Effectivity and clinical impact of $^{18}$F-FDG PET in the diagnosis of unsuspected second primary tumors

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Objectives: This study is aimed to determine the capacity and clinical impact of the $^{18}$F-FDG-PET to detect previously unsuspected second primary tumors.

Materials and methods: This is a retrospective cross-sectional study of 1984 consecutive scans performed between March 2004 and March 2005, identifying those studies that had reported the presence of hypermetabolic lesions that had not been previously suspected or detected and that could be suggestive of second primary tumors. Diagnosis was made histopathologically or by clinical and radiological follow-up for a period exceeding one year.

Results: 62 findings suggestive of second primary tumors were detected in 58 patients (3.1%). The reasons for the study for this group of patients were diverse, the most common being the differential diagnosis of solitary pulmonary nodules. A total of 43.5% of lesions were not followed-up. We confirmed the existence of 35 lesions, either by pathology study (21 lesions, 13 second primary tumors, the incidence in our population was 0.65%) or clinical and radiological follow-up (14 lesions, none of which corresponded to second primary tumors). The total clinical impact was the discovery of unexpected 14 lesions in 12 patients.

Conclusions: The presence of second primary tumors on $^{18}$F-FDG-PET is relatively common. These lesions should be monitored clinically for accurate diagnosis. In a high percentage, they correspond to unexpected second primary tumors in an early stage and therefore amenable to curative treatment or for which tumor treatment planning may be modified.

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Introduction

The possibility of a second primary tumor appearing in the same patient has been reported for decades and has been widely described in the scientific literature. Studies performed by the U.S. National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) have shown that multiple primary neoplasms make up 13.1% of the cancers in males and 13.7% of those in women. There is evidence that a person who has survived one cancer has twice the probability of developing a new primary tumor than an individual with the same age and genre with no previous oncologic history. The development of these tumors is increasingly more frequent due to the increase in the use of chemotherapeutic agents and radiotherapy, which raise the probability of the appearance of a new malignant tumor, and is also related to the intrinsic risk of the oncologic patient to develop these tumors, as well as genetic factors and the frequent association of different types of cancers with the same etiology. The detection of these tumors is also on the rise because of the technological advances in the diagnostic tools currently available which allow the detection of malignant involvement in early stages. In addition, these tools constitute an important prognostic factor in patients with cancer, being able to determine treatment failure and the increase in mortality of some specific types of oncologic disease. These lesions are often tumors with a poor prognosis which are frequently located in already treated or unexpected areas in which early diagnosis is difficult to achieve. Although the management of each patient is individual, the therapeutic options in these second or third primary tumors are generally compromised by the treatment of a tumor with a worse prognosis. Nonetheless, early diagnosis of these tumors may lead to successful treatment.

Positron emission tomography with $^{18}$F-fluorodeoxyglucose (PET-$^{18}$F-FDG) is a diagnostic technique which is successfully and increasingly used in the diagnosis and follow-up of the treatment of a rising number of malignant neoplasms, including their initial staging, restaging of recurrence and the monitoring of response to chemotherapeutic agents and radiotherapy. It is also used in the characterization of undetermined lesions such as the solitary pulmonary nodule (SPN) and in the investigation of tumors of unknown origin. Some reports have even described the capacity of this technique in the screening of some cancers and in the detection of new malignant tumors in a reduced fraction of asymptomatic patients. PET-$^{18}$F-FDG has demonstrated greater diagnostic precision than computerized tomography (CT) in the detection of metastatic lesions or unexpected tumoral recurrences of malignant tumors and has shown its capacity for the diagnosis of other primary tumors.

The objective of this study was to evaluate the capacity and clinical impact of PET-$^{18}$F-FDG in the diagnosis of unexpected second malignant primary tumors in 1984 PET-$^{18}$F-FDG studies performed in our unit from March 2004 to March 2005.

Material and methods

Study population

We carried out a transversal descriptive study including a cohort of 1984 consecutive whole body PET-$^{18}$F-FDG studies in our unit from March 2004 to March 2005. The aim of these studies was to achieve the initial staging or restaging of already known tumors, the differential diagnosis of benign/malignant lesions of undetermined nature or the evaluation of the response to treatment of tumors, with retrospective analysis of the results of these studies.
varied (Table 1), the most frequent being the differential diagnosis of benignancy-malignancy of SPN (27.60%), the restaging of lymphomas (20.7%), the study of initial staging of non small-cell lung cancer (18.9%) and the restaging of colon cancer (18.96%) (Fig. 2).

