Strahlenther Onkol 2013 · 189:445–447
DOI 10.1007/s00066-013-0331-4
Received: 7 February 2013
Accepted: 13 February 2013
Published online: 21. April 2013

H.T. Eich[1] · J. Kriz[1] · H. Schmidberger[2] · B. Böll[3] · B. Klimm[3] · M. Rancea[5] · R.-P. Müller[4] · A. Engert[3]

[1] Department of Radiation Oncology, University of Muenster, Münster
[2] Department of Radiation Oncology, University of Mainz, Mainz
[3] First Department of Internal Medicine, University of Cologne, Cologne
[4] Department of Radiation Oncology, University of Cologne, Cologne
[5] Cochrane Haematological Malignancies Group, First Department of Internal Medicine, University of Cologne, Cologne

The German evidence-based guidelines for Hodgkin's lymphoma

Aspects for radiation oncologists

The interdisciplinary guidelines (evidence-based) for diagnostics, treatment and follow-up were established in cooperation with several national societies (PSO, AIO, AGO, ARO, DGE-BV, DGIM, Deutsche Leukämie und Lymphomhilfe, DGN, DGP, DEGRO, DEGUM, DKG, DRG, KOK, CHMG, GMDS, GHSG, DNEbM and KML). Deutsche Krebshilfe, Deutsche Krebsgesellschaft, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) and Leitlinienprogramm Onkologie realized the funding. The main investigating society was the Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO). The guideline process was funded by the German Guideline Program in Oncology (grant no. 109230), an association of the Scientific Medical Societies in Germany, the German Cancer Society and German Cancer Aid that also provided methodological support. The guidelines are an evidence-based instrument for improving diagnostics, treatment and follow-up in Hodgkin's lymphoma (HL) patients. The present report summarizes the aspects relevant to radiation oncologists.

The German evidence-based guidelines use the Cotswolds-modified Ann Arbor staging system for patients with HL. The following risk groups are defined:

Early favourable stages:
- Patients in stages IA or IB and IIA or IIB without risk factors.

Early unfavourable stages:
- Patients in stages IA or IB and IIA with one or more risk factors.
- Patients in stage IIB with elevated erythrocyte sedimentation rate (ESR) and/or involvement of ≥3 lymph node areas.

Advanced stages:
- Patients in stage IIB with risk factors, extranodal involvement and/or bulky mediastinal mass.
- Patients in stages IIIA or IIIB.
- Patients in stages IVA or IVB.

Risk factors are defined as: elevated ESR, extranodal involvement, involvement of ≥3 lymph node areas and bulky mediastinal mass.

In general, all patients should be included into clinical trials unless there are exclusion criteria. The following sections outline stage-adapted treatments.

Early favourable stages

Treatment consists of a combined-modality approach, i.e. chemotherapy (CTX) followed by involved-field radiotherapy (IF-RT). RT alone should not be used to treat patients in early favourable stages as several studies have demonstrated the superiority of CTX followed by RT [1, 2, 3]. CTX comprises two cycles of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD). This regimen is used as standard because of its effectiveness and low toxicity [1, 4]. Other regimens—e.g. the Stanford V regimen—have been tested and the results are awaited [5].

RT is applied as IF-RT. The HD8 trial conducted by the German Hodgkin Study Group (GHSG) tested whether IF-RT is as effective as extended-field radiotherapy (EF-RT). The final analysis showed no statistically significant difference between the two treatment modalities, thus IF-RT—which is less toxic—is used as standard [6].

The recommended RT dose is 20 Gy. The GHSG HD10 trial tested 20 Gy versus 30 Gy IF-RT. In the final analysis, no statistically significant differences between 20 Gy and 30 Gy were observed [4].

Legend

- Arbeitsgemeinschaft für Psychoonkologie (PSO)
- Arbeitsgemeinschaft Internistische Onkologie (AIO)
- Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)
- Arbeitsgemeinschaft Radiologische Onkologie (ARO)
- Deutsche Gesellschaft für Endoskopie und Bildgebende Verfahren (DGE-BV)
- Deutsche Gesellschaft für Innere Medizin (DGIM)
- Deutsche Leukämie und Lymphomhilfe
- Deutsche Gesellschaft für Nuklearmedizin (DGN)
- Deutsche Gesellschaft für Pathologie (DGP)
- Deutsche Gesellschaft für Radioonkologie (DEGRO)
- Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM)
- Deutsche Krebsgesellschaft (DKG)
- Deutsche Röntgengesellschaft (DRG)
- Konferenz Onkologischer Kranken- und Kinderkrankenpflege (KOK)
- Cochrane Haematological Malignancies Group (CHMG)
- Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (GMDS)
- Deutsche Hodgkin Studiengruppe (GHSG)
- Deutsches Netzwerk Evidenzbasierte Medizin (DNEbM)
- Kompetenznetz Maligne Lymphome (KML)
- Deutsche Gesellschaft für Hämatoonkologie (DGHO)

The role of fluorodeoxyglucose positron-emission tomography (FDG-PET) in the treatment strategy for patients in early unfavourable stages is being tested in the ongoing GHSG HD16 trial. Although the high negative predictive value of a negative PET scan is well known [7, 8, 9, 10, 11], PET should not be used as a tool to stratify treatment outside clinical trials.

