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Hodgkin’s Lymphoma

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Hodgkin’s Lymphoma

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Compliance rules:

- Guideline
- Conflict of interests

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1 Definition and Basic Information

Hodgkin’s lymphoma is a malignant disease that affects the lymphatic system. In the majority of cases the neoplastic cells can be derived from B lymphocytes. Characteristic feature is a low number of malignant Hodgkin-Reed-Sternberg (H-RS) cells surrounded by numerous reactive cells (bystander cells).

Most common primary localizations are cervical (60-80%), mediastinal, and inguinal lymph nodes. Hodgkin’s lymphomas disseminate both via lymphatic vessels or *per continuitatem* into lymphatic organs as well as by blood vessels or *per continuitatem* into extralymphatic organs.

In 2012, an S3 Guideline was prepared under the guidance of the German Hodgkin Study Group (GHSG) for the diagnostics, therapy and follow-up of Hodgkin’s lymphoma in adult patients. It contains more detailed information on each of the various subjects and includes a comprehensive list of references.

1.1 Epidemiology

The incidence rate is at 2-3/100,000 per year. The age peak lies at approx. 32 years.

1.2 Classification

Classification of Hodgkin’s lymphomas is performed according to the WHO classification:

I. Lymphocyte-predominant Hodgkin’s lymphoma (NLPHL; synonyms: LPHD, nodular paragranuloma)

The NLPHL encompasses almost 5% of all Hodgkin’s lymphomas. As opposed to the classical Hodgkin’s lymphomas the malignant cells are referred to as L&H (lymphocytic and histiocytic) and most often display the B-cell antigens CD20 and CD79a.

II. Classical Hodgkin’s lymphoma (cHL)

- Nodular sclerosing (NS)
- Mixed cellularity (MC)
- Lymphocyte-rich (LR)
- Lymphocyte-depleted (LD)
- Not classified

Tumor cells of the classical Hodgkin’s lymphomas are referred to as Hodgkin and Reed-Sternberg cells (H-RS) and typically display CD30 and CD15 antigens. The histological subclassification within the cHL diagnosis is currently without therapeutic consequences.

Stage-adapted therapy allows long term cure in more than 80 percent of all patients. Hodgkin's lymphoma is one of the oncological diseases with the highest cure rates in adults.

2 Clinical Presentation

Patients frequently come to the physician and report of long-lasting, partially undulating lymphadenopathy which in most cases is painless. Fever sometimes under the form of Pel-Ebstein fever, night sweats, weight loss, or pruritus may occur as accompanying symptoms. Alcohol-induced pain is unusual (approx. 5%).

Changes in laboratory values, e.g. erythrocyte sedimentation rate or CRP increases, leukocytosis, eosinophilia, or lymphocytopenia are not characteristic of the disease. There is no specific laboratory parameter for Hodgkin's lymphoma which can be used for diagnostic or follow-up purposes.

3 Diagnosis

3.1 Diagnostics

The histological diagnosis should be based on the surgical extirpation of an entire suspicious lymph node. A fine-needle aspiration (cytology) is insufficient considering the low percentage of H-RS cells and the inability to evaluate the lymph node structure. As the diagnosis might present great difficulties to the pathologist, assessment by a reference pathologist is recommended. If "reactive alterations" have been initially diagnosed in spite of progressive clinical symptoms, another biopsy specimen should be taken.

As therapy of the Hodgkin's lymphoma strictly depends on the stage of the disease, a precise assessment of the initial stage (staging) is an absolute necessity, see Table 1.

