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Positron Emission Tomography Scanning in the Management of Hodgkin Lymphoma Patients: A Single-institution Experience

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of article

Abstract

Background. Positron emission tomography (PET-CT) has become a valuable implement in the management of Hodgkin lymphoma (HL). However, since PET-CT is a relatively new imaging method, its capabilities have not been fully explored.

Objectives. The aim of the study was to evaluate the role of PET-CT at different points in HL management.

Material and Methods. The medical documentation of 47 HL patients treated at the Comprehensive Cancer Center in Białystok, Poland, was analyzed retrospectively. The study group consisted of 15 men and 32 women, aged 18–59 years, in HL clinical stages II–IV, treated either with chemotherapy or sequential chemoradiotherapy.

Results. In 65.2% of the patients who underwent post-chemotherapy PET-CT scanning before their qualification for adjuvant radiotherapy (RT), PET-CT was decisive in qualifying them for RT, by establishing whether or not metabolic partial remission (PR) had occurred. With regard to the achievement of partial or complete response (CR), computed tomography (CT) and PET-CT results correlated in 45.5% of the patients after the completion of chemotherapy, and in 18.7% after the completion of the entire treatment (chemotherapy or chemoradiotherapy). Among the patients from the advanced-stage group (stages III/IV stage and/or bulky HL), morphological PR in CT scans after two to three courses of chemotherapy was more often associated with a lack of metabolic CR in post-treatment PET-CT scanning ($p = 0.022$) than in other patients. Post-treatment PET-CT scanning was shown to be highly prognostic of a relapse-free follow-up ($p < 0.0001$) and superior to post-treatment CT imaging in relapse prediction ($p < 0.0001$).

Conclusions. Compared to CT, PET-CT was more accurate in residual masses assessment. Notable ability of PET-CT in relapse-free follow-up prediction encourages to more common use of PET-CT in clinical practice. Further clinical research on the need for RT in patients with PR in CT parallel to CR in PET-CT is required (**Adv Clin Exp Med 2016, 25, 6, 1185–1192**).

Key words: computed tomography, Hodgkin lymphoma, positron emission tomography, residual masses.

Hodgkin lymphoma (HL) is a malignancy originating from the B lymphocytes of lymph nodes' germinal centers. It accounts for approximately 11% of all lymphomas [1]. In developed countries there are two peaks of HL prevalence: in young adults (20–30 years old) and in the older population (around 60 years old). Asymptomatic localized lymphadenopathy, particularly involving the cervical, supraclavicular and mediastinal regions, is known to be the major clinical presentation of HL [2]. In some cases bulky HL is diagnosed on the basis of imaging studies. Bulky disease refers to

the presence of a large mediastinal mass of at least 10 cm in width, or a mass occupying at least one-third of the internal transverse diameter of the thorax. It is known to be an adverse prognostic factor [3]. The treatment of patients suffering from HL, based on either chemotherapy alone or in combination with radiotherapy, depends on the clinical stage of the disease and prognostic factors [4].

Appropriate imaging is of essential importance throughout the diagnostic and therapeutic process. Computed tomography (CT) remains a standard imaging study in HL because it is gen-

erally available, reproducible and easy to perform, and there is credible evidence of its diagnostic significance [5]. It is used in the assessment of the extent of the primary disease, in monitoring disease regression during therapy and in determining the final response to the administered treatment (re-staging) [6, 7]. Nonetheless, some restrictions of CT usage in HL management are known. Firstly, minor lesions (less than 1.5 cm in diameter) are likely to be missed [7]. Moreover, determining the character of residual masses (i.e., differentiating between fibronecrotic scar tissue and a persistent lymphoma mass) is extremely difficult [8, 9].

By detecting cells' metabolic function, positron emission tomography-computed tomography (PET-CT) makes it possible to address the imperfections of CT scanning [8]. Owing to enhancement of the uptake of the radiotracer ^{18}F -fluorodeoxyglucose (^{18}F -FDG), not only is it feasible to detect even slight neoplastic areas that are imperceptible on CT scans, but residual masses can also be investigated (Fig. 1) [10]. An interim PET-CT carried out after two or three cycles of chemotherapy helps to evaluate the response to current treatment, and therefore allows for adjustment of the therapy to the individual case, if required. Likewise, the prognostic value of interim PET-CT has been demonstrated [11].

