EDITORIAL

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Positron Emission Tomography: Is There a New Diagnostic Approach in Paediatric Oncology?

Pozytronowa tomografia emisyjna: jaka jest jej rola w postępie diagnostyki nowotworów u dzieci?

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Abstract

The prognosis to survive malignant disease in childhood and adolescence is nowadays good or excellent. The five year event free survival of children suffering from childhood neoplasia has risen from 50% to 75% in the last twenty years. One reason certainly is the evaluation and optimisation of the current standardised therapy protocols. Diagnostic modalities used in these standardised therapy protocols are ultrasound, MRI and CT as well as scintigraphy according to single suspicion and its location. However, currently used radiological imaging not always answers clinical questions about tumour viability or possible tumour relapse. The use of positron emission tomography (PET) may give an opportunity to improve this diagnostic dilemma. The FDG-PET allows whole body metabolic image staging of the entire patient in a single investigation, with the chance to detect lesion spread in the entire patient, whereas with the use of conventional imagine modalities such as CT and MRI scan atypically located lesions may remain undetected. FDG-PET scans seem to improve diagnostic staging and therapy monitoring in children and thus may lead to higher survival of the little patients. But yet only few data exist about the use of FDG-PET scans in paediatric oncology. This article gives an overview of the current use of FDG-PET in paediatric oncology with a focus on malignant lymphomas and childhood solid tumours. Furthermore, it reviews currently available literature and outlines the German multicentric PET study "PET 2003" initiated in Berlin and performed by the Department of Paediatric Oncology and the Department of Radiology, Nuclear Medicine and Radiation Oncology of Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin (**Adv Clin Exp Med 2004, 13, 6, 875–883**).

Key words: positron-emission-tomography (PET), staging, response assessment, childhood cancer, PET Studie 2003.

Introduction

Childhood malignancies are rather rare, but potentially well curable nowadays. The aged standardised incidence in the last ten years (1992–2002) of childhood neoplasia per year is 13.9 in 100.000 children under fifteen years of age. At the moment 1800 new cases of childhood malignancies are registered in Germany per year [1]. Curative rates of 75% and more are possible today for neoplasia in German and European paediatric oncology [2]. Of course, individual survival differentiates rarely and depends on the specific tumour entity a child suffers from. The survival rate of acute leukaemia, for example, is today about 88% to 90%, the five year survival rate of malignant lymphoma is close to 90%, which can be considered an excellent result [3]. Event free survival of solid tumours in childhood at all is about 65% [3]. The epidemiological data is based on cumulatively registered children under the age of fifteen in Germany in the years 1980–2000 (number of all malignancies n = = 26 609) published 2001 [1].

The main reason for the improvement of survival rates is the use of multicentric therapy optimising treatment studies which are ruled either by national or European cooperative study groups. In Germany, almost 90% of children and adolescents

suffering from childhood cancer are included in those studies and receive treatment according to a standardised protocol. At the moment, there are 27 different study groups located in the German speaking countries (Austria, Germany and Switzerland) and managed within the framework of the GPOH (Gesellschaft für pädiatrische Onkologie und Hämatologie/German Society of Paediatric Oncology and Haematology). The GPOH has developed out of the BFM – study group (Berlin, Frankfurt, Münster) founded by H. Riehm in 1976, which gained international acknowledgement due to its successful treatment concept with raising curing rates for acute lymphatic leukaemia [4] and its relapses [5].

Fundamental for the development of new therapy protocols is their redesign and optimisation according to new scientific knowledge concerning tumour biology and the mechanism of single chemotherapy components, but also the evaluation of the results which have been accomplished by former therapy protocols. New therapy study designs are aimed to improve either the percentage of survival or to reduce the side effects of the therapy [6, 7].

