# 4th INTERNATIONAL WORKSHOP ON PET IN LYMPHOMA

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# POSTER SESSION

## A1. BASELINE METABOLIC TUMOR VOLUME PREDICTS PATIENT'S OUTCOME IN HODGKIN LYMPHOMA

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To investigate the prognosis impact of the metabolic tumor volume at baseline (MTV0) we compared the respective clinical usefulness and prognosis value of the MTV0 and the SUVmax reduction between baseline (PET0) and interim PET (PET2) performed after 2 cycles of chemotherapy (DSUVmaxPET0-2) in 59 consecutive patients with a first diagnosis of Hodgkin lymphoma (HL) treated in our institution. Therapeutic strategy was not modified according to PET2 result. MTV0 was measured with a semi-automatic method using various volume shapes and systematic 41% SUVmax thresholding. Median follow-up was 39 months (range: 6-62). MTV0 (≤ 225 vs > 225) was predictive of 3-year progression free survival (3y-PFS) (85% vs 42%; p = 0.001) and freedom from treatment failure (3y-FFTF) (88% vs 45%; p = 0.0015). Bulky tumor (>10cm) was also predictive of 3y-PFS (44% vs 78%, p <0.04), but of border line significance for 3y-FFTF (80% vs 53%, p = 0.09). In multivariate analysis, using the international prognosis score, DSUVmaxPET0-2 (>71% vs ≤71%), MTV0 and bulky tumor as covariates, only DSUVmaxPET0-2 and MTV0 remained independent predictors for PFS (p= 0.0005; RR= 6.4, and p< 0.007; RR= 4.2, for DSUVmaxPET0-2 and MTV0 respectively) and FFTF (p= 0.0002; RR= 8.2, and p= 0.01; RR= 4.4, for DSUVmaxPET0-2 and MTV0 respectively).

MTV0 is more relevant that tumor bulk to predict outcome of patients with HL, and adds significant prognosis insights to interim PET response assessment. The combination of MTV0 with DSUVmaxPET0-2 allows identifying 3 subsets of HL patients with significantly different outcomes that may help clinicians to guide therapeutic strategy.

## A2. INTERIM PET SUVMAX REDUCTION IS SUPERIOR TO VISUAL ANALYSIS USING 5-POINT SCALE CRITERIA TO PREDICT PATIENT'S OUTCOME IN HODGKIN LYMPHOMA

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We explored the respective prognosis value of interim PET response assessed according to visual analysis using the 5-point scale (5PS) or to SUVmax reduction (DSUVmax), in 59 patients with a first diagnosis of Hodgkin lymphoma (HL) treated in our institution. PET was done at baseline (PET0), after 2 (PET2) and 4 cycles of chemotherapy and therapeutic strategy was not modified according to the interim PET results.While visual PET2 and PET4 positivity (5PS ≥ 4) were associated to a lower 3-year progression free survival (3y-PFS) (45% and 33%) compared to PET2 and PET4 negativity (80%, p= 0.001 and 74%, p=0.0002, respectively), DSUVmaxPET0-2 (>71% vs ≤71%) and DSUVmaxPET0-4 (>75% vs ≤75%) were more accurate to identify patients with significantly different 3y-PFS (81% vs 30%; p<0.0001; HR = 6.77 and 77% vs 25%; p<0.0001; HR = 6.2). In multivariate analysis, using the international prognosis score, DSUVmaxPET0-2 and DSUVmaPET0-4 as covariates, DUVmaxPET0-2 remains the unique independent predictor for PFS (p = 0.0001; RR: 8) and for freedom from treatment failure (FFTF: p < 0.0001; RR: 10.4).

SUVmax reduction between baseline and interim PET was more accurate than visual analysis based on the 5-point scale to predict outcome of patients treated for HL. DSUVmax reduces the excess of positive results related to visual interpretation, and appears to be a better method to assess early PET response in HL. In addition SUVmax reduction seems to better identify patients with different outcomes after 2 than after 4 cycles of chemotherapy.

## A3. FDG-PET AS A BIOMARKER IN RESPONSE ASSESSMENT IN ABVD TREATED HODGKIN LYMPHOMA PATIENTS

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**Background:** Interim PET (iPET), performed early during therapy, is a strong predictor of treatment outcome in lymphoma. The use of different equipments, the lack of standardization in scanning protocols and the absence of shared simple rules for iPET interpretation hamper its use as a biomarker in clinical trials. For these reasons in 2009 an international validation study (IVS) was launched with a two-fold aim: (a) to validate the Deauville 5-point scale (5-PS) in iPET reporting (b) to confirm the predictive value of iPET results on failure free survival (FFS) in ABVD-treated advanced-stage Hodgkin Lymphoma (HL) patients.

**Methods:** Paired baseline and iPET images were collected using WIDEN®, verified for image quality in the central Core lab in Cuneo and distributed to reviewers with the Keosys network. PET images were reviewed by six independent blinded reviewers using 5-PS. An iPET scan with a 1-3 score was defined as negative, with a 4-5 score as positive.. Information related to scanning procedures was retrieved from the DICOM header for each patient.

**Results:** 260 patients (Group A) consecutively scanned from January 2002 to December 2009 in 17 centres worldwide were retrospectively enrolled in IVS and a total of 520 scans underwent central review. DICOM header data were retrieved for patient weight (n=431), uptake time (n=474) and injected activity (n=472). Injected activity was (359±85) MBq (range 85-699) and uptake time was (82±35) min (range 45-128). The adherence to EANM guidelines for PET scanning (uptake time of 60±10 min) was found only in 100 (38%) patients (Group B). Specificity and positive predictive value (PPV) of iPET in predicting treatment outcome were 0.94 and 0.73 in group A, 0.99 and 0.91 ($p<0.01$) in group B, respectively. 3-years FFS of iPET positive patients was 28% in group A and 14% in group B ($p<0.01$). The 3-y FFS for negative iPET was 95% in both groups.

**Conclusion:** The adherence to international guidelines for PET scanning proved to be essential in order to improve the prognostic value of iPET as a biomarker in clinical trials.

## A4. HD THERAPY CAN BE SAFELY REDUCED BASED ON EARLY INTERIM PET/CT FOR PATIENTS WITH ADVANCED HIGH-RISK DISEASE, BUT NOT FOR EARLY DISEASE

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Our multicenter ongoing study, initiated in 2006, prospectively evaluates outcome of HL pts (age 18-60 yrs, stages I-IV) receiving therapy tailored with regard to PET/CT done after 2 cycles of chemotherapy. Early disease (ED) is categorized as favorable (EF) or unfavorable (EU). After 2 ABVD cycles, EF pts with neg. PET/CT undergo INRT. EU pts get 2 more ABVD cycles (total 4) followed by INRT. Pts with pos. interim PET/CT receive 2 (EF) or 4 (EU) more ABVD cycles followed by INRT. Pts with advanced disease (AD) and IPS 0-2 initially get 2 ABVD cycles and pts with IPS≥3 receive 2 cycles of escalated BEACOPP (EB). If interim PET corresponds to Deauville score 1-2, 4 more ABVD cycles are given, with no radiation therapy (RT) to bulky mediastinal masses. If interim PET is pos. with no evidence of progression, therapy continues with EB for high-risk pts or is escalated to EB in standard-risk pts; RT is given to bulky mediastinal masses. To date, 275 pts have been enrolled: 26 progressed (5 with primary refractory disease). 2 pts died: 1 during auto BMT and 1 from acute MI 2 yrs after end of therapy. 4 of 13 relapsed pts had pos. interim PET. In 19 pts with ED or standard-risk AD, therapy was escalated after pos. interim PET/CT, 4 of them progressed. 88% of AD pts (standard and high risk) had neg. interim PET; therapy was reduced in 80% of AD high-risk pts. At a median follow-up of 24 months, a 2-yr PFS was 88% for the whole group (89% for ED, 84% for AD). NPV for neg. interim PET in ED and AD groups was 91% and 88%, respectively, showing that minimal chemotherapy with involved-site RT for ED and de-escalation for AD high-risk pts are feasible and safe.

## A5. ROLE OF PET/CT IN RELAPSED/ REFRACTORY HODGKIN LYMPHOMA (HL) TREATED WITH HIGH-DOSE THERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT (ASCT)

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**Background** : Chemosensitivity prior to ASCT is a powerful prognostic factor for outcome in HL. The prognostic significance of PET/CT in the ASCT setting has not been firmly established yet. Patients/Methods: CT and PET/CT were performed pre- and 3 months post-ASCT. Pts with residual FDG-avid lesions and SUVmax<4 were considered as minimal residual uptake positive (MRUp).

