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FDG PET/CT for metastatic squamous cell carcinoma of unknown primary of the head and neck

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ABSTRACT

Objective: The role of FDG PET/CT is uncertain in squamous cell carcinoma of unknown primary (SCCUP). Published data are limited by heterogeneity of pathology, varied diagnostic criteria, and small sample size.
Materials/methods: This retrospective study was conducted in 40 patients who had FDG PET/CT for SCCUP. Prior to PET/CT, patients had underwent standard clinical evaluations including flexible rhinolaryngoscopy. The majority of the patients had anatomic imaging. All subjects had histopathological investigations, and follow-up data after PET/CT.
Results: FDG PET/CT detected the primary in 16 of 40 patients (40%), and the most common locations of the primary were in the base of the tongue, palatine tonsil, and hypopharynx. There were 10 false positive and 6 false negative PET/CT scans. There was no difference in the mean SUVs of the suspected primary lesions between true and false positive groups. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy of FDG PET/CT for SCCUP in this patient cohort were 72.7% (16/22), 44.4% (8/18), 61.5% (16/26), 57.1% (8/14), and 60% (24/40), respectively. The tonsil was the site with the most false positive and false negative findings.
Conclusions: FDG PET/CT might be an effective single shot of whole-body imaging for detection of the primary in SCCUP. Low specificity remained the most notable weakness of FDG-PET in work-up for SCCUP. In addition to varied physiologic uptake or inflammatory related uptake in the common locations of the primary, the image indication bias might be another significant contributor of high false positive rate.

Introduction

Squamous cell carcinoma of unknown primary (SCCUP) of the head and neck is defined as isolated neck lymph nodes of squamous cell carcinoma without any evidence of the primary cancer after the standard diagnostic workup which includes the history, physical examinations, flexible optic endoscopy of the upper aerodigestive tract, and radiographic investigation with ultrasound, CT and/or MRI. SCCUP constitutes roughly 5% of all head and neck cancers [1,2]. In general, the prognosis of patient with SCCUP is unfavorable since they might only receive empirical treatment [3,4]. It is obvious that correct localization of primary tumor enable site-specific target therapy and may carry much better locoregional treatment and improved survival of the patient.

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has undergone explosive growth in oncologic applications. Today, FDG-PET is well established as an important imaging modality in oncology for tumor staging, restaging, detection of recurrence, and monitoring treatment response. PET-CT documents metabolic and function abnormalities which usually precede the anatomic changes. Another significant advantage of PET/CT is its routine whole body acquisition without additional radiation exposure to patients. The role of FDG PET/CT in the detection of an occult primary is uncertain. Published studies reported that FDG PET/CT is very helpful in detection of primary tumor of SCCUP [4–20], but the data are limited by heterogeneity of pathology, varied diagnostic criteria, and small sample size, with inconsistent results.

This retrospective study aims to investigate the value of FDG PET/CT in SCCUP, and discuss diagnostic pitfalls.

Materials and methods

Patients

This retrospective study was approved by the Institutional Review board. Relevant cases were identified through a search of a

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Table 1
Data of patients with true positive FDG PET/CT scans.

Patient No.	Age/sex	Metastatic SCC site	Image prior to PET/CT	FDG PET/CT findings	Additional image findings	Histopathological diagnosis
1	51/M	R. neck	Neck CT	R. BOT focus: 1.5 cm, SUV 8.2	5 mm lung nodule	SCC R. BOT
2	63/M	L. neck	Neck CT	L. palatine tonsil: asymmetric uptake, SUV 6.5	R. neck nodes	SCC L. palatine tonsil
3	62/M	R. neck	None	R. piriform sinus: 1.2 cm, SUV 4.1	None	SCC R. Hypopharynx
4	62/M	R. neck	Neck CT	LUL lung 0.9 cm nodule, SUV 3.3	None	Lung SCC
5	47/M	R. neck	None	R. palatine tonsil: asymmetric uptake, SUV 5.8	None	SCC R. palatine tonsil
6	40/M	R. neck	None	R. oropharynx: 2.4 cm, SUV 13	L. neck node	SCC R. oropharynx
7	51/M	L. neck	Neck CT	L. palatine tonsil: asymmetric uptake, SUV 8.1	R. neck nodes	SCC L. palatine tonsil
8	72/M	R. neck	Neck CT	R. supraglottis: 1.1 cm, SUV 7.2	L. neck node	SCC R. supraglottis
9	60/M	L. neck	Neck CT	L. BOT: 1.0 cm, SUV 5.0	None	SCC L. BOT
10	56/M	B/L neck	Neck CT	R. BOT: 1.2 cm, SUV 6.2	None	SCC R. BOT
11	52/M	L. neck	None	L. nasopharynx: asymmetric uptake, SUV 4.8	None	SCC L. nasopharynx
12	45/M	L. neck	None	L. palatine tonsil: asymmetric uptake, SUV 6.6	None	SCC L. palatine tonsil
13	55/M	R. neck	None	R. Hypopharynx: SUV 5.3	None	SCC R. piriform sinus
14	54/M	R. neck	None	R. piriform sinus: SUV 3.8	None	SCC R. piriform sinus
15	62/M	L. neck	None	L. BOT: SUV 5.5	R. neck node	SCC L. BOT
16	50/M	L. neck	Neck CT	L. BOT: asymmetric uptake, SUV 4.5	None	SCC L. BOT

