Analysis of predictability of F-18 fluorodeoxyglucose-PET/CT in the recurrence of papillary thyroid carcinoma

Suk Kyeong Kim1, Young So2,3, Hyun Woo Chung2, Young Bum Yoo4, Kyung Sik Park4, Tae Sook Hwang5, Bokyung Kim3,6 & Won Woo Lee7

1Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea
2Department of Nuclear Medicine, Konkuk University School of Medicine, Seoul, Korea
3Bioimaging Translational Open Innovation Center, Konkuk University School of Medicine, Seoul, Korea
4Department of Surgery, Konkuk University School of Medicine, Seoul, Korea
5Department of Pathology, Konkuk University School of Medicine, Seoul, Korea
6Department of Physiology, Konkuk University School of Medicine, Seoul, Korea
7Department of Nuclear Medicine, Seoul National University College of Medicine, Seoul, Korea

Keywords
F-18 fluorodeoxyglucose-positron emission tomography/computed tomography, lymph node metastasis, papillary thyroid carcinoma, prognosis, recurrence

Abstract
Whether preoperative F-18 fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) can predict recurrence of papillary thyroid carcinoma (PTC) remains unclear. Herein, we evaluated the potential of primary tumor FDG avidity for the prediction of tumor recurrence in PTC patients. A total of 412 PTC patients (72 males; 340 females; age: 47.2 ± 12.2 years; range: 17–84 years) who underwent FDG-PET/CT prior to total thyroidectomy (n = 350), subtotal thyroidectomy (n = 2), or lobectomy (n = 60) from 2007 to 2011 were analyzed. The predictive ability for recurrence was investigated among various clinicopathological factors, BRAFV600E mutation, and preoperative FDG avidity of the primary tumor using Kaplan–Meier (univariate) and Cox proportional hazards regression (multivariate) analyses. Of the 412 patients, 19 (4.6%) experienced recurrence, which was confirmed either by pathology (n = 17) or high serum thyroglobulin level (n = 2), during a mean follow-up period of 43.9 ± 16.6 months. Of the 412 patients, 237 (57.5%) had FDG-avid tumors (maximum standardized uptake value, 7.1 ± 7.0; range: 1.6–50.5). Kaplan–Meier analysis revealed that tumor size (P < 0.0001), larger tumor size (P < 0.0001), and more frequent extrathyroidal extension (P < 0.0001) were significant predictors for recurrence. However, only LN stage remained a significant predictor in the multivariate analysis (P < 0.0001). Patients with FDG-avid tumors had higher LN stage (P < 0.0001), larger tumor size (P < 0.0001), and more frequent extrathyroidal extension (P < 0.0001). In conclusion, FDG avidity of the primary tumor in preoperative FDG-PET/CT could not predict the recurrence of PTC. LN stage was the only identified predictor of PTC recurrence.

Introduction
In differentiated thyroid carcinoma patients, the role of F-18 fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) has been limited primarily to postoperative surveillance. FDG-PET/CT is known to be useful in the follow-up of differentiated thyroid carcinoma patients with elevated serum thyroglobulin levels and negative radioiodine whole body scans [1, 2]. Furthermore, some reports have shown that FDG-PET/CT could change the treatment plan in postoperative differentiated thyroid carcinoma patients [3, 4], and that the prognosis of metastatic thyroid carcinoma in the postoperative setting could be effectively predicted using preoperative FDG-PET/CT [5, 6]. However, the role of preoperative FDG-PET/CT in differentiated thyroid carcinoma has not yet been established, and FDG-PET/CT is currently not recommended...
in the preoperative work-up [7], owing to the fact that it does not appear to provide significant additional information on the T and N stages [8, 9] or supplemental information on the differential diagnosis of indeterminate thyroid nodules in these patients [10, 11]. On the contrary, a small number of studies have reported that preoperative FDG-PET/CT could reduce unnecessary surgery in patients with indeterminate thyroid nodules [12, 13]. Approximately one third of all incidentally detected thyroid nodules on FDG-PET/CT was malignant, thus requiring further evaluation [14, 15]. Furthermore, the FDG avidity of differentiated thyroid carcinoma has been shown to be associated with tumor size, lymph node (LN) metastasis, extrathyroidal extension, and lymphovascular invasion [16, 17], and these factors are known to be associated with a poor prognosis [9, 18]. Therefore, it can be speculated that preoperative FDG-PET/CT may be useful for the prediction of the prognosis of differentiated thyroid carcinoma.

