

The Significance of PET/CT in the Initial Staging of Hodgkin Lymphoma: Experience Outside Clinical Trials

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Abstract. Aim: To examine the real-life impact of baseline positron-emission tomography/computed tomography (PET/CT) in Hodgkin lymphoma (HL). Patients and Methods: A total of 162 consecutive patients with HL were retrospectively studied. Results: Disease was up-staged in 26 patients (16%) and down-staged in 9 (6%). However, treatment strategy was modified in only 10 patients (6% of total). Involved field radiotherapy was delineated according to PET/CT in 36/66 patients (59%). These treatment modifications did not significantly affect outcome. Moreover, three potent prognostic parameters were identified: the number of involved sites, maximum standardized uptake value (SUVmax), and the product of SUVmax and maximal largest lesion diameter, as a surrogate of total lesion glycolysis. All three significantly correlated with 5-year freedom from disease progression $p=0.004$, $p=0.009$ and $p=0.04$, respectively). Conclusion: Baseline PET/CT findings may lead to treatment modification in <15% of patients with HL without a significant impact on outcome. Certain PET/CT parameters have potent prognostic significance.

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Disease stage is the most powerful prognostic system in therapy of Hodgkin lymphoma (HL) and represents the main determinant of treatment strategy (1, 2). Conventional staging with clinical examination, whole-body computed tomography (CT) and trephine bone marrow biopsy (BMB) is considered the standard of care (1-3).

Positron-emission tomography using 2-deoxy-2-¹⁸F-fluoro-D glucose (FDG) combined with CT (PET/CT) has an established role in post-treatment evaluation of patients with HL, while several studies support the implication of interim PET/CT in the design of treatment strategy (4-13). Currently, PET/CT at diagnosis is considered essential for initial staging (14, 15) due to its ability to detect more disease sites compared to CT (16-21). The percentage of patients in whom stage is changed due to PET/CT findings ranges between 15 and 47.7% (16-20, 22, 23). Although baseline PET/CT is highly recommended (24), it is not always available or reimbursed. Furthermore, the effect of baseline PET/CT on the choice of first-line treatment has not been systematically studied outside clinical trials (15). Thus, in everyday practice, treating physicians may be confusing in decision making by evaluating both CT and PET/CT findings.

The aim of this retrospective study was to investigate the potential impact of baseline PET/CT on staging, modification of therapeutic strategy and radiotherapy field in everyday clinical practice. Moreover, we aimed to investigate the prognostic significance of several baseline PET/CT parameters in comparison to conventional CT.

Patients and Methods

We retrospectively studied 162 consecutive patients with HL, diagnosed and treated at a single Hematology Unit between 12/12/2006 and 25/7/2014. Their selection was solely based on PET/CT availability at diagnosis. The study was approved with the number 6685, 17/13-4-11 by the Ethics Committee of Laikon General Hospital, according to the Declaration of Helsinki. Patients underwent initial conventional staging including clinical examination, contrast-enhanced whole-body CTs and BMB.

PET/CT scans were performed at three different sites and were reviewed by a single nuclear medicine physician at each site. The majority were performed at the Nuclear Medicine Department, Evangelismos Hospital. No central review was undertaken. The standardized uptake value (SUV) was defined as the ratio of the tumoral tracer concentration to the average tracer concentration in the entire body and was used as a semi-quantitative measure of the degree of FDG uptake. All acquired and reconstructed images and their corresponding SUV calculation was carried out on Siemens Biograph 6 Syngo Software Workstation (Siemens AG Erlangen Germany) for each metabolic region detected in scanning (10, 17, 25-27). Ann-Arbor definitions were used both for clinical staging (CS) and PET/CT staging (1, 2). Bone marrow (BM) involvement by PET/CT was defined as multifocal or unifocal bone uptake without bone lesions in CT (3, 17, 28-30). The number of involved sites (NIS) was calculated by both imaging modalities as shown in Figure 1. Bulky disease was defined as any lymph node with largest diameter >7 cm or a mediastinal mass >10 cm in its transverse diameter by CT.

