Visually Discernible [^{18}F]Fluorodeoxyglucose Uptake in Papillary Thyroid Microcarcinoma: A Potential New Risk Factor

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Context: A significant number of papillary thyroid microcarcinomas (PTMCs), despite excellent prognosis, show aggressive features such as extrathyroidal extension (EE) and lymph node metastasis (LNM) that may not always be detected preoperatively or intraoperatively. The relapse rate appears also substantial.

Objective: To assess the value of [^{18}F]fluorodeoxyglucose (FDG) uptake in PTMC as a potential risk factor for preoperative risk stratification.

Methods: This retrospective study included 87 patients (17 males and 70 females; mean age = 51.2 yr, range 29–74 yr) with a unifocal PTMC who underwent preoperative FDG-positron emission tomography (PET)/computed tomography (CT)and total thyroidectomy and central lymph node dissection. Statistical analyses were performed to compare the gender, age, tumor size, and FDG uptake in PTMC with the presence of histopathologically proven EE and central LNM (cLNM).

Results: Of the 87 patients, 44 (51%) had EE, and 27 (31%) had cLNM. PET/CT showed visually discernible FDG uptake in 46 PTMCs (53%). FDG positivity of PTMCs was the only significant variable correlated with both EE and cLNM; there was a significant difference in the prevalence of both EE (70 *vs.* 29%) and cLNM (41 *vs.* 19.5%) between the FDG-positive and FDG-negative groups. In contrast, other already known risk factors, *i.e.* gender, age, and size, showed a correlation with only one or neither of EE and cLNM.

Conclusion: The results indicate that visual FDG positivity in PTMCs is a potential risk factor that can be useful for preoperative risk stratification. Prospective studies would be warranted to assess the long-term benefit and cost effectiveness of preoperative FDG-PET/CT. (***J Clin Endocrinol Metab* 95: 3182–3188, 2010**)

High-resolution ultrasound-guided fine needle aspiration biopsy has led to a rapid rise in the incidence of papillary thyroid microcarcinoma (PTMC), *i.e.* papillary thyroid carcinoma 1 cm or smaller. PTMCs have been largely perceived as tumors that are characterized by benign behavior, of little clinical significance, and do not affect patients' survival. However, it has been increasingly demonstrated that PTMCs show very diverse disease extent with widely varying reported frequencies of the aggressive features (1–5). In addition, the tumor characteristics, age-based recurrence rates, and/or prevalence of the aggressive features in patients with PTMC at diagnosis are reported to be similar to that in patients with larger papillary thyroid carcinomas (1, 6). Also, despite an extremely

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Abbreviations: CT, Computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; PTMC, papillary thyroid microcarcinoma; SUV, standard uptake value.

low risk for mortality, recurrent or persistent disease even after total or near-total thyroidectomy is surprisingly common, and some authors feel that the treatment of patients with PTMC should be no different from the treatment of patients with papillary macrocarcinoma (7, 8).

The extent of thyroid surgery for PTMC varying from a lobectomy alone to total thyroidectomy with central-compartment neck dissection is largely determined depending on the presence or absence of the risk factors/aggressive features (9). Therefore, the wide variability in the reported prevalence of aggressive features among different studies as well as no significant difference in the prevalence of aggressive features between micro- and macrocarcinomas are of concern, especially given that some of these histopathological features may not easily be detected by preoperative imaging or even by inspection at the time of surgery.

[^{18}F]Fluorodeoxyglucose (FDG) uptake in many malignant tumors on positron emission tomography (PET) has been shown to be a significant predictor of greater aggressiveness and a poorer prognosis (10–13). Also, in post-thyroidectomy thyroid cancer patients, radioiodine-negative/FDG-positive recurrences are known to be associated with dedifferentiated tumors and a grave prognosis (14–16). This well-known relationship between the FDG avidity and tumor aggressiveness/differentiation appears to be in line with the limited sensitivity of preoperative FDG PET in ruling in malignancy in patients with thyroid nodules because the majority of them are well differentiated (17). At the same time, it is quite perplexing and equally interesting that a large number of thyroid cancers, including incidentalomas and PTMCs, exhibit increased FDG uptake despite their well-differentiated histology. In addition, we observed that small nodules of 5 mm or smaller often showed increased FDG uptake, whereas those close to 10 mm or even some macrocarcinomas not included in this study exhibited no or minimal uptake. Constellation of these well-known facts and observations prompted us to speculate that FDG positivity may represent relative aggressiveness even in well-differentiated PTMCs.

