FDG PET positivity in papillary thyroid microcarcinomas is a useful way to identify lymph-node metastases and extracapsular tumor extension

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SUMMARY

BACKGROUND

Papillary thyroid microcarcinomas (PTMCs), which are generally indolent tumors ≤1 cm, comprise almost half of all thyroid cancers. Although these tumors generally have an excellent prognosis, a subset has more aggressive behavior, with lymph-node metastases and extrathyroidal tumor capsular invasion that can be associated with about a 5% tumor recurrence rate and occasional cancer-specific mortality of approximately 2%. The problem is that preoperative neck ultrasonography commonly does not identify lymph-node metastases in the central neck compartment and fails to identify tumor invasion. This is a retrospective study aimed at assessing the value of 18F-fluorodeoxyglucose (18F-FDG) uptake in PTMC as a potential risk factor for preoperative risk stratification.

PATIENTS AND METHODS

Study Subjects

The medical records of 4615 patients who had total thyroidectomy with central lymph-node dissection from 2005 through 2008 revealed 2311 patients (50%) with PTMC (the study group). Of this group of 2311 patients with PTMC, 145 (6.3%) had an 18F-FDG–positron-emission tomographic (PET) scan 3 months before surgery. Ten of the 145 patients had 18F-FDG–PET for screening of cancer that eventually led to a diagnosis of PTMC, whereas 18F-FDG–PET was performed after the diagnosis of PTMC in 134 patients; however, the latter 10 patients were excluded because they represent a different group that would introduce bias into the data.

Patients who had a diagnosis of PTMC before PET agreed to undergo PET imaging studies. Thus, 134 patients represented a randomly selected population. Of these 134 patients, three additional groups were excluded to avoid bias, and 8 patients were excluded because of a history of head and neck malignancies. Also excluded were 30 patients with multifocal carcinomas because it was not possible to determine which of the multiple nodules was responsible for lymph-node metastases if they were present, and if the degree of 18F-FDG uptake varied among these multiple nodules, the relationship between the 18F-FDG uptake and lymph-node metastases could not be determined. Finally excluded were 10 patients with diffuse 18F-FDG uptake by thyroid carcinomas, which might not be accurately measured. The final study group thus comprised 87 patients with pathologically confirmed unifocal PTMC, 70 (80.5%) of which were women and 17 (19.5%) men, with a mean age of 51.2 years (range, 29 to 74).

Image Interpretation

The nuclear medicine specialists who were unaware of the patients' clinical, statistical, and pathology reports performed semiquantitative analysis on the tumor nodules. 18F-FDG uptake in PTMCs was visually categorized as positive if there was visibly higher 18F-FDG uptake and as negative if there was no visibly higher 18F-FDG uptake than in surrounding thyroid tissue. 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 discernible 18F-FDG uptake was regarded as being positive for metastases. Lymph nodes in level VI were considered to be positive for metastases, according to the American Head and Neck Society.

RESULTS

Comparison of Results of Independent Variables with Extrathyroidal Extension (Figure 1)

The clinical and histopathologic characteristics of the 87 patients with PTMC are shown in Figure 1. Of the 87 PTMCs, 44 (51%) were confirmed by pathology specimens to have extrathyroidal extension of tumor.

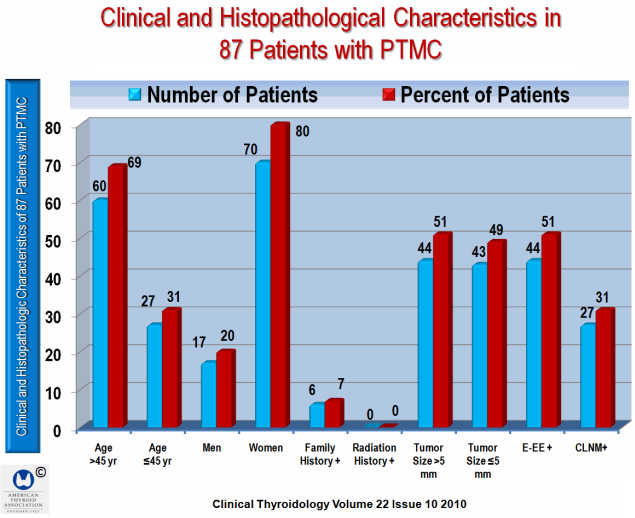

Figure 1. This figure shows the number and percent of clinical and histopathologic characteristics of 87 patients with PTMC. + = positive; CLNM = central lymph-node metastases; EE = extrathyroidal extension of tumor. This figure is derived from data in Table 1 of Yun et al.

