CARCINOMA OF UNKNOWN PRIMARY IN THE HEAD AND NECK: COMPARISON BETWEEN POSITRON EMISSION TOMOGRAPHY (PET) AND PET/CT

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Abstract: *Background.* Comparison of the diagnostic validity of positron emission tomography (PET) alone with integrated PET and CT (PET/CT) in the search for occult primary tumors in patients with cancer of unknown primary (CUP) site in the head and neck.

Methods. Thirty-nine consecutive patients with clinical CUP were investigated with PET and 38 patients with PET/CT. After initial diagnostic panendoscopy and histological confirmation of the cervical lymph node metastasis, either PET or PET/CT scanning was performed.

Results. Integrated PET/CT had a significantly higher overall detection rate than dedicated PET alone (55.2% vs 30.8%; $p = .039$) and positive prediction rate (93.3% vs 46.1%; $p = .01$).

Conclusion. Integrated PET/CT showed to be superior to PET in the detection of the primary site of clinically occult tumors in CUP syndrome. However, a negative result should still be investigated further by means of panendoscopy with tonsillectomy and blind biopsies. © 2010 Wiley Periodicals, Inc. *Head Neck* **33:** 1569–1575, 2011

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The definition of cancer of unknown primary (CUP) site in the head and neck is the histological confirmation of at least 1 cervical lymph node metastasis, when clinical diagnostic measures, including flexible endoscopy and imaging procedures, can find no evidence of a primary tumor.

The incidence of CUP accounts for as many as 3% to 7% of all head and neck tumors.[1,2] Up to now, the workup has consisted of thorough clinical examination, ultrasound scanning, CT and/or MRI, followed by panendoscopy. An ^{18}F-fluorodeoxyglucose (FDG)-PET is an imaging modality that has gained popularity in oncologic imaging, because metabolic information is provided that helps to unveil malignant lesions and differentiates viable tumor from successfully treated lesions. A drawback of PET imaging is the lack of morphological information, which is especially a problem in the head and neck region where anatomy is more difficult than in other regions of the body.[3] Software-based fusion of a diagnostic CT with PET performed at different sessions is possible, but differences in patient positioning can hamper the diagnostic value of such examinations.[4] Integrated PET/CT overcomes many of these limitations and has the additional benefit of a shorter examination time.[5] It combines the precise anatomical presentation and correlation of CT with the FDG accumulation in tumor tissue found on PET. In this way, the procedure makes the accurate and reliable localization of even very small tumors possible, a feature that may confer a key advantage, particularly in the anatomically very complicated and mobile region of the head and neck.[6] Visual/qualitative information from the PET can be quantified using the standardized uptake value (SUV).[5,7]

The purpose of this study was to compare the diagnostic impact of PET and integrated PET/CT in the detection of primary tumors in patients with CUP in the head and neck. In addition, we aimed to compare the maximum SUV in patients with and without tumors.

There are already several reports in the literature that indicate that combined PET/CT in the head and neck has advantages over dedicated PET alone, but no direct comparisons have yet been made in patients with CUP in the head and neck.[8–11]

MATERIALS AND METHODS

All patients that presented from January 2004 to September 2008 with CUP syndrome in the ear, nose, and throat department of our institution were included in this retrospective study. Each patient underwent a thorough clinical examination with a rigid or flexible endoscopy, ultrasound B-scanning, and contrast-enhanced CT of the head and neck region. An appointment was then made for a panendoscopy (pharyngoscopy, microlaryngoscopy, or esophagoscopy). In all cases without histologic confirmation of a space-occupying lesion in the neck, either a lymph node resection or core needle biopsy was performed during the panendoscopy. If there was no evidence of a primary tumor on the neck CT and panendoscopy, no specimens were taken for biopsy, and FDG-PET or, from December 2006 onward, FDG-PET/CT was performed. When the PET/PET-CT suggested a primary malignancy, multiple specimens were taken from this region for biopsy and verified by frozen section during a second panendoscopy; if the specimens were positive for malignancy, a tumor resection was performed, otherwise a "CUP panendoscopy" was carried out. This consisted of a bilateral tonsillectomy, tissue specimens from suspicious areas of mucosa were taken for biopsy, and 3 blind tissue biopsies of the nasopharynx and base of the tongue. All patients then underwent (modified) radical dissection of the neck.