The objective of this retrospective study was to: 1) assess the frequency of visual FDG positivity in PTMCs and 2) to compare the prevalence of extrathyroidal extension and lymph node metastasis between patients with FDG-positive and -negative PTMCs.

Patients and Methods

Patients (Table 1)

Our institutional review board approved the protocol for this retrospective study. The medical records of 4615 patients who underwent a total thyroidectomy with central lymph node dissection between 2005 and 2008 were reviewed, and 2311 patients had a diagnosis of PTMC. Of the 2311 patients with PTMC, 145 patients had a PET scan within 3 months before their surgery. Of the 145 patients, 10 patients had FDG PET for screening of cancer that eventually led to the diagnosis of PTMC, whereas FDG PET was performed after PTMCs were diagnosed in the other 134 patients. These 10 patients were excluded because they represent a different group, introducing bias to the data. Patients who had a diagnosis of PTMC before PET were advised of the availability of PET, its cost, potential but unproven benefit and efficacy of PET in the setting of PTMC, and possible benefit of finding second primary malignancies with PET reported in the literature. Of them, 134 patients elected to undergo PET imaging studies. Therefore, the 134 patients effectively represent a randomly selected population. Of the 134 patients, three groups of patients were additionally excluded to avoid bias. Eight patients were excluded because of a previous history of malignancies in the head and neck. Thirty patients with multifocal carcinomas were excluded because it would not be possible to determine which one(s) of the multiple nodules is (are) responsible for lymph node metastases, if present. And, if the degree of FDG uptake varies among these multiple nodules, the relationship between the FDG uptake and lymph node metastases cannot be determined. Lastly, 10 patients showing diffuse, nonfocal FDG uptake in their thyroid were excluded because FDG uptake by thyroid carcinomas may not be accurately measured. The remaining 87 patients with pathologically confirmed, unifocal PTMC constitute the study population (17 males and 70 females; mean age 51.2 yr, range 29–74 yr).

TABLE 1. Clinical and histopathological characteristics in 87 patients with PTMC

	No. of patients
Age (>45 yr/≤45 yr)	60 (69%)/27 (31%)
Sex (male/female)	17 (20%)/70 (80%)
Family history (present)	6 (7%)
Radiation history (present)	0 (0%)
Tumor size (>5 mm/≤5 mm)	44 (51%)/43 (49%)
Extrathyroidal extension (present)	44 (51%)
Central lymph node metastasis (present)	27 (31%)

Imaging procedures

PET/computed tomography (CT) images were acquired using the Phillips Gemini PET/CT scanner (Phillips-ADAC Medical Systems, Cleveland, OH). Patients were instructed to fast for more than 6 h, and then 5.18 MBq (0.14 mCi)/kg of FDG was iv injected into these patients. Images from the skull base to the proximal thigh were acquired 1 h later. Emission images were acquired for 3 min per bed, and transmission scans from low-dose CT were used for attenuation correction. Images were then reconstructed using the low-action maximal-likelihood algorithm.

Image interpretation and semiquantitative analysis

Two experienced nuclear medicine specialists visually reviewed PET/CT images using the Syntegra program (version 2.1E) and performed semiquantitative analysis on the nodules. The nuclear medicine specialists were blinded to the patients'

clinical status/surgical pathology; they knew only that the patients were diagnosed with thyroid cancer.

FDG uptake in PTMCs was visually categorized as positive if there was a discernible focal FDG uptake and negative if there was no discernibly higher FDG uptake than surrounding thyroid tissue. For semiquantitative analysis, a region of interest was drawn around these microcarcinomas, and the peak standard uptake value (SUV) was recorded. When a nodule was not visually discernible on PET, a region of interest was drawn according to the location of the nodule based on other anatomical images. Any central lymph node with visually discernible FDG uptake was considered to be positive for metastasis. Lymph nodes in level VI were considered to be central lymph nodes, according to the guidelines of the American Head and Neck Society (18).

