The role of positron emission tomography (PET) in the management of cervical lymph nodes metastases from an unknown primary tumour

Ruolo della tomografia ad emissione di positroni nel trattamento delle metastasi linfonodali laterocervicali a primitività ignota

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Parole chiave

Tumori della testa e del collo • Tumori a primitività ignota • Diagnosi • Tomografia ad emissione di positroni

Summary

Cervical lymph node metastases may be the initial manifestation of occult cancer. Despite a very exhaustive search, the primary site of approximately 2-10% of these tumours remain undetected. Evaluation of the patient includes: detailed physical examination of skin, upper airways (fiberoptic endoscopy), salivary glands and thyroid; fine-needle biopsy, multiple endoscopic biopsies, and imaging studies (ultrasonography, computed tomography scan or magnetic resonance imaging). Recently, positron emission tomography scan has been demonstrated to be a useful diagnostic imaging study in these patients. The records of 11 patients were reviewed. End-points were the usefulness of positron emission tomography in the detection of an unknown primary tumour and/or distant metastatic disease. In 5 patients, positron emission tomography detected a primary lesion, confirmed pathologically and revealed distant metastases in 2 patients. Two cases were false-positive and 1 false-negative. In 3 patients no primary tumour was found after 3 years follow-up. In conclusion, positron emission tomography was not of any significant advantage in detecting occult primary tumour *vs.* computed tomography scan or magnetic resonance imaging. Positron emission tomography, as "ab initio" total body examination, is important in detection of unsuspected distant diseases.

Riassunto

Le metastasi laterocervicali possono essere la prima manifestazione di un tumore a primitività ignota. La sede primitiva può non essere individuata malgrado le ricerche più accurate nel 2-10% dei casi a seconda dei vari Autori. La procedura diagnostica prevede una accurata valutazione delle prime vie aeree, della cute, delle ghiandole salivari e della tiroide; segue una biopsia ad ago sottile linfonodale laterocervicale, ed eventuali biopsie multiple di siti sospetti durante l'endoscopia delle vie aeree superiori. Si prosegue con uno studio radiodiagnostico con ecografia, TC e RMN. Recentemente si sono valutate le possibili applicazioni della PET in tali casi. In questo studio viene considerata una casistica di 11 pazienti e le possibilità da parte della PET di identificare il tumore primitivo o la presenza di metastasi a distanza. In 5 pazienti la PET ha permesso di localizzare il tumore primitivo successivamente confermato da rilievi istologici. In 2 pazienti sono state localizzate delle metastasi a distanza. Abbiamo rilevato 2 falsi positivi e un falso negativo. In 3 pazienti non è stato possibile identificare la sede primaria anche dopo tre anni di follow-up. In conclusione la PET sembra non aggiungere vantaggi significativi alle indagini TC o RMN. Solo si rivela importante quale metodica di imaging total body in prima istanza, per l'identificazione delle localizzazioni a distanza della malattia.

Introduction

Metastases, in cervical lymph nodes, may be the initial manifestation of cancer. Despite an appropriate diagnostic approach, the primary site of the disease remains unknown in about 2-10% of cases, at least in the early stage [1]. Histological investigations show that 60% of these lymph node metastases are from squamous cell carcinomas (SCC), 30% from adenocarcinomas and the remainder from undifferentiated cancers, probably from the thyroid gland or a melanoma.

Numerous diagnostic protocols have been suggested to overcome this clinical problem. The standard procedure starts with collecting a thorough clinical history which may reveal symptoms long underestimated by the patient. Next, a detailed physical examination of the skin, upper airways (by flexible fiberoptic endoscopy), salivary glands and thyroid must be carried out. The precise site of the lymphadenopathy can provide indications concerning the probable site of the primary in relation to the common pathways of lymphatic drainage (jugodigastric area suggests oropharyngeal disease; the posterior triangle is a

classic finding for a nasopharyngeal primary; supraclavicular node involvement suggests lung tumour, etc). It is useful to complete these early investigations with a fine-needle biopsy of the lymph node, which reveals the histological characteristics, in most cases. Open biopsy of a lateral neck lymph node is almost unanimously advised against. The histological type of the metastasis may also provide valuable information concerning the probable site of the primary. In fact, SCC suggests primary cancer of the head and neck, whereas adenocarcinoma is more likely to be from a primary cancer in the lungs, gastrointestinal tract, salivary glands, nasal mucosa, etc. Imaging studies – standard radiography, computed tomography (CT) and/or magnetic resonance imaging (MRI) – of the head and neck region and chest may then be performed. Ultrasonography and thyroid scintigraphy are generally reserved for those cases in which there is a suspicion of thyroid disease. If the rhinopharynx is suspected as the site of the primary, serological tests for EBV or polymerase chain reaction can be performed on the neck aspirate. Finally, multiple endoscopic biopsies, under general anaesthesia, may be taken from all the most common sites of undiagnosed primaries: nasopharynx, tonsil, base of the tongue, pyriform sinuses and post-cricoid region.

