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94 Abstract

The aim of the study was to assess sensitivity and specificity of FDG-PET/CT in different forms of childhood cancer. We retrospectively evaluated the results dedicated of 162 FDG-PET/CT examinations of 86 children treated with: Hodgkin lymphoma (HL; *n*=31), non-Hodgkin lymphoma (NHL; *n*=30) and other high grade solid tumors (*n*=25). Patients were admitted and treated in two departments of pediatric hematology and oncology in Hungary. FDG-PET/CT was performed for staging (*n*=25) and for posttreatment evaluation (*n*=137). Imaging was performed in three

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RESEARCH

Value of FDG-PET/CT Examinations in Different Cancers of Children, Focusing on Lymphomas

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Abstract The aim of the study was to assess sensitivity and specificity of FDG-PET/CT in different forms of childhood cancer. We retrospectively evaluated the results dedicated of 162 FDG-PET/CT examinations of 86 children treated with: Hodgkin lymphoma (HL; n=31), non-Hodgkin lymphoma (NHL; n=30) and other high grade solid tumors (n=25). Patients were admitted and treated in two departments of pediatric hematology and oncology in Hungary. FDG-PET/CT was performed for staging (n=25) and for posttreatment evaluation (n=137). Imaging was performed in three FDG-PET/CT Laboratories, using dedicated PET/CT scanners. False positive results were defined as resolution or absence of disease progression over at least 1 year on FDG-PET/CT scans without any intervention. In some cases histopathological evaluation of suspicious lesions was performed. Fals negative results were defined as negative FDG-PET/CT results in case of active malignancy. Positive predictive values (PPV) and negative predictive values (NPV) were calculated. NPV was 100 %. The highest PPV was observed in high grade solid tumors (81 %), followed by HL (65 %) and NHL (61 %). There was a major difference of PPV in different histological types of HL (50 % in HL of mixed-cellularity subtype, 90 % in nodular sclerosing, and 100 % in lymphocyte-rich and lymphocyte depleted HL). We treated one patient with nodular lymphocyte predominant HL, who had 5 false positive FDG-PET/CT results. PPV of T- and B-lineage NHL were similar (60 % and 62 %, respectively). We observed an interesting difference of PPV in different stages of HL and NHL. In HL PPV was higher in early than in advanced disease forms: 66 % in stage II HL and 60 % in stage III HL), whereas there was an inverse relationship between PPV and disease stages in NHL 0 % in stage I and II patients, 67 % in stage III and 100 % in stage IV patients). PPV was lower in males (54 %) than in females (65 %). PPV were 64 % vs. 58 % in patients under vs. over 10 years of age. Negative FDG-PET/CT results during follow-up reliably predict the absence of malignancy. Positive FDG-PET/CT scan results in general have a low PPV. The relatively high PPV in patients with histologically proven high grade solid tumors, advanced stages of NHL and with nodular sclerosing, lymphocyte-rich and lymphocyte depleted subtypes of HL warrant a confirmation by biopsy, whereas the watch-and-wait approach can be used in other forms of childhood cancer patients with a positive FDG-PET/CT result in course of follow-up examinations.

Keywords Childhood cancers · FDG-PET/CT · Hodgkin · Non-Hodgkin lymphoma · High grade solid tumors

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Introduction

Accurate disease staging and an objective assessment of response to therapy in childhood cancer is critically important in

course of the stratification of patients into prognostic risk groups and in defining risk-tailored therapy.