In 27 of the 62 incidental accumulations suggestive of unsuspected new tumors (43.5%) follow-up of the lesions was not carried out because of refusal of the patients to undergo further studies, the clinical stage or the loss of the patient to follow-up. Thus, the causative nosologic entity of these lesions remains unknown. The etiology of 35 incidental accumulations of FDG suspected to be second primary tumors was confirmed in the remaining 33 patients either by anatomopathological study or by clinical–radiological follow-up. This latter group without histopathological confirmation of the visual findings was made up of 14 lesions observed in 14 patients, none of which corresponded to second primary tumors. The anatomopathological study was performed in 21 incidental accumulations of FDG detected in 19 patients and suspected of being second primary tumors; 13 corresponded to unsuspected second primary tumors detected in 11 patients. It is of note that in two patients we detected two unsuspected primary tumors different from what was known. Thus, the incidence of second primary tumors or premalignant lesions in this population was of 37.14%, corresponding to 4 colorectal adenocarcinoma, 4 head and neck tumors, 3 differentiated thyroid tumors and 2 premalignant lesions (one in the colon and another in the head and neck). The remaining incidental FDG accumulations initially suspected to be second primary tumors corresponded to distant metastasis of the known primary tumor and 7 benign lesions (2 thyroid lesions, 4 adenomas in the colon and one ovarian lesion). Within the group of 35 PET findings with follow-up by histological study, 14 were of malignant origin (13 second tumors in 11 patients and one known primary metastasis), representing 40% of the same. Figure 2 shows the case of a patient referred for initial staging of lung cancer in whom, in addition to the known lesion, a second primary tumor of the sigma was found.

The detection of these lesions led to a change in both the medical and surgical therapeutic approaches undertaken in 36.4% of the patients (12 of the 33 patients with incidental FDG accumulations suspected of second primary tumors studied). This group included one patient in whom treatment was initiated on the detection of autoimmune thyroiditis and the 11 patients with 13 primary tumors found incidentally. The clinical impact determined by survival (Table 2) was limited to one patient in this group of 11 patients (patient in complete remission from lymphoma successfully operated for a follicular thyroid cancer), with a survival of less than 2 years in the remaining 10 patients.

Table 1
Reasons for consultation.

- Differential diagnosis of benignancy-malignancy of solitary pulmonary nodule: 16 patients (27.60%)
- Restaging of lymphoma: 12 patients (20.7%)
- Initial staging of lung cancer: 11 patients (18.96%)
- Restaging of colon cancer: 11 patients (18.96%)
- Restaging of head and neck cancer: 2 patients (3.46%)
- Restaging of lung cancer: 1 patient (1.72%)
- Initial staging of lymphoma: 1 patient (1.72%)
- Restaging of ovarian cancer: 1 patient (1.72%)
- Restaging of biliary tract tumor: 1 patient (1.72%)
- Restaging of prostate cancer: 1 patient (1.72%)
- Restaging of differentiated thyroid cancer: 1 patient (1.72%)

Discussion

There is abundant evidence in the scientific literature regarding the appearance of multiple tumors in a significant percentage of oncologic patients, the origin of which does not respond...
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DTC, differentiated thyroid cancer; SPN: solitary pulmonary nodule.
The worst prognosis. Nonetheless, early diagnosis of these second and third neoplasms may allow the implementation of successful treatment.

The use of PET-18F-FDG in oncology has clearly demonstrated its capacity for the diagnosis of second or third primary tumors and premalignant lesions. In a prospective study of 68 patients with malignant tumors of the oropharynx, Stokkel et al. showed that the PET-18F-FDG study is an important tool for the diagnosis of second primary tumors in patients with primary head and neck tumors, being detected in 12 cases (18%). Pandit-Taskar et al. followed patients with abdominal accumulations of 18F-FDG, not sufficiently explained in the history of natural dissemination of the primary tumor and incidentally found, to determine the cause and the clinical significance of these tumors and concluded that these findings responded to both benign and malignant processes (of the 14 cases with a definitive diagnosis, 7 were premalignant adenomas and 5 malignant tumors) not related to the known tumor.

