



A prospective cohort study to assess the role of FDG-PET in differentiating benign and malignant follicular neoplasms



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H I G H L I G H T S

- Earlier meta-analyses have not considered Hürthle cell neoplasm separate from other follicular neoplasm.
- Hürthle cell neoplasm are known to show high FDG uptake.
- FDG-PET/CT can help in differentiating benign and malignant non-Hürthle cell thyroid nodules.
- A cut-off SUVmax of 3.25 enhances the accuracy of FDG-PET/CT in identifying cancers in thyroid nodules.

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Background: Follicular and Hürthle cell neoplasms are diagnostic challenges. This prospective study was designed to evaluate the efficacy of [18F]-2-fluoro-2-deoxy-*d*-glucose (FDG) positron emission tomography/computed tomography (PET/CT) in predicting the risk of malignancy in follicular/Hürthle cell neoplasms.

Materials and methods: Fifty thyroid nodules showing follicular/Hürthle cell neoplasm on prior ultrasonography guided fine needle aspiration cytology (FNAC) were recruited into this study. A FDG-PET/CT scan, performed for neck and superior mediastinum, was reported by a single observer, blinded to the surgical and pathology findings. Receiver operating characteristic (ROC) curve analysis of maximum standardized uptake value (SUVmax) and the area under the curve (AUROC) were used to assess discrimination between benign from malignant nodules. Youden index was used to identify the optimal cut-off SUVmax for diagnosing malignancy. Sensitivity, specificity, predictive values and overall accuracy were used as measures of performance.

Results: Our study group comprises of 31 benign and 19 malignant thyroid nodules. After excluding all Hürthle cell adenomas, the AUROC for discriminating benign and malignant non-Hürthle cell neoplasms was 0.79 (95% CI, 0.64–0.94; $p = 0.001$); with SUVmax of 3.25 as the best cut-off for the purpose. PET/CT had sensitivity of 79% (95% CI, 54–93%), specificity of 83% (95% CI, 60–94%), positive predictive value (PPV) of 79% (95% CI, 54–93%), and negative predictive value (NPV) of 83% (95% CI, 60–94%). The overall accuracy was 81%.

Conclusions: FDG-PET/CT can help in differentiating benign and malignant non-Hürthle cell neoplasms. SUVmax of 3.25 was found to be the best for identifying malignant non-Hürthle cell follicular neoplasms.

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1. Introduction

Follicular and Hürthle cell neoplasms are diagnostic challenges

for pathologists both on fine needle aspiration cytology (FNAC) and frozen sections, as comprehensive assessment of thyroid nodule for capsular invasion is required for diagnosis [1]. This often requires a

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diagnostic hemi-thyroidectomy and a subsequent completion thyroidectomy (second surgery) for the patients with malignancy diagnosed on paraffin sections. If the malignant neoplasms could be differentiated from benign adenomas preoperatively, these patients could directly undergo one-stage total thyroidectomy. This would avoid a second surgery, treatment delays and additional health care costs.

[18F]-2-fluoro-2-deoxy-*D*-glucose (FDG) positron emission tomography/computed tomography (PET/CT) scan has been used to discriminate benign and malignant follicular/Hürthle cell neoplasms earlier with variable results and is not recommended for routine evaluation of thyroid nodules with indeterminate cytology [2,3]. This prospective study was designed to evaluate the efficacy of FDG-PET/CT scan in predicting the risk of malignancy in indeterminate follicular neoplasms.

2. Material and methods

2.1. Study cohort

This prospective study, approved by Research Ethics Board at the University of Manitoba (H2010:056), included 47 consecutive consenting patients with 50 follicular/Hürthle cell neoplasms, >5 mm in size, seen in the Thyroid clinic from July 2013 to December 2015, at a comprehensive cancer care centre associated with the University teaching hospital. In all, 49 patients were screened for this study and 2 patients did not consent for FDG-PET/CT scan. The minimum sample size ($N = 44$) was calculated for a power of 0.80 with alpha of 0.05, based on 20% risk of malignancy in follicular neoplasm nodules and 39% risk of malignancy in FDG-PET positive indeterminate nodules [2,4].