However, apart from serious life threatening events during cancer therapy, some patients (5% to 20%, depending on the tumour entity and on the side effects caused by radiotherapy) show secondary malignancies. After a time period of approximate 15 to 25 years secondary malignancies, which could be associated with the primary treatment, either caused as a side effect of chemotherapy or radiation, may occur [8, 9]. Therefore, it seems it is more and more important to be able to treat children suffering from childhood malignancies according to tumour adapted strategy. The future aim for treatment is therefore an individualised therapy which will be as little as possible but as much as necessary. FDG-PET, as a non invasive imagining method allows the analysis of a various number of tumour biological aspects depending on the differently used radiopharmaceuticals. The base for that is not only the demonstration of metabolic activity but also the proof of cell proliferation. For staging, restaging and therapy control of adult malignant lymphomas, FDG-PET shows a remarkable accuracy in numerous studies performed since the early 90^{s}. This accuracy and the further promising use of FDG-PET as a diagnostic tool led to the introduction of a diagnostic programme into clinical routine. At the 3rd German interdisciplinary PET conference in oncology (III. Deutsche interdisziplinäre Konsensus Konferenz 2000, Ulm), FDG-PET for staging and therapy control of adult malignant lymphomas received an evidence of "Ib" (meaning that clinical use is likely to be justified) [10]. For childhood malignancies, however, data concerning staging and therapy response for malignant lymphomas and solid tumours in childhood are still limited. This editorial reviews the current literature on FDG-PET in solid tumours and Hodgkin's disease in childhood and presents the study design of a new German multicentre study (PET Studie 2003) investigating the use of FDG-PET in common childhood tumours.

FDG-PET in the Diagnostic Staging of Malignant Lymphomas

Optimal therapy for patients with malignant lymphomas, especially Hodgkin's disease (HD), is determined by a number of prognostic factors, a major one being an accurate definition of the extent of disease (staging). Computed tomography (CT) is widely used in staging but cannot reliably evaluate normal sized lymph nodes and some extra nodal sites, e.g. liver, spleen and bone marrow. ^{18}F-FDG (^{18}Fluor-2-desoxyglucose) has been shown to concentrate preferentially in lymphoma sites (whether in nodal or extra nodal tissue) and therefore may be a useful role in staging procedures. Partridge et al. [11] from London St. Thomas' Hospital compared concurrent computerized tomography and FDG-PET in the staging of Hodgkin's disease in 44 adult patients and assessed the frequency of stage migration and possible changes in therapy related to the use of PET scanning. As a result, 18 (40.9%) patients were upstaged, nine of these by FDG-uptake in splenic or extra nodal sites not visualised by CT. Only three patients were downstaged by PET. Eleven patients (25%) had modified therapy due to FDG-PET scan findings. Significantly more sites of disease were identified by FDG-PET than by

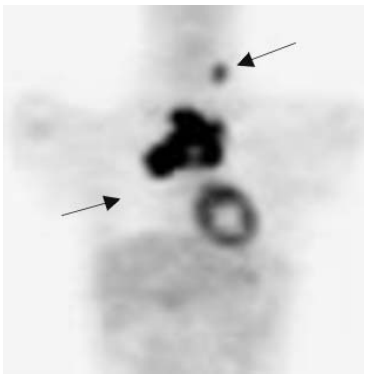

Fig. 1. Coronal slice of an 11-year-old girl suffering a relapse of a M. Hodgkin with cervical and mediastinal manifestation at restaging

CT resulting in staging changes and a modification of therapy in 25% of all patients. These are important implications not only for current patient management but also for the design of future clinical trials [11].

A various number of papers describing the diagnostic role of FDG-PET in primary staging and the follow-up assessment in adult oncology for malignant lymphomas (Hodgkin and Non-Hodgkin-Disease) have been published lately. Gambhir et al. [12] summarized all malignant lymphoma studies (n = 33) concerning the use and value of FDG-PET for initial lymphoma staging, published between 1997 and 2002 (literature research). 2227 patients suffering from Hodgkin or Non-Hodgkin Lymphoma were described. The cumulative sensitivity for FDG-PET was 90% and for conventional imaging modalities CIM (MRI, CT and nuclear medicine imaging modalities such like bone scintigraphy) 81%, the specificity for FDG-PET has been described to be about 93% while 84% for CIM. The summary of evidence for FDG-PET in malignant lymphoma is 1) For staging: an estimated 21% change was noted in management effect, based on 407 patient studies, 2) For recurrence: an estimated 10% change was noted in management effect, based on 158 patient studies.