computerized database of approximately 5500 patients who underwent PET/CT imaging at the Advanced Imaging Center, University Hospital between 01/2010 and 06/2017. Patients who had FDG PET/CT for SCCUP were selected for the study.

All patients had underwent standard clinical evaluation including history, complete physical examination with emphasis on the head/neck, and flexible rhinolaryngoscopy. Prior to FDG PET/CT, majority of the patients had regional image studies, mostly neck CT. If the primary lesions were not identified after these examinations, the patients were included into the study. All eligible subjects had available histopathological investigations, clinical and image follow-up data after the PET/CT.

Exclusion Criteria: 1. patients with non-SCC of unknown primary of the head and neck; 2. patients with a previous cancer; 3. patients who already received treatment of SCCUP; 4. patients with suspected primary lesion by the examinations and/or anatomic images, confirmed by histopathological findings; 5. patients without histopathological investigations of primary tumors after PET/CT; 6. patients without clinical and image follow-ups after negative histopathological examinations.

All patients had biopsies of the sites with positive FDG PET/CT findings, or random biopsies of oral cavity after negative PET/CT or if PET/CT suspected primary was not verified, which included the tonsils biopsy or tonsillectomy, biopsies of the nasopharynx, bases of the tongue, and supraglottis. Some patients had additional biopsy of the paranasal sinuses after negative PET/CT. All patients with negative biopsies had clinical and image follow-ups with the range 6 months to 7 years.

FDG PET/CT

Combined PET-CT was performed using a PET-CT scanner (Discovery LS, GE Healthcare, Milwaukee, Wisconsin, USA) and standard techniques. The patients fasted for at least 6 h prior to examination and their blood glucose level was less than 250 mg/dL. The patients received oral but not intravenous contrast media. Spiral low-dose CT (80 mA, 140 kV and 4 mm section thickness) was performed with the cranio-caudal direction covering the areas from the vertex to the mid-thigh for the purpose of attenuation correction and anatomic localization. Thereafter, emission scan was conducted in a reverse direction.

An image software Mim (Mim Software Inc, Cleveland, OH) was used for image display and analysis. The whole-body maximum-pixel-intensity projection was used for visual evaluation. Maximum standardized uptake value (SUV_{max}) of lesions was recorded.

Data analysis

In the first phase of the study, all cases of FDG PET/CT images for SCCUP were reviewed again to assure the accuracy of the initial interpretation and report. The reviewer was completely blinded to patients' histopathological or cytopathological results, follow-up findings, and final diagnoses at this phase.

In the second phase of the study, medical records were retrospectively reviewed for post-PET/CT information including the pathologic results, further image findings, follow-up history and clinical course. All information of the identified subjects was collected from Epic, Logician and PACS. Some cases were excluded from the analyses based on the exclusion criteria described above in this phase.

Diagnostic criteria. 1. True positive: FDG PET/CT suggested or suspected the primary which was verified by histologic examination; 2. False positive: FDG PET/CT suggested or suspected the primary which was proved to be benign on histologic examination, and subsequent long-term clinical/image follow-ups did not find the primary; 3. True negative: FDG PET/CT did not reveal the primary and subsequent histologic examination and series with no primary found on long term follow-ups; 4. False negative: FDG PET/CT did not suggest the primary, but subsequent histologic examination revealed the primary lesion.