In this study, we evaluated whether FDG avidity of the primary tumor upon preoperative FDG-PET/CT is a predictive factor for the recurrence of papillary thyroid carcinoma (PTC).

Materials and Methods

Patients

This study was approved by the Institutional Review Board. Patient consent was not required in this study. The records of patients with newly diagnosed PTC who underwent FDG-PET/CT prior to thyroid surgery at our institution from January 2007 to December 2011 were reviewed. We identified a total of 434 patients with PTC who underwent FDG-PET/CT within 3 months prior to operation. Of these 434 patients, 4 patients with initial distant metastases (3 lung metastases, 1 bone metastasis) were excluded. Eighteen patients who showed diffuse hypermetabolism at the thyroid gland on preoperative FDG-PET/CT were also excluded, since their primary tumor sites in the thyroid gland were difficult to determine. Therefore, a total of 412 PTC patients who underwent FDG-PET/CT prior to operation were finally enrolled in this study.

FDG-PET/CT scan procedure

All patients fasted for at least 6 h before FDG (4.8 MBq/kg) were intravenously injected in the resting state. An intravenous CT contrast agent was not administered in this study. The blood glucose level was checked in all patients and was lower than 120 and 200 mg/dL for non-diabetic and diabetic patients, respectively. PET/CT images were acquired 60 min after FDG injection with a GEMINI scanner (Philips Medical System, Cleveland, OH), with the patient positioned with both arms down. The CT scan comprised dual slice CT. The scan field of view was from the skull base to the mid-thigh level. The CT scan was performed using a standardized protocol of 120 kV X-ray voltage, 50 mA tube current, a 0.75-sec tube rotation time per rotation, 1.5 pitch, and a section thickness of 5 mm. Immediately after the CT scan, PET images were acquired using a conventional three-dimensional protocol with 2.5 min per frame.

Interpretation and analysis of FDG-PET/CT scan

Two nuclear medicine physicians with more than 10 years experience assessed the FDG-PET/CT images. FDG uptake in PTCs was categorized as FDG-avid tumor if there was a focal discrete FDG uptake in the thyroid that corresponds to the location recorded in pathological reports. If there was no discernible FDG uptake higher than surrounding thyroid tissue, it was categorized as non-FDG-avid tumor. In the case of multifocal tumors, the largest tumor was selected for interpretation. For FDG-avid tumors, the maximum standardized uptake value (SUVmax) was calculated. The SUV was defined as the decay-corrected radioactivity per unit volume divided by the injected radioactivity per body weight of the patient.

Treatment and follow-up of patients

Thyroid surgery was performed within 3 months of FDG-PET/CT. Of the total 412 patients, 350 patients underwent total thyroidectomy, 2 patients underwent subtotal thyroidectomy, and the remaining 60 patients underwent lobectomy. Cervical LN dissection was performed in 375 (91.0%) patients, and the mean number of dissected LNs was 13.2 ± 13.0 (range: 1–95). The BRAFV600E mutation status was evaluated in 301 patients (73.1%) by the pyrosequencing method, as described previously [19].

Radioactive iodine ablation therapy was performed in 302 patients; 71 patients received low-dose radioactive iodine ablation therapy (1.11 GBq), while the remaining 231 patients received high-dose radioactive iodine ablation therapy (up to 7.4 GBq).