Buchmann et al. [13], for example, published in 2001 an investigation of 52 malignant lymphoma patients with 1297 different lymph node lesions where significant differences between the sensitivity and specificity according to the tumours location, as shown in Table 1, were assessed. The authors evaluated prospectively the clinical value of FDG-PET in the detection and staging of malignant lymphoma compared with computed tomography (CT) and bone marrow biopsy (BMB). In these analyses, FDG-PET was significantly superior to CT ($P < 0.05$), except in infradiaphragmatic regions, in which the two methods produced equivalent results. Thus, FDG-PET is very accurate in the staging of malignant lymphomas. Compared with conventional modalities (CT and BMB), FDG-PET was significantly superior and led to changes in the therapy regimen for 8% of patients.

Table 1. Comparison of sensitivity and specificity for PET and CT in the initial staging of malignant lymphomas

	Sensitivity		Specificity	
Manifestation (in 1297 regions)	PET (%)	CT (%)	PET (%)	CT (%)
Extra nodal	99.2	83.2	100	99.8
Nodal	100	80.8	99.4	99.4
Supradiaphragmal	99.1	80.3	99.8	97.9
Infradiaphragmal	100	91.2	99.8	99.8

Not all of the above mentioned adult studies underline the promising idea of a general use of FGD-PET for staging, restaging or for follow-up-assessment for malignant lymphomas. Depending on the tumour entity (Hodgkin or Non-Hodgkin), the histological classification and its subtypes, the localisation of the lesion, the difference between primary lesion or metastases and the time of investigation (staging, restaging or therapy control) one is able to find very different and contradictory statements concerning the sensitivity and the specificity of FDG-PET as a diagnostic method [14–16]. There are similar descriptions explaining the role of FDG-PET in follow-up-assessment and the evaluation of post-treatment residual mass [17–22]. All the examples show that it is not possible to give a general statement concerning sensitivity and specificity of FDG-PET. Sensitivity and specificity vary from the anatomic region, from the investigated location and the time of investigation [12].

Opposed to the experience in adult lymphoma patients, knowledge of FDG-PET imaging Hodgkin's lymphoma in children is still limited yet. In the first study investigated by Montravers et al. from Hôpital d'enfant Armand-Trousseau, Paris, four out of seven children suffering from Hodgkin's lymphoma received an upgrade to a higher stage, but in only one case, therapy has been modified due to alterations in staging [15].

In Germany first consequences have already taken place in the new therapy protocol (GPOH HD 2003) treating children suffering from Morbus Hodgkin. The new Hodgkin study concept is to

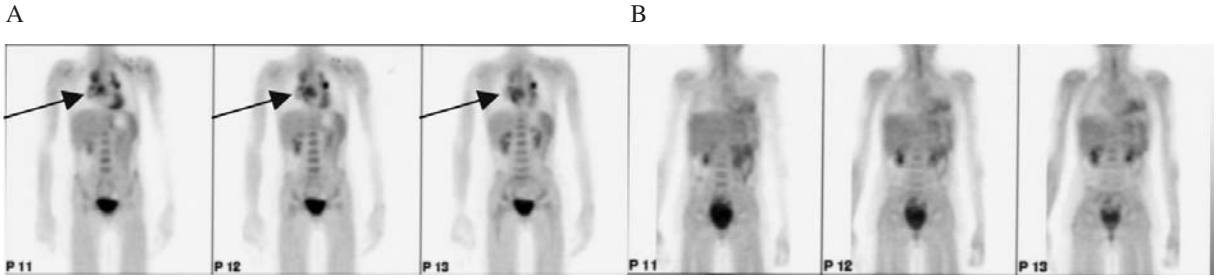

Fig. 2. M. Hodgkin Stage III B, ♀, 16 years of age. The above coronal projection slice shows the mediastinal expansion of the tumour before (A) and after two chemotherapy cycles of "OPPA" (B)

evaluate if radiotherapy after the two initial cycles of chemotherapy (2 x OEPA (for boys)/ 2 x OPPA (for girls)) can be omitted in patients of "group 1" in the treatment protocol with a negative FDG-PET scan and lead in conclusion to the same event-free survival. Additionally FDG-PET is going to be evaluated in the treatment "groups 2 and 3" to show if it could be evaluated as a predictive factor for early response in chemotherapy [23].

