Journal of Nuclear Medicine, published on October 12, 2017 as doi:10.2967/jnumed.117.198085

Title: ^{18}F-fluorodeoxyglycose-avid thyroid incidentalomas: the importance of contextual interpretation

Authors: David A. Pattison*[1,2] (MBBS, MPH, FRACP), Michael Bozin*[3,4] (MBBS, BAppSci), Alexandra Gorelik[5,6] (MSc), Michael S. Hofman[1,7] (MBBS, FRACP), Rodney J. Hicks[1,7] (MBBS, MD, FRACP), Anita Skandarajah[3,4] (MBBS, MD, FACS, FRACS).

** Denotes equal contribution to the preparation of this manuscript.*

1. Centre for Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Australia
2. Department of Nuclear Medicine & Specialised PET Services, Royal Brisbane & Women's Hospital, Brisbane, Australia
3. Department of Surgical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
4. Department of Surgery, University of Melbourne, Melbourne, Australia
5. Melbourne EpiCentre, Royal Melbourne Hospital, Melbourne, Australia
6. Department of Medicine, University of Melbourne, Melbourne, Australia
7. The Sir Peter MacCallum Department of Oncology, the University of Melbourne, Melbourne, Australia

CORRESPONDING AUTHOR:

Dr. David A. Pattison

Department of Nuclear Medicine & Specialised PET Services

Royal Brisbane & Women's Hospital,

Butterfield Street, Brisbane, Queensland, Australia 4006

T: +617 3646 7593

F: +617 3646 3502

Email: david.pattison@health.qld.gov.au

Word Count: 2589

Running Title: FDG-avid thyroid incidentalomas

ABSTRACT:

Background: FDG-avid thyroid incidentalomas (TI) are seen in approximately 2.5% of patients imaged for staging or response assessment of malignancy and represent thyroid cancer in approximately 35% of cases. Consequently, the 2015 ATA guidelines strongly recommend investigation of all FDG-avid nodules ≥1cm with US and fine needle aspiration cytology (FNA). This study aims to assess the overall and thyroid cancer specific survival in a large cohort of patients with FDG-avid TI with long-term follow-up to assess the validity of this approach.

Methods: Retrospective review of 45,680 PET/CT scans performed at a comprehensive cancer center from January 2007 to January 2015 identified 2,588 FDG PET/CT reports referring to the thyroid. After exclusion of non-avid thyroid nodules, diffuse FDG-uptake, known thyroid cancer, abnormalities adjacent to thyroid and repeat studies, 500 patients (1.1%) with TI were identified of whom 362 had confirmed death and/or > 12 months' clinical follow-up. Variables including age, gender, primary malignancy, overall survival, thyroid cancer-specific survival, FNA and histopathology were collected until January 2016. Multivariate logistic regression and survival analysis were performed.

Results: 362 analyzed patients (65% female) had median age 65-years (range 19-96) and follow-up of 24-months (range 1-103). Lymphoid, lung and colorectal malignancy were the most common staging indications. Median overall survival was 20-months (IQR 9.5-39). The majority of 180 observed deaths were due to the primary malignancy under investigation (92.2%) or non-cancer related causes (7.2%); one patient (0.6%) died from incidentally-detected medullary thyroid cancer. FDG-avidity in index malignancy, advanced stage of that malignancy 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). Of 131 patients suitable for cytological/histopathological evaluation, 47 (36%) had

incidental thyroid cancer (24 papillary, 11 malignant FNA, 5 oncocytic/Hürthle cell carcinoma, 2 medullary, 1 follicular and 4 metastases from underlying malignancy).

Conclusions: 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 and certainly before aggressive treatment. Active surveillance should be considered in this group of patients.

Key terms: FDG; PET/CT; incidentaloma; thyroid; oncology.

INTRODUCTION:

Fluorine-18 fluoro-deoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is an accurate functional imaging technique increasingly used for the diagnosis, staging and therapeutic monitoring of many common malignancies. The enhanced uptake of glucose (or its analogue FDG) by cancer cells due to inefficient aerobic glycolysis – termed the Warburg effect (1) – is the hallmark of *in vivo* cancer imaging with FDG PET/CT. However, incidental foci of FDG uptake unrelated to the primary malignancy pose a significant problem for the reporting nuclear medicine specialist, treating physician and surgeon. Our department has previously analyzed outcomes of incidental non-thyroidal FDG uptake and shown that most can be appropriately categorized as benign or of unlikely clinical significance by experienced PET readers, thereby avoiding the costs, anxiety and potential complications of unnecessary investigation (2). However, FDG-avid thyroid incidentalomas (TI) – defined as abnormal focal FDG uptake confined to the thyroid gland – are a relatively common finding (2.5%) and a large meta-analysis confirms these represent thyroid cancer in approximately 35% of investigated cases (3). Consequently, the 2015 American Thyroid Association (ATA) guidelines (4) strongly recommend investigation of such nodules ≥1cm with thyroid US and fine needle aspiration cytology (FNA) without consideration of the prognosis of the underlying malignancy.

Nevertheless, the overall outcome of most oncology patients with FDG-avid TI is likely determined by the underlying malignancy given the excellent prognosis associated with thyroid cancer, especially that detected incidentally on imaging. Therefore, the costs, anxiety and risks associated with investigation and surgical management of incidental FDG-avid thyroid cancer need to be carefully balanced. The relative clinical impact of an incidental, asymptomatic thyroid cancer in the context of active non-thyroidal malignancy is unknown but critically important information to guide the interpretation and management of this finding.

Our study aims to assess the clinically relevant outcomes of overall survival, thyroid cancer-specific survival and the risks of recurrent/metastatic thyroid cancer in a large cohort of patients with FDG-avid TI –

irrespective of investigation status – managed at a comprehensive cancer center with long-term follow-up. Secondary outcomes include determining predictors of mortality and the incidence of malignant, benign, Hürthle cell and metastatic disease within FDG-avid incidental thyroid nodules in this cohort.

