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HEAD AND NECK

18-FDG PET in the diagnosis of laterocervical metastases from occult carcinoma

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Abstract The management of patients with cervical node metastasis (CNM) from carcinoma of unknown primary (CUP) often includes several radiographic studies and invasive procedures that are only successful in detecting an occult primary tumour in less than 25% of the cases. In this prospective study we have assessed the role of total body positron emission tomography (PET) using an 18-F-fluorodesoxyglucose (FDG) in the detection of primary tumours in patients with metastases from CUP. Thirteen patients with lymph node metastases from cytologically verified CUP have undergone total body FDG PET which confirmed the possibility of lymph nodal lesion; all patients have also undergone conventional imaging with CT and/or MRI. The data obtained with the FDG-PET method have subsequently been confirmed both by the histopathological examination and by the clinical course of the disease. The current work aims at assessing and defining the effectiveness of the FDG-PET method during the diagnostic work-up of laterocervical metastasis from CUP conventionally examined with CT and/or MRI; based on our results, we recommend a flow-chart for the clinical-diagnostic management of the patient affected by laterocervical metastasis in the absence of known primary.

Keywords 18-F-fluorodesoxyglucose · Positron emission tomography · Unknown primary tumour · Metastatic disease

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Introduction

Carcinoma of unknown primary (CUP) with cervical node metastasis (CNM) poses a real diagnostic challenge and there is debate about the investigations to be employed in diagnostic work-up.

Metastasis from CUP is a diagnosis of exclusion: it can be used in the case of cervicocephalic metastatic disease when panendoscopic examination, radiological examination and biopsies of the most frequent otorhinolaryngologic areas for occult primary have failed to reveal a primary carcinoma [1].

The rate of CUP ranges between 2 and 9% of all head and neck tumours; a Danish study showed that the annual prevalence of CNM from squamous cell occult carcinoma is 0.34% from 100,000 inhabitants in a year and such effect has substantially been the same over the past 20 years [2].

Lymph nodes represent the most common organ for metastases from CUP and the laterocervical area is the region most frequently affected [3]. CUP can be "localised" when there is one or more lymph node metastases in one region or a solitary visceral metastasis; it can be "disseminated" when there is involvement of multiple lymph nodes and/or viscera [3].

High-resolution computed tomography (CT) or magnetic resonance imaging (MRI) allows the correct staging of

most primary tumours (77–81%), but the sensitivity of the two methods decreases with the detection of small T1 tumours [2–4]. CT or MRI can only detect 10–30% of T1 tumours smaller than 1 cm and located in sites which are not easy to explore like the nasopharynx, the base of tongue or the pyriform sinuses; clinical, panendoscopic and bioptic examinations prove to be more sensitive in their diagnosis than radiological imaging [4, 5].

The primary tumour can regress spontaneously after metastatic spreading [6] and/or radiotherapy, without having even been detected [7].

Fine needle aspiration cytology (FNAC) is preferred to incisional or excisional biopsy; the latter is recommended only when the FNAC result is non-diagnostic or when a lymphomatous/sarcomatous tumour or an adenocarcinoma is suspected [8].

Although the total body tomoscintigraphy was introduced more than 25 years ago, the use of the FDG-PET imaging for the clinical diagnosis of head and neck carcinoma is relatively recent [9–12].

PET is useful in different aspects of oncological investigations, from the assessment of disease extension to the restaging after treatment; however, it does not represent a very good diagnostic modality because, even though it has got high sensitivity, its specificity is not as high [13].

When the other methods failed in detecting the site of primary tumour, the FDG PET was successful in detecting CUP in 20–40% of the patients; in a series of patients its accuracy reached 73% [2, 14].

The conventional imaging modalities for patients with CNM include CT of head, neck and thorax. The FDG-PET method examines the part of the body located between the skull base and the proximal half of the femur.

In the pre-therapeutic staging, the FDG-PET method has also been used to assess the aggressiveness of head and neck tumours: high levels of FDG uptake have been observed in the most advanced neoplasms with worst prognosis [15].

