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SHORT COMMUNICATION

Interim FDG-PET/CT in Hodgkin lymphoma: the prognostic role of the ratio between target lesion and liver SUVmax (rPET)

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Abstract
Objective To evaluate the prognostic role of the ratio between target lesion and liver SUVmax (rPET) in patients with Hodgkin lymphoma (HL) undergoing interim FDG-PET/CT and to compare rPET with the 5-point Deauville Score (5p-DS).
Methods Sixty-eight patients with HL undergoing interim FDG-PET/CT after first courses of chemotherapy were evaluated. The receiver operating characteristic (ROC) approach was applied to identify the optimal cutpoint of rPET with respect to progression free survival (PFS). The prognostic significance of rPET was compared with 5p-DS (scores 4 and 5 considered as positive). Positive predictive value (PPV) and negative predictive value (NPV) were calculated using the presence of an adverse event as the gold standard.
Results The ROC analysis for rPET as a predictor of progression showed an optimal rPET cutpoint of 1.14. Both 5p-DS and rPET were strong outcome predictors ($p < 0.001$). Patients with negative 5p-DS and patients with rPET <1.14 had a similar two-year PFS (86 and 87 %, respectively). Patients with a positive 5p-DS had a 2-year PFS of 27 %, while patients with rPET >1.14 had a 2-year PFS of 15 %. 5p-DS and rPET cutoff of 1.14 showed a PPV of 58 versus 70 %, and a NPV of 85 versus 86 %, respectively.
Conclusions rPET could be considered an accurate prognostic factor in patients with HL undergoing interim FDG-PET/CT. Larger prospective studies are needed to confirm these data.

Keywords Hodgkin · FDG-PET/CT · Deauville · SUVmax · rPET

Introduction

Despite recent advances in Hodgkin lymphoma (HL) treatment, about 20 % of patients still die of progressive disease [1]. ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) is considered the standard regimen for first-line treatment. An important research goal is early identification of patients with poor prognosis, who could take advantage of an intensified therapy scheme. Interim 18F-Fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging after the first two cycles of ABVD has proved to be a powerful prognostic tool in patients with HL [1–3]. A 5-point scoring system using the Deauville criteria (5p-Deauville Score, 5p-DS) has been proposed as a qualitative visual method to evaluate interim FDG-PET/CT and been widely accepted to be the best predictor of outcome [4]. The ratio between semi-quantitative parameters (e.g., target lesion and liver SUV) has been recently proposed for the evaluation of interim FDG-PET/CT in patients with HL [5]. The ratio has some important advantages: it is independent of the amount of administered activity and body weight; it allows conversion of a visual qualitative scale (e.g., 5p-DS) to a continuous semi-quantitative scale; it permits evaluation of interim FDG-PET/CT through a well-determined semi-quantitative-based cutpoint [5]. To the best of our

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knowledge, no data about the prognostic role of the ratio between lesion and liver SUV in patients with HL undergoing interim FDG-PET/CT have been published until now. The aim of this retrospective study is to evaluate the prognostic value of the ratio between target lesion and liver SUVmax (rPET) in patients with HL undergoing interim FDG-PET/CT during the first-line chemotherapy and to compare rPET with 5p-DS.

Methods

Patients

Sixty-eight patients with HL, diagnosed between January 2007 and December 2014 at our institution, were retrospectively evaluated. All patients received ABVD chemotherapy according to the presence of risk factors defined by EORTC [6]. Treatment scheme was not changed on the basis of the interim FDG-PET/CT results. All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Interim FDG-PET/CT

