Title

Predictive value on advance Hodgkin Lymphoma treatment outcome of end-of treatment FDG PET/CT in the HD0607 clinical trial

Running title

End-of-treatment PET in Hodgkin Lymphoma

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Abstracts (150-250 words)

The Lugano classification for response assessment in lymphoma recommends the use of the 5-point-scale Deauville Score (DS) to assess response evaluation of end-of-treatment FDG-PET/CT (eotPET) in Hodgkin Lymphoma (HL); nevertheless, there is a paucity of data on its accuracy and reproducibility.

We focus here on the cohort of advanced stage IIb-IV HL patients enrolled in the HD0607 clinical trial (NCT identifier 00795613) that having had a negative interim PET performed 6 cycles of ABVD (Doxorubicin, Vinblastine, Vincristine and Dacarbazine) and then performed an eotPET. Negative patients were randomized to radiotherapy and no further treatment while positive patients were treated based on local policies. eotPET was re-evaluated independently by two readers evaluated and progression free survival was analysed (PFS).

eotPET of 254 patients were analysed. The median follow-up was 43 months. The best receiver operator characteristics cut-off values to distinguish positive and negative patients was 4. The area-under-the-curve was 0.81 (95%CI, 0.70-0.91). Three-years PFS was 0.95 (95% CI 0.90-0.97) in eotPET negative and 0.22 (95% CI 0.11-0.43) in eotPET positive. DS demonstrated a good reproducibility of positivity/negativity between the readers consensus and local site evaluation where the agreement occurred on 95.0% of patients.

The present study demonstrates that eotPET is an accurate tool to predict treatment outcome in HL and confirms the appropriateness of the Lugano classification for eotPET evaluation. Keywords: Advanced-stage Hodgkin Lymphoma, PET, Deauvile Criteria, End-of-treatment response assessment

Introduction

^{18}F-fluorodeoxyglucose Positron Emission Tomography combined with Computed Tomography (FDG-PET/CT, simply PET) is the standard-of-care for response assessment in FDG-avid lymphoma (1). Moreover it serves as a surrogate for other measures of clinical benefit, such as Progression Free Survival (PFS) or Overall Survival (OS) and as an essential guide in the choice of continuing or changing therapy (2).

In 2007 the International Working Group developed new recommendations for response criteria for aggressive malignant lymphomas, incorporating end-of-treatment PET (eotPET) for the definition of therapy responses. The overall accuracy of PET proved superior to contrast-enhanced CT scan, and patients with residual masses on CT but with negative FDG uptake were considered as a complete responders(3).

The consensus of the International Conference on Malignant Lymphomas Imaging Working Group held in 2014 confirmed that PET is the standard-of-care for treatment response assessment at interim and the end-of-treatment in FDG-avid lymphoma, and that the Deauville criteria are recommended for FDG-PET/CT reporting using a 5-point-scale using 5-point-scale Deauville score (DS) (4). According to the revised criteria for response assessment (named the Lugano classification by this consensus), a DS of 1, 2, or 3 with or without residual CT masses represents Complete Metabolic Response (CMR) (4).

Such recommendations were based on expert opinion consensus and, as of now, few validation studies have been published to confirm the predictive role on treatment outcome of eotPET in patients with Hodgkin lymphoma (HL) using the above-mentioned criteria.

The multi-centric prospective clinical trials RATHL(5), SWOG S0816(6) and GITIL/FIL HD0607(7) demonstrated that a PET-driven switch after two Doxorubicin, Vinblastine, Vincristine and Dacarbazine (ABVD) to escalated Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine and Prednisone (BEACOPP) is feasible and effective in high risk patients with advanced stage HL and DC are a robust and reproducible interpretation key for interim PET interpretation. In this work we evaluated eotPET in the HD0607 trial to support the use of DS 4 as a threshold for complete response both in terms of diagnostic accuracy, with respect to PFS, and the reproducibility of DS measured as the concordance agreement between reviewers and between reviewers' and local sites' evaluation.