Patients were uniformly treated as follows: Patients with early stages (IA/B, IIA and IIB without bulky mediastinum or extranodal extension) received 4-6 cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by 30-36 Gy involved-field radiotherapy (IF-RT) (31-36). Patients with advanced stages (III/IV) were treated with chemotherapy without preplanned RT, receiving either 6-8 cycles of ABVD or two cycles of ABVD and interim PET-guided treatment as follows: 4-6 further ABVD cycles (total 6-8) if interim PET was negative or six cycles of escalated therapy with bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) if the interim PET was positive (Deauville 5-point scale score ≥ 4) (37-39). RT was given selectively to patients with PET-positive residual lesions after chemotherapy. Patients with stage IIB HL with bulky mediastinum with or without extranodal extension followed the same schedule as those with stage III/IV with the invariable addition of IF-RT.

For the comparison of disease parameters, the appropriate non-parametric tests were used. The primary endpoint of the study was freedom from HL progression (FFP), calculated from treatment initiation to relapse, progression, or last follow-up. Deaths from unrelated causes without prior disease progression were censored at the time of death. Overall survival (OS) was calculated from treatment initiation to death from any cause or to last follow-up. Survival functions were estimated according to the Kaplan-Meier method and compared using the log-rank test. *p*-Values of less than 0.05 were considered statistically significant.

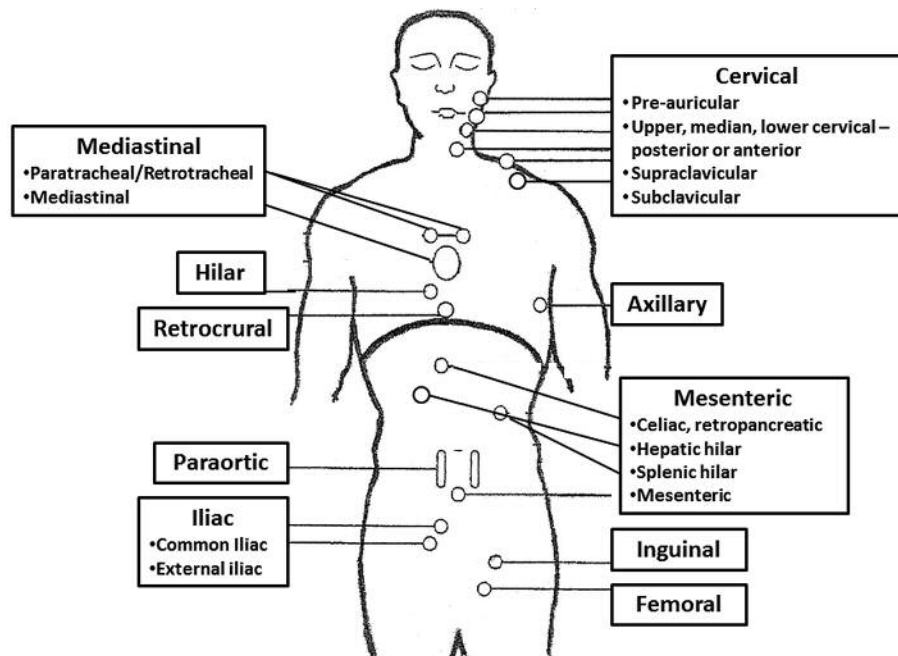


Figure 1. Enumeration scheme of disease involved sites. 1: Each rectangle represents one involved site. 2: Right and left lymph node areas were enumerated as separate sites for cervical, axillary, iliac, inguinal and femoral lymph nodes. 3: Bone involvement, whether multi- or unifocal, was enumerated as a single site. 4: Right and left lung were enumerated as separate sites.

Table I. Patient characteristics.