Positron emission tomography (PET) using 2-deoxy-2-(^{18}F) fluoro-D-glucose (FDG) tracer is considered more sensitive and specific than standard conventional imaging modalities as it exploits a distinctive biochemical feature of cancer cells, i.e. increased glucose uptake and elevated glycolysis [1]. Nowadays the state of the art method for PET investigations is PET/CT fusion imaging, a combined method in which PET is performed in parallel with computer tomography (CT) scan. FDG-PET/CT provides both matching metabolic and anatomical images, allowing the precise localization and differentiation of physiological and pathological foci characterized by an increased FDG uptake [2]. In contrast to extensive data in adults, there have been only a few studies in children, addressing usually one type of cancer, mostly lymphoma [3–17]. There is a growing consensus that FDG-PET/CT fusion imagining will play an important role in childhood and adolescent oncology similar to adult patients. Furthermore, the introduction of PET/CT scanners with increased sensitivity allow the reduction of both acquisition time and total administered dose decreasing radiation burden and eliminating movement artifacts. These achievements are highly desirable in the pediatric population [5].

Our retrospective study attempted to assess the value of FDG-PET/CT in the staging and in course of follow-up investigations of children and adolescent patients with lymphomas and in a course of small pilot study various forms of childhood cancer.

Materials and Methods

Patients

Evaluating 162 FDG-PET/CT examinations, we studied the clinical outcomes and results of 86 children (male:female = 55:31 age: 11.7±4.2 years, follow up time: 31±17 months, 3–100 months) treated with different forms of cancer: 31 Hodgkin lymphoma (HL), 30 non-Hodgkin lymphoma (NHL), and 25 with other histologically proven high grade solid tumors) between August 1, 2005 and March 15, 2010 at the Department of Pediatric Hematology-Oncology, Institute of Pediatrics, Medical and Health Science Center, University of Debrecen, and the 2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary (Table 1). Every primary tumor was proven by histopathologic examination at the time of diagnosis. Histopathological diagnosis was established by hematoxylin-eosin staining and immunohistochemistry according to standard methods. Staging was performed according to generally accepted definitions. FDG-PET/CT was performed for staging (n=25) and for posttreatment evaluation or for detection of disease recurrence (n=137).

Table 1 Disease distribution of high grade patients

Diagnosis	Number
Hodgkin lymphoma	31
Non-Hodgkin lyphoma	30
High grade bone tumors (Ewing/osteosarcoma)	16 (4/12)
High grade brain tumors	5
High grade PNET/Neuroblastoma	3
High grade germ cell tumor	1
Total	86

PNET primitive neuroectodermal tumor

Imaging

All studies were performed on dedicated PET/CT scanners. Patients were fasting for at least 6 h before administration of FDG to decrease physiologic glucose levels and to reduce serum insulin levels to near-basal levels. They were allowed to drink water. 3 MBq/kg FDG was injected intravenously 45–60 min prior to image acquisition and patients were asked to void urine immediately before acquisition. We used an optimized low-dose CT protocol in children to decrease the radiation dose, which was achieved by lowering the tube voltage and current. In addition, online dose modulation systems were used to lower radiation burden. FDG-PET/CT scans were displayed and reconstructed in the transaxial, coronal and sagittal planes. Sites of abnormal uptake were defined as focal accumulations greater than mediastinal blood pool uptake in lymphatic regions or focal uptake in extranodal localizations with or without morphologic abnormality. Images were analyzed by two physicians (radiologist and nuclear physician).

Any sites of abnormal uptake on FDG-PET/CT suspicious for a relapsed or a metastatic disease were evaluated by histopathology or by repeated imaging and serial clinical follow-up investigations for at least 12 months after completion of the FDG-PET/CT imaging study. False positive results were defined as resolution or absence of disease progression over at least 1 year on FDG-PET/CT scans without any intervention. In some cases histopathological evaluation of suspicious lesions was performed. False negative results were defined as negative FDG-PET/CT result in case of an active malignancy as proved by other methods. An increased FDG uptake on PET/CT due to metabolically active brown fat in typical locations and focal muscle uptake were not considered as positive lesions.

Positive predictive value (PPV) was defined as the proportion of patients who had positive test results and confirmed by either histopathological or clinical diagnosis as defined above. PPV was calculated as: true positive/true positive + false positive results. Negative predictive value was defined as the proportion of patients who had negative imaging results

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confirmed by clinical diagnosis as defined above. NPV was calculated according to true negative/true negative + false negative results. As a further step we calculated PPV and NPV of FDG-PET/CT for different tumor types, histological subtypes, stages, age groups and gender groups.