**Results :** Among 68 evaluable pts, 47% were treated for primary refractory disease, 41% at and 12% beyond first relapse; 75% had chemosensitive disease prior to ASCT. A PET/CT was available pre-ASCT in 55 pts, post-ASCT in 62 and at both time points in 53. Pre-ASCT PET/CT was positive/MRUp in 24/45 chemosensitive vs 10/10 chemoresistant pts (p=0.02). At a median follow-up of 30 mo, 2-year failure free survival (FFS) was 85% vs. 48% (p=0.005) in 21 pre-ASCT PET/CT-neg and 34 PET/CT-pos/MRUp pts. Chemosensitivity remained significant (2-year FFS 71% vs. 24%, p=0.0001) and could further stratify pre-ASCT PET-pos patients: 2-year FFS was 85% for chemosensitive PET-neg vs. 56% for chemosensitive PET-pos and 30% for chemoresistant PET-pos pts (p=0.002). Post-ASCT PET scan had the strongest predictive value for outcome: 2-y FFS was 91% for post-ASCT PET-neg/MRUp vs. 12% for PET-pos pts (p< 0.0001). Patients renderd PET-neg/MRUp post ASCT had excellent outcomes irrespectively of pre-ASCT PET/CT results (2-year FFS 86-93%).

**Conclusions :** Pre-ASCT PET/CT positivity does not preclude a favorable outcome in relapsed/refractory HL pts undergoing HDT/ASCT. Particularly pts who ultimately achieve PET-negativity post-ASCT have an excellent outcome. Conventional chemosensitivity is still a major determinant of the outcome.

## A6. CORRELATION OF INTERIM PET/CT (PET-2) FINDINGS AND INTERIM C-REACTIVE PROTEIN (CRP) LEVELS IN ADVANCED HODGKIN LYMPHOMA (HL)

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**Background :** PET-2 positivity following ABVDx2 is a strong prognostic factor in advanced HL. CRP levels are usually elevated in advanced HL, but they are rapidly normalized following ABVD. AIMS: To investigate whether (1) CRP levels decline in concordance to PET-2 and (2) CRP alterations may improve the discriminative ability of PET-2. METHODS: Among 32 pts with advanced HL 30 had sequential CRP levels (abnormal if >5 mg/L). RESULTS: Among 30 pts (median initial CRP 80.4, 90% elevated), 26 were PET-2(-) and 4 PET-2(+); 3/26 PET-2(-) pts have progressed/relapsed (FN). Among 4 PET-2(+) pts, 2 continued on ABVD and progressed and 2 switched to BEACOPP-esc remaining in remission. The correlation of interim CRP with PET-2 is shown in the table:

| | Pts with abnormal CRP levels* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| PET-2 | Ib | | IIa | | IIIa | | IVa | |
| True Negative (TN) | 7/20 | 35% | 3/20 | 15% | 4/22 | 18% | 2/17 | 12% |
| False Negative (FN) | 2/3 | 67% | 2/3 | 67% | 1/3 | 33% | 2/3 | 67% |
| Positive | 1/3 | 33% | 1/3 | 33% | 1/3 | 33% | | |
| Positive or FN | 3/6 | 50% | 3/6 | 50% | 2/6 | 33% | | |

*1 pt with normal intCRP and FN PET-2 had normal initial CRP

At 4-12 weeks (prior to IIa,IIIa,IVa), 12-18% of patients with TN PET-2 still had abnormal CRP levels, usually due to severe obesity. CONCLUSIONS: In this preliminary analysis, persistently abnormal CRP levels were associated either with FN PET-2 or with obesity in pts with TN PET-2. PET-2 positivity was not clearly associated with CRP persistence. Further research is needed to clarify whether CRP or other biomarker serial alterations may improve the predictive capacity of PET-2.

## A7. FDG-PET RESPONSE OF SKELETAL LESIONS IN PEDIATRIC HODGKIN´S LYMPHOMA (PHL) AFTER 2 CYCLES OF CHEMOTHERAPY

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**Aim**: PHL patients, treated in the EuroNet-PHL-C1 study, receive radiotherapy after chemotherapy only in case of positive interim PET after 2 induction cycles of OEPA. Our question was, whether there is an enhanced rate of - possibly false - residual PET positivity in skeletal lesions and therefore a need for separate response criteria for the skeleton.

**Methods:** 1068 PHL patients got central review for staging and response assessment using the International Harmonization Project criteria. Review process included evaluation and documentation of skeletal lesions in FDG-PET datasets, subdivided in bone marrow lesions (normal bone scan and/or CT) or bone lesions (lesion also visible in bone scan or CT).

**Results:** FDG-PET showed skeletal lesions in 149/1068 patients (14%). Most of these patients except from their skeletal lesions suffered from advanced stage disease and had large nodal tumor masses. At response assessment bone lesions were PET-negative in 39/63 patients (62%), bone marrow lesions in 70/86 patients (81%). For comparison, the nodal lesions were PET-negative in only 38% of these patients. Overall, 33% of this cohort of patients were completely PET-negative (no RTx indication). 21% were still PET-positive in both, nodal and skeletal lesions. 40% were PET-positive due to nodal tumor residuals only, whereas in only 6% residual skeletal lesions were responsible for positive interim PET.

**Conclusion:** In PHL patients with advanced stage disease and skeletal involvement the prominent reasons for PET-positivity after 2 cycles of CTx were nodal but not skeletal findings. Thus, in our opinion, definition of separate response criteria for the skeleton is not necessary.

## A8. INTERIM PET AFTER FRST AND SECOND ABVD CYCLE IN PATIENTS WITH HODGKIN LYMPHOMA (HL)-POLISH OBSERVATIONAL STUDY

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We launched in Poland in 2009 an observational study to examine the prognostic value of FDG-PET/CT after 1 ABVD cycle (PET1) and to assess the kinetics of FDG uptake after 2 ABVD cycle (PET2) in patients with PET1positive (+). PET were scored according to 5-point scale. We hypothesized that: PET1 would have good enough negative (NPV) and positive predictive value (PPV) to justify a treatment intervention based on PET1 result; and pts with PET1(+)PET2(-) would have a high risk of progression. 199 patients: 54 with early (I-IIA) and 145 with advanced stages (IIB-IV) HL were enrolled into the study. PET1 were scored locally. Only If PET1 was positive (score 4-5, POS) or equivocal (3-MRU), PET2 was performed. Subsequently, all scans are being assessed by the Polish-Italian panel of reviewers and compared to the initial local score. At the time of abstract submission only local scores are available. At a median follow-up of 19 months 80% of pts achieved a CR with or without radiotherapy, 20% (37) patients experienced a PFS event. Within an "early" group PET1 was (+) in 11(20%) pts. In 5 of them PET2 remained (+) after 2 ABVD. In advanced group PET1 was(+) in 47(32%) and remained (+) in 21(15%) after 2 ABVD. All" early" pts with PET1(-) remain in CR whereas 11(12,5%) advanced pts with PET1(-) progressed. NPVs were 100% and 88% whereas PPV were 44% and 48% in pts in early and advanced stages, respectively. 25 pts (5 early) with PET1(+) became PET2(-). At a median FU 16,7 months only 2 such pts relapsed.Our data confirm high NPV of PET1 whereas PPV is debatable in terms of possible treatment intervention.Longer FU is needed to assess the PPV of PET1.

## A9. POSITIVE INTERIM PET IN HODGKIN-LYMPHOMA = TREATMENTINTENSIFICATION ?

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**Introduction :** Excellent negative predictive value of 18FDG-PET/CT is known in Hodgkin-lymphoma, however less is known about the interim PET positive cases.

**Methods:** We investigated interim PET positive Hodgkin-lymphoma patients between January, 2007 and August, 2011 in the CHEAP (chemotherapy effectiveness assessed by PET) study. The difference have been analyzed between interim PET positive patients who relapsed and those who not, based on their clinicopathological features, baseline SUVmaxvalue, ΔSUVmax etc.

**Results :** 108 Hodgkin-lymphoma patients underwent staging, interim and restaging 18FDG-PET/CT in this period. Interim PET/CT was negative in 81 (74,31 %) patients. Negative predictive value was 0.938, positive predictive value was 0.592. 4-year progression-free and overall survival was significantly better in the interim PET negative group (93 v. 32%, and 97 v. 77%, $p<0,005$). 27 (24,77%) patients had positive interim PET/CT (based on the Deauville criteria), and 16 patients had relapsed in this group. The average follow-up time was 31,96 months (14-50 months). Single-factor analysis identified aged over 40 years ($p=0,055$), abnormal LDH ($p=0,022$) and cMC histological subtype (however not significant) as risk factors for relapse. By multivariate analysis, these risk factors showed significant ($p=0,049$) effects for relapse.

**Conclusion :** Positive interim PET/CT is not sufficient to decide about changing therapy by its own. Classical clinical features like histological subtype, LDH measured at the time of diagnosis and age could help identifying those patients by whom therapy change may be warranted.

## A10. PROGNOSTIC VALUE OF PRETHERAPY METABOLIC TUMOR VOLUME (MTV) AND EARLY RESPONSE ASSESSMENT (TWO CYCLES) IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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**Objectives:** To investigate 1)whether MTV as measure of metabolic tumor burden is a prognostic factor in patients with DLBCL 2) if combined with SUVmax reduction between base line and two cycles of chemo (delta SUV0-2) it improves the evaluation of the response at interim.

