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Practice guideline

Summary of the Standards, Options and Recommendations for the use of positron emission tomography with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDP-PET scanning) in oncology (2002)

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When positron emission tomography (PET) scanning was introduced at the end of the 1970s, its technical characteristics and biological potential aroused immediate interest. The available tracers at time (isotopes of oxygen, nitrogen, and carbon) made it possible to study blood flow, regional oxygen consumption, the main metabolic pathways and ligand–receptor interactions in the brain, heart and other major organs, without physiological perturbations. Although the promise of the technique was fulfilled, its use has not developed as rapidly as expected.

Positron emission tomography scanning was initially used to study the brain and the heart, but today it is used mainly in oncology. This is partly due to technological developments that allow whole-body examinations. There is also a growing number of publications suggesting that this technique is useful in the management of many cancers, from initial staging to post-therapeutic follow-up.

The tracer generally used is 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), which is a glucose analogue that competes with glucose at the level of transmembrane transporters. Although other tracers have been proposed ([^{11}C]methionine, [^{11}C]tyrosine and [^{11}C]thymidine), their use has not yet been validated, and the carbon-11 label is a limiting factor for extensive routine use. Nearly 70 years ago, Warburg demonstrated an increase in glycolytic activity in cancer cells, and this is the basis for use of FDG in oncology. Briefly, in most cancers, neoplastic transformation induces an increase in glucose transporters (particularly GLUT1) and in the activity of glycolytic enzymes (particularly hexokinase). These changes are responsible for an increase in glycolytic activity in cancer cells, under both aerobic and anaerobic conditions. The glycolytic activity is related to the viable tumour cell mass, as the increase in glucose transport reflects cell proliferation. Accumulation of glucose is not specific to malignant tumours but can also be increased in benign tumours and in inflammatory diseases, such as sarcoidosis and granulomatosis.

In 2001, there were only four operational PET scanners in France, dedicated to clinical use. Since then, the Government has authorised the installation of about 40 sites, with a final objective of 60 PET scanners so as to provide adequate access throughout the country.

The most important question about the use of PET scanning in oncology is: 'What is its usefulness in comparison with other imaging techniques?' The answer requires not only comparing the performance of PET scanning with that of other imaging techniques, but also evaluating the impact of use of PET on the management of patients with cancer. Although, many studies are under way, only a few publications specifically addressing the question are available.

As with most medical imaging techniques, the clinical use of PET has developed before its efficacy and efficiency have been clearly demonstrated. The fields of application of PET scanning are evolving continuously with new research findings. However, the rapid pace of technological improvements to PET scanning results in an ever increasing list of applications, but this also prevents the accumulation of convincing data for evaluation. In this context, it was decided that clinical practice guidelines were needed to define the potential and recognised indications for FDG-PET scanning in oncology.

OBJECTIVES

The objective was to review the available scientific data and to develop the Standards, Options, and Recommendations (SORs) for the role of and indications for FDG-PET scanning in oncology. The main steps in patient care that were studied were diagnosis of the primary disease, initial and secondary metastatic assessment, evaluation of treatment response, and detection of recurrent disease. The recommendations made relate to the primary cancer sites defined as priorities on the basis of the available scientific

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data: cancers of lung and pleural, melanoma, gynaecological cancers, gastrointestinal cancers, head-and-neck cancers, urological cancers, lymphomas, soft-tissue and bone sarcomas, and cancers of the thyroid, and also carcinomas of unknown primary site. For some cancer sites, the working group considered that an evaluation was either not timely or that the available data were inadequate. These topics, in particular cerebral tumours and childhood cancers, will be addressed when these recommendations are updated.

METHODS

The details of the methodology have been published previously (Fervers *et al*, 2001). For this particular SOR, a multidisciplinary group of experts was set up by the French National Federation of Cancer Centres (FNCLCC) and the French Society for Biophysics and Nuclear Medicine (Société Française de Biophysique et Médecine Nuclear, SFBMN) to critically appraise the available evidence on the role of and indications for FDG-PET scanning in oncology.

