Phil. J. Internal Medicine, 47: 71-75, March-April, 2009

PREVALENCE OF MALIGNANCY IN PATIENTS WITH THYROID INCIDENTALOMAS DETECTED BY ^{18}F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY

Juan Maria Ibarra O. Co, M.D.,* Michael L. Villa, M.D., FPCP**
and Jonas Y. Santiago, M.D.***

ABSTRACT

***Background*: Thyroid incidentalomas detected by ^{18}F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) have been reported in 1.1 to 2.9% of scans performed. Previous studies have determined the prevalence of thyroid malignancy in these patients to be 14-72%.**

***Objective*: We undertook a retrospective study to determine the prevalence of thyroid incidentalomas in our center, and evaluated the corresponding prevalence for malignancy in these patients.**

***Results*: A total of 2,912 FDG-PET scans were performed on 1,855 patients, of which 56 (3.0%) presented with a thyroid incidentaloma (40 focal and 16 diffuse). Among the 22 patients who had an ultrasound, 15 presented with solid nodules (10 focal and 5 diffuse), while 5 were negative for any lesions (4 focal and 1 diffuse). Of 13 patients who had a subsequent FDG-PET scan, 8 had resolution of the hypermetabolic foci (61.5%), of which 5 were focal and 3 diffuse. Only 1 of 6 incidentalomas whose histological diagnoses were available showed malignancy (papillary carcinoma). Other cytologic diagnoses include colloid goiter and lymphocytic thyroiditis.**

***Conclusion*: The prevalence of thyroid malignancy in focal incidentalomas is 1 in 12 (8.3%) and 1 in 17 in all incidentalomas (5.9%). Our experience indicates that the prevalence rates are much lower than that previously reported. Nevertheless, the prevalence rates are significantly elevated to warrant further evaluation, including an imaging procedure and fine needle aspiration biopsy.**

***Keywords*: Thyroid incidentaloma, thyroid carcinoma, positron emission tomography**

**Alumni, Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, St. Luke's Medical Center*

***Chief of Section, Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, St. Luke's Medical Center*

****Chairman, Department of Nuclear Medicine, St. Luke's Medical Center, Head, Positron Emission Tomography Center, St. Luke's Medical Center, Assistant Professor I, St. Luke's College of Medicine William H. Quasha Memorial*

Reprint request to: Juan Maria Ibarra O. Co, M.D., Department of Nuclear Medicine, St. Luke's Medical Center, Office Address: Medical Arts Building Room 122, St. Luke's Medical Center, E. Rodriguez Sr Blvd, Quezon City, Home: Juan Maria Ibarra O. Co, 35 Madison St, North Greenhills, San Juan, Metro Manila, 1503 Philippines, Contact number: +63 (917) 476-9095

INTRODUCTION

Positron emission tomography (PET) is a non-invasive method for screening and evaluating the whole body for various kinds of malignancies.[1] It requires the use of molecules that are labeled with radioactive nuclides, among which ^{18}F-Fluorodeoxyglucose is most commonly used. Because cancer cells exhibit increased rate of glycolysis, ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) is able to assess a fundamental alteration in the cellular metabolism of glucose that is common to all neoplasms. Increased cellular glucose uptake, and likewise ^{18}F-Fluorodeoxyglucose, is one of the key alterations associated with the high glycolytic rate of cancer cells.[2]

Incidentalomas have been reported on FDG-PET. A thyroid incidentaloma is defined as a newly identified thyroid lesion encountered during an imaging study.[3] One small series suggests a high rate of cancers in these incidentalomas, in which 5 of 7 patients (71.43%) presented with a malignant histology.[4] Larger studies have reported prevalence rates ranging from 14% to 50%. These studies are summarized in Table I.[3-11]

Corresponding standard uptake values (SUV) of incidentalomas are available, although its use in differentiating benign from malignant lesions has not been established. Kim *et al.* reported that there was no significant difference in maximum SUV between benign and malignant nodules, while Kang *et al.* concluded that incidentalomas with high standard uptake values (SUV) carry a higher risk of malignancy.[3,7] De Geus-Oei *et al.* recommended that SUVs not be relied on in the discrimination between malignant and benign thyroid lesions.[12]

Since its inception in 2001, the FDG-PET scan of the St. Luke's Medical Center in Manila has been used in a large number of patients in the region. Many thyroid incidentalomas have been discovered during the seven-year period, although few have undergone further evaluation. The objectives of the study are to identify the prevalence of thyroid incidentalomas identified by FDG-PET and the prevalence of malignancy in these patients.

