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Prognostic value of FDG-PET in Hodgkin lymphoma for posttreatment evaluation. Long term follow-up results.

Z. MOLNAR[1], Z. SIMON[2], Z. BORBENYI[3], B. DEAK[1], L. GALUSKA[4], K. KERESZTES[2], Z. MILTENYI[2], I. MARTON[3], A. ROSTA[1], T. SCHNEIDER[1], L. TRON[4], E. VARADY[1], A. ILLES[2]

[1]National Institute of Oncology, Budapest, Hungary, [2]Third Department of Institute for Internal Medicine, [4]PET center, Medical and Health Sciences Center, University of Debrecen, Hungary , e-mail: zsocogo@gmail.com, [3]Second Department of Medicine and Cardiology Center, Faculty of Medicine, University of Szeged, Hungary.

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Determining the viability of residual tumor masses is a great challenge after primary treatment of Hodgkin lymphoma. FDG-PET may play a crucial role in this procedure .

In this study, files of 128 Hodgkin lymphoma patients were reviewed, who were treated in three Hungarian hematology centers between January 1995 and February 2005. CT scan showed residual tumor mass by all of them. Their median follow-up was 75.5 months from PET examination. The number of true-positive, true-negative, false-positive, false-negative subjects were 29, 83, 10, 6, respectively. Sensitivity of post-treatment FDG-PET was 83 %, specificity 93 %, positive predictive value 74 %, negative predictive value 93 %, and accuracy 88 %.

The difference between the event free survival of PET positive and negative cases is highly significant (p=0.0000), according to the Mantel-Cox test. Our results in the largest cohort of patients, in accordance with literature, clearly indicates that patients with negative FDG-PET results are unlikely to progress or relapse during the longest follow-up.

Key words: FDG-PET, Hodgkin lymphoma, prognosis, long-term follow up

In the past few decades Hodgkin lymphoma (HL) has become a highly curable malignant disease. The response and survival rates have increased as a result of using modern polychemotherapy and irradiation. The problem of residual mass after induction therapy is often difficult in HL. Approximately in two-third of HL patients could be detected residual masses after completion of their planned treatment, but only 20-25 % will finally relapse [1]. These masses may contain residual lymphoma, which needs further treatment or may represent fibrosis or necrotic tissue, which will remain stable or continue to regress on further imaging without the need for more treatment. The early diagnosis of relapse, progression or incomplete response is an important indication to start salvage therapy with or without stem cell transplantation as soon as possible without waiting for clinically prooved relapse. Differentiation of active tumor from fibrosis or necrosis within residual radiographic masses represents a problem of interpretation for HL. In fact there are no reliable radiographic characteristics that permit differentiation. If the tumor is easily accessible, the questionable lesion can be excised and histologically analyzed, whereas a deep tumor can only be accessed by open thoracic or abdominal surgery, with a certain risk, owing to the necessity of anesthesia and surgery and a high failure rate considering the relatively small amount of tissue that can be gained by surgical or needle biopsies. It would also be desirable to identify patients who are cured to avoid the toxicity of additional unnecessary therapy. In the 1990s, positron emission tomography (PET) scanning was recognized as a powerful tool in the diagnosis and staging of tumors, including lymphomas, in the evaluation of recurrent or residual mass and in the early restaging of induction chemotherapy in lymphomas, due to the uptake of 2-[fluorine-18] fluoro-2-deoxy-d-glucose (FDG) in malignancies exhibiting increased metabolic activity [2, 3]. The effectiveness of FDG-PET to differentiate viable tumor tissue from necrosis or fibrosis has been shown in several studies in the past few years [1, 4, 5, 6]. Literature seems to be consistent in negative predictive value, however, as regards positive predictive value, contradictory results are displayed (Table 1).

In 1994, East Europe's first PET center began to work in Debrecen, Hungary. The residual tumor masses of HL patients have been examined since 1995. Thanks to the long follow-up,

Table 1. Studies of 18-fluoro-deoxy-glucose positron emission tomography (FDG-PET) for restagin of Hodgkin lymphoma

Authors	Number of patients	Follow-up (month)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
De Wit et al [5]	33	26	100	78	67	100	85
Ditmann et al [18]	26	6	87	94	87	94	92
Spaepen et al [19]	60	32	50	100	100	91	92
Weihrauch et al [20]	29	28	67	80	60	84	76
Guay et al [21]	48	16	79	97	92	92	92
Friedberg et al [22]	29	24	80	85	50	96	85
Panizo et al [23]	29	28	100	85	75	100	90
Molnar et al	128	75	83	93	74	93	88

Abrevations: PPV: positive predictive value, NPV: negative predictive value

our data are able to show the value of PET examinations in the treatment of Hodgkin's lymphoma. The aim of this retrospective study was to assess the value of FDG-PET for prediction of remission or relapse in HL in a rather large cohort of patients after a long follow-up.