In a retrospective study of 110 patients who underwent a PET-18F-FDG study and colonoscopy, Yasuda et al. found 59 adenomatous polyps in 30 patients, 14 (24%) of which were positive in the PET-18F-FDG study, with the detectability of the polyps increasing with the size of the adenoma. Thus, colonoscopy represented a reasonable step after observation of focal uptake of 18F-FDG in the PET study, similar to what Tatlıdil et al. concluded in the study of 27 cases with no known history of colorectal carcinoma and on comparing the findings of the PET-18F-FDG study with those observed in the colonoscopy and anatomicopathological studies. Diffuse intestinal uptake is associated with the absence of pathological findings on colonoscopy and high uptake in segments of the colon may correspond to inflammatory involvement.

Likewise, Gutman et al. retrospectively analyzed 1716 consecutive patients referred over one year for PET/CT-18F-FDG study of several malignant involvements and also concluded that the incidental finding of focal colonic uptake of FDG justifies the performance of colonoscopy with the aim of detecting premalignant lesions (which they found in 13 patients). These authors emphasized the capacity of the fusion of PET and CT images to determine the precise localization of these lesions and the utility of the study to differentiate physiological and pathological uptakes of 18F-FDG.

Tori et al. demonstrated the value of PET-18F-FDG studies in the early diagnosis of epidermoid carcinoma of the esophagus as a previously unsuspected second primary tumor.

Van Den Bruel et al. proved the important role of PET-18F-FDG study in the early diagnosis of thyroid neoplasms (medullary and differentiated carcinomas) based on the incidental finding of malignant lesions correctly identified in 5 PET-18F-FDG studies and with no relationship with the primary tumor.

The study by Kim et al. is of note. The objective of their study was to evaluate the prevalence of incidental uptake of 18F-FDG in PET studies and the role of SUV determinations to establish the benign or malignant character of these lesions by retrospectively studying the results of 4655 cases. These authors found a high prevalence of malignant lesions among the focal thyroid lesions incidentally found and concluded that cytologic or histologic diagnosis is necessary, despite the SUV values determined.

In another similar study, Kang et al. retrospectively analyzed the results of the studies performed in two different groups of patients, one of oncologic patients and another of healthy volunteers for the screening of cancer, and evaluated the risk of malignancy of the focal uptakes of FDG in the thyroid glands and their association with SUV values. The prevalence of unexpected focal thyroid lesions was of 2.2%, independently of the reason for the study, carrying a high risk of malignancy, especially if associated with high SUV values.
Ishimori et al. evaluated the capacity of the PET/CT-18F-FDG study for the detection of unexpected new primary tumors in patients referred for the study of known or suspected malignant tumors. To do this they evaluated the results of studies carried out in 1912 patients, determining the lesions of de novo appearance, that is, previously unsuspected prior to the study and with an atypical localization within the natural history of dissemination of the lesion under study, and compared these with the final diagnosis reported in the patient histories. They concluded that PET/CT-18F-FDG detected new unsuspected primary tumors in at least 1.2% of the patients with cancer.

On the other hand, Agress et al. performed another study with the objective of determining the clinical importance and malignant potential of the accumulations of hypermetabolism demonstrated by the PET-18F-FDG studies in oncologic patients. They reviewed the results of a total of 1750 studies and concluded that the identification of unexpected accumulations of hypermetabolism in the PET-18F-FDG study, not related to the known tumor for which the study was performed, may indicate the presence of other primary tumors and, therefore, emphasized the need for the follow-up of such findings.

More recently, Özol et al. retrospectively analyzed the results of 2370 studies undertaken in oncologic patients to demonstrate the malignant potential and clinical value of the pathological uptakes of 18F-FDG incidentally found in these studies and concluded that the detection of these findings may indicate unexpected malignant lesions either in relation to unusual malignant dissemination of the known primary tumor or to a synchronous tumor. These authors also concluded that the follow-up of these FDG deposits may lead to a significant change in the therapeutic management and in the early diagnosis requiring medical or surgical study.

Likewise, the aim of another study carried out by Beatty et al. was to determine the clinical impact of FDG deposits suggestive of second primary tumors in 3814 studies performed in 2219 oncologic patients. They concluded that these findings should be studied insofar as they determined changes in the treatment algorithm of the patients and in relation to the status of the primary tumor.

