

## Original Article

# Utility of metabolic heterogeneity factor in differentiating malignant versus benign parotid uptake on $^{18}\text{F}$ FDG PET-CT

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Received May 29, 2018; Accepted October 22, 2018; Epub December 20, 2018; Published December 30, 2018

**Abstract:** Differentiation of benign and malignant parotid uptake on Fluorine 18 Fluro-Deoxy-Glucose Positron Emission Tomography-Computed Tomography ( $^{18}\text{F}$  FDG PET-CT) is of paramount importance due to the poor prognosis of the later but usual quantitative measures such as standardized uptake value (SUV) are not reliable for this purpose. Metabolic heterogeneity, being a characteristic of malignant tumors, would potentially be able to make this distinction. In this study, seventy-one FDG-avid parotid lesions were retrospectively separated histologically into benign and malignant groups. The heterogeneity factor (HF) of all the lesions was then calculated and compared between the two groups. There was significant difference in HF between malignant (median -0.17) and benign group (median -0.03);  $P=0.0006$ . On receiver operating characteristic (ROC) analysis, a cut-off value of  $\leq -0.06$  for HF was associated with the highest sensitivity and specificity (sensitivity and specificity of 94.6% and 60.0%, respectively-  $\text{AUC}=0.789$ ;  $P=0.0001$ ). Hence, it was concluded that HF is a reliable value in distinguishing benign from malignant parotid uptake on  $^{18}\text{F}$  FDG PET-CT.

**Keywords:** Heterogeneity factor, parotid malignancy,  $^{18}\text{F}$  FDG PET-CT

## Introduction

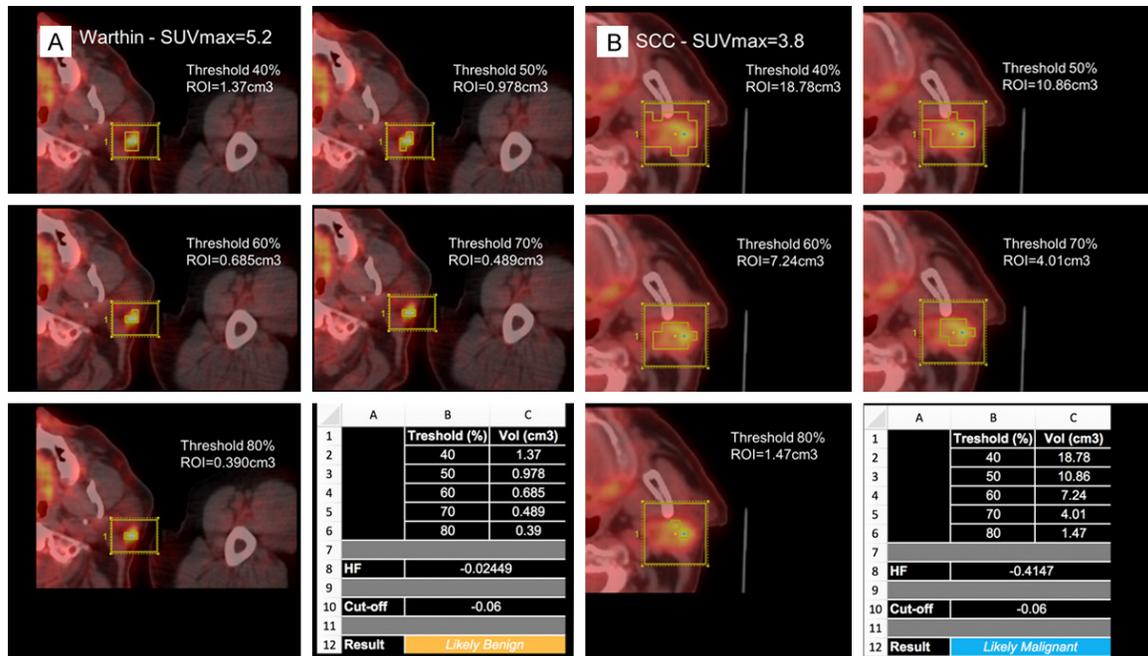
Incidental focal FDG uptake in the parotid is not uncommon and is seen in up to 0.4% of oncology  $^{18}\text{F}$  FDG PET-CT scans [1]. However, it may be difficult to differentiate the malignant from benign parotid tumors, which have significantly different survival outcome, by SUV only as some benign tumors may also show very avid FDG uptake (typically Warthin tumor), while some malignant tumors (typically adenoid cystic carcinoma, low grade mucoepidermoid carcinoma or necrotic squamous cell carcinoma) may have no significant FDG avidity [2-7]. Therefore, SUV is an unreliable parameter for differentiating malignant versus benign FDG uptake in parotid which necessitates the need for another more reliable imaging driven value for more reliable distinction.