	N	%
All patients	162	100
Median age in years (range)	33 (17-82)	
Male gender	83	51
Median number of involved sites by CS (range)	4 (1-14)	
Median number of involved sites by staging by PET (range)	5 (1-15)	
Clinical stage vs. stage by PET/CT		
I	16 vs. 10	10 vs. 6
II	69 vs. 66	42 vs. 41
III	39 vs. 39	24 vs. 23
IV	38 vs. 47	24 vs. 30
B-Symptoms	71	44
Splenic involvement by CS vs. PET-S	32 vs. 44	20 vs. 27
Extranodal disease: by CS vs. PET-S	54 vs. 72	34 vs. 45
1 site	41 vs. 55	25 vs. 34
2 sites	10 vs. 14	6 vs. 9
≥3 sites	3 vs. 3	2 vs. 2
Bulky disease	30	19
Median SUVmax (range)	11.5 (2.5-31.1)	

Table II. Correlation between clinical staging and staging by positron-emission tomography/computed tomography (PET/CT).

	PET/CT staging, n				Total N
	I	II	III	IV	
Clinical staging, n					
I	8	5	3	0	16
II	1	55	7	6	69
III	1	5	28	5	39
IV	0	1	1	36	38
Total N	10	66	38	48	162

Down-staged up-staged no change in stage

Table III. Number of involved sites by clinical staging (CS) and staging by Positron emission tomography/ computed tomography (PET/CT) in the different clinical stages.

Clinical stage	Median number of involved sites (range)	
	CS	PET/CT
I	1 (1-1)	1.5 (1-5)
II	2 (2-6)	4 (1-10)
III	5.5 (2-14)	7 (1-15)
IV	6 (3-11)	10.5 (3-14)

Table IV. Actual radiotherapy administered to our patient population.

Actual situation	Theoretical IF-RT field modification according to PET/CT, n		Total number
	No	Yes	
All patients	96	66	162
No change of IF -RT field according to CS	27	11	38
No RT, although down-staged by PET/CT	0	1	1
No change of IF-RT field according to CS, although up-staged by PET/CT	0	8	8
Change of IF-RT field according to staging by PET/CT	0	32	32
No RT due to up-staging by PET/CT	0	4	4
No RT due to advanced stage by CS and PET/CT	60	0	60
Not evaluable	8	7	15
Exact RT-field unknown	1	3	4

No change of RT field Change of RT field according PET/CT

RT: Radiotherapy, IF-RT: involved field radiotherapy, CS: clinical staging, PET/CT: positron-emission tomography/computed tomography.

Results

Correlations between CS and PET staging. The characteristics of the 162 patients are shown in Table I. According to CS compared with staging by PET, 16, 69, 39 and 38 patients *versus* 10, 66, 39 and 47 patients were classified as stage I/II/III/IV, respectively. The distribution of staging and NIS by PET compared with CS are shown in Table II and III. CS was highly correlated to staging by PET ($p < 0.0001$); however, HL in 26 patients (16%) was up-staged by PET and in nine patients (6%) was down-staged. The highest frequency of stage shift was observed in those with CS I, where HL in 50% of the patients were up-staged, followed by CS III, where 11/39 cases (28%) changed (5/39 up-staged and 6/39 down-staged). Among patients with CS II, 20% changed staging by PET, the majority of which were up-staged. Lastly, only 5% of CS IV cases were down-staged.

The median NIS by CS and by PET were highly correlated ($p < 0.0001$, Spearman's $\rho = 0.831$). However, the NIS by PET was significantly higher ($p < 0.0001$) and this was true

within each single CS ($p = 0.01$ for CS I and $p < 0.0001$ for all others). In total, 88/161 (54%) patients had additional involved sites shown by PET, 13 (8%) had fewer sites and 30 (19%) had other sites added and others removed. Finally, only in 30 (19%) patients was the NIS identical both by PET and CS. Within this latter group, 25/30 patients had early CS.

