2[18F]-fluoro-2-deoxy-D-glucose positron emission tomography is a sensitive tool for the detection of occult primary cancer (carcinoma of unknown primary syndrome) with head and neck lymph node manifestation

MARKUS JUNGEHÜLSING, MD, KLEMENS SCHEIDHAUER, MD, MICHAEL DAMM, MD, UWE PIETRZYK, PhD, HANS ECKEL, MD, HARALD SCHICHA, MD, and **EBERHARD STENNERT, MD,** Cologne, Germany

BACKGROUND: **The neck lymph nodes are a common site of metastases from carcinoma of unknown primary (CUP syndrome). 2[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (18-FDG-PET) has been shown to be a sensitive tool for detecting primary malignant lesions as well as metastatic spread. We have prospectively investigated the sensitivity of 18-FDG-PET in detecting occult primary carcinomas with manifestation in the head and neck lymph nodes.**

METHODS: **From May 1994 to July 1998, in 723 patients a cancer of the head and neck was diagnosed at the University of Cologne ENT outpatient clinic. The routinely performed staging procedures were chest radiography; full blood count; cervical and liver ultrasound; endoscopy of the nasopharynx, oropharynx, hypopharynx, larynx, and esophagus; and laboratory analyses. After the staging workup, in 27 of 723 patients (3.7%) CUP syndrome had to be presumed because the primary cancer could not be detected. In these patients 18-FDG-PET was performed, and images were reconstructed with a transmission-emission fusion technique.**

RESULTS: **In 7 of 27 patients (26%) 18-FDG-PET revealed an unknown primary: in 2 a bronchial carcinoma, in 2 a nasopharyngeal carcinoma, in 1 a squamous cell carcinoma of the parotid gland, in 1 a squamous cell carcinoma of the hypopharynx, and in 1 a carcinoma of the tonsil. In 4 of 7 patients the occult primary tumor was removed surgically. In 8 of 27 patients therapeutic strategy was changed as a result of the 18-FDG-PET findings.**

CONCLUSION: **18-FDG-PET should be performed in all patients with CUP syndrome after conventional diagnostic workup fails to identify the primary.** (Otolaryngol Head Neck Surg 2000;123:294-301.)

Today about 2% of all newly diagnosed malignancies are categorized as carcinoma of unknown primary cancer (CUP syndrome).[1,2] The prior localization of the first manifestation of CUP syndrome is in the whole body lymph nodes (37, and among them 31% are localized in the head and neck region).[1] CUP syndrome creates a dilemma for both patient and physician with regard to the adequate treatment. Therefore the detection of the occult primary is important, and the literature dealing with CUP syndrome is large (for an overview see Jungehülsing et al[3]).

But as diagnostic tools advance, diagnostic strategies are modified and become more accurate. For example, in 1950 Abrams et al[4] noted that of 1000 autopsied cases with proven malignancies 10% represented CUP syndrome. The introduction of new immunohistochemical staining methods[5] and cross-sectional imaging techniques[6,7] has diminished the percentage of occult primary cancer cases to 2% today.[1,2]

As a new diagnostic tool, 2[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (18-FDG-PET) has proved to be highly accurate in identifying malignant tumors.[8,9] The aim of our study was to determine the value of 18-FDG-PET after unsuccessful conventional diagnostic evaluation for patients with metastases from unknown primary cancer in the head and neck region.

METHODS AND PATIENTS

Patient Selection

From May 1994 until July 1998, in 723 patients malignant disease was diagnosed in the outpatient ENT unit of the University of Cologne, Germany. Whereas in 291 (40%)

From the ENT (Drs Jungehülsing, Damm, Eckel, and Stennert) and Nuclear Medicine (Drs Scheidhauer and Schicha) Departments, University of Cologne; and the Max Planck Institute for Neurologic Research (Dr Pietrzyk).

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Reprint requests: M. Jungehülsing, MD, Universitäts-Hals-, Nasen-, Ohrenklinik, 50924 Cologne, Germany.

