# ''Focus on...'' session: PET use in lymphoma

## 043 IS MARROW BIOPSY STAGING FOR HD AND DLBCL OBSOLETE IN THE PET-CT ERA?

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**Introduction:** Positron emission tomography using 18F fluorodeoxyglucose (FDG) combined with a co-registered CT (PET-CT) identifies lymphoma in extra-nodal sites not detected by other imaging, including bone marrow. Staging of Hodgkin's Disease (HD) and Diffuse Large B-Cell Lymphoma (DLBCL) by PET has changed how we view bone disease in lymphoma, as often being focal 'metastatic' disease rather than a diffuse infiltrate. Although seeking marrow involvement by iliac crest biopsy remains the standard, utilising the now routine PET-CT which images most of the skeleton seems more logical. We question whether bone marrow biopsy has additional value.

**Methods:** We retrospectively compared diagnostic reports of staging PET-CT scans and iliac crest biopsies from HD and DLBCL patients over a 2 year period. PET-CT imaging was performed using GE DST or VCT PET-CT scanners, 90 minutes after administration of 370MBq FDG. Biopsies were reported by experienced haematopathologists using standard immunocytochemistry. Bone marrow was considered involved based on a positive iliac crest biopsy, or FDG uptake in marrow at diagnosis which resolved on interval scan after treatment.

**Results:** Of 93 cases (DLBCL 65, HD 28) PET-CT demonstrated marrow disease in 25% (DLBCL 19, HD 4). In 22 of 23 with marrow disease on PET-CT, FDG uptake was focal (DLBCL 18, HD 4) representing localised disease, mostly in the axial skeleton. Just 1 patient (DLBCL) had diffuse marrow FDG uptake interpreted as marrow disease which was confirmed by iliac crest biopsy. In contrast only 32% (7 of 22) of focal PET+ve cases had disease detected by biopsy. An additional DLBCL patient had low volume interstitial marrow disease on biopsy not detected by PET-CT, which did not change IPI score. Sensitivity of PET-CT for bone marrow involvement in DLBCL was 95% (19/20 patients) compared to 40% (8/20) for iliac crest biopsy. PET-CT sensitivity for HD was also superior at 100% vs 25%. Iliac crest biopsy added additional information in only 1% (1/93) of patients.

**Conclusions:** We find that PET-CT has high accuracy for identifying marrow involvement by DLBCL and HD at diagnosis, when reported by experienced readers. The inadequacy of iliac crest biopsy is explained by the frequent focal nature of marrow involvement by these two diseases. In our experience, only diffuse marrow FDG uptake needs investigation by marrow biopsy, particularly in HD where reactive marrow change occurs without disease infiltration. Where marrow is negative or shows focal positivity on PET, routine iliac crest biopsy adds no clinically important diagnostic value in the PET-CT era.

## 044 THE GERMINAL CENTER B-CELL SIGNATURE IS ASSOCIATED TO A HIGHER [$^{18}$F]-FDG UPTAKE AND IMPROVES THE PROGNOSIS VALUE OF PET SCAN IN DIFFUSE LARGE B-CELL LYMPHOMAS (DLBCL) TREATED BY RITUXIMAB (R) AND ANTHRACYCLINES-BASED CHEMOTHERAPY

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**Introduction:** In addition to the molecular classification, [$^{18}$F]-Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging is essential to optimise initial staging or to predict prognosis of DLBCL. The aim of the study was to assess the relationship between cell of origin (COO) classification and PET scan features in DLBCL.

**Materials and methods:** Fifty seven cases treated by CHOP/CHOP-like+R were retrospectively analysed (median age = 65y, aaIPI 0-1 = 30%, 2-3 =70%). PET scan results at diagnosis (SUVmax), following 3/4 cycles of chemotherapy (interim PET) and at the end of treatment (final PET) were correlated to molecular features. Expression profile of 18 genes related to GCB/ABC signatures and 5 genes coding for glucose transporters (GLUT) was determined from frozen tissues using an Illumina platform and DASL technology (cDNA-mediated Annealing, Selection, Ligation and extension). Phenotypes were also assessed by immunohistochemistry (IHC) according to Hans algorithm.