MATERIALS AND METHODS

Subjects

The data and images from all FDG-PET studies conducted from 10 January 2002 to 31 December 2007 were analyzed retrospectively. FDG-PET is performed at our institution for several indications: as a cancer-screening program in presumptively healthy subjects; as the initial evaluation for a tumor visualized by another imaging procedure; as a method for establishing tumor extent or staging; as a means for assessing a patient's response to cancer treatment; and as a tool for determining tumor recurrence in patients treated for malignancies.

All scans during the study period in which a thyroid incidentaloma was reported were retrieved for inclusion in the study. Other data from the subjects included in the study were collected from the institution's central computer and physicians records, including results from laboratory procedures and other imaging studies. Subjects were grouped according to the appearance of the incidentaloma (focal vs. diffuse). Patients with pre-existing thyroid carcinoma were excluded.

FDG-PET Method

FDG-PET scans were obtained on a whole body PET scanner (GE Advance Nxi PET Scanner). All patients fasted for at least 6 hours prior to the study. Image acquisition for the whole body scan was performed from the head to the mid-thigh 60 minutes after administration of 10 to 20mCi ^{18}F-FDG. 5-minute positron emission and 3 minute transmission images were acquired. Transmission, attenuation and non-attenuation corrected images were processed and read. Maximum weight normalized SUVs were calculated around each lesion. All FDG-PET scans were interpreted by one reader (JS).

RESULTS

We reviewed 2,912 FDG-PET scans performed on 1,855 patients, and identified 56 (3%) with thyroid incidentalomas. The characteristics of selected patients with focal and diffuse thyroid incidentalomas are presented in Tables II and III, respectively. The evaluation of breast, lung and colon cancers were the most common indications for requesting a FDG-PET scan in these patients. The age distribution is presented in Figure 1.

Table I. Summary of Prevalence Rates of Malignancy in FDG-PET-Positive Thyroid Incidentalomas

Author	Prevalence rate of focal thyroid incidentaloma	Number of patients with focal thyroid incidentalomas and available histology	Prevalence rate of thyroid malignancy
Are *et al* [5]	2.9%	57	42%
Chen *et al* [6]	1.2%	50	14%
Kim *et al* [7]	1.1%	32	50%
King *et al* [8]	–	22	14%
Kang *et al* [3]	1.6%	15	26.7%
Cohen *et al* [9]	2.3%	15	47%
Chu *et al* [10]	1.2%	14	28.6%
Nam *et al* [11]	2.8%	12	41.7%
Van Den Bruel *et al* [4]	–	7	71.43%

Table II. Characteristics of Selected Patients with Focal Thyroid Incidentalomas. These Patients Underwent Any of the Following: Biopsy, A Normal Imaging Procedure or Resolution of Metabolic Foci on Repeat FDG-PET.

Age/Sex	SUV	Imaging	Cytology (FNAB)	Resolution on repeat FDG-PET
30/F	5.9	Nodules and cysts	Papillary CA	–
41/F	4.8	Complex nodules	Colloid goiter	–
43/F	6.9	Complicated cyst	Colloid goiter	–
56/F	5.5	–	Colloid goiter	–
51/F	3.2	Normal	–	–
58/M	3.6	Normal	–	–
68/M	8.7	Normal	–	–
69/M	5.6	Normal	–	Yes
50/F	4	–	–	Yes
21/F	6	–	–	Yes
68/F	5.4	–	–	Yes
65/F	R 6.5 / L 4.9	Nodules	–	Yes

Table III. Characteristics of Selected Patients with Diffuse Thyroid Incidentalomas. These Patients Underwent Any of the Following: Biopsy, A Normal Imaging Procedure or Resolution of Metabolic Foci on Repeat FDG-PET.

Age/Sex	Imaging	Cytology	Resolution on repeat FDG-PET
53/F	–	Colloid goiter	–
62/F	–	Lymphocytic thyroiditis	Yes
47/F	Normal	–	–
48/M	–	–	Yes
68/M	–	–	Yes