FDG-PET in Staging of Solid Tumours

First examinations of children and adolescents with malignant bone tumours showed that FDG-PET is also very well suited for the assessment of therapy response and for restaging for these tumour entities. The assessment of therapy response was investigated by Schulte et al. [24] and showed that response of preoperative chemotherapy controlled by FDG-PET correlated closely with the results of histological examination of the resected tumour tissue. For the detection of osseous metastases of Ewing's sarcoma, FDG-PET also showed advantages when compared to Tc-99m-diphosphonate scintigraphy [25, 26].

Franzius et al. [27] evaluated the potential of positron emission tomography using ^{18}F-fluoro-2--deoxy-D-glucose for the assessment of chemotherapy response of primary osseous tumours compared with the degree of necrosis determined histologically. Seventeen patients with primary bone tumours (11 osteosarcomas, 6 Ewing's sarcomas) were examined by FDG-PET and planar bone scintigraphy before neoadjuvant chemotherapy and before surgery. Tumour response was classified histologically according to Salzer-Kuntschik (grades I–II: good response; grades IV–VI: poor response). The conclusion of this examination is that FDG-PET seems to be a promising tool for the evaluation of response to chemotherapy in primary osseous tumours. In this preliminary study, FDG-PET was superior to planar bone scintigraphy [27].

Ewing's sarcoma patients with significantly proven poorer prognosis are those with detected metastases at the initial diagnosis as well as not responding to initial therapy or those who develop a tumour relapse [28]. Survival depends on the initial staging and its resulting stratified branch of therapy. Staging procedures as presently performed by conventional radiological imaging (MRI and CT scans as well as bone scintigraphy) identify 20% to 25% of the cases with metastatic lesions at the time of initial diagnosis. In the recently completed US CCG 7881 study, patients with bone or bone marrow (BM) metastases at the time of diagnosis had a 3-year disease-free survival of less than 15% compared to 22% for any metastatic site [CCG 7951 treatment manual, 1996]. Kushner reported that patients with primary pulmonary metastases fared better than patients with primary bone marrow involvement [29]. As shown in the Figure 3, the EFS for the patients suffering from an Ewing's sarcoma depends on metastases and its location. Yet unknown are the numbers of not detected metastatic lesions because of an insufficient initial staging.

As the following clinical example of a 13-year-old Caucasian girl shows, conventional imaging procedures (MRI and CT scan) performed according to the standards of therapy optimising protocol are able to detect metastatic lesions: During initial staging with MRI and CT scan extra located lung metastases has been seen next to primary Ewing's sarcoma tumour in the right humerus as shown in Figure 4 as well as by FDG-PET. As similar cases

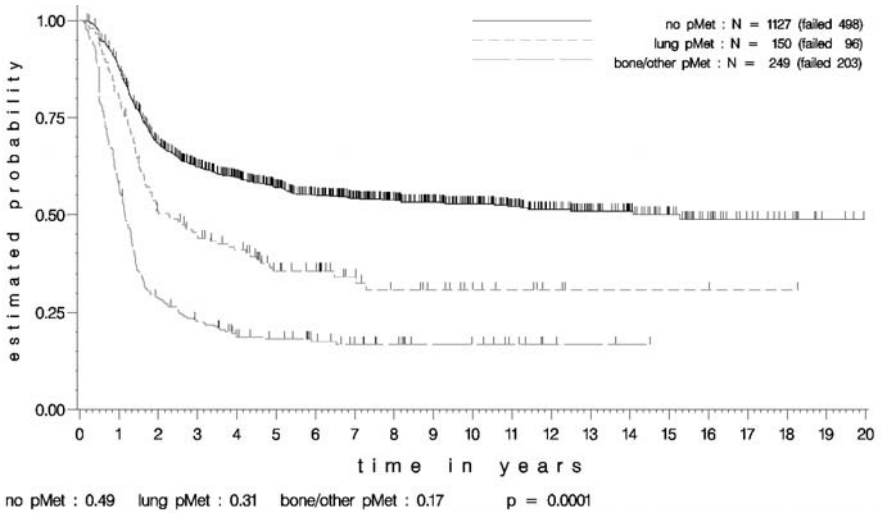

Fig. 3. EFS according to presence and sites of primary metastases (Data: 05/99), (Figure by EURO-E.W.I.N.G. 99-Study Group)

