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Combining 6-fluoro-[^{18}F]L-dihydroxyphenylalanine and [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography for distinction of non-carcinoid malignancies in carcinoid patients

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ARTICLE INFO

Article history:
Received 24 February 2009
Received in revised form 29 April 2009
Accepted 30 April 2009
Available online 22 May 2009

Keywords:
Carcinoid tumour
Second primary neoplasms
Positron emission tomography

ABSTRACT

Aim: Carcinoid patients frequently develop a second primary malignancy (SPM), which can deserve full treatment. Distinguishing a SPM from carcinoid lesions is therefore important. Differentiation can be achieved using the difference in uptake between different positron emission tomography (PET) tracers.

Methods and results: Between January 2005 and August 2008, 105 carcinoid patients were seen at the Department of Medical Oncology for treatment and follow-up. We identified 3 patients who presented with a new SPM in whom differentiation between carcinoid lesions and the SPM was guided by functional imaging of the catecholamine pathway with 6-fluoro-[^{18}F]L-dihydroxyphenylalanine (^{18}F-DOPA) PET and [^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET as radiotracer for the glucose metabolism. All 3 patients had metastatic carcinoid disease and localised adenocarcinoma based on the PET-scans. For the adenocarcinoma they received curative treatment.

Conclusion: The difference in uptake between these PET techniques can be used for decision making when a primary or metastatic SPM is suspected.

1. Introduction

Carcinoids are rare neuroendocrine tumours. They often display a relative indolent behaviour, resulting in a long survival. In up to 46% of patients with carcinoid tumours, another non-carcinoid primary malignancy is diagnosed.[1] Given the relative long survival, even in case of metastatic disease, such a second primary malignancy (SPM) can deserve full treatment. Distinguishing lesions of a SPM from a carcinoid metastasis is therefore important, and may have therapeutic consequences. We will illustrate this in three patients in whom decision making was guided by functional imaging of the catecholamine pathway, with 6-fluoro-[^{18}F]L-dihydroxyphenylalanine (^{18}F-DOPA) positron emission tomography (PET) and [^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET as radiotracer for the glucose metabolism.

2. Patients and methods

All carcinoid patients with metastatic disease seen between January 2005 and August 2008 at the Department of Medical

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.04.037

Oncology for treatment and follow-up were included in this retrospective study. The charts of all patients were reviewed to identify patients who had presented with a new SPM during this period. The patients with a new SPM who received both a ^{18}F-DOPA PET scan and a ^{18}F-FDG PET scan to distinguish between the carcinoid lesions and the SPM in order to make a decision about possible curative surgery were further analysed. Clinical follow-up data of these patients were obtained.

^{18}F-FDG PET was performed as described previously.[2] Since 2005 ^{18}F-DOPA PET is available at the University Medical Center Groningen and is used as part of the routine work-up for staging of carcinoid tumours. ^{18}F-DOPA was locally produced.[3] For the ^{18}F-DOPA PET scan the patients fasted for 6 h before the examination and were allowed to continue all medication. Whole body 2D-PET images were acquired 60 min after the intravenous administration of ^{18}F-DOPA (180 + 50 MBq), on a Siemens ECAT HR+ positron camera (Siemens, Knoxville, TN) with attenuation correction (7–10 bed positions of 5-min emission and 3-min transmission scan, total scanning time approximately 60 min). Images were reconstructed using the OSEM algorithm two subsets, eight iterations. One hour prior to the ^{18}F-DOPA injection patients received 2 mg/kg carbidopa orally to increase tumour-to-background ratio of tracer uptake.[4–6]

3. Results

One hundred and five patients with a metastatic carcinoid tumour were identified, 49 men and 56 women with an average age of 62 years. Median follow-up since diagnosis of the carcinoid tumour was 3 years. Fifteen patients (14%) had an additional diagnosis of a SPM, most commonly located in the gastrointestinal tract ($n = 4$ patients) and the genitourinary tract ($n = 4$ patients). In 6 patients a metachronous carcinoid was detected 2–22 years after the non-carcinoid malignancy, while in 4 patients a synchronous, asymptomatic carcinoid was discovered during surgery for a non-carcinoid malignancy. In 5 patients a metachronous SPM was discovered 2–10 years after diagnosis of the carcinoid tumour was made. In 3 of these patients the SPM was diagnosed between 2005 and 2008, after ^{18}F-DOPA PET became available in our hospital for the routine care of carcinoid tumours. These 3 patients underwent both a ^{18}F-DOPA PET and a ^{18}F-FDG PET scan.

