Recommendations on the use of $^{18}$F-FDG PET/CT in Oncology. Consensus between the Brazilian Society of Cancerology and the Brazilian Society of Biology, Nuclear Medicine and Molecular Imaging*

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Abstract The authors present a list of recommendations on the utilization of $^{18}$F-FDG PET/CT in oncology for the diagnosis, staging and detection of cancer, as well as in the follow-up of the disease progression and possible recurrence. The recommendations were based on the analysis of controlled studies and a systematic review of the literature including both retrospective and prospective studies regarding the clinical usefulness and the impact of $^{18}$F-FDG PET/CT on the management of cancer patients. $^{18}$F-FDG PET/CT should be utilized as a supplement to other conventional imaging methods such as computed tomography and magnetic resonance imaging. Positive results suggesting changes in the clinical management should be confirmed by histopathological studies. $^{18}$F-FDG PET should be used in the diagnosis and appropriate clinical management of cancer involving the respiratory system, head and neck, digestive system, breast, genital organs, thyroid, central nervous system, besides melanomas, lymphomas and occult primary tumors.

Keywords: FDG-PET; Oncology; Diagnosis; Clinical indications.

INTRODUCTION

Today’s medicine poses a number of challenges to clinical practice in daily care of patients. Increasing developments and advances in imaging methods for diagnosis and follow-up of disease have resulted in a considerable increase in costs associated with the incorporation of such new technologies into the health system. Thus, one of the greatest challenges that society is facing, is solving the problem of the utilization of more accurate diagnostic methods versus the costs associated with the incorporation of such new technologies.

In the mid-eighties, positron emission tomography (PET) utilizing $^{18}$F-Labeled 2-Deoxy-2-fluoro-D-glucose($^{18}$F-FDG) was introduced as an in vivo imaging method to demonstrate the human body metabolic...
activity. Since then, countless scientific publications have reported undeniable advances in oncologic clinical practice. Malignant cells, in their greatest majority, present high glycolytic metabolism as compared with healthy tissues. Such a difference in the glucose consumption favors the performance of PET/CT studies.

Because of the proven clinical effectiveness of the method and the absence of a consensus on the use of such method in the country, the Sociedade Brasileira de Biologia, Medicina Nuclear e Imagem Molecular – SBBMN (Brazilian Society of Nuclear Medicine and Molecular Imaging) and Sociedade Brasileira de Cancerologia – SBC (Brazilian Society of Cancerology) have joined efforts with the purpose of developing a List of Recommendations on the Use of \(^{18}\)F-FDG PET/CT in Oncology in order to define clinical guidelines for an appropriate utilization of the method. Experienced professionals in the areas of nuclear medicine and oncology, representing the respective medical societies participated in the effort for development of the present recommendations. A nuclear physician indicated by the Instituto Nacional de Cancer – INCA (National Cancer Institute) has also collaborated in this effort.

As a result of such joint effort, a well established list of recommendations on the use of \(^{18}\)F-FDG PET/CT in oncology was prepared. The participating societies had a great preoccupation in defining the clinical conditions in which \(^{18}\)F-FDG PET/CT could bring real impact to patients, reducing the cost of its utilization. The professionals participating in this effort believe that such a list of recommendations will be of great relevance, considering that it will provide guidelines for the indication of \(^{18}\)F-FDG PET/CT as it is a powerful tool for an appropriate approach to patients with different types of tumors.

The product from this effort, officially publicized during a special plenary session of the Brazilian Congress of Oncology held in October/2009 in the city of Curitiba, Brazil, with the participation of the presidents of the respective societies, members of the specialty committees, and INCA representatives.

The recommendations on the use of \(^{18}\)F-FDG PET/CT in oncology were established with basis on the search for best clinical evidences in the medical literature and categorized as: appropriate (Class IA), acceptable (Class IB), auxiliary (Class IIA), still unknown (Class IIB) and unnecessary or without sufficient data available (Class III). With the purpose of establishing a list of recommendations comprising the clinical conditions in which the \(^{18}\)F-FDG PET/CT could be of real value for patients with cost reduction, it was established that classes IA and IB present a solid basis for the utilization of \(^{18}\)F-FDG PET/CT in the medical practice.