**Results:** Gene expression profiling classified 30 DLBCL in the GCB subtype (2-year PFS=76%) and 27 in the ABC subtype (2-year PFS=51%, p=0.03), giving a concordance rate of77% with IHC. Expression of GLUT2 was significantly higher in DLBCL with SUVmax ≥ third quartile, regardless the GCB/ABC subtype. At base-line, SUVmax was higher in the GCB subtype as compared to the ABC subtype ($p = 0.029$) but was not predictive of the outcome. Interim and final FDG-PET (negative / positive) were highly predictive of the prognosis. Using semi-quantitative assessment of SUV decrease at interim PET (ΔSUV) fast (n=36) and slow (n=9) responders (ΔSUV ≥ or < 70%) were defined. In multivariate analysis, GCB/ABC(OR=5.1), aaIPI(OR=7.1) and slow/fast responses (OR=0.1) were independently correlated with PFS and OS. Using the GCB/ABC classification and interim PET, we identified patients with a very favourable outcome (2-year OS/PFS = 100%) characterized by a GCB phenotype and a fast metabolic response. Conversely, in the GCB group (defined by DASL or IHC), slow responders display a very poor prognosis (2-year OS=33%). Similarly, DLBCL with fast metabolic responses but belonging to the ABC subtype displayed an unfavourable outcome (2-year OS = 57%).

**Conclusion:** Molecular classification according to COO and interim PET scan are two strong and independent prognostic factors in DLBCL that should be incorporated in future clinical trials to tailor therapeutic strategies.

## 045 FDG-PET TO GUIDE RADIOTHERAPY IN ADVANCED-STAGE HODGKIN LYMPHOMA PATIENTS WITH RESIDUAL BULKY DISEASE AFTER CHEMOTHERAPY: RESULTS OF THE GHSG HD15 TRIAL

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**Introduction:** The role of additional radiotherapy after chemotherapy for advanced-stage Hodgkin lymphoma is unclear. The German Hodgkin Study Group (GHSG) thus performed the HD15 trial in which advanced-stage Hodgkin lymphoma patients having residual disease after 6-8 cycles of BEACOPP were evaluated by $^{18}$F-fluorodesoxyglucose positron emission tomography (PET) following chemotherapy.

**Methods:** Entry criteria for the PET question in HD15 were partial remission (PR) after the end of chemotherapy with at least one involved nodal site measuring more than 2.5 cm in diameter by computed tomography (CT). Calculations were restricted to those cases with either progressive disease (PD) or relapse within 12 month after PET or at least 12 months of follow-up. A total of 2,137 patients were included in HD15 of whom 728 had a tumor bulk ≥ 2.5 cm after BAECOPP chemotherapy an were qualified for the PET question. An expert panel performed the assessment of response and PET. Only PET-positive patients were scheduled for radiotherapy of residual disease. The negative prognostic value (NPV) of PET was defined as the proportion of PET-negative patients without progression, relapse or radiotherapy within 12 month.

**Results:** The full analysis set included 728 patients of whom 699 had at least 12 month of follow-up. Median age was 30 years, 57% were males and 66% had NS histology. Of the 728 qualified patients with residual disease ≥ 2.5 cm after BEACOPP, 74.2% were PET-negative and 25.8% PET-positive. In PET-negative group, a total of 28 patients relapsed or had radiotherapy despite being PET-negative resulting in a negative prognostic value of 94.6% (95% CI 92.7% to 96.6%). With a median follow-up of 38 months, the time-to-progression after PET at 3 years was 92.1% for PET-negative patients and 86.1% for PET-positive patients (95%-CI for difference-11.9% to -0.1%). Overall, only 11% of patients had additional radiotherapy as compared to 71% after $BEACOPP_{escalated}$ in our prior HD9 trial. Discussion The NPV of PET of 0.95 suggests that indeed only patients with residual disease after chemotherapy who are PET-positive need additional radiotherapy. PET-negative patients at least after BEACOPP can be spared from additional radiotherapy.