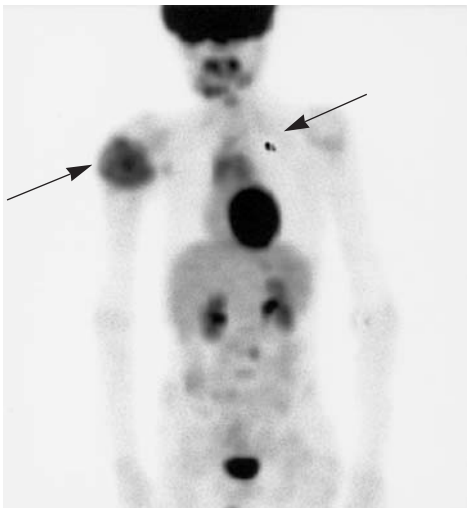

Fig. 4. Coronal slice of a 13-year-old girl suffering from Ewing sarcoma. The primary tumour is located as shown in the right humerus. Metastases are located in the upper part of the left lung

show, FDG-PET shows not only in one entire investigation next to the primary tumour, lung metastases as sensitive as CMI, but in addition it is also possible to detect unexpectedly bone marrow lesions. In another clinical case of a 16-year-old Turkish girl, additional bone marrow lesions in the left distal femoral bone were not detected by conventional radiological imaging methods but by FDG-PET only. After a biopsy of these foci took place an additional lesion could be classified. Due to this additional information the patient was switched into another branch of EURO-E.W.I.N.G. 99-protocol and is successfully treated in risk group R3 by now.

Additionally performed FDG-PET scans could give information about chemotherapy response of a specific tumour and it might indicate whether radiotherapy is necessary or not. Furthermore, in patients with an advanced stage of a malignant solid tumour disease, there will be the question if a sequential FDG-PET examination during the chemotherapy protocol is able to differentiate sick children into or within a single subgroup with a rather good or poor prognosis.

At the moment PET scans with ^{18}F-FDG are performed only if diagnostic or clinical questions are unable to be answered clearly by the standard diagnostic procedures defined by the therapy optimising studies or if the FDG-PET scan could give additionally promising information of the tumours dignity, its localisation and a probably metastasising or tumour recurrence [30]. Emphasising the above mentioned importance of initial staging, the correct stratification, the adequate therapy branch do have an important influence on the outcome and survival of most of the typical solid tumours in childhood (like neuroblastoma, nephroblastoma, osteosarcoma and Ewing's sarcomas). In summary presented clinical investigations show the high potential of FDG-PET for the detection of solid malignant tumours and malignant lymphomas in childhood. The possibility to characterise tumour tissue according to its metabolism seems to be the main advantage over conventional radiological imagines. Furthermore, the authors believe that FDG-PET is a useful tool for response assessment of therapy and for the differentiation between pretreated tissue cured by local therapy like radiotherapy or operation and viable tumour tissue. This is an important aspect where morphological imaging can give either no or inconclusive information.

FDG-PET Methodology

Positron-Emission-Tomography (PET) with ^{18}F-FDG is a functional nuclear medicine imaging procedure based on the imaging glucose metabolism *in vivo*. Thereby it can assess – in contrast to conventional radiological methods like MRI or CT – the metabolic activity and the viability of malignant tumours.

The standard FDG-PET protocol consisted of an 8-h fasting period. This is followed by confirmatory blood glucose testing to ensure that values are within the normal range (< 110 mg/dl). The intravenous injection of FDG is proportional to the child's body weight as shown in Table 2.

