original article

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# Hodgkin's lymphoma in remission after first-line therapy: which patients need FDG–PET/CT for follow-up?

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**Background:** The purpose of the study was to evaluate the impact of 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG–PET)/computed tomography (CT) during follow-up of patients with Hodgkin's lymphoma.

**Patients and methods:** Patients in complete remission or an unconfirmed complete remission after first-line therapy who received FDG–PET/CT during their follow-up were analyzed retrospectively. Confirmatory biopsy was mandatory in case of recurrence.

**Results:** Overall, 134 patients were analyzed. Forty-two (31.3%) patients had a recurrence. The positive predictive value of FDG–PET/CT was 0.98. Single-factor analysis identified morphological residual mass [$P = 0.0005$, hazard ratio (HR) 3.4, 95% confidence interval (CI) 1.7–6.6] and symptoms ($P < 0.0001$, HR 4.9, 95% CI 2.4–9.9) as significant risk factors for relapse. By multivariate analysis, morphological residual mass was the only significant risk factor for early follow-up (<24 months) ($P = 0.0019$, HR 7.6, 95% CI 2.1–27.3). Advanced stage ($P = 0.0426$, HR 3.6, 95% CI 1.1–12.3) and the presence of symptoms ($P = 0.0009$, HR = 14.6, 95% CI 3.0–69.7) were found to be significant risk factors for later follow-up (>24 months).

**Conclusions:** Asymptomatic patients without morphological residues and an early stage of disease do not need a routine FDG–PET/CT for follow-up. Asymptomatic patients with morphological residues should receive routine follow-up FDG–PET/CT for the first 24 months. Only patients with advanced initial stage do need a routine follow-up FDG–PET/CT beyond 24 months.

**Key words:** follow-up, Hodgkin's lymphoma, PET/CT



## introduction

The primary goal of follow-up in cancer patients is to identify early recurrent disease. In Hodgkin's lymphoma (HL), detection of early or even preclinical relapse would allow the timely administration of appropriate salvage therapy and eventually improve survival [1, 2]. Current guidelines for patients with HL recommend computed tomography (CT) to assess the remission status after first-line treatment and the only indication for additional radiographic investigations is the new onset of suspicious clinical symptoms [3]. 2-[Fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (PET) may be considered for pretreatment staging and for the evaluation of response during and after first-line treatment [4].

Only limited evidence exists to support the use of FDG–PET for routine follow-up of asymptomatic patients [5, 6]. One recent study evaluated serial FDG–PET for follow-up of HL and aggressive non-Hodgkin's lymphoma (NHL) patients prospectively [7]. A substantial subset of patients had recurrence of HL and NHL during follow-up, and the authors concluded that FDG–PET might be a valid tool for surveillance of these patients.

Several risk factors for relapse of HL after successful first-line treatment have been described in the last decade [8]. The goal of our study was to investigate the value of follow-up FDG–PET/CT in patients with HL after completion of first-line therapy and emphasize the impact of risk factors on the recurrence rates. We aimed to identify patients at risk for relapse and to define a subset of patients who would benefit from FDG–PET/CT imaging during follow-up.

## patients and methods

### patients

Patients with HL in complete remission after first-line treatment who received at least one FDG–PET/CT during their follow-up from the beginning of 2002 until the end of 2008 were included in this study.

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FDG–PET/CT imaging data were acquired on a combined PET/CT in-line system (Discovery LS, RX or Discovery STE, GE Health Systems, Milwaukee, WI), which permits the acquisition of coregistered CT and PET images in a single session.

All FDG–PET/CT scans were evaluated for the presence of abnormal FDG uptake and residual disease. All image analysis was routinely carried out by two dual-board-certified nuclear radiology physicians in consensus. Complete remission in these patients had to be documented by one appropriate imaging modality within 1 month after completion of first-line treatment (CT alone, CT and FDG–PET, or FDG–PET/CT). All imaging was carried out at our institution. CT scans were assessed for residual disease using the International Workshop Criteria (IWC) [9].

A residual morphological mass after the end of treatment was defined as a lesion that had regressed by >75% but was still >1.5 cm in its greatest axial diameter. We further documented the initial stage of disease using the Ann Arbor classification. Age, gender and signs of recurrence were assessed and recorded by the referring physician before the follow-up FDG–PET/CT imaging was carried out. Signs of recurrence included B symptoms or new suspicious masses. Relapse-free survival (RFS) was assessed in all patients from the initial date of diagnosis until the date of recurrence as documented by FDG–PET/CT. Histological confirmation was mandatory in all patients with suspected recurrent disease found with FDG–PET/CT. Our institutional ethics committee had approved the study. Due to the retrospective nature of the study, written informed consent of the patients was waived.