Recently, it has been suggested that positron emission tomography (PET) could be useful in these patients. PET is a technique based on the study of glucose turnover following administration of 18-F-labelled-fluoro-2-deoxy-D-glucose (FDG). Glucose turnover is particularly high in tissues with marked metabolic activity, such as neoplastic cells, which can thus be located by the labelled marker [2-11]. PET is able to localize tumours 0.3-0.6 cm in diameter located in the pharynx sites which are more difficult to investigate (rhinopharynx, palatine tonsil, base of tongue) [11].

This technique has been used in 11 patients who were referred to our unit with lateral cervical lymph node metastases of unknown origin, evaluating the significance of the findings in relation to information gained from the other imaging methods.

Patients and methods

Tomoscintigraphic imaging was performed using a total body GE Advance LS TC PET tomograph. Tomoscintigraphic scans were interpreted qualitatively, and semiquantitatively by calculating the absorption value of the relative tracer (Standardized Uptake Value: SUV) using the formula:

$$SUV = \frac{\text{dose corrected for decay/cm}^3 \text{ of tumour}}{\text{dose injected/weight of patient in grams}}$$

SUV values > 3 were considered indicative of increased metabolism.

The characteristics of the study population and the outcomes of the investigations performed are outlined in Table I.

A brief outline of each case is here with provided in order to illustrate the details of the investigations and particular situations that may occur.

Case 1

EDM, a 72-year-old male, presented with right-sided lateral cervical lymph node metastases and had been investigated in another hospital by CT of the head and neck without a primary neoplastic site being found. After having undergone pan-endoscopy of the upper airway and digestive tract with multiple biopsies which did not reveal the primary disease, the patient underwent lateral cervical lymph node excision. It was then decided to carry out PET. This investigation showed increased uptake of tracer in the left lung base (primary site), in both adrenal glands (distant metastases) and in the pericardial region (inflammatory reaction) (Fig. 1).

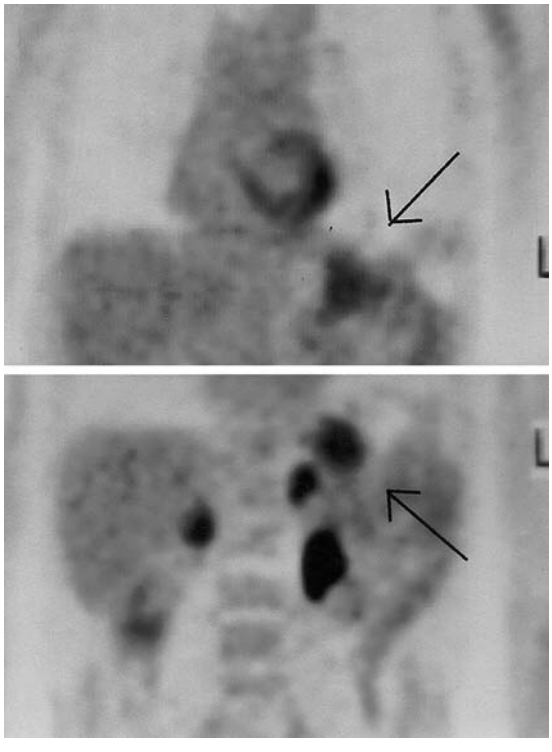

Fig. 1. PET imaging of patient 1: black arrows indicate distant metastases involving lung (upper arrow) and adrenal glands (lower arrow). Increased pericardial uptake due to inflammatory reaction is also visible.

Table I. Main characteristics of patient population.