The recommendations and practical guidelines developed by professional organizations on the use of \(^{18}\)F-FDG PET and \(^{18}\)F-FDG PET/CT in oncology are summarized on the next pages. It is important to observe that other clinical situations may be added to these recommendations provided they are based upon solid clinical evidences.

**CLINICAL RECOMMENDATIONS**

I – Respiratory tract cancers

1.1 – Non-small cell lung cancer (NSCLC)

Lung cancer presents the highest worldwide incidence. According to latest estimates, 1,438,916 deaths caused by lung cancer were reported in 2008, with 52% of the cases occurring in developed countries\(^1\). The estimated number of new cases of lung cancer in Brazil in 2008 was 27,270 corresponding to an estimated risk of 19 new cases per 100 thousand men, and 10 new cases per 100 thousand women. Unless the cases of non-melanoma skin tumors are considered, lung cancer is the third most frequent type of cancer in Brazil. Probably, NSCLC is the pathology in which \(^{18}\)F-FDG PET is most utilized\(^2\) with the following indications:

- Evaluation of solitary pulmonary nodules ≥ 1.0 cm (Class IA) – It must be taken into consideration that there are some situations (inflammatory/infectious diseases, granulomatous diseases) in which false-positives results may be observed. However the negative predictive value is above 90%.
- Nodal staging of NSCLC (Class IA) – The surgical approach with curative intent is essentially restricted for patients with disease staged as I to IIIA, lymph nodes evaluation being essential. With high sensitivity and specificity (around 90%), \(^{18}\)F-FDG PET is currently the most accurate imaging method for both nodal...
and extranodal staging in patients with NSCLC.

- In the restaging of NSCLC (Class IA) – Considering the structural imaging methods limitations, $^{18}$F-FDG PET can differentiate local recurrence from fibrosis in patients after surgery, with high sensitivity and specificity (around 90%).
- In the planning of radiotherapy for NSCLC (Class IB) – $^{18}$F-FDG PET/CT is preferable to CT alone for the definition of radiotherapy fields in the presence of poststenotic atelectasis.

### 1.2 – Mesothelioma

Malignant mesothelioma is a tumor that originates in the multitone mesothelial cells of the pleura. It is the main primary malignant neoplasia of the pleura and presents a high degree of malignancy, characterized by local invasion of soft tissues such as chest walls, pulmonary parenchyma, pericardium and regional lymph nodes, besides possible metastases to lungs, liver, pancreas, kidneys, adrenals and bone marrow, significantly reducing the mean survival of patients (approximately 12 months), regardless the type of therapy adopted. Mesotheliomas present high affinity with $^{18}$F-FDG. For this reason, studies with $^{18}$F-FDG PET are indicated:

- Initial staging in cases with no evidence of metastases at CT (Class IB).
- Post-chemotherapy follow-up (Class IIA).

### 3 – Gastrointestinal tract cancers

#### 3.1 – Esophageal cancer

The World Health Organization (WHO) has estimated 562,440 deaths caused by esophageal cancer worldwide in 2008. It is estimated that esophageal cancer caused 14,530 deaths in the United States in 2008. In Brazil, according to the latest INCA’s estimates indicate 10,550 new cases of esophageal cancer in 2009. In 2005, there were 6,457 deaths related to esophageal cancer in the country. $^{18}$F-FDG PET has shown to be efficient in the following situations:

- Staging (Class IA).
- Restaging (Class IB).
- Assessment of therapeutic response, particularly in patients treated with Imatinib, in whom the metabolic response evaluated by $^{18}$F-FDG PET may anticipate by weeks the response provided by anatomical methods (Class IA).