Patients and methods

This study represents a retrospective analysis of 128 patients who had residual masses on CT after completion of their planned treatment. All the patients were treated in the following three institutes: National Institute of Oncology, Budapest; Faculty of Medicine, University of Szeged; Medical and Health Sciences Centre, University of Debrecen. FDG-PET was performed between January 1995 and February 2005. Data collection was finished in January 2008, so time from the end of the examinations to data procession was 35 months, while the mean follow-up of the patients was 75.5 (20-156) months. The diagnosis was confirmed histologically first according to the REAL [7], later according to the WHO [8] classification in all patients. Patients were staged according to the Cotswolds modification of the Ann Arbor staging system [9] (Table 2). Clinically complete remission with residual mass was defined by the presence of residual mass on post treatment CT scan, no B symptoms and normal laboratory tests (CRu category). Progression or relapse were defined as histological verification of HL, progression on CT scan, or introduction of a new treatment. The patient characteristics are displayed in Table 1. Patients have been treated and reviewed according to the institutional protocols. Six patients were lost of follow-up. The median time between the end of the treatment and FDG-PET was 3.2 months (range 1.5-5). PET examinations were done with a GE 4096 Plus whole body camera (General Electric). A mean dose (80 μCi-2,96 MBq 2-[F-18]fluoro-2-deoxy-D-glucose (FDG) per body kg) of positron emission FDG 5,4±2,4 mCi (200±89 MBq) was applied. In the case of pharmacon accumulations that could not be explained as focal or physiological variants, decision was made on tumor to background ratio (TBR). If there was no involvement, the appropriate area of the opposite side or the neighbouring soft tissues at about the same depth were taken as background. Based on the results two categories were formed: if the TBR was equal or lower than 3 it was considered as negative, if it was higher than 3 it was positive [10]. The patients with negative and unconfirmed positive results were followed up closely. They were seen every month in the first year and every 3 months in the second and third year. After the third year, controll examinations were preformed every 6 month. The follow-up comprised a clinical examination, laboratory testing and cervical and abdominal ultrasound as well as chest radiography. CT scans of the affected regions were taken once or twice in the first year, than once a year if the size of residual masses was found to be unchanged by CT. In positive cases on PET, the patients received further treatment if independent regions were affected. PET positive patients were treated, if other signs of the the active disease were obvious. If no other sign of active disease was found biopsy was done, or thorough

Table 2. Clinical data of 128 Hodgkin lymphoma patients

Age (years)	27 (14-68)
Sex (Male/Female)	63 /65
B symptoms (No/Yes)	64/64
Clinical Stage (Number of patients)	
I	8
II	78
III	29
IV	13
Histology (Number of patients)	
NLPHL	1
NS	98
MC	27
LR	1
LD	1

Abrevations: NLPHL: nodular lymphocyte predominant Hodgkin lymphoma, NS: nodular sclerosis, MC: mixed cellularity, LR: lymphocyte rich, LD: lymphocyte depleted

