

THE DEVELOPMENT AND DISTRIBUTION OF PET, PET/CT IN ITALY

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Introduction

In recent years there has been a very impressive increase in the number of clinical applications for PET. Initially PET studies were mainly focused on brain metabolism and function, but since the advent of whole body PET the greatest development of clinical PET has been in oncology (1-4). At present almost 85-90% of the clinical activity in a standard PET center in Europe consists of oncologic PET studies. Also the range of neurologic, neuropsychiatric and cardiac applications has increased, albeit to a lesser extent.

The reasons why PET is successful in oncology

The most important reason why PET is successful in oncology is that it provides many diagnostic information very useful for the clinical management of patients. Neoplastic cells have some metabolic characteristics that coincide with the availability of ^{18}F -fluorodeoxyglucose (FDG), which is the most suitable radiopharmaceuticals for PET. FDG is worldwide used for the vast majority of clinical PET studies, particularly in oncology (5,6,7). Being a functional technique, PET is based primarily on metabolic activity rather than size in the detection of neoplasms; consequently, it is more sensitive than conventional anatomic modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). An interesting evaluation of the accuracy of FDG-PET across all oncologic applications taking into account the most qualified literature in oncology (lung cancer, colorectal cancer, melanoma, lymphoma, head and neck cancer, breast tumors, brain tumors, ovarian, cervical and uterine cancer, bladder cancer, gastroesophageal cancer, hepatocellular cancer, muscle and connective tissue tumors, pancreatic cancer, prostate cancer, renal cell cancer, testicular cancer, and thyroid cancer) estimated a sensitivity for PET ranging from 84% to 87% (among 18,402 patients), a specificity ranging from 88% to 87% (among 14,264 patients) and an overall accuracy ranging from 87% to 90%. These data were obtained from 419 articles and abstracts in which FDG-PET was reported (8). Another reason why PET has found such wide application in oncology is the intrinsic need of oncology itself, which requires both an improved detectability of cancer lesions with respect to the morphologic limits of conventional radiology and new parameters to describe the behavior of cancer tissue in terms of metabolism, differentiation, proliferation, and grade of malignancy (9).

Of course, FDG is not the only possible radiopharmaceutical for oncology. It is known that the avidity of tumors for FDG is not always optimal in all cancer types. Some tumors such as neuroendocrine tumors and other well-differentiated tumor types show a limited uptake of FDG (10). Furthermore, FDG shows a high degree of unspecific uptake in any cell type with a high glycolytic activity. FDG-PET accumulates in infectious and inflammatory processes (e.g. abscesses, TB, sarcoidosis, active granulomatosis, etc.) and this prevents sometimes the discrimination between tumor tissue and certain benign or inflammatory alterations (11). FDG also shows physiologic uptake in some normal tissues (brain, myocardium and other muscles, kidney and urinary system, gastrointestinal tract as well as thymus tissue); for instance, the high uptake of FDG by normal cortex renders FDG-PET relatively insensitive for the detection of small brain metastases (12). For all the aforementioned reasons other radiopharmaceuticals than FDG may in some cases be more appropriate to image certain cell pathways or specific structures. Several radiopharmaceuticals are available which explore various metabolic pathways such as amino acid uptake (^{11}C -methionine, ^{11}C -aminoisobutyric acid), membrane synthesis (^{11}C -choline, ^{18}F -fluorocholine), nucleic acid synthesis (^{11}C -thymidine), dopamine synthesis (^{18}F -fluorodopa), cancer cell hypoxia (^{11}C -fluoromisonidazole), hormone receptor expression (^{18}F -fluoroethyl estradiol), etc. (13-17). These PET tracers have been successfully investigated by various authors in oncology ; however, their use has not yet entered current clinical practice, except in a limited number of PET centers equipped with cyclotron and radiochemistry facilities.

