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Value of F-18-FDG PET in patients with cervical lymph node metastases of unknown origin

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Background. *Cancer of unknown primary is still a major diagnostic problem in patients with lymph node metastases despite a large variety of imaging modalities. Therefore, the aim of this study was to evaluate the impact of F-18-FDG positron emission tomography (PET) in these patients.*

Materials and methods. *A total of 28 patients aged 39 to 84 years with cervical lymph node metastases of squamous cell carcinoma (n=24) or an undifferentiated carcinoma (n=4) were investigated. Prior to PET a complete history, physical examination, ultrasound of the neck, panendoscopy, and CT of the head and neck region were performed in all patients without detection of the primary tumour site. All patients received 370 MBq F-18-FDG intravenously, and whole-body images were acquired at 60 min p.i. using an ECAT EXACT 47 (921) (Siemens, CTI). All lesions were evaluated either by histology or by subsequent CT/MRI.*

Results. *In 16/28 patients PET showed focal tracer accumulations corresponding to potential primary tumour sites located in the lungs (n=7), in the region of the palatine tonsil (n=5), the submandibular gland (n=1), the nasopharynx (n=1), the larynx (n=1), and at the base of the tongue (n=1). In 9 out of these 16 patients the primary tumour could be confirmed in the lungs (n=5), in the larynx, at the base of the tongue, the nasopharynx and the palatine tonsil in one patient each, respectively. In 6/16 patients PET lesions were false positive, predominantly located in the palatine tonsil (n=3). One patient denied further evaluation of PET findings. However, in 12/28 patients PET did not reveal tumour-suspicious lesions.*

Conclusions. *Since F-18-FDG PET detected the primary tumour site in approximately one third of the patients with cervical node metastases from an unknown primary (CUP-syndrome), F-18-FDG PET is a valuable diagnostic tool which might help to select a potentially curative treatment protocol in these patients.*

Key words: neoplasm, unknown primary; lymphatic metastasis, CUP-syndrome; tomography, emission-computed, fluorine radioisotopes, F-18-FDG PET

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Introduction

The enlargement of cervical lymph nodes is often the first manifestation of a tumour disease.[1] The palpation and localisation of these

enlarged lymph nodes may be helpful in determining their dignity and the origin of the primary tumour site.[2] An additional ultrasound-guided fine-needle aspiration cytology may give evidence of tumour cells in cervical masses.[1,3] Furthermore, morphological orientated imaging, *i.e.* MRI or CT is performed in order to assess the nodal status and to define the origin of the malignancy. However, despite an accurate diagnostic work-up the primary tumour site can not be detected in 1 to 12 % of all patients with cervical lymph node metastases.[4-9] They are called patients with CUP-syndrome (*c*ancer of *u*nknown *p*rimary). The cytological examination of patients often reveals squamous cell carcinomas or undifferentiated carcinomas.[4] This holds especially true for metastatic lymph nodes of the upper and middle cervical compartments, whereas lymph nodes of the inferior portion of the neck often bear adenocarcinoma cells.

In some cases the primary tumour is found *post mortem*. Common head and neck sites of lately diagnosed malignancies are the piriform sinus, the tonsils, the nasopharynx or the base of the tongue.[10] However, as much as 40 % of the occult primary tumours are located outside the head and neck region, predominantly in the lungs.[11]

Careful staging of patients with CUP-syndrome is of utmost importance since the therapeutic approach mainly depends on the extent of the tumour. The five-years-survival-rate of patients with an occult primary amounts to about 29-50 %.[12-16] In case of bilateral cervical lymph node metastases ($T_XN_{2C}M_0$) the five-years-survival-rate decreases to 17 to 28 %.[17-20] In contrast, in patients with localised squamous cell carcinoma of the head and neck region and bilateral lymph node metastases five-years-survival-rates of 55 % are reported.[21] This emphasises the necessity for an accurate diagnostic work-up in patients with unknown primary.

The value of positron emission tomography (PET) has already been reported in staging of head and neck tumors[22-24] as well as in therapy monitoring after irradiation.[25,26] Therefore, the aim of our study was to evaluate the use of F-18-FDG PET in the detection of the primary tumour in patients with cervical lymph node metastases and CUP-syndrome.

Materials and methods

In total, 28 patients (12 female, 16 male) aged from 39 to 84 years with cervical lymph node metastases of a squamous cell carcinoma (n=24) or an undifferentiated carcinoma (n=4) were included in the study. The diagnosis was established either by histology (n=10) or by fine-needle aspiration cytology (n=18). Seven patients underwent neck dissection prior to PET. Prior to PET a complete history, physical examination, ultrasound of the neck, panendoscopy as well as an additional computed tomography of the head and neck region were performed in each patient. However, the primary tumour site could not be detected. Thus, patients were assigned to have CUP-syndrome.