MATERIALS AND METHODS:

This study involved retrospective review of 45,680 consecutive PET/CT scans performed at a single comprehensive cancer center from January 2007 to January 2015 for the purpose of diagnosis, staging or treatment response in relation to their known or suspected malignancy. The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived. Keyword search of departmental database identified 2588 PET/CT reports referring to the thyroid and 1612 patients after exclusion of duplicate/follow-up PET/CT reports. 500 patients with TI were identified for survival analysis and histopathological / cytological outcome after exclusion of non-avid thyroid nodules, diffuse FDG uptake, known thyroid cancer, abnormalities adjacent to thyroid and use of non-FDG radiotracers (^{68}Ga-PSMA, ^{68}Ga-DOTATATE) based upon review of electronic medical records. 96 (19.2%) of these cases were referred to our center only for PET imaging without available clinical follow-up data, and 42 (8.4%) cases were lost to clinical follow-up. 362 patients had follow-up data to death or >12 months – necessary to capture a rapidly progressive poorly differentiated / anaplastic carcinoma, which would be expected to become clinically apparent during this period – and were included in the analysis until data cut-off in January 2016 (FIGURE 1). Variables including primary malignancy type and stage according to 7th edition of the American Joint Committee on Cancer (5) (AJCC), FDG-avidity within the primary malignancy on index PET/CT (i.e. first scan to identify an FDG-avid TI), extent of thyroid investigation (histological or cytological), overall survival, thyroid cancer-specific survival and structural incomplete response of thyroid cancer were collected. The etiology of investigated FDG-avid TI was classified according to histopathologic diagnosis (including size and presence of vascular invasion) and the result of FNA according to Bethesda classification (6) was used in cases where histopathologic diagnosis was not obtained.

Data analysis:

Univariate analysis using simple logistic regression was performed to assess any associations between mortality (dependent variable) and multivariate predictors (independent variables including presence of FDG avidity in non-thyroidal malignancy, AJCC tumor stage, TI investigation status, non-thyroidal malignancy type, age and gender). Factors found to be significant were included in the multivariate logistic regression model to determine whether they still predicted patient death. The Kaplan Meier curve was used to assess the individual impact of each predictor on survival time. Crude and adjusted odds ratios (OR) were calculated. Statistical analysis was performed using Stata12 (StataCorp, TX, USA). $P<0.05$ was considered statistically significant.

RESULTS:

362 patients (35% male and 65% female) met the inclusion criteria to assess the primary outcome of overall and thyroid cancer-specific survival, with a median age 65 years (range 19-96), and median follow-up of 24 months (IQR 13-46). Index PET/CT's of 272 (75%) patients demonstrated FDG-avidity associated with the underlying non-thyroidal malignancy, indicating the presence of persistent metabolically active disease. Lymphoid (19%), lung (16%) colorectal malignancy (12%) and melanoma (9%) were the most common diagnostic and staging indications (TABLE 1). Of 4 cases of carcinoma of unknown primary (1.5%), 2 FDG avid TI were confirmed papillary thyroid microcarcinoma and the PET/CT appearance of the remaining 2 was inconsistent with anaplastic thyroid carcinoma. 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 2). 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%]). One patient (0.6%) died from the incidentally-detected medullary thyroid cancer (FIGURE 2).

FDG-avidity and advanced stage of the known malignancy at the time of 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 crude OR 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 when all factors were included in the model, with adjusted OR of 4.0 (2.0-8.2), 2.5 (1.8-3.3) and 1.7 (1.04 -3.3) respectively ($P < 0.001$). The impact of these predictors on survival estimates are graphically demonstrated on Kaplan Meier survival curves (FIGURES 3A, 3B & 3C). Lymphoid neoplasm predicted improved survival relative to other malignancies, with crude and adjusted odds ratio of 0.3 (95% CI 0.1 – 0.5) and 0.3 (95% CI 0.2 – 0.8) respectively ($P < 0.001$). There was no statistically significant association between survival and other non-thyroidal malignancy types, age or gender (TABLE 3).

The majority (231) of the 362 patients with FDG-avid TI and adequate clinical follow-up 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 FNA, 5 oncocytic/Hürthle cell carcinoma, 2 medullary, 1 follicular and 4 confirmed metastases from underlying malignancy) (TABLE 4). 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 FNA without further evaluation. The incidence of FDG-avid thyroid nodules at our PET center was 1.1% during the 8-year study period.

DISCUSSION:

Our data demonstrates high mortality – median overall survival of 20 months – in this large cohort of patients with FDG-avid TI undergoing FDG PET/CT at a comprehensive cancer center. However, this appears to be almost exclusively due to the poor prognosis associated with the underlying malignancy rather than adverse

outcomes related to incidentally detected FDG-avid thyroid cancer. 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 of 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 a maximum standardized uptake value (SUVmax) threshold (7,8,9), many have found no such association (10,11,12) and a large meta-analysis by Bartegna et al (3) confirmed that there is significant overlap of FDG-avidity between benign and malignant lesions, without an SUVmax 'threshold' to guide the decision to biopsy. 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 recognized that oncocytic / Hürthle cell lesions (irrespective of benign or malignant etiology) demonstrate intense FDG-avidity (13) due to an intrinsic mitochondrial defect driving inefficient glycolytic metabolism (14,15). Other causes of very intensely FDG-avid benign TI include degenerate nodules (16), follicular adenomas and adenomatous hyperplasia (17). The limitation of this approach is evident by the low FDG uptake (SUVmax 4.4) in the only clinically significant thyroid cancer in our study (FIGURE 2) compared to the intensely avid benign follicular adenoma in the opposite lobe (SUVmax 16).

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 4) and emphasize the

need to consider the broader clinical context. 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 (18), gastroenteropancreatic neuroendocrine tumors (19), medullary thyroid carcinoma (20) and established metastatic differentiated thyroid carcinoma (21). This finding suggests that clinicians should take a cautious approach to investigating FDG-avid TI in the setting of FDG-avidity in a known or suspected malignancy, especially if metastatic as, unsurprisingly, advanced tumor 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 (22). 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 (16). This is plausible given that autopsy studies have identified incidental thyroid malignancy in up to 36% of specimens (23). 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 true FDG-avid incidental thyroid malignancy from 32% to 14% (24).

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' underlying malignancy likely did influence the oncologists'

decision to investigate incidentalomas in this cohort. The exceptionally low incidence of persistent clinically significant thyroid cancer in this series suggests that this decision was generally made appropriately. The proportion of investigated FDG-avid TI in other series (3) – mean 35% [range 11-100%] – is similar to our cohort (36%) and suggests that this principle is also applied variably in other centers.

