

# POSITRON EMISSION TOMOGRAPHY GUIDED OMISSION OF RADIOTHERAPY IN EARLY-STAGE UNFAVORABLE HODGKIN LYMPHOMA: FINAL RESULTS OF THE INTERNATIONAL, RANDOMIZED PHASE III HD17 TRIAL BY THE GHSG

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## Aims

Combined-modality treatment (CMT) comprising of chemotherapy and consolidation radiotherapy (RT) is standard of care for patients with early-stage unfavourable Hodgkin lymphoma (HLeu). However, the use of RT raises concern about long-term sequelae in this young patient cohort. We thus asked in the HD17 study, whether RT can be omitted in patients achieving a complete metabolic response after “2+2” chemotherapy (2x eBEACOPP followed by 2x ABVD) without loss of efficacy.

## Methods

Patients aged 18 to 60 years with newly diagnosed, HLeu were included in this international, randomized phase III trial. Patients were assigned to CMT with 4 cycles of chemotherapy followed by 30Gy involved-field RT or PET-guided treatment, omitting RT in PET4-negative patients (DS, Deauville score, <3). The German Hodgkin Study Group (GHSG) standard CTx is the “2+2” regime comprising of 2 cycles of eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) and subsequent 2 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). We aimed first to show non-inferiority of the PET4-guided strategy in a per protocol analysis regarding progression-free survival (PFS) with a non-inferiority margin of 8% and second to confirm PET4-positivity as risk factor for PFS in an intention-to-treat analysis of CMT-treated patients.

## Results

Between January 2012 and March 2017, we enrolled 1,100 patients. Of 979 patients with confirmed PET4 result, 651 (66.5%) were PET4-negative, 238 (24.3%) had DS3, and 90 (9.2%) DS4. Median observation time was 45 months (95%>CI, 43 – 47) for PFS and 47 months (95%>CI, 46 – 49) for overall survival (OS). In the standard CMT group (PP, n=428), 5-year PFS was estimated at 97.3% (95% CI, 94.5% to 98.7%), as compared to 95.1% (95% CI, 92.0% to 97.0%) in the PET4-guided treatment group (PP, n=477). The 5-year PFS difference between the two groups was – 2.2% (95%>CI, –5.3% to 0.9%), excluding the lower margin of –8%. Sensitivity subgroup analysis in PET4-negative patients (PP, n=597) confirmed non-inferiority with an estimated 5-year PFS of 97.7% (95%>CI, 93.6% to 99.2%) in the CMT group, and 95.9% (95%>CI, 92.4% to 97.9%) in patients treated without radiotherapy in the PET4-guided group (difference –1.7%, [95%>CI, – 5.3% to 1.8%]). In the CMT/CTx+RT group (n=646), 5-year PFS was estimated at 94.2% (95%>CI, 90.1% to 96.6%) for PET4 positive patients (n=328) as compared to 97.6% (95%>CI, 94.0% to 99.9%) for PET4-negative patients (n=318). The Hazard ratio for the difference was 3.03 (95% CI,

1.1% to 8.3%) confirming PET4 as significant risk factor. The difference was more pronounced when DS4 was used as cut-off for positivity: 5-year PFS rates were 81.6% (95%>CI, 67.9% to 89.9%) for DS4 patients versus 98.1% (95%>CI, 95.9% to 99.1%) in DS1–3 patients. 5-year overall survival rates (ITT) were 98.8% (95%>CI, 96.7% to 99.6%) in the standard CMT group and 98.4% (95%>CI, 96.2% to 99.3%) in the PET4-guided group. So far, 10 fatal events have occurred in HD17 including two HL-related events and one treatment-related death.

### **Conclusion**

PET4-negativity after treatment with “2+2” chemotherapy in patients with newly diagnosed early-stage unfavourable HL allows omission of consolidation RT without relevant loss of efficacy. PET-guided therapy thereby reduces the proportion of patients at risk for late effects from irradiation.

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