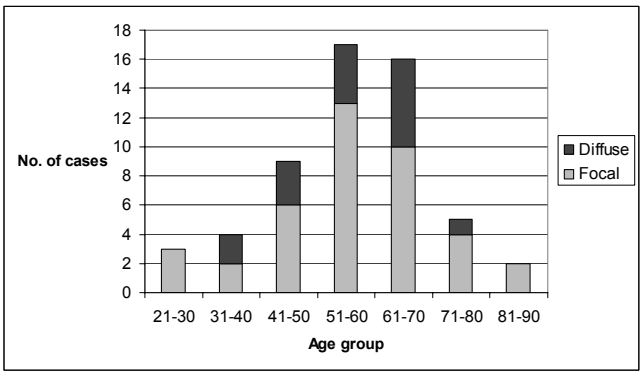

Figure 1. Age Distribution of Subjects with Thyroid Incidentalomas on FDG-PET

Of the incidentalomas, 40 (2.2%) were of the focal type and 16 (0.9%) were of the diffuse type. Among the patients with focal thyroid incidentalomas, 30 were female and 10 were male, with an average age of 56.8 years (range 21-89 years). Sixteen of the thyroid incidentalomas were located in the right lobe, 20 in the left lobe, and 4 in both lobes. The average standard uptake value (SUV) for all foci was 8.0 (range 2.9-19.8). Of the 15 patients whose thyroid ultrasound or CT scan was available, only 10 (66.67%) had a corresponding thyroid nodule. One (6.67%) patient had a complicated cyst, while the remaining 4 (26.67%) did not have any thyroid lesions.

In the patients with the diffuse thyroid incidentalomas, 11 were female and 5 were male. The average age was 57 years (range 36-69 years). Seven patients had a subsequent thyroid ultrasound done, among which five (71.4%) presented with a thyroid nodule or mass, one (14.3%) with a thyroid cyst and one (14.3%) with an unremarkable thyroid. Figure 2 shows an image of a patient with a diffuse thyroid incidentaloma.

Among the 13 patients who had a subsequent FDG-PET scan, 8 (61.5%) had resolution of the hypermetabolic foci (5 of which were of the focal type, and 3 of the diffuse type). Six patients underwent fine needle aspiration biopsy (4 from the focal group and 2 from the diffuse group). Fine needle aspirations were performed by different physicians, but examined by one cytologist. Both patients from the diffuse group had benign cytology (colloid goiter and lymphocytic thyroiditis). Three patients from the focal group were found to have colloid goiter on cytology, while one patient, a 34 year-old female with no prior malignancy and a maximum SUV of 5.9, presented with papillary cancer (Figure 3). The malignancy was later confirmed by surgical histology.

Figure 2. The Patient is A 68/F Who Underwent FDG-PET for Evaluation of A Previously Diagnosed Rectal Carcinoma. Diffuse Increased Uptake was Noted in Both Thyroid Lobes

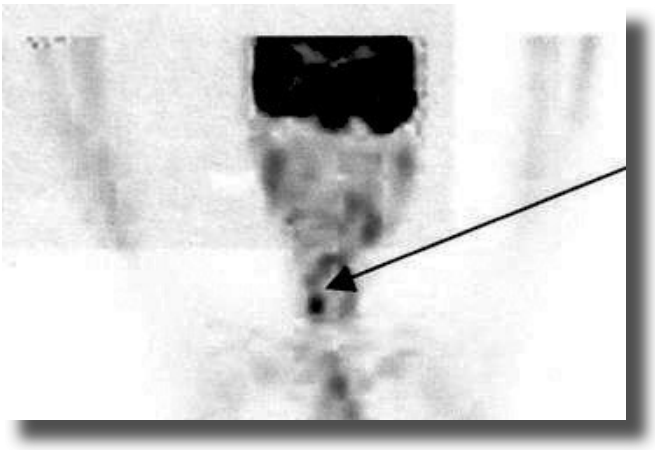

Figure 3. Patient is A 30/F Who Underwent FDG-PET As A Screening Procedure for Malignancy. A Hypermetabolic Focus was Noted On The Right Thyroid, with SUV 5.9. Fine Needle Aspiration Biopsy and Surgery were Performed, and Histopathology Revealed A Thyroid Carcinoma

DISCUSSION

Thyroid nodules are common disorders in Endocrinology. Prevalence studies estimate the rate of palpable thyroid nodules to be 3-7% in North America.[13] The prevalence of thyroid nodules on ultrasound has been estimated to be 20-76%. Despite the high frequency, malignant lesions account for only 5% of all thyroid nodules, independent of size.[14]

The prevalence rate of thyroid incidentalomas on FDG-PET ranges from 1.1-2.9% in an unselected population, and 1.6% in healthy subjects.[3-11] There has been no report about the prevalence of FDG-

PET-positive-thyroid incidentalomas in the general population. Given the high cost of a FDG-PET procedure and the low prevalence of an incidentaloma, it is unlikely that its use as a screening procedure for thyroid malignancies will be of significant benefit in the general population.

Previous studies on thyroid incidentalomas have centered only on focal hypermetabolic lesions rather than the diffuse type. In our study, 71.4% of the patients from the diffuse group who underwent a thyroid ultrasound had a solid nodule or mass, compared to only 66.67% from the focal group. Although only two of these patients had a subsequent thyroid biopsy, of which both were benign, we believe that further work-up of these incidentalomas remains warranted.