Our study findings support a more cautious contextual approach to the investigation and management of FDG-avid TI. In the first instance, we advocate an individualized approach to further investigation, recognizing that further evaluation of FDG-avid incidentalomas may be associated with patient anxiety, additional costs and potential morbidity associated with aggressive investigation (2). 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. We recommend limiting further investigation to patients with an otherwise favorable 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 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. As previously highlighted by Ginsberg, the reporting nuclear medicine specialist may practically convey this message by stating that 'incidental FDG-avid thyroid nodule is of doubtful clinical relevance in the context of FDG-avid metastatic malignancy'.[25]

If a diagnosis of papillary thyroid cancer is confirmed we strongly recommend consideration of active surveillance (26) (FIGURE 5), 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 realized (4). 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. Moreover, some of these patients will have serial FDG PET studies for the underlying malignancy providing a further opportunity for surveillance of the incidental thyroid lesion without performing additional investigations. 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 identified cases of FDG-avid TI were excluded from analysis. However, the majority of these are explained by the patient only attending our referral center for PET imaging without available clinical follow-up data, and only a modest 8.4% of the total identified cases received less than 12 months clinical follow-up. Furthermore, a prospective study would be challenging to implement for a relatively rare 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 for meaningful clinical outcomes in all patients (irrespective of the extent of thyroid investigation) is an advantage of our study design that eliminates the potential for verification bias seen in most prior studies of FDG avid incidentalomas. Referral bias to a comprehensive cancer center 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.

It is important to emphasize that our study only identified cases of FDG-avid thyroid cancer, and incidental non-FDG avid thyroid cancer was also likely to have been present in this patient population. Furthermore, metastatic thyroid cancer exists on a spectrum from well-differentiated (typically iodine-avid) to poorly differentiated (typically FDG-avid) disease described as the ‘flip-flop’ phenomenon (27). However, both types of disease may be present in the same patient due to metastatic disease heterogeneity and in one study up to 33% of metastatic lesions demonstrated both iodine and FDG uptake (28). This has important management implications in determining suitability for radioactive iodine therapy and consequently a

combination of both iodine and FDG PET/CT imaging has been advocated in the treatment of advanced thyroid cancer (29).

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.

CONCLUSION:

Overall survival in this large cohort of patients with FDG-avid TI was poor due to the prognosis associated with the underlying malignancy compared with minimal survival impact from FDG-avid TI. FDG-avidity in the known malignancy, and to a lesser extent advanced stage of this malignancy and a decision to not investigate the FDG-avid TI were significant predictors of overall mortality in this cohort. The prognosis of the underlying malignancy should be considered prior to investigation of FDG-avid TI because the potential benefits of intervention may not be realized due to the short life expectancy. Active surveillance of patients diagnosed with incidental FDG-avid papillary thyroid carcinoma should be considered.

DISCLOSURE STATEMENT:

No competing financial interests exist. Professor Hicks is supported by a National Health and Medical Research Council of Australia Practitioner Fellowship.

ACKNOWLEDGEMENTS:

We gratefully acknowledge assistance from Ms Elizabeth Drummond (research assistant) for access to database, Mr Jason Callahan (nuclear medicine technologist) for access to PET/CT workstation and Professor Michael Henderson (Deputy Director of the Department of Surgical Oncology).

REFERENCES:

[1] Warburg O 1956 On the origin of cancer cells. *Science* 123:309–314.

[2] Wang G, Lau EWF, Shakher R, et al. How do oncologists deal with incidental abnormalities on whole-body Fluorine-18 Fluorodeoxyglucose PET/CT? *Cancer.* 2007; 109:117-124.

[3] Bertagna F, Treglia G, Piccardo A, Giubbini R. Diagnostic and Clinical Significance of F-18-FDG-PET/CT Thyroid Incidentalomas. *J Clin Endocrinol Metab.* 2012; 97:3866-3875.

[4] Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid.* 2016; 26:1-133.

[5] Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. American Joint Committee on Cancer cancer staging manual (7th Edition). New York, NY: Springer; 2010.

[6] Cibas E, Ali SZ. The Bethesda System for Reporting Thyroid Cytology. *Am J Clin Pathol.* 2009; 132:658-665.

[7] Bloom AD, Adler LP, Shuck JM. Determination of malignancy of thyroid nodules with positron emission tomography. *Surgery.* 1993; 114:728–734.

[8] Kim BH, Na MA, Kim IJ, Kim SJ, Kim YK. Risk stratification and prediction of cancer of focal thyroid fluorodeoxyglucose uptake during cancer evaluation. *Ann Nucl Med.* 2010; 24:721–728.

[9] Ho TY, Liou MJ, Lin KJ, Yen TC. Prevalence and significance of thyroid uptake detected by 18F-FDG PET. *Endocrine.* 2011; 40:297–302.

[10] Hassan A, Riaz S, Zafar W. Fluorine-18 fluorodeoxyglucose avid thyroid incidentalomas on PET/CT scan in cancer patients: how sinister are they? *Nucl Med Commun.* 2016; 37:1069-1073.

[11] Kwak JY, Kim EK, Yun M, et al. Thyroid incidentalomas identified by 18F-FDG PET: sonographic correlation. *AJR Am J Roentgenol.* 2008; 191:598–603.

[12] Chen W, Parsons M, Torigian DA, Zhuang H, Alavi A. Evaluation of thyroid FDG uptake incidentally identified on FDGPET/ CT imaging. *Nucl Med Commun.* 2009; 30:240–244.

[13] Pathak KA, Klonisch T, Nason RW, Leslie WD. FDG-PET characteristics of Hürthle cell and follicular adenomas. *Ann Nucl Med.* 2016; 30:506-509.

[14] Pattison DA, Hofman MS. Role of Fluorodeoxyglucose PET/Computed Tomography in Targeted Radionuclide Therapy for Endocrine Malignancies. *PET Clin.* 2015; 10:461-476.

[15] Gasparre G, Porcelli AM, Bonora E, et al. Disruptive mitochondrial DNA mutations in complex I subunits are markers of oncocytic phenotype in thyroid tumors. *Proc Natl Acad Sci U S A.* 2007; 104:9001–9006.

[16] Pattison DA, Angel CA, Bozin M, Hofman MS, Hicks RJ. Oncocytic Thyroid Nodules are a Common Aetiology for Intensely 18F-Fluorodeoxyglucose-Avid Thyroid Incidentalomas. *Thyroid.* 2015; 25(S1): P-1-A-337 (abstract).

[17] Kim JM, Ryu JS, Kim TY, et al. 18F-Fluorodeoxyglucose Positron Emission Tomography Does Not Predict Malignancy in Thyroid Nodules Cytologically Diagnosed as Follicular Neoplasm. *J Clin Endocrinol Metab.* 2007; 92:1630-1634.