Patient 1 is a 56-year-old woman with a carcinoid of the ampulla of Vater and was treated with a pancreaticoduodenectomy. Four years later, a liver metastasis was found on a CT scan. Six years after initial diagnosis she experienced bloody stools due to a rectal adenocarcinoma. The known liver metastasis was reconfirmed on CT scan and ^{18}F-DOPA PET scan and was found to be stable (Fig. 1a). On the ^{18}F-FDG PET, faint uptake in the liver lesion and intense uptake in the rectum were seen (Fig. 1b). No other sites of increased ^{18}F-FDG uptake were visualised. At this moment no somatostatin receptor scintigraphy (SRS) was performed as 2 years earlier the SRS showed fewer lesions than the ^{18}F-DOPA PET at that moment. It was concluded that the liver metastasis originated from the carcinoid, and not from the adenocarcinoma. This was histologically confirmed by a liver biopsy. A curative resection of the rectal tumour was performed, which was histologically confirmed to be an adenocarcinoma of the rectum.

Patient 2 is a 61-year-old man with a carcinoid of the small intestine and liver metastases. Resection of the primary carcinoid tumour proved to be impossible because of its proximity to mesenterial arteries. Ten years later, he presented with bloody stools due to a rectal adenocarcinoma. ^{18}F-DOPA PET demonstrated uptake in the primary carcinoid tumour and liver metastases, while ^{18}F-FDG PET showed faint uptake in all carcinoid lesions, but intense uptake in the rectum and physiological uptake in the colon. No recent SRS was performed. It was concluded that the metastatic disease originated from the carcinoid, and not from the adenocarcinoma. A curative resection of the rectal tumour was performed, which was histologically confirmed to be an adenocarcinoma of the rectum. Three years have passed without any signs of new lesions originating from the adenocarcinoma.

Patient 3 is a 74-year-old man with a carcinoid of the small intestine and metastases in liver and abdominal lymph nodes. One year later, on a routine chest CT scan, a previously unknown lesion suspect for lung cancer was discovered. This patient was a smoker. The ^{18}F-DOPA PET showed uptake in a liver lesion and three abdominal lesions, while no lung uptake was observed (Fig. 1c). SRS showed the same liver lesion as was also seen on ^{18}F-DOPA PET and some vague uptake approximately in the midline of the abdomen on the site where the three abdominal lesions were seen on the ^{18}F-DOPA PET scan and no lung uptake. However, the lung lesion did show up on ^{18}F-FDG PET (Fig. 1d). It was concluded that the liver- and abdominal lesions originated from the carcinoid, and not from the pulmonary tumour. This lesion was surgically removed and histology showed a planocellular non-small cell lung cancer (NSCLC). Three years later no signs of metastases of the lung cancer have been discovered.

4. Discussion

The most common site of a SPM in carcinoid patients is the gastrointestinal tract, followed by the genitourinary tract and lung/bronchial system.[7] SPMs are usually the more aggressive malignancy. Consequently, most patients with both a carcinoid tumour and a SPM die from the SPM.[1] Differentiation between metastases from either the carcinoid, or the SPM, may be difficult. Our findings illustrate that combining two different radiotracers for functional PET imaging can be helpful in these cases. The absence of proof of metastases of the adenocarcinomas supported the decision for surgery with curative intent in all cases.

^{18}F-FDG PET imaging can detect fast-growing tumours with a high glucose metabolism (such as colorectal cancer and NSCLC), with a sensitivity of 95%.[8] In contrast, tumours with a low metabolic rate (such as carcinoid tumours) often show faint ^{18}F-FDG uptake and are poorly visualised by PET, with detection rates of 25–75%.[9–15]

Imaging with ^{18}F-DOPA is based on the exclusive property of neuroendocrine cells to take up and decarboxylate amine precursors. An excellent sensitivity of 96% for detection of