**Methods:** MTV was measured in 120 patients with a newly-diagnosed DLBCL, (all IPI categories) who underwent FDG PET at baseline and after 2 cycles of a rituximab-containing regimen, with no therapy change based on the latter. MTV was computed by summing the volumes of all lymphoma lesions after thresholding at 41% of the SUVmax using a semi-automatic software.

**Results:** Median follow-up was 39.8 months. Median baseline MTV was 304 cc . Interestingly, 2-y event free survival (EFS) was significantly higher in pts with MTV<550mL than in pts with MTV>550 mL (79% vs 53%, P=0.009), and prediction of 2-y overall survival (OS) was even higher (93% vs 64%, P<0.0001). Cox proportional-hazard regressions showed independency of MTV and deltaSUVmax (cutoff 66%), P=0.01 and P=0.0002 for EFS prediction, respectively, and P=0.0001 for each variable for OS prediction. Combination of MTV and deltaSUVmax allowed identification of 3 outcome profiles: 2-y OS was 93% in pts with MTV<550mL and deltaSUVmax>66% (n=68), 83% in pts with discordant MTV and deltaSUVmax (n=42), and 22% in pts with both MTV>550 mL and deltaSUVmax<66% (n=10, P<0.0001).

**Conclusions:** MTV is highly predictive of OS before initiation of therapy and, combined with interim FDG PET/CT response, allows identification of very good and very bad prognosis patients in 2/3 of cas. Baseline MTV would be helpful to identify 10-15% good responders who relapse.

## A11. BASELINE METABOLIC TUMOR VOLUME IS PREDICTIVE OF OUTCOME IN HIGH RISK PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA

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**Objective :** To assess the prognostic value of metabolic tumor volume measured on PET baseline in high risk DLBCL.

**Methods :**121 DLBCL patients (<60 years,aaIPI2-3 DLBCL) enrolled in the LNH07-3B trial (a PET driven therapeutic strategy trial) were analyzed. MTV was measured on FDG-PET/CT baseline with a 41% thresholding and ΔSUVmax0-4 between baseline and 4 cycles of immunochemotherapy: The tumour mass was measured on CT.

**Results :** Median follow-up was 28 months. Median baseline MTV was 303 cc. Patients with a baseline MTV ≥625 cc had a significantly (p=0.0032) inferior 2y-PFS of 57 % compared to 83% in those with a MTV < 625cc. A high baseline MTV≥625 cc was s(p=0.002) predictive of an inferior 2y-OS of 60% compared to 90% when MTV was< 625cc. By contrast the presence or the absence of a bulk >10cm was not predictive of outcome.
ΔSUVmax0-4 reduction (> 70% vs. ≤70%) predicted 2y-PFS (88% vs 40%; p<10-4) and 2y-OS (94% vs 59%; p<10-4). Combining MTV baseline to early response assessed by ΔSUVmax0-4 allows to split the group of good responders patients defined on the basis of ΔSUVmax0-4 >70% after 4 cycles of immunochemotherapy into 2 separated prognosis subsets (2y-PFS: 90% vs. 77%, p<10-4; 2y-OS: 96% vs. 77%, p<10-4). So far MTV could not significantly identify subgroups within the patients with ΔSUVmax≤70% even if patients with higher MTV base line had lower PFS and OS.

**Conclusions :** Baseline MTV was predictive of PFS and OS in high risk DLBCL although tumor bulk was not . MTV identified different risk categories of DLBCL patients within DLBCL patients with a good interim response (ΔSUVmax0-4 >70%) and may improve the negative predictive value of interim PET.

## A12. PROGNOSTIC VALUE OF INTERIM PET/CT IN PATIENTS WITH POOR RISK DIFFUSE LARGE B CELL LYMPHOMA (DLBCL). EXPERIENCE OF THE SPANISH GELTAMO GROUP

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**Backgroung :** Interim FDG-PET appears to be useful to guide risk stratification of patients with DLBCL, but remains controversial because the absence of consensus criteria for assessment. The reduction of maximum Standardized Uptake Value (SUVmax) between baseline and interim PET improves the accuracy and reproductibility of this method (Casasnovas, Blood 2011).

**Patients and Methods :** A prospective non randomized phase II trial (EudraCT:2006-005254-68) was undertaken in young patients (pts) newly diagnosed of poor risk DLBCL. Therapy was changed after 3 cycles of R- MegaCHOP based on PET (using local assesment and visual scale) ; pts with positive PET received early salvage therapy. Primary end points were Progression free survival (PFS) and Overalll survival (OS). Retrospectively, central review was done by three experts using visual assessment (Deauville criteria) and semiquantitative asessment. Baseline and interim SUVmax, and ΔSUVmax were evaluated (cutt off ΔSUVmax: 66%).Significance of PET parameters in OS was analyzed.

**Results :** 71 pts were enrolled and central review was possible in 50 pts, from which 80% have complete follow up (mean 37,6 months, 3.4-56.4). OS was significantly influenced by interim PET result, using visual (p=0.046) but mainly by semiquantitative analysis (p=0.0008). ΔSUVmax had impact on the overall survival (p=0.007) whereas basal SUVmax did not.

**Conclusions :** Our preliminary results show that outcome of DLBCL pts with a positive interim PET is worse despite change of therapy. Semiquantitative PET evaluation seems to be necessary, being ΔSUVmax a good prognostic parameter.

## A13. NEGATIVE INTERIM PET PREDICTS FOR BETTER OUTCOME OF DLBCL IN AN IAEA-SPONSORED, 9 COUNTRY INTERNATIONAL STUDY

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**Background :** Most studies of interim PET (iPET) for DLBCL outcome prediction report single centre experience in W. Europe or USA. Results have been variable and we hypothesised that inconsistency may be greater in non-Western countries, where ethnicity and environmental factors may affect disease biology, and advanced disease alter rate of response. To address this and inform clinical practice in countries where PET has been more recently introduced, we devised a prospective international cohort study with the International Atomic Energy Agency.

**Methods :** In participating countries (Brazil, Chile, Hungary, India, Italy, Philippines, Thailand, Turkey, Korea) patients were scanned in a single PET centre. All had PET scans before and after 2 or 3 cycles of R-CHOP. iPET was classified as negative (which included Minimal Residual Uptake) or positive. All MRU and PR scans were centrally reviewed. Treatment change in response to i-PET was not permitted.

**Results :** 395 patients aged 16-83 yrs. Countries recruited between 9 and 72 (median 50) cases; 54 excluded because of death before i-PET or protocol violation. i-PET was negative in 220 (145 neg, 75 MRU), positive in 121. At median 20.5 months follow up, progression had occurred in 12 (5%) iPET neg, and 43 (36%) i-PET pos subjects. 2 year EFS: i-PET neg 90% (95%CI 85–94%), i-PET pos 59% (49–68%); hazard ratio 4.9 (95%CI 2.8–8.6). There was no evidence that recruiting country influenced the prognostic value of i-PET.

**Conclusions :** This large study supports early i-PET as an independent predictor of outcome in DLBCL. The ability of i-PET to predict outcome appears to be generalisable to non-western populations and healthcare systems.

## A14. PRONOSTIC VALUE OF INTERIM FDG-PET/CT METABOLIC RESPONSE IN DIFFUSE LARGE B CELL LYMPHOMA TREATED WITH R-CHOP

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**Aim :** Evaluate interpretation criteria prognostic value of interim FDG-PET/CT (PETi) and its reproducibility. Also, impact of pretherapeutic pronostic criteria.

**Methods :** Retrospective analyse of first line DLBCL assessed by PET at baseline and after 2-4 cycles of RCHOP by two physicians after a join training. Qualitative (Deauville five-point scale (5-PS)) and quantitative assessment of maximal standardized uptake value reduction rate (∆SUVmax) were correlated to EFS and OS. ROC curve analysis of ∆SUVmax and Kappa correlation coefficient (k) were calculated. Genomic expression profil (GCB versus ABC) and IPI were correlated to outcome.

**Results :** 54 DLBCL with median follow up of 29,6 months. Two-years EFS rate using Deauville criteria was 84,9% for negative PETi (score 1 to 3) and 47,6% for positive PETi (score 4-5) (k=0,85); with a ∆SUVmax ≥ 66% and <66%, the 2-years EFS was respectively 80,1% and 18,1% (p<0,001) (k=0,94). ROC curve analysis of ∆SUVmax suggested highest sensitivity/specificity for a cutoff of 84% and 52% respectively.
EFS was significantly different in GCB versus ABC (p=0,02). Clinical staging between low IPI and high IPI did not show significant statistical difference in terms of EFS (p=0,06).
Patients combining ABC and ∆SUVmax<66% had particularly poor outcome whereas those who combined GCB-∆SUVmax ≥ 66% had excellent outcome.

**Conclusion :** Our study confirme strongest pronostic value of quantitative criteria, with an excellent reproducibility.
Integrating genomic expression profiles study improves the outcome prediction.