Table 1: Diagnostics

Test	Comments
Case history	B symptoms • Fever • Night sweats (change of night clothes) • Unintentional weight loss (<10% of body weight within 6 months)
Physical examination	• Palpable lymph nodes • Hepatosplenomegaly
Laboratory analyses	• Complete blood cell count, including leukocyte count with differential • Erythrocyte sedimentation rate • LDH, GOT, GPT, AP, Gamma GT, uric acid, creatinine
Imaging	• Chest X-rays • CT scan of the neck (with contrast medium) • CT scan of the chest (with contrast medium) • CT scan of the abdomen (with contrast medium)
Bone-marrow puncture	• Aspirate (cytology) • Biopsy (histology)

A liver biopsy will be indicated only if diffusive liver involvement is suspected (e.g. unclear increase of AP activity), provided that such information would have an influence on the selection of therapy. An involvement will have to be assumed if focal lesions in the liver (CT and/or sonography) are diagnosed during the staging procedure.

An explorative laparotomy with splenectomy is no longer recommended [II, A].

Positron emission tomography (PET) is not recommended as part of the initial staging, since no data indicate an influence on therapy outcome. However, PET may be considered in the event of suspicious lymph nodes in CT scan if an involvement would have an influence on therapy selection. In this case it must be kept in mind that inflammatory lymph nodes are also associated with an increased uptake of FDG in PET scans, eventually requiring histological confirmation.

Further tests are required to identify patients who have an increased risk for acute and/or late toxicity, see Table 2.

Table 2: Pre-Therapeutic Toxicity Tests

Organ	Tests
Lungs	• Lung function
Heart	• Electrocardiography • Cardiac echography
Fertility	• Consultation in reproductive medicine

3.2 Staging - Classification

Staging is performed according to the modified Ann Arbor Classification, see Table 3.

Table 3: Staging according to Ann Arbor Classification

Stage I	Involvement of a single lymph node region (I,N) or involvement of a single or localized extranodal site (I,E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm or involvement of an extranodal site or organ and one or more lymph node regions on the same side of the diaphragm
Stadium III	Involvement of two or more lymph regions and/or organs outside the lymphatic system on both sides of the diaphragm
Stadium IV	Non-localized, diffuse or disseminated involvement of one or several extralymphatic organs with or without involvement of lymphatic tissues.
Addendum A	No B symptoms
Addendum B	Presence of B symptoms

Lymphatic tissue: lymph nodes, spleen, thymus, Waldeyer’s tonsillar ring, appendix, Peyer’s glands.

B symptoms:

Fever of unknown origin > 38^{o}C

Night sweats of unknown origin (change of night clothes)

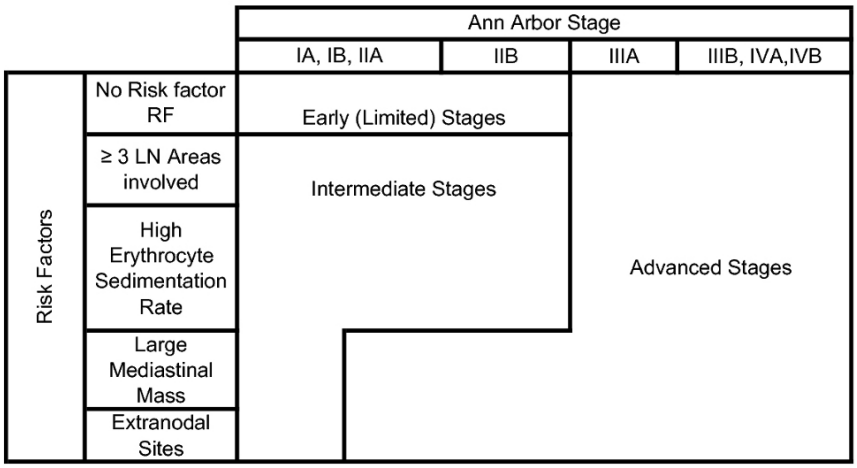
Unintentional weight loss of more than 10% of the body weight within a period of six months

3.3 Risk Groups (“Stages”)

Treatment stratification based on staging and risk factors is used by all international study groups [II-III, A]. Increasingly, the various European study groups (GHSG, EORTC,) are using similar approaches in recent years, so that only few differences exist by now. Studies by the

German Hodgkin's Study Group (GHSG) are based on the following classification which has proved successful in the practice, see Figure 1.