A number of patients with incidentalomas in our study presented with negative findings on ultrasound or CT scan as part of further evaluation (26.7% in the focal group, and 14.3% in the diffuse group). Such occurrence has also been reported by Yi *et al.*, in which 2 of 6 patients with FDG-PET thyroid incidentalomas were negative for nodules on CT or sonogram.[15] These lesions were therefore considered benign, and biopsy not indicated. The management guidelines for patients with thyroid nodules, as developed by the American Thyroid Association, recommends no further work-up for ultrasound-negative thyroid glands.[16] It may be acceptably safe to assume that despite hypermetabolic activity on FDG-PET, the absence of a lesion on ultrasound or CT is adequate evidence to rule out a malignant lesion.

Among subjects who had a subsequent FDG-PET scan, 61.5% had resolution of a reported hypermetabolic focus. Such occurrences have not been reported in the literature. Given the very high negative predictive value for detecting malignancy in the preoperative evaluation of thyroid nodules, the assumption that such foci are truly benign should be considered.[13,17-19] The question of why a foci was initially noted prompts us to review the principles of FDG-PET. FDG-PET preferably picks up malignant lesions because of the increased rates of glycolysis and glucose uptake. One of the glucose transport proteins, GLUT 1, has been found to be expressed at high levels in a variety of cancers. By immunostaining, GLUT 1 expression was frequently detectable in differentiated and anaplastic thyroid carcinoma, but not in benign nodules or normal thyroid.[4,20] FDG is not cancer specific, and will accumulate in sites with high levels of metabolism and glycolysis, such as in hyperactivity, active inflammation and tissue repair, which may explain the transient hypermetabolic foci seen in some patients.[2,21]

With the addition of several patients who may be assumed to have a non-malignant thyroid, either due to the absence of a lesion on ultrasound or CT scan or due to resolution of the focus on a subsequent FDG-PET scan, the prevalence of thyroid malignancy in focal incidentalomas is 1 in 12 (8.3%) and 1 in 17 in all incidentalomas (5.9%). Our experience indicates that the prevalence rates are much lower than that previously reported.

Despite these relatively lower results, the prevalence rates are significantly elevated to warrant further evaluation, including an imaging procedure, such as ultrasound, and corresponding fine needle aspiration biopsy.

Limitations of the study include the limited availability and potential inaccuracy of medical records used in a retrospective study. There is also a lack of priority in performing further diagnostic tests on thyroid incidentalomas, mainly because FDG-PET scans are requested for the evaluation of another malignancy, and priority is focused on the primary cancer. A more appropriate setting for such a study would be a prospective study.

CONCLUSION

Of the 1,855 patients who underwent FDG-PET scanning showed thyroid incidentaloma (40 focal and 16 diffuse). Patients who had an ultrasound from both groups presented with solid nodules (66.67% focal and 71.4% diffuse), indicating that further work-up may be warranted in both groups. Despite the lack of a definitive cytological or histopathological diagnosis in many patients, the assumption that malignancy can be ruled out in certain subjects indicates that the prevalence of thyroid malignancy in focal incidentalomas is 1 in 12 (8.3%) and 1 in 17 in all incidentalomas (5.9%). Our experience suggests that the prevalence rates are much lower than that previously reported.

REFERENCES

1. Strauss LG, Conti PS: The Application of PET in Clinical Oncology. J Nucl Med, 32(4):623, 1991.

2. Fletcher JW, Djulbegovic B, Soares HP, Siegel BA, Lowe VJ, Lyman GH, Coleman RE, Wahl R, Paschold JC, Avril N, Einhorn LH, Suh WW, Samson D, Delbeke D, Gorman M, Shields AF: Recommendations on the Use of ^{18}F-FDG PET in Oncology. J Nucl Med, 49(3):480, 2008.

3. Kang KW, Kim SK. Kang HS, Lee ES, Sim JS, Lee IG, Jeong SY, Kim SW: Prevalence and Risk of Cancer

of Focal Thyroid Incidentaloma Identified by ^{18}F-Fluorodeoxyglucose Positron Emission Tomography for Metastasis Evaluation and Cancer Screening in Healthy Subjects. J Clin Endocrinol Metab, 88:4100, 2003.

4. Van den Bruel A, Maes A, De Potter T, Mortelmans L, Drijkoningen M, Van Damme B, Delaere P, Bouillon R: Clinical Relevance of Thyroid Fluorodeoxyglucose-Whole Body Positron Emission Tomography Incidentaloma. J Clin Endocrinol Metab, 87(4):1517, 2002.