In the final phase, statistical analysis was conducted to evaluate the value of FDG PET/CT for SCCUP.

Results

Total 40 eligible patients were enrolled into the study: 33 males and 7 females, and mean age 53.9 ± 8.5 years (range 35–72 years). FDG PET/CT findings were categorized into one of four groups:

1. True positive. Table 1 summarizes the characteristics of 16 patients with true positive FDG PET/CT findings. Except for negative physical examinations including flexible optic endoscopy of the upper aerodigestive tract, 8 of 16 patients had diagnostic neck CT prior to FDG PET/CT, which did not detect the primary. FDG PET/CT identified or suspected the primary neoplasms, which were all confirmed by subsequent histopathological examinations. Mean SUV of the lesions was 6.1 ± 2.3 (range 3.3–13). The most common locations of the primary were in the base of the tongue (5 cases), palatine tonsil (4 cases), and hypopharynx (3 cases). There was one distant primary tumor site in the lung. Fig. 1 was an example of the true positive in the tonsil.
2. False positive. There were 10 cases with false positive FDG PET/CT findings (Table 2). Abnormally increased FDG uptake was suspicious for the primary lesion, but subsequent biopsy or surgical pathology did not identify the tumor (Figs. 2 and Fig. 3). Mean SUV of 10 false

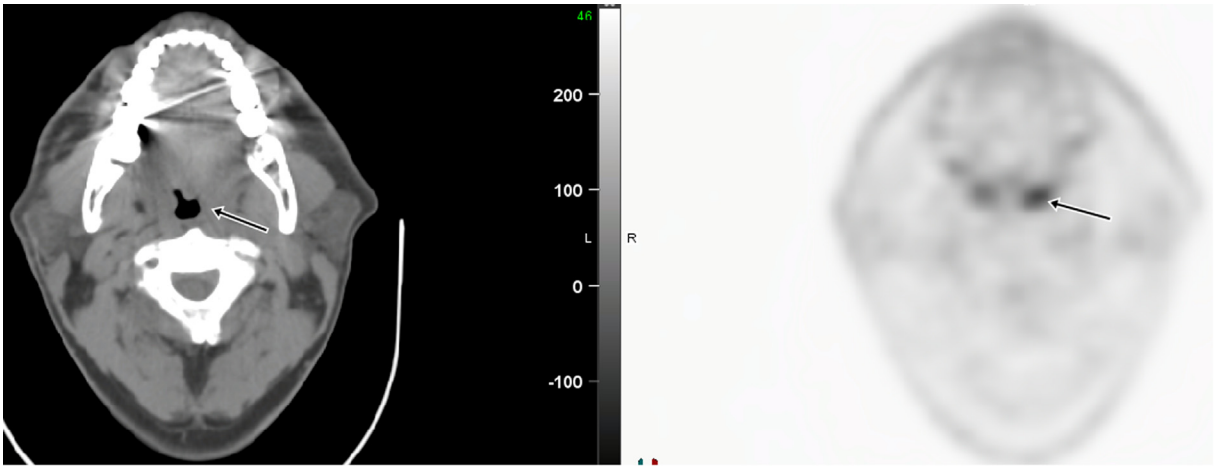

Fig. 1. True positive FDG PET/CT findings for patient 2 with metastatic SCC of the left neck. Diagnostic neck CT was negative for the detection of the primary. On FDG PET/CT, there was asymmetric fullness with increased uptake (SUV 6.5) in the left palatine tonsil (arrows), suspicious for the primary. Subsequent tonsillectomy confirmed SCC.

positive foci was 6.5 ± 2.4 (range 3.8–12), which was similar to that of confirmed primary lesions in the true positive group. The locations of the false positive were the tonsil (3 cases), supraglottis (2 cases), base of the tongue (1 case), nasopharynx (1 case), buccal space (1 case), distal esophagus (1 case), and lung (1 case). In 4 patients, increased uptake was from chronic inflammation. With 6 month to 7 year clinical and image follow-ups (mean 28.9 ± 25.8 months), the primary was still not identified in these patients. Therefore, no patient of this group could be counted as the false negative.

