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BACKGROUND
Patients with Hodgkin’s lymphoma might have persistent fatigue even years after treatment. However, knowledge of the development of fatigue persisting long after completion of treatment is limited. Therefore, we did a detailed analysis of fatigue in our first-line clinical trials for early-stage favourable (HD13 trial), early-stage unfavourable (HD14 trial), and advanced-stage (HD15 trial) Hodgkin’s lymphoma. Beyond the description of fatigue from diagnosis up to 5 years after treatment, we aimed to assess any effect of patient characteristics, disease characteristics, or treatment characteristics on persistent fatigue.

METHODS
In this longitudinal study, we included patients with early-stage favourable, early-stage unfavourable, and advanced-stage Hodgkin’s lymphoma from the HD13, HD14, and HD15 trials, respectively, aged between 18 and 60 years. Eligible patients for these trials had newly diagnosed, histologically proven Hodgkin’s lymphoma, an Eastern Cooperative Oncology Group performance status of 2 or lower, HIV negativity, and absence of comorbidity disallowing protocol treatment. We used the fatigue scale of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire to assess fatigue from diagnosis up to 5 years after the end of treatment. The primary outcomes of interest in this study were fatigue scores in the second and fifth year after end of treatment. We estimated the effect of different disease, patient, and treatment characteristics on fatigue with multiple regression analyses and identified fatigue trajectories with growth mixture models. The regression analyses and growth mixture models used robust and full information maximum likelihood estimates to account for missing data. The HD13, HD14, and HD15 trials are registered as international standard randomised controlled trials, ISRCTN63474366, ISRCTN04761296, and ISRCTN32443041, respectively.
FINDINGS
The HD13 trial enrolled patients with early-stage favourable disease from Jan 28, 2003, to Sept 30, 2009; the HD14 trial enrolled patients with early-stage unfavourable disease from Jan 28, 2003, to Dec 23, 2009; and the HD15 trial enrolled patients with advanced-stage disease from Jan 28, 2003, to April 18, 2008. 5306 patients were enrolled in these trials. We analysed 4215 patients with any valid fatigue assessment up to 5 years after the end of treatment. Patients with higher tumour burden at diagnosis had more fatigue at baseline (mean fatigue score in HD13: 30·8 [SD 28·0]; in HD14: 39·8 [29·4], and in HD15: 49·0 [30·2]). Fatigue scores (FA) in the second year after the end of treatment were 28·5 (24·7) in HD13, 28·8 (24·4) in HD14, and 30·7 (24·4) in HD15; in the fifth year after the end of treatment FA was 30·8 (26·0) in HD13, 27·1 (24·8) in HD14, and 28·2 (24·9) in HD15. Predictors of fatigue in the second and fifth year after end of treatment were baseline fatigue (p<0·0001) and age as a continuous variable (p<0·0001). In addition to preceding fatigue and age, patient sex and Hodgkin's lymphoma specific risk factors at baseline did not consistently and significantly improve the prognosis of fatigue in the first, second, and fifth year after end of treatment. There was no significant effect of treatment on fatigue scores in the second and fifth year after treatment.

INTERPRETATION
Our findings show a high incidence of severe acute and persistent fatigue in Hodgkin's lymphoma survivors, which is largely independent of tumour stage and treatment. Our results contribute to a better understanding of fatigue in patients with Hodgkin's lymphoma and Hodgkin's lymphoma survivors and could inform development of urgently needed intervention strategies.

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