All patients had a prior ultrasonography and ultrasound guided FNAC showing follicular/Hürthle cell neoplasms. A FDG-PET/CT scan was performed pre-operatively; for which, all patients were asked to fast for 4–6 h prior to administration of F-18 FDG injection. To minimize the examination time and substantially reduce the radiation exposure, only a half-dose of FDG (185 MBq) was administered and patients were scanned in a single bed position (neck and superior mediastinum). The acquisition time was increased by 60% (from 3 to 5 minutes per bed position) to compensate for the reduced dose. A standard acquisition protocol for the 3D-mode Biograph-16 (Siemens; Malvern, PA) PET/CT scanner was used for all patients. Helical CT was acquired with 3- to 5-mm section thickness, as described earlier [5]. All scans were reported by a single observer who was blinded to the surgical and pathologic findings. Recovery coefficient method for partial volume correction of PET images was used, as described earlier [6]. Metabolic tumor volume is the sum of estimated volumes of voxels with increased uptake (MTV; global MTV = volume of voxels with SUV > threshold SUV). MTV is defined as total tumor volume with SUVmax of 2.5 or greater. Total lesion glycolysis is the sum of the product of each lesion's MTV and the corresponding mean SUV over lesions within that MTV (TLG; global TLG = MTV × mean SUV) [7–9]. MTV and TLG were calculated for 30 lesions with SUVmax \geq 2.5. Histopathology results were considered as the gold standard for diagnosis.

The patient characteristics, FDG-PET/CT scan findings, and the tumor histology were recorded. The data were managed and analyzed using SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL). After checking for normality assumption, the mean and standard deviation were used to express normally distributed data (such as the age and the size of nodule), which were compared by analysis of variance (ANOVA). The median with interquartile range (IQR) was used for non-normally distributed data (such as the standardized FDG uptake value). Inter-group comparison of non-normally distributed data was made by Mann-Whitney nonparametric analysis. χ^2 test was used to compare categorical variables. A p -value <0.05 (two-sided) was considered to indicate statistical significance and 95% confidence intervals (95% CI) were used to express reliability in the estimates.

Receiver operating characteristic (ROC) curve analysis of maximum standardized uptake value (SUVmax) and area under the curve (AUROC) were used to assess discrimination between benign from malignant nodules. Youden index was used to identify the optimal cut-off SUVmax for diagnosing malignancy [10]. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy were used as measures of performance of FDG-PET/CT.

3. Results

The mean age of the patients in our study cohort was 58.7 ± 12.8 years and 72% of them were females. There were 23 follicular adenomas, 8 Hürthle cell adenomas, 11 papillary carcinomas, 6 follicular variant of papillary carcinomas and 2 follicular carcinomas. In all, 19 (38%) nodules were malignant. Hürthle cell neoplasms were identifiable by pre-operative FNAC in 6 (75%) cases. The mean size of the thyroid nodule was 2.6 ± 1.3 cm and there were 4 micro-carcinomas (tumor size = 7.0–8.5 mm). The patients' age ($p = 0.14$) and gender ($p = 0.43$) as well as the median SUVmax ($p = 0.10$) of benign and malignant nodules were not significantly different (Table 1) however, the malignant nodules were significantly smaller ($p = 0.01$) than the benign ones. The median SUVmax value of all thyroid nodules in the study cohort was 3.45 (IQR = 0–7.58) and the SUVmax distribution of the benign and malignant nodules is shown in Fig. 1. All 4 micro-carcinomas in this cohort had SUVmax over 3.25 (range = 3.6–5.9). The SUVmax did not change significantly by partial volume correction ($p = 0.55$). Median MTV was 4.70 (IQR = 1.71–19.95) and median TLG was 20.75 (IQR = 4.87–101.03) for lesions with SUVmax > 2.5. However, there was no statistically significant difference in MTV ($p = 0.116$) and TLG ($p = 0.187$) of benign and malignant follicular neoplasms. All Hürthle cell adenomas showed intense FDG uptake with SUVmax between 3.4 and 33.5 and median SUVmax of 9.3 (IQR = 6.9–19.9).

FDG-PET findings of benign and malignant neoplasms were significantly different ($p = 0.003$), as summarized in Table 2. Focal increased FDG uptake by thyroid nodule had sensitivity of 89% (95% CI, 65–98%), specificity of 35% (95% CI, 19–54%), PPV of 46% (95% CI, 30–63%), and NPV of 85% (95% CI, 54–97%) for diagnosing follicular/Hürthle cell neoplasms. The overall accuracy of FDG-PET/CT was 56%. After excluding Hürthle cell adenomas, the AUROC was

Table 1
Patient demographics and characteristics of benign and malignant follicular/Hürthle cell neoplasms.