Focal avid FDG uptake in the parotid gland is usually further investigated by clinical examination, ultrasound, fine needle aspiration cytol-

ogy (FNAC) or ultrasound guided core biopsy (USCB). Parotid FNAC and USCB, although minimally invasive procedures, still carry out a small risk of complications such as bleeding, hematoma, infection and tumor seeding; these procedures also occasionally lead to inconclusive or false negative results. If proven useful to distinguish between benign and malignant parotid uptake, measuring HF of a parotid incidentaloma on  $^{18}\text{F}$  FDG PET-CT could reduce the number of radiological investigations and invasive procedures which are currently being undertaken to discriminate between the two entities.

There is now established evidence of connection between histological intratumoural heterogeneity in malignant tumors and their microenvironment properties such as tumoral microbiology, vascular distribution, lack of oxygen, apoptosis and necrosis, cellular proliferation, cellular structure and inflammation [8-12]. However, this is also known that the distribution of these properties within a tumor is inhomogeneous

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**Figure 1.** Comparison between a benign (A) and a malignant (B) parotid lesion by measuring lesion's volume with different SUV thresholds and calculating the HF in a Microsoft Excel worksheet as explained in detail in the methods section of this article. HF of the benign lesion (Warthin's tumor) is calculated at -0.024 and the malignant lesion (SCC) at -0.41 (cut-off value for malignancy  $\leq -0.06$  as per our study results-the higher negative value indicates more heterogeneous uptake which favors malignancy). As illustrated, the SUVmax is not useful in distinguishing benign from malignant lesion in this example.

[13]. Therefore, analysis of a volume of interest (VOI) around the FDG-avid uptake in the parotid would allow for the assessment of intratumoural heterogeneity and calculation of HF which is further elaborated in the methods section of this article.

HF, which is derived from linear regression line and calculated the derivative  $[dV/dT]$  from volume-threshold function, has already been shown to be more useful than maximum standardized uptake value (SUVmax) and total lesion glycolysis (TLG) in differentiating malignant versus benign parotid lesions on  $^{18}\text{F}$  FDG PET-CT [14]. The aim of this study is to further investigate whether HF is a reliable parameter in distinguishing benign versus malignant parotid uptake on  $^{18}\text{F}$  FDG PET-CT.

### Methods

This study has been approved by Hunter New England Human Research Ethics Committee.

### Patients

Between January 2010 to January 2016, a total of 14,794  $^{18}\text{F}$  FDG PET-CT scans were per-

formed in our institution for various indications. All the reports were retrospectively searched for the word "parotid" and 525 scans were identified. These were then reviewed individually and all scans with focal avid FDG uptake in the parotid that underwent histopathological characterization were selected.

We excluded the patients who had diffuse uptake in the gland, lymphoma located at multiple sites and patients who has diagnostic or therapeutic invasive procedures prior to  $^{18}\text{F}$  FDG PET-CT. We did not exclude the patients whose final diagnosis of avid parotid lesion was determined as intra-parotid lymph node on histopathology.

