Focal skeletal FDG uptake indicates poor prognosis in cHL regardless of extent and first-line chemotherapy

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Summary

18F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) is used for staging classical Hodgkin lymphoma (cHL) with high sensitivity for skeletal involvement. However, it is unclear whether a single bone lesion carries the same adverse prognosis as multifocal lesions and if this is affected by type of chemotherapy (ABVD versus BEACOPP).

We reviewed the clinico-pathological and outcome data from 209 patients with newly diagnosed cHL staged by FDG-PET/CT. Patterns of skeletal/bone marrow uptake (BMU) were divided into 'low' and 'high' diffuse BMU (i.e. without focal lesions), and unifocal or multifocal lesions. Additional separate survival analysis was performed taking into account type of chemotherapy. Forty patients (19.2%) had skeletal lesions of which 20 were unifocal and 20 were multifocal. The 3-year progression-free-survival (PFS) was 80% for patients with 'low BMU', 87% for 'high BMU', 69% for 'unifocal' and 51% for 'multifocal' lesions; median follow-up 38 months, The presence of bone lesions, both uni- and multifocal, was associated with significantly inferior PFS (log rank p=0.0001), independent of chemotherapy type.

Thus, increased diffuse BMU should not be considered as a risk factor in cHL, whereas unifocal or multifocal bone lesions should be regarded as important predictors of adverse outcome, irrespective of the chemotherapy regimen used.

Key words: 18F-FDG PET/CT, classical Hodgkin lymphoma, bone marrow uptake, focal bone lesions, chemotherapy

Introduction

The prognosis for patients with advanced stage classical Hodgkin Lymphoma (cHL) has improved over the years(Engert*, et al* 2012, Gordon*, et al* 2013, Son*, et al* 2017). Advanced stage cHL, as determined by the Ann Arbor classification(Carbone*, et al* 1971), is treated with combination chemotherapy regimens such as Adriamycin, Bleomycin, Vincristine, Dacarbazine (ABVD) or more aggressive combinations like Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin, Procarbazine, Predisone (BEACOPP) escalated or BEACOPP-14. Because of the increased toxicity associated with aggressive treatment for advanced stage cHL, a search for prognostic factors identifying patients at particularly high risk of treatment failure is warranted. Moreover, these may represent a subset of patients in whom novel targeted drugs (e.g. brentuximab vedotin or immune checkpoint inhibitors) in the upfront setting may be particularly useful(Zander*, et al* 2002).

Demographic, clinical and biochemical factors are routinely used to stratify patients into high- or low-risk groups(Hasenclever and Diehl 1998, Zander*, et al* 2002). One of the most well established tools for the prognostic assessment of patients with advanced stage cHL is the International Prognostic Score (IPS), which includes age, sex, clinical stage, performance status and a range of biochemical variables(Hasenclever and Diehl 1998). However, previous studies using the IPS have not been able to identify satisfactorily a distinct group of advanced stage cHL patients at particularly high risk(Hasenclever and Diehl 1998, Munker*, et al* 1995). This may partly be due to the fact that older patients more often have abnormal biochemistry, regardless of Ann Arbor stage(Specht and Nissen 1989).

18F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) is now regarded as the standard imaging

modality for staging patients with newly diagnosed cHL Compared with CT alone, FDG PET/CT is better at detecting skeletal and bone marrow involvement(El-Galaly, *et al* 2012) and other sites of extra-nodal disease(Barrington, *et al* 2016). Consequently, FDG PET/CT classifies more patients as stage IV than stand-alone CT. However, FDG PET/CT may yield more information than merely imaging stage and localization of disease sites. FDG based measurement of total metabolic tumor volume (MTV) has gained considerable interest as an independent predictor of outcome in both Hodgkin(Kanoun, *et al* 2014, Song, *et al* 2013) and non-Hodgkin lymphomas(Kim, *et al* 2013, Sasanelli, *et al* 2014). Unfortunately, MTV measurements must still be performed manually using specialized software tools not readily available for everyday clinical practice. In the meantime, other routinely available PET metrics may be used to improve prognostic accuracy. It is still unclear whether diffusely increased bone marrow FDG uptake at diagnosis should be regarded as a disease-associated adverse feature(Adams, *et al* 2015, Agrawal, *et al* 2013, Chen-Liang, *et al* 2015, El-Galaly, *et al* 2012, Mittal, *et al* 2011, Salaun, *et al* 2009). FDG bone marrow uptake (BMU) can be visually assessed or be quantitatively measured as the ratio between FDG uptake (SUVmax or SUVmean) in representative sections of the bone marrow compared with the liver. Diffusely increased BMU has previously been found to be associated with a higher leukocyte count(El-Galaly, *et al* 2012) and increased CRP(Salaun, *et al* 2009). If diffusely increased BMU reflects disease activity and/or inflammation in the bone marrow, then BMU at the time of diagnosis may assist in risk stratification.

Furthermore, since the presence of focal skeletal lesions without CT or bone marrow biopsy correlates in patients with cHL has only been appreciated since the introduction of PET-based imaging, it remains unclear whether these lesions (unifocal

or multifocal) represent an adverse prognostic feature in ABVD and/or BEACOPP treated cHL.

The aim of the present study was to assess the prognostic impact of different patterns of skeletal uptake observed in staging FDG-PET scans evaluating the presence/absence of high diffuse BMU compared to the presence/absence of unifocal and/or multifocal bone lesions, respectively, in patients treated with ABVD and BEACOPP chemotherapy.

