard model) techniques), was undertaken to determine factors associated with time to death. Both analyses were adjusted for patients’ age and were performed using Stata12 (STATACORP, TX, USA). P<0.05 was considered statistically significant.
Methodology 2. Assessing the role of SUV-max as a predictor of thyroid cancer

Patients who were investigated for their thyroid incidentalomas by FNAC or surgery between 2009 and 2014 were further assessed to determine the utility of SUV-max as a determinate of malignancy. Only the index PET/CT scan was assessed. This was a single time-point cross-sectional analysis that was defined as the patients PET/CT scan that first identified the nodule and/or was the scan immediately prior to investigation with FNAC or surgery.

FDG-avidity parameter data was gathered using MIM imaging software (SUV-max, SUV-mean, dimensions of the thyroid nodule, SUV-mean of the liver as quality assurance and dose of FDG and uptake time). Fisher’s exact test was used to determine if SUV-max was significant for malignant nodules at a given uptake. A SUV-max threshold of 5 was used based on a similar study by Bertagna et al 2013 where an SUV-max of 4.8 yielded a sensitivity and specificity of 95.7 and 46.4% respectively. A receiver operating curve (ROC) analysis of the patients with a definitive diagnosis of thyroid malignancy was performed to determine the diagnostic performance of the test and identify a SUV cut-off useful in differentiating benign from malignant incidentalomas. Linear regression analysis was also performed to determine association of SUV-max, nodule size, malignant and benign nodules.

Methodology 3. Assessing oncocytic thyroid nodules as a common cause of FDG-avid thyroid incidentalomas

We performed a retrospective audit of Peter MacCallum Cancer Centre Department of Cancer Imaging Karisma software (Kestral, Perth, WA, Australia) imaging database for all 18F-FDG PET/CT reports from Jan 2007- Dec 2012 using the search term ‘thyroid’. The index PET/CT was the patients PET/CT scan that first identified the nodule and/or was the scan immediately prior to investigation with FNAC or surgery. The patient’s pathology report and thyroid specimen (histological subtype and location) were the comparison.
These were cross-referenced with patient histories in Verdi to identify patients with FDG-avid TI who had undergone surgical excision (lobectomy/total thyroidectomy). Patient demographic and cancer related variables included patient age, gender, duration of follow-up and overall survival. Thyroid specimens were retrieved from anatomical pathology archives to localise potential cause of focal FDG uptake (e.g. Hürthle cell adenoma, hyperplastic nodules or malignancy) within each section of sampled thyroid gland (upper-, mid-, lower-pole or isthmus). Histopathology results / thyroid pathology were documented in accordance with the WHO classification of endocrine tumours. Immunohistochemistry staining for GLUT family transporters on benign and malignant thyroid nodules was performed to identify likely candidate for incidental thyroid FDG uptake. Detailed histopathologic (location, size, diagnosis, percentage oncocyte density [POD]) and PET/CT imaging (location, size, SUVmax) review was performed by an independent head & neck oncologic pathologist and nuclear medicine physician respectively. The threshold of number of oncocytes in specimen to define a oncocytic tumour was 75%. Pearson R correlation was used to determine whether FDG-avidity within a detected nodule on PET/CT is related to the oncocytic density of a tumour identified on specimen.
Figure 9. Identification of TI available for PET/CT and pathological correlation
Chapter 3: Results (primary)

PET/CT behaviour, investigation and management of FDG-avid TI

Introduction

The primary outcome was to assess the impact on incidentally detected FDG-avid TI on PET/CT. The inclusion criteria to assess the primary outcome of overall and thyroid cancer-specific survival, with a mean age 65 years (range 19-96), and median follow-up of 24 months (IQR 13-46). The male to female ratio was 1:1.85. Index PET/CT’s of 272 (75%) patients demonstrated FDG-avidity, indicating the presence of residual metabolically active underlying malignancy. Lymphoid (19%), lung (16%), colorectal malignancy (12%) and melanoma (9%) were the most common diagnostic and staging indications (Table 8). Most patients had stage IV cancer (43%) as per AJCC staging, followed by stage III (28%), stage II (15%) and stage I cancer (13%) (Table 8).

Table 8. Baseline demographic and clinical data of study population

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>N=362</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>- Median</td>
<td>66</td>
</tr>
<tr>
<td>- Range</td>
<td>19-96</td>
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<tr>
<td><strong>Gender, N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>127</td>
</tr>
<tr>
<td>- Female</td>
<td>235</td>
</tr>
<tr>
<td><strong>FDG avid primary Ca on index PET/CT, N (%)</strong></td>
<td>272 (75)</td>
</tr>
<tr>
<td><strong>Primary malignancy, N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>- Lymphoma</td>
<td>69 (19)</td>
</tr>
<tr>
<td>- Lung</td>
<td>59 (16)</td>
</tr>
<tr>
<td>- Colorectal</td>
<td>43 (12)</td>
</tr>
<tr>
<td>- Melanoma</td>
<td>33 (9)</td>
</tr>
<tr>
<td>- Other</td>
<td>159 (44)</td>
</tr>
<tr>
<td><em><em>AJCC</em> stage of primary malignancy, N (%)</em>*</td>
<td></td>
</tr>
<tr>
<td>- 1</td>
<td>47 (13)</td>
</tr>
<tr>
<td>- 2</td>
<td>54 (15)</td>
</tr>
<tr>
<td>- 3</td>
<td>100 (28)</td>
</tr>
<tr>
<td>- 4</td>
<td>156 (43)</td>
</tr>
<tr>
<td><strong>Occult primary tumour, N (%)</strong></td>
<td>5 (1)</td>
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Incidence of thyroid malignancy amongst FDG-avid TI

Of 45,680 PET/CT scans between 2007 and 2014, 500 patients (1.1%) were identified to have FDG-avid thyroid incidentalomas.