Early unfavourable stages

Patients in early unfavourable stages are treated with a combined-modality approach. Standard CTX according to the final results of the GHSG HD11 and HD14 trials consists of two cycles of escalated-dose bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP), followed by two cycles ABVD [12, 13]. If escalated-dose BEACOPP cannot be applied due to medical reasons, four cycles of ABVD should be given instead.

Based on the results of the GHSG HD8 trial mentioned above, the standard RT volume is defined as the involved field [6].

The standard RT dose is 30 Gy, as demonstrated in the final analysis of the GHSG HD11 trial [13]. The HD11 trial tested 20 Gy versus 30 Gy IF-RT applied after either four cycles ABVD or four cycles BEACOPP. The combination of four cycles ABVD followed by only 20 Gy resulted in inferior progression-free survival compared to the other treatment arms [13].

The role of FDG-PET in risk stratification is not well established. Despite being a well-known independent marker, FDG-PET has not been used outside of clinical studies [14, 15, 16, 17]. The ongoing GHSG HD17 trial implements FDG-PET and a new RT volume—the involved-node radiotherapy (IN-RT) concept—into the treatment stratification [18]. Since the risk of late adverse effects of RT is related to radiation dose and the size of the irradiated volume, the goal is to reduce doses and field sizes as much as possible without reducing the probability of cure. As the IN-RT concept has never been tested in a randomized trial, the GHSG is comparing it to standard IF-RT in their HD17 trial. Other study groups are also testing its value, such as the European Organisation for Research and Treatment on Cancer (EORTC) in their H10 trial [19, 20].

Advanced stages

Standard CTX for patients under 60 years of age in advanced stages of disease consists of six cycles escalated-dose BEACOPP, based on the final results of the GHSG HD15 trial [21].

The role of RT after effective CTX is the topic of controversial discussion. There are several studies dealing with this aspect [22, 23, 24]. Results of the meta-analysis of 14 studies conducted by Loeffler have to be interpreted with caution, due to the extended treatment volumes and now obsolete techniques that were described [24].

Treatment volumes for patients in advanced stages are inherent. In Germany, local RT with 30 Gy to initial bulky disease or extranodal lesions is the standard care outside of clinical trials.

The GHSG HD12 trial tested whether consolidation RT is needed after CTX. The final analysis shows that patients with residual disease who received consolidative RT had improved progression-free survival rates [25].

The HD15 trial used PET for risk stratification in the treatment of patients in ad-

Strahlenther Onkol 2013 · 189:445–447
DOI 10.1007/s00066-013-0331-4

H.T. Eich · J. Kriz · H. Schmidberger · B. Böll · B. Klimm · M. Rancea · R.-P. Müller · A. Engert

The German evidence-based guidelines for Hodgkin's lymphoma. Aspects for radiation oncologists

Abstract
This report reviews aspects of the German evidence-based guidelines for Hodgkin's lymphoma relevant to radiation oncologists. Stage-adapted treatment is discussed with the focus on radiotherapy. Up-to-date literature citations provide an overview of current recommendations.

Keywords
Radiotherapy · Chemotherapy · Positron-emission tomography · Fluorodeoxyglucose · Risk factors

Die deutsche S3-Leitlinie für das Hodgkin-Lymphom. Aspekte für Radioonkologen

Zusammenfassung
Die vorliegende Analyse stellt wichtige strahlentherapeutische Aspekte der S3-Leitlinie für das Hodgkin-Lymphom zusammen. Diskutiert wird die stadiengerechte Behandlung mit dem Schwerpunkt Strahlentherapie. Die Auflistung der aktuellen Literatur gibt einen Überblick über derzeitige Empfehlungen.

Schlüsselwörter
Strahlentherapie · Chemotherapie · Positronenemissionstomographie · Fluorodeoxyglukose · Risikofaktoren

vanced stages. It was a multicentric study consisting of three treatment arms. Patients received either eight cycles escalated-dose BEACOPP, six cycles escalated-dose BEACOPP or eight cycles BEACOPP 14. After a restaging had been performed, patients with an FDG-PET-positive residual tumor ≥2,5 cm received local RT comprising 30 Gy. Patients with an FDG-PET-negative result were carefully followed up. The negative predictive value of PET was defined as 94% [21, 26].

The ongoing HD18 trial implements an early PET examination after two cycles of CTX into the treatment stratification. Patients with an FDG-PET-positive result after four to six cycles receive additional local RT with 30 Gy, according to the results of the HD15 trial. These results still have to be awaited.

Lymphocyte-predominant Hodgkin's lymphoma

The lymphocyte-predominant Hodgkin's lymphoma accounts for 5% of all HL and is distinguished from classical HL by its clinical course. Patients in stages IA without risk factors are treated with 30 Gy IF-RT. This treatment is based on retrospective studies conducted by the GHSG and the EORTC, where the IF-RT was equal to more extended RT volumes [27]. Patients in other stages are treated as patients with classical HL, using a combined-modality approach. The outcome is comparable to patients with classical HL [28].

