



Palatine tonsil SUVmax on FDG PET-CT as a discriminator between benign and malignant tonsils in patients with and without head and neck squamous cell carcinoma of unknown primary

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AIM: To analyse the maximum standardised uptake value (SUVmax) ratio between tonsils in patients with and without tonsillar carcinoma to determine useful diagnostic thresholds.

MATERIALS AND METHODS: Positron-emission tomography (PET)/computed tomography (CT) examinations of patients with suspected head and neck squamous cell carcinoma (SCC) and controls from April 2013 to September 2016 were reviewed retrospectively. Tonsillar SUVmax ratios (ipsilateral/contralateral for malignant tonsils, maximum/minimum for patients without [controls]) were calculated and used to construct a receiver operating characteristic (ROC) curve.

RESULTS: Twenty-five patients had tonsillar carcinoma (mean SUVmax ratio of 2, range 0.89–5.4) and 86 patients acted as controls (mean SUVmax ratio of 1.1, range 1–1.5). Using the ROC, the most accurate SUVmax ratio for identifying malignancy was >1.2 (77% sensitivity, 86% specificity). A potentially more clinically useful SUVmax ratio is ≥ 1.6 with 62% sensitivity and 100% specificity.

CONCLUSION: An SUVmax ratio between tonsils of ≥ 1.6 is highly suspicious for SCC and could be used to direct site of biopsy. Some malignant tonsils had normal FDG uptake; therefore, PET/CT should not be used to exclude tonsillar cancer. Minor asymmetrical uptake is frequently seen in non-malignant tonsils and does not necessarily require further investigation. Due to the single centre nature of this study and the recognised variation in SUV measurements between PET scans, other centres may need to develop their own cut-offs.

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Introduction

Head and neck (HN) squamous cell carcinoma (SCC) can present with neck lumps from cervical lymph node metastases, the presence of which is usually confirmed using fine-needle aspiration (FNA). If no primary is identified by outpatient examination of the HN and computed tomography (CT) and/or magnetic resonance imaging (MRI) then the patient is determined as having a cancer of unknown primary (CUP) of the HN.¹ However, identification of the primary tumour is important both for accurate staging and because optimum treatment for patients with CUP is uncertain. Some centres treat the neck disease alone, whereas others will treat some or all potential primary sites with radiotherapy +/- chemotherapy.²

Recent guidelines have recommended combined 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography (PET) – computed tomography (CT) as the imaging investigation of choice to non-invasively attempt to detect the primary tumour.^{1,2} In terms of the ability to diagnose a palatine tonsillar primary using PET-CT, Davison *et al.*³ compared the uptake in malignant and contralateral tonsils and found that the maximum standardised uptake value (SUVmax) ratio between sides had a better diagnostic accuracy (AUC: area under the receiver operating characteristic curve [ROC]) than SUVmax alone and SUVmax difference between tonsils. However, there is a discrepancy in the literature on the recorded range of values of tonsillar SUVmax ratio in patients with and without palatine tonsillar SCC. Davison *et al.*³ reported a complete separation of the ranges of SUVmax ratio between the groups with malignant and non-malignant tonsils, but Lee *et al.*⁴ reported an overlap. Whether or not there is overlap between the ranges is important as it affects the certainty with which PET-CT can be used to predict the presence or absence of tonsillar carcinoma. More in line with the findings of Lee *et al.*⁴ we have observed patients who had normal FDG uptake within their palatine tonsils who later had a tonsillar SCC proven at biopsy.

The primary aim of the present study was therefore to analyse FDG PET-CT examinations of patients evaluated for HN CUP and to analyse the SUVmax ratio between tonsils of patients with and without tonsillar carcinoma. This would allow the identification of SUVmax ratios that could be used to predict the likelihood of the presence or absence of tonsillar SCC.

