Positron emission tomography at the end of first-line therapy and during follow-up in patients with Hodgkin lymphoma: a retrospective study

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Background: Routine positron emission tomography (PET) in follow-up of Hodgkin lymphoma (HL) after treatment is still controversial. The aim of this retrospective study was to analyze the clinical impact of routine PET examination during the follow-up for relapse detection in PET-negative HL patients at the end of therapy.

Patients and methods: PET scans were carried out in 113 HL patients at the end of therapy and during the follow-up either in regular intervals or in a suspected relapse. Median follow-up of the group was 34 months.

Results: Overall 327 PET scans were evaluated in 113 patients (median three PET scans per patient). At the end of therapy, 94 (83.2%) patients were PET negative and 19 (16.8%) PET positive. Regular follow-up PET scans in 67 of 94 PET-negative patients correctly identified tumor in 6 of 155 PET scans (3.9%). In 27 of 94 patients with clinically suspected relapse, 5 of 27 PET scans (18.5%) confirmed tumor.

Conclusions: Our analysis showed that there is no need for regular follow-up with PET scans in PET-negative patients at the end of therapy: the ratio of true-positive PET scans during the follow-up is low (3.9%). Positive PET at the end of therapy and during follow-up should be evaluated with caution.

Key words: follow-up, Hodgkin lymphoma, PET

introduction

Follow-up guidelines in Hodgkin lymphoma (HL) vary due to lack of prospective data for the routine performance of imaging. Published studies reported 55%–81% of relapses that were detected in patients with symptoms and only 11%–23% of relapses were identified by means of routine physical examination or imaging methods including computed tomography (CT) [1, 2]. Routine surveillance CT scanning during the follow-up period is expensive and inefficient: CT detected only 2 of 22 relapses of HL [3].

Positron emission tomography (PET) can discriminate viable tumor from necrotic tissue and is strongly recommended for staging and post-treatment assessment of diffuse large B-cell lymphomas and HL [4, 5]. The International Working Group proposed revised response criteria for malignant lymphoma, which combine CT and PET for response assessment [6]. Revised International Workshop Criteria (IWC + PET) guidelines provide a more accurate response classification compared with International Workshop Criteria guidelines on the basis of CT [4, 7, 8].

PET has good diagnostic accuracy for assessing residual HL at the completion of first-line treatment [6]. Reported ranges for the sensitivity and specificity of PET in predicting disease relapse were 0.50–1.00 and 0.67–1.00. A high negative predictive value (NPV) of PET after therapy (85%–100%) was demonstrated in several studies [9–12]. The German Hodgkin Study Group HD15 study demonstrated an NPV of 94% after 6–8 cycles of combination therapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone for PET-negative patients at the end of chemotherapy [12]. However, negative PET at the end of therapy cannot exclude minimal residual disease, possibly leading to a later relapse [13]. According to revised response criteria for malignant lymphoma, PET is currently not recommended for routine post-treatment surveillance due to lack of data to support this issue [4]. Jerusalem et al. [14] identified one residual tumor and four early relapses using regular follow-up PET scans up to 3 years after the end of therapy, but there were six false-positive PET studies that required confirmatory PET scans. Zinzani et al. [15] prospectively assessed regular follow-up PET scans in 421 patients with HL, with aggressive non-Hodgkin lymphoma (NHL) and with indolent follicular NHL. PET correctly identified relapse of lymphoma in 118 patients during the follow-up and this study indicated PET as valid tool for
follow-up of patients with HL and NHL [15]. In this study, the information about the relapse is however missing, as well as detailed HL patients’ analysis. In patients with inconclusive-positive PET results, histologic confirmation is necessary.