All patients underwent interim FDG-PET/CT at around day 25 (mean 25, range 22–27) after the first ABVD course. Patients fasted for at least 6 h before FDG administration. Images were acquired at a mean 60 ± 10 min after intravenous injection of mean 270 MBq (range 150–320) of FDG according to body mass index. All studies were performed using one of three integrated PET–CT tomographs (31 patients on DUAL and 30 patients on GEMINI GXL distributed by Philips Medical System; 7 patients on BIOGRAPH distributed by Siemens). The CT acquisition protocol included a low-dose CT scan from the base of the skull to the mid-thigh for attenuation correction and anatomical localization. All FDG-PET/CT scans were acquired in three-dimensional mode with an acquisition time of 3 min per bed position. PET data were reconstructed using an iterative algorithm (3D-RAMLA) and corrected for dead time, decay, random coincidences, and attenuation. PET–CT images were evaluated by two nuclear medicine physicians (SA and VR) using a dedicated fusion and display software (SYNTEGRA by Philips). Interim FDG-PET/CT interpretation was based on visual assessment of FDG uptake, and scored for intensity of FDG uptake according to the 5p-DS. Interim FDG-PET/CT scans with a score of 4 (FDG uptake that moderately exceeds the uptake in the liver), and 5 (markedly increased uptake >liver and/or new lesions related to lymphoma) were considered positive [4]. Target lesion both in visual (5p-DS) and semi-quantitative evaluation was defined as the hottest lesion in each interim FDG-PET/CT. Eventual disagreement between observers in scoring by 5p-DS was solved in a consensus meeting. SUVmax was defined as the SUV value of the hottest voxel, examined by display software. rPET was defined as the ratio between SUVmax of the hottest lesion (target lesion) and SUVmax of the liver right lobe.

Statistical analysis

The primary end point was progression-free survival (PFS), with progression during treatment, lack of complete remission at the end of the first-line treatment, and relapse counted as adverse events. The receiver operating characteristic (ROC) approach was applied to identify the optimal cutpoint of rPET with respect to events, to calculate accuracy values and to define the area under the curve (AUC). Survival curves were estimated using the Kaplan–Meier product limit method. Log-rank tests were used to analyze for differences in PFS. Hazard ratios (HRs) and 95 % confidence intervals (95 % CI) were adjusted for multiple prognostic factors using the Cox proportional hazards model. Computations were performed using the Stata 10.0 software (Stata Corp., College Station, TX, USA). A value of $p < 0.05$ was considered statistically significant. Positive predictive value (PPV) and negative predictive value (NPV) were calculated using the presence of adverse events as the gold standard.

Results

Basic patients' characteristics are described in Table 1. Interim FDG-PET/CT data (5p-DS, rPET, lesion and liver SUVmax) in all patients and in the three different

Table 1 Basic patients' characteristics ($n = 68$)

Characteristics	Patients (%)
Age (median, range)	39, 16–72 years
Sex	
M	38 (56)
F	30 (44)
Stage	
I–IIa	38 (56)
IIb–IV	30 (44)
IPS	
<2	53 (78)
>2	15 (22)

IPS International Prognostic Score

Table 2 Interim FDG-PET/CT data in all patients ($n = 68$) and stratified in three different tomographs used (dual, Gxl, and biograph)

Characteristics	Overall (%), $n = 68$	Dual (%), $n = 31$	Gxl (%), $n = 30$	Biograph (%), $n = 7$
5p-DS				
1–3	56 (82)	28 (90)	22 (73)	6 (86)
4–5	12 (18)	3 (10)	8 (27)	1 (14)
rPET				
<1.14	58 (89)	29 (94)	23 (77)	6 (86)
>1.14	10 (11)	2 (6)	7 (23)	1 (14)
Lesion SUVmax (mean, range)	2.1 (1–10.6)	1.7 (1.1–4.3)	2.1 (1–5.4)	3.3 (1.4–10.6)
Liver SUVmax (mean, range)	2.8 (1.4–4.2)	2.7 (1.4–3.9)	2.8 (1.8–4.2)	3.0 (2.1–3.8)
rPET (mean, range)	0.73 (0.47–3.03)	0.61 (0.47–1.79)	0.77 (0.51–1.59)	1.04 (0.53–3.03)