3. True negative. There were 8 patients (patients 27–34) with true negative FDG PET/CT findings. With 2 to 7 year (mean 51 ± 19 months) clinical and image follow-ups, the primary tumors were still not detected in these patients.
4. False negative. There were 6 false negative FDG PET/CT scans (Table 3): 3 in the tonsils, 1 in the base of the tongue, 1 in the pre-hyoid soft tissue and 1 in the epiglottis. 4 of 6 cases had sub-centimeter lesions, 1 had low grade in situ tumor and 1 in the unusual pre-hyoid location.

FDG PET/CT correctly detected the primary neoplasms in 16 of 40 (40%) of the patients. but the primary tumors were detected in total 22 patients (55%) on post PET/CT histopathological examinations or random biopsy, including 16 true positive and 6 false negative FET/CT cases There were 10 false positive scans. There was no difference in the mean SUVs of the suspected primary lesions between true and false positive groups. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of FDG PET/CT for SCCUP in this patient cohort were 72.7% (16/22), 44.4% (8/18), 61.5% (16/26), 57.1% (8/14), and 60% (24/40), respectively.

In 18 patients with true negative or false positive PET/CT followed by random biopsies, the primary was still not identified after year-long clinical and image follow-ups. However these patients all received chemotherapy and radiation after PET/CT and negative histopathological investigation, which may have destroyed the primary.

The tonsil was the location with the most false positive and false negative findings in the SCCUP workup on FDG PET/CT.

In 12 of 40 (30%) patients, FDG PET/CT revealed more FDG avid lymphadenopathy suspicious for metastases in the contralateral neck, which would affect treatment options in surgical and/radiation fields. There was no finding of distant metastasis in all 40 patients of the cohort. 2 patients were found to have small pulmonary nodules, which were stable on the follow-up scans and therefore were considered benign.

Discussion

Cancer of unknown primary is a group of metastatic disease with different pathology, primary lesions and biological feature, with dominant adenocarcinoma [21]. Squamous cell carcinoma only accounts for 5% of cancer of unknown primary, most in the head and neck [21]. Fine-needle aspiration is usually used for diagnosis of metastatic SCC of cervical lymph nodes. Afterwards, physical examination, flexible nasopharyngoscope, and regional imaging are recommended for detection of primary. In general, endoscopic examination and directed biopsies under anesthesia are obtained after image studies.

CT or MRI is widely used for detection of the primary of SCCUP of the head and neck. However, the major limitations of these anatomic image modalities are regional images and low sensitivity for small or non-enhancing lesions. Although FDG PET/CT imaging is a standard care for most of solid tumors, its role in detection of SCCUP of the head and neck is uncertain. Johansen et al. [5] reported overall detection rate 29% of FDG PET/CT for the primary in a 22 patient study, with 87% sensitivity, 68% specificity, 61% PPV and 90% NPV, respectively. However some patients had biopsy of the suspected primary prior to PET/CT which would markedly affect image finding and interpretation. Other groups, including Rudmik [8], Keller [9] and Lee et al. [16], all reported a 55% primary detection rate by FDG PET/CT in 20, 39, and 56 patients with unknown primary of the neck, respectively, but pathology of the included cases was heterogonous. Majchrzak et al. [11] retrospectively analyzed 41 patients who all had physical examinations, neck dissection accompanied by panendoscopy consisting of bilateral tonsillectomy and blind tissue specimens taken from macroscopically suspicious areas before FDG PET/CT. The PET/CT was true positive in 9, false positive in 4 and false negative in 4 patients. The authors concluded a high effectiveness of FDG PET/CT in the diagnosis of the unknown primary. Recently, Cetin et al. [19] compared the performance of FDG PET/CT to conventional imaging methods including CT, MRI and mammography in 36 patients with cancer unknown primary, and showed that FDG PET/CT detected more primary tumors than conventional modalities. Noij et al. [20] reported that qualitative analysis of FDG PET/CT based on the uptake improved the diagnostic accuracy.

In a comprehensive review including 16 studies and 302 patients [22], the overall sensitivity, specificity, and accuracy rates of FDG-PET in detecting unknown primary tumors were 88.3%, 74.9%, and 78.8%, respectively. FDG-PET detected 24.5% of tumors that were not apparent after conventional workup. Most of these included studies, however, were limited in heterogeneity of pathology, small sample size,

Table 2
Data of patients with false positive FDG PET/CT scans.