The patients were followed by serum thyroglobulin (immunoradiometric assay kit; ZenTech, Angleur, Belgium) and thyroglobulin antibody (radioimmunoassay kit; BRAHMS, Henningsdorf, Germany) level evaluations, radioiodine whole body scan, thyroid ultrasonography, chest posteroanterior radiography, chest CT, and FDG-PET/CT. The mean follow-up period was 43.9 ± 16.6 months (range: 1.9–87.0 months).
Statistical analysis

Statistical analyses were performed to determine the predictive factors for recurrence among tumor size (micronodular vs. macronodular), FDG avidity of the primary tumor, multifocality of the primary tumor, extrathyroidal extension (none vs. microscopic vs. macroscopic), LN stage (pN0 vs. pN1a vs. pN1b), sex, age (<45 vs. ≥45 years), and BRAFV600E mutation status. First, univariate analyses were performed using the Kaplan–Meier method, with the significance of the differences between the disease-free survival curves tested using the log-rank (Mantel–Cox) test. Next, multivariate disease-free survival analysis for independent prognostic factors was performed using a Cox proportional hazards model with the significant univariate variables. Finally, the differences between FDG-avid and non-FDG-avid tumors were analyzed using either the independent sample t-test (tumor size, age) or chi-squared test (multifocality of the primary tumor, extrathyroidal extension, LN stage, sex, and BRAFV600E mutation status). MedCalc version 15.2.2 (MedCalc Software bvba, Ostend, Belgium) was used for the analyses. P < 0.05 was considered to be statistically significant.

Results

Patient characteristics

The clinicopathological characteristics of the 412 PTC patients are summarized in Table 1.

The PTC subtypes were classical, follicular variant, squamous metaplasia, tall cell variant, oncocytic variant, and Warthin-like type in 385 (93.4%), 20 (4.9%), 4 (0.97%), 1 (0.24%), 1, and 1 patients, respectively. Thirty patients had other malignancies, including breast cancer, stomach cancer, colon cancer, lung cancer, hepatocellular carcinoma, ovarian cancer, malignant melanoma, and invasive thymoma in 26, 7, 2, 1, 1, 1, and 1 patients, respectively, whereas there was no case of head and neck cancer. Of all 412 patients, 255 (61.9%) patients had microcarcinoma (≤1 cm), while the remaining 157 (38.1%) patients had macronodular (>1 cm).

The primary tumor sites were visible on FDG-PET/CT in 237 (57.5%) patients, and their mean SUVmax was 7.1 ± 7.0 (range: 1.6–50.5). The clinicopathological characteristics were compared between FDG-avid and non-FDG-avid tumors (Table 2). The size of FDG-avid tumors was greater than that of non-FDG-avid tumors (1.39 ± 0.79 vs. 0.64 ± 0.32 cm, P < 0.0001). Extrathyroidal extension was more frequently observed in FDG-avid tumors (none:microscopic:macroscopic = 116:107:14) compared to non-FDG-avid tumors (none:microscopic:macroscopic = 130:45:0, P < 0.0001). Furthermore, LN stage was higher in FDG-avid than non-FDG-avid patients (P < 0.0001) (Table 2). However, the multifocality of the primary tumor (P = 0.4483), sex (P = 0.5847), age (P = 0.2151), and BRAFV600E mutation status (P = 0.7070) did not significantly differ according to the FDG avidity of the primary tumor (Table 2).

Of the 412 patients, 19 (4.6%) experienced recurrence during the follow-up. The recurrence was confirmed by either pathology of dissected cervical LNs (n = 17) or by a high serum thyroglobulin level (n = 2). Table 3 shows a comparison of the clinicopathological characteristics of recurred versus not recurred PTC patients.