5. Are C, Hsu JF, Ghossein RA, Schoder H, Shah JP, Shaha AR: Histological Aggressiveness of Fluorodeoxyglucose Positron-Emission Tomogram (FDG-PET)-Detected Incidental Thyroid Carcinomas. Ann Surg Oncol, 14(11):3210, 2007.

6. Chen YK, Ding HJ, Chen KT, Chen YL, Liao AC, Shen YY, Su CT, Kao CH: Prevalence and Risk of Cancer of Focal Thyroid Incidentaloma Identified by ^{18}F-Fluorodeoxyglucose Positron Emission Tomography for Cancer Screening in Healthy Subjects. Anticancer Res, 25(2B):1421, 2005.

7. Kim TY, Kim WB, Ryu JS, Gong G, Hong SJ, Shong YK: ^{18}F-Fluorodeoxyglucose Uptake in Thyroid from Positron Emission Tomogram (PET) for Evaluation in Cancer Patients: High Prevalence of Malignancy in Thyroid PET Incidentaloma. Laryngoscope, 115(6):1074, 2005.

8. King DL, Stack BC: Incidence of Thyroid Carcinoma in Fluorodeoxyglucose Positron Emission Tomography-Positive Thyroid Incidentalomas. Otolaryngol Head Neck Surg, 137(3):400, 2007.

9. Cohen MS, Arslan N, Dehdashti F, Doherty GM, Lairmore TC, Brunt LM, Moley JF: Risk of Malignancy in Thyroid Incidentalomas Identified by Fluorodeoxyglucose-Positron Emission Tomography. Surgery, 130(6):941, 2001.

10. Chu QD, Connor MS, Lilien DL, Johnson LW, Turnage RH, Li BD: Positron Emission Tomography (PET) Positive Thyroid Incidentaloma: The Risk of Malignancy Observed in a Tertiary Referral Center. Am Surg, 72(3):272, 2006.

11. Nam SY, Roh JL, Kim JS, Lee JH, Choi SH, Kim SY: Focal Uptake of (18)F-Fluorodeoxyglucose by Thyroid in Patients with Nonthyroidal Head and Neck Cancers. Clin Endocrinol (Oxf), 67(1):135, 2007.

12. De Geus-Oei LF, Pieters GFFM, Bonenkamp JJ: Mudde AH, Bleeker-Rovers CP, Corstens FHM, Oyen WJG. ^{18}F-FDG PET Reduces Unnecessary Hemithyroidectomies for Thyroid Nodules with Inconclusive Cytologic Results. J Nucl Med, 47:770, 2006.

13. Hegedüs L. The Thyroid Nodule. N Engl J Med, 351:1764, 2004.

14. AACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. Endocr Pract, 12:63, 2006.

15. Yi JG, Marom EM, Munden RF, Truong MT, Macapinlac HA, Gladish GW, Sabloff BS, Podoloff DA: Focal Uptake of Fluorodeoxyglucose by the Thyroid in Patients Undergoing Initial Disease Staging with Combined PET/CT for Non–Small Cell Lung Cancer. Radiology, 236:271, 2005.

16. Cooper DS, Doherty GM, Haugen BR. Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM: Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid, 16(2):1, 2006.

17. Sebastianes FM, Cerci JJ, Zanoni PH, Soares J Jr, Chibana LK, Tomimori EK, de Camargo RY, Izaki M, Giorgi MC, Eluf-Neto J, Meneghetti JC, Pereira MA: Role Of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography in Preoperative Assessment of Cytologically Indeterminate Thyroid Nodules. J Clin Endocrinol Metab, 92: 4485, 2007.

18. Kresnik E, Gallowitsch HJ, Mikosch P, Stettner H, Igerc I, Gomez I, Kumnig G, Lind P: Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography in the Preoperative Assessment of Thyroid Nodules in an Endemic Goiter Area. Surgery, Mar;133(3):294, 2003.

19. Kim JM, Ryu JS, Kim TY, Kim WB, Kwon GY, Gong G, Moon DH, Kim SC, Hong SJ, Shong YK. ^{18}F-Fluorodeoxyglucose Positron Emission Tomography Does Not Predict Malignancy in Thyroid Nodules Cytologically Diagnosed as Follicular Neoplasm. J Clin Endocrinol Metab, 92:1630, 2007.

20. Haber RS, Weiser KR, Pritsker A, Reder I, Burstein DE: GLUT1 Glucose Transporter Expression in Benign and Malignant Thyroid Nodules. Thyroid, 7(3):363, 1997.

21. http://www.med.harvard.edu/JPNM/chetan/basics/basics.html accessed 22 Jan 2008.