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Importance of F18-Fluorodeoxy-D-2-Glucose Positron Emission Tomography (FDG-PET) for Staging and Therapy Control of Hodgkin's Lymphoma in Childhood and Adolescence – Consequences for the GPOH-HD 2003 Protocol

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Key Words

F18-fluorodeoxy-D-2-glucose positron emission tomography · FDG-PET · Hodgkin's disease · Child · Response assessment

Summary

The prognosis for children and adolescents with Hodgkin's lymphoma is excellent. However, many patients will show secondary malignancies 15–30 years after the initial diagnosis, which appears to be connected with the intensity of treatment during primary disease. In the GPOH-HD 95 trial, the indication for radiotherapy was limited to patients who did not show a complete remission after chemotherapy, as determined radiographically. In the future protocol, the indication for radiotherapy in patients with early-stage Hodgkin's lymphoma should be further refined by using FDG-PET for evaluating the response to chemotherapy. Furthermore, in patients at an advanced stage of the disease, it should be determined if sequential FDG-PET research during chemotherapy can separate patients into subgroups with an excellent or a poor prognosis. This article gives a review of the current literature on FDG-PET in patients with Hodgkin's lymphoma and outlines the consequences for future protocols.

Schlüsselwörter

F18-Fluorodesoxy-D-2-Glukose-Positronenemissionstomographie · FDG-PET · Morbus Hodgkin · Kinder · Therapieerfolg

Zusammenfassung

Die Heilungsaussichten beim Morbus Hodgkin im Kindes- und Jugendalter sind sehr gut. Demgegenüber besteht ein hohes Risiko, nach 15–30 Jahren Latenzzeit an einem Sekundärmalignom zu erkranken. Daher wurde in der GPOH-HD-95-Studie eine Response-adaptierte Therapie eingeführt und die Indikation zur Radiotherapie eingegrenzt. In der künftigen Studie soll durch die Anwendung der FDG-PET die Indikation zur Radiotherapie bei Patienten mit niedrigen Stadien weiter eingegrenzt werden und bei Patienten mit hohen Stadien des Morbus Hodgkin die Frage beantwortet werden, ob durch FDG-PET-Verlaufsuntersuchungen ein unabhängiger Prognosefaktor zur weiteren Differenzierung von Patienten mit ausgezeichneter und schlechter Prognose ermittelt werden kann. In dieser Arbeit werden daher der Stand der Forschung zur FDG-PET beim Morbus Hodgkin sowie die daraus resultierenden Überlegungen für die Erstellung des GPOH-HD-2003-Protokolls referiert.

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Introduction

The prognosis for children and adolescents with Hodgkin's lymphoma is excellent. The GPOH-HD 95 trial registered event-free survival rates after 5 years of 94, 87 and 83% for therapy groups 1, 2 and 3, respectively. Total survival was 97% [1]. Hence, the emphasis in the treatment of Hodgkin's lymphoma in childhood and adolescence now is on reducing the intensity of therapy. Recent reports [2, 3] on the long-term risks pointed out a dangerous tendency towards developing secondary malignancies after a period of 15–30 years after which a cumulative rate of 25% or even more patients exhibited secondary malignancies. More than chemotherapy, radiotherapy appears to be a significant risk factor.

The GPOH-HD 95 trial introduced the approach of therapy reduction upon good response. In this study, patients in whom imaging showed complete remission after the end of chemotherapy (volume reduction > 95%, residual tumor volume < 2 ml) received no radiotherapy. In patients with intermediate and advanced stage disease (therapy groups 2 and 3), but not in those with early-stage lymphoma (therapy group 1), foregoing radiotherapy was associated with a lowered probability of event-free survival [1]. In the next study, the approach of reducing the use of radiotherapy in therapy group 1 will be further investigated.