5p-DS 5-point Deauville Score, *rPET* ratio between lesion and liver SUVmax

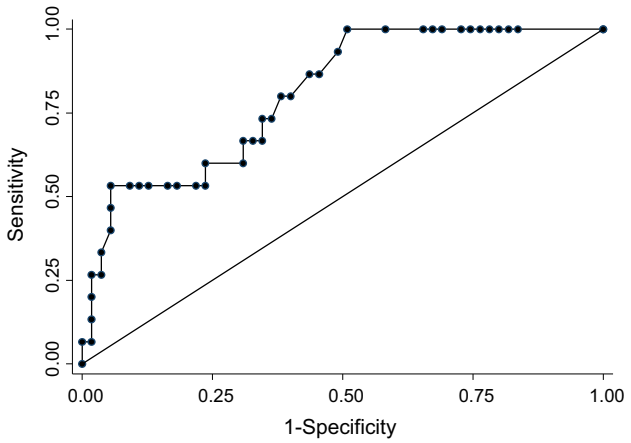

Fig. 1 ROC analysis for rPET values to predict progression. The area under the curve (AUC) of the ROC analysis is 0.81 (95 % CI 0.69–0.92)

tomographs used are listed in Table 2. No liver focal lesion was detected in our population. The ROC analysis for rPET as a predictor of progression showed an AUC of 0.81, with an optimal rPET cutpoint of 1.14 (specificity 95 %, sensitivity 53 %) (Fig. 1). Both 5p-DS (HR 9.2, SE 4.9, 95 % CI 3.3–25.9) and rPET (HR 4.9, SE 2.1, 95 % CI 2.1–11.3) resulted in strong outcome prediction ($p < 0.001$) (Fig. 2). Patients with negative 5p-DS and patients with rPET <1.14 had a similar 2 year PFS (86 and 87 %, respectively). Patients with a positive 5p-DS had a two-year PFS of 27 % (Fig. 2a), while patients with rPET >1.14 had a two-year PFS of 15 % (Fig. 2b). 5p-DS and rPET (cutoff of 1.14) were discordant in two patients, which had positive 5p-DS and rPET <1.14. Neither of these patients had any adverse events. 5p-DS and rPET cutoff of 1.14 showed PPV 58 vs 70 %, NPV 85 vs 86 %, respectively. Finally, a scatter graph of rPET in the study population is shown in Fig. 3.

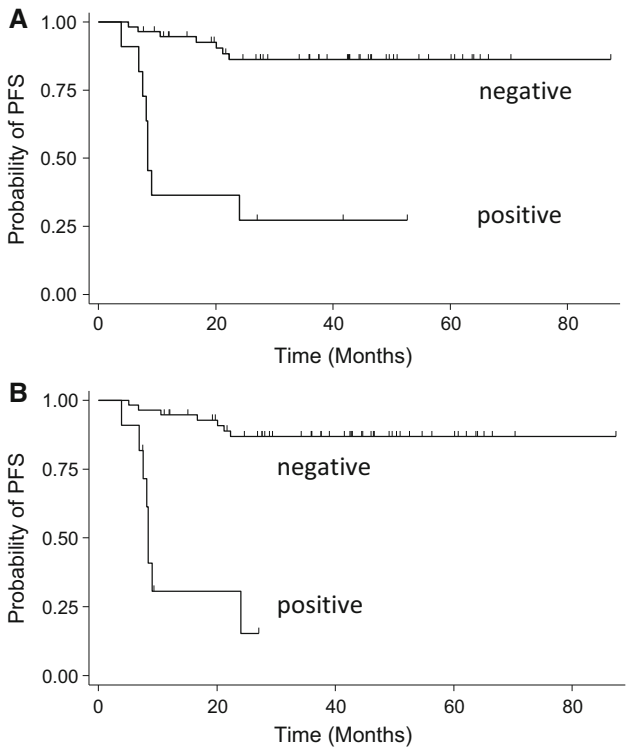

Fig. 2 Kaplan–Meier survival estimates for PFS according to **a** interim 5p-DS and **b** rPET cutoff of 1.14

Discussion

To the best of our knowledge, no data about the prognostic role of the ratio between lesion and liver SUV in patients with HL undergoing interim FDG-PET/CT have been published until now. The aim of this study was to evaluate the prognostic role of the ratio between the target lesion and liver SUVmax (rPET) in patients with HL undergoing