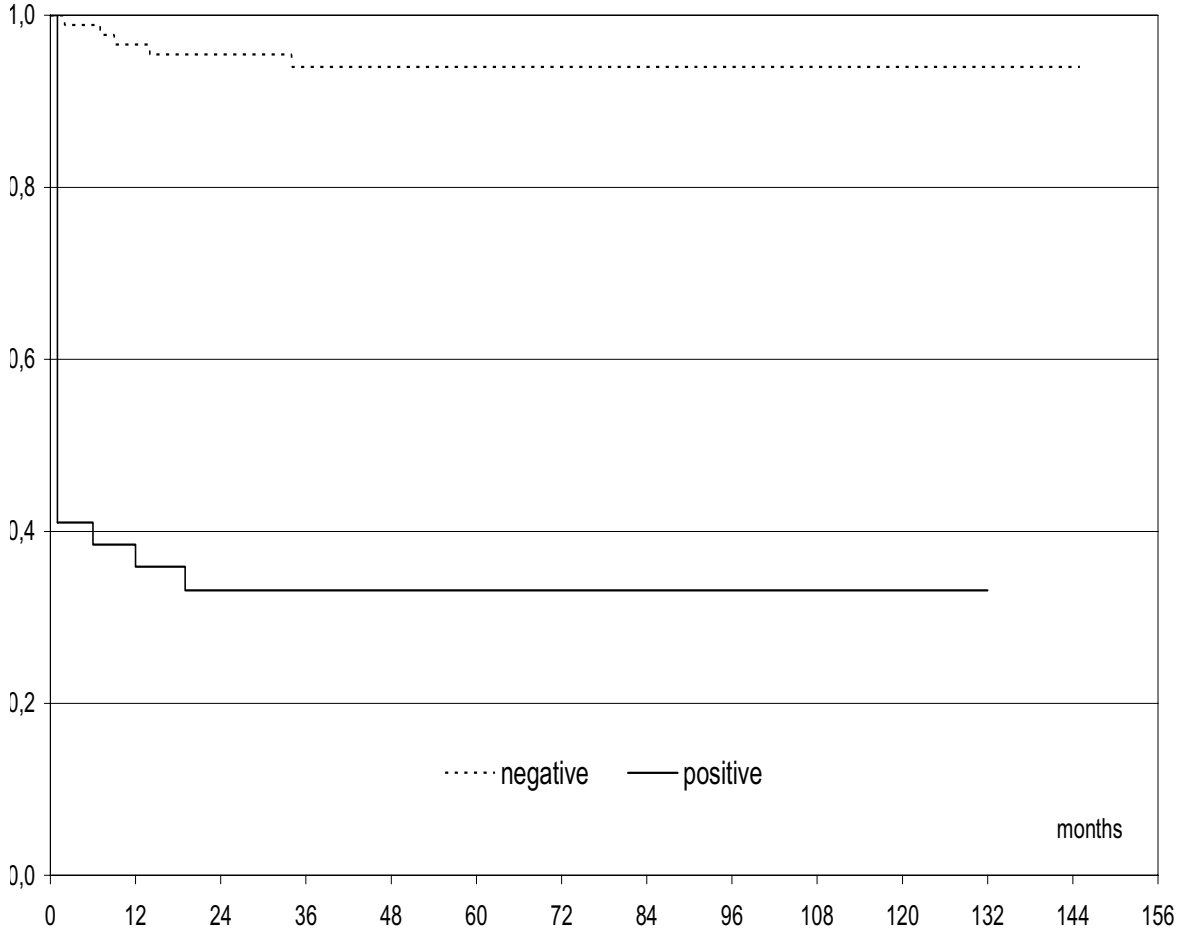

Figure 1. Event free survival according to the PET results in Hodgkin lymphoma patients

observation was choosen according to the clinical situation. The non-lyphomal activity intensification was thought to be false positive. We considered the result to false positive when it was caused by non-lymphomal activity intensification.

Specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV) and accuracy have been calculated according to literature [11]. Event free survival (EFS) has been calculated from the date of the PET scan to the date of documented relapse, death, or to the last follow-up visit.

EFS and OS rates were estimated by the Kaplan-Meier method. Mantel-Cox χ^2 probes were used for analyzing the effect of different parameters (age, stage, histologic subtype, the time between the end of treatment and PET and the date of PET examination) on the false results.

Results

The result of FDG-PET examinations was negative by 89 patients (70%) and positive by 39 patients (30%). The number of true-positive, true-negative, false-positive, false-negative subjects were 29, 83, 10, 6, (22.6, 64.9, 7.8, 4.7 %) respectively, which means that 6.7 % of 89 PET negative cases were false-negative, while 25.6 % of 39 PET positive cases were false-positive. Sensitivity of post-treatment FDG-PET was 83 %, specificity 93 %, positive predictive value 74 %, negative predictive value 93 %, and accuracy 88 %. The difference between the event free survival of PET positive and negative cases was highly significant (p=0.0000), according to the Mantel-Cox test (Figure 1). In the false negative group EFS from PET was 33, 34, 39, 54, 57 and 105 months, respectively. Regarding relapses, in 3 patients they were proved histologically, while in the other 3, with CT scans. Three patients died in this group, all of them because of progressive disease. One achieved a second complete remission (CR), one has NLPHL (nodular lymphocyte predominant Hodgkin lymphoma), he has active disease, but does not need any treatment, and one patient was lost of follow-up, after 54 month. She had progressive disease at that time. In the true negative group the median follow-up time is 67 months (range:

Table 3. The most frequent causes of false positive (non-lymphoma) result of 18 fluoro-deoxy-glucose positron emission tomography (FDG-PET)

sarcoidosis
tuberculosis
histoplasmosis
fungal infections
pyogenic abscess
thymic hyperplasia
hyperplasia of the bone marrow
pneumonitis

35-151), the results were proved by follow-up data. None of the patients died from that group. Two patients were lost of follow-up from that group. In 39 cases positive PET results were found, from them, in 10 cases the relapse was not likely, because of the clinical findings and the results of the conventional radiological methods, so in these cases throrough observation was chosen without treatment. In these cases during the 89 (49-147) months mean follow up time no relaps occured, so the result of PET was false positive. In 24 cases the clinical finding (signs, laboratory results, other radiological methods) corresponded with PET result, so it was accepted, and new treatment was applied. In the five doubtful cases biopsy was done to confirm the relapse. From the 29 true positive cases, 9 patients died because of progressive disease, 16 achieved CR with further treatment, and 3 were lost of follow up.