Patients and methods

The multi-centric HD0607 clinical trial (ClinicalTrial.gov identifier 00795613), assessed the clinical impact of dose intensification performed early during treatment in a subset of poor prognosis, advanced-stage (IIB-IVB) HL patients, defined by a positive interim PET (iPET) after two courses of conventional ABVD. After a

baseline lymphoma staging including PET (bPET), patients were treated with 2 ABVD courses, followed by an iPET. bPET and iPET were uploaded in the study website using the WIDEN® platform(8) and iPET reviewed in a blinded independent central review (BICR) (9) using the DC by a panel of expert nuclear medicine physicians. iPET positive patients (DS ≥ 4) (experimental arm), were randomized to receive either 4 cycles of escalated-BEACOPP (Be) plus 4 cycles of BEACOPP baseline (Bb) or Be+Bb (4+4) supplemented with Rituximab. Patients with a negative iPET (DS <4) (standard arm) stuck on ABVD treatment with four additional cycles and, upon confirmation of eotPET CMR entry, randomized to consolidation radiotherapy (cRT) on the sites of initial large nodal mass (LNM) or no further treatment (NFT). eotPET scans were reported locally by a PET imaging expert at the local site. In the present report, we focus on the eotPET negative patients entering in the randomized study. Since there was no difference in treatment outcome in terms of 6-years PFS for patients according to the randomization arm [10], in the present study we analyse both cohorts together, without distinction based on the post-chemotherapy assigned treatment.

PET imaging

PET scanning and imaging fulfilled the methodology required by the HD0607 trial, as previously described (10). We were able to retrieve from local databases and collect 246 PET/CT.

eotPET was reviewed along with bPET and iPET by two nuclear expert medicine physicians, blinded to patient history, clinical data and treatment outcome. A third reviewer was recruited to adjudicate the final result in case of discrepancies. For each patient the location of the most active residual lesion in eotPET (reference lesion) was identified and visually scored according to DS as described elsewhere(11); a consensus was reached in discordant cases. The reference lesion was identified as a lesion already present in bPET, with a DS ≥ 2. New, single lesions in eotPET, not recorded in bPET, were not deemed to harbinger lymphoma if the patient was responding to treatment in all the initially involved sites. DS 5 was assigned to lesion having an uptake higher than three-fold the average liver uptake. For each reference lesion d_{max}, the largest diameter on axial slice measured on the CT of PET, was reported. In supplemental material we report also data regarding qPET, the ratio between the lesion SUV_{peak} and the liver SUV_{mean}, rPET, the ratio between the lesion SUV_{max} and the liver SUV_{mean}, and Q_{max} the ratio between the lesion SUV_{max} and the liver $SUV_{max.}$ (see

supplemental material). The results of the local eotPET report were retrieved from the patient's record of the study.

Statistical analysis

Progression-free survival (PFS) was measured from the date of registration to the date of first appearance of disease progression, relapse or death for any cause; a treatment failure (for relapse of progression) could be considered a PFS event in presence of a documented second-line treatment. For each eotPET reviewed we evaluated the binary concordance between the two reviewers and between local and central review using the Cohen's kappa. The eotPET results were reported according to DS and the corresponding PFS values dichotomized in search of the optimal value. Differences in PFS between groups were estimated by log-rank test of the Kaplan-Meier curve. Accuracy (AC), sensitivity (SE), specificity (SP), negative predictive value (NPV) and positive predictive value (PPV) were computed in relation with PFS events. Confidence interval at 95% were obtained via bootstrapping. Clinical and PET variables were entered into a prognostic univariate and multivariate model (one for PFS and one for OS) based on Cox regression analysis. Proportional hazards assumption was checked by inspection of the scaled Schoenfeld residuals.

Results

The demographics and clinical parameters of the whole cohort of 296 patients that were interim PET negative within HD0607 clinical trial and the subset of 254 patients included in the present study is reported in Table I. No statistical relevant differences in the breakdown of the demographic and clinical parameters in the two groups were observed. Figure 1 present the CONSORT diagram of the population of this study.

Discordance in eotPET reporting among local investigators and central reviewers occurred in 14/254 (5.5%) of the patients. 11 patients locally reported as negative turned out to be positive upon central review and 3 patients locally reported as negative were evaluated as positive in central review. The Cohen's kappa between the central review and the local investigators was 0.65.