Spleen and extranodal involvement increased from 20% and 34% by CS respectively to 27% and 45% by PET respectively. PET/CT detected significantly more patients with BM involvement ($p < 0.0001$) compared to BMB. Thus, BM involvement increased from 8% by BMB to 17% by PET/CT. Impressively, there was no single patient with a negative PET/CT for BM involvement having a positive BMB, resulting in a negative predictive value of 100% for PET/CT. There were 24 patients with diffuse BM uptake, none of whom had a positive biopsy.

Treatment decision change due to staging by PET. According to our treatment policy, treatment strategy could have theoretically been changed in 23 patients (14%) on the basis

of staging by PET. However, only in 10 patients (6% of the whole group) did the treating physician decide to modify the therapeutic strategy from early- to advanced-stage treatment and *vice versa*. Among these 10 patients in whom treatment strategy was modified, six had advanced CS and four were down-staged by PET and received IF-RT. In the remaining 13 patients, treatment was administered according to CS; 12/13 cases were up-staged by PET. However, RT was maintained as an integral part of the treatment strategy.

Change of IF-RT due to staging by PET. There were 66 patients in whom the IF-RT field might have theoretically been modified according to staging by PET, the majority of which (n=55) had early CS (Table IV). Among them, IF-RT did not actually change in 20/66 (32%) patients and these received RT to the CT-defined IF. In 36/66 (59%), the IF-RT field was delineated according to PET/CT. Seven patients were non-evaluable due to the development of progressive disease before RT or early death. In the remaining three patients, the exact RT field was unknown. Table IV shows the RT actually received in detail.

Prognostic factor analysis. At a median follow-up of 56.7 months (range=5.2-119.6 months), the 5-year FFP and OS were 81% and 93%, respectively. The following potentially prognostic parameters were evaluated by univariate analysis: gender, CS, staging by PET, B-symptoms, spleen involvement, number of extranodal sites, bulky disease, BM involvement by PET, NIS, SUVmax, modification of treatment strategy according to staging by PET and modification of IF-RT field according to staging by PET.

The presence of B-symptoms had an adverse prognostic impact (5-year FFP 86% *vs.* 74%; $p=0.004$). Stage was a significant prognostic factor for FFP both by CS and staging by PET ($p<0.001$ for both). The 5-year FFP was 100%, 85%, 86% and 59% for those with CS I/ II/III/IV *vs.* 100%, 83%, 95% and 63% for those with PET stage I/II/III/IV, respectively (Figure 2). Notably, 5-year FFP for patients with stage III HL by PET was superior to that of those with stage II disease (95% *vs.* 83%), although not statistically significantly because no events were recorded in the 10 patients with HL up-staged from CS I/II to PET stage III and the single patient down-staged from CS IV to PET stage III. Of note, these patients were mainly up-staged due to small, isolated infradiaphragmatic lesions. Up-staging or down-staging by PET did not have any prognostic significance, with a 5-year FFP of 79% for patients without stage modification *vs.* 89% for those who were up-staged and 78% for those who were down-staged (Figure 3, $p=0.547$).

The NIS by PET was of prognostic significance at multiple different cut-offs (data not shown), meaning that three groups of patients were identified: The 5-year FFP was 100% *vs.* 80% *vs.* 69% for patients with ≤ 2 , 3-8 and >8 sites

by PET respectively ($p=0.004$, Figure 4). The NIS by CS was less predictive compared to staging by PET, being statistically significant only at the cut-offs of two and three sites ($p=0.02$ and $p=0.04$, respectively).

Likewise, the number of extranodal sites was highly significant for FFP both by CS and by PET ($p=0.001$ and $p=0.003$, respectively). When the number of extranodal sites was analyzed within patients with stage IV HL, the 5-year FFP for cases with 1, 2 and ≥ 3 sites was 67%, 50% and 33% by CS, and 73%, 50% and 33% by PET, respectively. However, these differences were not significant, most likely due to low patient number. Focal uptake of FDG by the BM was a highly significant adverse prognostic factor ($p<0.0001$) and more potent compared to BMB ($p=0.009$). Patients with diffuse or no BM FDG uptake had a 5-year FFP of 87% *vs.* 54% for those with uni- or multifocal skeletal uptake.