A short time (5 to 10 min) after the ^{18}F-FDG application 0.5 mg Furosemid per kg body weight with a maximum doses of 20 mg is given intravenously to gain a forced diuresis in order to lower

Table 2. Amount of radioactivity of 2-deoxy-2-^{18}fluoro-D-glucose (^{18}F-FDG-PET) according to the body weight per kg

3 kg	37 MBq	14 kg	133 MBq	26 kg	207 MBq	38 kg	270 MBq	50 kg	325 MBq
4 kg	52 MBq	16 kg	148 MBq	28 kg	215 MBq	40 kg	280 MBq	52–54 kg	333 MBq
6 kg	70 MBq	18 kg	163 MBq	30 kg	230 MBq	42 kg	290 MBq	56–58 kg	340 MBq
8 kg	85 MBq	20 kg	170 MBq	32 kg	240 MBq	44 kg	296 MBq	60–62 kg	355 MBq
10 kg	100 MBq	22 kg	185 MBq	34 kg	252 MBq	46 kg	303 MBq	64–66 kg	363 MBq
12 kg	118 MBq	24 kg	196 MBq	36 kg	263 MBq	48 kg	315 MBq	68 kg	366 MBq

≥ 68 kg KG = 370 MBq.

radiation exposure. After an uptake period of 60 to 90 minutes, attenuation-corrected whole-body PET scans (upper legs to skull) in two-dimensional mode are acquired using a full-ring PET scanner axial field of 8 min emission time and 4 min transmission per bed position. Normally 5 to 7 bed positions are needed for a whole body scan, taking 10 to 12 minutes for each bed position. Data reconstruction is performed with specific software using iterative data reconstruction (OSEM algorithm). Coronal, transaxial as well as sagittal slices are reconstructed from the data set. Images are interpreted by two experienced nuclear medicine investigators blinded to each other and compared to the results of the conventional imaging methods, histopathology and the clinical data.

FDG-PET Staging and Response Criteria

All primary PET scans are going to be performed within 1 week prior to the initiation of neoadjuvant chemotherapy treatment. For the time after chemotherapy, the use of FDG-PET seems to be critical. The European Organization for Research and Treatment of Cancer (EORTC) [31] recommends that PET scans should not be performed within a time period of one until two weeks after chemotherapy courses have been performed.

Therapy response is evaluated by comparing pre- with post-treatment maximal standard uptake values (SUV_{max}). SUV will be corrected to body surface area [32]. The maximal glucose uptake in the lesion prior to therapy is measured by using standardised circular ROIs (1.5 cm in diameter). Tumour mass will be identified by areas of pathologically increased glucose uptake on transaxial slices. Within these areas, the ROI is centred on the area of maximal metabolic activity on every transaxial slice showing tumour-related increased uptake. ROIs are placed in identical positions on post-therapeutic scans using predefined anatomical landmarks. SUVs are calculated by using average activity values in the ROI. SUV_{max} is defined as the ROI with the highest value in each study. According to the criteria published by the European Organization for Research and Treatment of Cancer (EORTC) [31], a change in SUV_{max} is chosen as the indicator for therapeutic response.

A third FDG-PET examination at the end of all chemo- or local therapy (tumour extirpation or radiation) will be performed as final examination in order to identify and/or exclude residues or tumour relapses. For children suffering from a solid tumour the final PET scan will be done close to the end of chemotherapy but for those patients suffering from a malignant lymphoma the authors are planning to perform the last FDG-PET between 4 and 6 weeks after the end of chemotherapy before radiation starts.

Nevertheless, in lymphomas for instance a rapid decrease of FDG accumulation in the tumour seems to be an important indicator of a good response to chemotherapy. Different studies where FDG-PET has been performed between the applications of chemotherapy courses have shown two important matters: 1) early response as an evident sign in a significant decrease of the standardized uptake value (SUV) within 7 days [32] or an inconspicuous PET scan after a certain amount of chemotherapy courses correlates with a very good prognosis [33] and 2) positive persistent PET findings correlate with a high relapse probability and a poor prognosis for the patient [33].