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (version 12.0; SPSS Inc., Chicago, IL). Univariate analyses were performed to determine the relationship between four independent variables, *i.e.* gender, age, tumor size, and FDG uptake in the PTMC, and two dependent variables, extrathyroidal extension (presence or absence) and central lymph node metastasis. All four independent and two dependent variables were dichotomized by gender (male or female), age ($\leq$45 or $>$45 yr), tumor size ($\leq$5 or $>$5 mm), and visually discernible focal FDG uptake in the PTMC (presence or absence), extrathyroidal extension (presence or absence), and central lymph node metastasis (presence or absence). Three of the four independent variables, *i.e.* age, tumor size, and FDG uptake expressed as SUV, as continuous variables were also correlated with the two dichotomized dependent variables.

Additionally, the relationship between dichotomized independent and dependent variables were assessed by two-tailed Fisher's exact test. Two-tailed independent Student's *t* test was used to assess the difference in the age and tumor size between the dichotomized groups of dependent variables. To assess the difference in the SUVs between the dichotomized groups of dependent variables, Mann-Whitney *U* test was used. For comparison of two continuous variables, Pearson's correlation analysis was performed.

Independent variables with a $P < 0.25$ identified from the univariate analysis or Fisher's exact test were included in the multivariate logistic regression analysis to assess possible interdependency. When both dichotomized and continuous variable of the same independent factor had a $P < 0.25$, then the more significant one of the two was chosen for multivariate analysis. The results were considered statistically different if the *P* value from the multivariate analysis was less than 0.05 and the 95% confidence interval of the odds ratio did not include 1. The sensitivity, specificity, positive predictive value, and negative predictive value of FDG positivity for prediction of the extrathyroidal extension and/or central lymph node metastasis were also calculated.

Results

Comparison of independent variables with extrathyroidal extension (Table 2)

Of the 87 PTMCs, 44 nodules (51%) were pathologically confirmed to have extrathyroidal extension. Table 2 provides the results from various analyses of the dichotomized and/or continuous independent variables with extrathyroidal extension. The gender and age were not significant independent variables. Also, there was no difference in the age between 44 patients with and 43 patients without extrathyroidal extension (mean age = 50.8 ± 9.3

TABLE 2. Correlation of independent variables with extrathyroidal extension (EE) in patients with PTMC

Variables	EE negative (n = 43)	EE positive (n = 44)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Gender						
Female	35 (50%)	35 (50%)	1			
Male	8 (47.1%)	9 (52.9%)	1.125 (0.389–3.252)	0.837,[a] 1.0[b]		
Age						
≤45 yr	14 (51.9%)	13 (48.1%)	1			
>45 yr	29 (48.3%)	31 (51.7%)	1.151 (0.464–2.857)	0.761,[a] 0.819[b]		
Age (continuous variable)			0.993 (0.954–1.034)	0.743[a]		
Tumor size						
≤5 mm	32 (74.4%)	11 (25.6%)	1			
>5 mm	11 (25%)	33 (75%)	8.727 (3.319–22.951)	<0.0001,[a] 0.000005[b]	5.95 (2.13–16.60)	0.0007
Tumor size (continuous variable)			1.711 (1.343–2.180)	<0.0001[a]		
FDG visual uptake						
Negative	29 (70.7%)	12 (29.3%)	1			
Positive	14 (30.4%)	32 (69.6%)	5.524 (2.200–13.866)	0.0001,[a] 0.0002[b]	3.04 (1.09–8.51)	0.034
FDG SUVs (continuous variable)			1.475 (1.109–1.962)	0.0013[a]		

CI, Confidence interval; OR, odds ratio.

[a] By univariate logistic regression analysis.

[b] By Fisher's exact test.

and 51.6 ± 11.9 yr, respectively, $P = 0.74$ by Student's *t* test).

The size of PTMC tumors based on histopathological specimen ranged from 2–10 mm with a mean size of 5.6 mm; 44 tumors were larger than 5 mm, and 43 tumors were 5 mm or smaller. There was a significant difference in the frequency of extra-thyroidal extension between the $>$ 5 mm and $\leq$ 5 mm groups (75% *vs.* 26%, $P = 0.000005$ by the Fisher's exact test). The tumor size in patients with extrathyroidal extension was significantly larger than those without extension (mean size = 6.8 ± 2.0 cm *vs.* 4.3 ± 2.2, $P < 0.0001$ by Student's *t* test).