The current work aims at assessing and defining the effectiveness of the FDG-PET method during the diagnostic work-up of laterocervical metastasis from CUP conventionally examined with CT and/or MRI; based on our results, we recommend a flow-chart for the clinical-diagnostic management of the patient affected by laterocervical metastasis in the absence of known primary.

Materials and method

Patients

During the period between January 2001 and September 2006 the authors observed 13 consecutive patients, 10 men and 3 women whose average age was 62 (range 46–82), who demonstrated at least one FNAC positive lymph node metastasis in the cervico-cephalic area, with a negative history for primary tumours (cT × N + M0).

The diagnostic work-up included clinical and panendoscopic examination of the upper aero-digestive tracts, anteroposterior and lateral chest X-ray, axial and coronal CT scan of the neck with contrast, MRI with gadolinium if the CT scan was inconclusive and finally ultrasound guided FNAC of the suspected mass.

If the biopsy showed a malignancy and panendoscopic examination and conventional imaging were negative, the patient underwent a total body FDG PET (Table 1).

FDG-PET method

The FDG-PET scans were performed by the Department of Nuclear Medicine at Padova University Hospital.

After explaining the details of the procedure the patients gave written consent to the investigation. Pregnancy and hypersensitivity towards radionuclide or excipients have been added to the criteria of exclusion from the study. The questionnaire filled in by the patients indicated conditions which may cause hyperglycaemia, such as corticosteroid drugs, catecholamine, phenytoin, carbamazepine, phenobarbital or valproic acid, which are responsible for a reduced sensitivity of the FDG-PET examination.

The FDG PET total body method has been carried out with a coincidence-detection hybrid gamma camera (Marconi IRIX), acquiring the images 60 min after the injection of 370 MBq of [18F]FDG.

After the intravenous injection, the patient has been invited to relax and avoid speaking, chewing, swallowing too much and performing muscular activities in order to minimise FDG uptake in the laryngeal muscles or in the chewing muscles. The acquisition of the images has been carried out from the orbito-meatal line down to the groin; the images have been reconstructed with repetitive algorithm, without correction of the attenuation.

Statistical analysis

The statistical analysis has been performed considering the definitions of sensibility, specificity, the positive predictive value (PPV), the PPV and accuracy; such definitions have therefore been applied to the conventional imaging CT, MRI and to the FDG PET, assessing the validity to detect the primary tumour or metastases (Table 1).

Given that the conventional and nuclear imaging in all 13 patients examined has confirmed the neoplastic nature of the metastasis already diagnosed with FNAC, only the capacity of the methods to detect the occult primary has been assessed.

Table 1 Validity of the CT/MRI imaging and of the FDG-PET method in the detection of the primary site of tumour

Patient	Sex	Age	CT/MRI[a]	FDG PET	Primary T	cTNM	Primary tumour
1	M	51	F+	F+, base of tongue	Occult	T × N3M0	Occult
2	M	62	F−	T+, nasopharynx	Nasopharyngeal Ca	T × N1M0	Nasopharyngeal Ca
3	F	73	T−	F+, tonsil	Occult	T × N3M0	Occult
4	M	51	F−	T+, tonsil	SCC tonsil	T × N1M0	SCC tonsil
5	M	56	T+[b]	T+, lung	Bronchogenic Ca	T × N3M1	Bronchogenic Ca
6	M	55	F−	F−	Nasopharyngeal Ca base tongue	T × N2cM0	Nasopharyngeal Ca base of tongue
7	M	65	T+	T+, clavicle	Fibrosarcoma	T × N3M0	Fibrosarcoma
8	M	57	F−	F−	SCC tonsil	T × N1M0	SCC tonsil
9	F	73	F−	F−	SCC base of tongue	T × N3M0	SCC base of tongue
10	M	46	T−[c]	T−	Occult	T × N1M0	Occult
11	M	82	T+	T+, tonsil	High-grade lymphoma	T × N3M0	High-grade lymphoma
12	M	65	F−	T+, tonsil	SCC Tonsil	T × N2aM0	SCC tonsil
13	F	64	F−	T+, base of tongue	SCC base of tongue	T × N2bM0	SCC base of tongue