In 163 out of 254 (64.2%) cases it was possible to identify a reference lesion in the eotPET with a DS≥2 while in 91/254 (35.8%) patients no reference lesion was identifiable (DS = 1). The overall DS scoring (number of

patients in brackets) was the following 1(91), 2(113), 3(24), 4(12) and 5(14). Patients in CMR, showing an EotPET with a DS ≤ 3, were 228/254 (89.8%). The best ROC cut-off values to distinguish positive and negative patients was DS score 4 (Figure S1 in supplemental material). The area-under-the-curve (AUC) of ROC was 0.81 (95%CI, 0.70-0.91), other parameters are reported in Table 2. The clinical characteristics of PET-2 negative patients showing a positive or a negative eotPET are depicted in Table 3.

After a median follow-up of 43 (6-95) months, 219/254 (86.2%) were in CR and 35/254 (13.8%) showed a PFS event (disease relapse, progression or death). Of the 26 patients with a positive eotPET (DS 4-5), 20 showed disease recurrence (true positive), while 6 were in CR (false positive). On the other hand, 15 patients showing disease recurrence were in CMR, with DS scores of 1 (4), 2 (8) and 3 (3), respectively. 5 patients died: with a. DS score of 1 (1), 2 (1), 3 (0), 4 (1) and 5 (2), respectively. The deaths were due to transplant related mortality (three patients), respiratory failure due to pulmonary infection (one patient), and progression, sepsis (one patient).

Figures 2 show the PFS according to DS score. 14/14 (100%) of the patients that had a DS 5 experienced progression while only 6/12 (50%) of those with a DS 4. Figures 3 and 4 show the dichotomized PFS and OS values for DS based on survival analysis. Three-years PFS was 0.95 (95% CI 0.90-0.97) in eotPET negative and 0.22 (95% CI 0.11-0.43) in eotPET positive. Log-rank was <0.001.

At multi-variate analysis with Cox model, including sex, WHO activity index, Ann Arbor stage, IPS, B-symptoms, large nodal mass, and DS, only eotPET DS was statistically relevant, p<0.0001, for PFS and OS.

Discussion

PET has become the standard diagnostic tool for post-treatment response evaluation for most lymphoma subtypes that proved FDG-avid. As a matter of fact, CMR is currently adopted as a widely used surrogate endpoint for progression free survival and overall survival.

Cerci et al. demonstrated that end-of-treatment lymphoma restaging with PET, classified as positive or negative according to the consensus recommendations of the Imaging Subcommittee of International Harmonization Project in Lymphoma (IHP), was superior to the conventional dimensional criteria to assess

tumor shrinkage on CT (12). After first-line treatment, approximately 40% of patients were considered in complete remission unconfirmed (RCU) or in partial response (PR) by end-of-therapy CT (eotCT). In their study Cerci et al has shown that eotPET clearly outperformed eotCT as demonstrated by AC, SE, SP, PPV, and NPV values of 0.96, 1.00, 0.92, 0.92, and 1, which proved significantly higher than the corresponding eotCT values, that were 0.77, 0.87, 0.74, 0.52, and 0.94 respectively [14]. This higher accuracy is due to ability of PET to differentiate viable tumour from fibrosis in residual masses.

A meta-analysis by Adams et al. including 1137 patients with early and advanced HL from 10 studies showed that in patients with a metabolic response defined by a negative PET, the disease relapse rate during follow-up ranged from 0% to 26.7%, with a weighted summary proportion of 7.5% (95% confidence interval: 3.9 -13.8) (13). However, the criteria to interpret the PET in the studies included in this meta-analysis were generally based on the 'old' IHP criteria that demonstrated generally a higher number of false positive results compared to the strict definition of CMR in the Lugano classification (14–16).