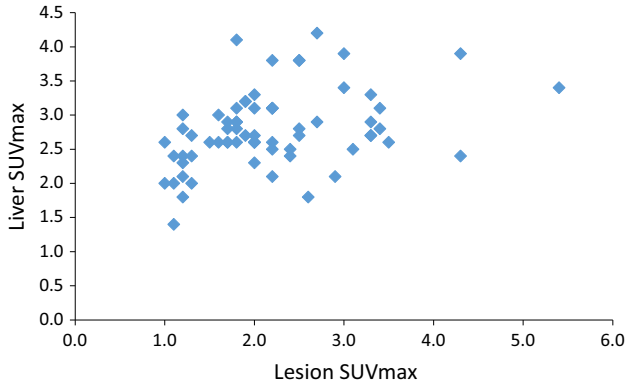

Fig. 3 Scatter graph of the ratio between lesion and liver SUVmax (rPET) in study population ($n = 68$)

interim FDG-PET/CT during the first-line chemotherapy and to compare rPET with 5p-DS.

According to the previous studies [4], 5p-DS was confirmed to be a strong prognostic factor in our population. With 5p-DS, target lesion uptake (usually the hottest lesion described) is compared with liver uptake (chosen as standard reference): a target lesion uptake higher than the liver (score 4 or 5) is considered positive and is a marker of aggressive disease [4]. Nevertheless, 5p-DS still shows many of the limits of visual image interpretation (such as inter-observer disagreement) [5, 7]. Moreover, it is still being debated which the best intra-patient reference organ is (liver or mediastinal blood pool) [8]. In this study, 5p-DS and rPET were obtained considering the same reference organ (liver parenchyma). Recent studies demonstrated that also semi-quantitative parameters (such as lesion SUVmax) have a prognostic significance in patients with HL [7, 9, 10]. In our population, rPET was documented to be a prognostic factor in patients with HL undergoing interim FDG-PET/CT. This ratio has some important technical and practical advantages over visual analysis: it is independent of the amount of administered activity and body weight; it allows conversion of a visual qualitative scale (as 5p-DS) in a continuous semi-quantitative scale; it permits evaluation of interim FDG-PET/CT through a well-determined semi-quantitative-based cutpoint [5]. Moreover, rPET could have significant diagnostic advantages over visual analysis (e.g., in terms of predictive value). Different from previous studies [5], we used the ratio between SUVmax of the target lesion and SUVmax of the liver (defined as rPET) in each interim FDG-PET/CT examination. Moreover, we did not use any other SUV parameters (such as SUVpeak or SUVmean) to avoid mistakes and misinterpretation related to ROI- or VOI-based measurement [11]. In our population, rPET demonstrated a good specificity in predicting PFS (95 % at a cutpoint of 1.14). We chose this cutoff, because it had the best specificity (95 %) and sensitivity (53 %) among values of rPET >1 (lesion SUVmax higher than liver SUVmax). In particular, patients with rPET >1.14 had a worse prognosis than patients with positive 5p-DS (PFS at 2 years of 15 and 27 %, respectively). 5p-DS and rPET results were in agreement in most of the patients (66/68, 97 %). Only two patients were discordant (positive 5p-DS and rPET <1.14), and neither of these patients had any adverse events, and therefore, these could be considered as false positives of 5p-DS. Consequently, the rPET cutpoint of 1.14 seems to be accurate to identify patients with aggressive disease (PPV 70 %, NPV 86 %).

This study has some limitations. First, it is a retrospective study about a small group of patients ($n = 68$). As is well known [11], SUV strictly depends on several technical, biological, and physical factors. In particular, the use of three different tomographs could be a limitation in the comparison of semi-quantitative parameters. Moreover, according to some authors [12, 13], the use of ratios could be a source of errors. Possible source of mistakes could also be the heterogeneity of liver parenchyma in the measurement of liver SUVmax [8, 14, 15]. Nevertheless, the use of ratios as rPET could mitigate heterogeneity between different tomograph in terms of lesion and liver SUVmax, because of the intra-examination normalization guaranteed by rPET.

Conclusion

rPET could be considered a prognostic factor in patients with HL undergoing interim FDG-PET/CT. rPET seems to be an accurate semi-quantitative alternative to 5p-DS in identifying patients with aggressive disease and to improving their treatment management. Larger prospective studies are needed to confirm these data.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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