T+ true positive; T−, true negative; F+, false positive, F−, false negative, SCC, squamous cell carcinoma

[a] Means axial and coronal CT of the neck with e.v. contrast medium, unless otherwise specified

[b] CT neck, thorax and abdomen with contrast medium

[c] CT neck with e.v. contrast medium and RMN with gadolinium; the results of the two examinations have turned out to be overlapping

Therefore, the cases with an area of increased FDG uptake and positive histology were considered *true positives*; the cases without FDG uptake, with negative "random" biopsies of the tonsils, base of tongue and nasopharynx have been considered *true negatives*.

The cases with increased FDG uptake but negative histology were considered *false positives*.

Finally, *false negatives* were the cases with positive histology, but negative FDG PET. (Table 1)

For the histopathological work-up of the primary tumour, four ipsi-lateral tonsillectomies were carried out; two of them were positive for squamous cell carcinoma during the intraoperative examination (frozen section), with prompted a more radical excision (or neck dissection).

Ten "random" biopsies were carried out in the most frequent primary sites (five to the base of tongue, three to the nasopharynx and two at tonsillar fossa) in those cases where imaging CT/MRI and FDG PET had not detected suspected areas of primary tumour.

In order to treat the lymphnode metastatic disease, 8 of 13 patients have undergone neck dissection (4 bilateral and 1 ipsi-lateral functional neck dissection; 2 ipsi-lateral radical neck dissection; 1 selective supraomohyod ipsi-lateral neck dissection) with histopathological confirmation of metastasis.

Results

In the period between January 2001 and September 2006, 13 patients with a metastatic laterocervical mass from occult primary came to the attention of the authors.

The histopathological examination of the suspected primary enabled to restage the disease (pTNM) and to determine sensitivity, specificity, PPV, NPV and accuracy of the physical (CT and/or MRI) and nuclear (FDG PET) imaging in the detection of the primary tumour.

The chest X-ray detected a pulmonary neoplasia in 1 of the 13 patients. This represented a diagnostic dilemma since the FDG PET showed only two hypercaptating areas in the pulmonary and laterocervical sites. A bronchoscopic biopsy confirmed the presence of a bronchogenic carcinoma.

Conventional radiography has detected the only case with a pulmonary neoplasia; thus, achieving 100% sensitivity and specificity.

The detection of the occult primary with conventional imaging CT/MRI has shown a sensitivity of 30%, a PPV of 75% and an accuracy of 38%. The FDG PET has achieved a sensitivity of 70%, specificity of 33%, PPV of 78%, NPV of 25% and accuracy of 62%.

It is important to consider that this study selected patients with laterocervical metastases, which explains the low values of specificity and NPV.

In 7 of 13 cases (54%), the FDG-PET method has correctly detected the occult primary carcinoma: 4 had oropharyngeal localisation (1 squamous cell carcinoma of the base of tongue, 2 tonsillar squamous cell carcinomas and 1 high-grade malignant tonsillar lymphoma), 1 showed nasopharyngeal site (nasopharyngeal carcinoma) and, finally, 1 turned out to be a primary fibrosarcoma of the clavicle.

In 3 of 13 patients (23%), the FDG PET failed to detect the primary; thus, the diagnosis and the staging of the disease remained unchanged.

As for the remaining 3 patients (23%), the FDG PET did not detect areas of uptake of the radionuclide, but thanks to random biopsies and/or tonsillectomy, the site of the primary was eventually detected; the intraoperative examination of "random" biopsies have diagnosed 3 primaries (2 squamous cell carcinoma in the base of tongue, 1 in the palatine tonsil) and have thus enabled the extension of the excision to the primary tumour site; 2 of 4 tonsillectomies were positive for squamous cell carcinoma at the intraoperative examination, with subsequent enlargement of the surgical exeresis.