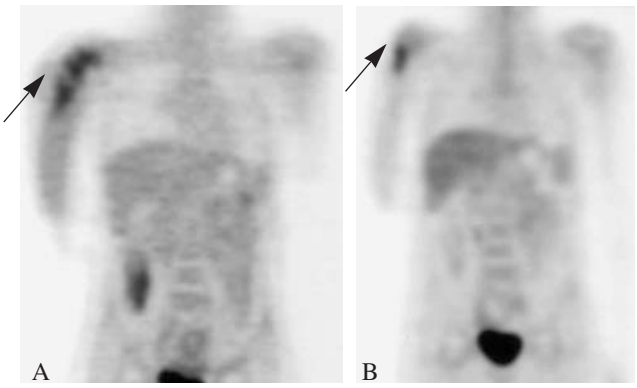

Fig. 5. Coronal slice of a 14-year-old boy suffering from an osteosarcoma of the right proximal humerus with a SUV_{max} of 12.8 at the initial diagnosis (A), restaging after 3 cycles of polychemotherapy according to COSS 96-protocol with a SUV_{max} of 4.3 (B)

PET Study 2003

As many questions concerning the general use of FDG-PET in paediatric oncology remain unanswered, the authors decided to start a multicentre, prospective study to evaluate FDG-PET as a diagnostic tool in childhood cancer. The authors first concentrate on a selected numbers of common solid childhood tumours and the – in adult medicine already well investigated – malignant lymphomas but for the case of success also plan to include other entities as well.

The intention of PET 2003 study group is to examine children and youth, who completed their first year of life, suffering from a solid malignant tumour or a malignant lymphoma with FDG-PET. Tumour response to chemotherapy should be assessed as well as the existence of relapses and/or residues after performance of the treatment. The FDG-PET results will be compared with the

appropriate radiological procedures (MRI and CT) of the tumour treatment protocols, the histopathology of resected tumours and the clinical data. Furthermore, the following hypothesis will be evaluated:

1. There exists a significant influence of FDG-PET for initial staging and restaging comparable to conventional radiological imagines (CIM).

2. A response to chemotherapy can be assessed more precisely by FDG-PET than by conventional radiological procedures.

3. The discrepancy between CIM and FDG-PET is significant and it is possible to identify and/or exclude residues or tumour relapses.

4. FDG-PET can be used as prognosis factor to separate patients into subgroups with excellent or poorer prognosis.

5. FDG-PET as a response control for malignant lymphomas is able to lower radiation or to prevent radiation at all.

In PET Study 2003 the FDG-PET investigation is, as well planned for initial staging, restaging during therapy and finally as a terminate investigation after the whole therapy. The restaging examinations will be done 2 weeks after the completion of the initial chemotherapy circles (according to each single multicentric therapy optimising treatment protocol) but before local therapy, like tumour extirpation or radiation is taking place.

The PET 2003 study established at the Campus Virchow Klinikum of Charité – Universitätsmedizin Berlin, will at least investigate 100 children, aged from 2 to 18 in cooperation of a multicentre-study design with the children's hospital in Charité-Universitätsmedizin Berlin, Cottbus, Düsseldorf, Greifswald, Leipzig, Rostock, Schwerin and Wroclaw. All patients suffering from initial or a relapse of neuroblastoma, nephroblastoma, soft tissue sarcoma, osteosarcoma, Ewing's sarcoma or a malignant lymphoma are supposed to be included in the study. The examination is ethically based on the Declaration of Helsinki and the principles of "good clinical practice". The study protocol is approved by the human studies and ethics committee of the Charité – Universitätsmedizin, Berlin.

Conclusion

FDG-PET seems to improve the diagnostic staging in childhood disease and therefore it may lead to higher survival rate of the little patients by a better and sufficient staging and a better and differentiated therapy control. FDG-PET allows metabolic imaging of the entire body in single investigation ("one shot image"), with the chance to detect lesions spread all over the body, whereas conventional radiological methods such as CT and MRI may not notice atypically located lesions. The PET technology represents the expanding knowledge of the pathology of paediatric disease, especially for paediatric oncological diseases.

Pursuing the PET technology with the development of new tracers in adult oncology, it seems that paediatric oncology patient management will profit in future in the same way adult patient already does. But by now only few data exist about the use of PET in paediatric oncology. However the authors anticipate that its use in paediatric oncology will increase in future.

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