### $^{18}\text{F}$ FDG PET-CT imaging

Images were obtained using a dedicated PET-CT camera (Discovery 690 PET/CT, GE Healthcare, Milwaukee, WI, USA). The images were displayed on an Advanced Workstation (Version 4.4, GE Healthcare, Milwaukee, WI, USA) and were analyzed by a Nuclear Medicine physician. Imaging was performed 60 minutes post intravenous administration of  $^{18}\text{F}$  FDG.

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**Table 1.** The histopathological characteristics of the study patients (n=71) along with measured heterogeneity factor and SUVmax on <sup>18</sup>F FDG PET-CT scans

Histopathology	Number of patients (%)	HF (range)	SUVmax (range)
<i>Malignant tumors</i>			
SCC (including metastatic)	32 (45.1%)	-1.6046 to -0.0166	2.0 to 39.0
Metastatic Melanoma	8 (11.3%)	-1.1492 to -0.0156	2.1 to 11.6
Neuroendocrine	4 (5.6%)	-2.1055 to -0.0754	3.3 to 27.6
Large cell undifferentiated carcinoma	1 (1.4%)	-0.1701	11.3
Mucoepidermoid carcinoma	1 (1.4%)	-0.3589	7.7
Epithelial-myoeepithelial carcinoma	1 (1.4%)	-0.0615	7.6
Dedifferentiated acinic cell carcinoma	1 (1.4%)	-0.1243	5.0
Malignant epithelial tumor	1 (1.4%)	-0.1703	7.4
Poorly differentiated carcinoma	3 (4.2%)	-1.2861 to -0.0606	6.1 to 13.5
Merkel cell carcinoma	1 (1.4%)	-0.1302	9.3
Epithelial tumor not otherwise specified	1 (1.4%)	-0.8821	3.3
Metastatic carcinoma	1 (1.4%)	-0.2172	41.8
Large B-cell lymphoma	1 (1.4%)	-0.2257	15.4
<i>Benign lesions</i>			
Warthin tumor	5 (7%)	-0.3374 to -0.0235	3.5 to 34.4
Pleomorphic adenoma	1 (1.4%)	-0.0127	6.1
Granulomatous inflammation	1 (1.4%)	-0.24253	4.7
Chronic suppurative sialadenitis	1 (1.4%)	-0.3512	10.1
Reactive node	1 (1.4%)	-0.0195	11.2
Benign intra-parotid node	2 (2.8%)	-0.0919 to -0.0262	6.6 to 10.5
Benign salivary gland with oncocytes	2 (2.8%)	-0.2098 to -0.0136	3.5 to 3.8
Benign parotid tissue	2 (2.8%)	-0.1789 to -0.1096	3.4 to 5.1

The emission scan time per bed position was 2 minutes and 8 bed positions were acquired.

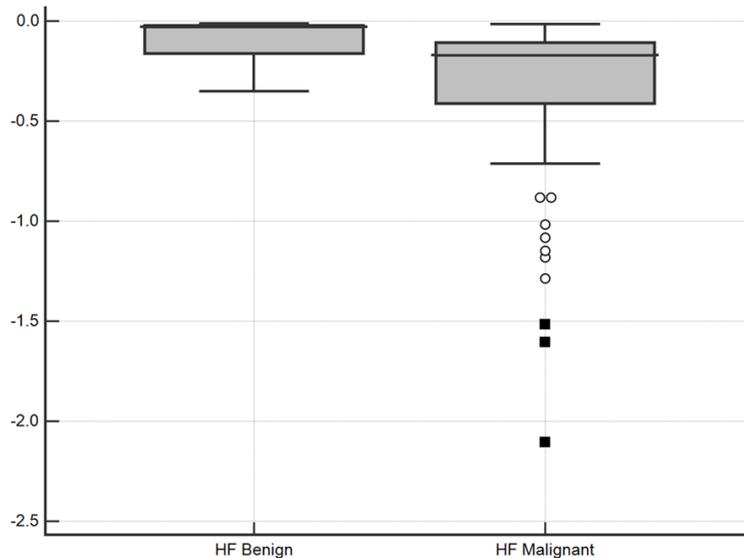
### *Measurement of heterogeneity factor*