Patients referred for FDG PET-CT for non-HN indications may also show incidental asymmetrical FDG uptake in their tonsils, leading to a concern that this could represent an incidental primary tonsillar malignancy. A secondary aim was therefore to identify the range of SUVmax ratios in patients with suspected HN CUP who did not have tonsillar SCC and in an additional group of patients referred for non-HN indications. This would facilitate more accurate PET-CT reporting and patient management when asymmetrical incidental tonsillar FDG uptake is observed.

Materials and methods

This was a retrospective analysis of palatine tonsillar appearances of patients who were referred for FDG PET-CT as part of their routine clinical care. Approval for the research was gained from the institution at which it was performed, but separate ethics approval and patient consent were not required and data were kept fully anonymised.

Patient selection

The FDG PET-CT images of all patients who had been referred with clinical codes of 'unknown primary' by the HN team between April 2013 and September 2016 were retrieved. Patients who underwent FDG PET-CT after pan-endoscopy and biopsy were excluded. Patients with previous tonsillectomy that was not due to cancer were included as SCC can arise in the tonsillar remnant⁵ and the patient's tonsillectomy status is frequently unknown at the time of PET-CT reporting. *N*=79 patients fitted the inclusion criteria. *N*=25 patients were diagnosed with a tonsillar primary (tonsil group) and *n*=50 patients had confirmed non-tonsillar primary (control group 1). Not all patients in control group 1 had HN SCC, however, these patients were still included as the FNA results and the final diagnosis is frequently not known at the time of PET-CT reporting. Excluding these patients would therefore result in the study not being a true representation of the PET-CT examinations undertaken and reported for potential HN CUP. Three patients were excluded as they had pathological uptake from a non-tonsillar primary site extending into the tonsil, and one patient was excluded as they had had previous tonsillar carcinoma and were referred with a second HN primary.

FDG PET-CT for a non-HN control group of 36 patients (control group 2), referred for variety of non-HN indications (such as lymphoma, lung cancer, or non-malignant pathologies) were analysed, three patients from each calendar month from July 2015 to June 2016. Patients who had lymphoma with suspicion of tonsillar involvement were excluded. Patients were selected equally across the calendar year to account for any possible change in tonsil appearances due to seasonal variation in viral upper respiratory tract infections.

PET-CT image acquisition and SUV measurements

Patients fasted for 6 hours. Blood glucose was measured prior to scanning to check this was within the range of 4–8 mmol/l. Patients were injected with 350 MBq of FDG and after an uptake time of 90 minutes they were scanned using GE Discovery 710 PET-CT systems in the three-dimensions acquisition mode. Patients were first scanned with a HN protocol from the midbrain to lung apex, with arms down, supine, head first, at two bed positions, 3 minutes per bed and an overlap of 11 sections. Once completed, a second PET examination immediately followed with a half-body protocol (6–9 bed positions, 3–4 minutes per bed, 11

sections overlap). Unenhanced helical CT was obtained for attenuation correction and localisation prior to each PET examination, with tube voltage 140kV, detector coverage 40 mm (64×0.625mm), helical thickness 2.5 mm, pitch 1.375, rotation speed 0.5 seconds. CT examinations for the HN had a fixed beam current of 70mA, and modulated current (SmartmA, noise index=40, range 15–100 mA) for the half-body scan. PET images were reconstructed using the iterative time of flight algorithm (GE Vuepoint FX) with voxel sizes 2.73×2.73×3.27mm. CT images were reconstructed with the adaptive statistical iterative (ASiR) algorithm.

SUV accuracy was maintained with a quarterly scanner normalisation and cross-calibration of the PET machines with the dose calibrator, daily checks on the cross-calibration, and an annual check of the patient scales accuracy.

Image analysis

Regions of interest (ROIs) were manually drawn around both tonsils and the SUVmax within each tonsil recorded using Hermes Gold 3 (Sweden) software. The SUVmax ratio between tonsils was calculated where:

$$\text{SUVmax ratio} = \text{SUVmax of ipsilateral tonsil} / \text{SUVmax of contralateral tonsil}$$

The ipsilateral tonsil was considered to be the tonsil on the same side as the pathological lymph nodes for the tonsillar carcinoma group. For the control groups 1 and 2, the tonsil with the highest SUVmax was considered the “ipsilateral” tonsil.