	Benign (N = 31)	Malignant (N = 19)	p-value
Mean age	60.9 \pm 12.8	55.3 \pm 12.3	0.13
Gender (Male:Female)	9:22	4:15	0.74
Mean size of the nodule	2.9 \pm 1.3 cm	2.0 \pm 1.1 cm	0.01
Median SUVmax	2.55; IQR = 0–7.60	4.60; IQR = 3.40–7.65	0.10

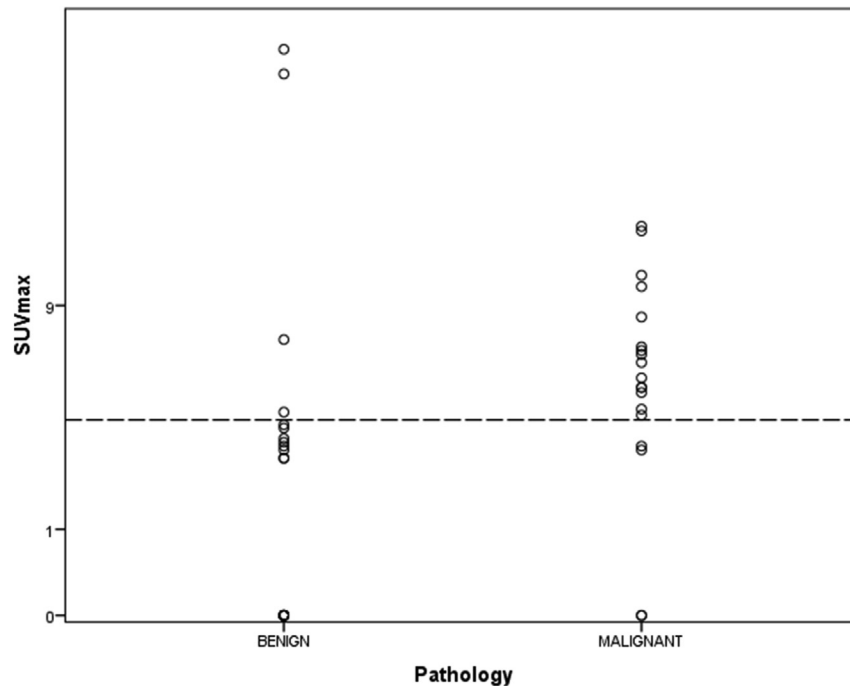


Fig. 1. Scatter plot of SUVmax in benign and malignant non-Hürthle cell follicular neoplasm. Y-axis shows the SUVmax on logarithmic scale (base 10) with reference (dashed) line indicating SUVmax = 3.25. SUVmax was undetectable in 2 malignant and 11 benign neoplasms (SUVmax = 0).

Table 2
FDG-PET/CT findings in follicular neoplasm.

	Carcinoma positive	Carcinoma negative	Total
FDG-PET positive	15	4 ^a	19
FDG-PET negative	4	19	23
Total	19	31	42

^a Excludes 8 Hürthle cell adenomas.

0.79 (95% CI, 0.63–0.94; $p = 0.002$) for discriminating benign from malignant nodules with 3.25 as the best SUVmax cut-off for the purpose. FDG-PET/CT had sensitivity of 79% (95% CI, 54–93%), specificity of 83% (95% CI, 60–94%), PPV of 79% (95% CI, 54–93%), and NPV of 83% (95% CI, 60–94%) with an improved overall accuracy was 81% with this SUVmax cut off.

4. Discussion

Although FNAC and ultrasonography are the mainstays of diagnosis of thyroid cancer, the differentiation between benign and malignant follicular neoplasms remains a challenge both on ultrasound and FNAC. Fifteen to 30% of the thyroid lesions that are reported as follicular neoplasm on FNAC are ultimately malignant [4]. The diagnostic role of FDG-PET scan in diagnosing malignant thyroid nodules has been studied earlier also with variable conclusions [11–18]. According to an earlier systematic review, 1 in 3 FDG-PET positive thyroid nodules was reported to be malignant with significantly higher ($p < 0.001$) mean SUVmax (6.9) as compared to the benign ones (4.8) [19]. We did not find any significant difference between the median SUVmax of benign and malignant thyroid nodules, as has also been reported earlier [14].

The metabolic activity of the thyroid nodule is expressed in terms of SUVmax. Various studies have considered different criteria for PET positivity; ranging from any focal increased uptake in the region of the thyroid nodule above background [11,12,17,18] to different SUVmax cut-offs ranging from 2 to 7 [13,15,20,21].

