Dual Modality of ^{18}F -Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography in Patients with Cervical Carcinoma of Unknown Primary

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Key Words

Unknown primary tumor · Positron emission tomography/computed tomography · Fluorodeoxyglucose · Dual modality

Abstract

Objective: To evaluate an optimized F-18-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) acquisition protocol for head and neck cancer and assess the usefulness of combined FDG-PET/CT in locating unknown primary tumors in patients with biopsy-proven cervical lymph node metastases.

Subjects and Methods: Twenty-one patients with cervical lymph node metastases of unknown primary tumors underwent staging with FDG-PET/CT. The images of FDG-PET alone, CT alone, FDG-PET/CT read side by side and fused and FDG-PET/CT were evaluated separately by 2 physicians. Imaging results were correlated with either histology (n = 14) or clinical follow-up (n = 7). **Results:** On the fused FDG-PET/CT images, primary tumors were identified in 12 patients (57%); with FDG-PET alone and FDG-PET and CT read side by side 11 (52%) primary tumors were found while CT alone identified 5 (23%) primary tumors. **Conclusion:** Our data indicate that fused

FDG-PET and CT images increased the sensitivity of detecting carcinoma of unknown primary (CUP) tumors compared to CT alone, but not to FDG-PET alone or FDG-PET and CT read side by side. Hence accurate fusion of functional and morphologic data by FDG-PET/CT is a promising imaging modality in the clinical workup of patients with cervical CUP tumors.

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Introduction

In about 2–10% of all newly diagnosed biopsy-confirmed malignancies the site of origin is not identified by routine clinical workup and they are thus categorized as carcinoma of unknown primary cancer (CUP) [1–4]. In 24–36% of these patients the prior localization of the first CUP manifestation are lymph nodes in the head and neck region [1, 3, 4]. While the prognosis of patients with CUP is generally unfavorable with average survival of only a few months, however, patients with cervical lymph node metastases are an exception to this rule [5–10] since they can be treated locoregionally. Furthermore, at least in patients with an upper- or mid-jugular lymph node metastasis, the corresponding primary tumor is likely (85%)

Table 1. Condensed data of imaging data and histological result of all patients (n = 21)

n	Age	CT	PET	PET and CT	PET/CT	Histology	Diagnosis
1	46	TP	TP	TP	TP	+	oropharyngeal carcinoma
2	48	FN	TP	TP	TP	+	bronchial carcinoma
3	54	FN	FN	FN	FN	+	oropharyngeal carcinoma
4	55						NPF
5	57	FP					NPF
6	60						NPF
7	62	TP	TP	TP	TP	+	laryngeal carcinoma
8	63		FP				NPF
9	65						NPF
10	68	FN	TP	TP	TP	+	non-Hodgkin's lymphoma
11	69	TP	TP	TP	TP	+	bronchial carcinoma
12	74	FN	FN	FN	FN	+	esophageal carcinoma
13	75	TP	TP	TP	TP	+	bronchial carcinoma
14	76	FP					NPF
15	94	FN	FN	FN	TP	+	salivary gland carcinoma
16	69	TP	TP	TP	TP	+	non-Hodgkin's lymphoma
17	69	FN	TP	TP	TP	+	oropharyngeal carcinoma
18	54	FP	FP	FP			NPF
19	63		TP	TP	TP		oropharyngeal carcinoma
20	63	FN	TP	TP	TP	+	medullary thyroid carcinoma
21	48	FN	TP	TP	TP	+	laryngeal carcinoma

TP = True positive; FP = false positive; FN = false negative; NPF = no primary found.

to be head and neck carcinoma [5] and thus is potentially curable.

