

Increased Relapse Rates in Early Stage Hodgkin Lymphoma (HL) Patients without Radiotherapy: The German Society of Radiooncology (DEGRO) Advises to Treat all Early Stage HL Patients with Radiotherapy

Ohne Radiotherapie erhöhte Rückfallrate bei frühen Stadien eines Hodgkin Lymphoms: Die Deutsche Gesellschaft für Radiooncologie rät zur Strahlentherapie bei allen Patienten mit frühen Stadien eines Hodgkin Lymphoms

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In the EORTC/LYSA/FIL H10 trial stage I/II HL patients with favorable and unfavorable risk profile and a negative 18-fluoro-desoxy-D-glucose positron emission tomography (FDG-PET) after 2 cycles of ABVD were randomized for radiotherapy (RT) vs. no radiotherapy after the end of chemotherapy. After an interim futility analysis the data monitoring and safety committee considered it unlikely to demonstrate non-inferiority of the experimental arm (with omission of RT) compared to the standard RT arm. Therefore the study was suspended. The decrease in the 1-year PFS with omission of RT was 3–5 %, but absolute PFS was still in the range of 95 %. The authors conclude their article “The final analysis will reveal whether this finding is maintained over time.... [5]”.

Recently, the German Society of Radiooncology (DEGRO) circulated a statement advising that all patients with early stage HL should receive RT based on the results of the H10 trial. Although the current evidence-based S3 guideline “Hodgkin's Lymphoma” of the German Cancer Society does advise involved-field radiotherapy with 20Gy following chemotherapy for all patients over 18 years of age – if treated outside of clinical trials [11] – the general recommendation of radiotherapy for all HL patients cannot be extended to pediatric patients.

The strategy of the upcoming EuroNet-PHL-C2 trial stands in striking contrast to the DEGRO's advice. In this upcoming trial the EuroNet-PHL group aims at a 5-year EFS rate of more than 90 % and at omitting radiotherapy in early favourable HL patients with a negative FDG-PET result (Deauville score <4) after 2 cycles of OEPA. In addition, early favourable HL patients treated without RT will receive one additional cycle of COPDAC, a regimen with a low toxicity profile [3], to minimize the decrease of event-free survival (EFS; including second cancers as events) in patients without RT. It is expected that more than 90 % of the early favourable HL patients will be PET negative. The patients with early unfavourable HL will be treated in group of intermediate stage patients. These patients will be randomized between standard COPDAC consolidation and an intensified DECOPDAC regimen. Again, patients who are PET-negative after 2 cycles of OEPA will not

receive RT. In the light of the results of the H10 trial and the advice of the DEGRO the EuroNet-PHL group has to ask:

Is our strategy still justified?

The trade-off which is made in all current HL trials investigating omission of RT in patients with good response to chemotherapy has to be considered in detail. Current studies suggest a decrease of EFS by omitting RT in adequate early FDG-PET responders in the range of 5 %, but applying RT to all early stage patients would probably be unnecessary in at least 75 % (up to 90 %) of these patients. Thus, from a clinical point of view and apart from biometrical considerations the important question is:

Under which circumstances is it allowed to risk a decrease of EFS in order to spare unnecessary radiotherapy in the majority of the patients?

The patients should be informed about the risks of omitting radiotherapy vs. applying radiotherapy. There is consistent evidence that radiotherapy – even at doses below 30Gy can cause solid secondary tumors (SST) in up to 25 % of the patients within 30 years after treatment [1,5]. Thus, the risk of SST might be higher in young people than in those over 50 years of age at time of diagnosis – merely because young people may live longer with the burden of radiation. In addition, the risk of certain SST may be higher in young people for biological, e.g. hormonal reasons. It has been shown that the risk of radiotherapy-induced breast cancer is highest before puberty and at young age [7]. In addition, heart dysfunction (coronary artery disease, valve dysfunction) is radiotherapy dose-related [8] and should be avoided for long-term survival. Modern radiotherapy techniques, dose reduction and small volumes may reduce the risk, but cannot exclude long-term side effects completely. Concluding these arguments it seems that omission of radiotherapy could be more beneficial in young people. Secondly, the patients have to be informed on the chance of cure if they relapse. Relapsing patients will receive a more intensive chemotherapy which may include high-dose chemotherapy and autologous stem cell transplantation [9]. In patients with limited stage relapse chemo-radiotherapy may also be justified [6]. This option might be limited to patients without radiotherapy in the first line and with good response to second

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line chemotherapy. Here again, achieving an EFS rate as high as possible by first-line treatment might be more important in older patients, especially in those where the clinical condition may not allow an intensive second-line treatment. However, in young people the situation seems to be different. Recently, Wolden et al. [10] reported the long-term results of the CCG 5942 trial. In this study, HL patients including those with stage I and II with favourable or unfavourable risk factor profile were randomized for radiotherapy or no further treatment if they showed complete response at the end of chemotherapy (>70% tumour volume reduction and a negative gallium scan). Like the H10 trial, this study was also suspended after an unfavourable interim analysis. The long term results, show a significant decrease in 10-year EFS (91.2 vs. 82.9% for patients with or without radiotherapy), but the 10-year OS (overall survival) was not different (97.1 vs. 95.9% for patients with or without radiotherapy). Thus, future analyses may even demonstrate more favourable survival rates for patients without RT since the risk of SST has been eliminated in these.

However, prevention of a relapse in patients in whom radiotherapy is omitted may be important to reduce the overall burden of treatment in individual patients. The results of the HD15 trial of the GHSG demonstrate the paradigm that intensification of chemotherapy could compensate for radiotherapy [2]. In this trial only about 10% of the advanced stage HL patients received radiotherapy and the results of those patients with good response to chemotherapy and no radiotherapy after completion of chemotherapy were excellent (5-year FFTF 89.3% using 6×BEA-COPPesc). In the EuroNet-PHL-C2 trial early favourable HL patients with adequate response to chemotherapy after 2 cycles of OEPA and omission of radiotherapy will receive an additional course of COPDAC to minimize the reduction of EFS.

In conclusion, the EuroNet-PHL-C2 strategy seems to be well considered and justified in the light of the argumentation above and the published results in young people.

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