The aim of this retrospective study was to analyze routine use of PET during the follow-up and in suspected relapse outside the clinical trial.

patients and methods

patients
PET findings and clinical outcomes were retrospectively evaluated in 113 HL patients after first-line treatment and during follow-up since 1999 till 2008. Median follow-up of the group since the end of therapy was 34 (range 3–109) months. Characteristics of patients are summarized in Table 1. First-line therapy consisted of chemotherapy alone (n = 47 patients), chemotherapy and involved-field radiotherapy (n = 65 patients) or radiotherapy alone (n = 1 patient).

methods
Conventional methods for restaging at the end of therapy and in suspected relapse included: physical examination, laboratory studies, chest X-ray, CT and/or ultrasound of neck, CT of chest, abdomen and pelvis and magnetic resonance imaging in selected cases.

Of 327 PET scans, 237 PET and 90 PET/CT studies were carried out according to standard procedures with a whole-body PET scanner ECAT EXACT BGO Siemens or PET/CT scanner Biograph Duo LSO Siemens MS. PET and CT data were not merged on PET studies only. PET scans were carried out in all patients at the end of therapy. CT and PET follow-up examinations were carried out either as regular restaging methods or in a suspected relapse. Follow-up procedures: CT preceded the PET scan 7–28 days and if PET/CT was carried out, no additional CT was indicated. Responses after treatment and relapses were evaluated according to International Working Group criteria for response assessment of HL [7]. PET studies were evaluated separately. Clinical follow-up was assessed by clinicians.

interpretation of imaging
PET, PET/CT and CT images were interpreted visually and analyzed using available clinical information. Standardized uptake value (SUV) was not used for evaluation of PET. For the purpose of this analysis, these arbitrary definitions were used:

- Positive PET finding: increased 2-[(fluorine-18)]fluoro-2-deoxy-D-glucose (FDG) uptake above background was described as concordant with tumor, or tumor was mentioned as a possible cause of increased FDG uptake.
- Negative PET finding: no evidence of increased FDG uptake above background or increased FDG uptake clearly concordant with nonmalignant lesion (e.g. perivascular extravasation of FDG).
- Positive PET conclusions required additional examinations in order to confirm or to exclude a tumor while in cases of negative PET findings, no further examinations were carried out.

On the basis of these results of additional examinations (if required), following arbitrary categories were used for the purpose of this study:

- confirmed positive PET: lymphoma or other tumor confirmed (increased FDG uptake corresponds with viable tumor);
- inconclusive positive PET: lymphoma or tumor was subsequently excluded, the etiology was nonmalignant: inflammation, etc) and
- negative PET: concordant with described finding.

Negative CT finding: no lymph nodes >1.5 cm and no hepatosplenomegaly or other abnormalities indicative of lymphoma.

New positive CT finding: pathologically enlarged lymph nodes had not been present in the past or had grown since previous measurements.

results

One hundred and eleven of 113 patients are alive, 2 (1.8%) patients died (1 lymphoma progression, 1 treatment toxicity in relapse) during the median follow-up of 34 months.

PET at the end of therapy

PET scans were carried out at the end of therapy in 113 patients: median 17 (range 7–26) days after chemotherapy and median 41 (range 24–287) days after radiotherapy. Figure 1 summarizes CT and PET findings at the end of treatment and clinical outcome during the follow-up: 94 (83.2%) patients were PET negative (9 patients subsequently relapsed, second tumor occurred in 2 patients) and 19 (16.8%) PET positive (5 progressed). Biopsy was not carried out in four of five patients due to rapid HL progression and salvage therapy was immediately initiated. In one patient, biopsy identified relapse of HL in a PET- and CT-positive lymph nodes. In 14 of 19 patients with inconclusive PET positivity, no relapse was identified: 6 inflammations (2 biopsy proven), 1 thymus hyperplasia, 6 postradiation changes (1 biopsy proven) and 1 postchemotherapeutic changes (Table 2).

Timing of positive PET scans in patients with HL progression at the end of first-line therapy: 24–83 days after radiotherapy in three patients and 25 days after chemotherapy in two patients.

Timing of PET scans at the end of therapy in patients with inconclusive PET positivities: 12–22 days after chemotherapy in six patients with inflammation and 13 days in one patient with postchemotherapeutic changes; 26 days after the end of chemotherapy in one patient with thymus hyperplasia and 24–30 days after radiotherapy in five patients and 102 days in one patient with postradiation changes.