## 046 PET-CT OF FOLLICULAR LYMPHOMA IN PATIENTS TREATED IN THE PRIMA STUDY: CENTRAL REVIEW OF SCANS USING THE 5PS

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**Background:** The role of FDG PET-CT in assessing response at the end of therapy in follicular lymphoma (FL) remains undetermined. We investigated the prognostic value of post-immunochemotherapy PET-CT in FL patients from PRIMA prospective study.

**Patients and Methods:** Results of PET-CT scans from patients treated with induction immunochemotherapy followed by observation or rituximab maintenance were collated. Patient characteristics and outcomes were analysed. The PET-CT studies available for central review were then examined by two independent nuclear physicians and re-classified as positive or negative for disease, according to the Deauville criteria: a 5 Point Scale (5PS) with use of the mediastinal blood pool activity (MBP) as a threshold (cut-off for positivity between grade 2 and 3).

**Results:** One hundred twenty-two PET-CT scans were performed at the end of the induction immunochemotherapy, and 32 (26%) were considered positive by the investigators on the basis of local criteria. This local classification was predictive of an inferior PFS 33 vs. 71% (P<.0001) and increased risk of death HR 7.0P=.0011 as previously reported at ASH 2010 (Trotman, abstract 855). Currently, 58 PET-CTs have undergone central review, with 13/58 (22%) considered positive. Four of these had been considered negative by the local investigator. Maximum standardised uptake value (SUVmax) of residual lesion in the 13 patients with positive scans ranged from 2 to 30 (median 5.7). In 5/13 the FDG uptake was intermediate between that of the MBP and liver, (grade 3 on 5PS). Forty-five PET-CT were negative, of which 7 were considered positive by the local investigator. In 6/7 there was minimal residual uptake below the MBP activity (grade 2) and one had grade 1 activity.

**Conclusion:** Standardized consensus criteria, need to be validated and applied for reliable interpretation of post-treatment FDG PET-CT in FL patients. Updated results of central PET review, based on consistent application of the 5PS criteria, will be correlated with patient outcomes.

## 047 INTERNATIONAL VALIDATION STUDY OF INTERPRETATION RULES AND PROGNOSTIC ROLE OF INTERIM-PET SCAN IN ADVANCED STAGE HODGKIN LYMPHOMA

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**Background:** Published data supports the prognostic role of interim-PET (iPET) in advanced-stage, ABVD-treated Hodgkin lymphoma (HL). Recently, in Deauville a consensus for interpretation of iPET scans was reached. The aim of this study was to validate these criteria for iPET using an international cohort of patients with scan reviewed by an expert panel (EP).

**Materials and Methods:** The inclusion criteria were: (a) HL (except lymphocyte predominance), stages IIB-IVB or IIA with adverse prognostic factors (apIIA); (b) ABVD treatment (6 cycles ±radiotherapy for bulky lesions); (c) iPET after 2 ABVD, with baseline PET (b-PET) and iPET done on the same PET/CT scanner; (d) no treatment change based on iPET; (e) pts whose treatment was intensified for ABVD resistant lymphoma were eligible if there was clinical and/or radiological evidence of disease progression; (f) follow-up (FU) > 1 year. bPET and iPETs were interpreted using visual assessment with the Deauville 5-point scale by EP. Scores 1 to 3 were regarded as 'negative' (-ve) and scores 4 and 5 as 'positive' (+ve). The six EP readers scored iPET independently, then met to reach consensus in discordant cases. Binary and overall concordance rates were calculated using k Cohen's and α Krippendorf's coefficients, respectively.