SUVmax was significant at different cut-offs. Three groups of patients were identified: patients with SUVmax ≤ 9 , 9-18 and >18 had 5-year FFP rates of 93%, 81% and 58% respectively ($p=0.009$; Figure 5a). Next we examined the product of SUVmax and maximal largest lesion diameter (Dmax) as an estimate of total lesion glycolysis (TLG). Three groups of patients with different outcomes were identified: There were 36 patients with values ≤ 35 , 66 patients with values ranging between 35.1 and 100, and 28 patients with values >100 . The corresponding 5-year FFP rates were 94%, 81% and 70% ($p=0.04$; Figure 5b).

Outcome according to modification of treatment strategy. Change of treatment strategy according to staging by PET did not have any impact on outcome: among the 23 patients in whom treatment strategy could have been changed according to staging by PET, the 5-year FFP was 92% for those for whom it did not change *versus* 80% for those for whom it did ($p=0.427$). Regarding the IFRT modification, among 63 patients in whom IF could have changed due to staging by PET, there were 20 patients for whom the IF was not actually modified and 36 for whom the IF changed. FFP was 90% *versus* 80% respectively ($p=0.48$). This difference remained non-significant, even when only early CS patients were evaluated ($p=0.468$).

Discussion

The present study compared baseline staging by PET to the established standard of care, *i.e.* CS with whole-body CT and BMB. Although baseline PET/CT is highly recommended, its impact on everyday clinical decision-making outside clinical trials has not been studied adequately. This retrospective study on 162 consecutive patients with HL with available baseline PET/CT provides some insight into the above issues. We found that staging