In a retrospective study, Metser *et. al* compared the accuracy of PET in assessing residual masses at the end of therapy for 43 patients with HL and 94 patients with non-HL by comparing IHP and Deauville criteria (17). The standard of reference was based on histopathology, or clinical follow-up and imaging surveillance. A positive biopsy or interval increase in size of the mass on surveillance was considered indicative of residual viable disease at time of PET. The AC, SE, SP, PPV, NPV and accuracy were 0.85, 0.95, 0.81, 0.70, and 0.97 using IHP and 0.94, 0.93, 0.94, 0.88, and 0.97 using Lugano classification. The authors concluded that the DS of 4 threshold they used to define eotPET positivity improves SP, yet maintains a high SE in identifying residual lymphoma. The agreement amongst readers in defining positive and negative eotPET with DS was excellent.

In a retrospective study on 35 HL and 66 non-HL, Fallanca *et al.* compared the diagnostic accuracy of IHP and DS for eotPET reading to predict progression and survival (16). Disease status was followed by reference to the available clinical and imaging information, identifying patients negative for the presence of disease and patients with relapse and/or progression of disease at follow up. Once more DS criteria

outperformed IHP criteria, with AC, SE, SP, PPV, NPV and accuracy values of 0.76, 0.97, 0.67, 0.57, and 0.98 for the former and of 0.86, 0.92, 0.87, 0.74, and 0.92 for the latter. The corresponding 2-years cumulative values of PFS and OS were 73% and 75% in negative patients and 20% and 36% in positive patients with the IHP criteria, and were 75% and 74% in negative patients and 49% and 53% in positive patients with DS values. The authors concluded that DS has a better performance and survival prediction results over the IHP criteria (10).

More recently Picardi et al. (18), in a retrospective study of 169 IIB-IV HL that underwent eotPET after 6 cycles of ABVD, showed that the NPV of eotPET was 0.94. Patients with a positive eotPET were addressed to observation or RT on residual nodes or salvage chemotherapy followed by Autologous Stem Cell Transplantation (ASCT) depending on DS and clinical condition. The thoroughness of the study consisted in the histopathological control of the accuracy of imaging results by core-needle cutting biopsy (CNCB) performed in all the patients showing a residual mass scored DS 4 and 5. In this study, CNCB confirmed the persistence of disease in 100% of DS5 and in only 16% of DS4.

As previously mentioned, the Lugano Classification adopts a DS threshold of 4 for a positive eotPET. But this assertion was based more on the consensus of the experts and in analogy with other subtypes of FDG-avid lymphoma rather than on a well-conducted clinical validation study. Nonetheless, both the aforementioned preliminary papers and our work support this DS threshold. Within this work we confirmed that the best cut-off values in ROC analysis to distinguish responder from non-responders was 4. Patients with a DS of 1, 2, and 3 with or without residual mass had a 3-year PFS of 0.95 while those with a DS 4 and 5 had a 3-years PFS of 0.22.

DS5, as shown in figure 2 had a PPV of 1. As a matter of fact, all patients with a DS 5 underwent progression while the latter occurred only in half of the DS4 patients. The reasons of FP results in patients with a residual mass with a DS 4 are still unclear. As a matter of fact Picardi et al, showed a much higher number of FP results in patients with a post-treatment residual mass undergoing fine needle biopsy in patients with a DS of 4 at eotPET compared to that observed in patients in the same clinical situation and DS of 5 at eotPET (18). A

reason could be the presence of granulomatosis or other inflammatory process reactive to CT induced tissue necrosis.

In this study we report the presence of patients who, despite having a negative interim PET showed a positive eotPET. This finding was recorded in 10% of the patients. We analysed the baseline characteristics in search of possible clinical variables associated to this switch to a positive eotPET, but we failed to find any relationship

Despite the lower number of the present analysis restricted to a patient subset in which eotPET scans were available for review among the entire cohort of PET-2 negative patients, that the scans were collected randomly, and the breakdown of prognostic factors in the patients included in the present study did not differ from that of the entire population enrolled in the HD0607 trial we do not expect that the reported results could suffer from bias of patent selection.

Conclusions

Our study confirms that Lugano classification should be the standard tool to evaluate eotPET for treatment response assessment in advanced-stage HL patients. DS provide an excellent NPV and a good PPV. The great reproducibility between the central and the local review confirms that the DS is a reliable tool in this setting.

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Declarations

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Conflict of Interest: the authors declare that they have no conflict of interest.