## A15. INTERIM FDG-PET/CT AS A PROGNOSTIC FACTOR IN DIFFUSE LARGE B-CELL LYMPHOMA

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**Aim :** Interim 18F-fluorodeoxyglucose positron emission tomography (PET) performed early during the course of therapy in diffuse large B-cell lymphoma (DLBCL) is highly predictive of outcome. However, interpretation criteria of interim PET are not yet appropriately defined for the evaluation of tumor response. The aim of our study was to assess whether interim PET may predict Overall Survival (OS) and Progression-Free Survival (PFS) in DLBCL patients according to 3 different sets of criteria: two qualitative (visual) methods and one semi-quantitative.

**Methods :** 50 newly diagnosed DLBCL patients were prospectively enrolled in this study. All patients had PET/CT at diagnosis and interim PET/CT after second cycle of chemotherapy. We use 3 methods of evaluation for interim PET/CT: qualitative in 3-Point Scoring (PS), qualitative Deauville's 5-PS and semi-quantitative (ΔSUV max). The therapy response on FDG-PET was correlated to PFS and OS using Kaplan-Meier survival analysis.

**Results :** In the analysis of visual 3 PS, there was not statistically significant difference in PFS and OS. The estimated 7 year PFS was 79% in patients with interim PET uptake ≤ liver and 50% for the patients with interim PET uptake > liver, and these difference was statistically significant. The optimal cut-off value of ΔSUVmax that could predict the PFS and OS difference in patients with DLBCL was 76% and 75%, respectively.

**Conclusions :** Our results support the use of liver uptake as an indicator in the qualitative evaluation of interim PET or a ΔSUVmax greater than 75% in semiquantitative analysis. Interim PET may predict PFS and OS and could be considered a prognostic factor in aggressive lymphoma.

## A16. INTERIM FDG-PET/CT DOES NOT PREDICT OUTCOME IN NEWLY DIAGNOSED MANTLE CELL LYMPHOMA PATIENTS TREATED WITH CHEMOTHERAPY ALONE OR ASCT

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**Background :** Mantle cell lymphoma (MCL) is a rare disease. FDG-PET/CT scans are often used to evaluate patients with MCL, although the impact of PET results on their outcome is not well established.

**Aims :** In this study we looked for correlation between PET results and outcome in a retrospective cohort of MCL patients.

**Methods :** We retrospectively reviewed the outcome of 58 consecutive MCL patients who were treated between 1998 and 2011. PET/CT scans, performed after 3-4 cycles and at the end of first line chemotherapy (prior to ASCT), were correlated with response and long-term outcome. Scans were scored as positive or negative based only on visual assessment.

**Results :** Forty four (76%) patients received RCHOP or RCHOP-like chemotherapy for induction, and 23 (40%) patients were also treated by BEAM followed by ASCT. After a median follow-up of 3.3 yrs (0.67-13.1) the estimated OS and PFS at 3 yrs for the entire cohort were 84% and 48 %, respectively. Interim PET was performed in 51/58 patients. Older age (≥60) was significantly more common in the interim-PET positive group (p=0.02). The estimated 3 yr OS for interim-PET negative (n=20) and interim-PET positive (n=31) patients were 85% and 90%, respectively (p=NS). The 3 yr PFS for interim-PET negative and positive were 57% and 44%, respectively (p=NS). A subset analysis of the patients who received consolidation with upfront ASCT showed that neither OS nor PFS at 3 yrs were predicted by interim or pre-transplant PET results.

**Conclusions :** interim FDG PET/CT results do not predict OS and PFS in MCL patients. In patients, who received consolidation with ASCT, neither interim nor pre-transplant PET results predict outcome.

## A17. INTERIM FDG PET CAN PREDICT OUTCOME OF MANTLE CELL LYMPHOMA IN ELDERLY PATIENTS TREATED BY GOELAMS' RIPAD+C SCHEME.

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Mantle cell lymphoma (MCL) is considered as an aggressive lymphoma, but may have a variable [18F] Fluorine-Deoxyglucose (FDG) avidity. Without proof of interest, , FDG - Positron Emission Tomography (FDG-PET) is not yet recommended in MCL. The French GOELAMS group recently published the results of a phase II prospective multicenter clinical trial evaluating RiPAD + C front-line combination including proteosome inhibitor (PS341-Velcade®) in association with chemotherapy and rituximab immunotherapy . The aim of our study was to determine the prognostic value of initial, interim and post-treatment FDG-PET evaluations in this group of homogeneously treated patients.

From June, 16th 2007 to December 22 nd 2008, 39 patients from 21 French centers were included. Three FDG-PET scans were recommended: at initial staging (IS), mid-treatment evaluation (MTE) after 4 cycles of chemotherapy and response assessment (RA) at the end of treatment. All available scanns were centrally reviewed by a single expert, using international response assessment criteria.

From the 39 patients, 78 FDG-PET scans were performed (31 IS, 28 MTE, 19 RA). The median progression free survival was 5 months for positive MTE versus 43 months for negative MTE (p= 0.0021). However, although there is a tendency, that doesn't translate to a better overall survival (OS) indeed, median OS was 25 months for positive MTE, versus not reached for negative MTE (p=0.15).

As it is able to predict patient outcome, mid treatment FDG-PET is a useful tool for early evaluation of MCL in elderly patients treated by GOELAMS' RiPAD + C scheme.

## A18. BASELINE SUVMAX AND ΔSUVMAX ANALYSIS IN HIGH-TUMOR BURDEN FOLLICULAR LYMPHOMA PATIENTS TREATED WITH IMMUNO-CHEMOTHERAPY : A PROSPECTIVE STUDY

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**Objective :** To assess the prognostic value of baseline SUVmax and ΔSUVmax in follicular lymphoma (FL) treated by immunochemotherapy

**Methods :** 121 FL patients with at least one criteria of high tumour burden have been prospectively recruited by 14 centers.PET have been performed at baseline, after 4 R-CHOP(PET4) and after 6 R- CHOP+2R(PET8).Base line SUVmax was measured in 109 patients. .ΔSUVmax were measured at PET4 (n= 106)and PET8(n=.100) and their prognostic value compared to visual PET reporting using the 5-point scale.

**Results :** Median follow up was 23 months.Median base line SUVmax was 9.5 (3.3-35.6). Patients with SUVmax>14.2 (n=27) had 2y-OS of 87% significantly lower($p<0.008$) than the 100%
2y-OS for patients with SUVmax<14.2(n=82). Moreover combined with FLIPI (considering only 2 groups 0-2 versus 3-5) the value of base line SUV max could identify one group of high risk patients (n=12, FLIPI 3-5 and SUVmax>14.2) who had a significant ($p<0.0001$) poorer outcome (71% 2y-OS) than the other groups (100% 2 y-OS for FLIPI 0-2,SUVmax>or<14.2 and FLIPI 3-5,SUVmax<14.2).
ΔSUVmax 0-4 reduction with a 43% cut off predicted 2y-PFS but not 2y-OS and ΔSUVmax 0-8 reduction with a 67% cut-off was predictive of 2y-PFS ($p<0.03$) and 2y-OS ($p<0.005$) but to a lesser extent than the predictive value found when PET was reported with the 5 point scale ($p<0.0001$).

**Conclusions :** In FL SUVmax baseline combined with FLIPI could identify different risk populations. The level of ΔSUVmax reduction under therapy is a good predictor of outcome and supports the results already reported with the 5 point scale analysis.

## A19. MID-TREATMENT 18F-FDG PET-CT SCAN FOR EARLY RESPONSE ASSESSMENT IN NK/T-CELL LYMPHOMA: A PROSPECTIVE STUDY FROM A SINGLE CENTER

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**Aim :** In a prospective study of newly diagnosed or relapsed histologically proven NK/T-cell lymphoma patients, we aim to determine the accuracy of mid-treatment 18F-FDG PET for response assessment using both visual and semi-quantitative analyses.

**Materials and Methods :** 23 patients (13M, 10F, mean age 49 +/-17 yrs) were referred to our unit for pre- and mid-treatment (after 2 cycles of standardised SMILE therapy) PET-CT scans using a standardised protocol. 18 were newly diagnosed and 5 were relapsed patients. PET-CT scans were analysed visually using the IHP criteria (+ or -) and the lesion with the highest SUVmax was recorded. Univariate and multivariate analysis of the predictive value of IPI and PET-CT scan findings were tested against patient outcome (OS and PFS). Mean follow up period was 25 mths (range 3-51 mths).

**Results :** By visual analysis, mid-treatment scan was negative in 14 and positive in 9 patients. Using univariate analysis, the following indices were predictive of outcome; IPI (sensitivity 100%, specificity 59%, accuracy 70%, p= 0.013 for PFS and 0.012 for OS), mid-treatment scan by visual analysis, and semi-quantitative analysis using best SUVmax cut-off of 2.3, showed identical results (sensitivity 83%, specificity 76%, accuracy 78%, p=0.004 for PFS and 0.003 for OS). The 2-year estimate for PFS was 93% in patients with negative scans compared to 42% in patients with positive scans. Multivariate analysis found mid-treatment PET-CT by visual analysis to be the only significant independent predictor of outcome (OS and PFS; p=0.006).