CT features on low-dose unenhanced CT were also examined. In patients with tonsillar SCC, CT appearances of the tonsils were recorded using the following categories: 1=no asymmetry; 2=mild asymmetry (asymmetry is present but, on CT appearances alone, it is not possible to accurately determine whether or not the asymmetry is likely to be pathological or physiological); 3=definite asymmetry (based on CT appearances alone it is highly likely to be pathological).

Statistical methods

GraphPad Prism (v7.03, <http://www.graphpad.com/>) was used to perform statistical analysis. The mean and standard deviation of the SUVmax ratio of the three groups of patients were calculated. ROC curves were constructed and used to determine the AUC and the optimal cut-off for the

detection of tonsillar primaries (defined as the minimum of the sum of squares of 1–sensitivity and 1–specificity, equivalent to the point nearest the top left corner of the ROC curve).

The Shapiro–Wilk test was used to test normality of SUVmax ratios in each group. SUVmax ratios in all three groups were found to deviate significantly from normality and this was not improved with a log-transform, hence non-parametric methods were used to analyse the data. The Kruskal–Wallis test was conducted to assess for any difference in SUVmax ratio between the three groups. Dunn’s test with multiple comparison corrections used to establish differences in mean rank between pairs of groups.

Results

Patient demographics for the three groups of patients are shown in Table 1. The final diagnosis for control group 1 is shown in Table 2. The tonsil SUVmax, SUVmax ratio and CT appearances are shown in Table 3. The Kruskal–Wallis test revealed a highly significant difference in SUVmax ratio between the three groups (Kruskal–Wallis statistic 27, $p < 0.0001$). Post-hoc Dunn’s test (with multiple comparison corrections) showed highly significant differences in mean rank between the tonsil group and control group 1 ($p < 0.0001$) and between the tonsil group and control group 2 ($p < 0.0001$). No significant difference was established between the control groups ($p = 1.0$). Figs 1 and 2 are examples of patients with FDG-avid tonsillar SCC and of CT appearances of the tonsils classified as 1 and 2. Three patients with tonsillar carcinoma had completely normal uptake with SUVmax ratios of 0.89, 1, and 1.1, the PET-CT appearances for one of these patients is shown in Fig 3. Fig 4 shows the range, interquartile range, and median for the SUVmax ratio between tonsils in all three groups of patients. As expected the median and range is much higher in the malignant group and the two control groups appear quite similar.

Fig 5 shows the ROC curve for the use of tonsillar SUVmax ratio for the diagnosis of tonsillar carcinoma. The AUC is 0.83 (95% confidence interval [CI]=0.71–0.96). The optimal cut-off ratio is 1.2, which has a sensitivity of 77% and a specificity of 86%; however, a potentially more clinically useful cut-off SUVmax ratio with a 100% positive predictive value (PPV) is ≥ 1.6 . This has a sensitivity of 62% and specificity of 100%.

Table 1
Patient demographics for the SCC and control groups.

Patient characteristics	Tonsillar SCC group (n=25)	Control group 1 (suspected HN SCC, non-tonsillar primary) (n=50)	Control group 2 (no HN pathology) (n=36)
Age (years) mean, range	61, 48–72	64, 28–92	62, 27–87
Gender			
Male (%)	69	71	50
Female (%)	31	29	50

HN, head and neck; SCC, squamous cell carcinoma.

Table 2
Final diagnoses for the patients in control group 1.

Diagnosis	Percentage
Base of tongue SCC	16
HN SCC of “true” unknown primary	12
Piriform fossa SCC	4
Oropharynx SCC (but not tonsil)	2
Supraglottic SCC	4
Vocal cord SCC	2
Vallecula SCC	2
Olfactory neuroblastoma	2
Nerve sheath tumour	2
Salivary gland pathology (parotid cancer, pleomorphic adenoma)	6
Thyroid cancer	6
Non-HN malignancy ^a	28
No malignancy found ^b	14

HN, head and neck; SCC, squamous cell carcinoma.