Correlation of Independent Variables with Extrathyroidal Extension (EE) in Patients with PTMC (Figure 2)

Figure 2 shows the results of various analyses of the dichotomized variables with or without continuous independent variables with extrathyroidal extension. Patient age and sex were not significant independent variables. Also, there was no difference in the age of 44 patients with and 43 without extrathyroidal expression (mean [±SD] age, 50.8±9.3 and 51.6±11.9 years, respectively; P = 0.74).

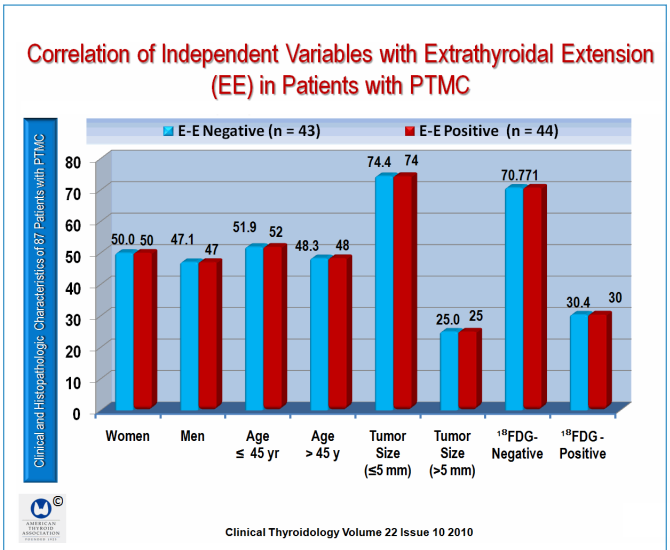

Figure 2. This figure shows the correlation of independent variables with EE in patients with PTMC. Sex and age were not significantly independent variables. Also, there was no difference in age among 44 patients with and 43 patients without EE. Mean (±SD) age was 50±9.3 and 51.6±11.9 years respectively. These data for this figure were derived from Table 2 of Yun et al.

The size of PTMC tumors ranged from 2 to 10 mm, with a mean of 5 mm; and 43 tumors were ≤5 mm (75% vs. 26%; P = 0.0005). The tumor size was significantly larger in patients with extrathyroidal extension (6.8±2.0 vs. 4.3±2.2 cm; P<0.001) *(Figure 2)*.

Visual Analysis of PET Scans

Visual analysis of PET scans showed discernible 18F-FDG uptake in 46 (53%) of the 87 PTMCs, and 41 did not have visible uptake. Extrathyroidal tumor extension was found in 32 of 46 (70%) of the 18F-FDG-positive group as compared with 12 of 41 (29%) of the 18F-FDG-negative group (P<0.0001). The SUVs in all 87 PTMCs ranged from 0.7 to 15.0, with a median of 2.1. The median SUV was 2.8 in 44 patients with extrathyroidal extension as compared with 1.8 in 43 patients without extension (P<0.0021).

Univariate and Multivariate Logistic-Regression Analysis (Figures 3 and 4)

Multivariate logistic-regression analysis revealed that tumor size and visual 18F-FDG positivity were significant independent variables that correlated with extrathyroidal extension as compared with 1 of 9 patients without tumor extension (P = 0.013). Ten of 12 patients with tumors >5 mm were associated with extrathyroidal extension, as compared with 3 of 8 patients with tumors ≤5 mm (P = 0.013). The diagnostic accuracy of 18F-FDG positivity was 73% for sensitivity, 67% for specificity, 70% for the positive predictive value, and 71% for the negative predictive value *(Figure 5)*.

Pathologically confirmed central lymph-node metastases occurred in 27 patients (31%). Figure 4 shows the results from univariate and multivariate analyses. Among the independent variables, visual 18F-FDG positivity in PTMCs and tumor size were the only significant variables in the multivariate analysis.