Looking for the reason of false results, we examined the association of treatment modalities (radiotherapy or chemotherapy or combined modality treatment) and PET outcomes, but no significant changes were found. Neither the variaty of time from treatment to PET explained these false results. (Data were not collected to separate tables)

We found increased activity of the thymus by three patients, sarcoidosis by two patients and pleuro-pneumonia by one case in the background of false PET positivity. The reason for false positivity cannot be explained from the medical files by the remaining four patients.

Discussion

Before FDG-PET was introduced for the clinical evaluation of patients with HL, tumor activity of residual masses after therapy could only be assessed by invasive procedures, such as core or surgical biopsy of lymphnodes or mediastinoscopy, or by regularly repeated CT scans. However, CT and MRI have a low sensitivity and specificity in this indication. Gallium scintigraphy has been used as a metabolic imaging technique to detect active tumor tissue, but it has several disadvantages, such as low specificity, especially in the abdomen [12], and moreover it takes at least three days to examine a patient thoroughly. FDG-PET has been reported to be superior to gallium in respect to sensitivity and specificity [13]. In a recent systematic review, Zijlstra [14] and colleagues summarized the results of 15 studies evaluating PET after the first line treatment in lymphoma. Subgroup analysis in 247 patients, who had HL, showed a sensitivity and specificity of 84% and 90% for the detection of residual lymphoma; our results are similar to the above mentioned numbers. The result of this trial clearly indicates that patients with negative FDG-PET results are unlikely to progress or relapse during a long follow-up. However, if FDG-PET was positive after treatment, only about 60 % of patients would relapse. According to our data, in accordance with literature, false positive uptake is a problem in HL patients [15, 16, 17]. We investigated the effect of age, histologic subtype, clinical stage and the type of treatment on the accuracy, but we could not find any significant difference based on these facts. However, the date of the investigation influenced the results: before 2000 the number of false results were significantly higher than after that time, which shows the importance of investigators'experience. The most frequent causes of false positivity are summarized in Table 3. The most common reason for false positivity was thymus hyperplasia, besides, sarcoidosis and inflammation also affected the examination. Unfortunately there was no acceptable reason by four patients. Attenuation correction as well as standard uptake value (SUV) were not calculated, however, SUV is not likely to help to distinguish active disease and inflammation. [17]. The false positive region was outside the residual tumor mass by five patients. In these cases, the recently installed PET-CT scan can be useful to evaluate the structure of lesions with increased metabolic activity. The diagnosis of relapse should be confirmed with additional, perhaps invasive diagnostic procedures, or with closer follow-up [24]. If clinical signs do not refer to relapse, it may be considered to repeat the FDG-PET scan within 4-12 weeks. False negative results should be eliminated, too, however, relapse was detected among these patients three years or later (33-105 months) after the scan. Refering De Wit et al [5], we also think that it is not correct to evaluate false negativity in relapses after three years, as it should be considered to the result of minimal residual disease, which cannot be detected by FDG-PET scan. The German Hodgkin Study Group evaluated the negative predictive value of PET scan by advanced stage HL patients in the HD15 survey. They defined the relapse after 12 months as a late event which cannot be predicted by PET. This way, negative predictive value should be adopted only to 12 months progression free survival [24]. However, FDG-PET improves the accuracy of restaging assessment over that of CT alone, so it is accepted as the most valuable tool for HL restaging. The new definition of complete remission is based on its results [25]. Its accuracy can be further improved by the use of PET/CT as well as calculatin SUV value and attenuation correction.

The installation of PET scan in the recent period opened a new possibility to evaluate residual tumor masses, and in this way to avoid the „overtreatment" of patients. It contributed the dissemination of risk-adopted therapies from patient-oriented view. PET/CT apparats that combines computed tomography and positron emission tomography, give further opportuni-

ties to detect residual tumor, which will decrease the number of false results. Novel examinations expanded the role of PET/CT in the treatment of Hodgkin lymphoma, as pretreatment and interim scans may determine the decisions about therapeutical approaches. It is easier to evaluate the residual mass if a pretreatment scan was performed formerly. It can be concluded that PET examinations help to plan individual, risk-adopted treatment modalities, which improves both the curability and the longterm quality of life in young people with Hodgkin lymphoma.

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