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Column: Retrospective Study

Reviewer#1

The authors present a manuscript which looks at thyroid incidentaloma in patients' images for other cancers with no known thyroid disease. The study is a retrospective study and all patients with focal metabolic uptake must also have ultrasound and histology or cytology available. The lesions (focal metabolic uptake) were classified as benign or malignant based on histology and cytology. Metabolic indices SUVmax, SUVpeak, SUVmean, MTV and TLG were determined and using statistical analysis the authors found out which of these could best discriminate malignant thyroid from benign thyroid nodule as a cause of focal hypermetabolic uptake.

The authors found SUVmax as the most useful parameters in distinguishing benign from malignant thyroid incidentaloma and determined that 8.5 was useful in making this distinction

Comments

1.Under methodology

Authors must please describe what was done is blood glucose was high. Was the scan rescheduled?

Answer: Thank you for your valuable comments. We generally follow the F-18 FDG PET-CT procedure standards established by Society of Nuclear Medicine and Molecular Imaging (SNMMI) and European Association of Nuclear Medicine (EANM). We check the blood glucose level of the patients when they arrive at the imaging centre and if the level is higher than or equal to 11 mmol/L (200 mg/dL), the scan is rescheduled. If the glucose level is lower than 4 mmol/L (about 70

mg/dL), we contact the relevant clinical department to control the level. We added these to the text.

2. Apart from Hurthle cell adenoma what were the other benign lesions the authors found causing hypermetabolic foci

Answer: According to the pathologic reports, of the twenty benign thyroid lesions, five were Hurthle cell adenoma/proliferative lesions with the highest SUVmax of 10.88 and the mean SUVmax of 6.97. The rest fifteen lesions were benign follicular nodule/lesion/neoplasm with the highest SUVmax of 12.71 (benign follicular lesion by pathology) and the mean SUVmax of 6.58. There was no statistically significant difference of SUVmax between benign Hurthle cell lesions and benign follicular lesions.

3. Under the discussion the authors comment that well differentiated thyroid cancer usually have lower hypermetabolic uptake anaplastic Hurthle cell. From their results most of their cases were papillary (22) or follicular. Could the authors comment whether these were dedifferentiated and whether that may have caused the other metabolic indices not achieve significant discriminating benign from malignant TIs.

Answer: There are many known mutations associated with thyroid cancer and one of them is BRAF mutation. The test for the oncogene BRAF V600E is available at our hospital and, of the 23 well-differentiated thyroid cancer lesions, 19 were BRAF positive and the test was not done for the rest 4 lesions. For the 19 lesions that were tested, 100% mutation was shown. Although it is still not completely sure whether this mutation resulted in a high FDG uptake, conversely, it was confirmed that the FDG-avid well-differentiated thyroid lesions of this study had a high rate of BRAF mutation. This could empower the notion that dedifferentiation is highly responsible for high FDG uptake. We added these to the text.

4. In this study, the authors excluded patient with known thyroid lesions-could this have influenced the lack of discrimination of benign and malignant nodules using TLG?

Answer: The patients with previous/known thyroid disease would be considered inappropriate for the research subjects “thyroid incidentaloma” of this study. If those were included, the positive rate might be affected. A volume is one of the components of the TLG calculation formula and there are reports saying the malignancy does not necessarily increase as the volume of thyroid lesion increases. For the same reason, it seems less likely that the differentiation power of TLG will improve regardless of whether or not the patients with existing thyroid disease are included.

5. The use of SUVmax to distinguish benign from malignant pathology can be challenging when there are granulomatous lesion (may give high values like malignant lesions). Do the authors envisage a similar problem in the thyroid TI?

Answer: We think it's possible enough. Fundamentally, FDG is taken up by cells with high glucose metabolism and it is difficult to differentiate malignant lesions from benign ones only by the amount of uptake. Therefore, if the metabolism of a certain nodule/mass (including granulomatous lesions) is increased, it is still a challenge to distinguish benign lesions from malignant ones.