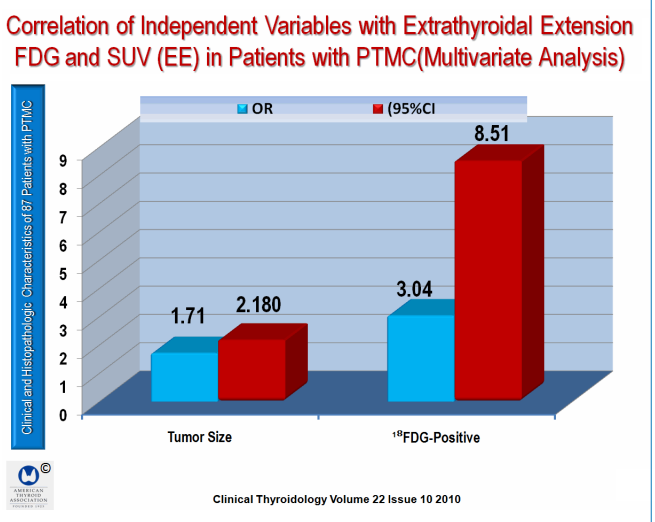

Figure 3. This figure shows the correlation of independent variables with extrathyroidal EE in patients with PTMC. Multivariate analysis logistic regression EE extension was present in 70% of the 18F-FDG-positive group as compared with 29% in the 18F-FDG-negative group. Tumor size ≤5 mm and > 5 mm is and FDG SUVs are significant independent variables. + = positive; CI = confidence interval; OR = odds ratio. The data for this figure were derived from table 2 of Yun et al.

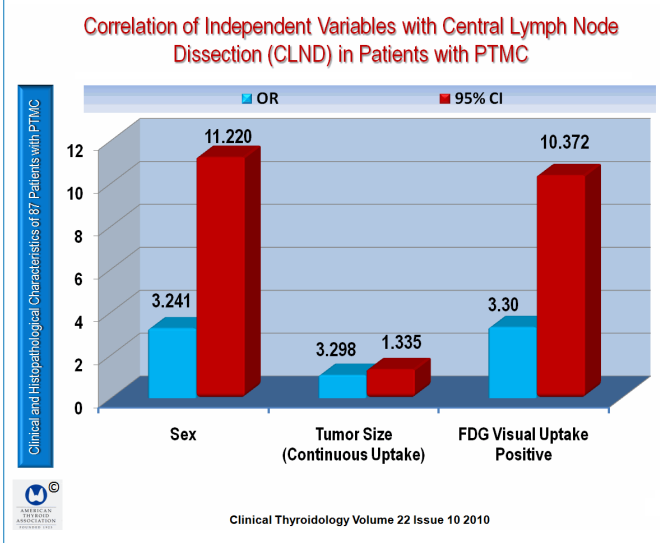

Figure 4. This figure shows the correlation of independent variables with central lymph-node dissections. CI = confidence interval; OR = odds ratio. The data for this figure are derived from Table 3 of Sun et al.

The frequency of central lymph-node metastases in the 18F-FDG-positive group was 19 of 46 (41%) as compared with 8 of 41 (20%) in the FDG-negative group (P = 0.037). The sensitivity, specificity, positive predictive value, and negative predictive value of 18F-FDG uptake for the diagnosis of central lymph-node metastases were 70, 55, 41, and 80%, respectively. Tumor size as a continuous variable almost approached statistical significance by univariate analysis (P = 0.063) but was found to be completely insignificant by the subsequent multivariate analysis (P = 0.534)