Patient no.	Age/sex	Metastatic SCC site	Image prior to PET/CT	FDG PET/CT findings	Additional FET/CT findings	Histopathological diagnosis	F/U period (months)
17	48/M	R. neck	Neck CT	R. nasopharynx: SUV 8.0	L. neck nodes	Inflammation of R. nasopharynx; Other bx: neg	12
18	64/M	L. neck	Neck CT	L. BOT: asymmetric uptake, SUV 5.8	None	All bx: neg	7
19	64/F	L. neck	Neck CT	Distal esophagus: SUV 5.8	lung nodules	Esophageal bx: inflammation Other bx: neg	12
20	53/F	L. neck	Neck CT	L. supraglottis: SUV 6.0	None	All bx: neg	12
21	35/M	L. neck	Neck CT	L. tonsil: asymmetric uptake, SUV 7.8	R. neck nodes	L. tonsilletcomy: inflammation; Other bx: neg	24
22	60/M	L. neck	Neck/chest CT	L. buccal space: SUV 3.8	None	All bx: neg	84
23	65/M	L. neck	Neck CT	L. tonsil and BOT: SUV 6.0	None	All Bx: neg	36
24	49/M	R. neck	Neck CT	LLL lung nodule: 0.8 cm, SUV 4.3	None	Chest CT in 2 m: no nodule All neck bx: neg	60
25	53/F	L. neck	None	L. supraglottis: SUV 12	R. neck	L. supraglottic inflammation Other bx: neg	36
26	61/M	R. neck	Neck CT	R. tonsil: SUV 5.2	None	Tonsillectomy: neg Other bx: neg	6

and varying results.

On the other hand, some results suggest a limited role for FDG PET or FDG PET/CT. In a study including 21 patients with FDG PET or FDG PET/CT from the University of Florida group [7], PET or PET/CT was found to have limited role in the management of patients with SCCUP. In the latest study reported by Dale et al. [10], 30 SCCUP patients had been through a standard workup prior to PET/CT, consisting of CT of the neck and chest, examination with flexible endoscopy with patient awake, panendoscopy and examination under general anesthesia, tonsillectomy and sometimes blind sampling biopsies, and MRI (floor of the mouth). Only 1/30 patients had their primary cancer detected by FDG PET/CT. The authors suggested that the lower detection rate of the primary might be secondary to better diagnostic equipment and more thorough investigation prior to FDG PET/CT.

The current study exhibited a 40% (16/40) detection rate of primary tumors by FDG PET/CT, comparable to that reported in the literature. Our results showed lower sensitivity than those reported on meta-analysis, which was most likely attributed to discrepancy of the workup and selection criteria of eligible patients in included 16 studies. The findings regarding primary tumor locations were consistent with those from previous studies. 21 of 22 patients with histopathological confirmed primary tumors had primary in the oral cavity, nasopharynx, hypopharynx and larynx. The tonsils and the base of the tongue were the most common sites of the primary. Compared to diagnostic CT, FDG PET/CT has ability to demonstrate small metabolically active tumor focus in the tonsil or base of the tongue where there is typically prominent lymphoid tissue which may obscure identification of abnormal enhancement on the diagnostic CT.

Although it is not quite common, SCCUP from non-head and neck origin should be a consideration of SCCUP workups. One patient in the study was found to have primary lung cancer, which highlights the advantage of the PET/CT workup with the whole-body acquisition. After negative standard diagnostic workups for SCCUP, a chest CT may be necessary to evaluate possible lung primary if FDG PET/CT is not obtained.

Low specificity remains the most notable weakness of FDG-PET in work-up for SCCUP. The current study showed false positive findings in 10 of 40 cases and lower specificity than the reported in the meta-analysis [22]. FDG-PET had notably low specificity and a high false-positive rate in the tonsils, which was consistent with previously reported [5–9,22]. Main reasons for the high false-positive rate in the tonsils are varied physiologic uptake and inflammation or tonsillitis. Less commonly, FDG accumulation can occur in patients with sarcoidosis, granulomatous disease, and benign tumors [23]. Greven et al. suggested that the high false-positive rate might also be attributable to sampling error in PET-directed biopsies [24]. Another significant factor of low specificity of FDG PET/CT in SCCUP is the image indication bias. When assessing for an unknown primary, radiologists or nuclear medicine physician might trend to call more abnormal findings on the images for SCCUP compared to those for other indications. Any subtle asymmetry on either PET and/or CT images may be interpreted as abnormal or the primary on SCCUP work-up. 3-D reviews of the axial, coronal and sagittal PET and CT slices are helpful to verify asymmetry or abnormality of the tonsils and bases of the tongue.