The majority (231) of the 362 patients with FDG avid TI whom met the inclusion criteria were not investigated at the time of index PET/CT scan.

Of the 131 patients who underwent histological and/or cytological investigation, 47 (36%) had incidental thyroid cancer (24 papillary, 11 malignant on FNAC, 5 oncocytic/Hürthle cell carcinoma, 2 medullary, 1 follicular and 4 confirmed metastases from underlying malignancy) (Table 9). This corresponded to a thyroid cancer incidence of 9.4% amongst patients with FDG-avid TI.

At completion of follow-up, 42 of 43 patients (98%) with confirmed thyroid cancer were either stable under observation or had no clinical evidence of disease recurrence. 72 (55.0%) of investigated nodules had benign pathology and 12 (9.1%) had non-diagnostic/indeterminate FNAC without further evaluation.

Table 9. Pathologic characteristics of malignant FDG avid thyroid incidentalomas

<table>
<thead>
<tr>
<th>Malignant cases, N (%)</th>
<th>N=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant on FNAC alone</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Papillary</td>
<td>24 (51)</td>
</tr>
<tr>
<td>Follicular</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Metastasis (from underlying malignancy)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Medullary</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Hürthle cell Ca / Oncocytic variant</td>
<td>5 (11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignancy histological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (mm)</td>
</tr>
<tr>
<td>- Median</td>
</tr>
<tr>
<td>- Range</td>
</tr>
<tr>
<td>Vascular invasion, N (%)</td>
</tr>
<tr>
<td>Capsule invasion, N (%)</td>
</tr>
</tbody>
</table>
Assessing thyroid cancer treatment response – structurally incomplete

Forty-six patients were found to have an excellent response to thyroid cancer treatment, as reflected by an absence of disease recurrence on ultrasound and PET/CT.

Only one patient (0.6%) died from incidental medullary thyroid cancer (Figure 10). In this patient, a FGG / $^{68}$Ga-DOTATATE PET/CT initially revealed concordant mild DOTATATE uptake in the right thyroid nodule and evaluation for medullary thyroid carcinoma was recommended, however the patient was lost to follow-up. A subsequent PET directed biopsy of the mildly FDG / DOTATATE avid thyroid nodule confirmed progressive medullary thyroid carcinoma with extrathyroidal extension and lymphovascular invasion. A total thyroidectomy confirmed the intensely FDG avid left thyroid nodule was a follicular adenoma. The patient passed away approximately 18 months later due to progressive metastatic disease (red arrows in Figure 10).

Figure 10. FDG PET/CT performed in a 61 year old woman with metastatic duodenal carcinoid tumour (blue arrow; Grade 2, Ki,67 15%) showed mildly avid right thyroid nodule and intensely avid left thyroid nodule.
Overall and thyroid cancer specific survival

The median overall survival from the primary malignancy was 20 months (IQR 9.5-39).

Overall, 180 (50%) patients died and the majority of these (166 [92%]) had positive FDG avidity on the index PET/CT scan (Table 10). The vast majority of deaths were due to the primary malignancy under investigation (166 [92.2%]) or other non-cancer related causes (13 [7.2%]).

Table 10. Summary of patient follow-up & clinical outcome data.

<table>
<thead>
<tr>
<th>Patients with follow-up &gt; 12 months or death (months)</th>
<th>N=362</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
</tr>
<tr>
<td>- Median</td>
<td>24</td>
</tr>
<tr>
<td>- Range</td>
<td>1-103</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
</tr>
<tr>
<td>- Median</td>
<td>20</td>
</tr>
<tr>
<td>- Range</td>
<td>0-93</td>
</tr>
<tr>
<td><strong>Survival status at last follow-up, N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>181 (50)</td>
</tr>
<tr>
<td>Death</td>
<td>181 (50)</td>
</tr>
<tr>
<td>- Primary cancer</td>
<td>166 (45.9)</td>
</tr>
<tr>
<td>- Incidental FDG avid TI</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>- Non-malignant aetiology</td>
<td>13 (3.6)</td>
</tr>
<tr>
<td><strong>FDG avid TI status at last follow-up, N (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Malignant TI</td>
<td>47 (13)</td>
</tr>
<tr>
<td>- Observation</td>
<td>11 (3)</td>
</tr>
<tr>
<td>- No clinically evident disease</td>
<td>31 (9)</td>
</tr>
<tr>
<td>- Recurrent/metastatic structural disease</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>- Metastasis (from underlying malignancy)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Non-diagnostic/indeterminate FNAC</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Benign TI</td>
<td>72 (20)</td>
</tr>
<tr>
<td>Not investigated</td>
<td>231 (64)</td>
</tr>
</tbody>
</table>
FDG avidity and advanced stage of the primary malignancy on the index PET/CT that detected the TI, and a decision by the clinician to not investigate the FDG avid TI were all statistically significant predictors of mortality with hazard ratios of 8.5 (95% CI 4.6-15.8), 3.0 (95% CI 2.3-3.9) and 3.3 (95% CI 2.0-5.0) respectively (P < 0.001). These associations persisted after multivariate analysis, with age-adjusted hazard ratios of 4.0 (2.0-8.2), 2.5 (1.8-3.3) and 1.7 (1.04 -3.3) respectively (P < 0.001). These findings are graphically demonstrated on Kaplan Meier survival curves (Figure 11).