Table 1. Clinicopathological characteristics of the 412 papillary thyroid carcinoma patients.

| Characteristic                        | Value                          |
|---------------------------------------|--------------------------------|
| Sex (male:female)                     | 72:340                         |
| Mean age (range), years               | 47.2 ± 12.2 (17–84)            |
| Operation (TT:STT:L)                  | 350:2:60                       |
| Mean primary tumor size (range), cm   | 1.07 ± 0.74 (0.20–5.0)         |
| Unifocal tumor:multifocal tumor       | 271:141                        |
| Extrathyroidal extension              | 246:152:14                     |
| (none:microscopic:macroscopic)        |                                |
| Lymph node stage (pN0:pN1a:pN1b)      | 214:121:40                     |
| BRAFV600E mutation (+:−)              | 277:24                         |
| RAI ablation (none:low:high)          | 110:71:231                     |
| FDG-avid:Non-FDG-avid tumor           | 237:175                        |

Table 2. Comparison of clinicopathological characteristics between FDG-avid and non-FDG-avid tumors.

|                          | FDG-avid tumors (n = 237) | Non-FDG-avid tumors (n = 175) | P value   |
|--------------------------|--------------------------|-------------------------------|-----------|
| Sex (male:female)        | 44:193                   | 28:147                        | 0.5847    |
| Age (years)              | 47.9 ± 13.2              | 46.4 ± 10.9                   | 0.2151    |
| Operation (TT:STT:L)     | 216:1:20                 | 134:1:40                      | 0.0002    |
| Primary tumor size (cm)  | 1.39 ± 0.79              | 0.64 ± 0.32                   | <0.0001   |
| Unifocal:multifocal tumor| 160:77                   | 111:64                        | 0.483     |
| Extrathyroidal extension (none:macroscopic) | 116:107:14             | 130:45:0                      | <0.0001   |
| Lymph node stage (pN0:pN1a:pN1b) | 108:76:37                | 106:45:3                      | <0.0001   |
| BRAFV600E mutation (+:−)  | 163:9                    | 114:15                        | 0.0700    |
| RAI ablation (none:low:high) | 43:29:165               | 67:42:66                      | <0.0001   |
| Recurrence (+:−)         | 17:220                   | 2:173                         | 0.0077    |

FDG, fluorodeoxyglucose; TT, total thyroidectomy; STT, subtotal thyroidectomy; L, lobectomy; RAI, radioactive iodine.
Univariate analysis (Kaplan–Meier method)

In the Kaplan–Meier analyses, tumor size ($P = 0.0054$), FDG avidity of the primary tumor ($P = 0.0049$), extrathyroidal extension ($P = 0.0212$), and LN stage ($P < 0.0001$) were found to be significant predictors of recurrence. However, multifocality of the primary tumor ($P = 0.1349$), sex ($P = 0.2742$), age ($<45$ vs. $\geq 45$ years) ($P = 0.9968$), and BRAFV600E mutation status ($P = 0.3139$) were not significant predictors of recurrence (Table 4 and Fig. 1).

Table 3. Comparison of clinicopathological characteristics between recurred and not recurred papillary thyroid carcinoma patients.

| Variable                      | Recurred (n = 19) | Not recurred (n = 393) | $P$ value |
|-------------------------------|-------------------|------------------------|-----------|
| Sex (male:female)             | 5:14              | 67:326                 | 0.4656    |
| Age (years)                   | 48.2 ± 15.5       | 47.2 ± 12.1            | 0.7208    |
| Operation (TT:STT:L)          | 332:2:59          | 18:0:1                 | 0.4714    |
| Primary tumor size (cm)       | 1.60 ± 0.98       | 1.05 ± 0.71            | 0.0015    |
| Unifocal:multifocal tumor     | 10:9              | 261:132                | 0.3227    |
| Extrathyroidal extension (none: microscopic: macroscopic) | 6:11:2 | 240:141:12 | 0.0183 |
| Lymph node stage (pN0:pN1a:pN1b) | 1:6:10 | 213:115:30 | $<0.0001$ |
| BRAFV600E mutation (+,-)      | 11:0              | 266:24                 | 0.6689    |
| RAI ablation (none:low:high)  | 2:0:17            | 108:71:214             | 0.0093    |
| FDG-avid:Non-FDG-avid tumor   | 17:2              | 220:173                | 0.0077    |
| SUVmax of FDG-avid tumors     | 7.56 ± 6.79       | 7.08 ± 7.04            | 0.7847    |

TT, total thyroidectomy; STT, subtotal thyroidectomy; L, lobectomy; RAI, radioactive iodine; FDG, fluorodeoxyglucose; SUVmax, maximum standardized uptake value.