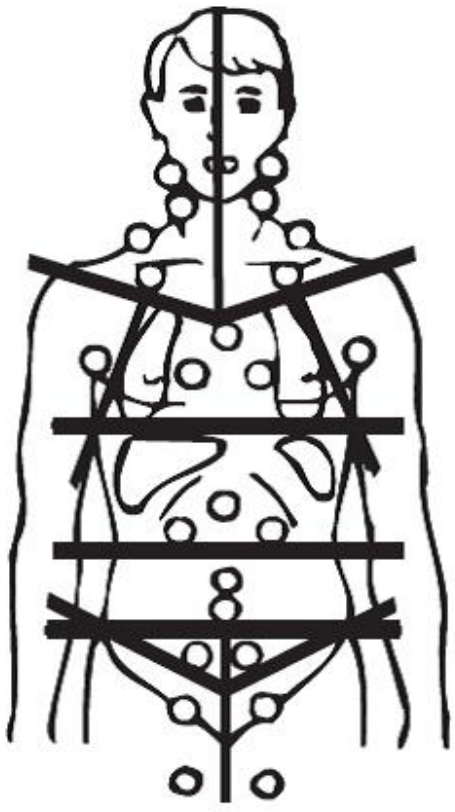
Figure 1: Risk Groups – Classification of the German Hodgkin Study Group (GHSG)



3.4 Risk Factors (acc. to GHSG)

- Involvement of 3 or more lymph-node regions (see Figure 1)
- High erythrocyte sedimentation rate (within the first hour: ≥50mm in the absence of B symptoms, ≥30mm in the presence of B symptoms)
- Large mediastinal mass (≥1/3 of the maximal chest diameter in conventional chest X-rays)
- Extranodal site