Currently, the assessment of HL therapy outcomes on the basis of anatomical imaging studies is done in accordance with revised Response Evaluation Criteria In Solid Tumors (RECIST) guidelines (v. 1.1) [12]. Complete response (CR) refers to the disappearance of all target lesions, with a simultaneous decrease in the short axis of any path-

ological lymph node to < 10 mm. Partial response (PR) is a 30% decrease (minimum) in the sum of the target lesions' diameters. Progressive disease (PD) is the designation when the sum increases by at least 20% or when a new lesion appears. A reduction or increase in diameter that cannot be classified either as PR nor as PD is designated as stable disease (SD). As pointed out in the revised RECIST guidelines, there is no undeniable data that discredits the substantial role of morphological assessment of tumor burden [12]. PET-CT imaging, however, could be a useful approach in the assessment process, provided further evidence for its role is obtained [12].

In the assessment of treatment response on the base of PET-CT imaging, the Deauville five-point scale is used. A visual interpretation of ^{18}F -FDG uptake is compared to uptake in the mediastinal blood pool and liver. Scores 1, 2 and 3 stand for CR; 4 and 5 are considered PR, unless there has been no significant change in ^{18}F -FDG uptake from baseline (SD), or if there is an increasing intensity or new malignant focus (PD).

So far the official worldwide guidelines regarding HL have referred to PET-CT use rather cautiously. However, a more and more appreciable role of PET-CT is being emphasized [13]. In its current recommendations of diagnostic and therapeutic proceedings in malignant tumors, the Polish Society for Medical Oncology encourages the use of PET-CT scanning at different points in HL management, particularly supporting it in the assessment of final post-therapy outcome [14].

Due to the relatively short history of its clinical usage in Hodgkin disease, the full capabilities and

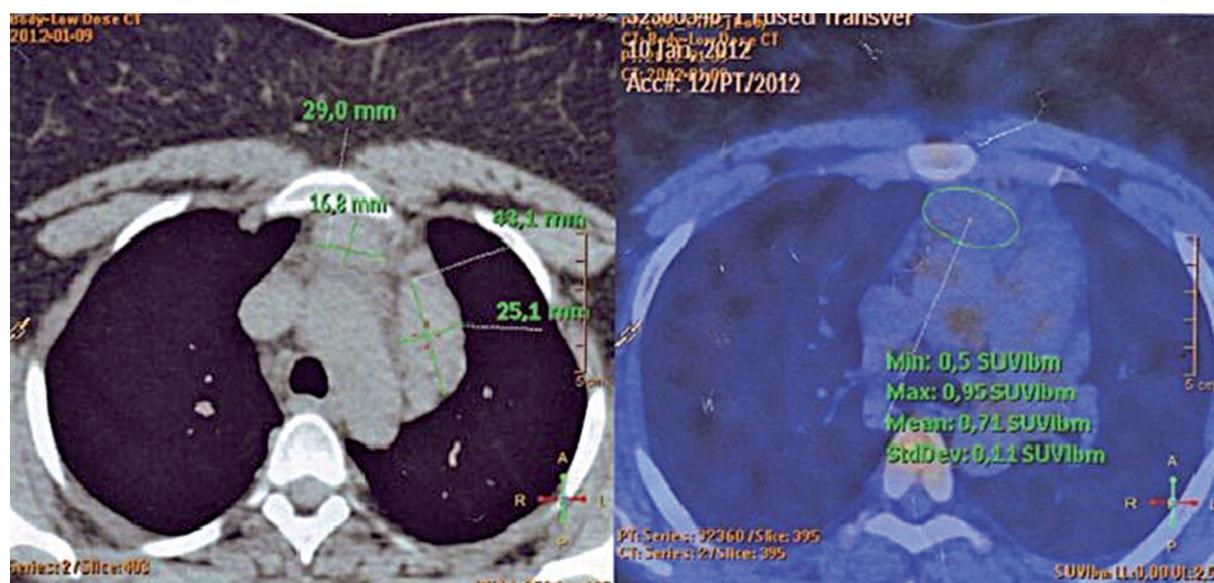


Fig. 1. A comparison of computed tomography (CT) and positron emission tomography (PET-CT) results in Hodgkin lymphoma patient after completion of chemotherapy. The CT (left) reveals residual masses, however no evidence of active disease is present on the PET-CT scan (right)

limitations of PET-CT still have been not thoroughly explored. Therefore, in order to unequivocally define the exact role of PET-CT in HL management, further clinical research should be performed.

