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Impact of whole-body ^{18}F-FDG PET on diagnostic and therapeutic management of Medical Oncology patients

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ABSTRACT

Aim: Most studies evaluating positron-emission tomography (PET) impact on decision making are based on questionnaires sent to referring physicians, with low response rates and potential bias. Studies directly evaluating influence of PET on routine management of Medical Oncology patients are scarce.

Patients and methods: We retrospectively studied all patients evaluated by whole-body ^{18}F-FDG PET during 1 year in a Haematology/Oncology Department. We collected information regarding indication, PET results, modification of diagnostic and therapeutic management and adequacy of therapeutic changes.

Results: One hundred consecutive patients having PET were evaluated. Diagnostic strategy was modified in 63% of patients (30% avoiding biopsy). Therapeutic management was modified by PET in 34% of cases: changes were classified as adequate in 30% and as inadequate in 4% of patients.

Conclusions: Our study shows a major impact of PET in the diagnostic and therapeutic management of cancer patients and supports its introduction as a routine diagnostic tool in Medical Oncology.

1. Introduction

Whole-body ^{18}F-FDG positron-emission tomography (PET) has demonstrated to be a useful test for oncological diagnosis in multiple settings. PET's ability to overcome the limitations of size criteria used in radiological tests and to provide functional imaging makes it an invaluable tool for cancer staging and treatment monitoring. Its diagnostic value and cost–benefit have been systematically evaluated for most types of tumours and several indications are now considered standard by national and international agencies.[1–3]

However, studies of PET impact on clinical decision making from the point of view of clinicians are less frequently published. Most of them are based on questionnaires sent to referring physicians, with response rates frequently below 50%, which makes it possible some bias to communication of significant results.[4–9] Only in a few studies is evaluation of clinical management modification by PET results directly based in medical records, although available publications have focused on specific diseases or clinical problems such as lymphoma, lung cancer or colorectal cancer metastases.[10–13] There are also some publications demonstrating the

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impact of PET on planning and therapeutic decision in radiation therapy services, with similar rates of treatment modification.[14]

The aim of this study was to establish the impact of whole-body ^{18}F-FDG PET on global diagnostic and therapeutic management of cancer patients in a single-centre Haematology and Medical Oncology Department.

2. Patients and methods

2.1. Design of the study

We retrospectively reviewed the clinical records from 100 consecutive patients studied by PET during 1 year (November 2005 to October 2006) in the Department of Haematology and Medical Oncology of a single centre. All patients had their diagnosis of malignant neoplasm histologically confirmed. Indication of PET was made at physician discretion, but it was our general policy to ask for the test only if a modification of diagnosis or treatment by its result was expected. So, according to clinical practice in our centre, PET was usually done at the end of the conventional diagnostic process.

PET indications were grouped as follows: (1) initial staging; (2) suspected recurrence, with unclear or negative imaging studies results; (3) tumour marker elevation, with unclear or negative imaging studies results; (4) evaluation prior to liver or lung metastasis resection; (5) treatment response evaluation; (6) post-treatment residual mass evaluation; and (7) other indications.

2.2. PET technical specifications

^{18}F-FDG PET scans were performed in a Cti Reveal XL PET scanner. Radioisotope (^{18}F-FDG) was generated offsite and injected within 6 h. of preparation at a dose of 150 μCi/kg. After a fasting period of at least 6 h. prior to the procedure, radioisotope was injected intravenously and the patient stayed resting in a quiet room during 60 min. Whole-body PET was performed from the head to the femur with 5 min acquisition time per bed (3 min emission/2 min transmission). The acquired images were processed using an iterative reconstruction algorithm. Standardised uptake value (SUV) was calculated according to the standard method as given by Hoekstra and colleagues.[15] All PET scans were interpreted by one nuclear medicine physician (PGC).

2.3. Diagnostic and evaluation criteria

PET results were evaluated qualitative- and semi-quantitatively and the test was considered positive if at least one area of FDG uptake showed SUV greater than 2.5; values below 2.5 were considered negative.

Results were classified as false negative or positive if there was discordance with biopsy results; when histological diagnosis were not available or clinically indicated, determination of false positive or negative results was based on radiological follow-up for at least 3 months to confirm or rule out neoplasm. False positive and negative results were evaluated for primary tumour and for metastatic disease (which included regional node metastasis for statistical analysis). Change of tumoural stage was diagnosed if PET results established a lower or upper stage with respect to stage as defined by all diagnostic tests.