On visual analysis of PET scans, 46 (53%) of the 87 PTMCs showed discernible FDG uptake, and 41 did not. Extrathyroidal extension was present in 70% (32 of 46) of the FDG-positive group compared with 29% (12 of 41) in the FDG-negative group ($P < 0.0001$). The SUVs in all 87 PTMCs ranged from 0.7–15.0 with a median of 2.1. The median SUV in 44 patients with extrathyroidal extension was 2.8 compared with 1.8 in 43 patients without extension ($P = 0.0021$ by the Mann-Whitney *U* test). Multivariate logistic regression analysis revealed that dichotomized tumor size and visual FDG positivity were two significant independent variables correlated with extrathyroidal extension (Table 2).

Even in a selected group of patients that is considered to be a low-risk group, *i.e.* 23 female patients age 45 yr or younger, visual FDG positivity and tumor size were found to be significant variables. Nine of 14 patients with visual FDG positivity in the PTMCs were associated with extrathyroidal extension compared with one of nine patients without extension ($P = 0.013$). Ten of 12 patients with tumor size larger than 5 mm were associated with extrathyroidal extension compared with three of eight patients with tumor 5 mm or smaller ($P = 0.013$).

The sensitivity, specificity, positive predictive value and negative predictive value of visual FDG positivity for evaluation of extrathyroidal extension in all 87 patients were 73, 67, 70, and 71%, respectively.

Comparison of independent variables with central lymph node metastasis (Table 3)

There were 27 (31%) patients with pathologically confirmed central lymph node metastasis. Table 3 shows the results from univariate and multivariate analyses. Among the independent variables, visual FDG positivity in the PTMCs was found to be the only significant variable multivariate analysis. The frequency of central lymph node metastasis in the FDG positive group was 41% (19 of 46) compared with 20% (eight of 41) in the FDG-negative group ($P = 0.037$). The sensitivity, specificity, positive predictive value, and negative predictive value of FDG uptake for the diagnosis of central lymph node metastasis were 70, 55, 41, and 80%, respectively. The tumor size as continuous variable nearly approached the statistical significance by univariate analysis ($P = 0.063$) but was found to be completely insignificant by subsequent multivariate analysis ($P = 0.534$).

Miscellaneous

PET/CT showed foci of increased FDG uptake, suggesting central lymph node metastases in only two of the 27 patients with confirmed lymph node disease. In the remaining 60 patients without central lymph node metas-

TABLE 3. Correlation of independent variables with central lymph node (cLN) metastases in patients with PTMC

Variables	cLN negative (n = 60)	cLN positive (n = 27)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Gender						
Female	51 (72.9)	19 (27.1)		1		
Male	9 (52.9)	8 (47.1)	2.386 (0.804–7.085)	0.121,[a] 0.145[b]	3.241 (0.936–11.220)	0.064
Age						
≤45	20 (74.1)	7 (25.9)		1		
>45	40 (66.7)	20 (33.3)	1.429 (0.518–3.940)	0.485,[a] 0.618[b]		
Age (continuous variable)			0.995 (0.953–1.039)	0.816[a]		
Tumor size						
≤5 mm	32 (74.4)	11 (25.6)		1		
>5 mm	28 (63.7)	16 (36.3)	1.662 (0.662–4.171)	0.276,[a] 0.257[b]		
Tumor size (continuous variable)			1.200 (0.983–1.460)	0.063[a]	1.072 (0.861–1.335)	0.534
FDG visual uptake						
Negative	33 (80.5)	8 (19.5)		1		
Positive	27 (58.7)	19 (41.3)	2.903 (1.100–7.658)	0.026,[a] 0.037[b]	3.298 (1.049–10.372)	0.041
FDG SUVs (continuous variable)			1.065 (0.881–1.287)	0.52[a]		

CI, Confidence interval; OR, odds ratio.

[a] By univariate logistic regression analysis.

[b] By Fisher's exact test.

tasis, the PET/CT was false positive in one and true negative in 59 cases. In all 87 patients, PET/CT showed no abnormalities outside the cervical region.

There appeared to be a moderate dependency of SUV on tumor size ($y = 0.4462 + 0.4592x$, where y = SUV and x = tumor size in millimeters; $r = 0.0478$; $P < 0.001$). Nevertheless, the tumor SUVs widely varied even among nodules of similar sizes. Furthermore, as shown above, the tumor SUV and size were found to be independent variables for the extrathyroidal extension by multivariate analysis. This seemingly dependent relationship between the SUV and tumor size most likely resulted from the well-known partial volume effect. This issue is discussed below.