Literature searches were performed for each cancer site in Medline®, from January 1996 to November 2001, and in the Cochrane® Library, Issue 3, 1999. The Cancerlit® database and the proceedings from American Society of Clinical Oncology conferences were also searched. The search excluded articles in languages other than English and French, as well as *in vitro* and animal studies. Studies in which tracers other than FDG were used were not specifically sought, although studies comparing FDG with other tracers were included for certain cancer sites, when they provided data for the relevant outcomes. The review met with a recurrent difficulty: multiple publication in different journals of the same study, with an increasing number of patients, and sometimes with the authors in a different order. In this situation, only the last publication, including the largest number of patients, was retained for this report.

The literature search was complemented with personal references supplied by the experts. In certain chapters, references published after November 2001 were added when the working group considered it necessary, especially when the new references had an impact on the definition of a standard or an option. The data analysis also included three reports of evaluations and recommendations for FDG-PET scanning (Adams *et al*, 1999; Robert and Milne, 1999; AETMIS, Agence d'évaluation des technologies et des modes d'intervention en santé, 2001) and the report of a German consensus conference (Reske and Kotzerke, 2001).

The working group selected and critically appraised pertinent references and then proposed the 'Standards', 'Options', and 'Recommendations' for the role of and indications for FDG-PET scanning in oncology, based on either the best available evidence or expert agreement.

'Standards' identify clinical situations for which there exist strong indications or contraindications for a particular FDG-PET application and 'Options' identify situations for which there are several alternatives, none of which have shown clear superiority over the others (Table 1). In any SOR, there can be several 'Options' for a given clinical situation. 'Recommendations' enable the 'Options' to be weighted according to the available evidence. Several FDG-PET applications can be recommended for the same clinical situation, so that clinicians can make a choice according to specific clinical parameters, for example, local circumstances, skills, equipment, resources, and patient preferences. Adapting the SORs to a local situation is possible if the reason for the choice is sufficiently transparent and this is crucial for successful implementation. Inclusion of patients in clinical trials is an appropriate form of patient management in oncology and is recommended frequently within the SORs, particularly in situations where evidence is too weak to support a particular FDG-PET application.

The type of evidence underlying any 'Standard', 'Option', or 'Recommendation' is indicated using a classification developed by the FNCLCC based on previously published models. The level of evidence depends not only on the type and quality of the studies reviewed, but also on the concordance of the results (Table 2). When no clear scientific evidence exists, judgment is made according to professional experience and consensus of the working group ('expert agreement').

In this particular situation, that is, a diagnostic test, it is sometimes difficult to classify levels of evidence. In addition, PET scanning is an emerging technique, for which many indications are

Table 1 Definition of Standards, Options and Recommendations

Standards	Procedures or treatments that are considered to be of benefit, inappropriate or harmful by unanimous decision based on the best available evidence
Options	Procedures or treatments that are considered to be of benefit, inappropriate or harmful by a majority, based on the best available evidence.
Recommendations	Additional information to enable the available options to be ranked using explicit criteria (e.g. survival, toxicity) with an indication of the level of evidence

Table 2 Definition of level of evidence

Level A
There exist a high-standard meta-analysis or several high-standard randomised clinical trial which give consistent results

Level B
There exists good quality evidence from randomised trials (B1) or prospective or retrospective studies (B2). The results are consistent when considered together

Level C
The methodology of the available studies is weak or their results are not consistent when considered together

Level D
Either the scientific data do not exist or there is only a series of cases

Expert agreement
The data do not exist for the method concerned, but the experts are unanimous in their judgement