Ethics approval and consent to participate: The study was conducted in accordance with the International Conference on Harmonization for Good Clinical Practice guidelines and the Declaration of

Helsinki. Written informed consent was obtained before enrolment. The study was approved by the Italian Pharmacology Agency (AIFA) and by the ethic committees of all the participating sites. The study was registered with the Eudract code 2007-007168-94 and at ClinicalTrials.gov, with the identifier number NCT00795613.

References

1. Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Mueller SP, et al. Role of imaging in the staging and response assessment of lymphoma: Consensus of the international conference on malignant lymphomas imaging working group. J Clin Oncol. 2014;32(27):3048–58.

2. Hutchings M, Barrington SF. PET/CT for therapy response assessment in lymphoma. in Publication Data ILC, editor. J Nucl Med [Internet]. 2010 May [cited 2011 Jun 20];50 Suppl 1(5):21S-30S. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19380407

3. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. Vol. 25, Journal of Clinical Oncology. 2007. p. 579–86.

4. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol [Internet]. 2014;32(27):1–10. Available from: http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.54.8800

5. Barrington SF, Kirkwood AA, Franceschetto A, Fulham MJ, Roberts TH, Almquist H, et al. PET-CT for staging and early response: Results from the Response-Adapted Therapy in Advanced Hodgkin Lymphoma study. Blood. 2016;127(12):1531–8.

6. Press OW, Li H, Sch H, Straus DJ, Moskowitz CH, Leblanc M, et al. US Intergroup Trial of

Response-Adapted Therapy for Stage III to IV Hodgkin Lymphoma Using Early Interim Fluorodeoxyglucose-Positron Emission Tomography Imaging: Southwest Oncology Group S0816. J Clin Oncol [Internet]. 2016;34(17):JCO.2015.63.1119-. Available from: http://jco.ascopubs.org/content/early/2016/04/07/JCO.2015.63.1119.abstract

7. Gallamini A, Tarella C, Viviani S, Rossi A, Patti C, Mule A, et al. Early chemotherapy intensification with escalated beacopp in patients with advanced-stage hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two abvd cycles: Long-term results of the GITIL/FIL HD 0607 tria. J Clin Oncol [Internet]. 2018 Feb 10 [cited 2019 Sep 1];36(5):454–62. Available from: http://ascopubs.org/doi/10.1200/JCO.2017.75.2543

8. Chauvie S, Biggi A, Stancu A, Cerello P, Cavallo A, Fallanca F, et al. WIDEN : A tool for medical image management in multicenter clinical trials. Clin trials [Internet]. 2014;11(3):1–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24711610

9. Chauvie S, Bergesio F. The Strategies to Homogenize PET / CT Metrics : The Case of Onco-Haematological Clinical Trials. Biomedicines. 2016;4(26):2124–30.

10. Chauvie S, Bergesio F, Fioroni F, Brambilla M, Biggi A, Versari A, et al. The68Ge phantom-based FDG-PET site qualification program for clinical trials adopted by FIL (Italian Foundation on Lymphoma). Phys Medica [Internet]. 2016 May [cited 2016 Aug 18];32(5):651–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27133138

11. Biggi A, Bergesio F, Chauvie S. Monitoring response in lymphomas: qualitative, quantitative, or what else? [Internet]. Jan 28, 2019 p. 302–8. Available from: https://www.tandfonline.com/doi/full/10.1080/10428194.2018.1480773

12. Cerci JJ, Trindade E, Pracchia LF, Pitella FA, Linardi CCG, Soares J, et al. Cost effectiveness of positron emission tomography in patients with Hodgkin's lymphoma in

unconfirmed complete remission or partial remission after first-line therapy. J Clin Oncol. 2010;

13. Adams HJA, Kwee TC. Proportion of false-positive lesions at interim and end-of-treatment FDG-PET in lymphoma as determined by histology: Systematic review and meta-analysis. Eur J Radiol. 2016;

14. Fischer BM, Olsen MWB, Ley CD, Klausen TL, Mortensen J, Højgaard L, et al. How few cancer cells can be detected by positron emission tomography? A frequent question addressed by an in vitro study. Eur J Nucl Med Mol Imaging [Internet]. 2006 Jun [cited 2015 Apr 1];33(6):697–702. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16612588