[18] Hicks RJ, Kalff V, MacManus MP, et al. 18F-FDG PET Provides High-Impact and Powerful Prognostic Stratification in Staging Newly Diagnosed Non-Small Cell Lung Cancer. *J Nucl Med.* 2001; 42:1596-1604.

[19] Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. 18F fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. *Clin Cancer Res.* 2010; 16:978–985.

[20] Verbeek HH, Plukker JT, Koopmans KP, et al. Clinical relevance of 18F-FDG PET and 18F-DOPA PET in recurrent medullary thyroid carcinoma. *J Nucl Med.* 2012; 53:1863–1871.

[21] Robbins RJ, Wan Q, Grewal RK, et al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. *J Clin Endocrinol Metab.* 2006; 91:498-505.

[22] Picardo A, Puntoni M, Bertagna F, et al. ^{18}F-FDG uptake as a prognostic variable in primary differentiated thyroid cancer incidentally detected by PET/CT: a multicenter study. *Eur J Nucl Med Mol Imaging.* 2014; 41:1482-1491.

[23] Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer*. 1985; 56:531-538.

[24] King DL, Stack BC, Spring PM, Walker R, Bodenner DL. Incidence of thyroid carcinoma in fluorodeoxyglucose positron emission tomography-positive thyroid incidentalomas. *Otolaryngol Head Neck Surg*. 2007; 137:400-404.

[25] Ginsberg LE. "If Clinically Indicated:" Is it? *Radiology*. 2010; 254:324-325.

[26] Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid*. 2014; 24:27–34.

[27] Feine U, Lietzenmayer R, Hanke JP, Wöhrle H, Müller-Schauenburg W. 18FDG whole-body PET in differentiated thyroid carcinoma. Flipflop in uptake patterns of 18FDG and I131. *Nuklearmedizin* 1995; 34: 127-134.

[28] Kelders A, Kennes LN, Krohn T, Behrendt FF, Mottaghy FM, Verburg FA. Relationship between positive thyroglobulin doubling time and 18F-FDG PET/CT-positive, 131I-negative lesions. *Nucl Med Commun* 2014; 35: 176-181.

[29] Pattison DA, Solomon B, Hicks RJ. A New Theranostic Paradigm for Advanced Thyroid Cancer. *J Nucl Med* 2016; 57: 1493-1494.

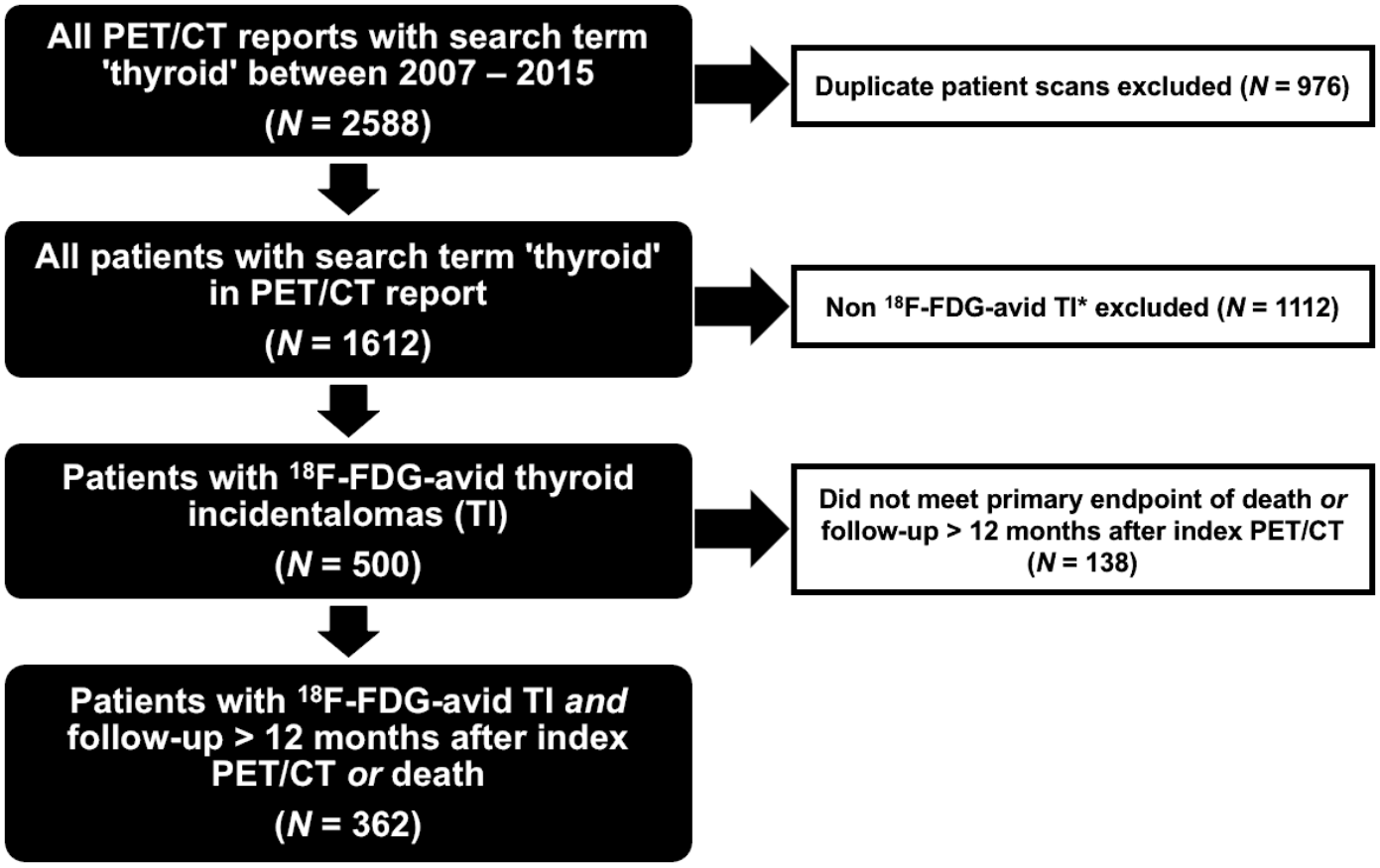


FIGURE 1. Consort flow diagram demonstrating identification & selection of study population. **Non-FDG-avid TI comprise non-avid thyroid nodules, diffuse thyroid FDG uptake, patients with known thyroid cancer, abnormalities adjacent to thyroid (parathyroid adenomas and lymphadenopathy) and use of non-FDG radiotracers (^{68}Ga-PSMA, ^{68}Ga-DOTATATE).*