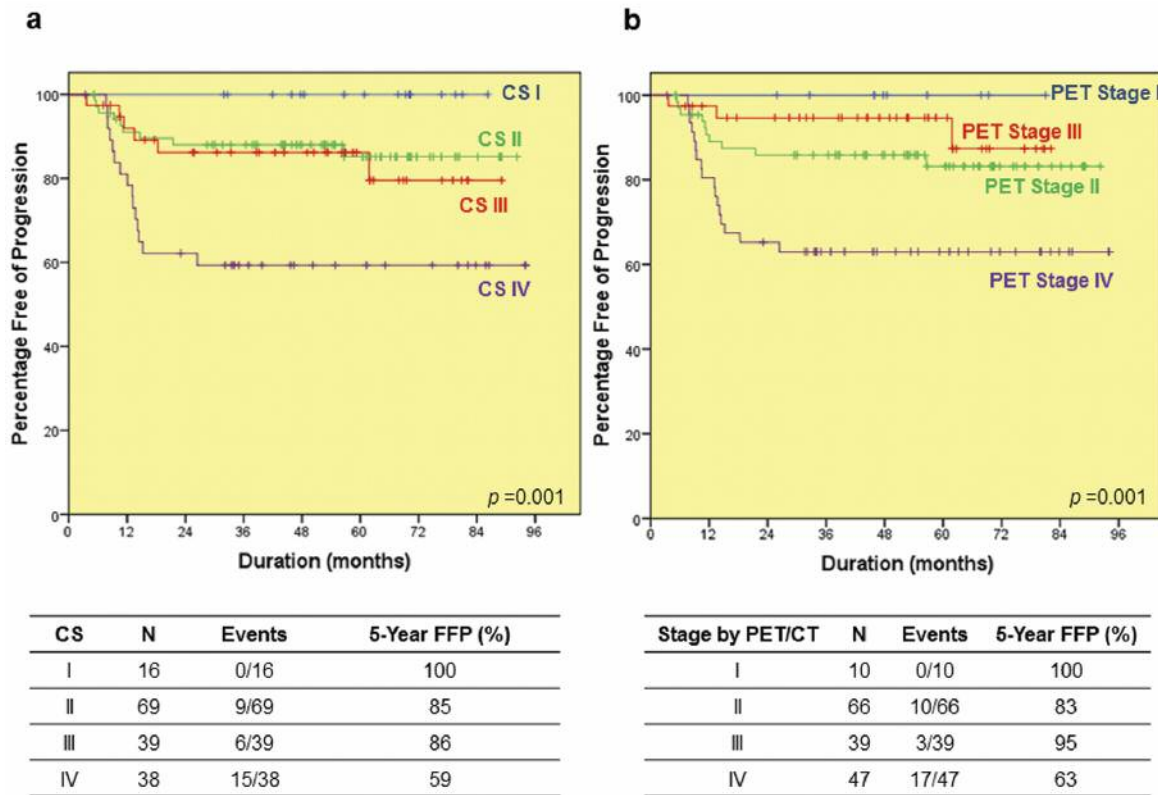


Figure 2. Freedom from progression according to clinical stage (CS) (a), and stage by positron-emission tomography/computed tomography (PET/CT) (b).

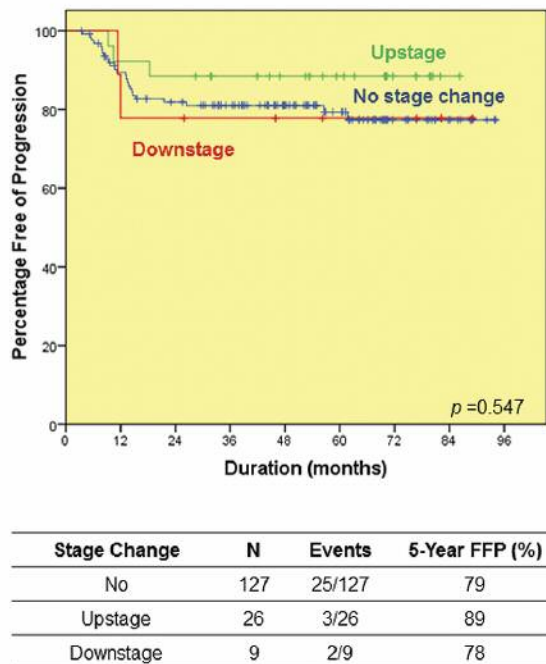


Figure 3. Freedom from progression according to upstaging and downstaging.

by PET altered disease stage in 22% of the patients (16% up-staged and 6% down-staged) compared to the standard approach. This finding is in accordance with earlier studies (16-20, 22, 23) and verified by the recent prospective RATHL trial (15). In this trial, in which cases with early favorable disease were excluded, 14% and 6% of the patients were up- and down-staged respectively which our results are in agreement with.

We found that sites of disease were added in 54% of the patients and in an additional 19%, involved sites were both added and reduced, whereas only in 19% were the involved sites exactly the same. The most frequent additional sites were lymph nodes, lung, skeletal (BM) lesions and spleen. These findings are consistent with those of Hutchings *et al.* (40) who reported 25-30% more lesions being identified by PET/CT. Moreover, we showed that BM involvement increased from 8% by BMB to 17% by staging by PET. More interestingly, none of the patients showing either no or diffuse BM uptake had a positive BMB, indicating that PET/CT is not only extremely sensitive but also has a 100% negative predictive value in accordance with published results (30). El Galaly *et al.* reported an increase of BM involvement from 6% to 18% by PET/CT and a 99%

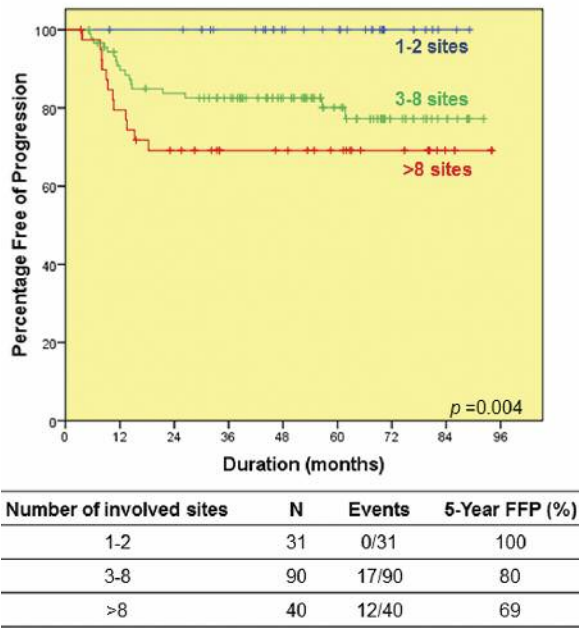


Figure 4. Freedom from progression according to the number of involved sites by positron-emission tomography/computed tomography (PET/CT).