Table 3 Summary of Standards, Options, and Recommendations for FDP-PET scanning

		Summary of Standards, Options and Recommendations by indication			
	Indications in French Product licence 1998	**Standard**	**Option**	**Further trials required**	**Situations where PET scanning is not indicated**
Cancers of the lung and pleura					
Lung	Differential diagnosis of pulmonary masses	Diagnosis of malignancy in a solitary pulmonary lesion larger than 1 cm, suspicious of malignancy on initial imaging (level of evidence: A)	Diagnosis of malignancy in a pulmonary lesion less than 1 cm (level of evidence: B2)	Evaluation of response to anticancer treatment (level of evidence: D)	Screen for cerebral metastases (standard, expert agreement)
	Staging and assessment of recurrent disease	Assessment of locoregional involvement and metastatic screen (particularly adrenal gland) (level of evidence: A)	Differential diagnosis of recurrence or residual disease from post-treatment fibrosis (level of evidence: B2) Optimisation of radiotherapy fields (in combination with CT scan) (level of evidence: B2)		
Pleura			Diagnosis of malignancy in pleural lesions (level of evidence: B2)	Local and distance metastatic screening in patients with malignant pleural lesions Contribution of determination of a biopsy site (level of evidence: D)	
Mediastinum					PET scanning is not indicated outside the setting of a clinical trial (standard)
Melanoma					
Cutaneous melanoma	Initial metastatic screen		Initial metastatic screen in patients with melanoma at high risk of metastases (Stage III AJCC) (level of evidence: B2) Assessment of operability in metastases thought to be solitary (level of evidence: B2)	Screen for recurrence as part of follow-up (level of evidence: C)	Screen for nodal micrometastases (level of evidence: B1)
Other melanomas					PET scanning is not indicated outside the setting of a clinical trial (standard)
Gynaecological malignancies					
Breast cancer			Locoregional and distant metastatic screen for patients with invasive tumours (level of evidence: B2) Suspicion of local or metastatic recurrence (level of evidence: B2)	Evaluation of response to neoadjuvant chemotherapy (level of evidence: D)	Diagnosis of malignant breast tumours (standard, level of evidence: B2) Detection of nodal micrometastases standard, (level of evidence: B2)

Table 3 *Continued*

	Indications in French Product licence 1998	Summary of Standards, Options and Recommendations by indication			
		Standard	**Option**	**Further trials required**	**Situations where PET scanning is not indicated**
Ovarian cancer				Suspicion of local or metastatic recurrence (level of evidence: C)	
Uterine cancer			Assessment of nodal involvement in patients with cancer of the cervix (level of evidence: B2)		Not indicated in patients with cancer of the endometrium or vagina outside the setting of a clinical trial (standard)
Gastrointestinal cancers					
Cancer of the oesophagus		Pretreatment evaluation of nodal and metastatic status to complement scans and endoscopic ultrasound (level of evidence: B2)			
Gastric carcinoma					No indication outside the setting of a clinical trial (recommendation, expert agreement)
Colorectal cancer	Assessment of operability of recurrent disease and metastases	Diagnosis of recurrence in patients with confirmed elevation of serum carcinoembryonic antigen (level of evidence: B2) Preoperative staging of local and metastatic recurrence (level of evidence: B2)		Preoperative initial staging (level of evidence: C)	
Pancreatic cancer		Differential diagnosis and staging in patients with normal serum glucose (level of evidence: B2)			
Hepatic carcinoma		Differential diagnosis of hepatic metastases, cholangiocarcinomas and benign tumours in patients with a solitary hepatic lesion (expert agreement)	Metastatic screen for patients with hepatocellular carcinoma (level of evidence: B2)	Early diagnosis of a cholangiocarcinoma in patients with sclerosing cholangitis (level of evidence: C)	
Neuro-endocrine tumours		Diagnosis and staging only in patients with a normal octreotide scan (expert agreement)			No indication for PET scanning as first-line imaging (level of evidence: B2)
Cancer of the head and neck					
	Initial metastatic screen for patients with cancer of the pharynx	Metastatic screen for patients with untreated cancers of the head and neck (level of evidence: B2)	Differential diagnosis between benign and malignant tumours when a biopsy has not been conclusive (level of evidence: B2)	Early evaluation of the efficacy of chemotherapy (level of evidence: C)	