Figure 2: Lymph-Node Areas



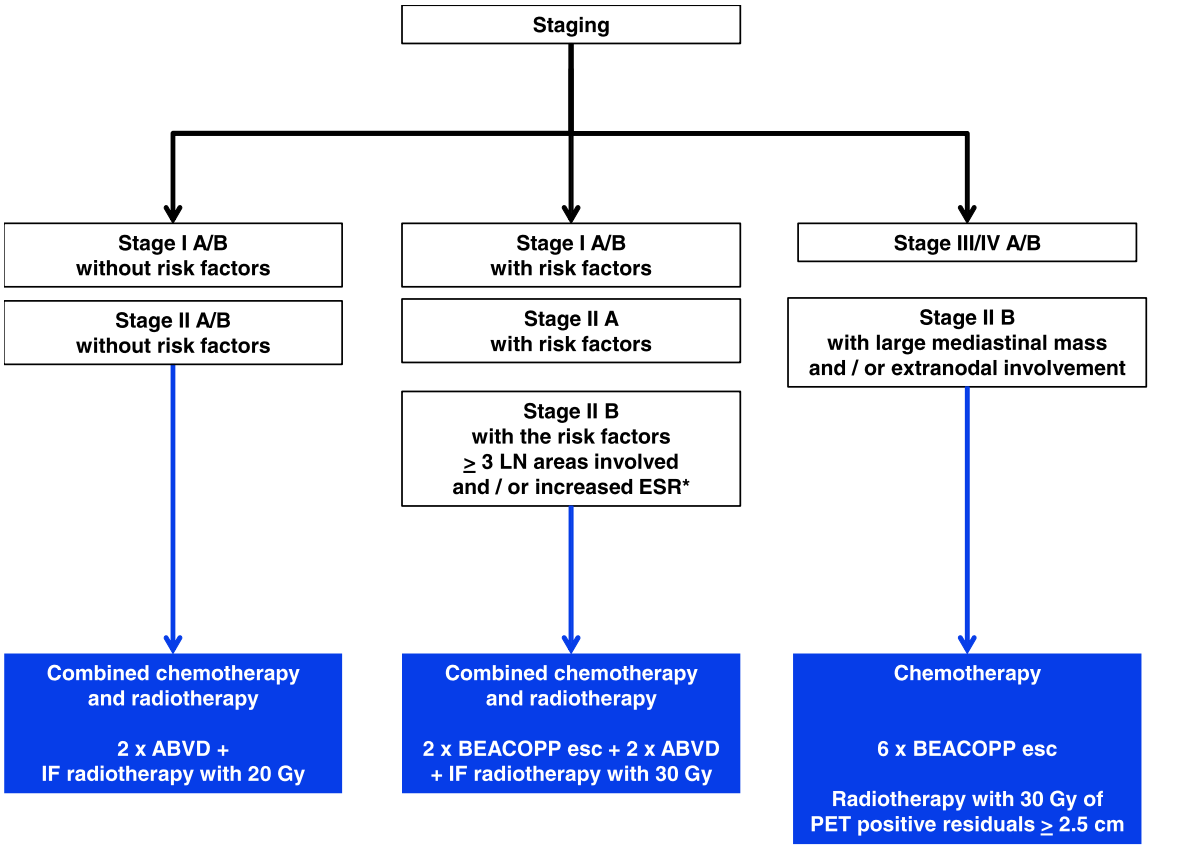
3.5 Diagnosis

Differential diagnostics include all inflammatory lymph-node enlargements of bacterial or viral etiology (e.g. tuberculosis, toxoplasmosis, Epstein-Barr virus, cytomegalovirus, HIV). In addition, other malignant lymphomas, lymph-node metastases of solid tumors, thymomas, germinal cell tumors, or sarcoidosis must also be either included or excluded in the process of differential diagnostic considerations.

4 Therapy

Whenever possible, patients with Hodgkin's lymphoma should be treated within clinical trials. Therapy should be started immediately after staging has been completed. As therapy is almost always performed in curative intent at the time of initial diagnosis, dose reduction should only be considered in case of strong indications. A primarily palliative strategy may be considered for extremely comorbid patients only. An algorithm for the therapy of patients aged between 18 and 60 years outside of clinical studies is shown in Figure 3.

Figure 3: Algorithm for Stage-Adapted First-Line Therapy in Patients Aged 18 to 60 Years (Outside of Clinical Trials)



Legend:

*Palliative therapy approach; Curative therapy approach; * ESR – Erythrocyte Sedimentation Rate*

Infertility, hypothyroidism, and coronary heart disease are observed as long-term sequelae of chemotherapy and radiotherapy. In addition, there is an increased risk for secondary malignancies (AML/MDS, NHL, solid tumors). This risk persists life-long and depends on the cumulative dose and the selection of cytostatic agents as well as dose and field size of radiotherapy.

4.1 Early Stages

The standard therapy for early stages is a combination therapy consisting of a short chemotherapy followed by involved-field radiotherapy (IF-RT). This combination is superior to radiotherapy or chemotherapy only for the control of tumor growth. Standard chemotherapy consists of two cycles of the ABVD regime. Standard dose of radiotherapy is 20Gy [I, A].

At present, the contribution of the single cytostatic agents within the ABVD regime is being reviewed by the GHSG in a clinical trial. Thus far, two of the four therapy arms (ABV and AV) have been prematurely closed because of an increased rate of events.

The question whether radiation therapy is indispensable in all patients, is currently under investigation in clinical trials such as the HD16 Study of the GHSG, see chapter 8.

4.2 Intermediate Stages

Standard therapy for intermediate stages is a combination therapy consisting of chemotherapy followed by involved-field radiotherapy (IF-RT). The most widely accepted standard therapy consists of four cycles ABVD followed by 30Gy IF-RT [I, A]. However, the final evaluation of the GHSG HD-14 Study demonstrated an improvement of tumor control (PFS after 5 years) from 89.1% to 95.4% when two cycles of BEACOPPescalated were, followed by two cycles of ABVD (2+2) and 30Gy IF-RT. The moderately increased toxicity of the BEACOPPescalated arm did not result in an increased mortality rate. Neither was fertility decreased in the “2+2” regime (2x BEACOPPescalated + 2x ABVD) as compared to 4x ABVD, nor was the rate of secondary hematological neoplasias increased. The benefit of the “2+2” regime is seen in all intermediate stage risk groups. Overall survival rates were not improved due to effective salvage treatment. Therapy with 4x ABVD is an acceptable alternative for patients who either are not eligible for BEACOPPescalated therapy due to limiting comorbidity or who refuse to undergo therapy with BEACOPPescalated.