Recently, Nachman et al. [4] pointed out a possible way to further reduce the indication for radiotherapy. Their study comprised a total of 829 patients. Those patients who showed a good partial remission at the end of chemotherapy (reduction of tumor volume > 70%) and who had no positive signal in Gallium-67 (^{67}Ga) scintigraphy were randomly selected for a radiotherapy vs. no radiotherapy trial. Although foregoing radiotherapy yielded clearly worse results, especially in the therapy groups 2 and 3, 89% of the patients from therapy group 1 showed stable remission [4]. These findings are encouraging, and a similar concept will be employed in the new Hodgkin's lymphoma trial.

At the 3rd German interdisciplinary conference 'PET in Oncology', FDG-PET for staging and therapy control in Hodgkin's lymphoma received a rating of Ib, meaning that clinical use is likely to be justified and that further studies are definitely needed [5]. Unlike the great experience with PET in adult lymphoma patients, scientific knowledge on PET in Hodgkin's lymphoma in children is limited. However, examinations in children and adolescents with malignant bone tumors showed that FDG-PET is very well suited for assessing therapy response and for restaging. Thus, Schulte et al. [6] demonstrated that assessment of therapy response following preoperative chemotherapy by FDG-PET correlated closely with the results of histological examination of resected tumor tissue. FDG-PET also was superior to Tc-99m-diphosphonate scintigraphy in detecting osseous metastases of Ewing's sarcoma [7, 8].

Since the above-mentioned research supports the feasibility and scientific importance of PET for children and adolescents with malignancies, and since there are solid data for adult patients with Hodgkin's lymphoma, our next therapy optimization study GPOH-HD 2003 will employ FDG-PET instead of ^{67}Ga scintigraphy. Furthermore, with its higher spatial resolution, FDG-PET can detect pathological lesions better than ^{67}Ga scintigraphy. This is especially advantageous for imaging of the abdomen and of smaller lesions where the sensitivity of ^{67}Ga scintigraphy is limited [9]. FDG-PET scans are also simpler to run, and the radiation burden is lower [10–12].

This paper reviews the current literature on FDG-PET in Hodgkin's lymphoma. Only those studies are included which clearly show therapy results of patients with Hodgkin's lymphoma. Studies which did not distinguish between Hodgkin's lymphoma and malignant non-Hodgkin's lymphoma were disregarded.

Table 1. The importance of PET for initial staging in Hodgkin's disease

Authors	PET-related changes		
	upstaging	down-staging	therapy change
Partridge et al., 2000 [13]	18/44	3/44	11/44
Weidmann et al., 1999 [14]	3/20	0/20	ND
Weihrauch et al., 2002 [15]	4/22	ND	1/22
Jerusalem et al., 2001 [17]	3/33	4/33	0/33
Montravers et al., 2002 [18]	4/7	0/7	1/7

ND = Not defined.

FDG-PET in the Diagnostic Staging of Hodgkin's Lymphoma

Whole-body FDG-PET gives an image of the entire body in a single run, making it possible to detect lesions scattered throughout the body, whereas with primarily local methods such as computed tomography (CT) and magnetic resonance imaging (MRI), lesions at unusual sites may remain undetected. In their study on 44 patients with Hodgkin's lymphoma, Partridge et al. [13] showed that by using PET 18 of 44 patients were assigned to a higher stage of illness and 3 to a lower one (table 1). The improved detection of spleen lesions and extranodal foci (e.g. bone) by PET was particularly impressive. Biopsies taken from some of the patients confirmed the PET diagnosis of tumor. Due to changes in staging, 11 of 44 patients received a different therapy. Similar results were also reported by Weidmann et al. [14] who upgraded 3 patients to a higher stage of illness following PET examination. Weihrauch et al. [15] upgraded the tumor stage in 4 of 22 patients following FDG-PET. Rifai et al. [16] found PET to be more sensitive than CT, especially for detecting lymphomas in the axilla and in bone. Jerusalem et al. [17] showed that no af-

Table 2. The importance of PET for assessing response to therapy

Authors	Follow-up period		Time period*	Cases**	Sensitivity, %	Specificity,%
	median	range				
Stumpe et al., 1998 [19]	ND	>6	ND	53	86	96
Lang et al., 2001 [20]	22.5	5–43	4–8 weeks	47	95	89
De Wit et al., 2001 [21]	25.6	2–45	10 ± 9 weeks	33	100	78
Weihrauch et al., 2001 [22]	28	16–68	≤4 months	29	67	80
Spaepen et al., 2001 [23]	32	ND	4–12 weeks	60	50	100
Naumann et al., 2001 [24]	37	15–58	1–24 weeks	43	100	64
Dittmann et al., 2001 [25]	ND	>6	≥3 weeks	26	88	94

*Time from the end of therapy.
**Patients or PET studies (if more than one PET/patient)
ND = Not defined.