The aim of the present study was to analyze current usage of PET-CT and its clinical usefulness in HL patients at one of the comprehensive cancer centers in Eastern Poland.

Material and Methods

A retrospective analysis of the medical documentation of 67 classical Hodgkin lymphoma patients treated at the Comprehensive Cancer Center in Białystok, Poland, between May 2007 and February 2014 was performed. In 47 cases, PET-CT scanning with 2-[F-18]-fluoro-2-deoxy-D-glucose (¹⁸F-FDG) was carried out at least once during HL management, therefore only those patients were included in the study group. The group was composed of 32 women and 15 men, aged 18–59 years at the time of diagnosis (mean age 33.38 ± 10.08) (Table 1). The extent of the disease, determined on the basis of the Ann Arbor staging system with the Cotswolds modifications, ranged between stages II and IV. Advanced-stage HL, defined as stages III/IV and/or the presence of bulky HL, was found in 25 cases (53.2%). The remaining patients (stages IIA and IIB) were included in the early-stage HL group. All the patients were treated with the doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) chemotherapy regimen, which was followed by radiotherapy (RT) in 80.9% of cases. Furthermore, in

Table 1. Study group characteristics

Characteristics	Patients	
	n	(%)
Sex		
male	15	(31.9)
female	32	(68.1)
Stage (Ann Arbor scale)		
II	28	(59.6)
III	13	(27.6)
IV	6	(12.8)
CS (clinical stage)		
early-stage HL	22	(46.8)
advanced-stage HL	25	(53.2)
Treatment modality		
CTh	9	(19.1)
CTh-RT	38	(80.9)

HL – Hodgkin lymphoma; CTh – chemotherapy; CTh-RT – chemoradiotherapy.

cases of progression (found in 5 patients), auto-hematopoietic stem cell transplantation (auto-HCT) was performed, preceded by salvage chemotherapy regimens: dexamethasone/cytarabine/cisplatin (DHAP) in three patients, and ifosfamide/carboplatin/etoposide (ICE) in two patients. Radiological studies performed at different points in HL management, included CT and PET-CT.

The initial CT result was considered positive when a nodal mass or extranodal lesion was found with the longest diameter greater than 1.5 cm and 1.0, respectively. RECIST guidelines (v. 1.1) were used to assess subsequent CT results and assign them to either the CT-positive group (PR, PD) or the CT-negative group (CR). Each PET-CT result was assigned to a particular group on the Deauville five-point scale. PR, SD or PD were designated as PET-CT positive, whereas CR was considered PET-CT negative.

A statistical analysis was performed using GraphPad Prism 5 software (GraphPad Software Inc., La Jolla, USA). The χ^2 test was used and a p-value less than 0.05 was considered statistically significant.

Privacy protection policies were abided by throughout the study and ethical approval was obtained from the Ethics Committee of the Medical University of Białystok, Poland.

Results

PET-CT scanning was performed once in 66% of the patients, twice in 21.2%, three times in 6.4% and four times in 6.4%. The various time points when PET-CT scans were performed are juxtaposed in Fig. 2. In the vast majority of cases (95.7%), PET-CT was used to evaluate the final response to the applied treatment (chemotherapy or chemotherapy followed by RT). The use of interim

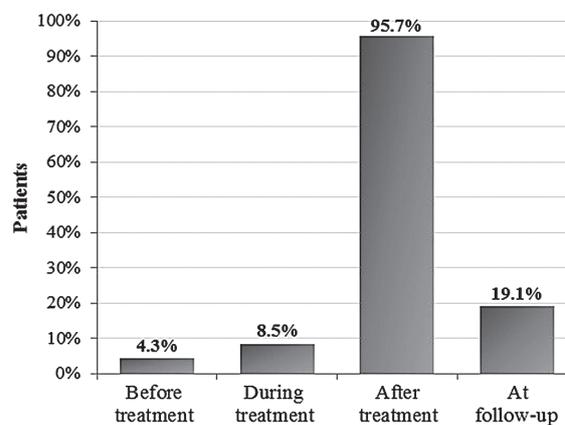


Fig. 2. Timing of PET-CT examinations in the management of Hodgkin lymphoma patients

PET-CT was noted in four patients (8.5%). In nine cases (19.1%), PET-CT was used at a follow-up evaluation, either routinely or to detect a recurrence suspected in clinical examination. This imaging method was found to be least frequently employed in initial staging process, being used for this purpose in only two patients (4.3%).