NPV of CT and PET in our group of patients at the end of therapy were comparable (91.2% versus 90.4%, statistically ns). Positive predictive value (PPV) of CT was lower when
compared with PET, but this was not statistically significant (16% versus 26%).

Follow-up PET scans in PET-negative patients at the end of therapy

In the group of 94 PET-negative patients at the end of therapy, 182 PET scans were carried out during the follow-up (Figure 2): 155 regular follow-up PET scans were carried out in 67 patients and the timing was on the basis of the physician’s decision. Three months interval of PET was chosen in 17 patients, 6 months interval in 33 patients and 12 months interval in 17 patients.

Twenty-seven PET scans were indicated in 27 patients in suspected relapse.

In 16 of 27 patients with suspected relapse, a negative PET scan ruled out tumor (Figure 2). PET positivity was found in 11 of 27 patients: 5 true PET-positive patients (4 relapses of HL, 1 second B non-Hodgkin follicular lymphoma, all biopsy proven). Four relapses of HL were identified 16–60 months after therapy and one second follicular lymphoma 30 months after completion of initial therapy. Inconclusive PET positivity was detected in six patients: four inflammations, one postradiation changes (biopsy proven) and one hip osteonecrosis.

In terms of relapse detection, the efficacy of regular follow-up PET scanning was low 3.9% (6 of 155 PET scans) but in clinically suspected relapse, 18.5% (5 of 27) PET scans confirmed tumor (Table 3), the difference is statistically significant (two-tailed P value = 0.02, relative risk = 0.21, 95% confidence interval 7% to 64%). In clinically suspected relapse, 59.3% (16 of 27) PET scans ruled out tumor (Table 3).

**discussion**

Patients with HL even in advanced stages have currently a better than 80% chance of being cured if appropriate and
adequate therapy is given [16]. Approximately two-thirds of the patients with HL have a residual mass on standard imaging methods during and at the end of treatment, but only 20% of these patients will eventually relapse [17]. Biopsy is not indicated in all patients with residual masses.

PET is an excellent tool to rule out relapse: NPV of PET at the end of therapy is high: 85%–100% [9, 18]. Reported post-treatment NPV of CT is 77% [19]. Our NPV of PET was 90.4% and this value was comparable with CT (91.2%).

PPV of PET after therapy for HL varies between 25% and 100% but it is higher when compared with PPV of CT (20%) [17, 20]. PPV of PET in our group of patients was 26% and this value was higher than PPV of CT (16%), although not statistically significant. Positive PET at the end of therapy with low PPV depends on the interpretation in the low range of published data. This can be explained by the definitions we used.

Few studies have investigated the value of PET and PET/CT in the follow-up setting [13–15, 21–26]. Most of these studies were on the basis of retrospective data, included only small numbers of patients with heterogeneous study population and the results were insufficient to draw any definitive conclusion regarding follow-up PET scanning. The largest prospective study published by Zinzani included 160 patients with HL and follow-up PET scans were scheduled every 6 months for the first 2 years and then on an annual basis. This study demonstrated the capability of PET to identify unsuspected relapse in 10% of scans in HL at 6 and 12 months, thus supporting the usefulness of carrying out a scan at these time points [15].

According to study published by Jerusalem, regular follow-up PET can be positive up to 9 months before histological

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**Figure 2.** Follow-up PET scans in 94 PET negative HL patients at the end of therapy. PET, positron emission tomography; pos., positive; neg., negative.