HF was calculated by drawing a region of interest (ROI) around the FDG avid lesion in the parotid fully including the primary lesion and a surrounding region of normal tissue as background. The tumor volume was determined with a series of SUV thresholds (40%, 50%, 60%, 70%, and 80% of SUVmax). These thresholds were chosen and aimed to exclude the background contribution within the parotid regions. The HF was derived from linear regression line and calculated the derivative (dV/dT) from volume-threshold function. It is shown as a negative value with a lower value representative of a more heterogeneous uptake (**Figure 1**). As HF is a purely image driven value, no adjustments were needed to be made for patient's age or gender. The HF was calculated by an experienced nuclear medicine physician. For inter-observer assessment purposes only, the val-

ues were calculated by a nuclear medicine registrar as well.

The volume of a hypermetabolic lesion on <sup>18</sup>F FDG PET-CT is dependent on SUV cut-off threshold. If the SUV cut-off threshold is reduced, the calculated volume would be higher as the low-grade area surrounding the lesion will also be included. The calculation and interpretation can be simplified in a Microsoft Excel worksheet. Threshold values (40%, 50%, 60%, 70% and 80%) are typed in B2, B3, B4, B5 and B6 cells and the metabolic volume corresponding to each threshold, which is derived from PET-CT reporting workstation, is charted in the next column in corresponding C2, C3, C4, C5 and C6 cells. The HF is then calculated in a separate cell (e.g. B8) by formula “=SLOPE (C2:C6, B2:B6)”. To simplify this for day to day use in clinical practice, another cell (e.g. B10) could be used for HF cut-off value and the final outcome could be further simplified by another formula in another cell (e.g. B12) “=IF (B8 ≤ B10, “Likely Malignant”, “Likely Benign”)”. Two examples of the above proce-

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**Figure 2.** Box Whisker plot of heterogeneity factors of the benign and malignant lesions.

dures in a patient with benign parotid lesion (Warthin's tumor) and another patient with malignant parotid lesion (SCC) are illustrated in (Figure 1).

This is a method of quantification of uniformity or heterogeneity of a lesion on  $^{18}\text{F}$  FDG PET-CT imaging. When there is uniform FDG uptake, the volume changes little with different thresholds resulting in a lower slope; with increased heterogeneity of a tumor though, the volume changes are more significant between different thresholds, so is the slope.

### Statistical analysis

Statistical analyses were performed using MedCalc Statistical Software (Version 17.2, MedCalc Software bvba, Ostend, Belgium). For statistical differences of HF between the benign and malignant parotid uptake a Mann-Whitney U test was performed. Receiver operating characteristics (ROC) analysis and Youden index was used to determine optimal cut-off values between benign and malignant FDG uptake in the parotids. The sensitivity, specificity and the area under curve (AUC) value of the HF were also calculated.

### Results

72 patients with focal avid  $^{18}\text{F}$  FDG uptake in the parotid underwent histopathological characterization; one lesion was reported as non-diagnostic on cytology hence was excluded

from the analysis. A total of 71 patients were selected for analysis, 56 lesions were malignant, and 15 lesions were benign. Patients with focal avid FDG uptake and a final diagnosis of intra-parotid lymph node on histopathology were not excluded; there were five such nodes with metastatic squamous cell carcinoma (SCC), two with metastatic melanoma and two with benign inflammatory changes. The histological nature of the benign and the malignant lesions are listed in (Table 1). The mean age of the patients in malignant group and benign group were 75 and 64, respectively.