Table 4. Univariate analysis results.

| Variable                      | Hazard ratio | 95% confidence interval | $P$ value |
|-------------------------------|--------------|-------------------------|-----------|
| Tumor size                    | 3.6051       | 1.4244–9.1245           | 0.0054    |
| FDG avidity                   | 6.2554       | 2.5182–15.5389          | 0.0049    |
| Mutplicity                    | 1.9577       | 0.7436–5.1544           | 0.1349    |
| Extrathyroidal extension (none vs. microscopic vs. macroscopic) | 2.6130 | 1.2691–5.3799 | 0.0212 |
| LN stage (pN0 vs. pN1a vs. pN1b) | 6.3677 | 3.0470–13.3074 | $<0.0001$ |
| Sex                           | 1.7542       | 0.5287–5.8211           | 0.2742    |
| Age                           | 1.0018       | 0.4071–2.4656           | 0.9968    |
| BRAFV600E mutation            | ND           | ND                      | 0.3139    |

Multivariate analysis (Cox proportional hazards model)

In the Cox proportional hazards model, including significant univariate variables (tumor size, FDG avidity of the primary tumor, extrathyroidal extension, and LN stage), only LN stage was found to be a significant predictive factor of recurrence ($P < 0.0001$, hazard ratio 6.3677, 95% confidence interval 3.0470–13.3074).

Discussion

In the current study, preoperative FDG-PET/CT was not proven to be useful for the prediction of PTC recurrence. However, the FDG avidity of the primary tumor was found to be highly associated with known prognostic indicators, including LN stage, the only independent predictor in this study. The relatively short follow-up period (mean: 44 months) and high proportion of microcarcinomas (61.9%) may have led to the low recurrent events (4.6%) compared to other studies. If we could have followed the patients for longer and enrolled more macrocarcinoma patients, more patients would likely have experienced recurrence, and FDG-PET/CT might have been shown to be a significant predictor for the recurrence of PTC. As LN stage remained the only significant predictor in the multivariate analysis, this indicates that LN stage has stronger statistical power than FDG-PET/CT for the prediction of short-term PTC recurrence.

There are two major reasons for the inclusion of such a high number of microcarcinomas in the current study. First, overdiagnosis of PTC by routine thyroid ultrasonography, and second, too generous coverage of FDG-PET/CT in our country. In South Korea, many health promotion centers have included thyroid ultrasonography in the routine health check program, and this has dramatically increased the detection rate of early differentiated thyroid carcinomas [20]. Furthermore, many patients with solid tumors, including differentiated thyroid carcinomas, have been able to receive insurance coverage from the national health insurance system for FDG-PET/CT from 2006. Since then, FDG-PET/CT scans have been widely performed in differentiated thyroid carcinoma patients before surgery, even in microcarcinoma patients. However, the policy has been changed not to cover preoperative FDG-PET/CT in differentiated thyroid carcinoma.

The patient inclusion criteria in the current study are another issue. In our study, lobectomy was performed in 60 patients with microcarcinomas. Although the extent of surgery is well known to affect recurrence and survival of PTC, this does not apply to microcarcinomas [21]. However, when we analyzed the remaining 352 patients...
after excluding the 60 patients who underwent lobectomy, similar results were obtained (data not shown).

Recently, Piccardo et al. reported on 54 FDG-avid primary differentiated thyroid carcinoma patients incidentally detected on FDG-PET/CT. The authors reported that the FDG avidity of the primary differentiated thyroid carcinoma was associated with the persistence or progression of the disease, although, on multivariate analysis, the FDG avidity did not add further prognostic information [22]. Unlike the report of Piccardo et al., our study enrolled both FDG-avid and non-FDG-avid tumors, and we evaluated only PTCs in a larger number of patients, thus enhancing the integrity of our study.