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Table 1. Conventional diagnostic procedure

1. Medical history
2. Physical examination
3. Chest radiography
4. Full blood count
5. Cervical and abdominal ultrasound
6. Panendoscopy (esophagoscopy, laryngoscopy, nasopharyngoscopy, oropharyngoscopy, hypopharyngoscopy)

Table 2. Investigations performed in patients with unsuccessful conventional diagnostic workup

1. Epstein-Barr virus serology
2. MRI respectively CT from the skull base to the diaphragm
3. Lymph node biopsy respectively neck dissection and immunohistochemical investigations
4. Gastroscopy, coloscopy, bronchoscopy, etc
5. Others

patients the guiding symptom was hoarseness, in 174 of 723 (24%) patients malignant lymphadenopathy was the cardinal symptom leading them to the ENT outpatient unit; fine-needle aspiration cytology (FNAC) or excisional biopsy was used to prove the diagnosis. All patients with proven malignancies underwent the conventional diagnostic workup listed in Table 1.

If after these diagnostic procedures the primary cancer still was not detected, MRI or CT from the nasopharynx to the diaphragm was performed, as well as Epstein-Barr virus serology. If findings were suspicious, tonsillectomy was performed as well. In patients in whom the FNAC had proved malignancy, excisional biopsy of a lymph node was performed with frozen-section analysis for histologic examination. Optionally, modified radical neck dissection was the most frequently used surgical intervention, following the guidelines of Byers,[10] Lefebvre et al,[11] and Abbruzzese et al,[6] thus providing a tissue specimen for immunohistologic investigations (cytokeratin, leukocyte antigen, neuron-specific enolase, chromogranin, β-chorionic gonadotropin, S-100, HMB45, prostate-specific antigen, and estrogen receptors).[5] These further investigations are summarized in Table 2.

In 27 patients the entire diagnostic evaluation (Tables 1 and 2) failed to disclose the site of the unknown primary cancer. This group consisted of 4 women and 23 men; the mean age was 60 years (36-74 years), and most patients (18/27) had squamous cell carcinoma (SCC). In 3 patients with adenocarcinoma, gastroscopy and coloscopy were performed without pathologic results. In patient 8, who had oat cell carcinoma, neither CT nor bronchoscopy showed signs of bronchial neoplastic disease (Table 3).

18-FDG-PET

All PET studies were performed with a Siemens CTI Ecat Exact whole-body positron camera. This device has a patient aperture of 56 cm in diameter and an axial length of 16.2 cm.

The spatial resolution of the system is 5 mm full width at half maximum transaxially in the center of the field of the view. FDG was produced by the method described by Hamacher et al.[12] A standard dose of 370 MBq (10 mCi) was injected intravenously after blood specimen collection for evaluation of the blood glucose profile (Table 3). All patients fasted at least 6 hours before the investigation. Whole-body images were obtained 60 to 90 minutes after injection. Forty-seven slices were acquired simultaneously without gap for a total of 15 minutes of emission and 10 minutes of transmission. Two to 3 bed positions (94-141 slices, respectively) were scanned: the head and neck region and the torso down to the diaphragm. Germanium 68 was used as an external positron emitter to correct for attenuation. PET images were reconstructed with filtered back-projection and displayed in coronal, sagittal, and transaxial projections with the commercial software MPITool (multipurpose imaging tool) described by Pietrzyk et al.[13] The PET findings indicative of a primary tumor were corroborated by FNAC, biopsy, or surgery.

RESULTS

Primary Tumors

In 27 of 723 (3.7%) patients with newly diagnosed malignancies, no primary tumor was found at the completion of the conventional evaluation. 18-FDG-PET revealed the primary tumors in 7 of 27 (26%) of these patients (Table 4). In total, 174 of 723 (24%) patients presented with cervical lymphadenopathy as guiding symptom. Patients with lymphadenopathy had a higher rate of unsuccessful conventional workup: in 26 of 174 patients (15%) the primary cancer was not detected. In our CUP syndrome group, only patient 11 had a metastasis located in the brain instead of the head and neck lymph nodes.