### assessment of risk factors and patient classification

CT scans after completion of first-line treatment were assessed for residual morphological masses at the initial lymphoma sites using the IWC criteria described above. Patients were assessed for advanced (IIIA–IVB) versus early (IA–IIB) stage by Ann Arbor classification, age (>45 and <45 years) and gender. Patient classification into the symptomatic or asymptomatic group was done on the basis of reported symptoms or referral notes by the treating physician.

### statistical analysis

Three groups of patients were analyzed: asymptomatic patients before referral for FDG–PET/CT, symptomatic patients before referral for FDG–PET/CT and all the patients combined. All three groups were analyzed according to the known risk factors such as a residual morphological mass after the end of treatment, advanced stage (greater than IIB), age >45 years and male gender. Log-rank tests and Kaplan–Meier analysis were used to assess the influence of single risk factors. Cox regression was used to assess partial influences of several risk factors. All statistical calculations were carried out with the Statistical Analysis Software SPSS 16 (SPSS Inc., Chicago, IL).

## results

### patients and disease status

We collected data from patients with HL who received one or more follow-up FDG–PET/CT scans from 2002 to 2008 at our institution. From 206 patients initially indexed, 72 patients had to be excluded from analysis due to incomplete follow-up data or administration of second-line treatment before FDG–PET/CT was carried out. Overall, 134 patients with HL (81 male, 53 female; mean age 34.12 ± 15.34 years) were eligible for analysis. All patients had initially received CT alone ($n = 33$), FDG–PET and CT ($n = 16$), or FDG–PET/CT ($n = 85$) at the end of their first-line therapy. The patient populations are listed in Table 1.

**Table 1.** Asymptomatic and symptomatic patient groups

| | *n* | % |
|---|---|---|
| A. Asymptomatic patients ($n = 83$) | | |
| Recurrence | | |
| Yes | 10 | 12.0 |
| No | 73 | 88.0 |
| Morphological residual mass | | |
| Yes | 41 | 49.4 |
| No | 42 | 50.6 |
| Stage of disease | | |
| Early (IA–IIB) | 51 | 61.4 |
| Advanced (IIIA–IVB) | 32 | 38.6 |
| Gender | | |
| Female | 36 | 43.4 |
| Male | 47 | 56.6 |
| Advanced age | | |
| <45 years | 64 | 77.1 |
| >45 years | 19 | 22.9 |
| B. Symptomatic patients ($n = 51$) | | |
| Recurrence | | |
| Yes | 32 | 62.7 |
| No | 19 | 37.3 |
| Morphological residual mass | | |
| Yes | 25 | 49.0 |
| No | 26 | 51.0 |
| Stage of disease | | |
| Early (IA–IIB) | 29 | 56.9 |
| Advanced (IIIA–IVB) | 22 | 43.1 |
| Gender | | |
| Female | 17 | 33.3 |
| Male | 34 | 66.7 |
| Advanced age | | |
| <45 years | 42 | 82.4 |
| >45 years | 9 | 17.6 |

Eighty-three (61.9%) patients had no symptoms and 51 (38.1%) patients were symptomatic before FDG–PET/CT. Forty-two (31.3%) patients had a recurrence during further follow-up. Disease recurrence was confirmed by histology and all relapsing patients received salvage chemotherapy. Ten (7.5%) patients in the asymptomatic patient group and 32 (23.9%) in the symptomatic patient group had recurrence as determined by FDG–PET/CT. The mean RFS in the patient group with recurrence ($n = 42$) was 26.9 months (4.6–191.5 months). The mean follow-up time of patients without recurrence from the end of first-line treatment until last negative FDG–PET/CT scan ($n = 92$) was 38.72 months (4.8–203 months). None of the patients with a negative follow-up FDG–PET/CT scan relapsed before the end of the study. FDG–PET/CT was able to detect relapses with a positive predictive value (PPV) of 0.98.

### risk factor assessment

*single risk factors.* In the whole patient population ($n = 134$), symptoms before follow-up FDG–PET/CT and morphological residual masses seen on CT after the end of treatment were predictive for recurrence ($P < 0.0001$, hazard ratio (HR) 4.886,

95% confidence interval (CI) 2.403–9.938 and $P = 0.0005$, HR 3.362, 95% CI 1.710–6.609; Figure 1A and B). Age >45 years at initial diagnosis, advanced stage of disease and male gender were not associated with a higher risk of relapse.