Discussion

Despite a very favorable prognosis, there is a wide variability in the clinical and pathologic characteristics of PTMC at the time of diagnosis among different studies, *i.e.* the prevalence of bilateral and/or multiple foci being observed in 2.9–56.8% and extracapsular invasion and/or lymph node metastasis at diagnosis ranging from nearly 0% up to over 60% (2–4, 19). Moreover, in a recent report analyzing more than 6000 patients with papillary thyroid carcinoma, microcarcinomas showed similar features to macrocarcinomas with respect to tumor characteristics and age-based recurrence rates (6). Another study also found no significant difference in the prevalence of multifocality, extrathyroidal extension, and lymph node metastasis in patients with PTMC at diagnosis compared with that in patients with larger papillary thyroid carcinomas (1). The relapse rate in patients with PTMCs is also substantial (7, 20, 21).

According to new 2009 American Thyroid Association guidelines, a thyroid lobectomy alone may be sufficient for PTMC without other risk factors (9). However, some authors seem to favor more aggressive surgery for patients with PTMC, despite its small size, as for those with papillary thyroid macrocarcinoma (7, 8, 22). Despite these different preferences among studies, most investigators seem to agree that preoperative risk stratification is important in determining the extent of surgery.

The known risk factors for the recurrent disease include the gender, age, tumor size, multifocality, extrathyroidal extension, and lymph node metastasis, although the significance level of individual factors varies among different reports (4, 5, 7, 19, 23–25). Moreover, some of the histopathological risk factors are often undetected preoperatively by imaging or clinically, or even by intraoperative inspection (4, 26). Therefore, it would certainly be desirable to have a risk factor that can be easily assessed preoperatively.

Although FDG positivity in recurrent thyroid cancer is well known to indicate more aggressive behavior (14–16), it is still unclear whether or not FDG positivity of primary well-differentiated thyroid cancers in the preoperative setting similarly indicates tumor aggressiveness. Jeong *et al.* (4) recently reported that SUV of PTMCs did not correlate with the presence of lymphatic metastasis, the multiplicity of primary tumor, or extrathyroid invasion but correlated only with the size of PTMCs. There is a remarkable similarity between our data and theirs, which is the moderate dependency of SUV on the tumor size with nearly identical r values (0.479 in our study and 0.481 in the previous study). However, measured SUV of lesions smaller than 3 cm falsely declines (especially more so when <2 cm), which is well known as the partial volume effect (27–29). For example, the measured activity of a 1-cm lesion is less than 50% of that of a 2-cm lesion despite the same concentration of activity in both lesions. We strongly believe that the seemingly significant dependency of SUV on the tumor size in both studies merely represents the partial volume effect rather than a true dependency. Instead of SUV, visual assessment is often relied upon for interpretation of small lesions. For example, SUV of 2.5 is the most widely adopted cutoff for differentiating malignant from benign pulmonary nodules. However, based on the experience accumulated over more than 10 yr, visually discernible FDG activity, regardless of SUV, in a small nodule is now generally considered suspicious for malignancy. Likewise, we suspected that visual analysis could be more meaningful than SUV for PTMC, which indeed turned out to be the case.

We found visually discernible FDG uptake in 53% of PTMCs. The sensitivity, specificity, positive predictive value, and negative predictive value of visual FDG positivity for extrathyroidal extension were 73, 67, 70, and 71%, respectively, and 70, 55, 41, and 80%, respectively, for central lymph node metastasis. Given these relatively low values, FDG positivity in PTMC cannot be used as a single predictor for extrathyroidal extension and central lymph node metastasis. Nevertheless, there was a significant difference in the prevalence of both EE (70 *vs.* 29%) and cLNM (41 *vs.* 19.5%) between the FDG-positive and FDG-negative groups. On the other hand, other known risk factors, *i.e.* gender, age, and size, showed a correlation with only one or neither of the extrathyroidal extension and central lymph node metastasis. These results suggest that FDG positivity can be as good as or possibly even better than other known risk factors for preoperative risk stratification in patients with PTMC.