Table 3. A comparison of the value of CT/MRI and PET for assessing the success of therapy

Authors	PET		CT/MRI	
	sensitivity, %	specificity, %	sensitivity, %	specificity, %
Lang et al., 2001 [20]	95	89	95	42
De Wit et al., 2001 [21]	100	78	70	26
Spaepen et al., 2001 [23]	50	100	70	28
Dittmann et al., 2001 [25]	88	94	25	56

fected lymph nodes > 1 cm were overlooked when using PET. In the same study, PET also detected foci which could not be found when using conventional staging. Unlike Partridge et al. [13], changes in staging did not lead to changes in therapy for any patient. Interestingly, the sensitivity of PET in detecting pathological lymph nodes seems to depend on their localization. Thus, sensitivity was 83% for peripheral and 91% for thoracic lymph nodes as well as 75% for lesions in the abdomen and pelvis. FDG-PET also seems to improve diagnostic staging in children. In a study by Montravers et al. [18], 4 of 7 patients were upgraded to a higher stage of illness, and in 1 case therapy was modified due to alterations in staging.

PET and Follow-Up Assessment

A number of papers also deals with the role of FDG-PET in follow-up assessment [19–25] (table 2). The time when after chemotherapy PET is used is critical. The EORTC [26] recommends that no PET scans should be done 1–2 weeks after chemotherapy since, in addition to possible false-positive results, higher rates of false-negative results have been observed in patients with malignant germ cell tumor [27]. However, in lymphomas a rapid decrease of FDG accumulation in the tumor is an important indicator of a good response to chemotherapy. Several studies where PET was employed between two applications of chemotherapy have shown that an early response – as evident from a significant decrease in the standardized uptake value (SUV) within 7 days [28] or an inconspicuous PET after one course of chemotherapy [29] – correlates with a very good prognosis while persistent positive PET findings correlate with a high relapse probability. Hence, for the above-cited reasons, in most of these studies on Hodgkin's lymphoma, PET scans were done between 3 and 6 weeks after the end of chemotherapy.

The sensitivity of PET (i.e., the probability of correctly identifying patients who will relapse) is variously reported at 50–100% and the specificity (the probability of correctly identifying patients who will not relapse) at 64–100%. In a total of 187 patients FDG-PET was examined after the end of therapy. For most of these studies, the median follow-up time was > 20 months. Assessment and follow-up observation yielded true-positive FDG-PET findings in 28 cases, true-negative results in 137, false-positive results in 13, and false-negative results in 9 cases. This gives an overall sensitivity of 75% and an overall specificity of 91.3% for all patients.

Due to the low prevalence of relapses and despite the relatively low sensitivity, this yields a negative predictive value of >90%. In the studies in which for those cases who relapsed despite inconspicuous PET findings also the tumor stage was given [22, 23, 25], these were shown to be exclusively patients at stages III and IV. The data of Cremerius et al. [30] also showed that negative and positive predictive values are higher for patients at lower stages of illness [30].

Most of the studies included patients in whom CT/MRI still revealed an obvious residual tumor. However, data obtained in these patients may have an unfavorable influence particularly on the negative predictive value of PET. Moreover, the

results of these studies suggest that PET, but not CT or MRI, is suited for giving information on the tumor's biological response (table 3). These findings are crucial when planning a response-oriented therapy.