**Conclusion :** Mid-treatment PET-CT is a valuable tool for early treatment response assessment in NK/T-cell lymphoma.

## B1 DUAL-POINT FDG-PET: A NEW SCANNING TECHNIQUE TO DISTINGUISH UNSPECIFIC AND NEOPLASTIC FDG UPTAKE IN HODGKIN LYMPHOMA

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**Background:** Interim $^{18}$F-FDG-PET (iPET) is the most important prognosticator in advanced-stage ABVD-treated Hodgkin Lymphoma (HL), but in early stage with or without bulky lesion a low PPV of iPET was reported. Moreover, a single residual FDG-avid mass (SFAM), commonly found at treatment (Tx) end in HL, was shown to reduce the specificity of PET in Tx response evaluation. Dual-point PET scan (2P-PET) has been proposed to discriminate unspecific inflammatory from neoplastic FDG uptake. **Aims** we report here preliminary results from a cohort of HL patients (p), scanned with 2P-PET with the aim to increase specificity and PPV of PET scan. **Methods:** from December 2008 till January 2012 25 HL p from Italian, French and Polish centers, most of them with bulky lesions, underwent 2P-PET at baseline (2P-PET-0), after 2 ABVD (2P-PET-2) and at Tx end (2P-PET-end). 2P-PET scan consisted in 2 consecutive image acquisitions 60' (+60) and 120'(+120) after single, standard-dose FDG injection. Tx was ABVD (x4 or x6) or BEACOPP (4+4) ± consolidation/involved-field radiotherapy (RT). In 23/25 p no Tx change was done based on iPET results and in 2 according to protocol. Bulky was defined as a mass with largest diameter ≥5 cm. Scans were reviewed by 2 expert readers in a consensus session. Standardized-Uptake Value $(SUV)_{MAX}$ was calculated both in +60 and +120 using single or multiple Volume of Interest regions (VOIs) drawn to encompass a single or multiple spots of FDG uptake within a single or multiple nodal mass. Retention Index (RI) was defined as $[(SUV_{MAX}+120-SUV_{MAX}+60)/SUV_{MAX}+120]$%. In case of multiple spots inside a single node or within different nodes, only the single focus with FDG uptake increase was considered. **Results** In 25 p (1 stage I,13 II, 4 III, 7 IV), 35 2P-PET were done. 10 p underwent 2P-PET-0: in 10/10 $SUV_{MAX}$ increased from +60 to +120 ($\Delta SUV_{MAX}$ 1-4.3). 15 p had a 2P-PET-2: 12 with a mean-follow-up of 18.36 months were evaluable. 3 were excluded because of too short ( +1, +5, +6 months) follow-up. 7/12 p showed an average RI reduction of 55% (200-14): all are in continuous CR (CCR). 5/12 p. showed an average 20% (11-26) RI increase: all progressed +1 to +9 months after Tx end. Overall 3/12 cases (1 false positive, 2 false negative, with a Deauville score of 4 and 2,3 respectively) were correctly classified after 2P-PET scan. Ten p with a SFAM had a 2P-PET-end: in the 6/10 with an increased average RI of 23% (9-43) a biopsy proved HL relapse. In 4/10 an average reduced RI of 29% (9-45) was found: in 2 biopsy disclosed presence of residual thymic along with inflammatory tissue and 2 were in CCR +4 to+10 months after Tx end. **Conclusion:** $SUV_{MAX}$ increased both in 2P-PET-2 and 2P-PET-end in all patients scanned at baseline and in relapsed patients. It decreased in 2P-PET-2 and 2P-PET-end in patients remaining in CCR. Interim and end-therapy 2P-PET scan showed a predictive value on treatment outcome of 100%.

## B2. PAEDIATRIC HODGKIN NETWORK (PHN) -TRANSFER AND STORAGE OF PET,PET/CT,CT AND MRI TO FACILITATE CENTRAL REVIEW (CR) WITHIN LARGE MULTICENTRIC TRIAL

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Children and adolescents with Hodgkin's Lymphoma from 18 European countries receive standardized diagnostic and treatment within the EuroNET-PHL-C1 trial. Structural core of the trial is the real time central review process deciding on staging and response, based on reference reading of all original images. As an established method CR guarantees the consistent application of image interpretation criteria, quality control and research work. Since evaluation of the images is time critical, a fast, easy to handle and secure data transfer is of high importance. Funded by the European Union, the PHN was established. Two main technical applications were developed: One for sending the images from the local site to the central server (CS) respecting EU data protection and patient integrity rules. The other one uses HERMES Medical Solutions platform for data integration and a multimodality processing application of the images. The mentioned solution enables the reviewer to access each imaging study from the CS. It is protected by firewalls (local site, CS) and the connections take place over a secure network protocol (HTTPS). In accordance with regulations a data protection concept was confirmed by the authorities.

129 sites in 13 European countries were joined and about 6300 imaging studies have been successfully transferred. In addition 3500 images of the previous GPOH-HD-2002 trial and from 2007/08 were uploaded. The overall data volume sums up to >2.0 terabyte. Images are safely stored on the CS and are quickly available (20-30 seconds) for re-evaluation, teleconferences or research purposes.

The established network is ready to be used also in other trials.

## B3. PROGNOSTIC FACTORS IN PATIENTS WITH HODGKIN LYMPHOMA (HL) AND A NEGATIVE PET/CT AFTER ABVD CHEMOTHERAPY

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**Background :** PET/CT negativity after ABVD is associated with favorable outcomes. However, prognostic factors for this subgroup have not been studied. Methods: Among 352 consecutive HL pts treated with ABVDx4-8, 327 responded, 287 underwent PET/CT and 229 became PET/CT(-) after ABVD.

**Results :** Dose intensity was nearly 100%. At a median follow-up of 31 mo, 12 pts relapsed and 1 died in CR1. 95% of stage I/II pts received radiotherapy (RT) vs. 11% advanced stage pts. Relapse free survival (RFS) was 94% and 92% at 3 and 4-6 years after the negative PET/CT. Inferior RFS was associated with advanced stage (3-year RFS 98% vs. 84% for stages I/II vs. III/IV, p=0.001) and involvement of ≥5 sites (p=0.05). For the 22 stage IV PET/CT(-) pts, 3-year RFS was 70% vs. 94% (and 88% 4-year RFS) for the 39 stage III pts. In multivariate analysis only stage III/IV was an independent prognostic factor for RFS (hazard ratio 6.6, p=0.01). At least 3/4 relapses in stages I/II and 1/8 in stages III/IV were detectable by clinical examination; 1/8 advanced stage pts relapsed in a previously bulky site.

**Conclusion :** A negative PET/CT after ABVDx4-6 predicts an excellent outcome in stage I/II pts, who are typically irradiated. The majority of the relapses in this subgroup may be detectable by clinical examination only. Although not usually irradiated, PET/CT(-) stage III pts have a slightly higher relapse risk, but stage IV pts, still remain in a considerable risk (up to 30%). Therefore, although stage IV (and probably stage III) PET/CT(-) patients may require regular monitoring with imaging studies, this can probably be avoided in stage I/II PET/CT(-) patients who have received RT.

## B4. IS THERE A ROLE FOR POSITRON EMISSION TOMOGRAPHY (PET/CT) IN THE INITIAL STAGING OF HODGKIN LYMPHOMA (HL)?

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**Introduction :** Although baseline PET/CT (bPET/CT) is recommended, it is not considered mandatory for the initial staging of HL. Furthermore, the role of bPET/CT on first-line treatment decisions is not clear. Patients/Methods: 67 HL pts, selected solely based on the availability of bPET/CT, were evaluated by conventional and PET-based methods.

**Results :** Pts' characteristics: median age 33 yrs; 60% males; 8,25,17 and 17 pts with clinical stage (CS) I,II,III,IV; median number of involved sites (NIS) 1, 2(1-5), 5(2-14), 7(4-11) for CS I,II,III,IV. Based on PET/CT, the corresponding figures were 2(1-5), 3(2-9), 7(2-14) and 11(5-14). CS or PET/CT-based NIS were highly correlated (Spearman's rho 0.80). PET/CT resulted to stage shift in 20 pts (30%; 17 upstaged and 3 downstaged). Similarly, PET/CT revealed higher NIS than CS in 50 pts (67%). Among 20 pts with potential stage shift, major treatment modifications could have been justified in 16 (24% of the total). However, in only 7/16 a different therapeutic strategy was actually applied due to PET/CT findings. Among 33 CSI/II pts, 21 (64%) actually received wider RT field, based on PET/CT-identification of more involved sites. Regarding bone marrow (BM) findings, 43 pts had no evidence of bone/BM uptake (all had negative BM biopsies), 11 had diffuse BM uptake (2 or 18% had positive BM biopsy), and 13 had multifocal bone/BM uptake (5 or 38% had positive BM biopsy).

**Conclusions :** PET/CT can identify a higher NIS in the majority of HL pts, with a 30% stage shift rate. The variable use of PET/CT for the initial HL staging and its heterogenous effect on treatment decisions may render comparisons of retrospective series difficult.