One of the limitations of our study is lack of direct correlation of FDG positivity in PTMCs with disease relapse rate because the follow-up is not long enough. Even after several more years of follow-up, we may still be un-

able to find any significant difference in the relapse rate between FDG-positive and FDG-negative groups because all our patients in both groups underwent extensive surgery, *i.e.* total thyroidectomy with lymph node dissection. In low-risk patients, it would be interesting to carry out prospective studies comparing recurrence rates between an FDG-negative group undergoing lobectomy and an FDG-positive group undergoing lobectomy, and/or between an FDG-positive group undergoing lobectomy and an FDG-positive group undergoing more extensive surgery.

PET/CT is an expensive procedure. However, its long-term cost effectiveness is unknown. Although the mortality rate associated with PTMCs is extremely low even in the presence of extended disease, the recurrence rate is not (7, 8). When the disease relapses, additional diagnostic and appropriate therapeutic procedures, which may include reoperation, will be required. This will, in turn, translate into increasing cost. In addition, there will be uncalculated cost due to the patient's decreased productivity resulting from hypothyroidism and time required for the diagnostic work-up and treatment. Perhaps even more importantly, the patients will suffer from psychological stress from having recurrent malignancy. Therefore, if positive clinical impact of a preoperative PET/CT examination can be demonstrated by prospective studies, this procedure may possibly turn out to be cost effective rather than expensive, despite its high initial cost. Assessment of long-term cost effectiveness also seems to warrant a prospective evaluation.

Other than the potential value of FDG positivity in the primary tumor, the yield of whole-body PET/CT in patients with PTMCs appears to be quite low. To date, detection of microscopic lymph node disease in malignant tumors has been a challenge for any diagnostic imaging modalities. The sensitivity and negative predictive value of PET for diagnosis of regional lymph node disease based on FDG uptake in the lymph node as the criteria was extremely low in our study as expected. The yield of PET/CT for evaluation of the rest of the whole body, regardless of its diagnostic efficacy, seems very low in patients with PTMCs simply because of the extremely low prevalence of distant metastatic disease in this population.

Conclusion

Visually discernible FDG uptake was observed in approximately one half of the unifocal PTMCs and associated with a significantly higher prevalence of extrathyroidal extension and central lymph node involvement compared with the FDG-negative group. This indicates that FDG positivity is a potential new risk factor that can be useful for preoperative risk stratification. Prospective studies would be warranted to assess the long-term benefit and cost effectiveness of preoperative FDG-PET.

Acknowledgments

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References

1. **Cappelli C, Castellano M, Braga M, Gandossi E, Pirola I, De Martino E, Agosti B, Rosei EA** 2007 Aggressiveness and outcome of papillary thyroid carcinoma (PTC) versus microcarcinoma (PMC): a mono-institutional experience. J Surg Oncol 95:555–560
2. **Roti E, degli Uberti EC, Bondanelli M, Braverman LE** 2008 Thyroid papillary microcarcinoma: a descriptive and meta-analysis study. Eur J Endocrinol 159:659–673
3. **Kim TY, Hong SJ, Kim JM, Gu Kim W, Gong G, Ryu JS, Kim WB, Yun SC, Shong YK** 2008 Prognostic parameters for recurrence of papillary thyroid microcarcinoma. BMC Cancer 8:296
4. **Jeong HS, Chung M, Baek CH, Ko YH, Choi JY, Son YI** 2006 Can [18F]-fluorodeoxyglucose standardized uptake values of PET imaging predict pathologic extrathyroid invasion of thyroid papillary microcarcinomas? Laryngoscope 116:2133–2137
5. **Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T, Ito K, Takami H, Takanashi Y** 2003 Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 237:399–407
6. **Noguchi S, Yamashita H, Uchino S, Watanabe S** 2008 Papillary microcarcinoma. World J Surg 32:747–753
7. **Chow SM, Law SC, Chan JK, Au SK, Yau S, Lau WH** 2003 Papillary microcarcinoma of the thyroid: prognostic significance of lymph node metastasis and multifocality. Cancer 98:31–40
8. **Pearce EN, Braverman LE** 2004 Papillary thyroid microcarcinoma outcomes and implications for treatment. J Clin Endocrinol Metab 89:3710–3712
9. **Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM** 2009 Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19:1167–1214
10. **Patronas NJ, Di Chiro G, Kufta C, Bairamian D, Kornblith PL, Simon R, Larson SM** 1985 Prediction of survival in glioma patients by means of positron emission tomography. J Neurosurg 62:816–822
11. **Vansteenkiste J, Fischer BM, Dooms C, Mortensen J** 2004 Positron-emission tomography in prognostic and therapeutic assessment of lung cancer: systematic review. Lancet Oncol 5:531–540
12. **Eubank WB, Mankoff DA** 2005 Evolving role of positron emission tomography in breast cancer imaging. Semin Nucl Med 35:84–99
13. **Kim CK, Alavi JB, Alavi A, Reivich M** 1991 New grading system of cerebral gliomas using positron emission tomography with F-18 fluorodeoxyglucose. J Neurooncol 10:85–91