**Conclusion**

Incidentally detected FDG-avid TI are detected in 1.1% of PET/CT scans. The incidence of malignancy was found to be 9.4%. Only one patient with malignancy had a structurally incomplete response, however this was on the basis of patient loss of follow-up rather than treatment failure. The median overall survival was poor at 20 months. At the completion of follow up, 46 of 47 patients with thyroid malignancy had an excellent response to treatment, as only one patient died from their thyroid malignancy.
Figure 11. Kaplan-Meyer survival distribution

A. Kaplan Meier survival distribution of patients with FDG avid primary disease at time of identification of FDG avid TI on index PET/CT (red line) and without FDG avid primary disease (blue line).

B. Kaplan Meier survival distribution among patients who did not undergo cytological or histopathologic investigation of FDG avid TI (red line), and those patients with further investigation (blue line).

C. Kaplan Meier survival distribution of patients stratified according to AJCC stage of primary malignancy, stage I (blue line), stage II (red line), stage III (green line) and stage IV (orange line).
Chapter 4: Results (secondary)

**SUV as a predictor of thyroid cancer**

The primary outcome is to determine if maximum standardized uptake value (SUV-max), representing the maximum uptake of 18-FDG, can be used as a surrogate measure of malignancy risk in thyroid nodules incidentally detected on PET/CT. Receiver operating curve (ROC) analysis of patients with a definitive diagnosis of thyroid malignancy performed to identify a SUV cut-off useful in differentiating benign from malignant incidentalomas.

A cross-sectional analysis of 99 patients with FDG-avid TI who have a cytological or histological proven benign or malignant thyroid nodules was performed. Forty-nine patients were found to have malignant thyroid nodules, with a median SUV-max of 14.5 (range 2.7 to 60.4) and an SUV-mean of 9.3. Fifty patients were found to have benign thyroid nodules, with a median SUV-max of 8.6 (range 1.9 to 48.2), and a SUV-mean of 6.4. Mean size (cm) of both malignant and benign nodules was 1.8, with similar volumes of 3.6 and 3.8cm$^3$ respectively.

Fisher’s exact test confirmed that malignant nodules had higher median SUV-max than benign nodules at a SUV-max threshold of 5, with a P-value of less than 0.0001. The sensitivity and specificity of SUV-max at this threshold was 70.91% (95%CI 57.1 – 82.4) and 77.22% (95%CI 62.2 – 88.5) respectively. This corresponded to a positive likelihood ratio of 3.12 (95%CI 1.8 – 5.5), a negative likelihood ratio of 0.38 (95%CI 0.24 – 0.59), a positive predictive value of 79.59% (95%CI 68.8 – 87.3) and a negative predictive value of 68.0% (95%CI 57.7 – 76.8). The disease prevalence was calculated to be 55.5% (Table 12).
A SUV-max cut-off of 9 was also assessed to determine if a higher value could improve the test's negative predictive value (P = 0.013), however this improved marginally to 74.0% (95%CI 63.6 – 82.2) (Table 12).

Receiver operator curve (ROC) analysis was performed to determine the diagnostic performance of SUV-max (Figure 12). The SUV-max threshold which was found to give the best possible separation of benign and malignant TI was 5.33. This demonstrated an area under the ROC curve of 0.66 (95CI 0.55 to 0.77), with a P-value of 0.005. This threshold demonstrated a sensitivity and specificity of 73.47 and 46.94 respectively.

**Table 11.** FDG-avid thyroid nodule characteristics based on SUV-max and size

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>SUV &lt; 5 (N)</th>
<th>SUV &gt; 5 (N)</th>
<th>Median SUVmax [Range]</th>
<th>SD</th>
<th>SUV mean</th>
<th>Size (cm)</th>
<th>Vol (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignant</strong></td>
<td>49</td>
<td>10</td>
<td>39</td>
<td>14.5 [2.7 - 60.4]</td>
<td>12</td>
<td>9.3</td>
<td>1.8</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Benign</strong></td>
<td>50</td>
<td>34</td>
<td>16</td>
<td>8.6 [1.9 - 48.2]</td>
<td>8.2</td>
<td>6.4</td>
<td>1.8</td>
<td>3.8</td>
</tr>
</tbody>
</table>

**Table 12.** Sensitivity and specificity of SUV-max at given cut offs

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NVP (%)</th>
<th>Prevalence (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUV-max</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>70.91 [57.1 - 82.4]</td>
<td>77.27 [62.2 - 88.5]</td>
<td>79.59 [68.8 - 87.3]</td>
<td>68.0 [57.7 - 76.8]</td>
<td>55.56%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>9</td>
<td>65.79 [48.7 – 80.4]</td>
<td>60.66 [47.3 – 72.9]</td>
<td>51.02 [41.3 – 60.5]</td>
<td>74.0 [63.7 – 82.2]</td>
<td>38.38</td>
<td>0.013</td>
</tr>
</tbody>
</table>

[95% confidence intervals]; PPV = positive predictive value; NPV = negative predictive value
Oncocytic thyroid nodules

Oncocytic nodules as a potential cause of varying rates of malignancy

Amongst studies included in systematic reviews of FDG-avid TI by Bertagna et al and Nayan et al, there is marked heterogeneity of the incidence of malignancy (ranging between 8% to 55%) (28,30). Importantly, the percentage of TI which underwent further investigation (FNAC or surgery) varied between 11% to 100%. This suggests significant verification bias confounded by either clinical factors (patients deemed not suitable for further investigation with FNAC) or radiological risk factors for malignancy – such as small or less avid thyroid nodules - that are not accounted for by clinicians.