All tissue removed was sent to pathology for examination. Exclusion criteria were a history of cancer in the head and neck, lymph node metastases that showed histology other than squamous cell carcinoma, diabetes, pregnancy, and severe obesity.

Seventy-seven consecutive patients (68 men, 9 women; aged 40–80 years; mean age, 60.0 ± 9.6 years) were included in this study.

Between January 2004 and October 2006, the first 39 consecutive patients (4 women, 35 men; aged 40–80 years; mean age, 58.8 ± 9.4 years) were investigated in a dedicated whole-body PET scanner (Ecat Emerge, Siemens, Erlangen, Germany).

The following 38 patients (5 women, 33 men; aged 43–78 years; mean age, 61.2 ± 9.5 years) were investigated, between December 2006 and September 2008, using a PET/CT scanner (Biograph 64, Siemens, Erlangen, Germany). This scanner combines a dedicated PET scanner with a 64-slice spiral CT.

The PET or PET/CT investigation was carried out when the patient was normoglycemic (70–130 mg/dL), after fasting for at least 6 hours. After adequate rest and 20 mg Buscopan, 240 to 380 MBq (6.5–8.8 mCi) of ^{18}F-FDG were injected according to their body weight. One hour later, PET was performed from head to proximal thigh, in 6 to 8 bed positions, depending on the patient's height. Both attenuation-corrected and uncorrected slice images and maximum intensity projections were evaluated and documented. With PET/CT, a contrast-enhanced CT of the PET positions displayed was also acquired for attenuation correction and anatomical mapping. Whole-body CT scanning was performed in spiral mode with 100 mAs, 120 kV, a section width of 5 mm, 0.75 mm collimation, and a table feed of 15 mm/gantry rotation, immediately preceding the acquisition of PET emission data (3 minutes per bed position). FDG-PET images were reconstructed using CT data for attenuation correction. Visible lesions with increased tracer uptake were identified and their uptake was quantified.

The PET and PET/CT examinations were evaluated by 2 specialists in nuclear medicine (R.L. and T.K.) and a specialist in head and neck radiology (M.L.) and assessed as either positive or negative for occult primary cancer. Clearly visible, asymmetrical FDG accumulation in the head and neck was taken to indicate a tumor and corresponding tissue asymmetry in the PET/CT was also taken into consideration.

In addition, the SUV was measured in the region of maximum metabolic activity and the corresponding area on the contralateral side. If there was no obvious hypermetabolic area, as a rule, the SUV was measured in the tonsillar area and base of the tongue, as empirically these are the areas where a tumor is most likely to be found.[12] The mean value and SD was calculated for the SUV_{max} and asymmetry (highest SUV/SUV on the contralateral side) and compared for patients with and without primary tumors using an unpaired t test.

The gold standard was the histologic demonstration of a primary tumor. PET or PET/CT scans positive for primary tumors were considered to be true positives when the histology showed a carcinoma in the corresponding biopsy. True-negatives were defined as PET or PET/CT scans assessed as negative/no suspicion of a primary tumor, with no primary detected in the CUP panendoscopy. False positives were PET or PET/CT scans reported as being suspicious of tumor although the presence of a primary was not confirmed on biopsy. Conversely, false negatives were taken to be PET or PET/CT scans assessed as negative/no suspicion of a primary tumor but where a primary tumor was subsequently found in the CUP panendoscopy.

The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET and PET/CT for the diagnosis of occult primary tumors in patients with clinical CUP in the head and neck were calculated and compared using the Fisher exact test.

Carcinomas were staged (T and N classifications) using the 6th Union Internationale Contre le Cancer classification.[13] All statistical analyses were performed with the SPSS 16.0 program (SPSS, Chicago, IL).

The procedure had previously been discussed and agreed upon by an interdisciplinary tumor board.

Table 1. Classification of patients according to N classification.

| N classification | No. of patients | | Total no. of patients |
	PET	PET/CT	
N1	4 (10.3%)	5 (13.2%)	9
N2a	11 (28.2%)	5 (13.2%)	16
N2b	13 (33.3%)	16 (42.1%)	29
N2c	4 (10.3%)	1 (2.6%)	5
N3	7 (17.9%)	11 (28.9%)	18
Total	39	38	77

Abbreviation: PET, positron emission tomography.