When analyzing the groups of symptomatic and asymptomatic patients separately, a documented morphological residual mass after first-line treatment remained the only significant risk factor for relapse [asymptomatic:

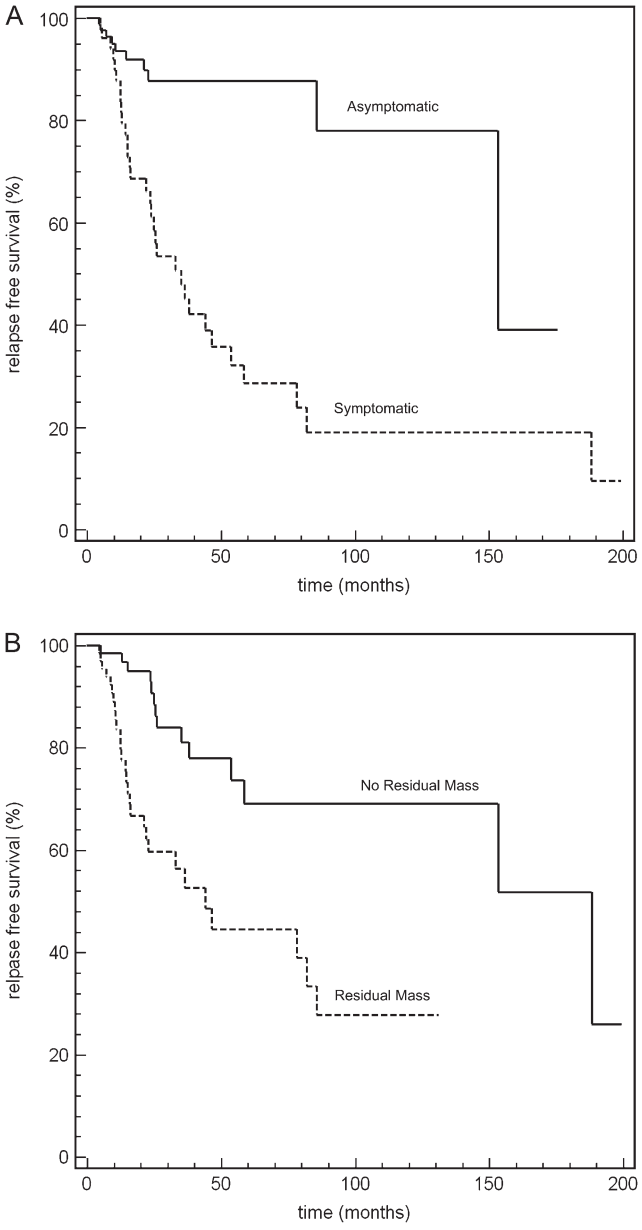


**Figure 1.** (A) Kaplan–Meier analysis of the relapse-free survival of asymptomatic patients compared with symptomatic patients during follow-up; $P < 0.0001$, HR 4.886, 95% confidence interval (CI) 2.403–9.938 (solid line: asymptomatic patients and dashed line: symptomatic patients). (B) Kaplan–Meier analysis of the relapse-free survival of patients with and without morphological residual mass after end of first-line treatment; $P = 0.0005$, HR 3.362, 95% CI 1.710–6.609 (solid line: patients with no morphological residual mass and dashed line: patients with morphological residual mass).

$P = 0.0011$ (HR = 9.033, 95% CI 2.418–336.700); symptomatic: $P = 0.01802$ (HR = 2.4068, 95% CI 1.1667–4.9647)].

*multiple risk factors.* Cox regression was used to assess the association between several risk factors and hazard of recurrence. Analyzed covariates were age >45 years at time of diagnosis, a morphological residual mass, gender, advanced stage of disease and symptoms before referral for FDG–PET/CT. The overall model fit shows a significant chi square 42.067, 5 *df*, $P < 0.0001$. Significant covariates were morphological residual mass ($P = 0.00016$, HR = 3.8387, 95% CI 1.9158–7.6915), advanced stage ($P = 0.03644$, HR 1.9900, 95% CI 1.0478–3.7794) and symptoms before referral ($P < 0.0001$, HR 5.1161, 95% CI 2.5002–10.4688) (Table 2).

These risk factors were added (zero to three risk factors) and used in the Kaplan–Meier method and the log-rank test. Symptoms, a morphological residual mass, advanced stage of disease or a combination of these factors identified patients at risk for recurrence ($P < 0.0001$). No asymptomatic patient without a morphological residual mass and an early stage of disease showed recurrence on the FDG–PET/CT and none of them recurred during later follow-up. The median RFS was not reached in patients without any of these risk factors. In patients with one risk factor present the RFS was 153.4 months, with two risk factors 35.2 months and with three risk factors 16.2 months (Figure 2). We also used the Cox proportional hazards regression within the first 24 months (patients $n = 69$) and after 24 months (patients $n = 65$). In the first 24 months, the only significant risk factor was morphological residual mass ($P = 0.0019$, HR 7.5994, 95% CI 2.1170–27.2796). Risk factors for recurrence after 24 months were symptoms ($P = 0.0009$, HR = 14.5627, 95% CI 3.0398–69.7657) and advanced stage ($P = 0.0426$, HR 3.6144, 95% CI 1.0569–12.3601) (Tables 3 and 4).