However, some studies did not find a SUVmax cut-off to be a definite predictor for malignancy [22]. Area under SUVmax curve >175.5 or the heterogeneity factor of FDG uptake >2.751 have also been considered to define FDG-PET positivity [16,23]. In our study group increased focal FDG uptake by thyroid nodules (irrespective of the SUVmax) had a high sensitivity of 89% (95% CI, 65–98%) and specificity of 35% (95% CI, 19–54%) for detecting cancer, similar to those reported in the two meta-analysis: 89.0% (95% CI, 79.0–95.0%) & 55.0% (95% CI, 48.0–62.0%) [24], and 95% (95% CI, 86–99%) & 48% (95% CI, 40–56%) [2], respectively. Selecting an appropriate cut-off value for any diagnostic test is challenging, as lowering the cut-off improves the sensitivity of the test; but does so at the cost of specificity. However, this will increase the number of false positives and lower its PPV, which in this case may result in unnecessary thyroidectomies. On the other hand, if the cut-off is set too high to make the test more specific, the test can miss some thyroid cancers (lower NPV) but will avoid unnecessary thyroidectomies. Ideally a cut-off with best overall accuracy should be considered. Based on the ROC analysis the SUVmax of 3.25 was identified as the optimal cut-off value to discriminate between benign and malignant nodules, which is slightly higher than the recommended cut-off of 2.05 reported in the recent meta-analysis, with much higher specificity (83% vs 42%) [24].

The meta-analyses, however, did not consider Hürthle cell neoplasm separate from other follicular neoplasm, even though all Hürthle cell neoplasm, in the pooled data, showed high FDG uptake [2,24]. We also found intense FDG uptake in Hürthle cell adenomas (median SUVmax = 9.3). Increased FDG uptake in Hürthle cells and poorly differentiated components have been reported earlier to be independent predictive factors of high (≥ 5) SUVmax [20]. Increased FDG uptake by benign Hürthle cell neoplasms [25,26] can often be mistaken for malignancy (false positive). We have recently reported the difference in PET characteristics of follicular and Hürthle cell adenomas [1]. The use of SUVmax cut-off of 3.25 and exclusion of Hürthle cell neoplasms improves the overall accuracy of FDG-PET/CT to 81% from 56% obtained by the use of increased

focal FDG uptake and 60% reported in meta-analysis [2]. The FDG-PET/CT with a PPV 79% (95% CI, 54–93%), observed in this study was much higher than 39% (95% CI, 31–47%) reported in the meta-analysis [2].

To the best of our knowledge, this is the first study which prospectively looked into the impact of intense focal FDG uptake by benign Hürthle cell neoplasms (false positivity), as a cause for lower specificity and PPV of FDG-PET in identifying malignant follicular neoplasms. We found that a cut-off SUVmax of 3.25 provided a higher accuracy with reasonably high sensitivity, specificity, PPV and NPV for predicting malignancy in FDG-PET positive non Hürthle cell follicular neoplasms, as compared to any increased focal FDG uptake by thyroid nodule. The limitation of this study, that we can envision, is the lack of correlation of FDG-PET/CT findings with the molecular markers [27–30], that are recommended for consideration in indeterminate thyroid nodules by the current American Thyroid Association Guidelines [3]. FDG-PET/CT has been reported to offer cost advantage in diagnosing malignant follicular neoplasm as compared to the alternatives of diagnostic thyroidectomy or molecular markers [31]. Use of only a half-dose of FDG could be a potential confounding factor however the same dose was used for all the patients. Further, to compensate for the reduced dose of FDG (185 MBq) to reduce the radiation exposure, the acquisition time was increased by 60%.

To conclude, FDG-PET/CT can help in differentiating benign and malignant non-Hürthle cell thyroid nodules. A cut-off SUVmax of 3.25 enhances the accuracy of FDG-PET/CT in identifying cancers in thyroid nodules. A larger multi-centre study is recommended to confirm these conclusions.

Ethical approval

Research Ethics Board, University of Manitoba (H2010:056).

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None.

Author contribution

Kumar A. Pathak: Study design, data collections, data analysis, writing.

Andrew Goertzen: Data analysis, writing.

Richard W Nason: Study design, writing.

Thomas Klonsch: Study design, writing.

William D Leslie: Study design, data collections, data analysis, writing.

Conflicts of interest

None.

Consent

All patients signed informed consent approved by the Research Ethics Board, University of Manitoba.

Guarantor

Kumar A. Pathak.

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