6. The first part of the discussion takes about higher metabolic uptake from dedifferentiated thyroid cancer however the study or findings do no address this authors should please attempt to explain some of their finding in light of this otherwise that explanation becomes irrelevant to the current study

Answer: We mentioned “dedifferentiation” just to explain that a silent indolent well-differentiated thyroid cancer could be discovered as a visually identified hypermetabolic incidentaloma as tumour progresses (dedifferentiated). In this study, BRAF mutation was found in 100% of all 19 well-differentiated malignant

thyroid lesions which underwent the mutation test, however, dedifferentiation itself is not a major concern of this study. Nevertheless, considering that this study was conducted on hypermetabolic lesions discovered with the naked eye, lesions not yet advanced (low probability of high FDG uptake) had less chance to be observed on images and eventually excluded from the study. This unrecognised selection bias probably resulted in a high FDG uptake even in the well-differentiated thyroid cancer. Conversely, if thyroid cancer was diagnosed histopathologically first and then FDG PET-CT was performed, there would be more lesions with low FDG uptake. We added these to the text.

7. There appears to be lack of space between certain words in the document such as “diseaseby’

Answer: We are sorry about that. We are going to check it again and correct all.

Reviewer#2

Comment

It is a interesting manuscript and retrospective study. I sugesting that the authors discribe if in literature has others comparatives studies.

Answer: There are papers analysing F-18 FDG PET-CT parameters such as standardised uptake value (SUV), metabolic tumour volume (MTV), and total lesion glycolysis (TLG) for thyroid incidentaloma. To introduce some examples:

i. The Role of Metabolic Volumetric Parameters in Predicting Malignancy in Incidental Thyroid Nodules Detected in (18)F-FDG PET/CT Scans.,Erdogan M et al., Mol Imaging Radionucl Ther 2021; 30: 86-92 [PMID: 34082507 DOI: 10.4274/mirt.galenos.2021.75983]

In the study, the authors concluded that TLG was useful for the evaluation of thyroid incidentaloma.

ii. Radiomics Analysis of [(18)F]-Fluorodeoxyglucose-Avid Thyroid Incidentalomas Improves Risk Stratification and Selection for Clinical Assessment., Ceriani L et al., *Thyroid* 2021; 31: 88-95 [PMID: 32517585 DOI: 10.1089/thy.2020.0224]

The authors concluded that TLG and maximum SUV might provide useful information for the management of thyroid incidentalomas.

iii. Diagnostic Value of Volume-Based Fluorine-18-Fluorodeoxyglucose PET/CT Parameters for Characterizing Thyroid Incidentaloma., Shi H et al., *Korean J Radiol* 2018; 19: 342-351 [PMID: 29520193 DOI: 10.3348/kjr.2018.19.2.342]

The authors concluded that TLG and MTV could potentially have clinical value in differential diagnosis of thyroid incidentaloma along with SUVmax.

iv. Diagnostic Value of FDG PET-CT Quantitative Parameters and Deauville-Like 5 Point-Scale in Predicting Malignancy of Focal Thyroid Incidentaloma., Thuillier P et al., *Front Med (Lausanne)* 2019; 6: 24 [PMID: 30809525 DOI: 10.3389/fmed.2019.00024]

The authors concluded that none of the parameters were significant predictors of malignancy of focal thyroid incidentalomas.

v. Diagnostic value of metabolic tumor volume assessed by 18F-FDG PET/CT added to SUVmax for characterization of thyroid 18F-FDG incidentaloma., Kim BH et al., *Nucl Med Commun* 2013; 34: 868-876 [PMID: 23797273 DOI: 10.1097/MNM.0b013e328362d2d7]

The authors concluded that a combination of maximum SUV and MTV with a SUV threshold of 4 might be more useful for the differentiation of malignant from benign thyroid incidentaloma.

Each study shows slightly different results from the others. In our study, only

maximum SUV was a significant parameter in differentiating malignant focal hypermetabolic thyroid incidentalomas from benign ones, and the two volumetric parameters, MTV and TLG, were not significant.

We deeply appreciate your attentive review, advice, and valuable time.

Thank you.