Oncocytic nodules and pathological misclassification

Pathological misclassification of incidentally identified occult thyroid carcinoma within the surgical specimen, which does not correlate with the site of focal FDG uptake on PET/CT.

Figure 12. Diagnostic performance of SUV-max determined by receiver operator curve (ROC) analysis
caused by a separate benign lesion, is another potential explanation of the variability in malignancy incidence. This has been the anecdotal experience of nuclear medicine physicians at Peter MacCallum Cancer Centre to date. Notably, a study of FDG avid TI by King et al. reported an incidence of papillary thyroid carcinoma in only 14% (reduced from 32%) after four incidental microcarcinomas (<5mm in diameter not possibly associated with the imaged abnormality) were excluded (41). The majority of TI that were incongruous with pathological specimens and received the diagnosis of thyroid cancer represented clinically insignificant microcarcinomas. There are no studies to our knowledge that have specifically correlated PET/CT, histopathological or immunohistochemical (IHC) findings to verify pathological misclassification as a potential source of heterogeneously reported incidence of thyroid cancer detected on PET/CT. Therefore, a more thorough investigation of FDG avid TI is necessary to identify the precise mechanism and its clinical relevance.

To explain the observed variability in malignancy rates in FDG-avid TI, we correlated the focal FDG uptake with histological findings to identify the most likely cause of the FDG avid TI in each case – by pathological misclassification or highly avid Hürthle cell tumours.

Cross-sectional analysis of histological and PET/CT findings
The retrospective analysis identified 263 patients with FDG-avid TI. FNAC was selectively performed in 68 patients and surgical pathology (hemi- or total thyroidectomy) was available for pathological review in 24 FDG-avid nodules in 22 patients (18 women and 4 men), with a median age of 61.5 years (range 28-80).

Five nodules (20%) necessitated revision of diagnosis on correlative histopathologic-imaging review. Two presumed malignant FDG-avid TI (nodules 2 and 24) found on imaging were
correlated to non-malignant Hürthle cell adenomas on pathology. This indicated misclassification by location – with the original diagnosis being attributed to micropapillary carcinomas (<5mm) not detectable on PET/CT.

Two other diagnosed malignancies (nodules 8 and 14) correlated to location, but not to pathological diagnosis – with both nodules demonstrating high percentage oncocyte density and therefore being re-classified as Hürthle cell carcinomas. One nodule (case 16) was found to be a separate incidental PTC in a region of the thyroid gland initially diagnosed as thyroiditis.

Table 13. Correlation of 18-F-fluorodeoxyglucose (FDG) avid lesions with pathological review, including percentage oncocyte density (POD)

<table>
<thead>
<tr>
<th>PET review of index lesion</th>
<th>Pathology review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Size</td>
</tr>
<tr>
<td>Isthmus</td>
<td>12</td>
</tr>
<tr>
<td>R lower</td>
<td>6</td>
</tr>
<tr>
<td>R middle</td>
<td>10</td>
</tr>
<tr>
<td>L middle</td>
<td>28</td>
</tr>
<tr>
<td>L lower</td>
<td>11</td>
</tr>
<tr>
<td>R middle</td>
<td>15</td>
</tr>
<tr>
<td>L lower</td>
<td>9</td>
</tr>
<tr>
<td>L lower</td>
<td>36</td>
</tr>
<tr>
<td>L middle</td>
<td>15</td>
</tr>
<tr>
<td>L lower</td>
<td>14</td>
</tr>
<tr>
<td>R middle</td>
<td>410</td>
</tr>
<tr>
<td>L middle</td>
<td>8</td>
</tr>
<tr>
<td>R lower</td>
<td>14</td>
</tr>
<tr>
<td>L lower</td>
<td>11</td>
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<tr>
<td>R lower</td>
<td>8</td>
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<td>R lower</td>
<td>8</td>
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<td>R upper</td>
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<tr>
<td>R lower</td>
<td>16</td>
</tr>
<tr>
<td>R upper</td>
<td>12</td>
</tr>
</tbody>
</table>

*FDG = Fluorodeoxyglucose; POD† = Percentage oncocyte density
The final thyroid lesion diagnosis in this surgical population was 13 malignant (oncocytic 6, PTC 6, MTC 1) and 11 benign (oncocytic 9, parathyroid adenoma 1, thyroiditis 1). Fifteen of twenty-four FDG-avid lesions demonstrated significant (≥60%) oncocyte density. The median/range SUVmax of benign (11.3/ [3.7-37]), malignant (5.5/ [3.4-54]), oncocytic (12.8/ [3.6-54]) and non-oncocytic (5.3/ [3.4-42]) lesions were ascertained. There was no correlation ($r^2=0.11$) between POD and SUVmax. In this selected cohort deemed suitable for surgery, 5 patients died from comorbidity within a median follow-up of 56 months from index FDG PET/CT; there were no thyroid cancer related deaths.