Therefore, the detection of the occult primary is important. To date [^{18}F]-2-fluoro-2-deoxy-*D*-glucose positron emission tomography (FDG-PET) has been shown to be the most efficient method capable of localizing unknown primary tumors. Detection rates ranging from 24 to 90% have been described in the literature [4, 11–14]. Consequently, the German consensus conference on FDG-PET recommends its use in patients with an unknown primary tumor [13]. However, the inability to localize foci of increased activity of FDG-PET can be challenging in respect of diagnosis, biopsy verification, and subsequent treatment planning. The combination of anatomical and metabolic imaging may overcome these shortcomings [15–18]. However, one has to be aware of pitfalls like artifacts of beam-hardening due to bones or metallic implants [19]. Furthermore the use of intravenous and oral contrast agents that are mandatory to acquire a diagnostic CT might be problematic and can lead to artifacts in PET imaging [20]. Hence, optimized acquisition protocols are needed for dedicated indications for PET/CT imaging in patients with head and neck pathol-

ogy [21–23]. The aim of our study was to determine the benefit of coregistration of FDG-PET and CT data in restaging of patients with head and neck CUP verified by histology. The second objective was to compare the sensitivity of whole-body FDG-PET/CT versus FDG-PET and CT alone or interpreted side by side with visual fusion to identify the localization of the primary tumor.

Subjects and Methods

Subjects

Twenty-one patients (16 men, 5 women, mean age 64 years, range 46–94 years), with histologically or cytologically proven cervical lymph node metastases who underwent clinical, endoscopic, sonographic, and planar radiological staging were included. None of the patients had received a dedicated head and neck CT before. All patients were examined by whole-body dual-modality FDG-PET/CT imaging from November 2001 to August 2003. Cytology revealed squamous cell carcinoma in 14 patients, adenocarcinoma in 4 patients and undifferentiated malignancy in 3 patients (table 1).

Image evaluation was performed retrospectively. Written informed consent was obtained from all patients. The study was performed in accordance with guidelines issued by the local institutional review board.

FDG-PET/CT Imaging

Dual-modality FDG-PET/CT was performed on a Biograph™ (Siemens Medical Solutions, Hoffman Estates, Ill., USA), which is based on a dual slice helical CT and a dedicated full-ring PET tomograph with BGO detectors. The Biograph provides two separate data sets for CT and PET, which are intrinsically coregistered [16]. The PET component of the combined imaging system offers an effective in-plane spatial resolution of about 8 mm and an axial field of view of 15.5 cm for one bed position.

A split acquisition protocol was used to perform a highest quality head and neck CT and a diagnostic CT of thorax, abdomen and pelvis by optimized use of intravenous contrast agents and by reducing beam-hardening artefacts in CT [23]. Total examination time of the split FDG-PET/CT was approximately 60 min.

Head and Neck FDG-PET/CT Imaging. After a fasting period of at least 10 h, 360 MBq (9.7 mCi) of FDG was administered intravenously after blood samples verified a blood glucose level within the normal range (<160 mg%). One hour after injection the patients were laid supine with arms down attached to the body and a CT topogram was performed to define the area of the head and neck scan (256 mm). Afterwards CT images were acquired over the predefined area with 160 mAs, 130 kV, a slice width of 3 mm, and a table feed of 5 mm per rotation while holding breath. For vascular and parenchymal delineation 60 ml of an iodinated contrast agent (Xenetix 300 mg iodine/ml, Guerbet GmbH, Sulzbach, Germany) was administered intravenously with an automated injector (XD 5500, Ulrich Medical Systems, Ulm, Germany) at 3 ml/s. Thereafter emission data were acquired in 3-dimensional mode for 6 min per bed position over two bed positions. CT data were used for PET attenuation correction [24]. Total examination time was a maximum of 15 min. Image reconstruction of the corrected emission data was performed after Fourier rebinning (AWOSEM, 4 iterations, 8 subsets, 3 mm Gaussian filter) [23].

Whole-Body FDG-PET/CT Imaging. After head and neck imaging (70–75 min p.i.) a whole-body FDG-PET/CT was performed in the supine position with the arms elevated above the head in a supporting device. In a topogram, a whole-body scan from thorax to pelvis were defined over five to eight bed positions. Small bowel delineation was accomplished by administration of either 1,000 ml of barium at a concentration of 1.5 g barium sulfate per 100 ml (Micropaque CT, Guerbet GmbH, Sulzbach, Germany) or by ingestion of a solution containing 0.2% of locust bean gum and 2.5% of mannitol diluted in 1.5 liters of water [25]. For vascular and parenchymal delineation 90 ml contrast agent was administered. CT images were acquired with 100 mAs, 130 kV, a slice width of 5 mm, and a table feed of 8 mm per rotation. Thereafter emission data were acquired in 3-dimensional mode for 3 min per bed position. Image reconstruction of the corrected emission data was performed after Fourier rebinning (AWOSEM, 2 iterations, 8 subsets, 5 mm Gaussian filter).