Methods

Patients

Retrospective review of consecutive patients with newly diagnosed cHL treated at Aarhus University Hospital (2008-2014) and Uppsala University Hospital (2005-2014) was undertaken. Inclusion criteria were treatment naïve cHL, first line treatment with ABVD or BEACOPP-like chemotherapy, an evaluable set of clinical data, laboratory test results, and a staging FDG PET/CT available for image review and analysis.

Patient data at diagnosis, biochemical analyses and histology were retrieved from the national lymphoma and pathology registries, local databases and hospital records. Follow-up status (relapse or death) was obtained through the national lymphoma registry and a review of medical records.

The Danish and Swedish Data Protection Agencies, and the national ethics authorities approved the data collection and analysis for this study.

Whole-body FDG PET/CT

PET/CT acquisition. Staging FDG PET/CT scans were carried out in accordance with local protocols and manufacturer guidelines. After unenhanced CT scans for attenuation

correction and anatomic co-registration, FDG PET/CT imaging was performed, followed by a contrast-enhanced CT if not already performed prior to the staging PET. Both PET and CT images were stored locally. Image reports from the time of the original scans were not used for the study analysis.

Image analysis. FDG PET/CT scans were retrieved from local databases at Aarhus and Uppsala University Hospitals and reviewed *de novo* by two experienced nuclear medicine physicians using a Hermes workstation in Aarhus and a GE workstation in Uppsala.

Images were reviewed specifically for bone marrow involvement taking note of focal and intense FDG uptake in the skeleton, irrespective of the presence or absence of osteolytic or non-osteolytic lesions. Criteria for FDG uptake in bone marrow to be classified as due to HL were: 1) FDG uptake above liver, 2) no anatomical changes to suggest alternative 'benign' bone pathology, and 3) to have resolved in parallel with nodal disease during treatment(Khan*, et al* 2013).

Bone lesions were categorized as multifocal if more than one lesion was present. Average FDG uptake in the bone marrow was visually graded (BMUvisual) as either below, equal to, or above liver uptake. The maximum standardized uptake value (SUVmax) was measured in the vertebral column (L3/L4 level) and in a large region in the right lobe of the liver. The ratio of SUVmax in the vertebral column and the liver was considered as a continuous variable indicating diffuse bone marrow FDG uptake (BMUcalc). For survival analysis, patients were divided into two groups: above (highBMUcalc) and below (lowBMUcalc) the median BMU value (Fig 1).

Statistics

A chi-square test was used to determine whether a significant relationship existed between the presence of focal skeletal FDG uptake (categorical variable) and visually increased BMU (categorical variable). A multivariate regression analysis was performed with the continuous variable BMUcalc as the dependent variable and parameters of the IPS as independent variables (age, leukocytes, lymphocytes, albumin, hemoglobin and sex). Receiver operating characteristic (ROC) curve analysis was carried out to determine the optimal threshold of BMUcalc to predict the presence of focal bone lesions.

Progression-free survival (PFS) was defined as the time from diagnosis to the first relapse, progression, death from any cause, or date of the latest follow-up. Overall survival (OS) was defined as the time from diagnosis to death from any cause or date of latest follow-up. PFS and OS were estimated using the Kaplan-Meier method and differences between groups were compared by the log-rank test. Subgroup analyses were tested for interaction, and no interaction was found to be present between the bone marrow uptake and presences of bone lesions ($p=0.44$). Furthermore, no interaction was demonstrated between treatment group (ABVD vs BEACOPP-based chemotherapy) and the presence of bone lesions ($p=0.37$).

To evaluate the prognostic impact of focal (uni- or multifocal) bone uptake or diffuse 18F-FDG BMU, Cox proportional hazards models were used, adjusted for known risk factors of the IPS: age, leukocytes, lymphocytes, albumin, hemoglobin and sex. The IPS factors were dichotomized accordingly. Ann Arbor clinical stage was omitted from this analysis due to its inherently strong correlation with focal skeletal FDG uptake (by definition, the finding of focal skeletal FDG uptake implied allocation to Ann Arbor stage IV). A p-value <0.05 was considered significant. All analyses were carried out using STATA version 15.1 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

A total of 288 patients (173 from Aarhus and 111 from Uppsala) were originally reviewed for inclusion in the study. Due to insufficient follow-up data, and/or inaccessible FDG PET/CT scans and/or missing biochemistry, the final study population comprised 209 patients (134 from Aarhus, 75 from Uppsala) with a complete set of clinical, biochemical and imaging data. Table I shows their baseline demographic characteristics and treatment background.

Frequency and intensity of focal and diffuse bone marrow FDG uptake

Focal bone lesions were present in 40/209 patients (19.3 %), a frequency comparable to previous descriptive reports(Agrawal*, et al* 2013, Chen-Liang*, et al* 2015, El-Galaly*, et al* 2012, Salaun*, et al* 2009). 14 patients were classified as stage 4 due to extranodal disease other than skeletal. Twenty of the forty focal bone lesions (50%) were unifocal. Unifocal and multifocal bone lesions were evenly distributed between men and women, but patients with multifocal bone lesions had a significantly higher median age than those with unifocal lesions [56 years ± 19 (multifocal) vs. 38 years ± 16 (unifocal), p=0.006]. The median BMUcalc value among all patients (SUVmax(L3/L4)/SUVmax(liver)) was 1.15 (range 0.52 – 5.57).

