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-[18F]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 ([11C]methionine, [11C]tyrosine and [11C]thymidine), their use has not yet been validated, and the carbon-11 label is a limiting factor for extensive routine use. Nearly 70 years after, 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
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 Nucleaire, 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 conference references 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 trials 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 |

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| Indications in French Product licence 1998 | Summary of Standards, Options and Recommendations by indication |
|------------------------------------------|---------------------------------------------------------------|
| **Cancers of the lung and pleura**       |                                                               |
| **Lung**                                 |                                                               |
| Diagnosis of malignancy in a pulmonary mass | Diagnosis of malignancy in a pulmonary mass smaller than 1 cm, suspicious of malignancy on initial imaging (level of evidence: A) |
| 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 solitary pulmonary lesion larger than 1 cm, suspicious of malignancy on initial imaging (level of evidence: A) |
| Differential diagnosis of pulmonary masses | Evaluation of response to anticancer treatment (level of evidence: D) |
| Staging and assessment of recurrent disease | Evaluation of response to anticancer treatment (level of evidence: D) |
| Assessment of locoregional involvement and metastatic screen (particularly adrenal gland) (level of evidence: A) | Evaluation of response to anticancer treatment (level of evidence: D) |
| **Pleura**                               |                                                               |
| Diagnosis of malignancy in pleural lesions (level of evidence: B2) | Diagnosis of malignancy in pleural lesions (level of evidence: B2) |
| Local and distance metastatic screening in patients with malignant pleural lesions | Local and distance metastatic screening in patients with malignant pleural lesions |
| Contribution of determination of a biopsy site (level of evidence: D) | 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) | 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) |
| Initial metastatic screen                | Initial metastatic screen in patients with melanoma at high risk of metastases (Stage III AJCC) (level of evidence: B2) |
| Susicion of operability in metastases thought to be solitary (level of evidence: B2) | Diagnosis of nodal micrometastases (level of evidence: B2) |
| **Other melanomas**                      |                                                               |
| PET scanning is not indicated outside the setting of a clinical trial (standard) | 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) | Locoregional and distant metastatic screen for patients with invasive tumours (level of evidence: B2) |
| Evaluation of response to neoadjuvant chemotherapy (level of evidence: D) | Evaluation of response to neoadjuvant chemotherapy (level of evidence: D) |
| Diagnosis of malignant breast tumours (standard, level of evidence: B2) | Diagnosis of malignant breast tumours (standard, level of evidence: B2) |
| Suspicion of local or metastatic recurrence (level of evidence: B2) | Suspicion of local or metastatic recurrence (level of evidence: B2) |
| Indications in French Product licence 1998 | Summary of Standards, Options and Recommendations by indication |
|------------------------------------------|---------------------------------------------------------------|
| **Ovarian cancer**                       | **Standard**  | **Option** | **Further trials required** | **Situations where PET scanning is not indicated** |
|                                         | **Suspicion of local or metastatic recurrence** (level of evidence: C) | Assessment of nodal involvement in patients with cancer of the cervix (level of evidence: C) | Not indicated in patients with cancer of the endometrium or vagina outside the setting of a clinical trial (standard) |
| **Uterine cancer**                       | Pretreatment evaluation of nodal and metastatic status to complement scans and endoscopic ultrasound (level of evidence: B2) | No indication outside the setting of a clinical trial (recommendation, expert agreement) |
| **Gastrointestinal cancers**             | Diagnosis of recurrence in patients with confirmed elevation of serum carcinoembryonic antigen (level of evidence: B2) | Preoperative initial staging (level of evidence: C) |
| **Cancer of the oesophagus**             | Assessment of operability of recurrent disease and metastases | Early diagnosis of a cholangiocarcinoma in patients with sclerosing cholangitis (level of evidence: C) |
| **Gastric carcinoma**                    | Pretreatment evaluation of nodal and metastatic status to complement scans and endoscopic ultrasound (level of evidence: B2) | No indication outside the setting of a clinical trial (recommendation, expert agreement) |
| **Colorectal cancer**                    | Preoperative staging of local and metastatic recurrence (level of evidence: B2) | No indication for PET scanning as first-line imaging (level of evidence: B2) |
| **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) | |
| **Neuro-endocrine tumours**              | Diagnosis and staging only in patients with a normal octreotide scan (expert agreement) | |
| **Cancer of the head and neck**          | Initial metastatic screen for patients with cancer of the pharynx | 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 |
|------------------------------------------|---------------------------------------------------------------|
| **Cancers of the head and neck** | **Standard** | **Option** | **Further trials required** | **Situations where PET scanning is not indicated** |
| 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) | Early evaluation of response to treatment (level of evidence: D) |  |  |
| Diagnosis of residual disease (level of evidence: B2) |  |  |  |  |
| **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 |
|------------------------------------------|------------------------------------------------------------------|
| **Prostate carcinoma**                   |                                                                  |
|                                          | Standard                                                        |
|                                          | Further trials required                                         |
|                                          | Situations where PET scanning is not indicated                  |
|                                          | Initial locoregional and distant metastatic screen (level of evidence: C) |
|                                          | Diagnosis of a primary prostate cancer (standard, level of evidence: B2) |
|                                          | Suspicion of local recurrence (level of evidence: C)            |
|                                          | Diagnosis of suspicious abnormalities on bone scan (level of evidence: D) |
|                                          |                                                                  |
| **Testicular cancer**                    |                                                                  |
|                                          | Standard                                                        |
|                                          | Option                                                          |
|                                          | Further trials required                                         |
|                                          | Situations where PET scanning is not indicated                  |
|                                          | Detection of malignancy in post-treatment residual mass (level of evidence: B2) |
|                                          | Initial metastatic screen (level of evidence: C)                |
|                                          | Diagnosis of a primary testicular tumour (standard)              |
|                                          | Search for recurrent disease in patients with increased serum concentrations of tumour markers at follow-up (Level of evidence: C) |
|                                          | 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).

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Appendix

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Standards, Options and Recommendations for FDP-PET scanning

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