Data Analysis. FDG-PET data sets were evaluated by 2 experienced nuclear medicine physicians in consensus (L.S.F., S.J.R.), while CT images were read by 2 radiologists (T.E., G.A.). The evaluating physicians were blinded to the other imaging modality. Interpretation of FDG-PET and CT images side by side was performed by the same physicians using the same images, which were manually misregistered by a 5th physician (S.J.R.) to simulate the clinical situation of FDG-PET and CT acquired in two separate examinations. Finally, fused FDG-PET/CT data sets were viewed by the same physicians in consensus. FDG-PET images were eval-

Fig. 1. Transverse CT (A) and fused PET/CT (B) images of a patient referred for PET/CT due to CUP syndrome with a right cervical metastasis. CT showed a cervical lymph node metastasis but revealed no primary tumor. Fused PET/CT revealed focally increased glucose metabolism (maximum SUV 3.9, mean SUV 3.2) in the right larynx diagnosed as the primary tumor (arrow) and a cervical lymph node metastasis. Diagnosis was later confirmed by histology.

uated for regions of focally increased tracer uptake. Thus, tumors were primarily identified by qualitative interpretation of the PET images. In all identified lesions, the maximum standard uptake values (SUV) were determined for tracer uptake quantification [26, 27]. As quantitation of FDG uptake using SUV shows significantly higher tracer concentrations for malignant than benign lesions, a maximum SUV of >2.5 was considered to represent malignancy in otherwise equivocal findings. CT images were evaluated for contrast-enhancing masses or asymmetries typical of malignancies. Histopathology (n = 14) and clinical follow-up over ≥ 9 months (n = 7) with subsequent panendoscopy with biopsy of the most probable tumor sites (n = 7), ultrasound (n = 7), CT (n = 6), MRI (n = 6), diagnostic tonsillectomy (n = 4) and additional biopsies (n = 4) served as the reference standard.

Statistical Analysis

Sensitivity regarding the detection of the primary tumors was calculated for the different imaging procedures. The three modalities (FDG-PET, CT, and FDG-PET/CT) of all patients were compared with each other, resulting in 2 × 2 contingency tables. Differences in diagnostic performance were assessed with the McNemar Test. A confidence level below 0.05 was considered statistically significant.

Fig. 2. Transverse PET (**A**), fused PET/CT (**B**) images, and reconstructed coronal CT images (**C**) of a patient referred for PET/CT due to CUP syndrome with a left cervical metastasis. PET showed focal tracer uptake (maximum SUV 5.4, mean SUV 4.9) in the right vocal cord (black arrow) misinterpreted as laryngeal carcinoma. Coronal CT image shows a raised left diaphragm (gray arrow) as a sign of phrenic palsy. The tracer uptake in the right vocal cord is a sign of physiologic activation.

Results

In 14/21 patients all staging procedures yielded histology of the primary tumor: oropharyngeal carcinoma: $n = 4$; bronchial carcinoma: $n = 3$; laryngeal carcinoma and non-Hodgkin's lymphoma: $n = 2$; and 1 each with esophageal carcinoma, medullary thyroid carcinoma and salivary gland carcinoma, respectively. In 7 patients, no primary tumor was found by either diagnostic tool and follow-up revealed no additional information as the patients underwent combined radiochemotherapy.

The condensed patient data of imaging results are presented in table 1. With CT alone 5 primary tumors (23%) were correctly diagnosed with 3 false positive results (14%). Figure 1 is an example of a small primary tumor site that was missed with CT alone. FDG-PET alone correctly detected the primary tumor in 11 patients (52%) and incorrectly in 3 (14%, false positive) that were due to an activated vocal cord in contralateral paresis of the phrenical nerve (fig. 2), oropharyngeal inflammation, and also caused by misinterpretation of lymph node metastases as the primary tumor site. Evaluating FDG-PET and CT images side by side led to the identification of the pri-