15. Marom EM, Munden RF, Truong MT, Gladish GW, Podoloff D a, Mawlawi O, et al. Interobserver and intraobserver variability of standardized uptake value measurements in non-small-cell lung cancer. J Thorac Imaging [Internet]. 2006 Aug;21(3):205–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16915065

16. Fallanca F, Alongi P, Incerti E, Gianolli L, Picchio M, Kayani I, et al. Diagnostic accuracy of FDG PET/CT for clinical evaluation at the end of treatment of HL and NHL: a comparison of the Deauville Criteria (DC) and the International Harmonization Project Criteria (IHPC). Eur J Nucl Med Mol Imaging [Internet]. 2016;43(10):1837–48. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27154522

17. Metser U, Mohan R, Beckley V, Moshonov H, Hodgson D, Murphy G. FDG PET/CT Response Assessment Criteria for Patients with Hodgkin's and Non-Hodgkin's Lymphoma at End of Therapy: A Multiparametric Approach. Nucl Med Mol Imaging (2010) [Internet]. 2016 Mar [cited 2019 Sep 29];50(1):46–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26941859

18. Picardi M, Fonti R, Della Pepa R, Giordano C, Pugliese N, Nicolai E, et al. 2-deoxy-2[F-18]

fluoro-D-GLUCOSE POSITRON EMISSION TOMOGRAPHY Deauville scale and core-needle biopsy to determine successful management after six doxorubicin, bleomycin, vinblastine and dacarbazine cycles in advanced-stage Hodgkin lymphoma. Eur J Cancer [Internet]. 2020;132:85–97. Available from: https://doi.org/10.1016/j.ejca.2020.03.008

Table 1. Main clinical characteristic of the population included in this study compared with the entire population of the HD0607 trial.

	HD0607 PET2 negative	*Study population*	*p-value*
N. of patients	630	254	
Median age (range)	31 (14-60)	30 (17-60)	0.885
Sex			0.869
Female	333 (52.9%)	132 (52.0%)	
WHO Activity Index			1.000
0-1	576 (91.4%)	232 (91.4%)	
>1	54 (8.6%)	22 (8.6%)	
Ann Arbor Stage			0.971
IIb	229 (36.3%)	91 (35.8%)	
III	208 (33.0%)	86 (33.9%)	
IV	193 (30.6%)	77 (30.3%)	
IPS			0.381
0-1	251 (39.8%)	89 (35.1%)	
2-3	311 (49.4%)	133 (52.3%)	
>3	68 (10.8%)	32 (12.6%)	
B symptoms present	511 (81.1%)	205 (80.7%)	0.965
Large nodal mass			0.531
No	277 (44.0%)	102 (40.2%)	
5-7 cm	123 (19.5%)	46 (18.1%)	
7-10 cm	117 (18.6%)	52 (20.5%)	
> 10 cm	113 (17.9%)	54 (21.2%)	

Table 2. Accuracy metrics for DS. 95% CI are not reported (could be found in supplemental material Table S1) since are completely overlapping for all variables and all metrics.

	Cut-off	*True positive*	*True negative*	*False positive*	*False negative*	*Accuracy*	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*
DS	4	20	213	6	15	0.92	0.57	0.97	0.77	0.93

Table 3. Clinical characteristics of eotPET positive versus negative patients.

	eotPET positive	*eotPET negative*	*p-value*
N. of patients	26	228	
Median age (range)	35 (19-59)	30 (17-70)	0.3551
Sex			0.8321
Female	13 (50.0%)	119 (52.2%)	
WHO Activity Index			0.0587
0-1	21 (80.8%)	211 (92.5%)	
>1	5 (19.2%)	17 (7.5%)	
Ann Arbor Stage			0.1782
IIb	7 (26.9%)	84 (36.8%)	
III	7 (26.9%)	79 (34.6%)	
IV	12 (46.2%)	65 (28.5%)	
IPS			0.1556
0-1	6 (23.1%)	83 (36.4%)	
2-3	14 (53.8%)	119 (52.2%)	
>3	6 (23.1%)	26 (11.4%)	
B symptoms present	24 (92.3%)	181 (79.4%)	0.1136
Large nodal mass			0.3326
No	13 (50.0%)	89 (39%)	
5-7 cm	2 (7.7%)	44 (19.3%)	
7-10 cm	7 (26.9%)	45 (19.7%)	
> 10 cm	4 (15.4%)	50 (21.9%)	