Results

A total of 162 FDG-PET/CT studies were performed in 86 children and adolescents during the time period of the study. Some of the patients were subjected to imaging several times (mean 2 FDG-PET/CT scans/patient, range 1–6 FDG-PET/CT scans/patient). All negative FDG-PET/CT results proved true negative ones, because all patients with a complete metabolic remission in FDG-PET/CT were in remission as confirmed by serial clinical investigations; therefore, NPV of PET/CT was 100 %.

We calculated PPV in different clinical situations. PPV was 61 % in NHL, 65 % in HL and 81 % in histologically proven high grade solid tumor patients (Table 2). PPV were different in different histological types of HL: mixed-cellularity subtype had much lower PPV (50 %) than nodular sclerosing (90 %), lymphocyte-rich and lymphocyte depleted subtype (100 %). We treated one patient with nodular lymphocyte predominant HL (NLPHL), who had 5 false positive FDG-PET/CT results. In NHL PPV of T cell- and B cell-lineage lesions was similar (60 % and 62 %, respectively). We have observed an interesting difference of PPV in different stages of HL and NHL. In HL PPV was higher in early than in advanced disease forms (66 % in stage II HL and 60 % in stage III HL), whereas there was an inverse relationship between PPV and disease stages in NHL (0 % in stage I and II lesions, 67 % in stage III and 100 % in stage IV lesions). PPV was lower in males (54 %) than in females (65 %). PPV were 64 % vs. 58 % in patients under vs. over 10 years of age. All positive FDG-PET/CT results in Ewing sarcoma and germ cell tumor patients were true positive ones.

In primitive neuroectodermal tumor (PNET) patients we found 2 true negative results and in neuroblastoma a true negative and a true positive result/lesions were negative on meta-iodobenzylguanidine (MIBG) scans in both cases/. In high grade brain tumor patients we found 1 true positive and 4 true negative result. PPV was 63 % (5/8) in osteosarcoma patients.

Twenty three lesions turned out to be false positive ones based on histopathology or clinical follow up studies. The majority of these comprised lymph nodes of different regions of lymphoma patients: submandibular/neck (n=3), inguinal (n=4), mediastinal (n=4), retroperitoneal (n=1) lymph nodes and tonsilla (n=1). Focal bowel uptake was observed in 4 lymphoma patients, and one pulmonary lesion proved false positive. In one patient FDG-PET/CT misclassified thymus. In one patient more than one regions were false positive. In osteosarcoma patients suspicious lesions in the skeletal system, both at the primary tumor site (n=2) and at a new site (1), and in the lungs were false positive findings.

Table 2 Positive predictive value (PPV) in different histologic types of high grade tumors

Diagnosis	PPV	PPV
Hodgkin MC	3/6	50 %
NS	9/10	90 %
lymphocyte-rich and lymphocyte depleted	5/5	100 %
Hodgkin stage II	3/5	60 %
stage III	4/6	66 %
Non-Hodgkin T cell	3/5	60 %
B cell	8/13	62 %
Non-Hodgkin: stage I–II	0/4	0 %
stage III	6/9	67 %
stage IV	5/5	100 %
High grade osteosarcoma	5/8	63 %
High grade Ewing sarcoma	5/5	100 %
High grade brain tumors (medulloblastoma, corpus pineale germinoma)	2/2	100 %
High grade PNET/Neuroblastoma	1/1	100 %
High grade germ cell tumor	1/1	100 %