negative predictive value for PET-based BM involvement (29). These data indicate that BMB may be omitted in the PET/CT staging era (3).

Although sites of disease were added in more than half of the patients and stage altered in approximately 20% of them, the percentage of patients in whom the therapeutic strategy changed was relatively small (9, 40). In our study, according to our treatment policy, treatment strategy could theoretically have been changed due to staging by PET in only 23 patients (14%). However, only in 10 (6% of the whole patient population) did the treating physician actually decide to change the treatment strategy due to staging by PET. In the remaining 13 patients, treatment was based on CS. It is of interest that among these 13 patients, HL in the vast majority (12/13) had been up-staged by PET. In our Institution, patients with early stages routinely receive IF-RT after the end of chemotherapy, whereas those with advanced stages receive chemotherapy only, unless a PET-avid residual lesion is present. Thus, physicians were reluctant to abandon IF-RT for CS I and II, even if patients were up-staged by PET due to additional infradiaphragmatic lymph nodes or splenic lesions. The same pattern was evident in the 10 patients for whom treatment strategy was

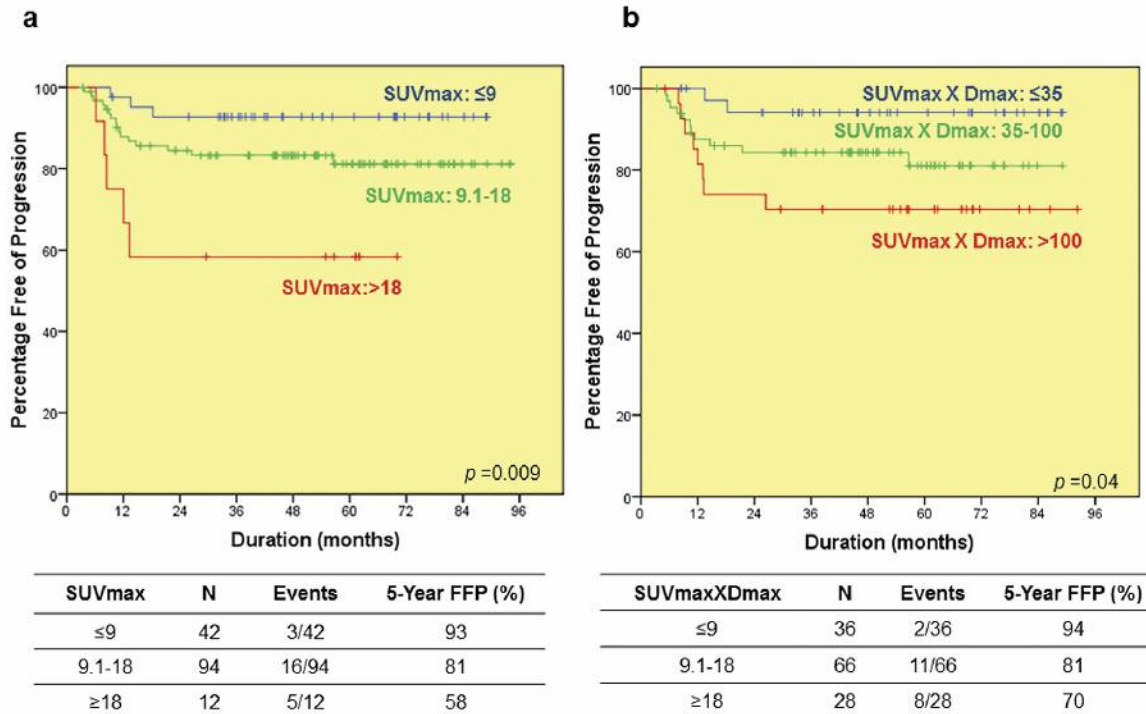


Figure 5. Freedom from progression according to maximum standardized uptake value (SUVmax) (a), and the value of the product of SUVmax and maximal diameter of the largest lesion (b).