^a Lung cancer, oesophageal cancer, lymphoma, prostate cancer, endometrial cancer, poorly differentiated adenocarcinoma, skin SCC, melanoma.

^b After comprehensive work-up including FNA of neck lump if present.

Discussion

SUVmax ratio and PET-CT appearances of tonsillar carcinoma

A range of SUVmax ratios (0.89–5.44) were identified in patients with proven tonsillar SCC. This is nearly identical to the range reported by Lee *et al.*⁴ of 0.85–5.45, but different to the range of 1.48–8.31 reported by Davison *et al.*³ This is an important finding as it provides further evidence that there is an overlap in the range of SUVmax ratios between malignant and non-malignant tonsils, and that PET/CT cannot be used to exclude tonsillar carcinoma. However, an SUVmax ratio of ≥ 1.6 has 100% specificity and PPV for malignancy; therefore, this SUVmax ratio could be used to predict that the tonsil is a likely primary site. This could obviate the need for panendoscopy and directed biopsies, and the associated morbidity in terms of pain, dysphagia and bleeding risk. This ratio of ≥ 1.6 is similar to the SUVmax ratio of 1.48, which had 100% specificity reported by Davison *et al.*,³ although they reported a 100% sensitivity for this ratio and the present study found a sensitivity of 62%. The difference in sensitivity between the present study and that of Davison *et al.* is likely because Davison *et al.* only analysed patients with known tonsillar SCC, they did not specify if they included patients who initially presented with CUP. The poor sensitivity of 62% should not be a cause for

concern because, when imaging has not detected a primary tumour, according to UK guidelines,¹ the patient should still proceed to panendoscopy, directed biopsies, and bilateral tonsillectomy, and this would ensure that a tonsillar primary will be detected if it exists.

All three patients who had no detectable increased FDG uptake in their malignant tonsil had T1 disease. This can help explain why they were FDG negative, it is expected that smaller tumours are more likely to have lower uptake of FDG due to technical factors such as partial volume effects, the 6–8 mm resolution of PET and count rate statistics. Increased FDG uptake that could occur in small tumours may also be more difficult to detect when it is occurring in the tonsils as they frequently have normal physiological increased FDG uptake. Higher false-negative rates in smaller tumours was also found by Lee *et al.*⁶ who reported false-negative results on FDG PET-CT in 22.3% of patients with T1 HN SCC, but only 2.2% of T2 tumours.

Additionally human papilloma virus (HPV)-positive primary tumours have been found to demonstrate lower FDG avidity than HPV-negative tumours.⁷ Although a limitation of this study is that HPV status was not recorded in all tumours, three patients with no detectable increased FDG uptake in their malignant tonsil were all positive for HPV.

A more minor, but useful, finding from this study is that normal CT appearances should not be used as evidence that there is not a tonsillar primary, as 56% of patients with tonsillar carcinoma had no CT asymmetry and a further 20% had only very mild asymmetry. Although it should be noted these were unenhanced, low-dose CT examinations and that the discriminatory power of CT on diagnostic contrast-enhanced CT may be better.

SUVmax ratio of non-malignant tonsils

The range of tonsillar SUVmax ratios is 1.0–1.48 in patients with HN pathology and 1.0–1.28 in patients without. These results are similar to Davison *et al.*³ who reported an SUVmax ratio range of 1–1.48 in their control group of patients with non-tonsillar HN SCC and to Lee *et al.*⁴ who reported 0.86–1.25 in patients with non-tonsillar HN SCC and 1.01–1.49 in patients without cancer, but with risk factors for HN SCC.

Therefore, the present study has provided additional evidence that mild asymmetrical tonsillar FDG uptake occurs in a population without tonsillar carcinoma or other HN pathology. Taking into account other published ranges, the upper limit of this ratio is 1.5; however, as shown in the

Table 3
Maximum standardised uptake value (SUVmax) and the range, mean and standard deviation of the SUVmax ratio for malignant tonsils and controls.