**Table 3.** Follow-up PET scans in 94 PET-negative patients at the end of therapy

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Number of PET scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular follow-up</td>
<td>67</td>
<td>155</td>
</tr>
<tr>
<td>PET negative</td>
<td>49</td>
<td>137</td>
</tr>
<tr>
<td>PET positive</td>
<td>18/67 (9%)</td>
<td>6/155 (3.9%)</td>
</tr>
<tr>
<td>True PET positive</td>
<td>6/67 (9%)</td>
<td>6/155 (3.9%)</td>
</tr>
<tr>
<td>Inconclusive PET positive</td>
<td>12/67 (17.9%)</td>
<td>12/155 (7.7%)</td>
</tr>
<tr>
<td>Suspected relapse</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>PET negative</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>PET positive</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>True PET positive</td>
<td>5/27 (18.5%)</td>
<td>5/27 (18.5%)</td>
</tr>
<tr>
<td>Inconclusive PET positive</td>
<td>6/27 (22.2%)</td>
<td>6/27 (22.2%)</td>
</tr>
</tbody>
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PET, positron emission tomography.
confirmation of an asymptomatic relapse [14]. In our study, tumor was detected by PET in 16 patients but it was carried out concurrently with CT and we did not observe earlier detection of preclinical relapse by PET. Regular follow-up PET scanning led to tumor detection in only 3.9% of PET scans. We observed a high ratio of inconclusive-positive PET results in 32 patients (28.3%): 14 patients (12.4%) at the end of therapy and 18 patients (15.9%) during the median follow-up of 34 months. SUV was not used for the interpretation of PET/CT or PET as this is a retrospective study summarizing PET findings over a decade. Moreover, according to the International Working Group’s revised response criteria for malignant lymphoma, visual assessment currently is considered adequate for determining whether a PET scan is positive and use of the SUV is not necessary [4]. False PET-positive findings reported in literature range between 35% and 63% [14, 22, 23]. Twelve of 32 inconclusive PET-positive findings (either at the end of therapy or during the follow-up) were in mediastinum and reflected post-therapeutic changes: postradiation, postchemotherapeutic or nonspecific inflammation. Early PET scanning 24–30 days after radiotherapy possibly led to inconclusive PET-positive findings. Chemotherapy can induce false PET positivity as well according to our results (six patients with nonspecific inflammation and one patient with postchemotherapeutic changes) within the range 12–22 days after treatment.

We observed rebound thymus hyperplasia in 23- and 25-year-old women. These mediastinal findings were identified not only early after therapy but also even 22 months after therapy. Our data support the observations and recommendations of Zinzani and Schaefer that positive PET scan of the mediastinum during the follow-up of lymphoma is not sufficient to determine uniquely a relapse of HL in view of its lack of discrimination between lymphoma and benign findings and histological confirmation should be carried out [26, 27].

Nine (9.6%) of 94 PET-negative patients at the end of therapy subsequently relapsed with HL and in 2 patients, second tumor was confirmed during the median follow-up of 34 months. PET scans during the regular follow-up detected HL within 18 months after therapy. In suspected relapse, first detection of HL using PET scan was 16 months after therapy.

PET is recommended if new clinical symptoms appear or if a change is seen using conventional staging methods [28]. Due to low number of events in patients who reached PET-negative complete remission, it is unlikely that prospective studies will demonstrate the benefit of routine follow-up with PET in all HL patients.

We did not observe false negative PET in our group of patients during the median follow-up of 34 months. The reported rate of false-negative PET scans during the median follow-up of 40 months after chemotherapy was 14% and after combination of chemotherapy and radiotherapy was 4% [29].

PET/CT is associated with substantially fewer false-or inconclusive-positive findings and also greater sensitivity compared with PET alone and surveillance PET/CT should be validated in patients who are at particular risk of early relapse (e.g. patients in advanced stages of HL with international prognostic score 4–7 or PET-positive patients after two cycles of initial therapy) in prospective clinical trials.

conclusions
Our analysis showed that there is no need for regular follow-up with CT and PET examinations in PET-negative patients at the end of therapy with low ratio of true-positive PET scans (3.9%). Positive PET at the end of therapy and during follow-up should be evaluated with caution.

Based on our experience, PET should be carried out during the follow-up in clinically suspected relapse: negative PET scan can exclude tumor, none of our PET-negative patients relapsed, and in all cases of tumor, PET was positive.

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disclosure
The authors declare no conflict of interest.

references