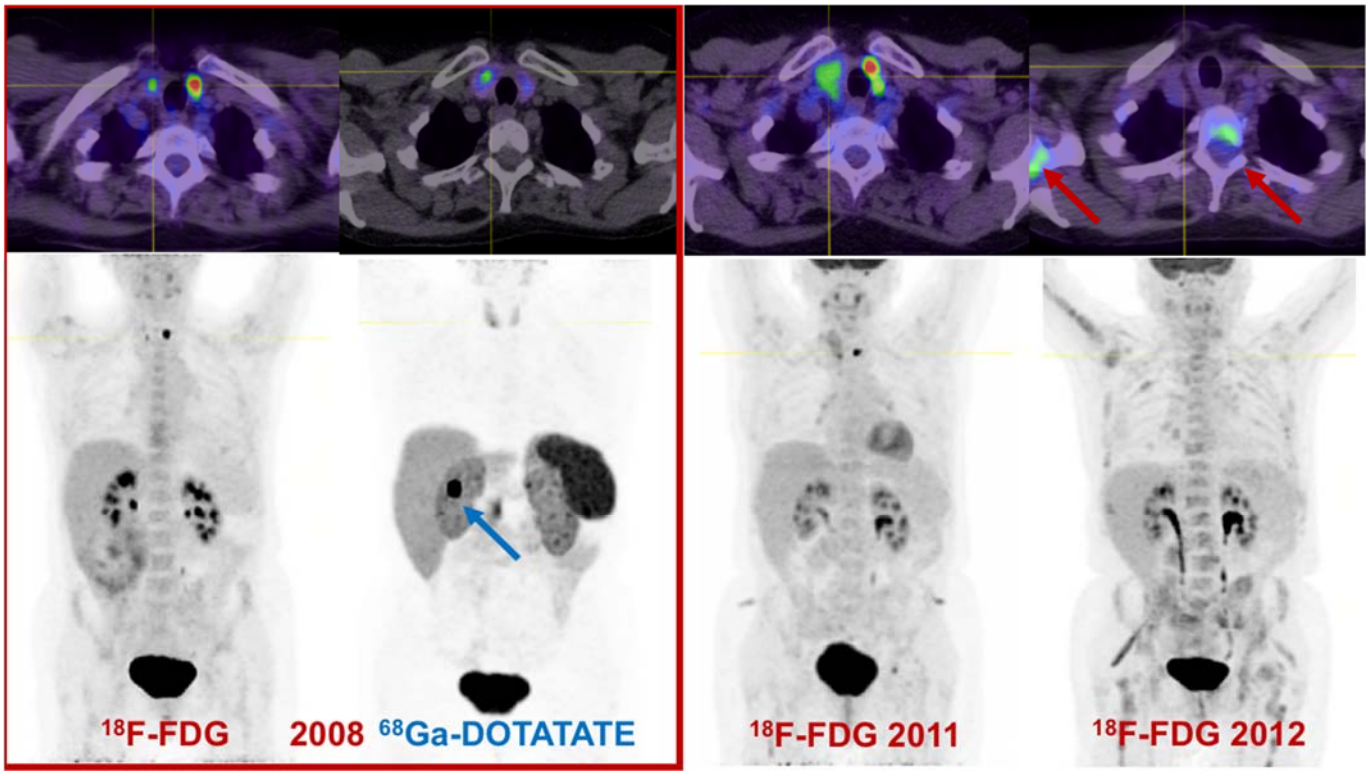
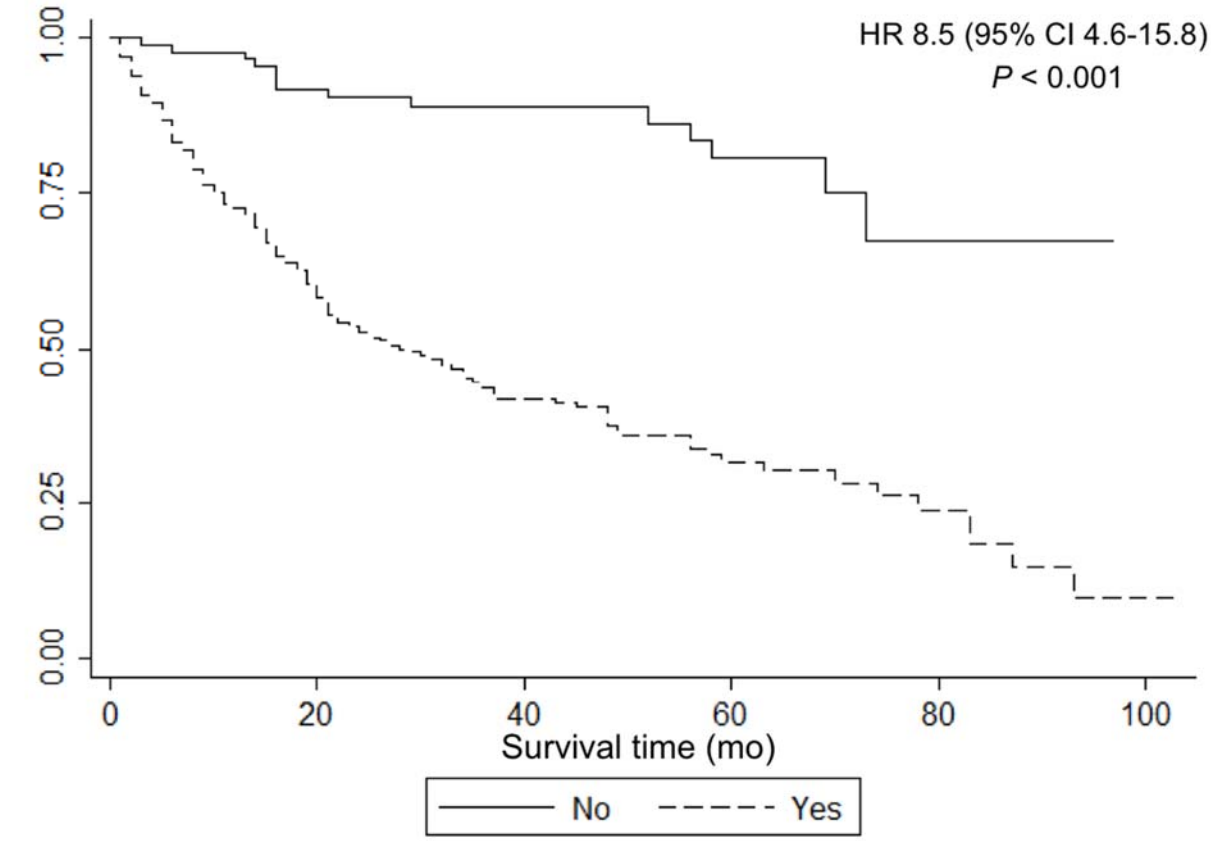