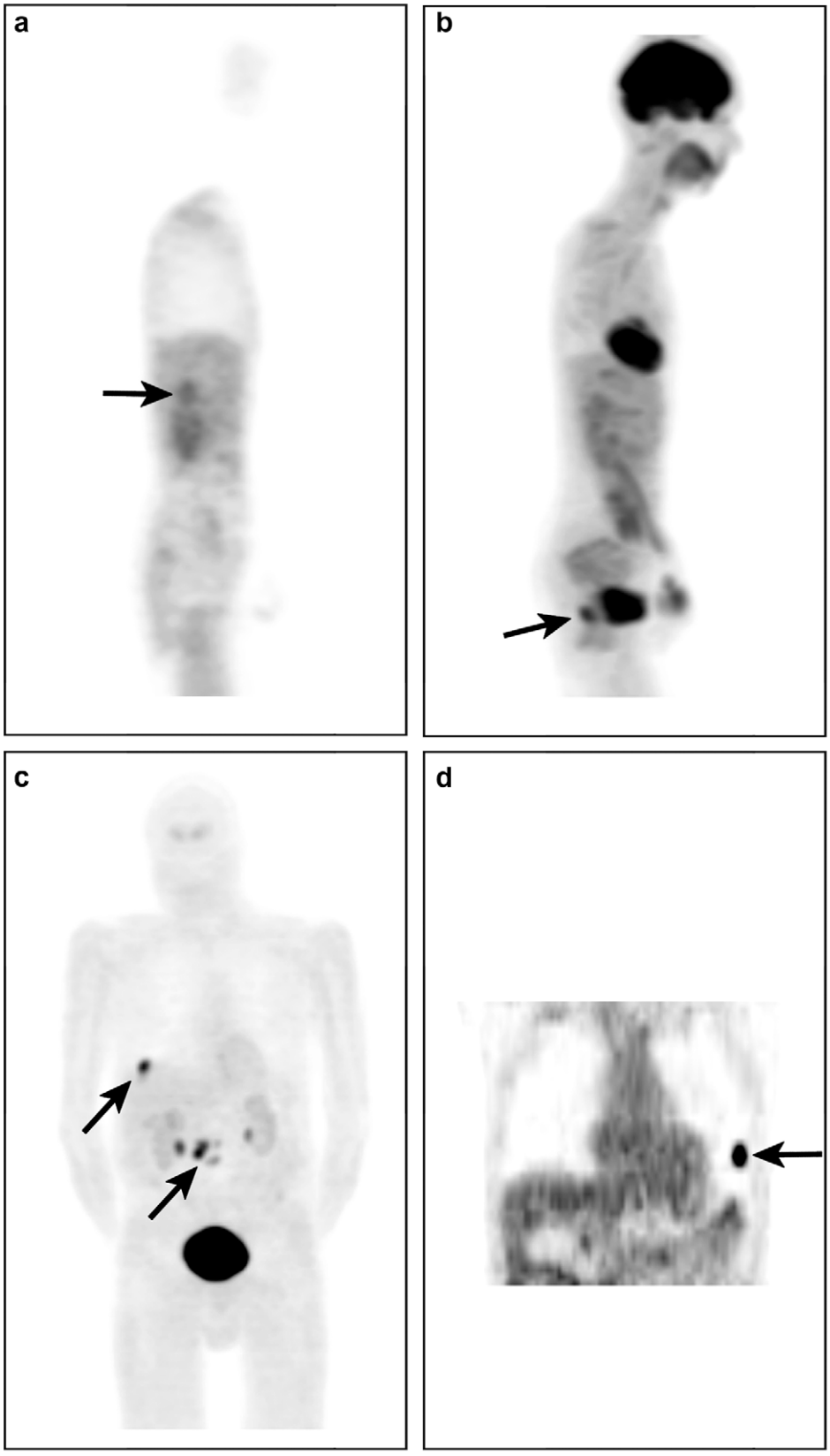

Fig. 1 – Patient 1 (a,b): (a) On 6-fluoro-[^{18}F]L-dihydroxyphenylalanine (^{18}F-DOPA)-positron emission tomography (PET) one liver lesion (arrow). (b) [^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG)-PET shows faint uptake in liver lesion, intense rectal-uptake (arrow). Patient 3 (c,d): (c) ^{18}F-DOPA-PET reveals four abdominally located metastases (arrows). (d) ^{18}F-FDG-PET showing uptake in left lung (arrow).

carcinoid tumour lesions is obtained with ^{18}F-DOPA PET, which is higher than that of SRS.[16–18]

The previous studies have shown that less differentiated neuroendocrine tumours, as determined by a higher Ki-67 index, are more likely to show higher uptake of ^{18}F-FDG on PET, while showing lower uptake on imaging, which specifically shows neuroendocrine tumours, such as SRS.[9,15,19] Theoretically, lesions on ^{18}F-FDG PET might also be due to de-differentiation of secondary lesions which were initially a well-differentiated carcinoid. However, the ^{18}F-FDG PET-positive lesions in our patients were not previously seen, for example on ^{18}F-DOPA PET, which should have been the case if they were indeed initially a well-differentiated carcinoid. Secondly, to our knowledge, no studies exist describing de-differentiation of carcinoid tumours. In this study we did not take biopsies of all metastatic lesions to rule out the possibility of a false-negative ^{18}F-FDG PET scan, as cytological and histological verification runs a risk of bleeding complications in the highly vascular carcinoid lesions. While this risk has to be accepted certainly for establishing an initial diagnosis, during the course of the disease in case of several metastatic lesions using the combination of PET tracers can be extremely helpful. Especially considering the excellent sensitivities of the PET techniques and the fact that no new or rapidly growing lesions have been discovered so far, the chance of a false-negative ^{18}F-FDG PET scan seems small. The possibility of distinguishing lesions without the need of taking biopsies with the associated risks is the great advantage of the combined use of these two radiotracers.

In conclusion, the difference in uptake between ^{18}F-FDG and ^{18}F-DOPA in tumour lesions can be used to make the distinction between metastases from the carcinoid tumour or from the SPM. This may clearly have therapeutic consequences, allowing curative treatment for non-metastasised SPMs, even in case of metastatic carcinoid disease.

Conflict of interest statement

None declared.

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