Table 3 *Continued*

	Indications in French Product licence 1998	Summary of Standards, Options and Recommendations by indication			
		Standard	**Option**	**Further trials required**	**Situations where PET scanning is not indicated**
Cancers of the head and neck		Diagnosis of recurrence (level of evidence: B2)	Search for a second concurrent malignancy (level of evidence: B2) Search for a primary tumour in patients with metastatic cervical lymphadenopathy with unknown primary site (level of evidence: C)		
Cancers of the salivary glands					No indication outside the setting of a clinical trial (standard)
Lymphomas					
	Initial staging, follow-up for early treatment and search for residual disease	Initial metastatic screen and as a complement to conventional imaging in HD, high-grade NHL and follicular lymphomas (level of evidence: B2) Diagnosis of residual disease (level of evidence: B2		Early evaluation of response to treatment (level of evidence: D)	
Sarcomas					
Soft-tissue sarcomas			Search for local recurrence (level of evidence: B2) To guide biopsy (level of evidence: B2)		
Osteosarcoma				Characterisation of suspected primary bone tumour (level of evidence: C)	
Urological cancers					
Renal cell carcinoma			Search of local recurrence or distant metastases in patients with symptoms (level of evidence: C)	Diagnosis of a primary renal cell carcinoma (level of evidence: C) Initial metastatic screen (level of evidence: C)	

HD=Hodgkin's disease; NHL=non-Hodgkin's lymphoma.

Table 3 *Continued*

Indications in French Product licence 1998	Summary of Standards, Options and Recommendations by indication			
	Standard	**Option**	**Further trials required**	**Situations where PET scanning is not indicated**
Prostate carcinoma			Initial locoregional and distant metastatic screen (level of evidence: C) Suspicion of local recurrence (level of evidence: C) Diagnosis of suspicious abnormalities on bone scan (level of evidence: D)	Diagnosis of a primary prostate cancer (standard, level of evidence: B2)
Testicular cancer		Detection of malignancy in post-treatment residual mass (level of evidence: B2) Search for recurrent disease in patients with increased serum concentrations of tumour markers at follow-up (Level of evidence: C)	Initial metastatic screen (level of evidence: C)	Diagnosis of a primary testicular tumour (standard) Differential diagnosis between a fibrous mass and a mature teratoma (standard)
Bladder cancer				No indication outside the setting of a clinical trial (standard)
Carcinoma of unknown primary site				
		Search for primary tumour in patients with metastatic cervical lymphadenopathy (level of evidence: C)		
Cancers of the thyroid				
Well-differentiated thyroid cancer	Suspicion of residual disease or recurrence when standard imaging results (including radioactive iodine scans) are not conclusive (level of evidence: B2)			Diagnosis of thyroid nodules (standard, level of evidence: B2)
Medullary cancer of the thyroid		Preoperative staging if further surgery is indicated for persistent or recurrent disease (level of evidence: B2)		

still being evaluated. The working group, therefore, decided to identify not only standards and options for protocols being evaluated but also indications that require confirmation. The standards are based on levels of evidence A or B and represent indications for which the working group considered that PET scanning is essential for the care of patients. The options are usually based on a high level of evidence (B2), whereas the indications that require confirmation are those for which published data are scarce or insufficient (levels of evidence C, D, and expert agreement). For certain indications, despite a low level of evidence, the clinical usefulness of PET scanning was considered by the working group to be high, thus the indication is classified as an option (expert agreement).

The document containing the SORs was then reviewed by a group of independent experts (see the Appendix) and after taking into consideration their comments, the guidelines were validated by the working group.

This English-language version is based on the summary version, which was itself based on the French full text version (Bourguet *et al*, 2003). The French full text and summary versions are available on the FNCLCC web site (http://www.fnclcc.fr).

A working group has been set up to monitor new scientific data on FDG-PET systematically. These clinical practice guidelines will be updated when new evidence becomes available or if there is a new consensus among the experts. In addition, patient-targeted information is being developed by the SOR SAVOIR PATIENT project, based on the specialist information (available late 2003). The SORs for use of FDG-PET scanning in oncology are summarised in Table 3.

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Appendix

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