The 2 patients with nasopharyngeal carcinoma did not show any elevated levels on Epstein-Barr virus serology. A 52-year-old woman (patient 11) had hemiparesis and aphasia at presentation, and a brain metastasis from an undifferentiated carcinoma was discovered and removed after conventional staging. The diagnostic evaluation did not reveal any primary tumor site, but 18-FDG-PET showed slight tracer uptake in the nasopharynx. Abrasion of the nasopharynx revealed a nasopharyngeal carcinoma. Subsequently, the postsurgical radiation field was extended to the nasopharynx. The other patient exhibited multiple cervical lymph node metastases, but neither panendoscopy nor CT and MRI revealed the primary cancer.

18-FDG-PET scanning showed strong tracer accumulation in the nasopharynx, and nasopharyngeal abrasion led to the diagnosis of an undifferentiated carcinoma

Table 3. Patient characteristics, site of metastasis, date of first examination, histopathologic findings in lymph node specimen

Patient No.	Age (y)	Sex	Glucose (mg%)	Site of metastasis	1st exam date	Diagnosis made by	Histopathologic/ cytologic findings in metastases
1	65	M	120	Right CLN	5/94	EB	SCC GIII
2	74	M	80	Right CLN	1/97	EB	SCC GIII
3	57	M	104	Left CLN	2/97	EB	SCC GIII
4	60	M	100	Left CLN	11/94	EB	SCC GIII
5	69	M	122	Left CLN	1/98	EB	Adenocarcinoma
6	71	M	80	Left CLN	10/95	FND	SCC GIII
7	66	M	89	Left CLN	2/98	FNAC	SCC GIII
8	66	M	80	Left CLN	3/95	EB	Oat cell Ca
9	67	M	80	Left CLN	12/96	FNAC	SCC GII
10	62	F	120	Left CLN	8/96	EB	SCC GII
11	56	F	90	Brain metastasis	10/94	Brain surgery	Adenocarcinoma
12	69	M	70	Left CLN	7/94	FNAC	Adenocarcinoma
13	75	M	120	Right CLN	8/94	EB	SCC GII
14	53	F	90	Left CLN	3/97	RND	SCC GIII
15	36	M	100	Left CLN	8/95	EB	Myoepithelial Ca
16	60	M	119	Left CLN	5/97	FNAC	SCC GIII
17	38	M	80	Left CLN	6/95	FNAC	SCC GIII
18	64	M	80	Left CLN	9/96	EB	Undifferentiated Ca
19	66	M	70	Left CLN	5/94	RND	SCC GIII
20	50	M	97	Left CLN	11/97	FNAC	SCC GII
21	65	M	124	Right CLN	1/98	EB	SCC
22	62	M	133	Right CLN	12/97	FNAC	SCC GII
23	63	M	100	Right CLN	11/97	FNAC	SCC GIII
24	43	M	100	Right CLN	10/95	FNAC	SCC GIII
25	70	F	80	Right parotid gland region	1/96	FNAC	Solid Ca
26	49	M	80	Left CLN	4/97	EB	Undifferentiated Ca
27	46	F	88	Left submandibular gland tumor metastasis	6/98	EB	Undifferentiated Ca

Glucose refers to the level of blood glucose before 18-FDG-PET scan.
CLN, Cervical lymph nodes; *EB,* excisional biopsy; *FND,* functional neck dissection; *RND,* radical neck dissection; *GII,* intermediate differentiation; *GIII,* poor differentiation; *Ca,* carcinoma.

of the nasopharynx. Combined radiotherapeutic and chemotherapeutic treatment with a carboplatin/5-fluorouracil regimen and 70-Gy radiation was administered rather than surgery.[3]

One of the 2 patients (No. 21) with bronchial carcinoma did benefit from the discovery of the occult tumor in so far as partial pulmonary resection was performed; he has had no tumor recurrence for 6 months. In the other patient (No. 19) resection seemed not to be promising because of the central site of the tumor; radical neck dissection was performed for histopathologic diagnosis, and a combined radiotherapeutic and chemotherapeutic regimen was performed at our internal medicine section.