Where PET is available, its main applications in oncology cover a number of indications involving different clinical steps in the diagnostic workup of cancer patients. At present the most frequent clinical indications are: a) establishing the tumor burden (extent of primary tumor and identification of distant metastases); b) treatment monitoring (measuring response after radiotherapy or chemotherapy); c) detecting suspected recurrences and restaging relapsed patients in order to plan correct cancer treatment (18,19). Other applications are not so common in the clinical routine as those already mentioned, but they have been investigated and are adopted when required in different cancer types to: a) establish the grade of malignancy; b) predict tumor response at an early stage, perhaps after one or two cycles of chemotherapy; c) identify primary disease in the presence of a tumor of unknown origin; d) localize biopsy sites; d) plan radiotherapeutic treatment since it identifies the area of viable cancer. The development of this subgroup of applications is affected by the still limited availability of PET facilities in various countries, and for this reason most referrals today are for the most common rather than for all potential routine applications.

PET shows certain limits in sensitivity and cannot be used to identify microscopic disease. This is due to the resolution limits of dedicated PET scanners, which theoretically is not less than 4-5 mm (20-22). This problem in the future can be partially overcome as the technology of PET will continue to improve both from the instrumentation and radiopharmaceutical standpoint. However until now, the clinical evidences derived from the application of FDG-PET in oncology have confirmed that

the lesion detectability of PET is good, often higher than that of CT and MRI. This makes PET cost-effective in spite of the relatively high cost of a PET scan. Many economic analyses (cost-analysis, cost-effectiveness analysis, cost-utility analysis) have been published and they demonstrate the advantages of the clinical use of PET (23-30). An impressive body of information shows that FDG-PET is able to provide unique information in patients with cancer that cannot be obtained with other current techniques. The practical advantages of PET compared to conventional morphologic modalities allow clinicians to change the management of patients on the basis of the FDG-PET results. Based on an evaluation of a series of 5,062 patients, the average management changes across all oncologic applications have been estimated to be around 30% (8) (**Table 1**).

TABLE 1. *Changes in patients management on the basis of PET studies**

Tumor type	PET applications	Patients No.	Changes of management (%)
Lung cancer	Staging	1867	37
Colon cancer	Restaging	1387	32
Colon cancer	Staging	236	36
Oesophageal cancer	Staging	545	20
Melanoma	Staging	283	26
Lymphoma	Staging	407	21
Lymphoma	Restaging	158	10
Breast cancer	Staging	111	24
Breast cancer	Restaging	23	40
Head and neck cancer	Staging	30	33
Total		5047	30.8

* Elaboration from Gambhir SS, et al. J Nucl Med, 2001, 42, 5.

This is particularly true in cancer with a high relapse rate after so-called radical surgery, for instance in patients with small metastatic localizations not identified by conventional modalities. Some groups of patients should not undergo an attempt at curative surgery without a previous PET scan, as the preoperative demonstration of nonresectable tumor may avoid unnecessary surgery. Beside this, PET also has the potential to evaluate the response of cancer to therapy, even at an early stage, e.g. after one or two cycles of chemotherapy. This permits a change to more effective treatment in patients who are not responding, avoiding morbidity from inappropriately prolonged treatment.

It easy to understand that on these basis PET is going to have a role more and more important in oncolgy. This evolution goes through the continous development and improvement of the scanners, the discovery of new radiopharmaceuticals, the policy of radiopharmaceutical regulation and reimbursement, the availability of resources related to the organization of PET centers, the adequate learning programs for nuclear medicine technologists and physicians trained in PET (31). As more PET imaging instrumentation becomes available, a further large experience will improve and better define the clinical indications of PET. There is no doubt that it should be appropriately included in the practice diagnostic guidelines for many cancer types. However, considering the

data from the literature and our daily routine experience at present it is possible to say that, when PET is available, a great number of referrals is absolutely essential to the oncologist in the choice of the appropriate clinical strategy.