**Results:** bPET and iPET from 402 pts diagnosed between 11/2001 and 01/2010 from 21 centers around the world were received but only 262 pairs of scan with good-quality images were reviewed. 148 pts (56%) had stage IIB-IVB, 53 (20%) apIIA 79 (30%) bulky disease, and 78 (30%) extra-nodal disease. In stages III-IV, IPS distribution was 9, 38, 45, 29, 17,8. On independent review the Cohen's k and Krippendorf α mean concordance rates were 0.77 and 0.76, respectively. There was 'true' discordance (3-ve vs. 3-ve reports) in only 8/262 (3%) pts. There were 48 +ve (18%) and 214 -ve (82%) iPET results. 223 pts (85%) were in CCR and 39 (15%) had progressed or relapsed with a median FU of 22.5 months. The 3-year PFS of iPET -ve and iPET +ve pts was 95% and 38%, respectively; PPV and NPV were 0.63 and 0.96, respectively. Sensitivity, specificity and accuracy were 0.77, 0.92 and 0.89.

**Conclusions:** the prognostic role of iPET in advanced-sage HL is confirmed. The Deauville criteria for reporting iPET are feasible and show a very good concordance among reviewers.

## 048 CLINICAL USEFULNESS AND PROGNOSTIC SIGNIFICANCE OF INTERIM $^{18}$F-FDG PET/CT FOR THE TREATMENT OF PERIPHERAL T CELL LYMPHOMAS

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Although interim $^{18}$F-fluoro-2-dexoy-D-glucose-positron emission tomography (FDG-PET)/computerized tomography (CT) scan has emerged as a powerful prognostic tool in predicting treatment outcome in Hodgkin's lymphoma (HL) and diffuse large B cell lymphoma (DLBCL), the prognostic value of interim PET/CT scanning has not been determined in patients with peripheral T cell lymphoma (PTCL). The sequential interim PET/CT was prospectively investigated to determine whether it provided additional prognostic information and could be a positive predictable value for the treatment of PTCL.

**Patients and Methods:** Sixty-three patients with newly diagnosed PTCL were enrolled from Sep. 2005 to Feb. 2010 in a single institution. The PET/CT analysis was performed at the time of diagnosis, the mid-treatment and completion of CHOP/CHOP-like or other chemotherapy. Patients that had mild or diffuse FDG uptake at any site were considered negative for intensities lower than or equal to that of the mediastinal blood pool structures with SUVmax cut-off value of 3.0. The clinical stage and response of the patients were assessed according to revised response criteria for aggressive lymphomas (Cheson, J Clin Oncol, 2007).

**Results:** Median age was 57 years (range: 23-82). 38 patients (60.3%) presented with advanced stage disease and 15 (23.8%) had bone marrow involvements. The histological subtypes were 38.1% PTCL-unspecified (n=24), 12.7% angioimmunoblastic T cell (n=8), 34.9% nodal or extranodal NK/T cell (n=22), and others. At diagnosis, 30 patients (47.6%) were classified as high-risk by the international prognostic index (IPI) and 29 (46%) were classified as high-risk (more than 2 factors) by the prognostic index for PTCL (PIT). 54 patients could be assessed the interim response and28 patients (44.4%) remained positive metabolic uptakes in interim PET/CT. The patients with positive interim PET/CT showed a significantly higher relapse rate (71.4%) than those with negative interim PET/CT (38.5%) ($P$ =0.027). After following median 12.2 months (range, 0.4-73), the positivity of interim PET/CT was significantly prognostic factor in both OS and PFS, with a hazard ratio of 3.79 (1.66 – 8.65) and 3.19 (1.48 – 6.89), respectively. The 2-year OS and PFS rate was significantly different in the patients with positive (22.3 and 25.6%) and negative (67.3 and 63.2%) interim PET/CT, respectively ($P$<0.01). Eight patients (12.7%) who determined to have positive interim PET/CT were revealed false-positive uptakes by locoregional biopsy (positive predictive value of 0.83).

**Conclusions:** Interim PET/CT has a significant predictive value for disease progression and survival of PTCL.The patients with positive interim PET/CT response should be considered an intensive therapeutic plan for overcoming their poor clinical outcome.