Figure 1 Consort diagram of the population of the study

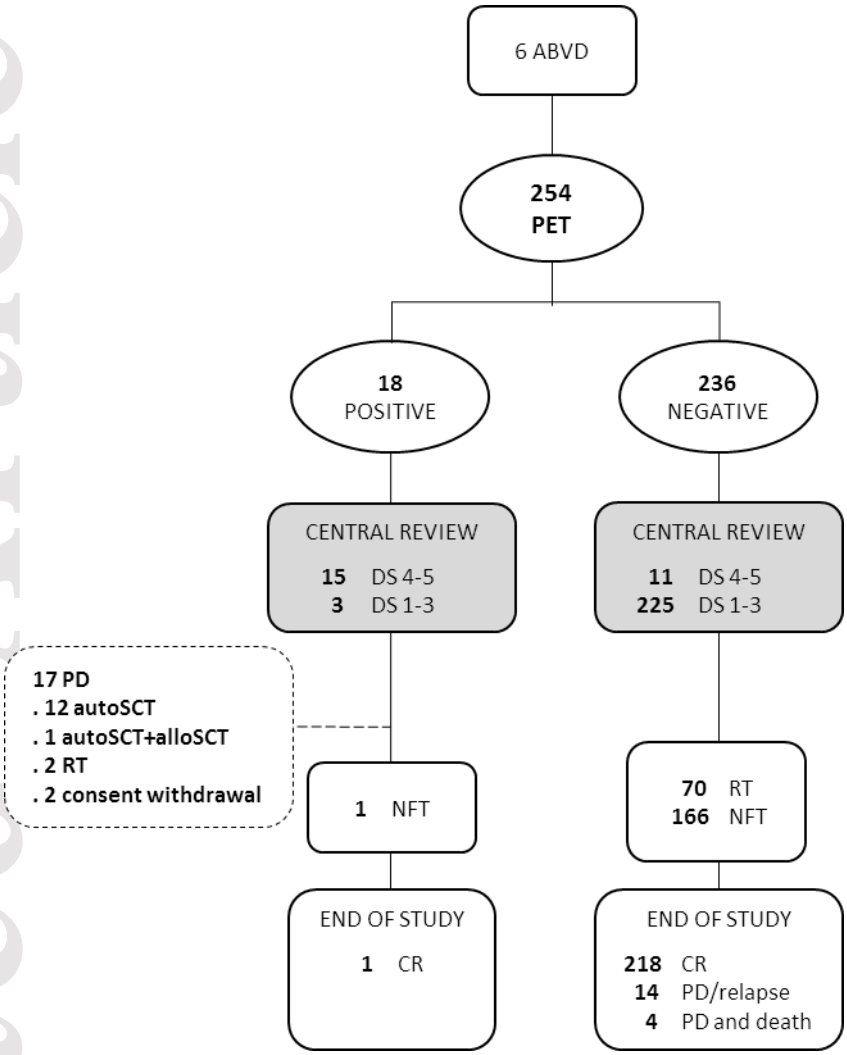

Figure 2. Kaplan-Maier for PFS for patients with different DS at eotPET. Dotted line represents the 95% confidence interval.