Determinants of diffuse bone marrow FDG uptake

A range of biochemical and demographic variables known to impact bone marrow activity and thus 18F-FDG BMU, including the IPS factors, were tested for their relationship to BMU in a univariate and multivariate analysis (Table II). In the

multivariate model, low hemoglobin, increased leukocyte count, low plasma albumin levels and the presence of focal bone lesions were all independent predictors of increased BMU. The remaining IPS factors (age, lymphocyte count and sex) were not. We also found that visually increased bone marrow uptake (BMUvisual) was overrepresented in the group of patients with focal bone lesions (χ^2 p=0.001).

Is there a threshold value of BMU indicative of focal bone lesions?

Since both BMUcalc and BMUvisual were increased in patients with focal bone lesions, we performed a ROC-analysis to determine which BMUcalc level should prompt suspicion of focal bone lesions. The area under the ROC curve was 0.70, p<0.01 with a cut-off BMUcalc=1.20, yielding a sensitivity of 0.74 and a specificity of 0.65 to detect the presence of focal bone lesions. With a prevalence of focal bone lesions in our patient cohort of 40/209, this translates into a positive predictive value of 33 % and a negative predictive value of 91 %.

Impact of focal bone lesions and diffusely increased bone marrow uptake on outcome

Median follow-up times for patients without bone lesions (n=169) or with focal bone lesions (n=40) were 3.14 years and 3.43 years (reverse Kaplan-Meier method), respectively. To test the appropriateness of pooling data from the two centers, we compared PFS and OS between Aarhus and Uppsala and found no difference (PFS, p=0.65 and OS, p=0.52).

The 3-year PFS rates, 83% (no-lesion), 69% (unifocal), and 51% (multifocal), were significantly different (p<0.001). The presence of focal bone lesions (unifocal or multifocal) was associated with a significantly poorer PFS (log-rank

p<0.001) when compared with the no-lesion group (Fig 2A). No significant difference in PFS between unifocal and multifocal lesions was observed (log-rank p=0.24). Similarly, the 3-year OS rates, 93% (no-lesion), 83% (unifocal), and 84% (multifocal), were also significantly different (p=0.001). The presence of focal bone lesions (unifocal or multifocal) was also associated with a significantly poorer OS (log-rank p=0.002) when compared with the no-lesion group (Fig 2B). No significant difference in OS between unifocal and multifocal lesions was observed (log-rank p=0.22). The 3-year PFS rates of patients with uni- or multifocal bone lesions were similar to those of patients with stage 4 disease without bone involvement, i.e. 69%, 51% and 71%, respectively (log-rank p=0.51; Fig 2C). Similarly, 3-year OS rates for the same patient subsets were 83% (unifocal), 84% (multifocal) and stage 4 disease without bone involvement (log-rank p=0.95; Fig 2D).

In patients with no focal bone lesions, PFS rates were similar for patients with high vs. low diffuse BMU (log rank p=0.62) (Fig 3).

In addition, we examined the impact of different chemotherapy regimens on PFS and OS in patients with unifocal or multifocal bone lesions, and found that focal bone lesions were associated with a poorer prognosis, regardless of treatment given (i.e. ABVD vs. BEACOPP-like) (Fig 4).

On multivariable analysis, including the individual parameters from the IPS-score, only the presence of focal bone lesions and age >45 years were independently associated with a significantly inferior PFS and OS (table III).

Discussion

The main findings of this study are that diffusely increased BMU was independently correlated with IPS parameters reflecting increased bone marrow turnover. Although

more frequently observed in patients with focal bone lesions, diffuse bone marrow uptake was not in itself associated with inferior outcome. This finding is corroborated by the poor performance of the ROC-based BMUcalc threshold to predict the presence of focal bone lesions. Our study also highlights the importance of detecting single FDG-avid bone lesions, since these patients had as poor a prognosis as patients with multiple bone lesions. Finally, we observed equally poor outcome in patients with focal bone lesions regardless of whether they had been treated with ABVD or BEACOPP-like chemotherapy, further underlining the notion, that focal bone lesions should be considered indicative of lymphoma in the bone/bone marrow irrespective of whether there is corroborative evidence on CT and/or a bone/bone marrow biopsy.

Diffuse bone marrow 18F-FDG uptake is likely to be reactive/inflammatory

Diffusely increased bone marrow FDG uptake (BMUcalc) correlated with a range of biochemical factors known to reflect bone marrow activation. Thus, low haemoglobin, albumin and lymphocyte count, as well as increased total leukocyte count and erythrocyte sedimentation rate, were associated with increased BMU. These parameters are often increased in states of inflammation and infection, but are also factors that are included in the IPS stratification index. It was, therefore, a main aim of this study to determine, whether diffusely increased BMU could be used as a surrogate PET prognostic risk marker. This was not the case, since the only IPS factors that remained independently correlated to BMU in the multivariate analysis were low haemoglobin and increased leukocyte count. It is possible that the observed *negative* relationship between BMU and age may explain this. Age >45 is a risk factor in the IPS and could cancel out the prognostic value of pooling other IPS factors into a single PET based

BMU metric. Furthermore, both PFS and OS were similar in patients regardless of the degree of BMU, only the presence of focal bone lesions being associated with poorer outcomes. Thus, our data support previous reports in which diffusely increased BMU is taken as indicative of non-malignant bone marrow inflammation and reaction(El-Galaly*, et al* 2012, Salaun*, et al* 2009), and expands this notion by demonstrating that increased BMU is not associated with inferior outcomes. It was also our experience that visually evaluated diffuse BMU tended to underestimate the number of patients with uptake levels above the liver, when compared with diffuse BMU calculated by the use of SUVmax in the vertebra and liver. Therefore, we recommend that BMU, whenever requested, is categorized as either normal or increased by the use of SUV values.