In the current cohort, 4 of 6 patients with false negative PET/CT had subcentimeter lesions. It is well known that small tumors might be below the resolution of FDG PET. The most common site of false-negative FDG-PET findings in the current analysis was the tonsil, which was different from previously reported observations that the base of the tongue was the most false negative location [22]. In addition to high grade physiologic uptake of the tonsils, small size of the lesions was the major reason of the false negative FDG PET/CT. High uptake of the tonsillar lymphatic tissue may overlap uptake from the small tumor. Therefore, bilateral tonsil biopsies or tonsillectomies may be needed in patients with negative FDG PET/CT workup. In addition, it is well known that well differentiated tumors have been shown to have a lower

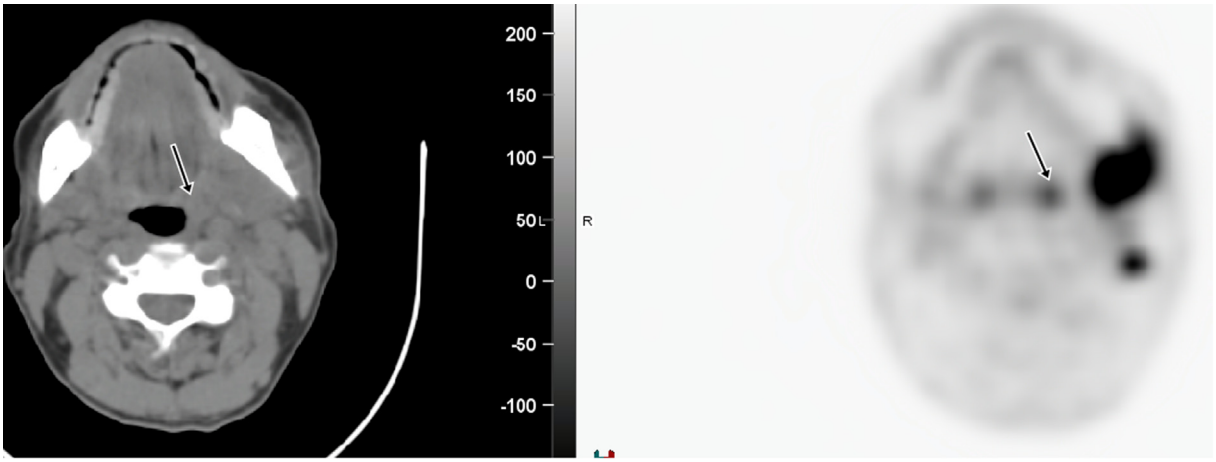

Fig. 2. False positive FDG PET/CT findings for patient 18 with metastatic SCC of the left neck. Although diagnostic neck CT was unremarkable, FDG PET/CT showed asymmetric uptake (SUV 5.8) in the left base of the tongue (arrows), suspicious for the primary. However, subsequent biopsy was negative. The primary was not identified on random biopsies of the oral cavity and year-long follow-ups.

rate of FDG uptake and possible false negative findings [25].

Some of published studies showed the ability of FDG PET/CT to detect new metastases. The detection of unknown distant metastases occurred in 11% of all patients reviewed [22]. The current study did not show distal metastasis in any case. However, FDG PET/CT demonstrated more ipsilateral nodal lesions and/or contralateral nodal metastases. Of 40 patients, 12 (30%) had contralateral nodal metastases on PET/CT except for known neck lesions. Even in cases of regional disease, the detection of the contralateral lymphadenopathy could lead changes in surgical procedures and/or targeted delineation of radiation therapy.

Compared to previously reported studies, the current study focused on a single pathology type of unknown primary: squamous cell carcinoma, which is the most dominant in the malignancies of the neck. Similarly, there are a few significant limitations associated with the study: retrospective analyses and small sample size, which made the statistical analysis less powerful.

To date, there is no consensus or guideline in the approach to the diagnostic evaluation of SCCUP [26,27]. Recently, Golusinski et al. proposed a new, evidenced-based protocol for workup of SCCUP of the head and neck [27]. For patients who present with SCCUP, FDG PET/CT should be requested immediately in the CT/MRI does not identify the primary site. As the primary diagnostic modality, FDG PET/CT is a viable alternative.