In 23 patients (48.9%) PET-CT was ordered after chemotherapy and before they were qualified for RT. For the majority of these patients (15 cases, 65.2%), the PET-CT result was decisive either for foregoing RT (when complete metabolic remission was observed) or administering (when complete metabolic response had not been achieved). There were eight patients (34.8%) who were qualified for RT irrespective of their PET-CT results. Among them, seven were administered RT despite PET-CT negativity (complete response), primarily due to either bulky disease at the baseline or considerable residual masses in CT scans after chemotherapy. All patients diagnosed with bulky disease (10, or 21.3%) were qualified for RT. Post-chemotherapy PET-CT was carried out in only 4 of them, and metabolic CR did not change the decision regarding RT administration in any of these patients.

Residual masses were revealed in 17 of the 19 patients in whom post-chemotherapy CT was performed. Subsequently, 10 of them underwent PET-CT examinations and CR was found in five patients. Two of them were spared irradiation due to PET-CT negativity.

Both CT and PET-CT were performed after completion of the planned chemotherapy in 11 patients (23.4%); on average, the CT scans were performed four days after the completion of chemotherapy and the PET-CT scans 5.9 weeks after. A discrepancy between the results of the two tests was observed in 54.5% of the patients: mostly, while the CT scans revealed morphological PR, metabolic complete remission (CR) was shown in the PET-CT scans (Table 2a). One case of progressive disease was also detected by PET-CT where CT indicated morphological PR. In the remaining cases the PET-CT and CT results were concordant.

Completion of the planned therapy (chemotherapy or chemoradiotherapy) was followed by both CT and PET-CT in 16 patients (34%); on average, the CT scans were performed 6.4 weeks after the completion of treatment and the PET-CT scans 12.25 weeks after. PET-CT and CT results were dissonant in 13 cases (81.3%) (Table 2b), and again, the most prevalent variance was CT positivity (PR) while the PET-CT showed that metabolic CR had been achieved.

There were 30 patients (19 from the advanced-stage group and 11 from the early-stage group) in whom CT scans were performed after

Table 2. Comparison of PET and CT results (a) after chemotherapy and (b) after completion of the entire treatment (chemotherapy or chemoradiotherapy) in Hodgkin lymphoma patients

(a)

		CT	
		CR	PR
PET	CR	1	5
	PR	–	4
	PD	–	1

(b)

		CT		
		CR	PR	PD
PET	CR	2	9	1
	PR	–	1	–
	PD	–	3	–

PET – positron emission tomography; CT – computed tomography; CR – complete remission; PR – partial remission; PD – progressive disease.

two or three cycles of chemotherapy, as well as PET-CT following the completion of the planned treatment. It was found that among the advanced-stage HL patients, partial morphological response in CT was significantly more often associated with the absence of complete metabolic remission in PET-CT ($p = 0.022$) (Fig. 3), compared to early-stage patients.

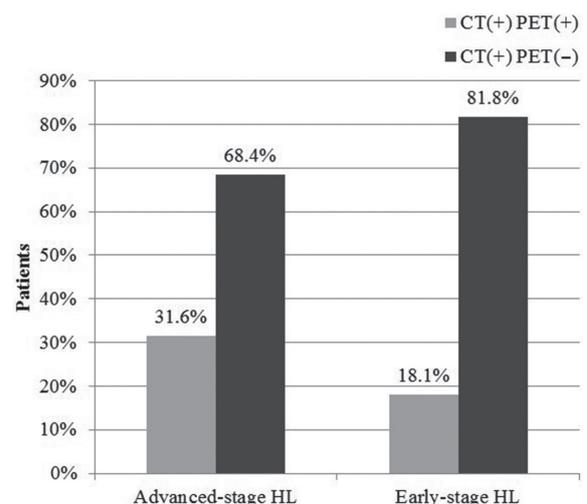


Fig. 3. A juxtaposition of results of computed tomography (CT) after 2–3 cycles of chemotherapy and positron emission tomography (PET-CT) after the completion of treatment (chemotherapy or chemoradiotherapy) in Hodgkin lymphoma patients. CT(+) – partial remission in CT; PET(+) – partial remission in PET; PET(–) – complete remission in PET

Table 3. Post-treatment (chemotherapy or chemoradiotherapy) PET results in relation to relapse occurrence in Hodgkin lymphoma patients

PET result \ Relapse	n = 30	
	Relapse n (%)	Relapse-free n (%)
PET(+)	4 (13.3)	1 (3.3)
PET(-)	0	25 (83.3)

PET – positron emission tomography; PET(+) – partial remission in PET; PET(-) – complete remission in PET.