## B5. STAGING FDG-PET MIGHT REPLACE BONE MARROW BIOPSY IN DIFFUSE LARGE B-CELL LYMPHOMA. RESULTS FROM A MULTI-CENTER IAEA-SPONSORED STUDY.

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**Objectives :** To assess the impact of staging 2-[18F]-FDG PET in the evaluation of bone marrow involvement in patients with diffuse large B-cell lymphoma (DLBCL) in an international study sponsored by the International Atomic Energy Agency (IAEA) in nine countries.

**Methods :** All patients were submitted to pre-treatment staging with PET-CT, or CT and PET scans; the studies were performed in each participating PET centre. Clinical factors comprising RIPI and bulky disease were recorded. Bone marrow biopsy (BMB) results were compared to staging PET results. PET in bone marrow was classified as completely negative, with mild diffuse uptake (also considered negative), moderate to severe diffuse uptake and presence of focal uptake.

**Results :** 374 participants with median age 53.3 (range 16–84) years were recruited. Individual countries recruited between 9 and 72 (median 50) cases. No bone marrow uptake was seen in 279 (74.6%), of those 263 (70.3%) patients presented negative BMB and 16 (4.3%) patients presented positive-BMB. Of the 95 (25.4%) patients with PET-positive BM uptake, 66 (17.6%) presented focal uptake and 29 (7.8%) with diffuse uptake. Of the 16 patients with BMB-positive and PET-negative results, half were already classified as stage IV by PET due to other lesions. The real impact of BMB, regarding clinical staging, was seen in only 8/374 (2.1%) patients.

**Conclusion :** This large study shows that FDG-PET might replace BMB in the evaluation of bone marrow commitment in BLBCL.

## B6. PROGNOSTIC SIGNIFICANCE OF POST-RITUXIMAB-CHOP (R-CHOP) PET/CT IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL)

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**Background :** The use of PET-Scan as a potent method to detect residual active disease in PMLBCL is based on the projection of data derived from Hodgkin and aggressive B-cell lymphomas. Patients/Methods: Among 78 consecutive pts with PMLBCL responding to R-CHOP, 65 underwent PET/CT. Progression Free Survival (PFS) was measured from the time of PET.

**Results :** The median post-PET follow-up was 25 months; 40 pts were PET-neg (62%) and 25 (38%) PET-pos. Among 40 PET-neg pts, 23 (58%) did not receive RT and 17 (42%) received a median of 3460 cGy. Three (3/23) non-irradiated pts relapsed (mediastinum and 2 isolated CNS relapses) vs. 0/17 irradiated pts. Among 25 PET-pos pts, 22 (88%) were irradiated (median 4000 cGy): 6/25 pts relapsed (all irradiated). The 2-year PFS was marginally superior for PET-neg vs. PET-pos pts (92% vs. 72%, p=0.07). Among PET-neg pts, 2-year PFS was 95% vs. 100% for 23 non-irradiated and 17 irradiated pts (p=0.37, when isolated CNS relapses were censored). Among PET-pos pts, 2-year PFS was 92% vs. 45% (p=0.03) for patients with SUVmax<5 (1/13 relapsed) and SUVmax≥5 (5/11 relapsed) respectively.

**Conclusions :** Discussion: PET/CT remains positive in ~40% of R-CHOP responders with PMLBCL. PET/CT positivity was only marginally associated with inferior PFS, when additional RT was administered, but higher SUVmax might predict a higher risk of relapse. Among 23 non-irradiated, PET-neg pts, only 1 relapse would be preventable by RT. According to these data: (1) R-CHOP responders with PMLBCL should not be forwarded to ASCT simply based on a positive PET/CT; (2) RT can be spared in the majority of PET-neg pts, but selection criteria still need to be defined.

## B7. PET/CT RESPONSE ANALYSIS IN PRIMARY MEDIASTINAL DIFFUSE LARGE B-CELL LYMPHOMA (PMBL): RESULTS OF THE IELSG-26 STUDY

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**Aim :** The endpoint of the study was to assess the 18FDG-PET-CT response rate following immunochemotherapy (ICHT), with or without mediastinal irradiation (IFRT) in a single cohort of PMBL patients (pts).

**Methods :** The study enrolled 125 pts with PMBL who received R-CHOP/R-MACOP-B(-like) regimens. 6 pts were excluded for early progression of disease during ICHT and 105 also underwent IFRT. PET-CT scan was performed at baseline and 3-4 weeks after the end of ICHT. In the case of residual disease, the imaging was also repeated >2 months after completion of IFRT. PET-CT Complete Response (CR) was defined by a negative scan or one having minimal residual uptake (MRU) </= mediastinal blood pool (MBP) activity. Central review of the PET-CT images has been completed in 115 pts.

**Results :** The PET-CT scans showed metabolic CR in 54/115 pts (47%): in 12 cases (10%) the PET-CT scan was completely negative but in 42(37%) there was MRU </=MBP. At a median post treatment follow-up time of 24 months 53/54 pts are in stable CR. Among the 61 pts (53 %) with positive PET-CT scan there were 9 relapses and 3 cases were switched to early intensification with front-line ASCT (12/61-20%). Out of 61 positive PET-CT scans after ICHT 29(48%) became negative after IFRT and have stable CR. Nevertheless also all pts with positive PET-CT with MRU >MBP but </=liver uptake after ICHT(27/115, 23%) or IFRT(9/115,8%) remained in CR.

**Conclusions :** Using the MBP as reference the number of positive PET-CT scan after ICHT is high with low PPV in the prediction of clinical response rate to the treatment. A MRU </=liver uptake showed high NPV similar to that of a PET negative scan both after ICHT and IFRT.

## B8. FEASABILITY OF PARAMETRIC IMAGING FOR LONGITUDINAL MONITORING BY FDG PET/CT IN DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)

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**Introduction:** Tumor response assessment based on FDG PET/CT is widely used in lymphoma. Currently, treatment response is assessed by analysing visually or quantitatively (e.g SUV) each FDG PET/CT. We introduce the feasability of a parametric imaging method to compare FDG PET/CT during therapy.

**Material and methods:** Data from three DLBCL patients with different response characteristics and long-time follow-up were retrospectively analyzed. Each patient underwent PET/CT at baseline (pretreatment) and during treatment for a total of N PET/CT. For each patient, all PET volumes (limited to an anatomic region) were registered using the CT data. The resulting time series of N registered PET volumes were analyzed using an automatic factor analysis (FA), estimating the characteristic time function (factors) for each tumor and the associated parametric images. Truncated time series including only 2 up to N-1 PET scans were also analyzed.

**Results:** For each patient, FA identified a constant factor corresponding to regions without significant change in SUV over time, and/or a decreasing factor (DF) corresponding to tumors responding to therapy, and/or an increasing factor (IF) showing tumor progression. FA results were consistent with conventional analysis (visual + SUV variation) confirmed by follow-up. In addition, associated parametric images depicted regions with different response rates for one large tumor.

**Conclusion:** In this preliminary study, the feasibility of parametric imaging in DLBCL longitudinal monitoring was confirmed. Furthermore, the parametric imaging may provide information on response heterogeneity of tumor volumes and is straightforward to determine the metabolic tumor volume. This study justified further investigations to highlight the clinical benefit of parametric imaging on treatment response assessment.

## B9. INSTITUT BERGONIE'S EXPERIENCE IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) OF THE ELDERLY TREATMENT RESPONSE ASSESSMENT BY PET/CT SCAN

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We retrospectively investigated the usefulness and characteristics of PET/CT for the assessment of DLBCL treatment response in the elderly. This population often leads to interpretation challenges due to frequents agressive, recurrent DLBCL and intercurrents infectious or inflammatory diseases.

We enrolled from database 82 patients aged > 70y and 111 aged < 70y for comparison. Inclusion criteria were histologically proven DLBCL, the undergoing of at least one PET/CT for treatment response (interim or end-point) between october 2005 and february 2012 at the Institut Bergonie, Bordeaux and follow-up > 6 months. Data collected were gene expression profile, stage, type of treatment, clinical outcome. PET/CT judgement criteria were Deauville for interim and Cheson for end-point. We focused on the locations, biopsy results and follow-up of residuals uptakes.

Early results tend to show good performances of the PET/CT despite a significant rate of false-positive residuals uptakes in the elderly population. Definitive results will be exposed during the congress.

Knowledge of particulars patterns of PET/CT in the elderly can lead to higher accuracy of the exam.

## B10. INTEREST OF 18 FDG-PET (PET) TO CONFIRM COMPLETE RESPONSE (CR) AFTER INDUCTION CHEMOTHERAPY IN PAEDIATRIC BURKITT'S LYMPHOMAS (BL).

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**Objective**: BL is rare and highly aggressive form of B cell lymphomas but one of the more curable form using intensive chemotherapy. Obtaining a CR at the end of induction chemotherapy is one of the major prognostic factor. The objective of this study was to evaluate, retrospectively, the interest of PET to confirm CR after induction chemotherapy in paediatric BL.