RESULTS

Both PET and PET/CT identified all the existing lymph node metastases that were present in 52 of the 77 patients. The other patients previously had a solitary lymph node metastasis that had been removed before the PET or PET/CT examination, and subsequent dissection of the neck revealed no further lymph node involvement. PET and PET/CT in these cases showed only postoperative inflammatory uptake. Table 1 gives the N classification of the 77 patients.

Twenty-eight (36.4%) primary tumors in the head and neck were confirmed on histology, 20 of these had been correctly identified by PET or PET/CT and 8 were found only by the CUP panendoscopy. In addition, a distant metastasis or primary tumor beyond the head and neck region was found with the help of PET or PET/CT in 15 of the 77 patients (19.5%).

In the first PET scan group, histopathology of the biopsies confirmed a malignant tumor in 10 patients. Pathological FDG accumulation was found on PET in 6 of these positive cases (3 tonsils, 1 nasopharynx, 1 base of the tongue, and 1 hypopharynx), as shown in Table 2. Four of these 6 cases could also be identified on panendoscopy; 1 tumor (nasopharynx) was submu-

Table 3. TNM classification of patients investigated with PET.

| T classification | No. of patients by N classification | | | | | Total no. of patients |
	N1	N2a	N2b	N2c	N3	
T0	3	8	11	4	3	29
T1	1	3	2	–	2	8
T2	–	–	–	–	2	2
Total	4	11	13	4	7	39

Abbreviation: PET, positron emission tomography.

cosal and discovered only by the PET, and 1 patient died before a panendoscopy could be performed, although the tumor was confirmed at autopsy. In addition, PET scans found a further 8 tumors (5 lung, 1 liver, 1 testis, and 1 renal pelvis) below the clavicles; 2 of these patients also had a histologically confirmed tumor in the head and neck. A PET scan has a detection rate of 15.4% (6 of 39) for primary tumors in the head and neck, 20.5% (8 of 39) in the rest of the body, and 30.8% (12 of 39) overall.

Four of the 10 histologically confirmed tumors were diagnosed only on CUP panendoscopy (1 epiglottis, 1 hypopharynx, 1 base of the tongue, and 1 parotid). The tumors not identified on PET scan were 8 to 15 mm in size. The PET scan also gave false-positive results in 7 cases (6 tonsils, and 1 base of the tongue), as shown in Table 2. The TNM classification of the 39 patients investigated with a PET scan is shown in Table 3.

Calculated from these results, a PET scan has a sensitivity of 60.0%, specificity of 75.8%, and accuracy of 71.8%. The positive predictive value was 46.2%, and the negative predictive value 84.6%.

In the second PET/CT scan group, 18 primary tumors were confirmed on histology. As Table 4 shows, 14 of these were identified by PET/CT scans (5

Table 2. PET scans that were assessed as positive for a primary tumor.

Patient no.	Location of positive PET	PET assessment	Location of positive histology
2	Tonsil	False positive	No tumor
3	Pharynx	True positive	Pharynx
4	Tonsil	False positive	No tumor
6	Tonsil	False positive	Submandibular gland
9	Tonsil	False positive	No tumor
17	Tonsil	True positive	Tonsil
22	Base of the tongue	True positive	Hypopharynx
23	Tonsil	True positive	Tonsil
24	Tonsil	False positive	No tumor
25	Tonsil	False positive	No tumor
29	Base of the tongue	False positive	No tumor
32	Tonsil	True positive	Tonsil
35	Nasopharynx	True positive	Nasopharynx

Abbreviation: PET, positron emission tomography.

Table 4. PET/CT scans that were assessed as positive for a primary tumor.