Overall, benign and malignant oncocytic lesions may have intense FDG uptake and are a common cause of FDG-avid TI. The incidence of FDG-avid malignancy may be overestimated without careful imaging / histopathologic correlation. Although pathological misclassification occurred in 20% of cases, only two cases (8%) necessitated downgrading in diagnosis from malignant to benign. In addition, only a further two cases (8%) were upgraded to Hürthle cell carcinomas.
Chapter 5: Discussion

PET/CT behaviour, investigation and management of FDG-avid TI

Concomitant thyroid nodules and cancer found on FDG PET/CT in patients being investigated or staged for malignancy have been progressively encountered in daily practice, as well as increasingly reported in the literature. This can pose significant management challenges for cancer clinicians and their patients. The population differences of patients encountered at a dedicated cancer centre such as Peter MacCallum Cancer Centre (PMCC) compared to most other tertiary referral centres can contribute to these challenges. This is not only in respect to their primary cancer diagnosis, but also their stage of cancer at the time of referral. In addition, the interface that patients have with clinical trials and translational cancer research to improve their cancer-specific survival also gives clinicians, researchers and patients inspiration and hope to pursue further treatment options. Therefore, determining a patient’s potential outcome and balancing cancer-specific survival whilst minimising potential harm can be difficult and a challenging discussion with the patient.

Unfortunately, despite the provision of excellent care in cancer, our data demonstrates high mortality – median overall survival of 20 months. This is due to the poor prognosis associated with the underlying malignancy in this large cohort of patients with FDG avid TI undergoing FDG PET/CT at a comprehensive cancer centre. In contrast, there was no discernible clinical impact – excluding that associated with medical investigation and management of this asymptomatic incidental finding – of the FDG avid TI in 361 (99.7%) of 362 patients after a median of 24 months’ follow-up; it is uncertain if earlier intervention would have prevented the single death from incidental medullary thyroid carcinoma. This highlights the importance of considering the prognosis of the underlying malignancy when
deciding upon whether further investigation and management is appropriate because the potential benefits of intervention may not be realized due to the short life expectancy.

Efforts to identify the cohort of patients who will potentially benefit from further evaluation and treatment have not been successful. Most previous studies have focused upon attempting to identify the patients at highest risk of thyroid cancer to guide the decision to biopsy using the intensity of focal FDG uptake. Whilst some studies have indicated an SUV threshold (49,77,78), many have found no such association (50,73,79) and a large meta-analysis by Bertagna et al confirmed that there is significant overlap of FDG avidity between benign and malignant lesions, without an SUV-max ‘threshold’ to guide the decision to biopsy (33). This is consistent with growing body of literature that FDG avidity of TI is often driven by mechanisms other than poorly differentiated malignancy. For example, it is increasingly recognised that oncocytic / Hürthle cell lesions (irrespective of benign or malignant aetiology) demonstrate intense FDG avidity due to an intrinsic defect mitochondrial defect driving inefficient glycolytic metabolism (80,81). Other causes of very intensely FDG avid benign TI include degenerate nodules, follicular adenomas and adenomatous hyperplasia (82). The limitation of this approach is evident by the low FDG uptake in the only clinically significant thyroid cancer in our study (Figure 11) compared to the intensely avid benign follicular adenoma in the opposite lobe.

In contrast, our study findings enable identification of those cases with a poor prognosis from underlying malignancy in which further evaluation is unlikely to be of clinical benefit (Figure 12). The presence of FDG avidity within the underlying malignancy conferred a significant crude hazard ratio of 8.5 for mortality (p<0.001) beyond the overall poor prognosis seen in our entire patient cohort. This finding is consistent with the large body of literature confirming the superior prognostic value of FDG avidity across a spectrum of malignancies, including non-small cell lung carcinoma (83), gastroenteropancreatic neuroendocrine tumours (84), medullary thyroid carcinoma (85) and established metastatic differentiated thyroid carcinoma.
This finding suggests that clinicians should take a cautious approach to investigating FDG avid TI in the setting of residual FDG avidity in the primary malignancy. Unsurprisingly, advanced tumour stage according to AJCC criteria was also a statistically significant prognostic indicator with crude hazard ratio 3.0 (95% CI 2.3-3.9).

Whilst this high prognostic value of FDG avidity in oncology has contributed to a level of anxiety associated with FDG avid TI, the lack of an SUV threshold for these lesions is supported by increasing evidence that FDG avidity associated with incidentally detected thyroid cancer does not add prognostic value beyond TNM staging (32). A potential explanation for this paradox is that a proportion of incidentally detected apparently FDG avid thyroid malignancies actually represent incidental findings in pathology specimens, further supporting a more conservative approach to managing FDG-avid TI. A careful histopathologic and imaging correlation revealed that 20% (3/15) of presumed FDG-avid incidental thyroid carcinomas in fact represented incidental malignancies identified by the pathologist, and did not correlate to the avid lesion at all (17). This is plausible given that autopsy studies have identified incidental thyroid malignancy in up to 36% of specimens (87). Exclusion of such microcarcinomas in another study on the basis that they were clearly not associated with the imaged abnormality due to partial volume artefact, reduced the incidence of malignancy from 32% to 14% (41).