**Materials and methods:** 18 children, median age 9 years, with BL stage II (n=2), stage III (n=9) and stage IV (n=7), treated according to French LMB 2001, between 2005 and 2011 were included. 19 PET were performed in addition to conventional imaging (CI) after 2 (stage II), 3 (stage III) or 4 (stage IV) courses of chemotherapy. PET were interpreted according to IHP criteria. The gold standard was histology and / or follow up.

**Results:** PET were negative in 11 children and were in agreement with CI in 9/11 cases. The two discordant cases, confirmed by histology, were considered as true negative for PET. The negative predictive value of PET was 100% versus 81% for CI. PET and CI were both positive in 7 children. According to histology, only 1/7 was considered as a true positive: it was the only case with residual mass uptake higher than liver background. In one case, PET was positive with an uptake higher than liver background whereas CI was negative. In this relapsing patient, PET was considered as true positive with progression of disease confirmed a few weeks later by PET and CI. According to IHP criteria, the positive predictive value of PET was 25 % versus 11% for CI.

**Conclusion:** PET seems to be interesting to confirm CR at the end of induction chemotherapy and could limit the systematical use of biopsy. However, using IHP criteria, biopsy remains essential to characterize PET positive residual masses, especially when residual uptake is lower than liver background.

## B11.THE ROLE OF FDG PET/CT IN IMMUNOCOMPETENT PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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**Purpose :** To determine the usefulness of FDG PET in the management of primary central nervous system lymphoma (PCNSL).

**Methods :** We enrolled 25 consecutive PCNSL immunocompetent patients who underwent FDG PET at staging (PET1). The maxSUV was measured into the most active CNS lesion (T) and a normal gray matter area (N). FDG PET was performed in 13 of them after 2 cycles of chemotherapy (PET2) and in 5 out of 6 patients who relapsed (PET3). The results were compared to the clinical and conventional imaging data. The correlation between T, T/N and respectively progression free survival (PFS) and overall survival (OS) was analyzed.

**Results :** The sensitivity of PET1 for CNS lesions was 92 %. Two patients were false negative. The median T and T/N were 12,1 (5,1-41,6) and 2 (1,1-4,8). PET1 revealed systemic spread of lymphoma in 2 patients. The mean follow-up was 28,7 months (7,4-40). PET2 was negative in 13/13 patients whereas MRI found residual gadolinium-enhancement lesion in 7 of them. Four patients who were PET2- and MRI+ relapsed into the CNS (n=2) and/or outside (n=2). PET3 detected all the sites of relapse. At last follow-up, 17 patients had no evidence of disease, 7 were died and 1 was treated for relapse. No correlation between T, T/N and respectively PFS (p = 0,8758; p=0,5495) and OS (p = 0,8803, p=0,7470) was observed.

**Conclusion :** FDG PET has a high sensitivity for PCNSL and can detect any systemic spread at staging and in case of relapse. However, we don't find an adjunct role of FDG PET to MRI in CNS lesions. Pretreatment T and T/N have no prognosis value in our study and FDG PET seems not to predict relapse when it is performed after 2 cycles of chemotherapy.

## B12. PROGNOSTIC IMPACT OF 18F-FDG PET/CT METABOLIC TUMOR VOLUME, MTV, IN PRETHERAPEUTIC MANTLE CELL LYMPHOMA

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**Aim:** Mantle cell Lymphoma (MCL) is a rare Non Hodgkin's Lymphoma subtype with heterogenous behaviour. MCL-specific international prognostic index (MIPI) identifies prognosis groups. Data have shown an interesting prognostic impact of SUVmax before chemotherapy. New technological FDG-PET/CT (PET) tools such as Metabolic Tumor Volume (MTV) are also promising. Our objective was to assess the prognostic value of MTV and SUVmax in MCL before chemotherapy.

**Methods:** Retrospective analysis of 26 patients with biopsy-proven MCL assessed by PET. SUVmax, MTV40% and MIPI were correlated to overall and progression-free survivals (PFS).

**Results:** Eighteen patients (14 male) had PET before chemotherapy, five for restaging. Median age was 68.5 years(48-92). Most patients had advanced disease (Ann Arbor stade I: 2; III: 4; IV: 12). R-CHOP or R-DHAP was used in 17/18 followed by autologous stem cell transplantation (ASCT) in 3 patients. Median follow up was 42 months. Median SUVmax and MTV was 6.88[5.4-14.7] and 623ml[31-2889]. Relapse occurred in 14/18 and two deaths occurred. Four patients are still in complete remission, three of whom after ASCT. In the group with MTV<570ml, PFS was longer than 2 years, except for one patient who relapsed 16 months after the end of chemotherapy, while patients with MTV >570ml relapsed earlier or died, except one patient with 1711 ml MTV still in complete remission 3 years after ASCT. No cut-off for SUVmax was identified for prognosis. There was a trend for correlation between MTV and MIPI.

**Conclusion:** In MCL, MTV before chemotherapy could predict outcome and requires further investigation towards designing risk-adapted strategies, in particular ASCT.

## B13. THE USEFULNESS OF 18-FDG PET (PET) IN FOLLICULAR LYMPHOMA (FL)

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**Purpose :** PET is a powerful post therapy prognostic tool in HL and DLBCL but its interest in FL remains indeterminate. This study aims at assessing the usefulness of PET in restaging and its correlation with PFS and OS of patients with FL.

**Patients and Methods :** We retrospectively studied data from 17 patients with FL at diagnostic or at relapse. A negative PET is defined by the absence of visual metabolic activity or by a lesion with a SUVmax inferior to the mediastinal vascular background activity. Characteristics of patients show : sex ratio 1,1, median age 56 years (43-79), median FLIPI 2.5 (1-4), median Ann Arbor staging 3 (2-4) and median follow-up 49 months (7-145). Treat-ments are divided in 6 R-CHOP, 6 R-CVP, and 3 R-chemothera-py followed by autologous SCT.

**Results :** Initial PET at diagnostic (n=11) or at relapse (n=6) are positive. PET show more lesions than TDM (73%) and involve an Ann Arbor up restaging (40%) without modification of the FLIPI score. PFS and OS of the 13 patients with a negative end treatment PET (ePET) (38 and 44 months) are higher than PFS and OS of the 4 patients with a positive PET (19 and 31 months). In 33% of cases PET permit to affirm a complete res-ponse contrary to TDM. An intermediary PET (iPET) is also avai-lable for 7 patients. PFS and OS of the 5 patients with a negati-ve PET (43 and 49 months) are higher than PFS and OS of the 2 patients with a positive PET (26 months).

**Conclusion :** This study is a small monocentric series. Initial PET show a more exhaustive description of initial lesions than TDM. EPET appears to be a good predictor of PFS. A larger prospec-tive study is needed to evaluate the interest of an iPET.

## B14. FDG-PET/CT IN THE POST-THERAPY EVALUATION OF LYMPHOMA PATIENTS IN PRIMARY SJOGREN'S SYNDROME: A PILOT STUDY

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Six consecutive patients with primary Sjogren's syndrome and associated lymphomas with salivary glands involvement (4 MALT, 1 DLBCL and 1 SLL case),were prospectively enrolled after completion of immunochemotherapy. All had FDG-PET/CT post-therapy evaluation.Imaging studies were combined with minor salivary gland biopsies (including histology and immunohistochemistry) as the reference index, to evaluate both Sjogren's activity(Tarpley score and inflammatory foci as number of infiltrates/4mm2) and residual lymphoma.

Median SUVmax of the parotid gland was 3.05 (range 2.1-3.8), Tarpley score 2.5(1-3) and biopsy focus score 3 (0.7-8)/4mm2. Only one patient had residual MALT disease of the salivary glands, with a SUVmax of 3.8. Tarpley score had a strong positive correlation with SUVmax (Spearman's rho=+0.83, p=0.04).Foci biopsy score had also a positive association of marginal significance (rho=+0.71, p=0.10). Using a strict positivity criterion of SUVmax>3.0 for parotid uptake (mean normal 1.90 + 3 x SD, where SD=0.4 as previously reported in the literature), the corresponding sensitivity and specificity for detecting residual lymphoma are 1.0 and 0.60 respectively. No other sites of pathological uptake were noted.

This pilot study suggested that Sjogren's syndrome may have a confounding effect in the post-therapy, FDG-PET assessment of related lymphomas in the salivary glands.This may be attributed to the strong correlation of inflammation grading with FDG tracer uptake. Imaging should be complemented by salivary gland biopsy data to confirm lymphoma remission, until optimal cut-off data are gathered to permit omission of biopsy procedures in selected patients.

## C1. BONE MARROW ACTIVITY ON 89ZR-RITUXIMAB IMMUNOPET/CT PREDICTS HEMATOLOGICAL TOXICITY IN LYMPHOMA PATIENTS TREATED WITH RADIOIMMUNOTHERAPIE

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**Introduction :** Toxicity observed with radioimmunotherapy is primarily hematological and difficult to predict. The aim of this study was to evaluate whether bone marrow (BM) activity on immuno-PET with 89Zr-rituximab was correlated to hematological toxicity in lymphoma patients treated with 90Y-rituximab.