#### 3.2 – Colorectal carcinoma

As regards incidence, colorectal cancer is the third most common cause of cancer-related deaths worldwide, causing 694,847 deaths in 2008. The estimated number of new cases of colorectal cancer in Brazil for 2008 is 12,490 cases in the male population and 14,400 cases in the female population, corresponding to an estimated risk of 13 new cases per 100 thousand men and 15 new cases per 100 thousand women. One of the first indications for $^{18}$F-FDG PET occurred in the eighties for evaluation of local recurrence in a case of colorectal cancer. With excellent sensitivity and specificity (> 90%), $^{18}$F-FDG PET is fundamental in the detection of lymph node metastases, peritoneal involvement, hepatic and pulmonary metastases. Thus, the applications of $^{18}$F-FDG PET in colorectal cancer include:

- Initial staging (Class III).
- Increased CEA (carcinoembryonic antigen) levels, without evidence of lesions by conventional imaging methods (Class IA).
- Assessment of metastases resectability (Class IA).
- Detection of recurrence in the event of inconclusive radiological findings, even in the absence of CEA levels in non-secreting tumors (Class IA).

#### 3.3 – Gastrointestinal stromal tumor (GIST)

Mesenchymal tumors are the most frequently found neoplasms in the intestinal submucosa and comprise 1% of the tumors in the gastrointestinal tract. These tumors present an unpredictable behavior, and most of times are asymptomatic, being accidentally found during endoscopic or radiological examination. The occurrence of such tumors is evenly distributed among men, women and individuals aged above 50 years. In approximately two thirds of the cases the tumor is located in the stomach. In 25% of cases, the tumor is located in the small bowel, one third of them in the duodenum. Colorectal involvement occurs in about 10% of the cases. Gastrointestinal stromal tumors also present an intense $^{18}$F-FDG uptake. Thus the main indications for $^{18}$F-FDG PET are the following:

- Staging (Class IA).
- Restaging (Class IB).
- Assessment of therapeutic response, particularly in patients treated with Imatinib, in whom the metabolic response evaluated by $^{18}$F-FDG PET may anticipate by weeks the response provided by anatomical methods (Class IA).

### 4 – Breast cancer

Breast cancer is the second most frequent type of cancer in the world and the most common among women. Every year, 22% of all new cases of tumors in women are breast cancers. In 2008, there were estimated 559,081 deaths related to breast cancer worldwide. According to the National Cancer Institute (NCI), 194,280 new cases will be diagnosed in the United States. In 2008, 49,400 new cases of breast cancer were estimated in Brazil with an estimated risk of 51 cases per 100 thousand women. The applications of $^{18}$F-FDG PET in cases of breast cancer, considering ductal carcinoma, include:

- Detection of metastatic or recurrent breast cancer in patients under clinical suspicion (Class I).
- Restaging in patients with loco-regional recurrence or metastasis (Class IA).
- Evaluation of treatment response in patients with locally advanced disease or metastatic cancer (Class IA).
- Post-treatment follow-up (Class III).

### 5 - Melanoma

Melanomas occur less frequently than other skin tumors (basal cell and squamous...
cells tumors), however their lethality is higher. The WHO estimates that annually 132,000 new cases occur worldwide, with estimated 72,901 related deaths. In the United States, 68,720 new cases are estimated for 2009, while in Brazil 5,920 new cases are estimated for the same period. The applications of PET in cases of melanoma include\(^{(6,19,20)}\):

- Staging in high-risk patients (Breslow > 1.5 mm) (Class IA).
- Restaging of high-risk patients with melanoma, or candidates for metastasectomy, except for very small lesions (< 3 mm in diameter) and central nervous system lesions (Class IA).

6 – Genital cancers

6.1 – Ovarian cancer

In 2008, 155,326 deaths related to ovarian cancer were estimated in the world. In the United States, 21,550 new cases were expected for 2009. Approximately 90% of all ovarian cancers are of epithelial type and originate from cells on the ovarian surface. The remaining 10% are of germinal-cell type and stromal tumors. The five-year survival rate is 92% for in cases of focal disease, but distant metastasis occurs in 30% of cases. Clinical applications include\(^{(21)}\):

- Restaging following first-line treatment (Class IA).
- Increased CA125 levels, with no lesion identified by conventional imaging methods (Class IB).