Our finding that the clinical decision to not investigate an FDG-avid TI is also associated with a worse overall prognosis confirms that the patients’ prognosis does influence the oncologists’ decision to investigate incidentalomas in this cohort. The exceptionally low incidence of persistent clinically significant thyroid cancer in this series confirms that this decision is often made appropriately. The proportion of investigated FDG avid TI in other series (33) – mean 35% [range 11-100%] – is similar to our cohort (36%) and suggests that this principle is also applied variably in other centres.
Our study findings support a more cautious approach to the investigation and management of FDG avid TI. In the first instance, this data supports an individualized approach to further investigation, recognising that further evaluation of FDG avid incidentalomas may be associated with patient anxiety, additional costs and potential morbidity associated with aggressive investigation (88). Notably, our findings suggest that the management of incidental thyroid cancer in this setting is likely to have negligible impact on the patient’s outcome despite additional risks associated with potentially unnecessary surgery and delay of definitive treatment of underlying malignancy. This data supports limiting further investigation to patients with an otherwise favourable prognosis for whom diagnosis of incidental thyroid carcinoma may be clinically relevant. This involves careful consideration of factors associated with the patient (including age and non-oncologic morbidity), underlying malignancy (persistent FDG avidity, stage, etc.) and local features such as adjacent FDG avid neck nodes on PET scan. In many patients (particularly those in which FDG-PET/CT is routinely used in restaging such as lymphoma) investigation of the FDG avid TI can be deferred until after successful treatment of the underlying malignancy (Figure 12).

If a diagnosis of papillary thyroid cancer is confirmed this data supports the consideration of active surveillance (26), consistent with the recommendations of the ATA guidelines for patients with a relatively short life expectancy in whom the benefits of intervention may be not be realised (1). A period of observation provides a clearer understanding of the prognosis associated with the underlying malignancy in addition to the biology of the incidental thyroid carcinoma. It is important that all clinicians from the PET reporting nuclear medicine specialist to the referring oncologist, endocrinologist & thyroid surgeon are informed of this approach from the outset to provide a consistent message to the patient.

The retrospective nature of the study is a potential limitation and 28% of potentially eligible patients were lost to follow-up. However, a prospective study would be challenging to implement for an incidental pathology in this patient cohort and the overall proportion of
investigated patients is similar to that seen in other studies. Importantly, the follow-up of clinical outcomes in all patients (irrespective of the extent of investigation) eliminates the potential for verification bias seen in most prior studies. A minimum of 12-month follow-up in surviving patients was necessary to clinically capture a rapidly progressive poorly differentiated / anaplastic thyroid carcinoma which would be expected to become clinically apparent during this period. Referral bias to a comprehensive cancer centre is a possible limitation of this study, however we believe the results remain generalizable because malignancy remains the most common PET indication and the majority of PET scans were performed for standard approved indications.

A strength of this study is the focus upon the presence of clinically meaningful thyroid cancer outcomes of structural incomplete response or death in this patient population with limited lifespan. Furthermore, the large size and long duration of follow-up of 362 patients for a median of two years adds to the validity of the study findings.
**SUV as a predictor of thyroid cancer**

Relating specifically to thyroid cancer, the role of F-18-FDG PET/CT has expanded since its introduction and initial application for investigating high-risk patients with elevated serum thyroglobulin levels and negative radioiodine 131 imaging for recurrent DTC (89). This role has since expanded to establish the diagnosis of thyroid cancer prior to treatment, such as in patients who have repeated indeterminate results on FNAC and patients with FDG-avid TI (33). The utility of SUV-max as a surrogate marker of predicting thyroid malignancy is variably reported within the literature.

Observing patients with established cytological and histological diagnosed thyroid nodules, our data demonstrates that SUV-max does not reliably predict thyroid cancer, with an overall sensitivity of 70.9% to 73.4%; and specificity of 46.9 to 77.2%. This is at an SUV-max cut-off of 5. The performance of SUV-max on ROC analysis was also poor, reflected by area under the curve (AUC) of 0.66 (whereby perfect separation of groups is reflected by an AUC of 1.0 and no separation of groups reflected by an AUC of 0.5). Therefore, the utility of an SUV-max cut-off to differentiate benign and malignant FDG-avid TI is currently not a safe method.

This finding is consistent with the large body of literature that SUV-max cut-offs are not a reliable means of predicting thyroid cancer. The largest sum of evidence published by Bertagna et al. demonstrates that approximately one half the number of studies investigating the utility of SUV-max show a statistically significant difference between benign and malignant nodules, whereas the other half show no difference (33). Bertagna also studied the power of SUV-max retrospectively across three nuclear medicine centres in a total of 211 patients (124 benign, 72 malignant, 4 non-diagnostic and 11 indeterminate nodules) and demonstrated a very broad sensitivity of 57.1 to 95.7% and specificity of 46.4 to 79.3% across three centres at cut-offs of 4.8, 5.3 and 7. AUC ranged from 0.62 to 0.75, which
confirmed the broad overlap of SUV-max between patients with benign and malignant TI (28).