Except for the FDG avidity of the primary tumor and BRAFV600E mutation status, all other clinicopathological prognostic factors analyzed (tumor size, multifocality of the primary tumor, extrathyroidal extension, LN stage, sex, and age) are well-known prognostic factors for PTC. However, in the univariate analyses of our study, only the tumor size, FDG avidity of the primary tumor, extrathyroidal extension, and LN stage were found to be significant predictors of recurrence, while the multifocality of the primary tumor, sex, age, and BRAFV600E mutation status were not. This result is partly backed up by the findings of a recent systemic review and meta-analysis of 13 original articles published from 2005 to 2014 on the risk factors influencing the recurrence of PTC [23]. In this review, age and multifocality were not significantly correlated with recurrence, in contrast to sex, extrathyroidal extension, LN stage, tumor size, distant metastasis, thyroid surgery type, and I-131 therapy.
Finally, there are a number of studies that have shown the correlation between BRAFV600E mutation and poor prognosis of PTC [24], with a recent study reporting a correlation between BRAFV600E mutation and poor prognosis of papillary thyroid microcarcinomas [25]. In our study, among the 301 patients subjected to BRAFV600E mutation status analysis, 277 (92.0%) patients showed a positive result (Table 1). This high proportion of positive test results may have influenced the statistical analysis, since the hazard ratio and its 95% confidence interval could not be determined in the univariate analysis (Table 4). Hence, we consider that a large-scale study is needed in the future to explain this result.

In conclusion, although FDG avidity of primary tumor in preoperative FDG-PET/CT correlated with clinicopathological parameters, including LN stage, it could not predict the recurrence of PTC independently. LN stage was the only identified predictor of PTC recurrence.

Acknowledgments

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI15C1540).

Conflict of Interest

There is no conflict of interest to declare.

References

1. Feine, U., R. Lietzenmayer, J. P. Hanke, J. Held, H. Wöhrle, W. Müller-Schauenburg. 1996. Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. J. Nucl. Med. 37:1468–1472.
2. Wang, W., H. Macapinlac, S. M. Larson, et al. 1999. [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography localizes residual thyroid cancer in patients with negative diagnostic (131)I whole body scans and elevated serum thyroglobulin levels. J. Clin. Endocrinol. Metab. 84:2291–2302.
3. Rosenbaum-Krumme, S. J., R. Gorges, A. Bockisch, et al. 2012. (18)F-FDG PET/CT changes therapy management in high-risk DTC after first radioiodine therapy. Eur. J. Nucl. Med. Mol. Imaging 39:1373–1380.
4. Lee, J. W., S. M. Lee, D. H. Lee, et al. 2013. Clinical utility of 18F-FDG PET/CT concurrent with 131I therapy in intermediate-to-high-risk patients with differentiated thyroid cancer: dual-center experience with 286 patients. J. Nucl. Med. 54:1230–1236.
5. Wang, W., S. M. Larson, M. Fazzari, et al. 2000. Prognostic value of [18F]fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. J. Clin. Endocrinol. Metab. 85:1107–1113.
6. Robbins, R. J., Q. Wan, R. K. Grewal, et al. 2006. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. J. Clin. Endocrinol. Metab. 91:498–505.
7. Haugen, B. R. M., E. K. Alexander, K. C. Bible, et al. 2015. American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid doi: 10.1089/thy.2015.0020.
8. Choi, W. H., Y. A. Chung, E. J. Han, et al. 2011. Clinical value of integrated [18F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in the preoperative assessment of papillary thyroid carcinoma: comparison with sonography. J. Ultrasound Med. 30:1267–1273.
9. Pak, K., S. J. Kim, I. J. Kim, et al. 2013. The role of 18F-fluorodeoxyglucose positron emission tomography in differentiated thyroid cancer before surgery. Endocrinol. Relat. Cancer 20:R203–R213.
10. Vriens, D., J. H. de Wilt, G. J. van der Wilt, et al. 2011. The role of [18F]-2-fluoro-2-deoxy-d-glucose-positron emission tomography in thyroid nodules with indeterminate fine-needle aspiration biopsy: systematic review and meta-analysis of the literature. Cancer 117:4582–4594.
11. Wang, N., H. Zhai, and Y. Lu. 2013. Is fluorine-18 fluorodeoxyglucose positron emission tomography useful for the thyroid nodules with indeterminate fine needle aspiration biopsy? A meta-analysis of the literature. J. Otolaryngol. Head Neck Surg. 42:38.
12. Giovanella, L., S. Suriano, M. Maffioli, et al. 2011. 18FDG-positron emission tomography/computed tomography (PET/CT) scanning in thyroid nodules with nondiagnostic cytology. Clin. Endocrinol. (Oxf.) 74:644–648.
13. Vriens, D., E. M. Adang, R. T. Netea-Maier, et al. 2014. Cost-effectiveness of FDG-PET/CT for cytologically indeterminant thyroid nodules: a decision analytic approach. J. Clin. Endocrinol. Metab. 99:3263–3274.
14. Chen, W., M. Parsons, D. A. Torigian, et al. 2009. Evaluation of thyroid FDG uptake incidentally identified on FDG-PET/CT imaging, Nucl. Med. Commun. 30:240–244.
15. Soelberg, K. K., S. J. Bonnaema, T. H. Brix, et al. 2012. Risk of malignancy in thyroid incidentalomas detected by 18F-fluorodeoxyglucose positron emission tomography: a systematic review. Thyroid 22:918–925.
16. Yun, M., T. W. Noh, A. Cho, et al. 2010. Visually discernible [18F]fluorodeoxyglucose uptake in papillary thyroid microcarcinoma: a potential new risk factor. J. Clin. Endocrinol. Metab. 95:3182–3188.
17. Byun, B. H., U. G. Jeong, S. P. Hong, et al. 2012. Prediction of central lymph node metastasis from papillary thyroid microcarcinoma by 18F-fluorodeoxyglucose PET/CT and ultrasonography. Ann. Nucl. Med. 26:471–477.