Focal skeletal lesions are associated with poor prognosis

In our study, 19.4% of patients with newly diagnosed Hodgkin lymphoma had focal FDG uptake in the bones. This fraction is consistent with recent reports where focal FDG uptake in the skeleton is considered diagnostic for bone marrow involvement(Agrawal*, et al* 2013, Chen-Liang*, et al* 2015, El-Galaly*, et al* 2012, Salaun*, et al* 2009). However, it is considerably higher than the proportion reported by Munker et al. who, in the era preceding pre-therapeutic PET/CT, only detected bone marrow involvement (BMI) by iliac crest biopsy in 4.8 – 5.9% of patients(Munker*, et al* 1995).

It was not an aim of this study to determine the diagnostic accuracy of FDG PET/CT to diagnose bone marrow involvement, since others have convincingly done this(El-Galaly*, et al* 2012). On the other hand, it was the purpose of this study to characterize the frequency and the prognostic impact of skeletal lesions in cHL, a clinical presentation of cHL, which has emerged only after the introduction of PET/CT

imaging as part of the routine diagnostic work-up in HL. It is noteworthy that the presence of focal bone lesions carried a poor prognosis, regardless of whether these were unifocal or multifocal. A possible explanation for this could be that lymphomas involving the bone/bone marrow or other extra-nodal sites are characterized by a more aggressive tumor biology, rendering the number of metastases less important. This is supported by Munker et al. who observed no difference in overall survival among stage IV patients with BMI, compared with those without(Munker*, et al* 1995). This finding was also consistent with the findings in the present study (Figs 2C and D). It is also possible, that patients with a unifocal bone lesion on PET/CT might actually have multiple bone lesions, but that they are too small to be detected by the PET scan.

It has previously been demonstrated that more than half of the cHL patients that present with biopsy-proven BMI also harbour non-neoplastic lesions in the bone marrow such as non-necrotising granulomas or fibrosis(Sovani*, et al* 2014). Therefore, it can be speculated whether the highly avid bone lesions observed on PET-CT scans represent malignant disease, or whether they could in fact be caused by non-malignant manifestations. However, our findings strongly suggest that focal bone lesions found in cHL do indeed represent true malignant lymphoma, given the poor prognosis of these cases. This interpretation of our data is corroborated by the equally poor outcome in patients with focal bone lesions, regardless of whether they had been treated with ABVD or BEACOPP-like chemotherapy.

Limitations

Retrospective studies, including this one, are inherently hampered by a lack of rigorous inclusion criteria and standardized PET/CT protocols. Firstly, patients in our study were diagnosed and had their pre-treatment FDG PET/CT performed over a time range from

2005 to 2014, during which preferred first-line treatment may have changed. However, the vast majority of our patients were treated with either ABVD or BEACOPP-like chemotherapy, which are still the most commonly used treatments for advanced stage cHL. Secondly, FDG PET/CT has evolved considerably since 2005, with higher resolution PET/CT introduced during the inclusion period in the two participating centres. Therefore, it is conceivable that smaller unifocal lesions may not have been detected on older scans. Thirdly, although diffusely increased BMU was not associated with inferior outcome and, therefore, most likely represents a benign reactive lesion, no histological confirmation of this inferred conclusion was available.

Conclusion

The presence of diffusely increased FDG uptake should alert the reading clinical nuclear medicine physician about the possibility of bone lesions, but should not in itself be reported as suspicious for BMI. Moreover, our data emphasize the importance of detecting bone lesions, irrespective of the number, since these are associated with a significantly poorer outcome regardless of the primary treatment regimen (i.e. ABVD or BEACOPP.like). Whether cHL associated with bone lesions also presents specific biological and tumor microenvironmental features that may explain the skeletal findings is not clear, but these findings warrant correlative biological studies, which are currently ongoing.

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Authorship contributions

Contribution: M.A.P. participated in data collection and drafting the manuscript; L.C.G. is the corresponding author and participated in concept design and manuscript writing and review; P.K. participated in data analysis and revision of the manuscript; C.W. and A.A. participated in data collection; M.D.A., S.F.B., P.J., S.H.D., R.M.A., G.E. and D.M. assisted in data collection and revision of the manuscript; F.A. conceptualized the study and revised the final manuscript.

Competing interests

M.A.P., L.C.G., P.K., C.W., D.M., G.E., A.A., P.J., S.F.B., S.H.D., R. M.A., and F.A. have no competing interests.

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Tables:

Table I Patient demographics			
	No lesion (n=169)	Focal lesion(s) (n=40)	Total (n=209)
Characteristic			
Male/female	88/81 (52/48%)	24/16 (60%/40%)	112/97 (54/46%)
Mean age (range)	40 (14-83)	47 (8-80)	42 (8-83)
Elevated LDH*	49 (30%)	18 (45%)	67 (33%)
Haemoglobin (g/l)** Mean (range)	132.1 (77.3-172.4)	119.2 (87.0-153.1)	130.5 (77.3-172.4)
Platelets (10^9/l)*** Mean (range)	338 (9-817)	293 (10-541)	329 (9-817)
Leucocytes (10^9/l)**** Mean (range)	9.7 (0.5-39.2)	8.9 (1.8-19.4)	9.5 (0.5-39.2)
Lymphocytes (10^9/l)***** Mean (range)	1.7 (0.1-12.4)	1.3 (0.2-2.9)	1.7 (0.1-12-4)
ESR (mm)^ Mean (range)	36 (0-110)	53 (4-116)	39 (0-116)
Albumin (g/l)^^ Mean (range)	38 (18-53)	32 (14-47)	37 (14-53)
B symptoms (N/Y)^^^	95/69 (58/42%)	11/27 (29%/71%)	106/96 (52/48%)
Performance status ≥ 2 (WHO)^^^^	6 (4%)	6 (16%)	12 (6%)
International Prognostic Score > 2	33 (57 %)	25 (43%)	58 (28%)
BMUcalc	1,2(0.52-3.45)	1,56 (0.83-5.57)	1.28 (0.52-5.57)
BMUvisual	35 (65%)	19 (35%)	54 (26%)
Histology	N=166	N=40	N=206
NS	122 (73%)	27 (68%)	149 (72%)
MC	31 (19%)	8 (20%)	39 (19%)
LD	2 (1%)	0 (0%)	2 (1%)
cHL NOS	11 (7%)	5 (12%)	16 (8%)
Ann Arbor stage	N=169	N=40	N=209
I	19 (11%)	0 (0%)	19 (9%)
II	98 (58%)	0 (0%)	98 (47%)
III	38 (22%)	0 (0%)	38 (18%)
IV	14 (8%)	40 (100%)	54 (26%)
Treatment	N=168	N=39	N=207
ABVD/COPP-based	126 (75%)	24 (62%)	150 (73%)
BEACOPP-based	31 (18%)	11 (28%)	42 (20%)
Other (CHOP, OEPA, radiation only)	11 (7%)	4 (10%)	15 (7%)

* N=163 (No lesion (NL)), N=39 (Focal lesion (FL)), N=202 (Total (T))
** N= 163 (NL), N=39 (FL), N=202 (T)
*** N=161 (NL), N=39 (FL). N=200 (T)
**** N=163 (NL), N=39 (FL), N=202 (T)
***** N=156 (NL), N=37 (FL), N=193 (T)

^N=151 (NL), N=34 (FL), N=185 (T)
^^N=154 (NL), N=37 (FL), N=191 (T)
^^^N=164(NL), N=38 (FL), N=202 (T)

Legend: cHL NOS = classical Hodgkin lymphoma, not otherwise specified; LD = lymphocyte-depleted classical Hodgkin lymphoma; MC = mixed cellularity classical Hodgkin lymphoma; NS = nodular sclerosis classical Hodgkin lymphoma.

Table II Univariate and multivariate predictors of diffuse BMU				
	Univariate Coefficient	**p-value**	**Multivariate Coefficient**	**p-value**
Sex (male)	-0.105	p=0.14	0.026	p=0.74
Age	-0.005	p=0.01	-0.002	p=0.30
Hemoglobin	-0.165	p<0.001	-0.096	p=0.05
Platelet count	0.001	p<0.001	0.001	p=0.12
Leucocyte count	0.033	p<0.001	0.020	p=0.01
Lymphocyte count	-0.067	p=0.03	-0.035	p=0.22
ESR	0.004	p<0.001	-0.002	p=0.19
Albumin	-0.028	p<0.001	-0.013	p=0.04
Focal Bone lesion (no/yes)	0.347	p<0.001	0.234	p=0.02

Legend: Univariate and multivariate predictors of diffuse bone marrow uptake (BMU).

Combined model r^2=0.27, p<0.0001

Table III Predictors of PFS		
Risk factor	**HR, 95 % CI (univariate) PFS**	**HR, 95 % CI (multivariate) PFS**
Bone lesion (PET)	3.30 (1.74 – 6.27), p<0.001	3.11 (1.40 – 6.93), p=0.005
BMU (upper median)*	0.82 (0.37 – 1.82) p=0.63	
Age (above 45)	2.93 (1.53 – 5.62), p=0.001	2.97 (1.30 – 6.79), p=0.01
Male sex	1.50 (0.79 – 2.85) p=0.21	1.11 (0.53 – 2.33), p=0.78
Low hemoglobin (<104.7 g/l) (<6.5 mmol/l)	1.98 (0.94 – 4.17), p=0.07	0.62 (0.17 – 2.26), p=0.47
Low albumin (<40 g/l)	0.48 (0.21 – 1.08), p=0.08	0.73 (0.30 – 1.77), p=0.49
Leucocytes (>15 x 10^9/l)	1.00 (0.35 – 2.83) p=1.00	1.52 (0.47 – 4.93), p=0.48
Lymphocytes (<0.6 x 10^9/l OR <8% of leucocytes)	4.35 (1.67 – 11.30) p=0.003	2.93 (0.75 – 11.40), p=0.12

Legend: Hazard ratios (HR) were calculated using Cox proportional hazard analyses.

BMU was not included in the multivariate analysis due to co-linearity with Bone lesion.

Figure legends:

Fig 1: **Patterns of bone marrow FDG uptake.** Examples of BMU level with relation to bone lesion status. Black arrows represent nodal involvement of cHL. Grey arrows represent focal bone lesions.

Fig 2: Outcome depending on the presence of extranodular disease. Kaplan-Meier plots of PFS and OS. A and B: Patients with no lesions vs. unifocal vs. multifocal. The 3-way p-value was subsequently broken down into unifocal vs. multifocal (p=0.24 and p=0.22 for PFS and OS respectively) and focal lesion vs. no lesion (p=0.0001 and p=0.002 for PFS and OS respectively). C and D: Patients with stage 4 disease of non-skeletal vs. skeletal type (C and D).

Fig 3: Outcome in patients with only diffuse bone marrow FDG uptake. Kaplan-Meier plot of PFS in patients with no bone lesions and low vs high BMU.

Fig 4: Outcome depending on primary chemotherapy. Overall survival in patients with or without bone lesions related to primary treatment.