In a 75-year-old man (patient 13) FNAC revealed malignancy in a right cervical lymph node (region III[14]). Neck dissection was performed, and a lymph node metastasis was disclosed that descended from an undifferentiated SCC. After the routine diagnostic evaluation was inconclusive, 18-FDG-PET revealed strong tracer accumulation in the deep portion of the right parotid gland. Total parotidectomy with facial nerve preservation was performed and revealed a primary parotid gland SCC, which is a rare entity (1.6% of all salivary gland tumors). Unfortunately the patient died 17 months later during a cardiac arrest. Until then there was no disease recurrence.

In a 46-year-old woman (patient 27), a tumor emerging from the left submandibular gland had to be removed; rapid section histology proved malignancy, and the surgical intervention was modified radical neck dissection. Histopathologic examination demonstrated the tumor to be metastatic from a basaloid SCC. Panendoscopy and multiple biopsy specimens did not reveal any mucosal lesions (Fig 1). Findings of the entire diagnostic evaluation, including MRI of the head and neck (Fig 2*A* and *B*), mammography, and gastroscopy/coloscopy were negative. 18-FDG-PET showed focal tracer uptake in the left tonsil (Fig 3). The tonsil was removed subse-

Table 4. 18-FDG-PET findings

Patient No.	Histopathologic/ cytologic findings in metastases	Known lymph node metastasis visualized	Unknown metastases visualized	Occult primary cancer visualized	Therapy	Therapeutic strategy change after 18-FDG-PET	Survival as of 7/98 (mo)	Cadaver dissection
1	SCC GIII	+	–	—	RND R	—	12*	No result
2	SCC GIII	+	–	—	RND R	—	17	—
3	SCC GIII	+	–	—	RND L, RT	—	15	—
4	SCC GIII	+	+	—	FND, RT	—	43	—
5	Adenocarcinoma	– (after excision)	+	—	RND L, RT	Extended field radiation	6	—
6	SCC GIII	– (after excision)	–	—	FND L	—	37	—
7	SCC GIII	+	–	—	RND	—	2	—
8	Magnocellular Ca	+	–	—	RND, RT	—	11*	Bronchial Ca
9	SCC GII	+	–	—	RND L, RT	—	18	—
10	SCC GIII	+	+	—	RND L, RT	Extended field radiation	22	—
11	Adenocarcinoma	+	–	Nasopharyngeal Ca	RND L, RT	Extended field radiation	24*	Not performed
12	Adenocarcinoma	+	+	—	RND L, RT	—	21*	Not performed
13	SCC GII	+	–	R parotid gland Ca	FND R	Total parotidectomy	17*	Not performed
14	SCC GIII	– (after excision)	–	—	RT	—	20*	Bronchial Ca
15	Myoepithelial Ca	+	+	—	FND R, RT	—	13	—
16	SCC GIII	+	–	Hypopharyngeal Ca	RT	Laser tumor resection	36	—
17	SCC GIII	+	–	—	RND L, CRT	—	22	—
18	Undifferentiated Ca	+	+	Nasopharyngeal Ca	CRT	Conservative instead of surgical approach	49	—
19	SCC GIII	– (after excision)	–	R bronchial peripheral Ca	RND R	Partial lung resection	8	—
20	SCC GII	+	–	—	FND, CRT	—	5	—
21	SCC	– (after excision)	–	L hilar bronchial Ca	FND L	—	6	—
22	SCC GII	+	–	—	FND R, RT	—	7	—
23	SCC GIII	+	–	—	FND R	—	33	—
24	SCC GIII	+	+	—	RND, RT	—	30	—
25	Solid Ca	+	–	—	RND R, RT	—	15	—
26	Undifferentiated Ca	– (after excision)	–	—	None	—	1	—
27	SCC GIII	– (after excision)	–	L tonsil Ca	FND L, CRT scheduled	Tonsillectomy	1	