It was considered that PET modified diagnostic management if an additional diagnostic test was triggered or avoided only due to PET results. Diagnostic plan modifications were classified into five groups: (1) avoidance of biopsy; (2) indication of biopsy; (3) avoidance of nuclear medicine or imaging diagnostic tests; (4) indication of nuclear medicine or imaging diagnostic test; and (5) other modifications of diagnostic plan. A diagnostic test was considered unnecessary if it was triggered by a false positive PET result.

Treatment modification by PET was defined as a PET result, confirmed or not by other diagnostic test, which changed the original treatment plan. PET results supporting or confirming previous treatment planning (as metastasis or post-treatment residual masses resection) were not included in this group. Treatment modifications were classified into six groups: (1) avoidance of radical treatment of the primary tumour; (2) avoidance of metastasis surgery; (3) indication of chemotherapy; (4) indication of radiation treatment; (5) avoidance of chemotherapy; and (6) other treatment modifications.

2.4. Statistical design and literature search

Differences of frequency variables (false positive and negative results, diagnostic and treatment modifications) between groups (stage, tumour, ECOG and PET indication) were analysed with χ^2-test. Validity analysis was performed to evaluate diagnostic value of PET for primary tumour and for metastatic sites; results were obtained for each PET indication and primary tumour. Data were analysed using SPSS (SPSS for Windows, version 14.0).

References concerning PET clinical impact were selected after searching MEDLINE and PubMed using the key terms 'PET', 'clinical management', 'clinical utility, and 'Oncology'. Only reports published in English or French between 1998 and 2008 were selected.

3. Results

3.1. Patients and results of PET examinations

Between November 2005 and October 2006, 100 consecutive patients were studied with whole-body ^{18}F-FDG PET. Characteristics of patients are listed in Table 1. Median age was 56 years (range: 12–82). Most of them (58%) had good performance status (ECOG 0-1). Predominant histological types were adenocarcinoma (57%) and lymphoma (17%). The most frequent primary sites were colorectal, lung and nodes (non-Hodgkin lymphoma and Hodgkin disease). With conventional imaging diagnostic tests, 30% of patients were classified as stage IV.

Indications and results of PET are listed in Table 2. The most frequent indications were initial staging (22%) and response evaluation (22%). Sixty-three percent of exams were positive (25% in the primary tumoural location, 38% in metastatic sites and 15% in both locations). Percentage of positive results was independent of primary tumour, but there was a trend (χ^2; $p = 0.06$) to association between positive results

Table 1 – Patient's characteristics

Characteristics	*n*
Number of eligible patients	100
Age (years)	
Median (range)	56 (12–82)
Sex	
Male	62
Female	38
Primary tumour	
Colorectal	30
Lymphoma	17
Lung	16
Digestive non-colorectal	12
Breast	5
Ovarian	4
Head and neck	3
Testicular	3
Other primary locations	10
Disease stage	
Stage I	32
Stages II–III	34
Stage IV	30
Performance status	
ECOG 0-1	58
ECOG $\geqslant 2$	10
Not available	32

Table 2 – Indications and results of whole-body ^{18}F-FDG PET

Indication	Negative result	Positive result	Total
Initial staging	9	13	22
Suspected recurrence	4	16	20
Tumour marker elevation	6	5	11
Surgery of metastasis	3	13	16
Response evaluation	13	9	22
Residual mass evaluation	2	6	8
Other indications	0	1	1
Total number	37	63	100

and type of indication (suspected recurrence or evaluation of post-treatment masses). Stage was modified by PET results in 40% of cases: upstaging in 20% and down-staging in 20%.

Comparison of PET staging with stage determined by conventional examinations was performed in all patients and showed 22% of false positive and 19% of false negative results. Findings were confirmed by histological diagnosis for half of the patients and by diagnostic imaging follow-up for the other half (11/11 for false positive and 9/10 for false negative results). Validity analysis for all locations (primary and metastatic) showed a sensitivity of 81% and a specificity of 78%. For primary tumour locations, sensitivity was 97% and specificity 85%. For metastatic sites, false positive and false negative rates were higher; thus, a lower sensitivity (73.4%) and specificity (64.4%) were observed.