A recent large single centre study conducted by Yoon et al combining the Thyroid Imaging and Reporting Data System (TIRADS) scoring on ultrasound with SUV demonstrated that combined these tests improved sensitivity and negative predictive value, compared to SUV alone (97.5% and 95%, compared to 65% and 70%) (73). However, when compared with TIRADS alone, the specificity and positive predictive value of the combined tests was reduced. The AUC on ROC analysis demonstrated an overall reduced performance of the combined test compared to TIRADS alone (0.724 and 0.737 respectively) (73). This demonstrates that SUV-max should also not be used as an adjunctive tool to increase the accuracy pre-existing validated tools for thyroid cancer risk stratification.

The pathophysiology relating to the utility of SUV-max is related to the Warburg effect (discussed above) combined with the theory that cellular de-differentiation in thyroid cancer results increased glucose transporter gene expression and reduced iodine uptake (27,90). Type 1 glucose transporters (GLUT-1) are found to be increasingly expressed in thyroid cancer proportionally with increasing de-differentiation and aggressive histological features as discovered by Grabellus et al. This is combined with proportionally increasing FDG-avidity (and therefore higher SUV-max) in well differentiated (lowest), poorly differentiated (intermediate) and anaplastic (highest) thyroid cancer (91). Cellular uptake of iodine in thyroid follicular cells is mediated by the Na⁺/I⁻ symporter, which is an important physiological step in normal iodination of thyroglobulin to form thyroxine (T4) and tri-iodothyronine (T3) (92). When cells have increased glucose uptake, the Na⁺/I⁻ symporter reduces in activity, which has been termed the ‘flip-flop’ phenomenon. This inverse pattern is also seen in escalating SUV-max and thyroid de-differentiation and has formed the basis of using FDG-PET/CT to investigate for recurrent thyroid cancer in the setting of high thyroglobulin levels and negative radioiodine-131 scans (91,93,94).
Despite the above findings by Grabelles et al, the majority of FDG-avid TI are represented by DTC in the form of PTC. As these well-differentiated tumours can demonstrate high uptake, this suggests that there may be alternate metabolic mechanisms other than cellular de-differentiation that contribute to high FDG-uptake in thyroid nodules. In a small series of patients with PTC incidentally detected on PET/CT, phosphatase and tensin homolog (PTEN), an oncosuppressor frequently mutated in thyroid cancers, was found to be lost in the majority of investigated cases and associated with intense GLUT-1 expression (95).

The use of 18-FDG PET/CT has also been used to help define thyroid nodules that are repeatedly indeterminate or non-diagnostic on FNAC. This is a similar approach to investigating FDG-avid TI which do not have a definitive benign or malignant diagnosis with SUV-max. A systematic review and meta-analysis conducted by Vriens et al in order to assess the pre-operative value of PET/CT and whether negative 18-FDG PET/CT can select patients who have a low suspicion of malignancy and avoid surgery (96). This study demonstrated that PET/CT had varying accuracy in diagnosing malignancy between 41.7 and 79% amongst six studies with small sample sizes ranging from 15 to 51 patients, with most false positive nodules were less than 15mm. The greatest impact from this study was the finding that a negative PET/CT (defined as no uptake) in nodules >15mm which had a low false negative rate of 3.6% (96). The comparison of this data against TI demonstrates PET/CT remains an unsafe measure of malignancy amongst FDG-avid nodules. A negative PET/CT as defined by Vriens et al may provide some reassurance to patients with repeatedly indeterminate FNAC, but unfortunately provides no reassurance to patients, endocrinologists, nuclear medicine physicians and surgeons when encountered with FDG-avid TI.

There are potential confounders of highly avid thyroid nodules which contribute to the broad overlap between benign and malignant TI. Hürthle cell nodules and follicular adenomas compared to other benign conditions. The association with high SUV in Hürthle cell nodules
owes to impairment of respiratory chain complexes and consequent upregulation of oxidative phosphorylation and high mitochondrial density (16,17,19).

Technical factors that can also contribute to varying SUV include level of fasting serum glucose, length of fasting period prior to examination, volume of FDG-injected, time of radiotracer administration and uptake (33). PET/CT scanners are designed to measure the in-vivo radioactivity concentration within cancer cells, which is proportional to FDG concentration. FDG uptake is dependent on the concentration of FDG injected into a patient and patient size (97). The SUV standardises these variables by dividing the radioactivity concentration measured by the PET scanner (kBq/ml), by the proportion of decay-corrected amount of injected radiolabelled FDG (kBq) per the weight of the patient (g) (98). In order to provide a reproducible SUV, additional variables that require standardisation include imaging physics (image resolution), the biophysical status of the patient, the scan protocol (injection time and duration of scan), data processing, and analysis methods (99).

The biophysical status of the patient is one important modifiable variable that can affect the SUV. Blood glucose levels have been shown to inversely affect SUV in a linear manner, therefore patients failing to comply with caloric restriction prior to imaging may have diffusely increased levels of FDG in muscle due to increased GLUT4 levels, resulting in less FDG available for uptake in tumour cells (100,101). Conversely, medications such as chemotherapeutic agents can impair glomerular filtration rate, and therefore increase the concentration of FDG available for tumour cell uptake (100). In this study however, these factors were standardized by measuring the SUV-mean of the liver as quality assurance to ensure equal FDG uptake between studies.

Another variable is the analysis method of FDG-uptake. SUV-max is one such analysis method. Although SUVmax has a higher reproducibility as compared to other techniques
SUV-mean and region of interest analysis), it may be a value determined from only one pixel (97).