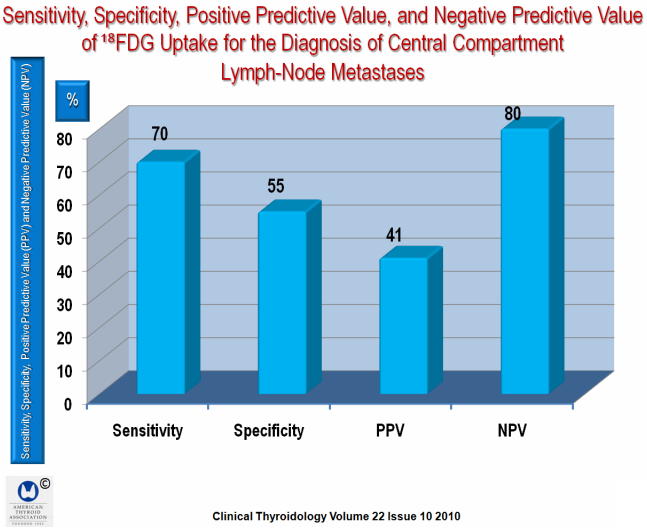

Figure 5. This figure shows the sensitivity, specificity, PPV (positive predictive value), and NPV (negative predictive value of 18F-FDG).

Miscellaneous Findings (Figure 4)

PET–computed tomography (CT) revealed foci of increased 18F-FDG uptake, suggesting central lymph-node metastases in only 2 of the 27 patients with confirmed lymph-node disease. Of the remaining 60 patients without central lymph-node metastases, PET–CT was false positive in 1 patient and true negative in 59 patients. In addition, PET–CT revealed no abnormalities outside the cervical region in all 87 patients. There was a moderate dependency of SUV on tumor size (P<0.001). Still, the tumor SUVs varied even among nodules of similar sizes. Moreover, the tumor SUV and size were found to be independent variables for the extrathyroidal extension by multivariate analysis *(Figure 4)*.

CONCLUSION

Visually apparent 18F-FDG uptake was observed in approximately half of the unifocal PTMCs and is associated with a significantly higher prevalence of extrathyroidal extension and central lymph-node metastases as compared with the 18F-FDG-negative group. The authors conclude that 18F-FDG positivity is a potential new risk factor that may be useful for predictive risk stratification.

COMMENTARY

Papillary microcarcinoma is being diagnosed with increasing frequency (1). Although it carries a low risk for cancer-specific mortality, the risk is not nil. The 10-year cancer-specific mortality rate in a study of 52,173 patients with papillary thyroid cancer found a 2% 10-year cancer-specific mortality rate for PTMC (2). Moreover, recurrent disease after total or near-total thyroidectomy is surprisingly common, with a 10-year recurrence rate of 5% for PTMC.

Not surprisingly, the management of PTMC continues to provoke substantial debate (3-5). Recommendation 26 of the 2009 American Thyroid Association Guidelines suggest that thyroid lobectomy alone may be sufficient treatment for small (<1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or with radiologically or clinically involved cervical lymph-node metastases. Recommendation rating: A.

There is a significantly different opinion concerning the extent of surgery and the use of radioiodine in the management of these small tumors (3;4). A recent study has classified microcarcinomas into two categories: low-risk and very-low risk PTMC (6), with the latter comprising unifocal tumors with no lymph-node metastases or extrathyroidal tumor invasion, whereas low-risk PTMCs may have extrathyroidal tumors or other features that portend a less favorable outcome, such as lymph-node metastases, extrathyroidal tumor extension, and tumor multifocality. For example an editorial by Pearce and Braverman(7) concerning the study by Pellegriti et al. (8) suggested that routine total or near-total thyroidectomy and postoperative radioactive iodine thyroid remnant ablation was suggested in patients with one or more of the following: tumor multicentricity, positive lymph nodes, or capsular or vessel invasion, which may improve recurrence rates and facilitate the use of serum thyroglobulin concentrations for postoperative risk assessment. They also argue for near-total or total thyroidectomy in patients with multinodular goiter or dominant benign nodules, given the relatively high rate of incidentally discovered PTMC, which prompts reoperation for completion thyroidectomy and recurrent contralateral benign nodular disease.

The study by Yun et al. found that visually discernible 18F-FDG uptake was apparent in approximately half of the unifocal PTMCs, and was associated with a significantly higher prevalence of extrathyroidal extension and central lymph-node metastases as compared with the 18F-FDG-negative group. The authors' conclusion that FDG can be useful for preoperative risk stratification is a reasonable conclusion, and the caveat that prospective studies are warranted to assess the long-term benefit and cost-effectiveness of preoperative 18F-FDG–PET is warranted.

— Ernest L. Mazzaferri, MD, MACP

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