MC mixed cell, *NS* nodular sclerosing, *PNET* primitive neuroectodermal tumor

Discussion

Apart from several case reports and review articles about the application of FDG-PET and PET/CT in pediatric oncology few studies describe systematic evaluations of the diagnostic efficacy of FDG-PET/CT as a new imagining modality for detection of primary malignancies and their metastases [8–13]. The low incidence and the broad range of cancer in children and adolescents, as well as the relatively conservative implementation of FDG-PET/CT in pediatric patients have made it difficult to collect comprehensive PET/CT data on pediatric malignancies. Most of the previously published studies have focused on childhood lymphomas [2, 14]. Miller and colleagues recently reported a high NPV of FDG-PET/CT for the therapy response of lymphomas in pediatric patients [14]. Our data with a 100 % NPV confirm their findings and extend to other forms of childhood cancers, like PNET/neuroblastoma, osteosarcoma and high grade brain tumors. A positive result on FDG-PET/CT imaging however, requires a thorough consideration. FDG can accumulate in brown fat, lymphoid tissues, glandular tissues, activated muscles, in the gastrointestinal and genitourinary tracts. False positive FDG-PET and PET/CT scans are usually associated

with infection or inflammation. Sometimes there is no known clinical correlation and the area of positivity resolves spontaneously. However, clinical history, examination and the pattern of FDG uptake may aid in differentiating inflammatory from malignant PET positive foci. We have found a 61–81 % PPV in different forms of currently analyzed childhood cancers (Table 2.). The low PPV in mixed-cellularity subtype of HL, as compared to the nodular sclerosing, lymphocyte-rich and lymphocyte depleted subtypes was an unexpected new finding of this study which needs to be confirmed within the frames of prospective, multicentric trials involving a higher number of patients. It was also a surprising finding, that in a patient of a rare, but good prognostic group (NLPHL) we found 5 false positive results. Similarly, the different association between PPV and disease stages in HL vs. NHL requires further investigations. In adult NHL patients Schöder et al. found different FDG uptake in indolent and aggressive forms of the disease, but similar data are not available in childhood [15].

Our investigations involved pediatric patients with different solid tumors in addition to children with HL and NHL during a small pilot study. Only a few publications were dedicated to FDG-PET and PET CT investigations in childhood sarcomas [12, 16]. Mody et al. found a higher PPV and a lower NPV than we did in our sarcoma patients. The difference may be caused by the higher number of sarcoma patients observed in their study [16].

The role of FDG-PET/CT in brain tumors is controversial, because of the high basal glucose uptake of normal brain tissues. In this group of patients, methionine PET is the preferred form of functional imaging; however, FDG PET/CT can be useful in detecting metastases or relapses in high grade CNS tumors [17]. Use of FDG-PET/CT in brain tumors has helped to distinguish viable, residual, or recurrent tumor from post-therapeutic changes and necrosis. High-grade tumors show high uptake of FDG at diagnosis. FDG-PET/CT results may also not accurately correlate with tumor progression after intensive radiation therapy.

Lack of MIBG positivity may characterize some patients with neuroblastoma [18]. In these cases tumor cells may uptake alternative tracers, like FDG. In our cohort FDG-PET/CT was able to detect and to exclude residual tumor in two cases of MIBG negative neuroblastoma [19].

Conclusion

Our study showed that negative FDG-PET/CT scan results provide a strong evidence of the absence of active disease in children and adolescents with different forms of cancer. Positive FDG-PET/CT scan results in general have a low PPV, indicating that results should be interpreted with caution. The relatively high PPV in patients with advanced stages of NHL and with nodular sclerosing, lymphocyte-rich and lymphocyte depleted subtypes of HL and other high grade solid tumors warrant a confirmation by biopsy, whereas the watch-and-wait approach can be used in other forms of childhood cancer patients with a positive FDG-PET/CT result in course of follow-up examinations. FDG-PET/CT can afford very valuable information above standard imaging techniques in MIBG negative neuroblastoma and high grade brain tumor patients to detect or exclude residual tumor, but further evaluations are necessary to determine the prognostic role and usefulness of FDG-PET/CT as compared to conventional imaging modalities in the evaluation of different types of pediatric malignancies.

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