SUV-max has been shown in several studies to be a more robust metric for assessing treatment response. Reassuringly, test-retest studies involving repeated scanning of a patient using the same scanning system and protocol demonstrate a coefficient of variation of approximately 10%. This therefore demonstrates that SUV is a highly repeatable and useful tool for monitoring treatment response in individual patients, rather than a predictor of malignancy(102).

Our study therefore helps validate Bertagna’s findings that SUV-max is not a safe tool to discriminate benign from malignant TI and should remain a theoretical adjunctive tool for predicting thyroid cancer. Ultrasound and FNAC should remain the gold standard investigation tool of thyroid nodules.
Oncocytic thyroid nodules

Highly avid-TI are potentially more likely to be investigated for thyroid cancer. This is due to many cancers having a higher uptake of glucose on the basis of the Warburg effect (27). At a molecular level, positive correlation between FDG uptake and cellular glucose transporter (GLUT1) expression is well established for many cancers, but is not clearly defined in differentiated thyroid cancer (103–105). This may be reflective of analysis of thyroid cancer tissue with unquantified FDG avidity or due to an alternative explanation of FDG uptake. The loss of Phosphatase and Tensin homolog (PTEN) expression - a protein that is encoded by the PTEN tumour suppressor gene - has been associated with intense GLUT1 expression in a small series of FDG avid thyroid carcinoma(95). The BRAF-V600E mutant protein within the occurs in approximately 45% of papillary thyroid carcinomas and is associated with poor
Clinicopathological outcomes and reduced iodine avidity. A ‘flip-flop phenomenon’ of reduced iodine avidity and increased FDG uptake has been linked to BRAF-V600E mutant thyroid cancers through increased expression of GLUT1 mRNA and reduced expression of molecular markers of differentiation (106).

Similar tumours that demonstrate a high level of GLUT1 expression and express high FDG avidity are oncocyctic tumours. These including Hürthle cell adenomas and carcinomas. Hürthle cells (otherwise known as oncocyctic or oxyphillic cells) are characterised by the cytoplasmic accumulation of abundant mitochondria that frequently display abnormal morphology (16). These cells (albeit not designated as such) also occur in other oncocyctic tumours of the body such as renal oncocyotosmas and oxyphillic carcinoma of the parathyroid gland (16). They are not normally occurring cells and only occur during states of chronic inflammation and tumorigenesis. Despite the inconsistent nomenclature, these cells are believed to share similar pathogenesis – due to imbalance between increased mitochondrial proliferation and reduced mitochondrial destruction (107). This may be as a result of elevated reactive oxygen species produced during normal thyroid metabolism and mutations in mitochondrial DNA (108–110). The overall outcome is high FDG uptake on PET/CT owing to consequent upregulation of oxidative phosphorylation and high mitochondrial density (17).

A recent meta-analysis conducted by Wang et al observing the utility of FDG-PET/CT in indeterminate thyroid nodules after FNAC biopsy is an example of how Hürthle cell tumours can act as potential confounders. Amongst seven peer-reviewed articles, Hürthle cell adenomas contributed to 41.6% of false positive tumours (111).

Overall, we found that benign and malignant oncocyctic lesions may have intense FDG uptake and are a common cause of FDG-avid TI. The incidence of FDG-avid malignancy may be overestimated without careful imaging / histopathologic correlation. Although pathological misclassification occurred in 20% of cases, only two cases (8%) necessitated downgrading in
diagnosis from malignant to benign. Unfortunately, these two patients died within 20 months of their index PET/CT imaging. In addition, only a further two cases (8%) were upgraded to Hürthle cell carcinomas. Reassuringly, these patients had an excellent outcome, being alive at completion of their follow up (66 and 72 months) after completion thyroidectomy.

Therefore, the heterogeneity of the incidence of malignancy seen between studies of FDG-avid TI is likely to be explained more by verification bias rather than pathological misclassification and highly avid oncocytic TI.

**Conclusion**

Cancer patients who underwent Fluorine-18 fluorodeoxyglucose (FDG) PET/CT for the purpose of diagnosis, staging and assessment of treatment response were found to have incidental thyroid nodules at a rate of 1.1%. The overall survival with FDG-avid TI was poor (median 20 months) due to the prognosis associated with underlying malignancy. The stage, extent and treatment response of a patient’s primary must be considered prior to investigation of FDG-avid TI with ultrasound and FNAC. Therefore, active surveillance (observation with the intention of treatment if cancer remission is achieved) should be considered in this group
of patients. This is based on the finding that most malignant TI are papillary thyroid cancers, which have an excellent 5-year-survival.

As FDG-avid TI can demonstrate variable uptake of FDG with an overall sensitivity of 70.9% to 73.4%; and specificity of 46.9 to 77.2%, SUV-max is not a safe tool to discriminate benign from malignant TI. SUV-max should remain a theoretical adjunctive tool for predicting thyroid cancer and ultrasound and FNAC should remain the gold standard investigation tool of thyroid nodules.

Benign and malignant oncocytic lesions are a common cause of FDG-avid TI. The incidence of FDG-avid malignancy may be overestimated without careful imaging and histopathologic correlation. Therefore, the heterogeneity of the incidence of malignancy seen between studies of FDG-avid TI is likely to be explained more by verification bias rather than pathological misclassification and highly avid oncocytic TI.
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