6.2 – Uterine cervix cancer

With approximately 500 thousand new cases/year worldwide, uterine cervix cancer is the second most common type of cancer among women, causing 286,451 deaths per year. The rate of incidence is approximately two times higher in less developed countries as compared with developed countries. In Brazil, the number of new cases of uterine cervix cancer in 2008 was 18,680, with estimated risk of 19 cases per 100 thousand women. Approximately 43% of patients diagnosed with locally advanced disease (III e IV A) are candidates for systemic treatment. The initial clinical staging of uterine cervix cancer is notoriously inaccurate. In this context, \(^{18}F\)-FDG PET has demonstrated to be extremely useful in patients with locally advanced disease, particularly through the characterization of apparently normal retroperitoneal lymph nodes at CT or magnetic resonance imaging (MRI). In the assessment of therapeutic response of patients submitted to radiotherapy and chemotherapy, \(^{18}F\)-FDG PET presents a higher accuracy than anatomic imaging methods and a complete metabolic response has a high prognostic value. Another contribution of the \(^{18}F\)-FDG PET study can be observed in the restaging of patients with suspicion of disease recurrence\(^{(21)}\). The clinical applications of \(^{18}F\)-FDG PET/CT in cases of uterine cervix cancer are the following:

- Initial staging of locally advanced disease (Class IB).
- Restaging and evaluation of therapeutic response (Class IB).
- In the suspicion of disease recurrence (Class IIA).
- In radiotherapy planning (Class IIA).

6.3 – Testicular cancer

Indicated in the evaluation of seminomas\(^{(22,23)}\):

- Restaging, in the evaluation of residual masses, after orchietomy and chemotherapy (Class IA).

7 – Thyroid cancer

Differentiated thyroid carcinomas present increased \(^{18}F\)-FDG uptake. Several studies have reported high sensitivity and specificity (75–85% and 90%, respectively) in the detection of metastasis in patients with well-differentiated thyroid carcinoma, with negative or dubious \(^{131}I\)-WBS (Class IA).

8 – Central nervous system tumors

\(^{18}F\)-FDG PET presents good results in the evaluation of recurrent high-grade primary CNS tumors. In the evaluation of gliomas recidivation, the structural images (CT and MRI) present difficulties in the differentiation between viable tumor cells, edema and fibrosis, while \(^{18}F\)-FDG PET demonstrates a significant increase in the \(^{18}F\)-FDG uptake by the recurrent high-grade tumor. Therefore, \(^{18}F\)-FDG PET was classified as Class IIA for the detection of recurrent high-grade gliomas\(^{(25,26)}\). In cases of low-grade gliomas, whose \(^{18}F\)-FDG uptake is only moderately increased, the study with \(^{18}F\)-FDG is not indicated.

9 – Lymphomas

Lymphomas are the fifth most frequent neoplasias in the USA, and comprise a heterogeneous group of lymphocytic neoplasias, basically divided into two categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). It is estimated that 74,490 cases were diagnosed in 2009, causing 359,993 deaths in 2008. With the exception of low-grade NHLs, NHLs and HLs, lymphomas present intense \(^{18}F\)-FDG uptake. In the staging, \(^{18}F\)-FDG PET presents higher sensitivity and specificity in the detection of nodal and extranodal involvement. In the restaging, particularly in the evaluation of residual masses, \(^{18}F\)-FDG...
PET presents excellent accuracy in the noninvasive characterization of lymphomas\(^{27,28}\). Particularly in Brazil, this method is highly cost-effective\(^{29}\). Thus, the clinical recommendations for the use of \(^{18}\)F-FDG PET in cases of lymphomas are the following:

- Initial staging (Class IA).
- Restaging following first-line treatment (Class IA).
- Evaluation of early response to chemotherapy (Class IIa).
- Follow-up (Class III).

### 10 – Identification of occult primary tumor

The detection of unknown primary neoplasias represents a challenge for oncologists and imagiologists. In many cases, the patients present with evident metastatic disease. The diagnosis of primary neoplasia is relevant, as it will define the type of treatment. Several reports are found in the literature about the utilization of \(^{18}\)F-FDG PET in this clinical condition\(^{30,31}\).

- Identification of occult primary tumor (Class IIA).

### REFERENCES