Patients fastened for at least 6 hours prior to PET-scanning in order to minimise blood insulin levels and glucose utilisation of normal tissue.[27] Whole-body images were acquired 60 min after i.v. injection of 370 MBq F-18-FDG using an ECAT EXACT 47 (921) scanner (Siemens/CTI) with an axial field-of-view of 16.2 cm. No attenuation correction was performed. Emission data were reconstructed by filtered back projection using a Hanning filter with a cut-off frequency of 0.4 of the Nyquist frequency. Thus, transaxial spatial resolution was approximately 12 mm. PET-images were printed on transparency film (Helios 810, Sterling) using a linear grey scale with highest activity displayed in black. Images were displayed with

an upper threshold of five times of the mean activity in the lung. Standardised documentation included both 20 transversal and 20 coronal slices with a slice thickness of 13.5 mm each, and Maximum-Intensity-Projections (MIPs) in anterior, left lateral, right-anterior-oblique, and left-anterior-oblique view as published previously.[28] Whole-body images were interpreted by simple visual inspection.

All lesions were evaluated either by histology or by subsequent conventional imaging.

Results

In 16/28 patients PET showed pathological tracer accumulations corresponding to potential primary tumour sites (Table 1). In nine out of these patients F-18-FDG accumulations were localised in the head and neck region with an increase of FDG uptake in the palatine tonsils in five patients and in the submandibular gland in one patient. Moreover, three patients showed an increased tracer uptake of the larynx, the nasopharynx or the base of the tongue, respectively. In addition, seven patients demonstrated pathological tracer uptake outside the head and head region, *i.e.* in the lungs. Moreover, one patient with increased uptake of F-18-FDG in the lungs showed decreased tracer accumulations of both occipital lobes. However, in 12/28 patients PET did not reveal tumour-suspicious lesions (Table 1).

PET correctly identified the primary tumour site in four out of nine patients with tumour-suspicious lesions of the head and neck region (Figure 1). Based on biopsy findings, the primary cancer was confirmed in the nasopharynx, the larynx, the base of the tongue, and the palatine tonsil, respectively. However, PET was false positive in three patients with tumour-suspicious tracer accumulations of the palatine tonsil and in one

Table 1. PET-findings of 28 patients investigated correlated to localisation of tumour-suspicious lesions and to true positive (TP) and false positive (FP) results

F-18-FDG PET (number)	localisation (number)	TP	FP
Negative (12)			
Positive (16)	lungs (7)	5	2
	palatine tonsil (5)	1	4*
	submandibular gland (1)	∅	1
	nasopharynx (1)	1	∅
	larynx (1)	1	∅
	base of the tongue(1)	1	∅

*one of these patient denied further investigations.

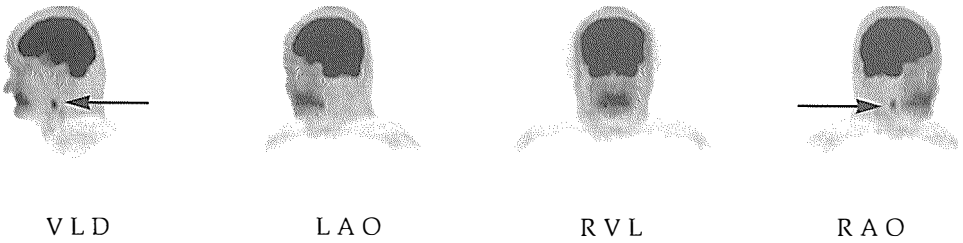

Figure 1. MIPs of a 58-year-old patient with histologically confirmed right-cervical lymph node metastases of a squamous cell carcinoma of unknown origin. Note focal uptake of F-18-FDG in the right palatine tonsil (arrows). Histological evaluation confirmed a squamous cell carcinoma of the right palatine tonsil.

patient with suspect for a primary tumour in the submandibular gland. One patient with increased uptake of F-18-FDG in the palatine tonsil refused biopsy. Thus, PET findings could not be evaluated in this patient.

In five out of seven patients with increased tracer uptake of the lungs PET correctly identified the primary tumour site (Figure 2). Moreover, in one patient with additional decreased tracer uptake of both occipital lobes, PET detected cerebral metastases which were confirmed by subsequent MRI imaging. In two out of the latter seven patients PET imaging was false positive concerning the localisation of the primary tumour site.

In 19 out of 28 patients investigated PET revealed a focal uptake of F-18-FDG in the neck region. These findings corresponded to known metastatic lymph nodes. Two out of the latter 19 patients underwent neck dissection prior to PET. However, PET findings turned out to be consistent with findings of physical examination of recurrent or remaining tumour tissue in the area pre-treated surgically.

PET showed no cervical lymph node uptake in nine patients. In five out of the latter nine patients a neck dissection was performed prior to PET. Thus, PET findings confirmed total resection of cervical lymph node metastases. In four out of these nine patients diagnosis was established by complete resection of metastatic lymph nodes prior to F-18-FDG PET imaging.