Pt. (sex)	Name	Age (yrs)	N	PET T	PET M	CT T	Endoscopy	Cytology N	Multiple biopsy
1 (M)	EDM	72	lc R	Lung	Adrenal glands	Negative	Negative	Ca undifferentiated	Negative
2 (M)	CC	66	lc R	Negative	Negative	Negative	Negative	Ca spinocellular	Negative
3 (M)	BG	54	lc R	Rhinopharynx	Negative	Negative	Negative	Ca undifferentiated	Negative
4 (M)	MM	58	lc L	Negative	Paratracheal nodes (brain metastases not seen)	Negative	Negative	Melanoma	Not performed
5 (M)	MP	46	lc R	Rhinopharynx	Negative	Negative	Positive	Ca moderately differentiated	Positive
6 (M)	UN	47	lc R	Negative	Negative	Negative	Doubtful (Rhinopharynx)	Ca undifferentiated	Negative
7 (M)	FG	50	lc B	Rhinopharynx	Negative	Positive	Positive	Ca undifferentiated sarcoidosis	Positive
8 (M)	SA	62	lc R	Vestibulo-oral, R mandible	Negative	Doubtful	Negative	Ca spinocellular	Negative
9 (F)	CL	46	lc R	Thyroid	Left breast	Positive	Negative	Ca medullary	Positive (FNAB)
10 (M)	FD M	60	lc R	Rhinopharynx	Negative	Positive	Positive	Ca undifferentiated	Positive
11 (M)	EG	68	lc L	Negative	Negative	Negative	Negative	Ca undifferentiated	Negative

Lc = Lateral cervical nodes; R = Right, L = Left, B = Bilateral

Case 2

CC, a 66-year-old male, presented with right-sided lateral cervical lymphadenopathy caused by metastasis of a well-differentiated primary spinocellular carcinoma of unknown origin for more than 2 years. Following the first cytological diagnosis, multiple endoscopic biopsies, CT and PET all failed to identify the primary site. No further information on the primary was gained from the periodic controls over the subsequent 2 years.

Case 3

BG, a 54-year-old male: after a fine-needle biopsy of right-sided lateral cervical lymph nodes had shown that these were involved by undifferentiated carcinoma, PET was carried out leading to the suspicion of a rhinopharyngeal primary, not, however, confirmed by CT and multiple biopsies.

Two years later, there is no evidence of active neoplastic disease of the rhinopharynx or any other site.

Case 4

MM, a 58-year-old, presented with left-sided lateral cervical lymphadenopathy, positive, by fine-needle biopsy, for melanoma. A dermatological examination with mapping (Fotofinder) was carried out and two of the equivocal sites were biopsied but found not to contain neoplastic foci. Fundus oculi examination was negative. CT was negative but PET was positive for secondary paratracheal lymph node involvement.

One year after complete excision of lateral cervical and paratracheal lymph nodes, there is still no evidence of the primary site of the disease, but brain metastases were shown by CT but not by PET.

Case 5

MP, a 46-year-old male, had right-sided lateral cervical lymphadenopathy, positive by fine-needle aspiration biopsy for a moderately differentiated carcinoma. The patient underwent CT and PET. Only PET detected the rhinopharyngeal localization. Endoscop-

ic investigations revealed a suspicious ulceration on the right pharyngeal wall which, when biopsied, was confirmed to be the site of the primary neoplasm.

CASE 6

UN, a 47-year-old male, had metastatic right-sided lateral cervical lymph nodes showing undifferentiated carcinoma involvement. CT and PET resulted negative. Endoscopic rhinopharyngeal examination was suspicious but multiple biopsy negative. Two years later, there is no evidence of active neoplastic disease.

CASE 7

FG, a 50-year-old male presented with a diagnosis of sarcoidosis made from an open biopsy of a left lymph node, carried out elsewhere. The extent of the lymphadenopathy, particularly on the left, limited movements of the neck. For this reason, the patient completed left cervical lymph node dissection. Post-operative histological examination revealed the presence of metastatic undifferentiated carcinoma. Endoscopic, CT and PET localized a rhinopharyngeal tumour. PET showed high metabolic activity in the rhinopharynx and contralateral lateral cervical lymph nodes. The patient, therefore, underwent complete excision of the contralateral lymph nodes and a rhinopharyngeal biopsy confirmed the PET-localised primary site of the cancer.

CASE 8

SA, a 62-year-old male had been previously treated (1995) for cancer of the left base of the tongue with partial glossopharyngectomy and excision of the ipsilateral cervical lymph nodes, followed by adjuvant radiotherapy. The patient returned 7 years later with right lateral cervical lymphadenopathy positive by fine-needle aspiration biopsy for spinocellular carcinoma. CT gave equivocal findings, whereas PET was positive for recurrence in the right mandible. Subsequent biopsy was negative for neoplastic recurrence, showing radiotherapy-induced osteonecrosis (Fig. 2).