The median HF in the malignant group was -0.17 (95% confidence interval-CI-for median -0.27 to -0.13, range -2.11 to -0.02) and in the benign group was -0.03 (95% CI for median -0.16 to -0.02, range -0.35 to -0.01);  $P=0.0006$  (Figure 2). At a cut-off value of  $\leq -0.06$ , the sensitivity and the specificity were 94.64% (95% CI, 85.1-98.9) and 60% (95% CI, 32.3-83.7), respectively. The inter-observer agreement for HF calculation (Intraclass Correlation Coefficient-ICC) between the nuclear medicine physician and the registrar was 0.84 on a single measurement (95% CI 0.75-0.90) and 0.91 on average (95% CI 0.86-0.95).

### Discussion

Intra-tumoural heterogeneity is a significant feature of malignant tumors and many factors such as the microenvironment biology of the tumor, vascularity, low oxygenation, necrosis, cellular proliferation, cellular composition and inflammation contribute to tumor heterogeneity and FDG uptake [8-12]. Several studies have documented that metabolic heterogeneity has an important role in predicting survival or response to the therapy in malignancies [15-18].

We found a statistically significant difference in HF between the malignant and the benign parotid lesions on  $^{18}\text{F}$  FDG PET-CT;  $P=0.0006$ . At a cut-off HF value of  $\leq -0.06$ , the sensitivity and the specificity to differentiate the two was 94.64% and 60%, respectively. Kim BS et al.

demonstrated that HF on  $^{18}\text{F}$  FDG PET-CT has statistically higher value in differentiating malignancy in parotid than other parameters such as SUVmax. They showed that at a cut-off value of  $\leq -0.084$ , the HF had 100% sensitivity (95%, CI 81.5-100) and 89.2% specificity (95%, CI 71.8-97.7) in distinguishing malignant FDG uptake in parotid [14]. The median HF in their study in benign group was -0.06 (compared to -0.03 in our study) and in the malignant group was -0.30 (compared to -0.17 in our study).

Relative to Kim BS et al. study, we had a larger sample size (71 patients versus 46), particularly in the malignant group (56 patients versus 18); acknowledging that we had lesser patients in the benign group (15 patients versus 28), and a broader spectrum of the underlying pathologies in the parotid, particularly in the malignant group, as shown in (Table 1). The difference in the cut-off values between the two studies is most likely due to (but not limited to) the difference in the sample size and the large variation between the histopathology of the benign and malignant lesions between the two studies.

Additionally, we also demonstrated that measuring HF is simple and practical with a high level of inter-observer agreement (Intraclass Correlation Coefficient of 0.84 on a single measurement, 0.91 on average) between the two different readers.

This retrospective study had several limitations. Firstly, the bias introduced by our selection criteria resulting in many FDG-avid lesions without histopathological evaluation to be excluded. In fact, this in addition to the high incidence of squamous cell skin cancer and melanomas in Australia have resulted in a somewhat unnatural distribution of the parotid malignancies in our study when reference is made to the incidence reports in the literature. However, when the metastatic melanoma scans were reviewed, only one patient had further metastasis in the lung and the remainder 7 patients only had disease in the parotid gland (or an intra-parotid node). Similarly, following reviewing the pathology reports of SCC patients, there was only one cutaneous SCC with deep invasion into the parotid. Of the remainder 31 patients with SCC in the parotid (or an intra-parotid node), 9 were reported to have metastatic SCC of which only two had evidence

of extra-parotid malignancy (both pulmonary) on the  $^{18}\text{F}$  FDG PET-CT. Secondly, this study had a relatively small sample size. Additional studies with larger patient population and a broader spectrum and more even distribution of benign and malignant pathologies are needed to form further consensus particularly in regard to a more standardized cut-off value for HF.

### Conclusion

This study supports the hypothesis that HF on  $^{18}\text{F}$  FDG PET-CT is a reliable parameter for differentiating between benign and malignant FDG uptake in the parotid. Additionally, knowing that intratumoural heterogeneity is a prominent feature of many other malignancies, HF may also have a role in distinguishing benign versus malignant FDG-avid lesions in other organs such as thyroid, lung and adrenal which could potentially be the next research endeavor.

### Disclosure of conflict of interest

None.

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