Link: http://www.awmf.org/leitlinien/aktuelle-leitlinien.html

Corresponding address

Prof. Dr. H.T. Eich
Department of Radiation Oncology,
University of Muenster
Albert-Schweitzer-Campus 1, 48149 Münster
Germany
HansTheodor.Eich@ukmuenster.de

Conflict of Interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

References

1. Engert A, Franklin J, Eich HT et al (2007) Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. J Clin Oncol 25:3495–3502
2. Ferme C, Eghbali H, Meerwaldt JH et al (2007) Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 357:1916–1927
3. Noordijk EM, Carde P, Dupouy N et al (2006) Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. J Clin Oncol 24:3128–3135
4. Engert A, Plutschow A, Eich HT et al (2010) Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 363:640–652
5. Gordon L, Hong F, Fisher R et al (2010) A randomized phase III trial of ABVD vs. Stanford V/+ radiation therapy in locally extensive and advanced stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperatve Oncology Group (E2496) (abstr 6). Blood 116
6. Engert A, Schiller P, Josting A et al (2003) Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 21:3601–3608
7. Wit M de, Bohuslavizki KH, Buchert R et al (2001) 18FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's lymphoma. Ann Oncol 12:29–37
8. Weihrauch MR, Re D, Scheidhauer K et al (2001) Thoracic positron emission tomography using 18F-fluorodeoxyglucose for the evaluation of residual mediastinal Hodgkin disease. Blood 98:2930–2934
9. Spaepen K, Stroobants S, Dupont P et al (2001) Can positron emission tomography with [(18)F]-fluorodeoxyglucose after first-line treatment distinguish Hodgkin's disease patients who need additional therapy from others in whom additional therapy would mean avoidable toxicity? Br J Haematol 115:272–278
10. Naumann R, Vaic A, Beuthien-Baumann B et al (2001) Prognostic value of positron emission tomography in the evaluation of post-treatment residual mass in patients with Hodgkin's disease and non-Hodgkin's lymphoma. Br J Haematol 115:793–800
11. Sher DJ, Mauch PM, Van Den Abbeele A et al (2009) Prognostic significance of mid- and post-ABVD PET imaging in Hodgkin's lymphoma: the importance of involved-field radiotherapy. Ann Oncol 20:1848–1853
12. Von Tresckow B, Pluetschow A, Fuchs M et al (2012) Dose-Intensification in Early Unfavorable Hodgkin Lymphoma: Final analysis of the GHSG HD14 Trial. J Clin Oncol 30(9):907–913
13. Eich HT, Diehl V, Gorgen H et al (2010) Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol 28:4199–4206
14. Gallamini A, Hutchings M, Rigacci L et al (2007) Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol 25:3746–3752
15. Hutchings M, Loft A, Hansen M et al (2006) FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 107:52–59
16. Hutchings M, Mikhaeel NG, Fields PA et al (2005) Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma. Ann Oncol 16:1160–1168
17. Terasawa T, Lau J, Bardet S et al (2009) Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma: a systematic review. J Clin Oncol 2009 27:1906–1914
18. Eich HT, Muller RP, Engenhart-Cabillic R et al (2008) Involved-node radiotherapy in early-stage Hodgkin's lymphoma. Definition and guidelines of the German Hodgkin Study Group (GHSG). Strahlenther Onkol 184:406–410
19. Girinsky T, Specht L, Ghalibafian M et al (2008) The conundrum of Hodgkin lymphoma nodes: to be or not to be included in the involved node radiation fields. The EORTC-GELA lymphoma group guidelines. Radiother Oncol 88:202–210
20. Girinsky T, Maazen R van der, Specht L et al (2006) Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. Radiother Oncol 79:270–277
21. Engert A, Haverkamp H, Kobe C et al (2012) Reduced Intensity of Chemotherapy and PET-giuded Radiotherapy in patients with advanced stage Hodgkin lymphoma: an open-label, randomised phase 3 trial. Lancet 379:1791–1799
22. Aleman BM, Raemaekers JM, Tirelli U et al (2003) Involved-field radiotherapy for advanced Hodgkin's lymphoma. N Engl J Med 348:2396–2406
23. Aleman BM, Raemaekers JM, Tomisic R et al (2007) Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 67:19–30
24. Loeffler M, Brosteanu O, Hasenclever D et al (1998) Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. International database on Hodgkin's Disease Overview Study Group. J Clin Oncol 16:818–829
25. Borchmann P, Haverkamp H, Diehl V et al (n d) Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage Hodgkin's lymphoma: final analysis of the HD12 trial of the German Hodgkin Study Group. J Clin Oncol
26. Kobe C, Dietlein M, Franklin J et al (2008) Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma. Blood 112:3989–3994
27. Nogova L, Reineke T, Eich HT et al (2005) Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). Ann Oncol 16:1683–1687
28. Nogova L, Reineke T, Brillant C et al (2008) Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. J Clin Oncol 26:434–439