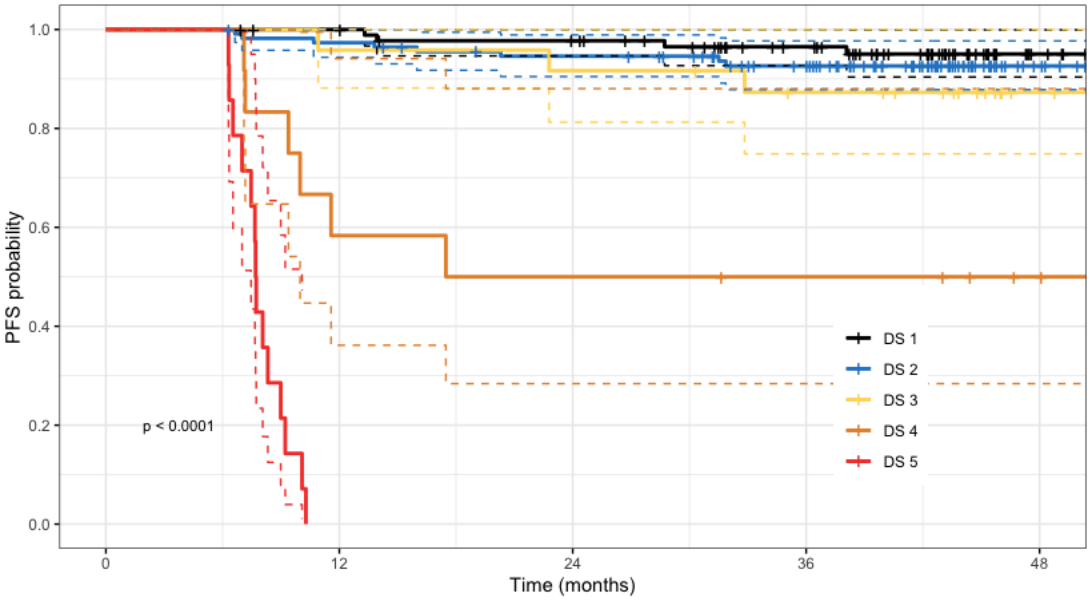

Figure 3. Kaplan-Maier for PFS of negative (DS 1-3) and positive (DS4-5) eotPET patients. Dotted line represents the 95% confidence interval.

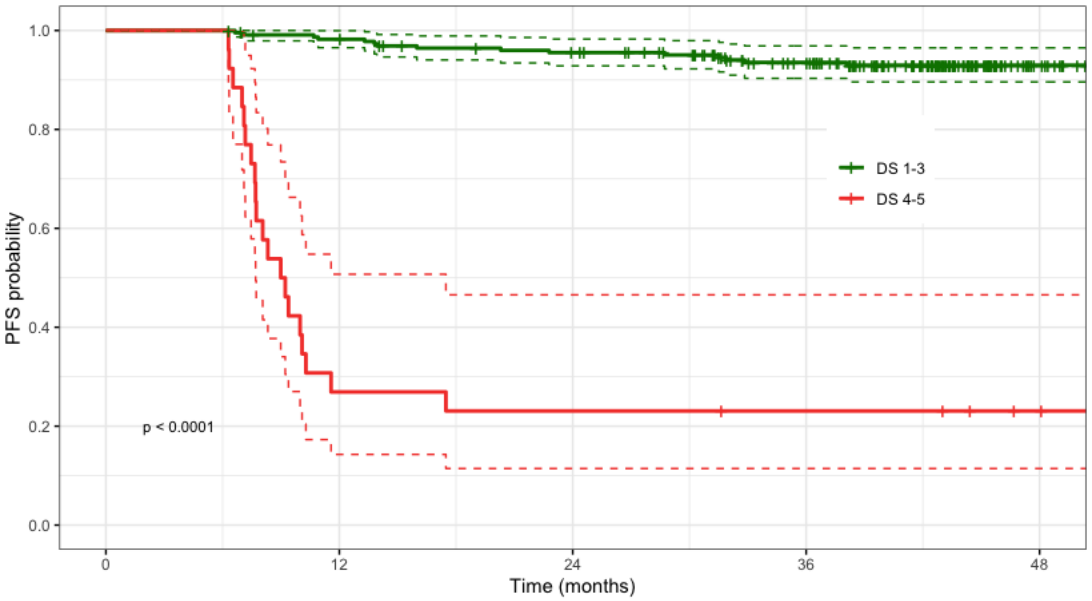

Figure 4. Kaplan-Maier for OS of negative (DS 1-3) and positive (DS4-5) eotPET patients. Dotted line represent the 95% confidence interval.