Conclusion

The current study demonstrated that FDG PET/CT was a useful adjunct in the work-up of patients with SCCUP. While the role of anatomic image modalities is limited by regional images and low sensitivity for small or non-enhancing lesions, FDG PET/CT might be an effective single shot of whole-body imaging for detection of the primary in SCCUP. The tonsils and the base of the tongue were the most common sites of the primary. Low specificity remains the most notable weakness of FDG-PET in work-up for SCCUP, which was prominently in the tonsils mainly due to varied physiologic uptake and inflammation. Another significant factor of low specificity of FDG PET/CT for SCCUP is the image indication bias. Radiologists or nuclear medicine physician might trend to call more abnormal findings on the images for SCCUP when looking for an unknown primary compared to those for other indications. On the other hand, the most common site of false-negative FDG-PET findings was the tonsils as well. High grade physiologic uptake and small size of the lesions were the major reasons of the false negative FDG PET/CT.

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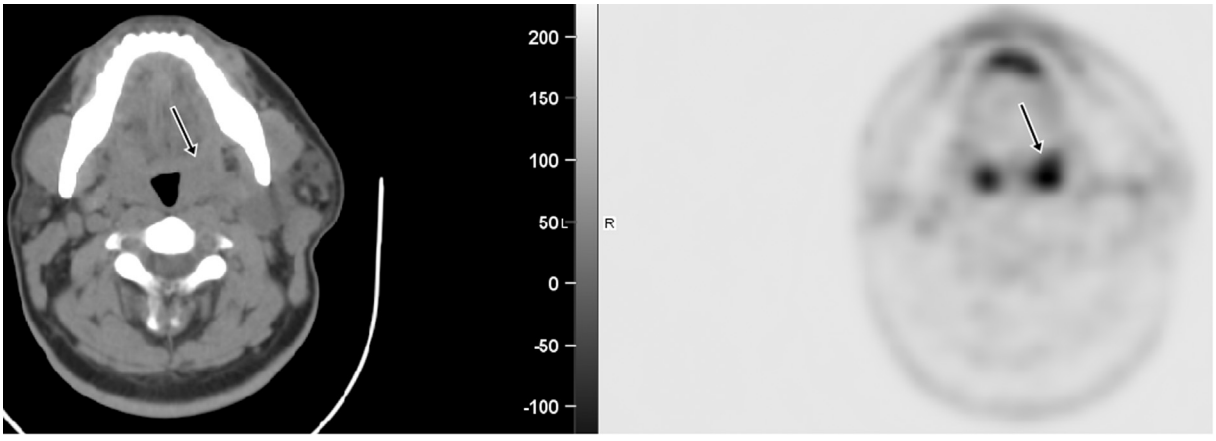

Fig. 3. False positive FDG PET/CT findings for patient 21 with metastatic SCC of the left neck. There were enlargement and increased uptake (SUV 7.8) of the left palatine tonsil (arrows), highly suspicious for the primary. Subsequent left tonsillectomy suggested chronic tonsillitis.

Table 3
Data of patients with false negative FDG PET/CT scans.

Patient no.	Age/sex	Metastatic SCC site	Image prior to PET/CT	FDG PET/CT findings	Additional image finding	Histopathological diagnosis	Comments
35	62/M	R. neck	Neck CT	Symmetric tonsillar uptake	None	1.0 cm R. tonsil SCC	Small tumor in tonsil
36	52/M	R. neck	Neck CT	Symmetric tonsillar uptake	None	0.7 cm R. tonsil SCC	Subcm tumor in tonsil
37	48/M	Submental	Neck CT	Unremarkable	None	1.5 cm SCC within pre-hyoid fibroconnective tissue	Unusual location
38	50/F	R. neck	Neck CT	Non-FDG avid R. epiglottic thickening	None	SCC in situ of R. epiglottis	Low grade tumor
39	47/M	R. neck	Neck CT	Symmetric tonsillar uptake	None	0.3 × 1.0 cm tumor in R. tonsil	Subcm tumor
40	72/M	L. neck	Neck US and CT	Unremarkable	None	0.4 × 0.5 cm tumor in L. BOT	Subcm tumor

Conflicts of interest

None declared.

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