CASE 9

CL, a 46-year-old female presented with right lateral neck adenopathy which fine-needle biopsy showed to be due to metastatic carcinoma although the histotype was unclear. CT and ultrasound neck examinations revealed a right thyroid nodule which subsequent fine-needle biopsy and calcitonin assays demonstrated to be a medullary carcinoma. PET confirmed the presence of thyroid neoplasia and the neck metastases, but also indicated a metastatic focus in the left breast. Ultrasonography of the breasts then revealed the presence of further metastases in the right breast. The disease evolved very rapidly, with the development of lung metastases within 3 months.

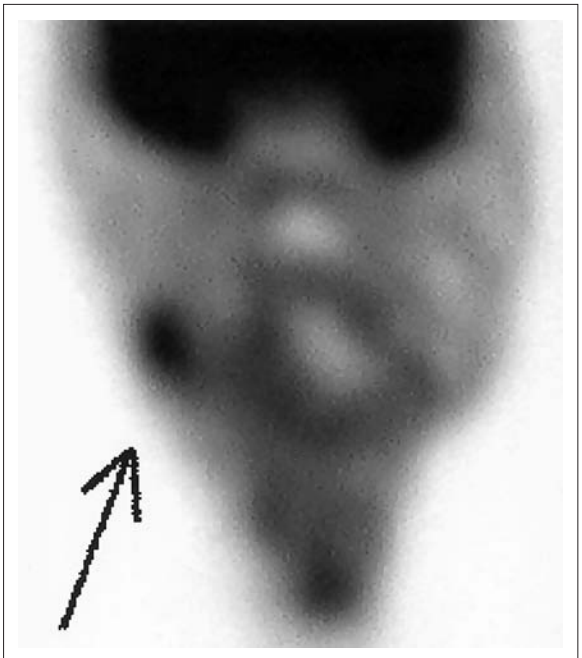

Fig. 2. PET showing a false-positive image of mandibular localization. Patient who presented radionecrosis underwent RT for mouth floor cancer.

CASE 10

FDM, a 60-year-old male, had right cervical lymphadenopathy which fine-needle biopsy showed to be an undifferentiated carcinoma; both CT and PET demonstrated a rhinopharyngeal primary site (left lateral wall) that was confirmed by endoscopy and biopsy (Fig. 3).

CASE 11

EG, a 68-year old male presented with a 4-year history of metastatic left-sided lateral cervical lymph node involvement from an unknown primary site. The first cytological finding (undifferentiated carcinoma) was followed by endoscopic investigation and multiple biopsies, CT and PET without, however, detecting the primary neoplasm. No further information was gained, in the periodic controls, over the subsequent 4 years.

Discussion

Of the various imaging techniques used in evaluating patients with cancer of the head and neck, CT and MRI now have some recognized indications. The advantages of CT are its excellent capacity to identify single or multiple metastases and to evaluate metastatic lesions (intra-nodal necrosis, extra-nodal

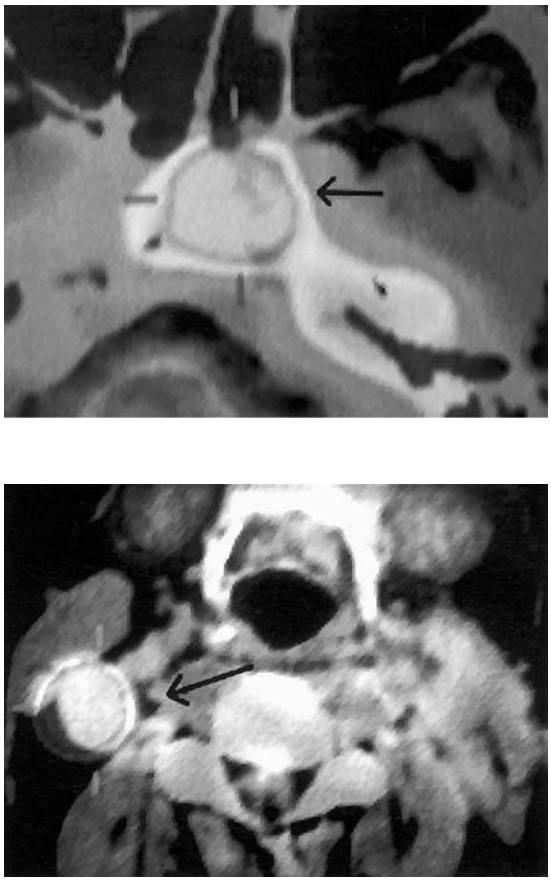

Fig. 3. PET showing primary lesion localised in rhinopharynx (left lateral wall) in patient with contralateral neck metastases as first clinical manifestation.

extension, involvement of the jugular vein, carotid artery or musculature).