## discussion

We evaluated the role of FDG–PET/CT for patients with HL after first-line therapy. Our study population included symptomatic as well as asymptomatic patients after first-line therapy. All patients were analyzed with regard to the

**Table 2.** .Cox proportional hazards regression with risk factors as covariates in all patients (overall model fit chi square 42.067, 5 *df*, significance level $P < 0.0001$)

| Factor | Significance (*P* value) | Hazard ratio | 95% CI of hazard ratio |
|---|---|---|---|
| Age > 45 | 0.4463 | 0.7241 | 0.3168–1.6550 |
| Stage > IIB | 0.0364 | 1.9900 | 1.0478–3.7794 |
| Male gender | 0.8551 | 0.9414 | 0.4941–1.7938 |
| Residual disease | 0.0002 | 3.8387 | 1.9158–7.6915 |
| Symptoms | <0.0001 | 5.1161 | 2.5002–10.4688 |

Advanced stages, residual disease and symptoms are predictive factors for recurrence in the follow-up of HL patients in FDG–PET/CT.
CI, confidence interval; HL, Hodgkin's lymphoma; FDG–PET, 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography; CT, computed tomography.

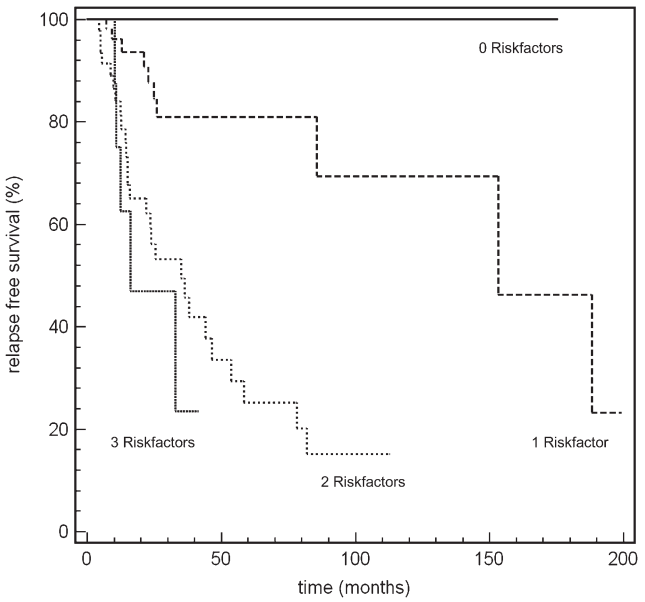


**Figure 2.** Kaplan–Meier analysis of the relapse-free survival of patients with the risk factors symptoms, morphological residual mass and advanced stage (solid line: zero risk factors, dashed line: one risk factor, points: two risk factors and dashed line and points: three risk factors), $P < 0.0001$.

**Table 3.** Cox proportional hazards regression with risk factors as covariates in all patients within the first 24 months (overall model fit chi square 18.230, 5 *df*, significance level $P = 0.0027$)

| Factor | Significance (*P* value) | Hazard ratio | 95% CI of hazard ratio |
|---|---|---|---|
| Age > 45 | 0.5553 | 0.7027 | 0.2189–2.2556 |
| Stage > IIB | 0.5225 | 1.3443 | 0.5453–3.3140 |
| Male gender | 0.7825 | 0.8872 | 0.3810–2.0659 |
| Residual disease | 0.0019 | 7.5994 | 2.1170–27.2796 |
| Symptoms | 0.0925 | 2.1438 | 0.8859–5.1881 |

Residual disease and symptoms are predictive factors for recurrence in the early follow-up (<24 months) of HL patients in FDG–PET/CT.
CI, confidence interval; HL, Hodgkin's lymphoma; FDG–PET, 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography; CT, computed tomography.