3.2. *Change of diagnostic management*

Diagnostic management was modified by PET results in 63% of the patients. In 30% of cases, a biopsy was avoided; in 15% of patients, PET examination generated a new biopsy. Radiological or nuclear medicine exams were avoided in 9% and 8% of cases, respectively. Unnecessary additional diagnostic examinations were generated by PET results in 12 patients (8 biopsies and 4 radiological tests).

Frequencies of diagnostic changes according to indication are listed in Table 3. Changes in the diagnostic process were more frequent when the reason to perform PET examination was suspected recurrence (95%) or residual mass evaluation (87.5%). Modification of diagnostic planning was also relevant for the rest of PET indications, as shown in the table. There was no relationship between the type of primary tumour and diagnostic test modification (χ^2; $p = 0.075$).

3.3. *Modification of therapeutic management*

Therapeutic management was modified by PET results in 34% of cases, as shown in Table 4. The most frequent type of treatment change (18% of cases) was the decision to administer chemotherapy (as a single therapeutic modality or as a treatment previous to any type of local treatment). In 6% of patients, PET results demonstrating more extensive neoplastic disease avoided surgical resection of metastasis or primary tumour. In another 26% of cases, PET supported previous treatment decision (surgery of metastasis or residual mass). No relationship between treatment modification and performance status ($p = 0.69$) or primary tumour ($p = 0.60$) was demonstrated.

Frequency and type of therapeutic modification were different according to the reason why PET had been performed (χ^2; $p = 0.002$ and $p < 0.001$, respectively). Impact on treatment plans was especially remarkable when PET had been indicated for initial staging or residual mass evaluation. Metastasis resection (mostly liver metastasis) planning was modified by PET results in 25% of cases.

Impact of treatment modification by PET on overall or progression-free survival was not determined. However, further follow-up of patients allowed us to evaluate patient outcome and treatment adequacy. False positive results generated an erroneous treatment decision in a patient with non-small cell lung cancer, in which a false positive in mediastinic nodes due to inflammatory changes motivated substitution of initial surgical treatment by radio-chemotherapy. False negative results on PET examination also motivated an inadequate change of treatment in three patients: two patients (one with a NHL and other with an ovarian cancer) did not receive chemotherapy in that moment, but treatment was administered later, when follow-up confirmed active disease. In another patient with NHL, a second advanced solid cancer was not discovered on PET, delaying chemotherapy treatment for the second tumour. Overall, PET results generated incorrect therapeutic decisions in 4% of patients and treatment modification was adequate in the rest of cases (30%).

Table 3 – Modification of diagnostic management according to ^{18}F-FDG PET indication

Diagnostic strategy modification	PET indication							Total
	Initial staging	Suspected recurrence	High tumoural marker	Surgery of metastasis	Response evaluation	Residual mass evaluation	Other indications	
No modification	10	1	4	9	12	1	0	37
Avoidance of biopsy	5	11	3	1	7	3	0	30
Indication of biopsy	2	5	1	3	2	1	1	15
Avoidance of imaging test	3	1	2	2	1	0	0	9
Indication of imaging test	2	2	0	1	0	3	0	8
Other modifications	0	0	1	0	0	0	0	1
Total	22	20	11	16	22	8	1	100

Table 4 – Modification of therapeutic management by ^{18}F-FDG PET results

PET indication	Treatment modification						
	No change	No local treatment	No metastasis resection	Indication of chemotherapy	Indication of radiotherapy	No chemotherapy	Other modification
Initial staging	10	2	0	7	2	0	1
Suspected recurrence	11	0	1	4	1	1	2
High tumoural marker	11	0	0	0	0	0	0
Surgery of metastasis	12	0	2	2	0	0	0
Response evaluation	19	0	0	2	1	0	0
Residual mass	3	0	0	3	1	1	0
Other indications	0	1	0	0	0	0	0
Total	66	3	3	18	5	2	3

4. Discussion

In the last 15 years, much evidence has been accumulated, indicating the usefulness of ^{18}F-FDG PET as a diagnostic tool in Oncology. PET has demonstrated its value in accurate staging, response evaluation, recurrence detection and evaluation of viability for post-treatment residual masses. Thus, PET has become a routine test in several neoplastic diseases as lung cancer, lymphomas, head and neck tumours, GIST and oesophageal cancer. In a wide range of tumours, PET is also a good adjunct to diagnosis and can frequently avoid invasive procedures in doubtful clinical situations.[1–3] However, clinical usefulness varies depending on disease and indication, and some warnings have been issued regarding limitations of the test and poor performance in some situations.