GII, intermediate differentiation; *GIII*, poor differentiation; *Ca*, carcinoma; *FND*, functional neck dissection; *RND*, radical neck dissection; *R*, right; *L*, left; *CRT*, combined radiotherapy and chemotherapy, *RT*, radiotherapy.
*Dead.

quently (Figs 4 and 5), and histopathologic examination revealed a 7-mm undifferentiated basaloid SCC.

In patient 16, a T1 hypopharyngeal carcinoma was detected only after 18-FDG-PET during a second panendoscopy. It was situated at the wall of the left piriform sinus and was completely covered by normal mucosa. The submucosal lesion measured 5 × 8 mm and was removed by CO_2 laser. On the whole, in 6 of 7 patients primary cancer discovery caused therapeutic strategy modification.

Metastases

In 20 of 27 patients, known metastases were reliably depicted by 18-FDG-PET (Fig 6). In 7 of 27 patients 18-FDG-PET detection was not possible because the metastasis had not yet been removed for diagnostic reasons. In 7 of 26 patients, additional metastases were detected by 18-FDG-PET: in 5 patients they were situated in the neck lymph nodes and in 1 patient in the mediastinal lymph nodes (patient 5, primary cancer not detected). One patient exhibited metastasis to the clavicle (patient 10, primary cancer not detected), which was verified by conventional radiographs. In the patients with mediastinal and clavicular bone metastases, the radiation field was extended subsequently to cover the additionally detected metastases.

In 20 patients unilateral radical or functional neck dissection was performed after 18-FDG-PET imaging.

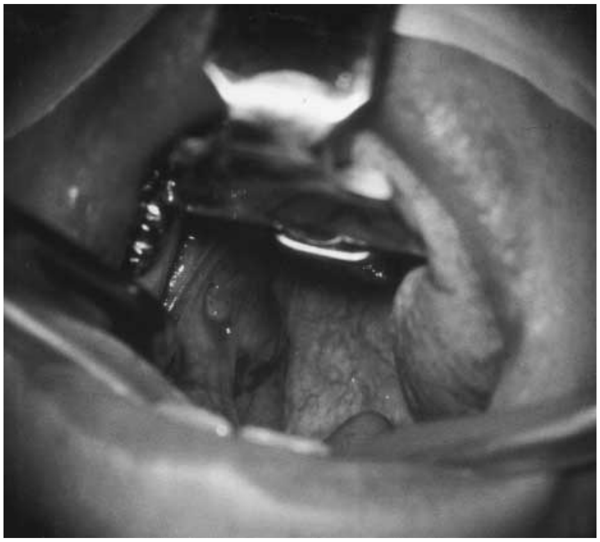

Fig 1. Suspension oropharyngoscopy in patient 27, a 46-year-old woman, shows normal size and extension of the left tonsil (photograph taken during the second panendoscopy).

Histopathology of the 20 specimen revealed 3 additional metastases in different lymph node regions[14] that were not detected by 18-FDG-PET. They all measured below 7 mm in diameter. There were no false-positive findings with 18-FDG-PET.