Patient no.	Location of positive PET/CT	PET/CT assessment	Location of positive histology
1	Larynx	True positive	Larynx
6	Epiglottis	True positive	Epiglottis
10	Vallecula	True positive	Hypopharynx
12	Larynx	True positive	Larynx
17	Vallecula	True positive	Vallecula
19	Hypopharynx	True positive	Hypopharynx
20	Base of the tongue	True positive	Base of the tongue
25	Tonsil	True positive	Tonsil
28	Tonsil	True positive	Tonsil
29	Vallecula	False positive	No tumor
31	Tonsil	True positive	Tonsil
33	Tonsil	True positive	Tonsil
34	Hypopharynx	True positive	Hypopharynx
36	Tonsil	True positive	Tonsil
38	Base of the tongue	True positive	Base of the tongue

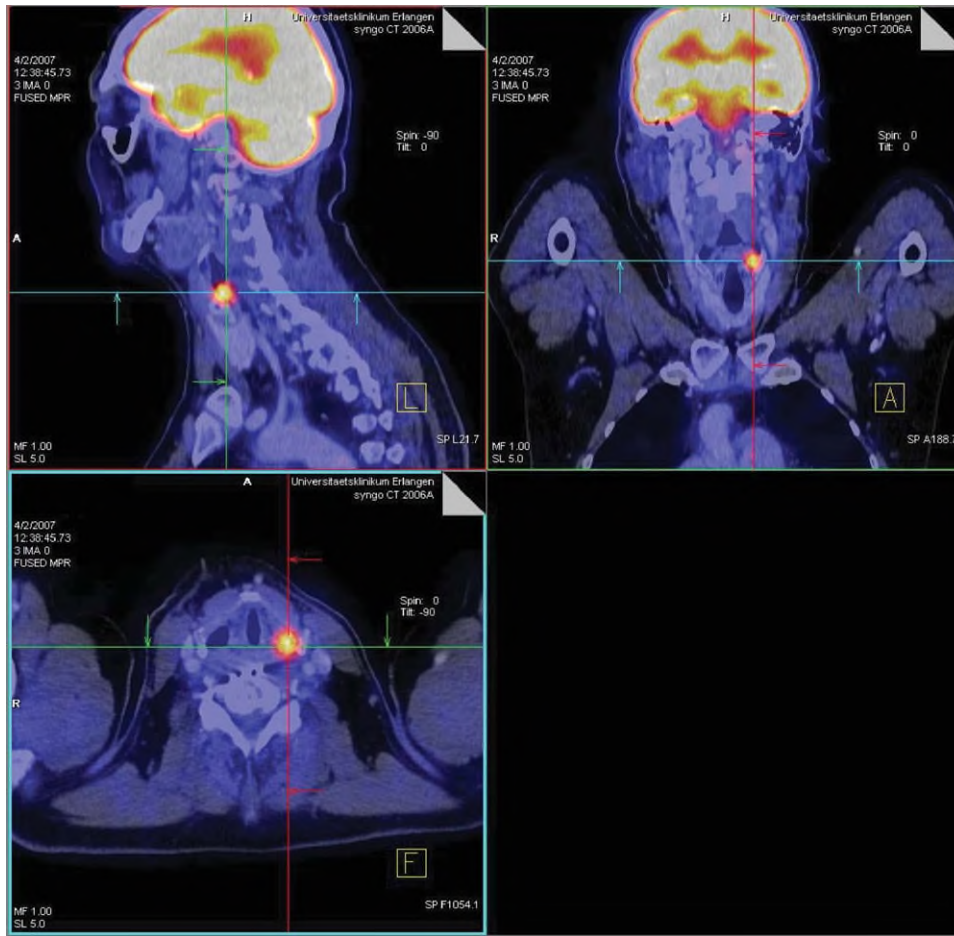*Abbreviation: PET, positron emission tomography.*

FIGURE 1. Sagittal, coronal, and axial sections of a PET/CT scan showing a small primary tumor in the left piriform fossa. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

tonsils, 2 hypopharynx [Figure 1], 2 endolarynx, 2 base of the tongue, 2 vallecula, and 1 epiglottis). In 4 cases, the tumor was found only on CUP panendoscopy (3 tonsils, 1 oropharynx; 5–15 mm in size). Accumulation at the base of the tongue/vallecula was wrongly interpreted as a tumor in 1 case. PET/CT scans detected 7 tumors in the rest of the body (3 lung, 1 liver, 1 sigmoid colon, 1 prostate, and 1 pancreas). This gives a detection rate of 36.8% (14 of 38) for the head and neck, 18.4% (7 of 38) for the rest of the body, and an overall detection rate of 55.3% (21 of 38).