Figures:

Fig 1:

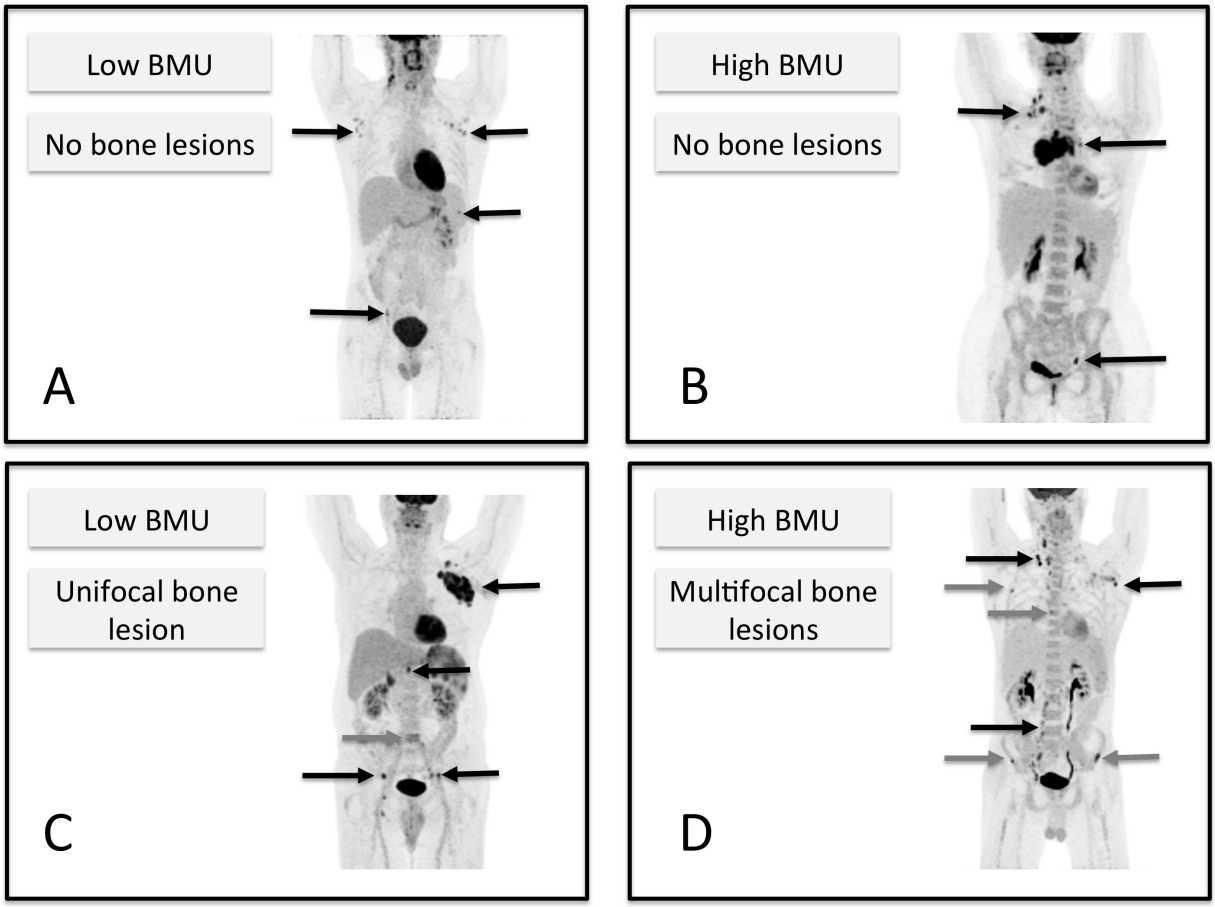


Fig 2:

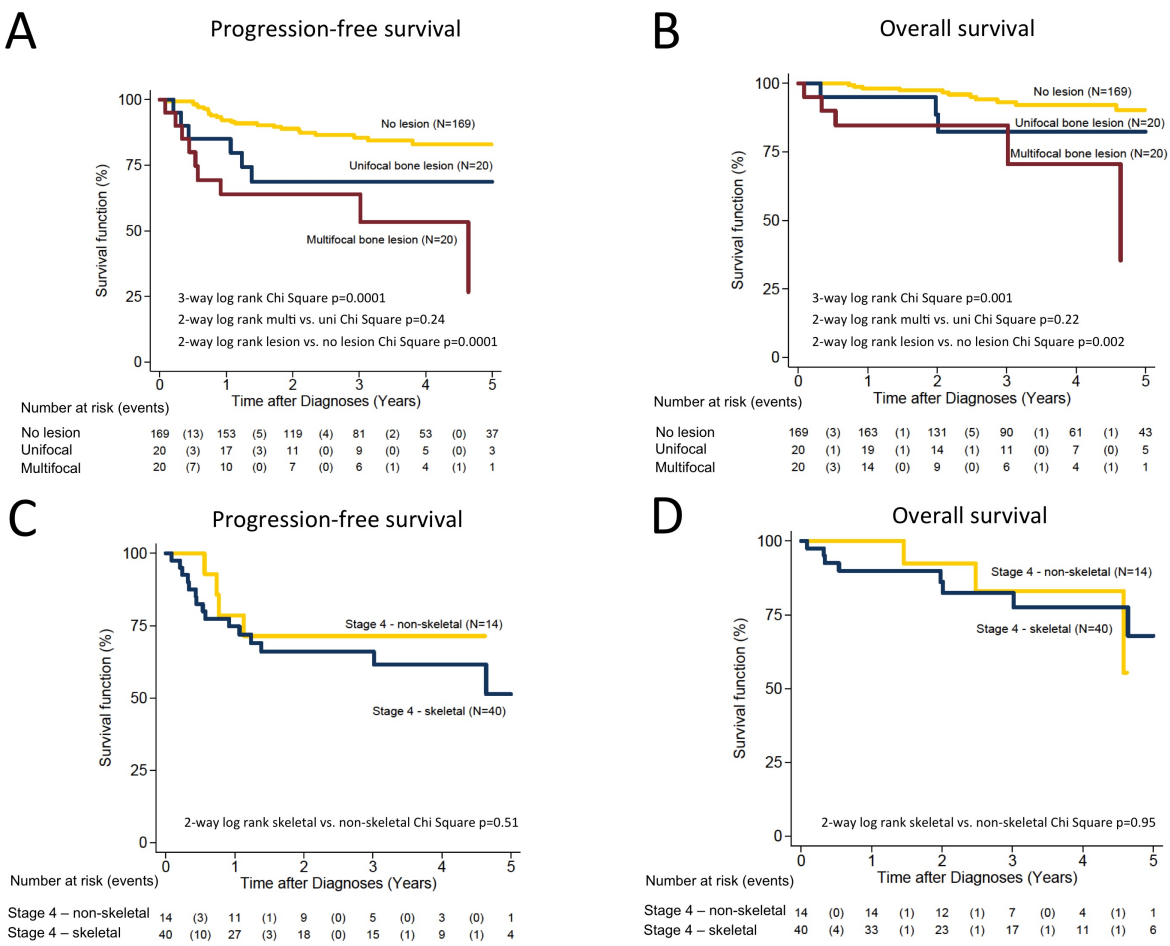

A
Progression-free survival
Survival function (%)
100
75
50
25
0
No lesion (N=169)
Unifocal bone lesion (N=20)
Multifocal bone lesion (N=20)
3-way log rank Chi Square p=0.0001
2-way log rank multi vs. uni Chi Square p=0.24
2-way log rank lesion vs. no lesion Chi Square p=0.0001
0 1 2 3 4 5
Time after Diagnoses (Years)
Number at risk (events)
No lesion 169 (13) 153 (5) 119 (4) 81 (2) 53 (0) 37
Unifocal 20 (3) 17 (3) 11 (0) 9 (0) 5 (0) 3
Multifocal 20 (7) 10 (0) 7 (0) 6 (1) 4 (1) 1
B
Overall survival
Survival function (%)
100
75
50
25
0
No lesion (N=169)
Unifocal bone lesion (N=20)
Multifocal bone lesion (N=20)
3-way log rank Chi Square p=0.001
2-way log rank multi vs. uni Chi Square p=0.22
2-way log rank lesion vs. no lesion Chi Square p=0.002
0 1 2 3 4 5
Time after Diagnoses (Years)
Number at risk (events)
No lesion 169 (3) 163 (1) 131 (5) 90 (1) 61 (1) 43
Unifocal 20 (1) 19 (1) 14 (1) 11 (0) 7 (0) 5
Multifocal 20 (3) 14 (0) 9 (0) 6 (1) 4 (1) 1
C
Progression-free survival
Survival function (%)
100
75
50
25
0
Stage 4 - non-skeletal (N=14)
Stage 4 - skeletal (N=40)
2-way log rank skeletal vs. non-skeletal Chi Square p=0.51
0 1 2 3 4 5
Time after Diagnoses (Years)
Number at risk (events)
Stage 4 – non-skeletal 14 (3) 11 (1) 9 (0) 5 (0) 3 (0) 1
Stage 4 – skeletal 40 (10) 27 (3) 18 (0) 15 (1) 9 (1) 4
D
Overall survival
Survival function (%)
100
75
50
25
0
Stage 4 - non-skeletal (N=14)
Stage 4 - skeletal (N=40)
2-way log rank skeletal vs. non-skeletal Chi Square p=0.95
0 1 2 3 4 5
Time after Diagnoses (Years)
Number at risk (events)
Stage 4 – non-skeletal 14 (0) 14 (1) 12 (1) 7 (0) 4 (1) 1
Stage 4 – skeletal 40 (4) 33 (1) 23 (1) 17 (1) 11 (1) 6

Fig 3:

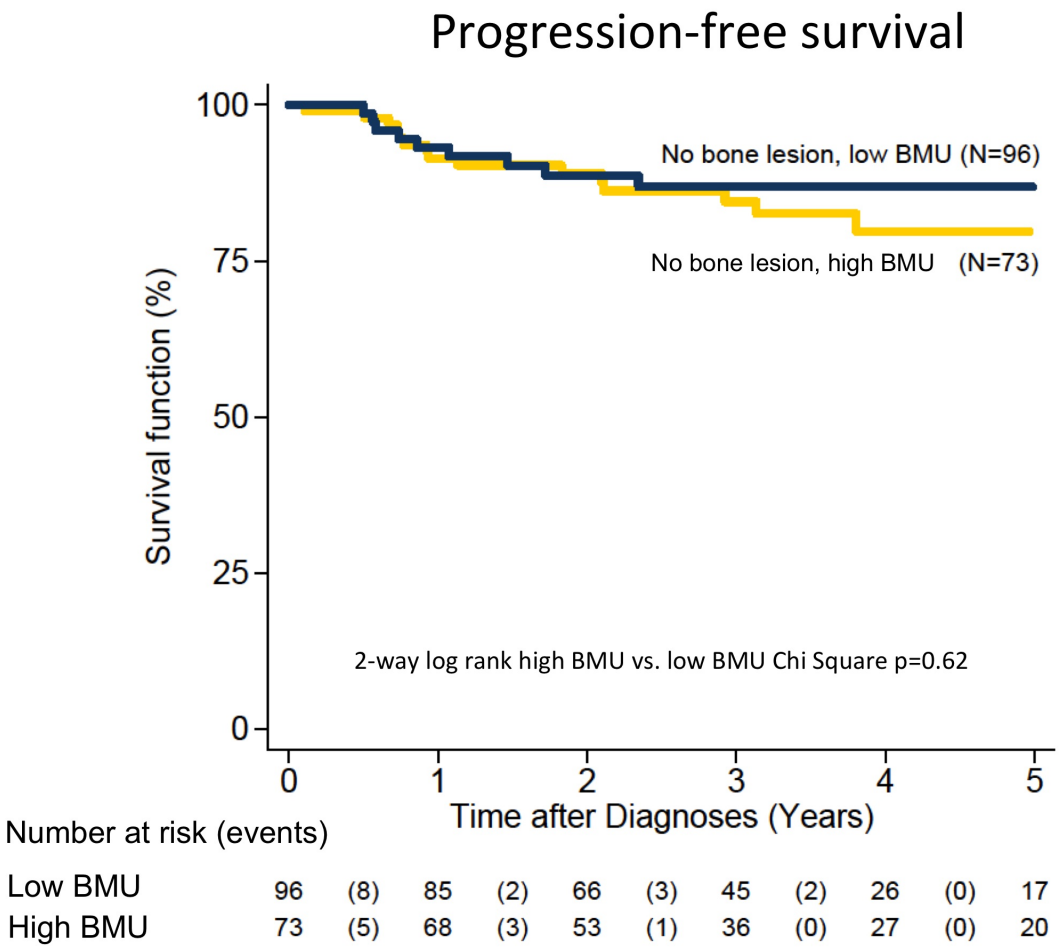
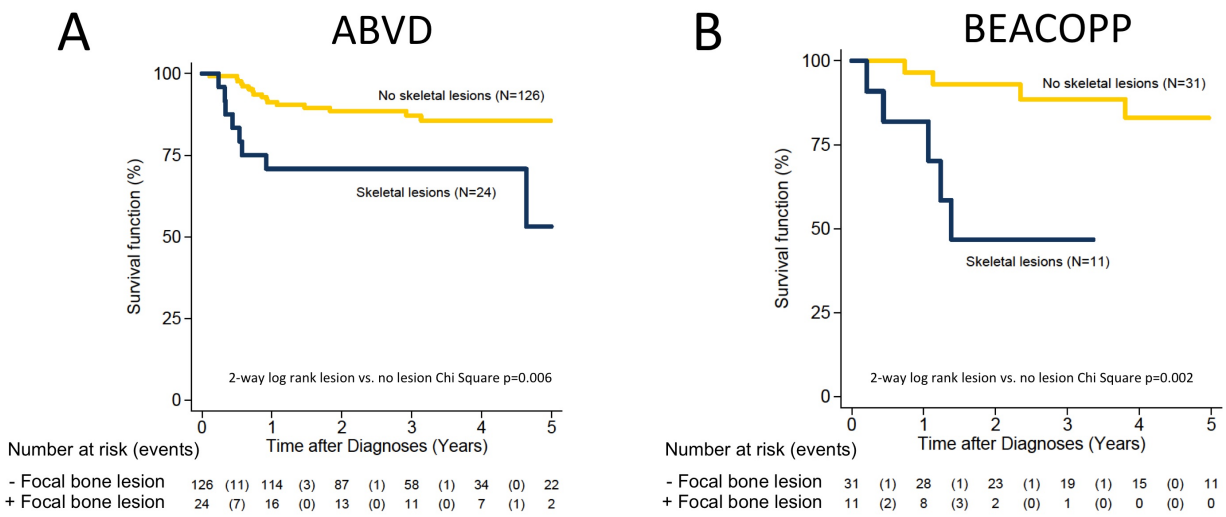

Progression-free survival
100
75
50
25
0
Survival function (%)
No bone lesion, low BMU (N=96)
No bone lesion, high BMU (N=73)
2-way log rank high BMU vs. low BMU Chi Square p=0.62
0
1
2
3
4
5
Time after Diagnoses (Years)
Number at risk (events)
Low BMU 96 (8) 85 (2) 66 (3) 45 (2) 26 (0) 17
High BMU 73 (5) 68 (3) 53 (1) 36 (0) 27 (0) 20

Fig 4:


A
ABVD
100
75
50
25
0
Survival function (%)
No skeletal lesions (N=126)
Skeletal lesions (N=24)
2-way log rank lesion vs. no lesion Chi Square p=0.006
0
1
2
3
4
5
Time after Diagnoses (Years)
Number at risk (events)
- Focal bone lesion 126 (11) 114 (3) 87 (1) 58 (1) 34 (0) 22
+ Focal bone lesion 24 (7) 16 (0) 13 (0) 11 (0) 7 (1) 2
B
BEACOPP
100
75
50
25
0
Survival function (%)
No skeletal lesions (N=31)
Skeletal lesions (N=11)
2-way log rank lesion vs. no lesion Chi Square p=0.002
0
1
2
3
4
5
Time after Diagnoses (Years)
Number at risk (events)
- Focal bone lesion 31 (1) 28 (1) 23 (1) 19 (1) 15 (0) 11
+ Focal bone lesion 11 (2) 8 (3) 2 (0) 1 (0) 0 (0) 0