**Table 4.** Cox proportional hazards regression with risk factors as covariates in all patients after the first 24 months (overall model fit chi square 21.53, 5 *df*, significance level $P = 0.0006$)

| Factor | Significance (*P* value) | Hazard ratio | 95% CI of hazard ratio |
|---|---|---|---|
| Age > 45 | 0.4831 | 0.6272 | 0.1714–2.2947 |
| Stage > IIB | 0.0416 | 3.6144 | 1.0569–12.3601 |
| Male gender | 0.6469 | 0.7782 | 0.2676–2.2633 |
| Residual disease | 0.1998 | 2.1595 | 0.6696–6.9648 |
| Symptoms | 0.0009 | 14.5627 | 3.0398–69.7657 |

Only symptoms are predictive for recurrence in the later follow-up (>24 months) of HL patients in FDG–PET/CT.
CI, confidence interval; HL, Hodgkin's lymphoma; FDG–PET, 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography; CT, computed tomography.

established risk factors: advanced stage of disease, advanced age, gender and morphological residual mass after first-line treatment.

Symptoms as the reason for patient referral were the most important risk factor. However, a few asymptomatic patients also had unsuspected recurrence. Further prognostic risk factors were tumor residues at the end of treatment and advanced stage of disease. None of the patients with initial early-stage disease and without a residual mass relapsed during follow-up. In our study, the high diagnostic yield of FDG–PET/CT for the follow-up is evident by the PPV of 0.98.

In a recent study by Zinzani et al., a large prospective trial with 421 patients, FDG–PET found 41 relapses at 6 months, 30 relapses at 12 months, 26 relapses at 18 months and 10 relapses at 24 months. This study concludes that FDG–PET is a valid tool for follow-up of patients with HL and NHL [7]. However, this conclusion is debatable because of rising concerns over the limitless use of imaging modalities regarding patient safety and economic costs [10]. Using the patient population of the latter study, 842 scans were done after 1 year identifying 71 relapses. Therefore, 11.86 scans were needed to identify one relapse. Using the full 2-year period, a total of 1684 FDG–PET scans identified 107 relapses. This equals 15.73 FDG–PET scans to identify one relapse of HL or NHL. Several studies have shown that diagnosis of recurrence is made on clinical grounds in 80% of all cases; it is the patient or the physician who indicates the possibility of relapse on clinical grounds, before confirmation by routine imaging studies [11–13].

We observed 10 (12%) recurrences in the asymptomatic patient group ($n = 83$), corresponding to 8.3 scans for detection of one relapse in asymptomatic patients. This result is similar to the data presented by Zinzani et al. In the symptomatic patient population ($n = 51$), we observed 32 (63%) recurrences. Accordingly, 1.59 scans were necessary to find one true recurrence in patients with new suspicious symptoms.

By combining the three parameters morphological residual mass after first-line treatment, symptoms and advanced stage of disease to create a risk score, we can assess the risk of relapse for a patient and the benefit of further imaging. While we observed no recurrences in patients without any of the three parameters, the RFS decreased markedly in patients who had a higher risk score. By using such risk-adapted strategy for the follow-up of patients with HL, the need for FDG–PET/CT scanning could be optimized and lead to reduced radiation exposure for our patients and savings of health care costs.

We also found a time delay of the risk factor 'symptoms before referral' in the prediction of recurrence. Cox proportional hazards regression in the first 24 months identified only morphological residual mass to be predictive for recurrence. After 24 months, symptoms before referral and advanced stage of disease were predictive for recurrence but residual morphological masses were not predictive. This finding highlights the importance of morphological residual mass as a risk factor in early follow-up, as demonstrated by a recent prospective trial [14]. Accordingly, surveillance of asymptomatic patients with FDG–PET/CT may be useful during early follow-up, while the probability of a relapse decreases after the first 24 months. On the other hand,

symptoms may be important during later follow-up and FDG–PET/CT should be considered in symptomatic patients.

The retrospective nature of this study is its most important limitation. It does not allow us to draw definitive conclusions. Furthermore, not all patients had FDG–PET at the end of first-line treatment. The Revised Response Criteria for Malignant Lymphoma published in Journal of Clinical Oncology 2007 includes FDG–PET at the end of first-line therapy [9]. Current oncology guidelines do not include mandatory FDG–PET after the end of therapy and our patient data reflect a normal HL patient collective. The RFS for our collective patient data is low compared with the data usually reported in the literature. This reflects a patient referral for PET/CT due to suspected recurrence by the treating physician and reflects a bias. However, the goal of our study was to develop a rationale and cost-effective strategy for the use of FDG–PET/CT imaging in a well-defined patient population after completion of first-line therapy.

In conclusion, FDG–PET/CT reliably detects recurrent HL after first-line therapy. However, it should only be considered in patients with clinical signs of recurrence at any time point, in patients with morphological residual mass within the first 24 months and in patients with advanced initial stage (greater than IIB) after 24 months after end of first-line treatment.

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