Panendoscopy identified 12 of 18 primary tumors, but was unsuccessful in 6 patients. Together, PET/CT scans and a panendoscopy detected 47.4% (18 of 38) of the primary tumors in the head and neck. The TNM classification of the 38 patients investigated with PET/CT is shown in Table 5.

Sensitivity was 77.8%, specificity 95.0%, accuracy 86.8%, positive predictive value 93.3%, and negative predictive value 82.6%.

Statistical analysis showed that, in comparison with PET alone, integrated PET/CT had a significantly better overall detection rate (55.2% vs 30.8%; p = .039) and detection rate of primary tumors in the head and neck (36.8% vs 15.4%; p = .033), a significantly better positive prediction rate (93.3% vs 46.2%; p = .01) and a trend to increased specificity (95.0% vs 75.9%; p = .118). The accuracy, sensitivity, and negative prediction rate were not statistically significantly different.

The SUV_{max} and the asymmetry were compared between the 28 patients with primary tumor and the 49 patients without. Both parameters were significantly higher in the patients with tumors, but no definitive

Table 5. TNM classification of patients investigated with PET/CT.

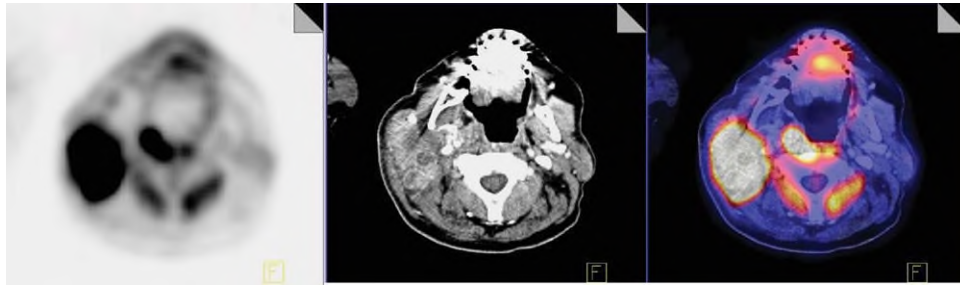| T classification	No. of patients by N classification					Total no. of patients
	N1	N2a	N2b	N2c	N3	
T0	1	5	6	–	8	20
T1	3	–	6	1	2	12
T2	1	–	4	–	1	6
Total	5	5	16	1	11	38

Abbreviation: PET, positron emission tomography.

FIGURE 2. Comparison of axial sections of positron emission tomography (PET), CT, and PET/CT scans of a large cervical lymph node metastasis and primary tumor in the right tonsil. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

cutoff could be determined to distinguish between the 2 groups.

DISCUSSION

The diagnostic and therapeutic management of an unknown primary cancer in the head and neck is still controversial. Reasons for this include the still largely unknown pathophysiology of CUP, the rarity of the disease, the lack of multicenter studies, the continual improvement of existing diagnostic procedures, and the development of new ones that are very promising but available only in a few reference centers.[14]

An intensive search for the tumor when there is a clinical CUP is justified by the following facts. The identification of a primary tumor can result in targeted treatment that not only increases the patient's chances of survival,[15] but also lowers morbidity by reducing the field of irradiation. The detection of a distant metastasis or second malignancy can also lead to changes in treatment.

This study showed that a PET/CT scan, in comparison with PET alone, had a clearly higher detection rate (36.8% vs 15.4%) of primary tumors in the head and neck in patients with clinical CUP. This remains higher than the average detection rate of 24.5% found for PET scans in 16 studies[14] and is comparable with other studies using PET/CT scans.[16]

The whole body PET tumor detection rate of 30.8% in our study is in accordance to the literature.[2,17–19] Integrated PET/CT performed considerably better (55% detection rate), but this higher rate, ranging from 32% to 68%, has also been reported by other groups.[11,20–23]

The specificity of a PET/CT scan also tended to be higher than a PET scan alone (95.0% vs 75.8%; $p =$ .118).

Six of the 7 false-positive FDG foci on PET scans were found in the tonsils and 1 at the base of the tongue. The only false-positive finding on a PET/CT scan was in the transitional zone between the base of the tongue and the vallecula, which showed clearly increased FDG uptake (SUV = 10.4) and asymmetry

(7.3). The morphology also showed unilateral hyperplasia with resulting asymmetry.