14. **Rivera M, Ghossein RA, Schoder H, Gomez D, Larson SM, Tuttle RM** 2008 Histopathologic characterization of radioactive iodine-refractory fluorodeoxyglucose-positron emission tomography-positive thyroid carcinoma. Cancer 113:48–56
15. **Wang W, Larson SM, Fazzari M, Tickoo SK, Kolbert K, Sgouros G, Yeung H, Macapinlac H, Rosai J, Robbins RJ** 2000 Prognostic value of [18F]fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. J Clin Endocrinol Metab 85: 1107–1113
16. **Feine U, Lietzenmayer R, Hanke JP, Held J, Wöhrle H, Müller-Schauenburg W** 1996 Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. J Nucl Med 37:1468–1472
17. **Mitchell JC, Grant F, Evenson AR, Parker JA, Hasselgren PO, Parangi S** 2005 Preoperative evaluation of thyroid nodules with 18FDG-PET/CT. Surgery 138:1166–1174; discussion 1174–1165
18. **Robbins KT, Shaha AR, Medina JE, Califano JA, Wolf GT, Ferlito A, Som PM, Day TA** 2008 Consensus statement on the classification and terminology of neck dissection. Arch Otolaryngol Head Neck Surg 134:536–538
19. **Ito Y, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A** 2007 Risk factors for recurrence to the lymph node in papillary thyroid carcinoma patients without preoperatively detectable lateral node metastasis: validity of prophylactic modified radical neck dissection. World J Surg 31:2085–2091
20. **Baudin E, Travagli JP, Ropers J, Mancusi F, Bruno-Bossio G, Caillou B, Cailleux AF, Lumbroso JD, Parmentier C, Schlumberger M** 1998 Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. Cancer 83:553–559
21. **Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR, Bergstralh EJ** 1992 Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. Surgery 112:1139–1147
22. **Pellegriti G, Scollo C, Lumera G, Regalbuto C, Vigneri R, Belfiore A** 2004 Clinical behavior and outcome of papillary thyroid cancers smaller than 1.5 cm in diameter: study of 299 cases. J Clin Endocrinol Metab 89:3713–3720
23. **Besic N, Pilko G, Petric R, Hocevar M, Zgajnar J** 2008 Papillary thyroid microcarcinoma: prognostic factors and treatment. J Surg Oncol 97:221–225
24. **Lim DJ, Baek KH, Lee YS, Park WC, Kim MK, Kang MI, Jeon HM, Lee JM, Yun-Cha B, Lee KW, Son HY, Kang SK** 2007 Clinical, histopathological, and molecular characteristics of papillary thyroid microcarcinoma. Thyroid 17:883–888
25. **Min HS, Choe G, Kim SW, Park YJ, Park do J, Youn YK, Park SH, Cho BY, Park SY** 2008 S100A4 expression is associated with lymph node metastasis in papillary microcarcinoma of the thyroid. Mod Pathol 21:748–755
26. **Roh JL, Kim JM, Park CI** 2008 Central cervical nodal metastasis from papillary thyroid microcarcinoma: pattern and factors predictive of nodal metastasis. Ann Surg Oncol 15:2482–2486
27. **Srinivas SM, Dhurairaj T, Basu S, Bural G, Surti S, Alavi A** 2009 A recovery coefficient method for partial volume correction of PET images. Ann Nucl Med 23:341–348
28. **Kim SC, Machac J, Krynyckyi BR, Knesaurek K, Krellenstein D, Schultz B, Gribetz A, DePalo L, Teirstein A, Kim CK** 2008 Fluorodeoxy-glucose positron emission tomography for evaluation of indeterminate lung nodules: Assigning a probability of malignancy may be preferable to binary readings. Ann Nucl Med 22:165–170
29. **Rousset OG, Ma Y, Evans AC** 1998 Correction for partial volume effects in PET: principle and validation. J Nucl Med 39:904–911