PET distribution and growth

The conclusion of this short paper on the increasing impact of PET in clinical oncology is that PET today has assumed a primary role in oncology. The advantages offered by this high technology are demonstrated by the impressive increased number of FDG-PET studies in oncology both in the US and Europe. This progressive trend is based on the fact that there is a clear evidence that a number of treatment strategies are often adjusted on the basis of PET studies. Moreover PET has been shown to be cost-effective, therefore the facilities available for PET imaging have shown a steady increase over the years. As far as the distribution of PET facilities is concerned, at present there are two PET scanners per 1,000,000 inhabitants in the US and one per 1,000,000 inhabitants in some parts of Europe (e.g. Germany). In Italy the number of PET scanners increased from 4 in 1995 to 34 in 2003, and the number of PET examinations from 2000 in 1996 reached 24000 in this year (Fig 1 and Fig. 2). Nearly 93% of PET scans are related to the oncological problems, the rest is carried out in neurology and cardiology. The ratio between the PET scanners and population is 0.6 per 1,000,000 inhabitants. Unfortunately there are several strict regulatory rules that do not allow to produce, distribute and sell FDG outside the hospital. Since FDG is not still registered in Italy, there not exists any national commercial distribution of the radiopharmaceutical through the Industry. This represents a very strong limitation in the development of PET centers. In fact about 36 PET scanners have been installed and the number of cyclotrons is 17; it is evident that the ratio PET/cyclotron is not in favour of a correct economic balance that can be achieved by adopting few centers of radiopharmaceutical production connected with different PET centers by a network for FDG distribution. There is no doubt that the expected improved availability of FDG through a national commercial distribution is essential to make it easier to plan an adequate policy in promoting clinical PET in every site. In this way nuclear medicine imaging will have a more and more substantial impact on the diagnosis of cancer and consequently on the correct choice of the most effective therapy for many malignancies.

Anyhow, the clinical use of PET has to be considered still in its infancy, and a major effort has yet to be made to accurately delineate the clinical indications for PET, by integrating PET in the practice guidelines of the diagnostic protocols for cancer patients. In this area the scientific and professional nuclear medicine associations should collaborate with oncologists, surgeons and all other physicians working in the field of oncology. The information obtained from PET has to be optimized by excluding ineffective procedures and inappropriate clinical answers. We have enough elements to affirm that the present of PET is good and its future will be bright, also because the understanding and perception of the clinical value of PET is continuously growing among

oncologists, and the technology of PET will continue to improve. Today CT scanners have been combined with PET scanners, and new hybrid equipments are capable to perform radiological and nuclea medicine images, automatically merging the the morphological and biological data to form a composite imaging (32). By uniting metabolic function with anatomic form, fusion imaging depicts the human body with a level of precision never before achievable. Today four companies manufacture hybrid PET-CT systems (CPS Innovations, GE Medical Systems, Philip Medical Systems and Siemens Medical Solutions). Combined these four Companies ahd installed approximately 300 PET-CT world-wide by mid-2003. In Italy 11 out of 36 PET scanners installed, 11 are PET-CT and the new installations are absolutely oriented towards the hybrid systems. Although the number of PET-CT machines is still small today, it is expected to increase in the next few years. In part the demand will be driven by the technology's potential to depicts and localize many images unsolved by the conventional imaging modalities and to revolutionize treatment planning for radiation therapy. A PET-CT scan gives radiation therapists a more accurate anatomical reference point for IMRT (intensity modulated radiation therapy) to deliver very high doses of cancer-killing radiation directly to cancers. In the next future we should also expect that also PET images will greatly ameliorate, as has been demonstrated by the experimental use of microPET scanners in animal models. These instruments are able to operate at a resolution of 2 mm or less, and the resolution of the future generation of PET scanners will likely be around 1 mm. A higher resolution means better lesion detectability, and it is a general concept in oncology that cancer is more curable when it is detected at an early stage. It is clear that all these technologies are relatively expensive, and the developments described above require resources that may not always be available. However, on the basis of the advances made in the last decade, there is no doubt that physicians will need more PET facilities in order to improve patient care. We are absolutely sure that many of the problematic diagnostic issues that we face every day in cancer patient management cannot be solved without the contribution of PET.