The GHSG HD11 Study investigated the potential reduction of radiation dose from 30Gy to 20Gy after 4 cycles of ABVD. The final evaluation revealed a decrease of FFTF (-4.7% after 5 years), so that even inferiority cannot be excluded. After four cycles of ABVD radiation with 30Gy IF should therefore be applied. The question whether the size of radiation fields could be further decreased (involved-node RT), is currently being investigated by clinical trials (HD17 Study of the GHSG).

4.3 Advanced Stages

Standard therapy in advanced stages consists of intensive chemotherapy with BEACOPPescalated. [I, A]. As compared to ABVD this regimen results in a distinct improvement of tumor control. The HD15 Study of the GHSG showed that just six cycles of BEACOPPescalated are less toxic but more effective than the previous standard consisting of eight cycles BEACOPPescalated (FFTF 89.3% vs. 84.4%; OS 95.3% vs. 91.9%).

Bauer et al. conducted a systematic review for comparison between ABVD and BEACOPPescalated. A total of 2,868 HL patients in intermediate or advances stages from four randomized studies were evaluated. All studies compared BEACOPPescalated to ABVD or its variants. As far as PFS was concerned, a significant benefit of BEACOPPescalated could be demonstrated, more pronounced in advanced stages than in intermediate stages (hazard ratio at 0.53 with a number-needed-to-treat (NNT) of 7). The same also applied to the rate of complete remissions, however, not to overall survival. There were more toxicities and more secondary leukemias under BEACOPPescalated than under ABVD. However, no significant differences were seen in the total number of secondary neoplasias and in therapy-associated mortality. The authors concluded

that a better tumor control could be achieved with BEACOPPescalated. A longer follow-up is needed to assess the impact on overall survival.

The concept of ABVD induction and PET-guided therapy adaptation is also being examined in clinical trials. The HD15 Study of the GHSG further investigated whether radiation could be limited to patients with residual PET-positive lymphomas of ≥2.5cm after chemotherapy. It showed that patients with PET-negative residual lymphomas ≥ 2.5cm, even without additional radiotherapy, had a prognosis identical to those who had a CR/Cru after completion of chemotherapy. The negative predictive value (NPV) of PET in this situation is 94%. Whether this also holds true subsequent to an ABVD-based strategy still remains uncertain.

Patients with PET-positive residual lymphomas should receive a local radiation therapy with a dose of 30Gy. On account of the good prognosis of these patients (PFS after 4 years: 86.2%) an intensification of therapy, for example, by means of high-dose therapy is not justified. The question whether PET scans conducted at an early stage in the course of therapy could lead to a significant reduction of chemotherapy is currently under investigation in clinical trials (HD18 Study of the GHSG).

4.4 Patients >60 Years

Patients above the age of 60 years should not be treated with BEACOPPescalated because of its increased toxicity. It is recommended to treat these patients stage-adapted with 2, 4 or 6-8 cycles of ABVD [I-II, A].

Alternatively, 6-8 cycles of PVAG can be applied in intermediate or advanced stages in the event of contraindications for single componentsof the ABVD regime.

Patients in early or intermediate stages should receive radiation with 30Gy IF-RT, whereas patients in advanced stages should undergo a local radiation of residual lymphomas ≥1.5cm.

4.5 NLPHL

Stage IA patients without risk factors have an excellent prognosis. These patients require IF radiation therapy with 30Gy, only [III, A].