DISCUSSION

18-FDG-PET has been shown to be a sensitive diagnostic tool in head and neck cancer (for a review see Keyes et al[15]).[16,17] Its different way of tumor delineation (visualization of metabolism rather than structure[18]) distinguishes the method for several diagnostic approaches in oncology.[19-22] 18-FDG-PET depicts the glucose utilization, which shows a high tumor-to-background ratio,[23] suggesting its application to patients with CUP syndrome. Consequently, several studies have been performed to evaluate the method for detection of the unknown primary cancer.[23-25] It is inherent that a statistical view of the diagnostic tools for the detection of an unknown primary is difficult: the diagnostic method being successful excludes the patient from the group of interest because he or she no longer has an occult tumor. Schipper et al[25] found occult cancer in 7 of 16 patients, Braams et al[23] in 5 of 13 patients, and Kole et al[24] in 7 of 29 patients. Patients in the study by Braams et al seemed to be part of the study group of Kole et al. They did not find any statistical relevance concerning the prognosis between detected and nondetected primary tumors in their 17 and 29, respectively, CUP syndrome patients.

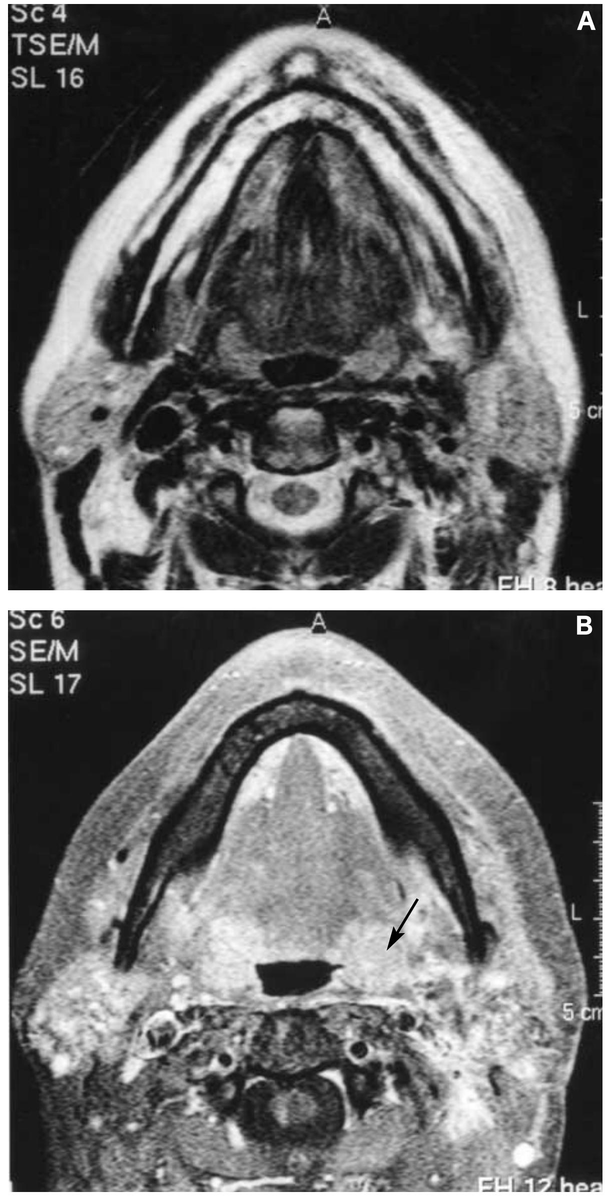

Fig 2. High-resolution MRI without **(A)** and with **(B)** gadolinium-DTPA shows a small lesion in the upper part of the left tonsil (diameter about 8 mm) *(arrow).* (Head coil, field of view = 240 mm, slice thickness = 2 mm, echo time = 16 ms, repetition time = 500 ms.)

Our own CUP syndrome patient group is too small to be suitable for statistical analysis (only 27 patients). The histopathologic findings and tumor stages are heterogeneous, and the follow-up is short.