**Methods :** 25 patients with relapsed CD20+ B cell lymphoma received IV rituximab (250 mg/m²) followed by 89Zr-rituximab (111-148 MBq), with immunoPET/CT performed 1h, 3 and 6 days after tracer injection. One week later, the same infusion of cold rituximab was followed by the injection of 90Y-rituximab (14.8 MBq/kg). BM activity was assessed by automatic segmentation of the skeleton on CT images using OWS® 1.0 and imported in Pmod® 2.75 for quantification of average BM activity concentration (Bq/cc) on 89Zr-immuno-PET/CT of day 6. Average BM activity concentration was standardized for the injected activity and patient's weight.

**Results :** Hematological toxicities grade 3 and 4 were observed in 8 (32%) and 5 (20%) patients respectively. On 89Zr-immunoPET, the median BM activity concentration was 0.05 Bq/cc (range 0.03-0.20 Bq/cc) per injected MBq/kg. BM activity concentration was significantly higher in patients who developed grade 3 and 4 toxicity (median 0.05 Bq/cc and 0.10 Bq/cc respectively) as compared to patients who did not develop grade 3 or 4 toxicity (median 0.04 Bq/cc) (p=0.0009). The area under the ROC-curve of BM activity concentration for predicting grade 3-4 and grade 4 toxicities were 0.88 and 0.92 respectively.

**Conclusion :** BM activity assessed on 89Zr-rituximab immuno-PET is highly predictive of hematological toxicity in patients treated with 90Y-rituximab.

## C2. HARMONISING SUVs IN MULTICENTRIC TRIALS USING 18F-FDG PET FOR THERAPY MONITORING IN NON HODGKIN LYMPHOMA PATIENTS

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**Aim :** to evaluate a strategy for harmonisation of SUVs within the framework of multicentric trials, which is based on the production of protocol-specific images to meet EANM quantitative harmonising standards, in addition to images optimised for diagnostic purpose.

**Materials and methods :** PET data were acquired on a PET/CT equipped with point spread function (PSF) reconstruction. The NEMA NU-2 phantom was used to determine the optimal filter to apply during PSF reconstruction in order to obtain recovery coefficients (RCs) as close as possible to those recommended by EANM's guidelines (latter referred to as PSFeanm). Patients' data were reconstructed with PSF reconstruction optimised for diagnostic purpose, PSFeanm, and with an OSEM algorithm known to produce RCs close to EANM's expected values. In order to validate our strategy, we mimicked a situation in which a patient would undergo a pre-treatment scan on a former generation PET system and a post-treatment scan on a PET equipped with an advanced algorithm, by comparing SUVs of OSEM reconstruction to SUVs of PSF and then PSFeanm reconstructions.

**Results :** overall, 252 lesions were analysed in 12 consecutive NHL patients. Bland-Altman analysis demonstrated that the mean ratio between PSF and OSEM data was 1.48 (95% CI: 1-1.96) for SUVmax. When applying our strategy, the mean ratio between PSFeanm and OSEM data was 1.04 (95% CI: 0.93-1.14).

**Conclusion :** this strategy reduced reconstruction-dependent variation in SUVs and would be useful when using SUVs in multicentric trials for therapy monitoring in sites equipped with multiple scanners, or as a diagnostic/ prognostic tool.

## C3. CLINICAL IMPACT OF CONTRAST-ENHANCED COMPUTED TOMOGRAPHY (CECT) COMBINED WITH LOW-DOSE FDG PET/CT ON LYMPHOMA PATIENT MANAGEMENT

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**Goal :** Routine management of lymphoma patients usually requires performing both CECT and low-dose FDG PET/CT, which increases radiation exposure. This study sought to evaluate the clinical impact of this approach.

**Methods :** Over a 1-year period, 237 CECT were performed in 163 patients after low-dose FDG PET/CT on the same day and same scanner. Scans were performed in various types of lymphoma, for staging (n=41), interim evaluation (n=73), post-therapy evaluation (n=115), and follow-up (n=8). After injection of 325+/-71 MBq FDG, low-dose CT (100 kV/60 mAs) was acquired from skull top to mid-thigh and CECT (120 kV/100 mAs) was acquired from skull base to groin after injection of 80 mL low-osmolarity contrast media. Clinical impact was determined from the multidisciplinary committee reports.

**Results :** CECT delivered an average 33+/-4 mSv vs. 18+/-3 mSv for low-dose FDG PET/CT (183% additional dose). CECT had no clinical impact on patient management in 219 cases (92%). A positive impact was noted in only 7 cases, i.e. diagnosis of deep vein thrombosis which required onset or extension of anticoagulants (n=5) and up-staging of lymphoma due to spleen involvement (n=2). To note, DVT was seen in 9 additional cases without impact on planned anticoagulation. A debatable impact was noted in the remaining 11 cases, consisting of complementary investigations, without therapeutic impact (documentation of PET-negative lesions, n=8), resulting in delay of therapy onset (n=2) or resulting in ablative surgery (n=1).

**Conclusions :** Clinical impact of CECT seems limited in our series. In the era of PET, imaging of lymphoma patients probably needs optimization to reduce radiation exposure.

## C4. ROLE OF 18F-FDG PET-CT UPTAKE PATTERNS IN WALDEYER'S RING TO DIFFERENTIATE THE BENIGN LESIONS TO THE MALIGNANT IN NHL

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**Aim :** evaluate 18F-FDG uptake with characteristic patterns and intensities in Waldeyer's ring could improve ability to differentiate benign to malignant lesions.

**Materials and Methods :** 50 patients with NHL and suspected presence of disease in Waldeyer was observed. The CT scan, performed in all patients was positive in the Waldeyer's ring in 5 cases.

**Results :** PET images showed pathological uptake (SUV 8) in pharyngeal tonsil (first pt), second pt had hyperfixation in right palatine tonsil (SUV6), the third case the hyperfixation was on palatine tonsil (SUV 7), some lateral cervical nodes (SUV 8), the fourth pt hyprfixed on lingual tonsil (SUV 14), left palatine tonsil (SUV 21), of the soft palate (SUV 16) and of some right backmandibular lymph nodes (SUV 8), of right lateral cervical (SUV 15), of sub chin (SUV 4) and of left supraclavicular (SUV 7); the last case showed uptake in both palatine tonsils (SUV 7), in the lingual tonsil (SUV 20), in right lateral cervical lymph nodes (SUV 12) and in the left paratracheals (SUV10).Overall (in our's 5 cases) the uptake appears mainly asymmetric on the Waldeyer's ring structures and all the accumulation showed a SUV greater then 4; finally 3 cases showed the involvement of lateral cervical lymph nodes.In 45/50 cases PET showed a symmetric uptake in Waldeyer's ring , a SUV lower than 4 without lateral cervical lymphonodes involvement.

**Conclusions :** an asymmetric distribution of the radiopharmaceutical of Waldeyer ring , the involvement of adjacent lymph nodes and a significant increase of up-take greater than 4 are suspected parameters for disease involvement in Waldeyer and could change staging and therapeutic plans.

## C5. WIDEN: A TOOL FOR MEDICAL IMAGING CLINICAL TRIAL MANAGEMENT.

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**Background**
Recently a novel clinical trial generation based on a therapeutic strategy driven by early treatment response assessment by functional imaging was conceived and a central review of the images became necessary. WIDEN ® (Web-based Imaging Diagnosis by an Expert Network) is a an electronic tool for online imaging review that has been set-up for the prospective multicenter Italian clinical trial HD0607, in which treatment is adapted to early interim PET scans result.

**Methods**
In the HD0607 clinical trial patients affected by advanced-stage Hodgkin Lymphoma (HL) are treated with standard ABVD therapy for 2 courses, followed by an interim PET scan (PET-2). PET-2 along with the baseline scan (PET-0) is uploaded to a dedicated web site thanks to WIDEN ® and hence made available for review. Reviewers report the scans on their own workstation within 72 hours from the upload and determine treatment choice: to switch to escalated BEACOPP in case of a positive result or to continue with ABVD for a negative PET-2 (NCT identifier 00795613).

**Results**
508 patients have been enrolled n the study. 476 of them already underwent interim PET. The average (median) time per scan upload and download were 13’23” (3’06”) and 6’56” (3’50”) respectively. The average (median) PET scan size was 132.6 MB (121.1 MB), with a minimum size of 51.2 MB and a maximum size of 469.8 MB. The average (median) time frame between the files upload by the submitting centre and the availability of the review results was 48h 53‘ (40h 40’). 9% of the scans were reviewed in days 4 and 5; 3% of the cases were reviewed after the fifth day. The overall concordance among reviewers shows a Krippendorf’s alpha of 0.777. Binary concordance between reviewers measured with Cohen’s kappa ranged 0.73-0.87.

**Conclusions**
WIDEN ® proved to be an effective tool for medical imaging exchange, review and analysis. Data security, simplicity, low cost, feasibility and prompt scan review were demonstrated. Its applicability in any clinical trial in which imaging is decisional for treatment modulation is warranted.

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