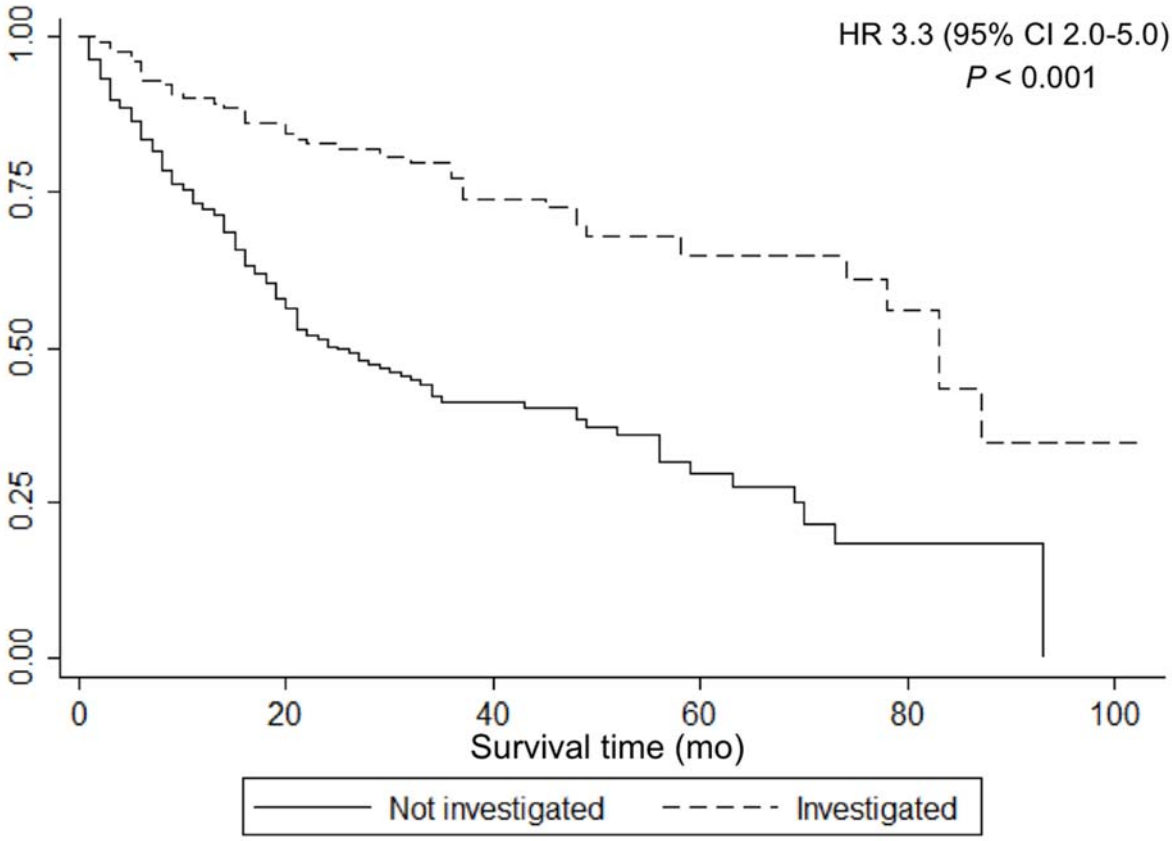