changed: 6/10 were down-staged from advanced to early stages and received IF-RT. Thus, there is a prevailing trend for IF-RT to be included in the treatment plan by the treating physicians whenever there is a discrepancy between CS and staging by PET. Moreover, change of treatment strategy according to staging by PET did not have any impact on outcome. However, the small number of patients who were affected by staging by PET may not have been enough to demonstrate a significant difference in outcome.

The next question that we tried to answer was the impact of baseline PET/CT on the delineation of the IF-RT field, mainly by including additional lesions. PET/CT is considered extremely useful in planning RT, in order to spare toxicity to adjacent tissues (41-45) as well as to include occult disease sites not evident by CT. In this study, IF-RT might have been theoretically modified to include sites defined by staging by PET in a considerable percentage (41%) of the cases. Finally, the IF-RT field was actually changed in more than half of them (57%) while, interestingly, the modification of the IF-RT field did not affect outcome positively. This is understandable in the context of systemic chemotherapy and suggests that designing the RT field by PET/CT might increase the risk of secondary cancer by adding further involved sites. These issues have not been resolved and further follow-up is needed to draw conclusions about the best method to design RT fields.

Staging by PET did not have a more potent prognostic significance compared to CS. However, staging by PET revealed two strong prognostic parameters, namely, the NIS and SUVmax. On the contrary, the NIS by CS did not strongly discriminate different risk groups. Thus the NIS by PET seems to improve the already known prognostic significance of this parameter in traditional CS (33,36,46-48). Furthermore, the higher the SUVmax, the worse the outcome is. SUVmax was able to identify three prognostic groups (≤ 9 , 9.1-18 and >18) with corresponding 5-year FFP of 93%, 81% and 58%, respectively. We also found an easily calculated parameter as a surrogate of TLG: the product of SUVmax and Dmax showed that product values ≤ 35 , 35.1-100 and >100 were able to stratify patients into three different prognostic groups. Recent evidence (49-51) indicates the importance of metabolic tumor volume (50) and TLG (52) as prognostic factors for patients with HL.

A limitation of the present study was its retrospective nature and the fact that PET/CTs were not centrally reviewed. In addition, the limited number of patients in whom stage and therapeutic strategy was altered, prevents firm conclusions to be drawn. Clinical trials incorporating initial staging by PET are carefully and elaborately planned but their findings do not necessarily apply in the community setting. Thus, our findings reflect real-world decision-making where physicians may be misled when there is a discrepancy between CS and staging by PET. Moreover, the construction

of IF-RT in early CS is even more problematic. The trend of PET-guided RT field delineation seems to prevail but follow-up is needed in order to assess long-term effects.

In conclusion, staging by PET leads to identification of additional involved sites in more than half of cases and change of stage in approximately 25% of them, even though modification of therapeutic strategy affects only a small percentage of patients. Although in the majority of early-stage cases the RT field is delineated according to PET/CT involved sites, the impact of such a procedure on outcome is questionable: inclusion of more disease sites by PET/CT may affect the incidence of secondary cancer. This highlights the need for optimal delineation of the RT field according to the involved sites and dose. CS using conventional staging methods has been the long-standing standard of care in HL. However, certain parameters related to PET/CT, such as the NIS, SUVmax, metabolic tumor volume and TLG, are emerging as potent prognostic parameters. As PET is being used more and more frequently for baseline staging, we need to obtain more accurate information regarding the use of traditional parameters of tumor burden in the PET era.

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