The low specificity of a PET scan, arising from the high false-positive rate, was reported to be one of the most obvious weaknesses.[17] The tonsils are the most likely site of false-positive FDG accumulation.[12,14] The higher metabolism in the tonsillar lymphatic tissue causes an intensive and frequently inhomogeneous uptake of FDG, which may overlap with the uptake by malignant tumors.[24] Similar problems are seen in other areas of Waldeyer's throat ring.[25] Other reasons for false positives in the head and neck are inflammatory processes, asymmetrical production of saliva and swallowing, cervical brown fat tissue, systemic granulomatous diseases, and benign salivary gland tumors.[10,26] The improved specificity of PET/CT scans can be explained by the precise anatomic mapping of the area of high FDG uptake. This is particularly important in patients with large cervical metastases (N3), which considerably shift endopharyngeal structures from their normal anatomic positions (Figure 2), making a correct anatomic correlation much more difficult.

PET and PET/CT scans showed comparable sensitivity (60.0% vs 77.78%). The reason for this is that a CT scan cannot minimize the false-negative results of PET scans. In most cases, it relates to small tumors (5–15 mm in this study) that are on the borderline of PET scan resolution. Well-differentiated squamous cell carcinomas may also be wrongly interpreted as negatives, because they take up less FDG.[27] In this study, 4 of 10 primary tumors were not identified with a PET scan and 4 of 18 primary tumors were not found with a PET/CT scan. They were detected only by means of CUP panendoscopy. A negative PET or PET/CT scan does not, therefore, exclude a primary tumor, and panendoscopy remains an indispensible tool in the diagnosis of CUP.

One very important feature of both whole-body PET and PET/CT scans is the detection of malignancy outside the head and neck region (distant metastases or synchronous second malignant tumors). The detection rates below the clavicles (18.4% with PET/CT

scan vs 20.5% with PET scan) were comparable and higher than the rates (11.2%) found with a PET scan in other studies.[14] Sensitivity and specificity cannot be calculated for these cases, as not all findings were checked with histology and the patients were not followed up clinically for a sufficient length of time. Data on synchronous and metachronous second malignancies from the literature show rates of 13% to 22%,[28,29] which are very close to our detection rates. The major importance of detecting a second malignancy is the change in treatment planning, usually from curative to palliative. In this way, not only can morbidity and subsequent reduction in quality of life be avoided, but also the expense of unnecessary treatment.[27]

Visual/qualitative assessment of FDG accumulation in the various regions of the head and neck require great experience on the part of the examiner. The semi-quantitative parameters based on the SUVs (eg, SUV-$_{max}$ and SUV-asymmetry) provide certain objectivity, and thus improve the diagnostic efficiency of the investigation.[12,30]

Our current management in the presence of a cervical space-occupying lesion was previously described. This procedure has 2 advantages. First, only those patients in whom no primary cancer has been found after maximum clinical and conventional radiological examination are investigated by a PET scan. Second, the initial panendoscopy does not make the evaluation of the PET scan more difficult, as no mucosal biopsies are taken at this stage. Such biopsies would make an accurate assessment of the PET more difficult or even impossible because of reactive/inflammatory uptake increasing the SUV.

This work has 2 major limitations. It is a retrospective study and the 2 diagnostic modalities were not compared in the same patient population. Therefore, a one-to-one comparison between a PET scan and a PET/CT scan is not possible and the results could be affected by the inhomogeneity of the 2 patient groups. Furthermore, someone cannot be absolutely sure that the negative findings in a PET or PET/CT scan are truly negative because the patients were not followed up after the initial diagnostic imaging. These problems could be solved by a prospective study with sufficient follow-up of the patients.

CONCLUSION

Both PET and PET/CT scans improve the diagnosis in the search for the primary tumor in cases of clinical CUP. The detection rate and positive predictive value of integrated PET/CT scanning are significantly increased; specificity shows a trend to significance. The higher costs of the examinations are therefore justified. It must be emphasized, however, that careful clinical examination, diagnostic imaging with ultrasound scan, CT or MRI scans (when dedicated PET scan alone is carried out), and especially panendoscopy with bilateral tonsillectomy, blind biopsies

from the nasopharynx and base of the tongue are all part of a complete CUP workup.

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