FIGURE 2. FDG PET/CT performed in a 61-year-old woman with metastatic duodenal carcinoid tumor (blue arrow; Grade 2, Ki,67 15%) showed mildly avid (SUVmax 4.4) right thyroid nodule and intensely avid (SUVmax 16) left thyroid nodule. ^{68}Ga-DOTATATE PET/CT revealed concordant mild DOTATATE uptake in the right thyroid nodule and evaluation for medullary thyroid carcinoma was recommended. Subsequent PET directed biopsy of the mildly FDG / DOTATATE avid thyroid nodule confirmed progressive medullary thyroid carcinoma with extrathyroidal extension and lymphovascular invasion. Total thyroidectomy confirmed the intensely FDG-avid left thyroid nodule was a benign follicular adenoma. The patient passed away approximately 18 months later due to progressive metastatic medullary thyroid cancer (red arrows).

A


HR 8.5 (95% CI 4.6-15.8)
P < 0.001
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
Survival time (mo)
No
Yes

B


HR 3.3 (95% CI 2.0-5.0)
P < 0.001
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
Survival time (mo)
Not investigated
Investigated

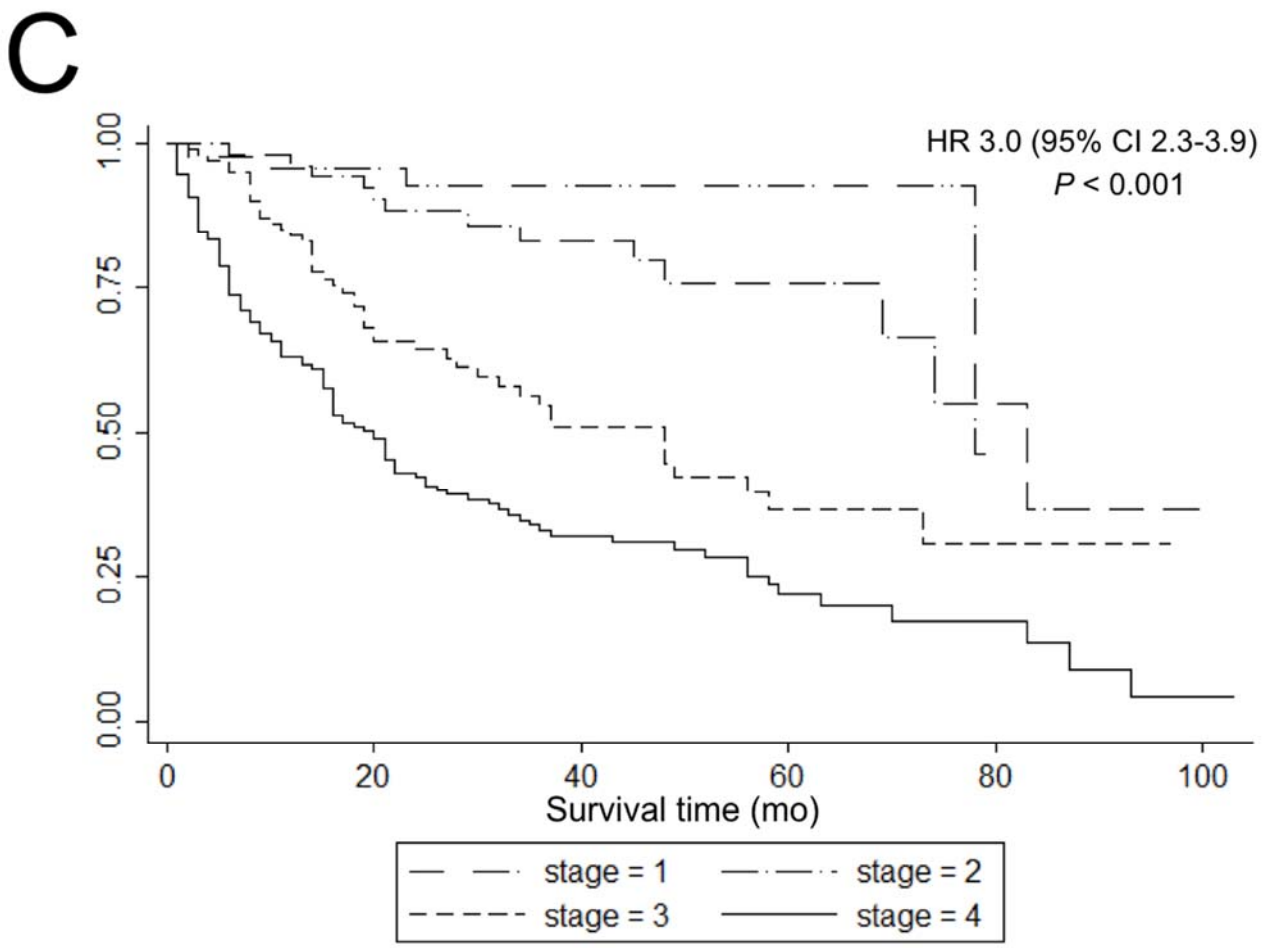


FIGURE 3A. Kaplan Meier survival distribution of patients *with* FDG-avid (SUVmax>3) primary disease at time of identification of FDG-avid TI on index PET/CT (Yes, dashed line) and *without* FDG-avid primary disease (No, solid line). FIGURE 3B. Kaplan Meier survival distribution among patients who *did not* undergo cytological or histopathologic investigation of FDG-avid TI (solid line), and those patients who *did* undergo further investigation (dashed line). FIGURE 3C. Kaplan Meier survival distribution of patients stratified according to AJCC stage of primary malignancy, stage I (long dash), stage II (dash-dot), stage III (short dash) and stage IV (solid line).

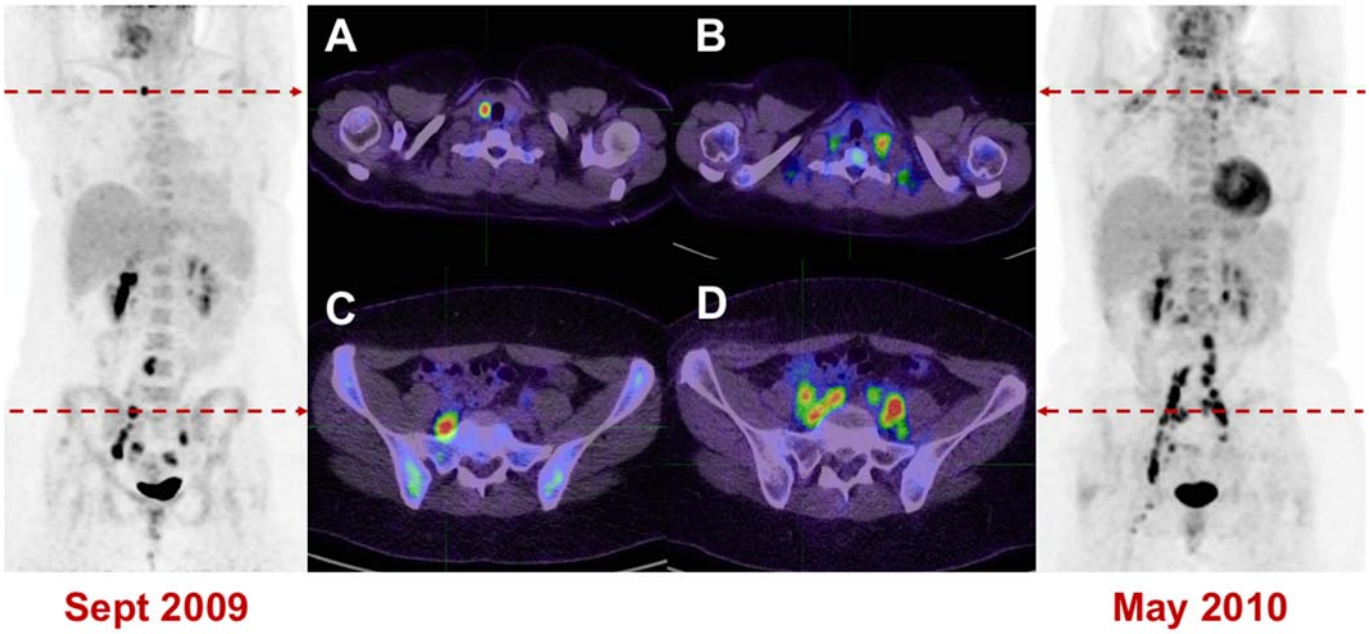


FIGURE 4. Intensely FDG-avid TI (SUVmax 16) was identified on a staging FDG PET/CT scan of a 28-year-old woman with Stage IIIB poorly differentiated cervical carcinoma & persistent FDG-avid pelvic nodal disease. Ultrasound-guided cytologic evaluation demonstrated papillary thyroid carcinoma treated with total thyroidectomy (5mm PTC with no adverse features). Upper images demonstrate (A) baseline FDG-avid thyroid nodule & (B) subsequent cervical carcinoma metastases to supraclavicular nodes. Lower images demonstrate (C) baseline FDG-avid pelvic lymphadenopathy with (D) subsequent disease progression. She passed away 10 months after the baseline PET/CT scan from progression of metastatic poorly differentiated cervical carcinoma.