MRI is superior to CT in defining mucosal involvement, but less accurate in evaluating nodal status. As a consequence, and also bearing in mind cost-containment, most clinicians consider it more appropriate to use CT than MRI.

In the particular situation of lateral cervical lymph node metastases the primary origin of which is unknown, a combination of endoscopy, CT and MRI has shown a 20-50% success rate in identifying the primary site, according to various Authors [12]. The ability of PET to locate the primary tumour ranges from 8-53% of cases, in the various series (Table II). The mean detection rate, in the more important reports in the literature is 32%, thus the results emerging from the present series (5/11) are slightly higher. It does not appear, therefore, that the results obtained with PET are significantly different from those with the previous imaging methods. Only in two particular situations could PET be clearly superior. First, since this is, "ab initio", a total body investigation, it is a significant aid in identifying unsuspected distant disease, as reported by Fogarty et al. [13] and as we were able to witness in cases n. 1 and 9 described here. Furthermore, the diagnostic potential of PET is particularly evident in the follow-up phase. In fact, after surgical or radiotherapy significant anatomical alterations may be found which often make it difficult to evaluate persistence or recurrence of disease by conventional imaging.

We recorded 2 false positive cases (patients 3 and 8) Nevertheless, it is well known that the risk of false-positive findings is relatively high in the head and neck region on account of physiological FDG uptake in salivary glands, lymphatic tissue and vocal cords. Likewise, the outcome of previous radiotherapy (os-

Table II. Recent reports of PET detection of a primary tumour in patients with metastatic cervical lymph nodes.

References	Patients (n.)	Primary found (n.)	Percentage found (%)
This study	11	5	45
Fogarty et al., 2003 [13]	21	8	38
Johansen et al., 2002 [17]	42	10	24
Jungehulsing et al., 2000 [9]	27	7	26
Bohuslavizki et al., 2000 [10]	44	15	34
Hanasono et al., 1999 [4]	20	7	35
Greven et al., 1999 [5]	13	1	8
AAssar et al., 1999 [6]	17	9	53
Stokkel et al., 1999 [7]	10	5	50
Safa et al., 1999 [8]	14	3	21
Kole et al., 1998 [3]	29	7	24
Braams et al., 1997 [2]	13	4	31
Total	261	81	32

teitis in case 8) may give rise to diagnostic doubts that can be resolved only by biopsy studies [14].

PET was unable to identify a primary site in 4 of the present cases. In all these patients CT, endoscopy and multiple biopsy were also negative. These data confirm the high sensitivity of this technique. Nevertheless, while this statement is correct regarding the primary site, it was not supported by findings regarding metastases. In fact, in case 4, CT revealed brain metastases not detected by PET; and, in case 9, ultrasonography detected bilateral breast metastases not shown by PET which revealed only a one-side localization. Since, in this case, the patient presented a thyroid medullary tumour, unexpectedly PET did not completely reveal a neoplasia. In fact, thyroid differentiated tumours (papillary or follicular carcinoma) or their metastases display a good iodine uptake, but poor FDG uptake, thus the sensitivity of FDG PET is low. Anaplastic and medullary thyroid carcinoma, on the other hand, display predictable PET patterns of high FDG uptakes proportionate to the biological aggressiveness of the tumour [15 16].

These data led us to reconsider the statement of Johansen et al. [17], namely, that if PET is negative, the probability that the disease is located exclusively in the sites identified is so high as to be able to plan a specific treatment strategy with a consequent reduction in treatment-induced morbidity. For this reason, Johansen et al. hold that the surgeon can avoid submitting the patient to contralateral neck dissection if PET does not reveal lymph node foci, the radiotherapist can limit the irradiation field, or the oncologist can vary the radiotherapy and chemotherapy strategy in relation to the single or multiple sites of the neoplasia (i.e., lymphoma). Unfortunately, in our data, PET was not as reliable and only association with other clinical and radiological investigations permitted a higher safety level and, consequently, correct therapeutic planning.

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