This study also sought to determine whether there is any correlation between PET-CT results after the completion of therapy and subsequent relapse occurrence. There were 30 cases in which it was possible to investigate both PET-CT scans following the completion of treatment and follow-up data (Table 3). The average time of observation was 19.9 months (3–53 months). In 26 patients no relapse was observed. Among them, CR in PET-CT was achieved in 25 cases and PR in one case. Conversely, in one patient who experienced disease recurrence, the post-treatment PET-CT scan showed PR. PET-CT scans performed as part of post-treatment evaluation showed high predictive value regarding possible relapse occurrence ($p < 0.0001$).

For comparison, the results of CT scans following therapy were available in 16 cases (mean time of observation: 17.4 months; 3–52 months).

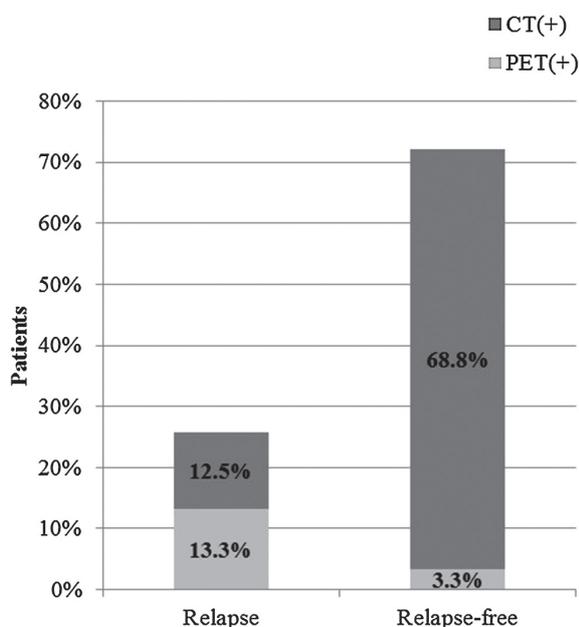


Fig. 4. Positron emission tomography (PET-CT) and computed tomography (CT) results after the completion of treatment (chemotherapy or chemoradiotherapy) in relation to relapse occurrence among Hodgkin lymphoma patients. CT(+) – partial remission in CT; PET(+) – partial remission in PET

Although in 11 cases (69%) morphological CR was not achieved, no relapses were noted in the follow-up. In another three patients (18.75%), relapse-free follow-up was preceded by CR in post-treatment CT imaging; recurrence was experienced by the remaining two patients (12.5%) whose post-treatment CT scans were positive.

A comparison of positive post-treatment CT and PET-CT results in relation to future relapse occurrence (Fig. 4) showed the superior predictive value of PET-CT in this respect ($p < 0.0001$).

A general increase in the number of PET-CT examinations was observed in the time period reflected in the study. In 2008 only five PET-CT studies were performed, whereas in 2010 the number rose to 14. In 2013 PET-CT was performed over four times more often than in 2008 (21 studies).

Discussion

In this study CT was the imaging method of choice during the initial HL staging process. The very rare implementation of PET-CT in staging (only 4.3% of the patients) is conspicuous. This probably results from the higher costs of PET-CT compared to CT, the small number of PET-CT centers in the region, and the lack of well-defined recommendations concerning PET-CT implementation in routine practice. It is noteworthy that in one recent study PET-CT imaging – in comparison with CT alone – was shown to upstage the disease among patients initially diagnosed as stage I or II [15]. However, the official recommendations concerning the use of PET-CT in initial HL staging are slightly inconsistent. The National Comprehensive Cancer Network (NCCN) defines PET-CT as an integral part of this procedure [13], whereas in the European Society for Medical Oncology (ESMO) guidelines PET-CT is considered only an additional tool that may be included in the staging process [16].