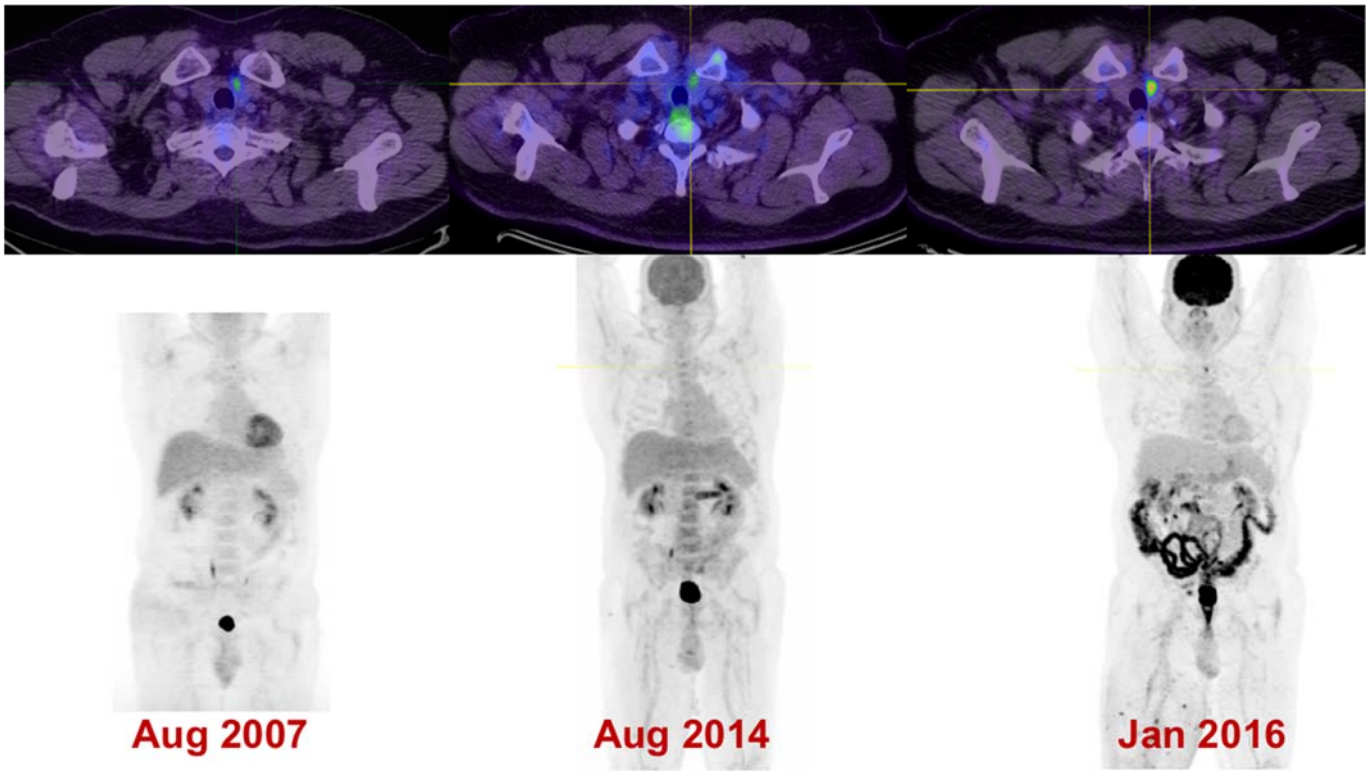


FIGURE 5. Mildly avid FDG-avid TI (SUVmax 3.1) was initially identified on staging FDG PET/CT of a 59-year-old man with metastatic melanoma in 2007. FNA (performed to exclude metastatic melanoma) confirmed an incidental papillary thyroid malignancy which remains stable under surveillance imaging and of limited clinical significance in the setting of metastatic melanoma under active treatment.

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

TABLE 1. Baseline demographic and clinical data of study population.

Patients with follow-up > 12 months or death *(months)*	**N=362**
Follow-up	
- *Median*	24
- *Range*	1-103
Survival	
- *Median*	20
- *Range*	0-93
Survival status at last follow-up, *N (%)*	
Alive	181 (50)
Death	181 (50)
- *Primary cancer*	*166 (45.9)*
- *Incidental FDG-avid TI*	*1 (0.3)*
- *Non-maligant aetiology*	*13 (3.6)*
FDG-avid TI status at last follow-up, *N (%)*	
Malignant TI	47 (13)
- *Observation*	*11 (3)*
- *No clinically evident disease*	*31 (9)*
- *Recurrent/metastatic structural disease*	*1 (0.3)*
- *Metastasis (from underlying malignancy)*	*4 (1)*
Non-diagnostic/indeterminate FNA	12 (3)
Benign TI	72 (20)
Not investigated	231 (64)

TABLE 2. Summary of patient follow-up & clinical outcome data.

Independent predictors	Simple logistic regression, Crude OR (95%CI)	Multivariate logistic regression, Adjusted OR* (95%CI)
FDG avidity (Non-thyroid malignancy)	8.5 (4.6-15.8)	4.0 (2.0-8.2)
AJCC Stage	3.0 (2.3-3.9)	2.5 (1.8-3.3)
Not-Investigated	3.3 (2-5)	1.7 (1.04 -3.3)
Non-thyroid malignancy		
- *Lymphoma*	0.3 (0.1-0.5)	0.3 (0.2-0.8)
- *Lung*	1.7 (0.9-3.2)	1.3 (0.6-2.7)
- *Colorectal*	1.1 (0.5-2.2)	1.3 (0.6-3.1)
- *Melanoma*	1.5 (0.7-3.3)	1.1 (0.5-2.8)
- *Others*	1	1
Age	1.0 (0.99-1.01)	1.0 (0.98-1.02)
Gender		
- *Female*	1	1
- *Male*	1.0 (0.7-1.6)	1.1 (0.6-1.8)

TABLE 3. Results of simple and multivariate logistic regression – outcome death.

Malignant cases, *N (%)*	**N=47**
Malignant on FNA alone	11 (23)
Papillary	24 (51)
Follicular	1 (2)
Metastasis (from underlying malignancy)	4 (9)
Medullary	2 (4)
Hurthle cell Ca / Oncocytic variant	5 (11)
Malignancy histological features	
Size *(mm)*	
- *Median* - *Range*	*15* *2-50*
Vascular invasion, *N (%)*	3 (6)
Capsule invasion, *N (%)*	9 (18)

TABLE 4. Pathologic characteristics of FDG-avid thyroid incidentalomas.