PET Scans Prior to High-Dose Chemotherapy

PET data before high-dose chemotherapy in patients with Hodgkin's disease is scarce. Negative FDG-PET findings prior to high-dose chemotherapy were reported by Becherer et al. [31] in 2 of 6 patients with Hodkin's disease. These patients remained in remission after high-dose chemotherapy (follow-up at 17 and 20 months). Of the 4 patients with positive PET findings prior to high-dose chemotherapy, 2 relapsed, one died of transplant-related toxicity.

Consequences for the Conception of the GPOH-HD 2003 Trial

The future study concepts are to evaluate if radiotherapy after two cycles of chemotherapy can be omitted in patients of treatment group 1 with a negative PET result without worsening event-free survival rate. In addition, it should be evaluated in patients of treatment groups 2 and 3 if early response to chemotherapy demonstrated by PET might be of predictive value. Thus, in view of the observations mentioned above, the conception of the new protocol must consider the following:

Initial Staging

- PET detects more foci than conventional radiological methods which lead to a change in stage status and a modification of the therapy. Hence, all study patients must be given an initial PET scan to avoid bias.
- The importance of PET for initial staging of children and adolescents has not been sufficiently determined yet. This is why the initial PET data in the planned study must be seen in the context of PET evaluation. This means that positive PET findings can only be considered pathological if they agree with data obtained using conventional imaging methods, which are still accepted as the standard. If there is any doubt (e.g., lymph nodes < 1.5 cm) or no correlation, then stage status should not be changed since excellent event-free survival rates are also achieved using conventional imaging methods. In such patients, special attention should be paid during follow-up if there are relapses at suspected sites. These analyses will be useful when evaluating PET data from initial staging in the future.
- Since in a minority of patients conventional imaging shows positive tumor signal at some sites at initial staging while PET is negative at the same site, these patients should receive radiotherapy in treatment group 1 after chemotherapy if lymphoma has not completely disappeared at these sites.

Follow-Up Assessment

- Given that a treatment course of omitting radiotherapy was successful in the majority of early-stage patients who responded well to chemotherapy and who showed a negative ^{67}Ga scintigraphy after chemotherapy, and in view of the fact that FDG-PET was repeatedly shown to be more accurate than ^{67}Ga scintigraphy, it is hoped that the answer to the question surrounding therapy group 1 – 'Can radiotherapy be omitted if PET findings after chemotherapy are negative?' – will be 'yes'.
- According to the EORTC recommendations and the data reported in the literature, a postchemotherapy period of 2 weeks should be observed to ensure a valid FDG-PET follow-up assessment. There are no indications that chemotherapy can influence PET beyond this period. The mean time for beginning radiotherapy in the GPOH-HD 95 study was 39 days after the end of chemotherapy. Hence, in the study planned, PET scans will be done between 14 and 17 days after chemotherapy, possibly followed by radiotherapy. By planning and scheduling appointments for the beginning of the 2nd course of chemotherapy, we also hope to shorten the time between the end of chemotherapy and the beginning of radiotherapy.
- Several studies have shown that PET scans after one or two courses of chemotherapy are suited to improve the prognosis of Hodgkin's and non-Hodgkin's lymphoma. The HD 2003 study is intended to ascertain whether sequential FDG-PET for patients in therapy groups 2 and 3 should be done before, during or after chemotherapy for early differentiation of subgroups with a particularly poor or good prognosis.

High-Dose Chemotherapy

- Since there are no solid data yet, the prospective evaluation of remission status using FDG-PET before high-dose chemotherapy and autologous stem cell therapy is important to determine the role of this method for a future response-adapted salvage therapy. At the moment, PET data still cannot be used as a basis for treatment decision in patients undergoing salvage therapy.

Planning the Multicenter Study

For a successful study, in addition to the above-mentioned points, the following must also be kept in mind:

- PET examinations must be conducted according to standards followed equally by all departments.
- PET examinations must be conducted observing a uniform time frame.
- PET data must be evaluated by the various participating centers in a noncentralized manner, following which it will be analyzed at study headquarters, now centralized. The final prospective evaluation will be made by the tumor conference at study headquarters.

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