It is known from larger studies dealing with conventional diagnostic modalities that detection of the so far occult tumor before definite therapy improves patient prognosis.[26,27]

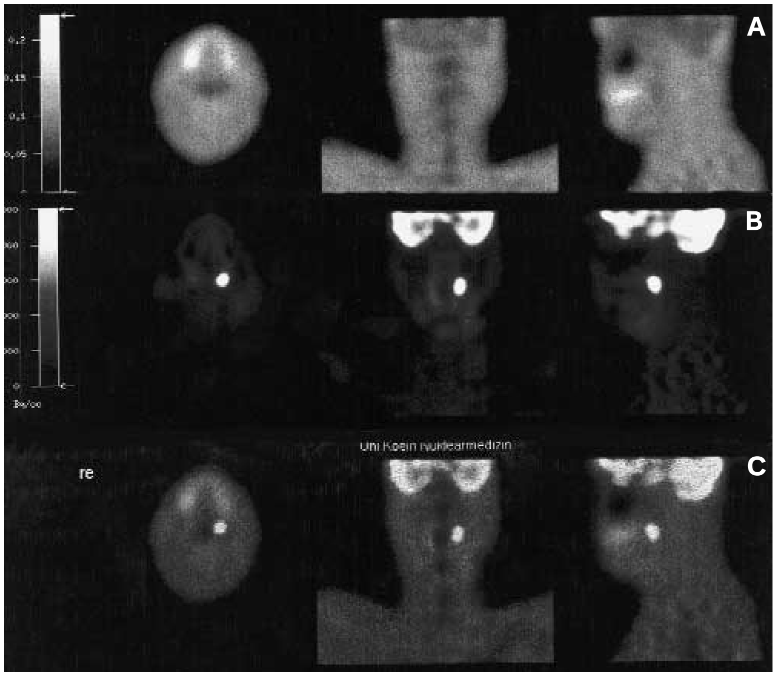

Fig 3. A 370 MBq 18-FDG, 60 minutes after intravenous injection in patient 27. PET: **A,** transmission; **B,** emission; **C,** fusion technique. Note high local retention of 18-FDG in the region of the left tonsil.

Fig 4. Left tonsillectomy specimen in the same patient showing a small, resistant lesion in its upper part.

Fig 5. Cut through the left tonsil. Notice the small, whitish, compact tumor.

Possible Reasons for Unsuccessful Primary Tumor Search

Several reasons for not being able to locate the primary tumor have been postulated. Spontaneous regression,[28] immune-modulated destruction of the primary cancer,[29] faster proliferation rate of the lymph node metastases,[30] and removal of the primary site by sloughing of a necrotic tumor from the gastrointestinal tract are discussed.[28] Branchiogenic carcinoma[31] mistaken for a lymph node metastasis could also be an explanation for an unsuccessful primary tumor search.[3] In our patients the 7 detected primary cancers corroborate the theory of a faster proliferation rate of the lymph node metastases[30] because the primary cancers were all

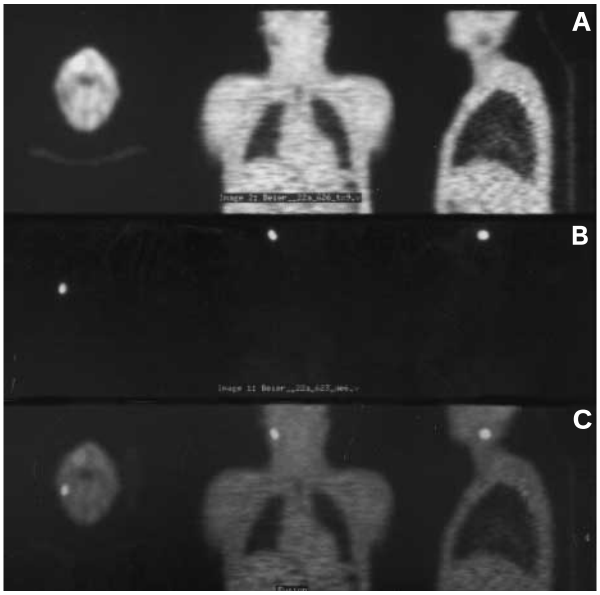

Fig 6. A 370 MBq 18-FDG 90 minutes after intravenous injection in patient 2. PET: **A,** transmission; **B,** emission; **C,** fusion technique. Note clearly depictable metastasis in upper part of right neck lymph node chain (Medina region II). No primary cancer was detected.