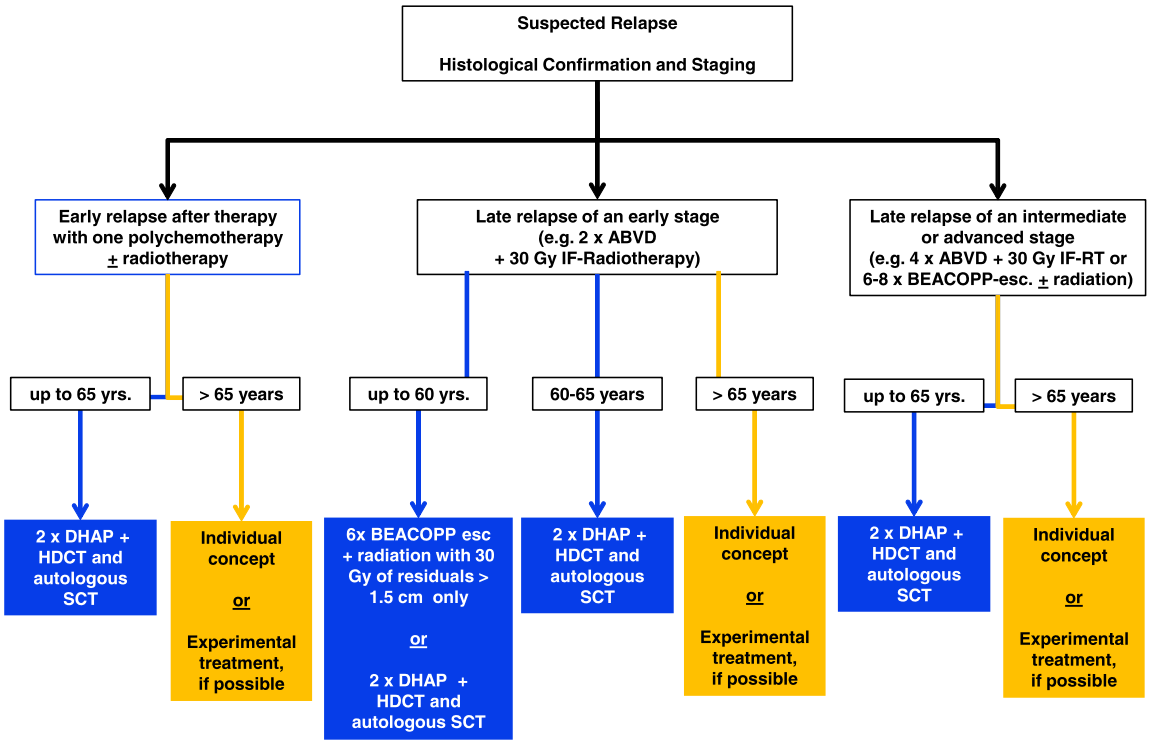
Patients with more extensive disease should be treated stage-adapted, in analogy to the therapy recommendations that apply to cHL.

Due to the expression of CD20 the application of an anti-CD20 antibody (off-label use) is an option for relapsed patients, in addition to the recommendations for cHL [III, B].

4.6 Relapses

In general, patients with an early relapse (3-12 months after termination of primary therapy) are distinguished from those with late relapse (>12 months after termination of primary therapy). The prognosis in patients with an early relapse is worse than in those with late relapse. Figure 4 shows an algorithm for patients treated in first relapse outside of clinical trials.

Figure 4: Treatment Algorithm for First Relapse (Outside of Clinical Trials)



Legend:

Palliative therapy approach; Curative therapy approach;

Re-induction therapy followed by high-dose chemotherapy with subsequent autologous stem cell transplantation is the treatment of choice for most patients in first relapse [I, A]. This concept is superior to a single conventional chemotherapy as far as relapse-free survival is concerned.

Chemotherapy regimens such as DHAP or IGEV can be used for re-induction and stem cell mobilization. The efficacy of other chemotherapy has only been poorly studied.

The final evaluation of the GHSG HD-R2 Study demonstrated that two cycles of DHAP followed by HDCT/APBSCT constitute the standard. A further intensification of induction therapy prior to HDCT did not improve the outcome.