Discussion

In 1 to 12 % of all patients with cervical lymph node metastases the primary tumour site can not be detected despite an accurate diagnostic work-up.[16] Therefore, the therapeutic approach remains to be controversial in these patients.[6] The primary objective in patients with CUP-syndrome is the treatment of both cervical lymph node metastases and the primary tumour site. Therefore, the therapeutic approach includes an irradiation of both sides of the neck as well as an irradiation of potential sites of the tumour bearing mucosa. Other authors advocate an ipsilateral neck treatment alone either by irradiation or by surgery.[29] The variety of therapeutic approaches underlines the diagnostic and therapeutic difficulties in patients with CUP-syndrome. An important necessity is the accurate diagnostic work-up since the prog-

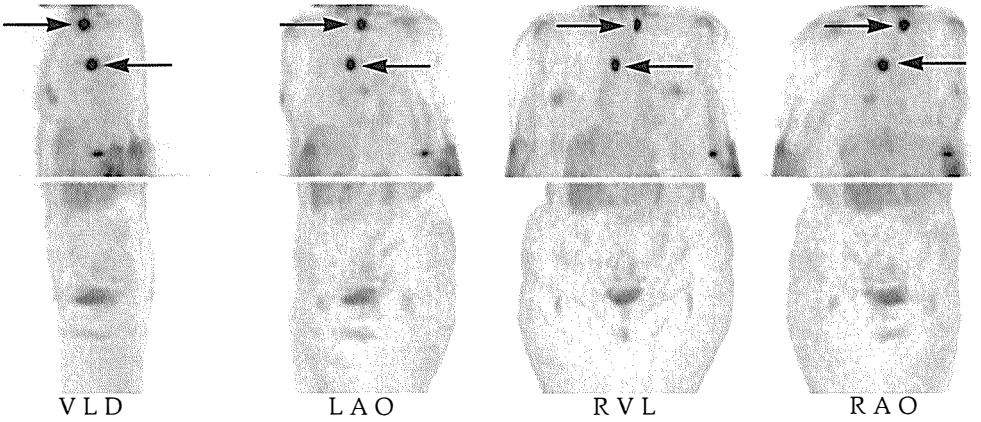

Figure 2. MIPs of a 59-year-old patient with cytologically confirmed left-supraclavicular lymph node metastases of a squamous cell carcinoma of unknown origin. Note focal uptake of F-18-FDG in the area of the known lymph node metastases (upper arrows) as well as a second focal tracer uptake in the right central lung (lower arrows). Histological evaluation confirmed a primary lung cancer.

nosis and the survival-rate mainly depend on the detection of the primary tumour site. Thus, five-years-survival-rates of patients with localised squamous cell carcinoma and bilateral cervical metastases are significantly higher as compared to patients with unknown primary tumour site and comparable lymph node status.[15, 17-21]

Initial studies using F-18-FDG PET showed its value in staging and therapy monitoring in patients with head and neck tumors.[22,24-26] The glucose analogue, F-18-FDG is accumulated and trapped within metabolic active cells. Thus, F-18-FDG can be used to identify higher glycolytic rates of many neoplasms when compared to normal glycolytic rates of non-malignant transformed tissue.

In 16 out of 28 patients PET revealed pathologic accumulations of F-18-FDG corresponding to potential primary tumour sites. In seven out of the latter 16 patients these tracer accumulations were localised outside the head and neck region, i.e. in the lungs. In nine out of 28 patients PET clearly identified the primary tumour lesion. In five patients lung cancer was confirmed as the primary tumour site. Thus, based on PET findings the therapeutic approach was changed in these patients. Of the nine patients with tumour-suspicious lesions of the head and neck region five were localised in the palatine tonsil. However, in three out of these patients PET was false positive, and one patient denied further evaluation of PET findings by biopsy. Thus, primary cancer of the palatine tonsil was only confirmed in one patient. The higher tracer accumulations of the palatine tonsils remained unclear. In contrast, PET clearly identified primary cancer of the larynx, the nasopharynx, and the base of the tongue in one patient, respectively. However, in 12 out of 28 patients PET could not identify tumour-suspicious lesions.

Moreover, PET findings were correlated to clinical findings of cervical lymph node metastases. In 19 out of 28 patients PET confirmed known tumour tissue, in nine patients with previous surgical resection of the metastatic lymph nodes PET findings corresponded to total resection of lymphatic tumour tissue. Thus, in the assessment of cervical metastases PET had no additional clinical impact in our patients. However, in this study PET imaging was helpful in approximately one third of all patients resulting in a change of the therapeutic approach.

Although F-18-FDG PET is an expensive diagnostic modality it allows the screening of the whole-body. This is especially important in patients with occult malignancies as in 40 % of malignant cervical lymph nodes the primary is localised below the clavicles with the most common site in the lungs.[11] However, the detection of the primary tumour site is the basis for an effective and curative therapy.

Previous reports suggested the usefulness of F-18-FDG PET in patients with CUP-syndrome. Braams and coworkers[30] investigated 13 patients with cervical lymph node metastases of unknown origin. PET was true positive in four patients detecting cancer of the oropharynx, of the larynx and of the lungs in one patient, respectively. Moreover, in one patient a plasmocytoma was identified as the primary tumour. Schipper and coworkers[18] reported a rate of 25 % true positive PET findings in 16 patients with cervical metastases of unknown origin.

Conclusion

Since F-18-FDG PET detected the primary tumour site in approximately one third of the patients with CUP-syndrome, F-18-FDG PET is a valuable diagnostic tool which might help to select a potentially curative treatment protocol in these patients.

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