smaller than 1 cm in diameter, and the metastases were much larger (>1 cm). Concerning the 20 patients without occult tumor detection, the reasons for unsuccessful 18-FDG-PET scanning may be those mentioned above, but it is also possible that the applied 18-FDG-PET technique was not sufficient. We focused the 18-FDG-PET examination on the region between the skull base and diaphragm because metastatic spread to the neck lymph nodes from below the diaphragm is rare,[32,33] and more bed positions would have prolonged the examination time (each bed position for 30 minutes). Moreover, former PET studies covering the whole body did not reveal any occult tumor below the diaphragm, except 1 case of an adenocarcinoma in the colon.[34]

Kole et al[34] ruled out that an emission-transmission fusion technique would perhaps ameliorate results of the occult primary search; we did use this technique in our study and had no better results (24% of detected tumors vs 26% of detected tumors); however, we believe that scans obtained with the fusion technique allowed a more exact anatomic projection, as shown in Figs 1 through 5 (patient 27).

Relevance

18-FDG-PET from the skull base to the diaphragm reduced the number of unidentified primary sites of cancer by 26% in our series of 27 CUP syndrome patients. This does not seem overwhelming, but we have to consider that all other diagnostic tools, including the modern cross-sectional imaging techniques like MRI, CT, and ultrasound, did not detect these occult tumors.

The reason for this finding was that in 7 patients the detected primary lesions were too small to be recognized as malignant tumors for these morphometric imaging modalities; for example, in patient 27 the small tonsil tumor was clearly depictable on a high-resolution MRI, which was performed after the 18-FDG-PET scan (Fig 2); measuring 7 mm in diameter, it was too small to fit the accepted MRI criteria for malignancy.

18-FDG-PET is a technique based on the visualization of metabolism rather than structure, and the unfavorable pixel resolution of 18-FDG-PET is overcome by a favorable tumor-to-background ratio and the lack of purely morphometric criteria of the conventional cross-sectional techniques.[23] However, in 20 of 27 patients 18-FDG-PET did not delineate the occult primary cancer, as well as the other diagnostic tools; the reason for this is not yet clear. In 2 of our 27 patients, cadaver dissection revealed bronchial carcinoma 11 months (patient 8) and 20 months (patient 14) after 18-FDG-PET imaging. Perhaps in these patients the primary tumor size was too small to be recognized by 18-FDG-PET.

Metastases were depicted with high accuracy in our CUP syndrome patients; 18-FDG-PET resulted in a change in the therapeutic strategy in 2 of them. This is in line with the existing literature describing high sensitivity and specificity for detecting lymph node metastases with 18-FDG-PET.[35,36] Three metastases smaller than 5 mm were missed.

Differentiation between metastatic and primary tumors did not cause any problems in our CUP syndrome patient group. The identified primary tumors were situated at anatomic sites where lymph node metastases are rare and less probable than primary tumors; moreover, our patients did not exhibit multiple metastases, which perhaps would have caused confusion.

Differentiation between SCC emerging from a cervical cleft (branchiogenic carcinoma[31]) and SCC lymph node metastasis remains impossible with 18-FDG-PET as well as with the conventional diagnostic tools.

CONCLUSION

We were able to identify 7 originally occult primary tumors and 7 unknown additional metastases in 13 of 27 patients with CUP syndrome. For these patients the results allowed more accurate decisions regarding treatment. 18-FDG-PET diminishes only the CUP syndrome percentage of the total number of malignancies. However, we think that even a lower percentage of primary tumors remaining occult is favorable. In our opinion, 18-FDG-PET should be performed after the defined conventional diagnostic workup (Table 1) but before all other diagnostic approaches (Table 2); thus it would render further diagnostic approaches more specific—and probably more cost-effective—in a certain percentage of patients (26% in our CUP syndrome patients).

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