An intensified conventional chemotherapy, for example, with six cycles of BEACOPPescalated [IV, B] might be taken into consideration for a small subgroup (first-line therapy with two cycles ABVD plus IF-RT, late relapse).

Radiation therapy only may be considered for patients with localized relapse, no B symptoms or anemia and relapse outside the initial radiation field [IV, B].

No standard has been defined for patients with relapse after HDCT/APBSCT. Choice of therapy selection should take into account the general condition of the patient, previous therapies, and comorbidity.

In 2011, the antibody-drug-conjugate (ADC) brentuximab vedotin was authorized in the United States for relapse therapy subsequent to autologous stem-cell therapy. Marketing authorization in Europe is expected in 2012.

Allogeneic stem cell transplantation is not a standard therapy for HL patients with relapse after APBSCT. However, it may be taken into consideration in young patients who are sensitive to chemotherapy and are in good general health [II-III, B]. This therapy should be performed within clinical trials. An important requisite is a very good (ideally a complete) remission prior

to the start of conditioning. Reduced intensity conditioning (RIC-allo) markedly decreased transplantation-associated mortality, however, relapse rates continue to be high.

A second high-dose chemotherapy followed by APBSCT may be considered for patients with a late relapse after APBSCT [IV, B].

Therapeutic options in palliative concepts include local radiation therapy, monotherapy with gemcitabine (off-label use), vinblastine, vinorelbine (off-label use), low-dose etoposide either alone or in combination with steroids.

At present, the efficacy of monoclonal antibodies, immunotoxins, histone deacetylase inhibitors (HDAC), or immune modulators (e.g. lenalidomide) are tested in phase I/II trials.

5 Monitoring

Monitoring of therapy response should be performed after the first half of chemotherapy has been completed, and after the termination of all therapeutic measures. In early stage disease monitoring should be performed after two cycles of chemotherapy. Mandatory elements of monitoring are the physical examination, laboratory analysis, and CT scans. Objective is the identification of patients who fail to respond to chemotherapy.

After termination of therapy, a pathologically increased uptake of FDG in PET scans may reveal persistent lymphoma, however, false-positive results have to be excluded (e.g. sequelae of radiation therapy, inflammatory or autoimmune diseases). In unclear situations, histological confirmation may be required.

6 Long Term Follow-up

In addition to the identification of relapse, long term follow-up has the purpose of detecting late toxicity or secondary neoplasias.

In the first year follow-up examinations should take place every three months, every six months until the fourth year, and later on annually.

Follow-up procedures routinely include a physical examination and analyses of laboratory parameters (complete blood cell count, including leukocyte count with differential, erythrocyte sedimentation rate, clinical chemistry). In addition, monitoring of thyroid gland function, particularly after radiation exposure of the cervical lymph node region, should be done in regular intervals (1, 2 and 5 years after therapy). CT scans should be performed about three months after termination of therapy only in patients who are not in complete remission (CRu, PR, SD). Further CT scans should be done only in patients with clinical symptoms suspicious of relapse. In most cases relapses will be noticed by the patients themselves. The diagnosis of a relapse will require histological confirmation.

It is recommended to interrogate patients specifically about symptoms of late-onset toxicity, especially as far as the heart and the lungs are concerned. Patients should be particularly informed about the benefits of non-smoking. Smoking tobacco significantly adds to the risks of late-onset toxicities of chemo-radiation therapy. Patients with lipid metabolism disorders should also be closely surveyed as they have a distinctly increased cardiovascular risk. Patients should participate regularly in cancer screening programs. The benefit of the routine use of PET scans in follow-up is still uncertain and is therefore not recommended.

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10 Active Studies

www.ghsg.org/studien

15 Links

Malignant Lymphoma Competence Network
www.kompetenznetz-leukaemie.de

Deutsche Leukämie – und Lymphom – Hilfe e. V.
www.leukaemie-hilfe.de

German Hodgkin Study Group
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17 Disclosures

according to the rules of the responsible Medical Societies.