18. Duntas, L., and B. M. Grab-Duntas. 2006. Risk and prognostic factors for differentiated thyroid cancer. Hell J. Nucl. Med. 9:156–162.

19. Kim, S. K., D. L. Kim, H. S. Han, et al. 2008. Pyrosequencing analysis for detection of a BRAFV600E mutation in an FNAB specimen of thyroid nodules. Diagn. Mol. Pathol. 17:118–125.

20. Ahn, H. S., H. J. Kim, and H. G. Welch. 2014. Korea’s thyroid-cancer “epidemic”–screening and overdiagnosis. N. Engl. J. Med. 371:1765–1767.

21. Bilimoria, K. Y., D. J. Bentrem, C. Y. Ko, et al. 2007. Extent of surgery affects survival for papillary thyroid cancer. Ann. Surg. 246:375–381; discussion 81-4.

22. Piccardo, A., M. Puntoni, F. Bertagna, et al. 2014. (1)8F-FDG uptake as a prognostic variable in primary differentiated thyroid cancer incidentally detected by PET/CT: a multicentre study. Eur. J. Nucl. Med. Mol. Imaging 41:1482–1491.

23. Guo, K., and Z. Wang. 2014. Risk factors influencing the recurrence of papillary thyroid carcinoma: a systematic review and meta-analysis. Int. J. Clin. Exp. Pathol. 7:5393–5403.

24. Tufano, R. P., G. V. Teixeira, J. Bishop, et al. 2012. BRAF mutation in papillary thyroid cancer and its value in tailoring initial treatment: a systematic review and meta-analysis. Medicine (Baltimore) 91:274–286.

25. Chen, Y., P. M. Sadow, H. Suh, et al. 2016. BRAFV600E is correlated with recurrence of papillary thyroid microcarcinoma: a systematic review, multi-institutional primary data analysis, and meta-analysis. Thyroid 26:248–255.