	SUVmax of tonsils	Range of ratio (I/C) (Max/min)	Mean (SD) of ratio	CT appearances of tonsil group
Malignant tonsils <i>n</i> =25	3.3–18.3	0.89–5.44	2.0 (1.17)	1=56%, 2=20% 3=24%
Control group 1 (with HN SCC) <i>n</i> =50	2.1–11.4	1.00–1.48	1.1 (0.10)	
Control group 2 (non-HN SCC) <i>n</i> =36	2.0–9.7	1.00–1.28	1.1 (0.07)	

CT, computed tomography; HN, head and neck; SCC, squamous cell carcinoma.

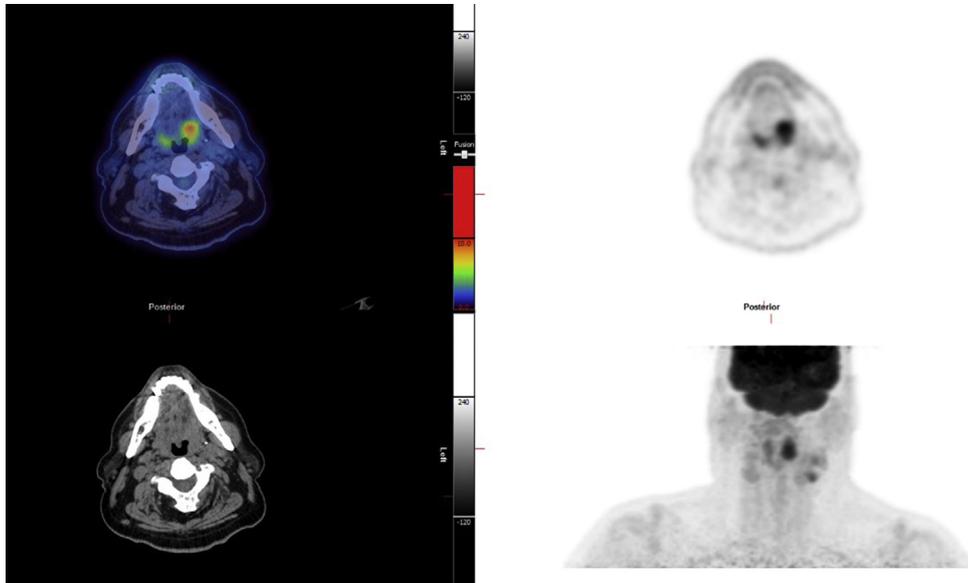


Figure 1 A left-sided tonsillar primary SCC with normal CT appearances.

present study, there is no SUVmax ratio that can exclude tonsillar carcinoma. Therefore, using an upper limit of SUVmax ratio to choose not to further investigate could miss a tonsillar carcinoma; however, a limit is still required to prevent unnecessary intervention and biopsy/tonsillectomy in a large proportion of the population who do not have tonsillar carcinoma.

Limitations

When using SUVs to guide management, it is important to be aware that differences in scanner type and reconstruction techniques can produce different SUVs. In particular, the use of point spread function, time of flight,⁸ and newer algorithms that allow fully convergent PET image

reconstruction but without excessive noise⁹ have all been shown to increase the SUV, particularly in smaller lesions, which is pertinent to the tonsils. This might have an effect on ratios if the reconstruction effect is greater in FDG avid tissue. Different uptake times and body mass index can also affect SUVs.¹⁰

Another potential limitation is that this is a single centre study and the SUVmax ratio was measured in a relatively small sample of patients and controls. However the present results are very similar to the published studies described above demonstrating that these results are still likely a good representation of the patient and control population. As already mentioned, HPV-positive and -negative lesions were not analysed separately, and this would be an interesting area of future work.