On comparing the common results of the last 4 studies in reference to ours, we observed that the incidence of second primary tumors or premalignant lesions with anatomicopathological results was of 0.65% (13/1984), being 1.7% in the study by Agress, 1.2% in that by Ishimori, 1.5% in the study by Özol and 1% (41/3814) in the report by Beatty. The differences in this parameter may be attributed to the percentage of lesions without follow-up, which was 43.5% (27/62) in our study, 22.4% in that by Agress, 38.8% (47/121) in the study by Özol, and Beatty did not follow 36% of the patients. The loss to follow-up of these lesions represents an important limitation of the study similar to the study by Ishimori. Correct and especially anatomicopathological identification may increase not only the number of malignant lesions observed but also the number of lesions which are not malignant. We frequently observed how the requesting clinician focused the study on the evaluation of the known primary tumor, clearly considering the investigation of these findings to be of less priority. With regard to the percentage of lesions suggestive of the presence of second primary tumors or premalignant lesions in PET-18F-FDG studies, the incidence in our study was of 3.1% (62/1984) and was similar to that obtained in the studies by Agress and Cooper (3.3%), Ishimori et al. (4.1%) and Özol et al. (5.1%). If we consider the percentage of lesions correctly identified as second primary tumors or premalignant lesions by PET-18F-FDG among those confirmed anatomicopathologically, the value obtained in our study was 61.9% (13/19), being 71% in the study by Agress and Cooper and 49% in that by Özol et al. Differences are also found in regard to the type of secondary primary tumors found. We detected a total of 13 lesions correctly identified as second primary tumors: 4 colorectal tumors, several of the head and neck, 3 differentiated thyroid carcinomas and 2 premalignant lesions. The study by Agress and Cooper reported 27 lesions: 18 adenomas of the colon, 2 breast cancers, 2 of the head and neck, one bladder cancer, another of the endometrium, one ovarian, another of the Fallopian tubes and one differentiated thyroid carcinoma.

The study by Ishimori et al. described 23 lesions: 7 lung cancers, 6 differentiated thyroid carcinomas, 4 colon cancers, 2 breast cancers, 2 of the esophagus, one of the biliary tract and another of the head and neck. The study by Özol et al. found 19 second primary tumors (3 colorectal, 5 of the lung, 1 renal, 2 of the prostate, 1 uterine, 2 head and neck, 1 esophageal, 1 of the pancreas, 1 sarcoma, 1 of the adrenal glands and 1 lymphoma) and 3 premalignant lesions in the colon. Beatty et al. reported 41 lesions: 10 lung cancers, 3 head and neck, 2 esophagus/stomach, 2 musculoskeletal, 3 gynecological, 5 colorectal, 7 of the breast, 2 of the thyroid glands, 1 skin cancer and 2 hematological carcinomas. The differences among the 3 studies in the type of tumors found and in the percentage of each observed may be based on possible local epidemiological factors, the presence of synchronic primary tumors, often genetically associated and the appearance of which depends on the medium under study and, particularly, the differences are probably due to a selection bias in our study due to the strict clinical selection criteria for the performance of PET-18F-FDG studies in our unit.

The main reasons for consultation in our study were the investigation of spin, the restaging of lymphoma, the initial staging of lung cancer and the restaging of colon cancer, being mainly lung cancer and the study of the SPN in the study by Agress and Cooper, and the proportion of each individual tumor was similar (colon, lung and breast cancer, lymphoma) in the study by Ishimori et al. In the study by Özol et al. the reasons for consultation were lung, breast, colorectal, head and neck, pancreas, esophageal, biliary tract, adrenal gland, and gynecological cancer, melanoma, lymphoma and gastrointestinal carcinomas. One of the anatomicopathologically confirmed lesions in our study was a metastasis of the primary tumor, with no similar case being reported in the study by Ishimori et al. and with 14 in that by Özol et al. However, no metastasis was observed in our study in the group in whom follow-up was performed without anatomicopathological diagnosis. Therefore, within its fundamental characteristics, this study demonstrates the impossibility of PET to differentiate the uptake of 18F-FDG by the metastasis of the primary tumor from that of second primary tumors, basing this differentiation on the distribution, characteristics and localization of each individual lesion. Likewise, another important limitation is the impossibility of differentiation from some benign tumors processes of local inflammatory involvement, thereby underlining the importance of the correlation of the uptakes with the previous clinical history and the added value of the new hybrid equipment. We consider that findings which are false second primary tumors may lead to additional invasive studies, although one of the advantages of the PET-18F-FDG study is that it provides a point for selective biopsy of the lesion. Nonetheless, the benefits of correct identification of true second or third primary tumors justify the follow-up of this type of suspected lesion.

Conclusions

The presence of incidental tumors in PET-18F-FDG is relatively frequent (3%). These lesions should be clinically followed for precise diagnosis. A high percentage of these tumors (37%) correspond to unexpected second primary tumors in an early phase and are, therefore, susceptible to curative treatment or may modify the therapeutic approach to the already known tumor.
Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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References