Fig. 1

PET scanners' development in Italy

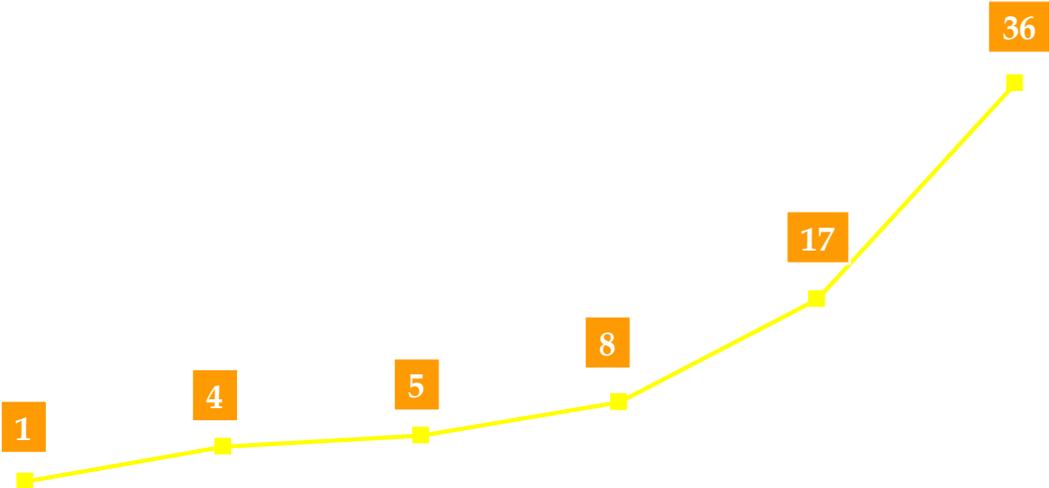


Fig. 2

PET examinations in Italy



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The recent development of combined PET/CT instrumentation is an important evolution in imaging technology. Since the introduction of the first prototype computed tomography (CT) scanner in the early 1970s, tomographic imaging has made significant contributions to the diagnosis and staging of disease. Rapid commercial development followed the introduction of the first CT scanner in 1972, and within 3 years of its appearance more than 12 companies were marketing, or intending to market, CT scanners; about half that number actually market CT scanners today. In modern nuclear medicine, planar scintigraphy has been extended to tomography by the development of Single Photon Emission Computed Tomography (SPECT), which can be helpful for certain clinical applications. The reliability of the PET/CT imaging information in cancer patients depends on trustworthy and consistently applied protocols. This issue has current relevance in drug discovery and development, where PET/CT imaging with FDG and other radiotracers is viewed by the pharmaceutical industry as potentially useful for shortening the process of clinical validation of new drugs. The IAEA wishes to thank the contributors to the drafting and review of this book for contributing their knowledge, time and effort.

Archival and Distribution of Data
12. Quality Control
13. Imaging-associated Risks and Risk Management

APPENDICES
Appendix A: Acronyms and Abbreviations
Appendix B: References

The FDG-PET/CT subgroup of the Uniform Protocols for Imaging in Clinical Trials (UPICT) Working Group (now part of QIBA initiative), consisting of imaging physicians and medical physicists worldwide with expertise in early drug development from academic research organizations, government and industry, together with imaging specialists, has met regularly through in-person meetings and weekly conference calls over the last 5 years to develop these evidence-based consensus guidelines for the use of FDG-PET/CT in oncology clinical trials. The European Commission launched a four-year pilot testing period for both the non-food and food sectors through a multi-stakeholder process to develop product-specific rules, Product Environmental Footprint Category Rules (PEFCRs), and organisation-specific rules, Organisation Environmental Footprint Sector Rules (OEFSRs). In May 2014, the European Commission approved the pilot project to develop PEFCRs for prepared pet food for cats and dogs. The Technical Secretariat (TS) charged with developing the PEFCR is composed of the following organisations: FEDIAF, C&D Foods, FACCO, Mars PetCare Eur...