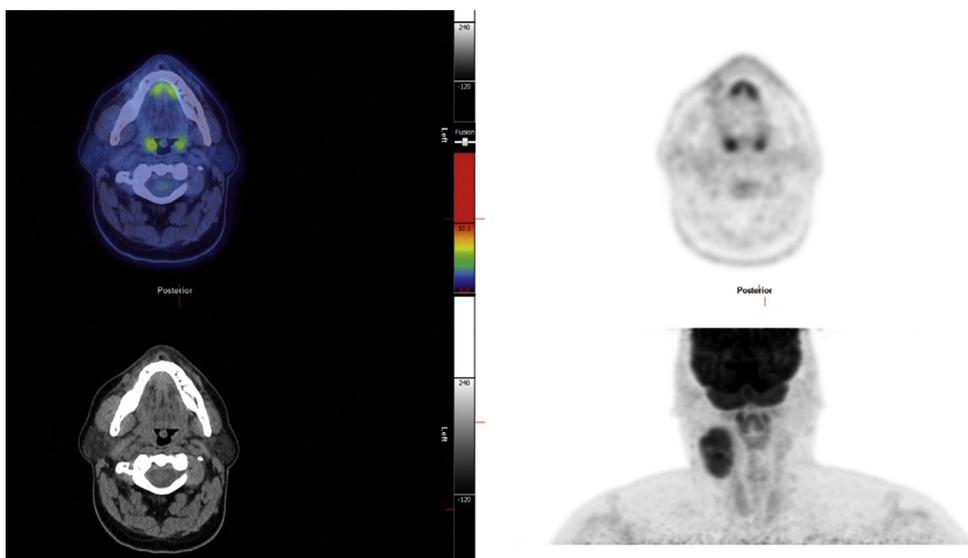


Figure 2 A right-sided tonsillar SCC with mildly increased FDG uptake and mild soft-tissue asymmetry on CT (CT appearances 2).

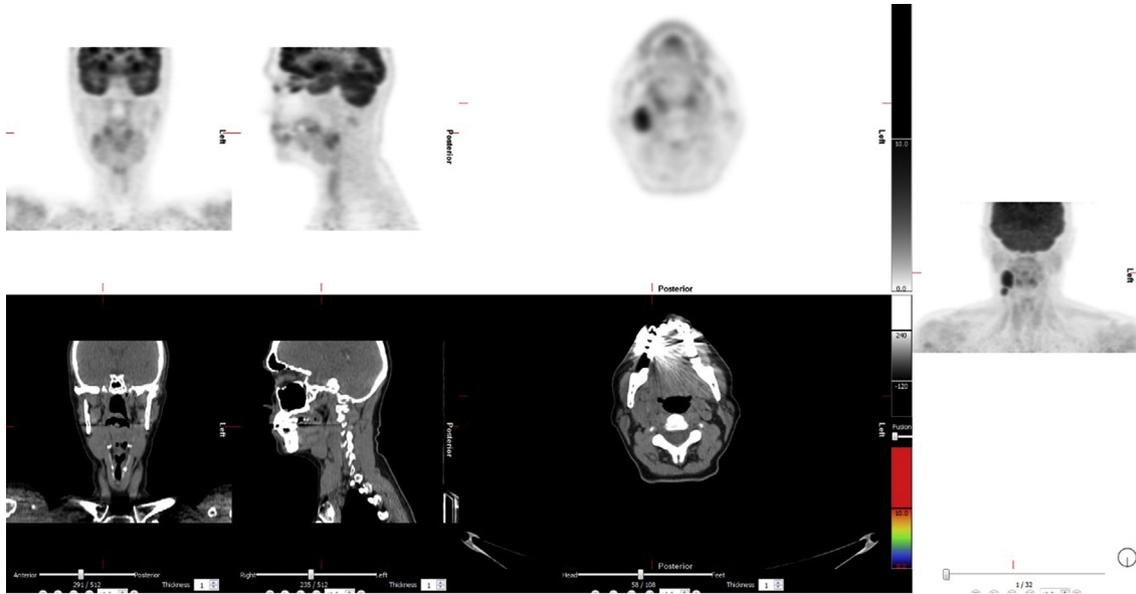


Figure 3 PET and CT images of a patient with normal FDG uptake within a proven right tonsillar SCC. Increased FDG uptake in the right sided metastatic nodes can also be seen.