Table 2. Sensitivities of CT, PET, PET and CT read side by side, and fused PET/CT for detection of the primary tumor in all patients with cervical CUP ($n = 21$)

	CT scan	PET	PET and CT	PET/CT
Sensitivity, %	29	52	52	57

mary tumor in 11 of 21 patients (52%) and incorrectly in 1 patient due to oropharyngeal inflammation. Based on intrinsically fused FDG-PET/CT, primary tumors were identified in 12 of 21 patients (57%). Compared to FDG-PET and CT images read side by side, a carcinoma of the right submandibular gland was diagnosed that was misinterpreted as a lymph node metastasis in CT and FDG-PET alone (fig. 3). In 9 patients (43%) the primary site was not detected in the fused FDG-PET/CT images.

FDG-PET alone, FDG-PET and CT read side by side as well as fused FDG-PET/CT were superior to CT image reading alone (table 2) for the detection of cervical CUP. However, only the difference in diagnostic performance

Fig. 3. Transverse CT (**A**), PET (**B**), and fused PET/CT (**C**) images of a patient referred for PET/CT due to CUP syndrome with a right cervical metastasis. Fused PET/CT revealed focally increased glucose metabolism (maximum SUV 3.9, mean SUV 3.6) in the right submandibular gland (gray arrow), diagnosed as the primary tumor. Diagnosis was confirmed by histology. On PET as well as side-by-side image evaluation, FDG uptake was misinterpreted as a lymph node metastasis.

between CT alone and fused FDG-PET/CT was statistically significant ($p = 0.03$). The differences between FDG-PET and FDG-PET and CT read side by side as well as fused FDG-PET/CT were not statistically significant.

Discussion

Accurate identification and localization of the primary tumor in patients with CUP is crucial for initiation of an optimized tumor- and stage-adapted therapy [8]. CT-based diagnostic workup of CUP patients has been shown to be rather limited in the identification of primary tumor sites in CUP patients [11, 13, 28]. Compared to most reports, the CT results of this study were quite favorable: 5 of 21 primary tumors (23%) were identified when interpretation was based on CT images alone.

In contrast FDG-PET is superior in locating CUP with varying detection rates from 23% up to 90% depending on the preselected patient population [4, 11–14, 29–34]. As until now, no consensus has been established on how routine clinical workup should be done in patients with CUP. Thus, there is no standardization. This explains the reported differences in the accuracy for FDG-PET applied in the search for the primary tumor site. In our study, 11 primary tumors corresponding to a success rate of 52% were correctly identified similar to previous reports [4, 11–14, 29–34].

In our view, the superior diagnostic performance of FDG-PET compared to CT justifies the recommendation of several groups to employ FDG-PET as the imaging modality of choice in the diagnostic workup of CUP patients [13, 35]. However, especially in the head and neck area FDG-PET imaging is limited by the lack of anatomical landmarks for correct anatomical location. The simultaneous availability of functional PET and morphologic CT data sets enhanced the diagnostic power of both

with regard to the number of true positive and false positive findings in other oncologic patient groups [36–38]. Due to exact anatomical landmarking of the glucose metabolism in combined FDG-PET/CT, we found a primary tumor in 1 patient, suggesting an additional benefit compared to FDG-PET and CT side by side. Furthermore, the simultaneous availability of CT data helped to reduce the number of false positive FDG-PET findings. Thus, functional and morphological data is of great advantage for optimized primary tumor detection as well as the guidance of any subsequent surgical intervention. To gain as much information as possible interpretation of PET/CT should be read by a specialists in nuclear medicine and radiology.

Nevertheless, the failure rate of 33% of nondetectable primary cancers requires improvement in diagnostic strategies in CUP patients. In most cases, the primary tumor remains unidentified during lifetime [39]. Our data show unequivocally that FDG-PET/CT help in further improving the staging in head and neck CUP.

Conclusion

Our data indicate that FDG-PET/CT significantly improved sensitivity in staging of head and neck CUP compared with CT alone but not compared with FDG-PET alone or FDG-PET/CT read side by side. Hence FDG-PET/CT imaging is a promising technique to further improve staging of head and neck CUP. Further studies are required to assess the potential impact of the FDG-PET/CT-associated increased sensitivity in therapy and patient survival.

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