Discussion

The CNM from unknown primary unfavourably affects the prognosis: the detection of occult origin of the metastatic spread allows for better planning of the therapeutic strategy.

The percentage of primary tumours detected with the FDG PET was 54% in the patients examined.

The sites where the primary tumour has been found more frequently with the FDG PET according to the data from the literature [2], are in decreasing order, the tonsillar region (3 cases), the base of the tongue (1 case), the nasopharynx (1 case), the lung (1 case) and a fibrosarcoma of the clavicle.

In the only two false positive cases using the FDG-PET scan (15% of all patients), the "tumour" was incorrectly identified at the base of the tongue and tonsillar fossa; this can be explained by considering that the oropharyngeal region has physiologically an increased uptake of radionuclide [2, 16, 17].

In this respect, the FDG-PET method has some advantages over the other imaging modalities as it allows to detect the tumour in relation to its metabolic activity, regardless of its size, from the site (superficial or submucosal) and from the induced changes to the surrounding tissues.

The FDG PET cannot detect neoplastic microemboli; however, if used together with the CT, it enables to define the metabolic particularity of areas which are suspect for malignant repetitiveness [1, 13, 18]. Lymph nodes smaller than 1 cm that were not shown on CT or MRI but displayed a high FDG uptake have been restaged in 3 of 13 patients (23%); this has modified the clinical staging and has allowed to plan the therapeutic strategy: two cN1 were restaged as cN2b cases and one cN1 as cN2a case.

The detection rate of primary tumour with CT/MRI imaging did not exceed 15–20%; a recent review showed that FDG PET has an overall staging accuracy of 69–78%, a PPV of 75–83%, an NPV of 75–86%, a sensitivity of 63–100% and a specificity of 90–94% [2].

In those cases with negative clinical examination and conventional imaging, the FDG-PET method allows the detection of the primary tumour in 5–43% of the patients [2].

Even if the results we have obtained do not reach such high absolute values, higher diagnostic sensitivity and accuracy of the FDG-PET method (70 and 62%, respectively), compared with the physical imaging (CT/MRI) of the neck (30 and 38%, respectively), are confirmed.

In this regard, it is worth remembering that the equipment used shows counting sensitivity and resolution lower than PET dedicated equipment. Moreover, more centres are now using CT-PET equipment, which produces images of much better quality due to a precise anatomic localisation from the immediate superimposition of the PET and of the CT.

The 18-FDG PET has shown to be an efficient examination also with regards to extracervical regions since it can carry out a total body assessment; thus, it has allowed to exclude the presence of extraregional metastases, which represent an absolute contraindication to any surgical intervention with therapeutic purposes.

One aspect which is often overlooked in the literature is the possibility offered by the FDG PET to discriminate between metastatic disease from unknown primary in the localised or disseminated phase.

One patient in our series that showed localised CUP with conventional studies was restaged as M1 (disseminated disease) after FDG PET which avoided unnecessary radical treatment.

Conclusions

The detection of the primary tumour is fundamental for the planning of the most efficient therapeutic strategy for patients with lymph nodal metastasis from occult carcinoma in the cervico-cephalic region.

The detection of the primary site with the conventional imaging modalities is reached in 15–40% of the cases; the use of the 18-FDG PET scan in our study has increased the sensitivity and the accuracy to 70 and 62%, respectively.

Although our study included a small number of patients and did not employ a dedicated PET tomography but a coincidence-detection hybrid gamma camera, it shows nevertheless that the 18-FDG PET scan detected the primary site of the neoplasm 54% of the times, enabling us to plan the best therapeutic strategy.

We hope that further studies in larger series of patients with the use of integrated CT-PET equipment will succeed in improving the understanding of the neoplastic disease in the cervico-cephalic region.

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