Due to the limitations described above, it is suggested that other centres may need to develop their own cut-offs of SUVmax ratio between tonsils to help discriminate between benign and malignant tonsils.

In conclusion, the palatine tonsillar SUVmax ratio in patients with histologically proven tonsillar SCC was 0.89–5.4. This is consistent with a previously published result and provides further evidence that FDG PET-CT cannot be used to exclude the presence of a tonsillar primary SCC; however, it could be used to conclude there

is a tonsillar primary, obviating the need for panendoscopy and directed biopsies. A ratio of ≥ 1.6 is suggested for this purpose, which had a 100% PPV in the present study.

Patients without tonsillar carcinoma or other HN pathology can have mildly increased SUVmax ratios, and an upper limit is required when deciding when to further investigate patients in whom asymmetrical tonsillar uptake is incidentally observed. In line with other studies, an upper limit of 1.5 is suggested.

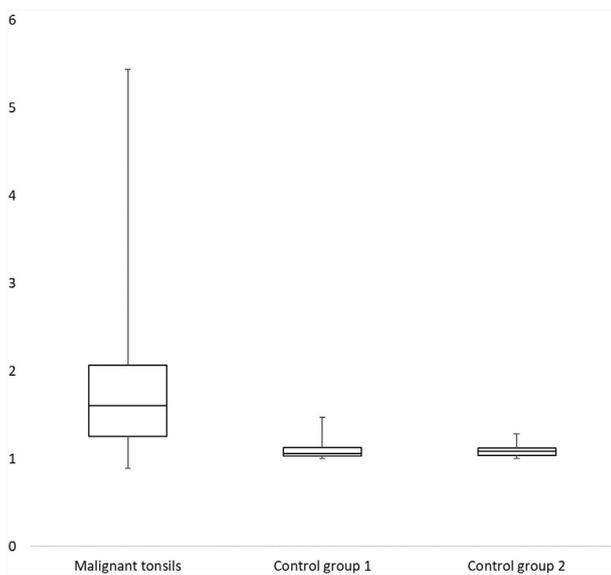


Figure 4 Box and whisker plot (showing the median, interquartile range and range) of SUVmax ratios between tonsils in the three groups of patients.

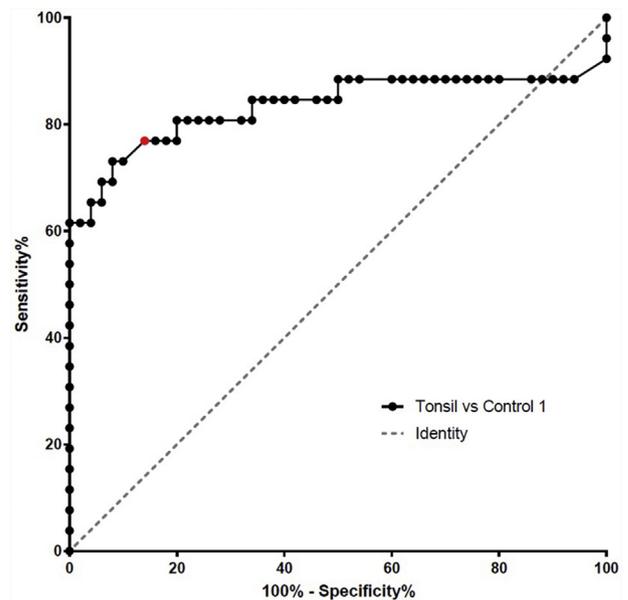


Figure 5 ROC curve of tonsil SUVmax ratios in patients with suspected HN SCC (tonsil group versus control group 1). Optimal cut-off point is shown in red.

Conflict of interest

The authors declare no conflict of interest.

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