Interim PET-CT is a promising implement that could make the treatment of HL patients more individualized. It has been reported to predict treatment failure in advanced-stage Hodgkin disease [11]. An early PET-CT examination and its role in further treatment stratification are being investigated by the ongoing HD18 trial [17]. However, since evidence from randomized trials is still being collected, interim PET-CT has not been established as a standard yet. The Consensus of the Imaging Subcommittee of the International Harmonization Project in Lymphoma stated that for now the use of this imaging method to monitor treatment during therapy should be confined to clinical trials or prospective registries [9].

It was difficult to investigate the usefulness of interim PET-CT in the present study, since its implementation was rare.

The need for RT use among advanced-stage HL patients with initial bulky disease and/or residual lesions in post-treatment imaging studies still remains unclear. According to the current ESMO guidelines, the standard treatment for advanced-stage HL comprises chemotherapy followed by RT only when residual post-chemotherapy masses are found [16]. In the present study this standard scheme was implemented in the vast majority of advanced-stage HL patients. However, as the German Hodgkin Study Group (GHSG) HD15 trial has recently showed, RT could be omitted – irrespective of residual masses – when PET-CT negativity is demonstrated in patients treated with the BEACOPP chemotherapy regimen [18]. Similarly, Savage et al. reported that omitting consolidative RT did not increase the risk of relapse in advanced-stage HL patients who had received ABVD-based chemotherapy, provided PET-CT scans showed complete response [19]. Furthermore – unlike the GHSG HD15 trial – the study by Savage et al. referred to cases with bulky HL at the baseline, and found that in cases of post-chemotherapy PET-CT negativity there was no statistically significant difference between non-irradiated bulky and non-bulky patients in terms of three-year time-to-progression [19]. Although these results seem promising, and avoiding RT-related toxicity would be definitely very beneficial, further PET-CT-exploiting research on the need for RT among advanced-stage HL patients is still required. In cases where post-chemotherapy RT is considered inevitable, PET-CT has been found essential in planning radiotherapy [20]. It could decrease both the irradiation volume and target misses.

As far as the role of PET-CT in surveillance is concerned, it has been recognized in the NCCN guidelines as unnecessary [13]. Likewise, recent research is providing a growing body of evidence of the limitations in PET-CT usage in follow-up. For instance, a substantial number of false-positive PET-CT results was revealed in routine surveillance among patients who had achieved remission after first-line therapy, which is particularly unfortunate considering the high costs involved [21]. Maeda et al. also reported that PET-CT has low positive predictive value in surveillance [22]. In contrast, in an investigation of clinically suspected relapse Hutchings reported that PET-CT has high nega-

tive predictive value and considered it eligible for this purpose [23]. The present study seems to reflect Hutchings's results, since among five patients who were clinically suspected of relapse at follow-up (mean 7.2 months after completing treatment) PET-CT accurately determined the character of the suspicious lesions, whereas none of the patients in whom PET-CT was implemented in routine surveillance was shown to relapse (mean 25 months of observation).

The present study revealed a striking discrepancy between morphological and functional response to chemotherapy and chemoradiotherapy. The most prominent discordance was a complete metabolic response in PET-CT parallel to a partial morphological remission in CT. Although the mean time after treatment completion differed between the two types of scan, these results seem to point to the need for combined interpretation of PET-CT and CT in the assessment of treatment outcome. This is of particular importance since most evidence-based recommendations concerning the treatment of HL patients are derived from randomized trials based on CT assessment.

The present study showed that post-treatment PET-CT results are highly predictive of relapse occurrence in the future, which is in line with previous reports [24, 25]. Moreover, it was found to be incomparably superior to CT imaging as a predictor of relapse.

Undoubtedly, the high cost of PET-CT examinations is a drawback that stands in the way of broader usage of this imaging method in clinical practice. Furthermore, although the availability of PET-CT is improving, it is still less accessible than CT scanning. Since the results of clinical studies on the role of PET-CT in HL are very promising and the use of PET-CT is expected to increase, steps should be undertaken to address the problems with costs and accessibility.

In conclusion, in the present study PET-CT results were decisive for further management decisions. PET-CT was found to be superior to CT in determining the character of residual masses. Unlike CT, post-therapy PET-CT imaging was found to be a good predictor of relapse. A number of issues concerning PET-CT, such as the need for RT in patients with positive CT scans parallel to negative PET-CT results, necessitate thorough investigation.

The weak points of the present study are its retrospective nature, the small number of patients and the heterogeneity of the study group.

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