If on a disease by disease basis clinical usefulness of PET is clear, its global impact on clinical decision making in Oncology has not been exactly established. Studies based on questionnaires sent to referring physicians show rates of treatment modification in the range of 25–40%. However, since response rates are usually below 50%, a communication bias to significant results by referring physician can not be ruled out.[4–9] Thus, obtaining data directly from the medical records could give more accurate and objective results about the impact of PET in patient management. Such a study was published by Dizendorf and colleagues; in his series, 202 patients referred for evaluation to a Radiation Therapy Department were studied with PET and a major impact on the intention, the planning and the indication of treatment was demonstrated.[14]

Our work confirms the global impact of PET both in diagnostic and therapeutic management of cancer patients in Medical Oncology practice. In a series of 100 patients comprising a wide range of primary tumours and different clinical situations, PET modified diagnostic management in two-thirds of patients and caused changes of treatment in another third of cases. Regarding diagnostic evaluation, PET avoided biopsy in 30% of patients, especially after demonstrating functional activity in metastatic or post-treatment residual disease. However, concerns about false positive results motivated biopsy in 15% of patients after positive results. These results are similar to previous data from questionnaires-based studies[4–8] and from studies focusing in a specific neoplasm as lung[11], breast[16] or kidney cancer.[17]

In our opinion, the main finding of our study was a high rate of treatment modification, confirming the results of previous publications. Results were especially determinant in the setting of potentially resectable metastatic disease. Also, PET was clearly useful in initial evaluation of tumoural extension, in which demonstration of metastatic disease frequently changed treatment to chemotherapy instead of local treatment. A similar work was published by Hillner and colleagues, with more cases ($n = 248$) and a prospective design.[18] However, indications were not restricted to a Medical Oncology setting (only 39% of cases), the study was representative of an American centre, and it was again based in questionnaires,

although with a high response rate (more than 90%). In their series, Hillner and colleagues showed that PET results changed their intended management in 61% of cases. In 32% of patients, there was a change to a non treatment policy. However, as the authors point out, the main limitation of the study was the impossibility to determine if changes in management were or not appropriate. By the contrary, although our work is limited by a retrospective design, its main strength is the use of medical records and a longer follow-up that permitted us to evaluate patient outcomes. Similarly, evaluation of real decisions and not of the theoretically planned decisions, as in other publications, makes results more relevant for oncology daily practice. The 4% rate of inadequate PET-based therapeutic decisions raises concerns about the potential for overconfidence in PET findings. However, adequate changes of treatment, especially in the metastatic disease setting, clearly compensate for this risk and make PET a safe procedure in which clinical decisions can be based.

This study has some limitations. The limited number of patients does not allow us to determine the relative value of PET in the different type of tumours, although the objective of the study was a global evaluation of its utility. Second, and more important, the single-centre character of the series and the indication of the PET at the discretion of each physician limit the external validity of the results. However, limited access to the technique meant that indication of PET was established at the end of diagnostic process and only when a change in diagnosis or treatment was expected depending on the results, a situation probably still common to many centres in Europe. Finally, results were obtained with a PET equipment, with worse spatial definition than newer PET-CT machines; technical improvements in combined functional and radiological imaging will probably yield better diagnostic performance,[19,20] thus making PET-CT-based clinical management more accurate.

An additional caveat of this work and of other similar reports is the intrinsic limitation of the level of outcomes evaluated. According to Fryback and Thornbury's hierarchical model of efficacy of diagnostic imaging, our study assesses diagnostic and patient management relevance, that are only surrogate measures for patient outcomes and societal benefits.[21] Assessment of the value of PET at these levels is beyond the scope of our work and it would require a multi-institutional effort and a more comprehensive research design.

In conclusion, this study shows a major impact of PET utilisation in the diagnostic and therapeutic management of the cancer patients evaluated in a Medical Oncology setting. Better definition of PET validity in each clinical scenario, improvement in PET-CT equipment and use of clinical judgment to avoid over-interpretation of PET results are necessary conditions to obtain the maximum benefits of this diagnostic technique. Although more studies are needed to evaluate the consequences of management changes induced by PET results on patient outcomes and efficiency variables, our work supports the introduction of this technique as a routine diagnostic tool in Oncology.

Conflict of interest statement

None declared.

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