Lymphomas

76

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76.1 Principle Considerations

The role of surgery in the treatment of children with lymphomas (Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) is limited to diagnostic biopsies and treatment complications. There are no indications for performing major tumour resections or debulking procedures, since chemotherapy is so effective and major surgery delays may complicate chemotherapy. Only in children with ileocecal intussusceptions due to Burkitt's lymphoma complete resection of the involved bowel segment is advised. Second-look surgery is also generally not recommended. Particularly, children with NHL may have rapidly growing tumors that can cause life-threatening complications requiring prompt intervention and treatment. Thus, a rapid diagnosis with the least invasive procedure should be done. In case of suspected lymphoma other options to establish the diagnosis before surgery should be considered like examination of blood and bone marrow and in case of pleural effusion/ascites puncture with cytologic and immunophenotypic examination. If the diagnosis with these simple measures cannot be established the most peripheral suspected lesion should be biopsied, e.g. in case of mediastinal tumor the nearest extrathoracic lymph node. The optimal way is that the surgeon, the pediatric oncologist and the pathologist cooperate in planning the biopsy, so that the biopsy material can be taken over by the pathologist already in the operation room for further appropriate processing.

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76.2 Non-Hodgkin Lymphoma (NHL)

76.2.1 Classification and Pathology

Early classification systems in use have been confusing for clinicians and also led to disagreement even between expert pathologists, since non-Hodgkin lymphoma (NHL) is a heterogenous collection of diseases and their description was solely on cytomorphologic features. Immunophenotyping, cytogenetic and molecular studies now allow for a more precise classification according to the lineage of the malignant cells (WHO and REAL classification).

In contrast to the wide diversity of adulthood NHL, childhood NHL can mainly be divided among four major subgroups: Burkitt and Burkitt-like-lymphomas, diffuse large B-cell-lymphomas, anaplastic large cell lymphomas and lymphoblastic precursor T- and B-cell-lymphomas. The malignant cells in childhood NHLs appear to arise from different lymphocyte precursors at various stages of maturation or from mature lymphocytes. Approximately 40–50% of childhood NHL are either from T-cell lineage or from mature B-cells expressing surface immunoglobulin, whereas fewer than 10% are of early B-cell origin lacking surface immunoglobulin (Table 76.1).

Table 76.1 Correlation of histopathology, immunophenotype, clinical features, cytogenetic and molecular features in childhood non-Hodgkin lymphoma*

Histology	Immunology	Clinical features	Cytogenetics	Genes involved
Burkitt and Burkitt-like	B cell (slg^+)	Abdominal masses, gastrointestinal tract tumors, involvement of Waldeyer's ring	t(8;14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q24;q11)	lgH-c*MYC* lgκ-c*MYC* lgλ-c*MYC*
Diffuse large B-cell (DLBCL)	B cells of germinal center or post germinal center	Abdominal masses, gastrointestinal tract tumors, involvement of Waldeyer's ring	t(8;14)(q24;q32) t(2;17)(p23;q23)	lgH-c*MYC* *CLTC-ALK*
Mediastinal large B-cell	B cells of medullary thymus	Mediastinum		
Anaplastic large cell (ALCL)	T cell (mostly), null cell or NK cell ($CD30^+$)	Skin, nodes, bone	t(2;5)(p23;q35) t(1;2)(q21;p23) t(2;3)(p23;q21) t(2,17)(p23;q23) t(X;2)(q11–12;p23) inv 2 (p23;q35)	*NPM-ALK* *TPM3-ALK* *TFG-ALK* *CLTC-ALK* *MSN-ALK* *ATIC-ALK*
Precursor T lymphoblastic (pT-LBL)	T cell (thymocyte phenotype)	Anterior mediastinal mass with upper torso adenopathy	t(1;14)(p32;q11) t(11;14)(p13;q11) t(11;14)(p15;q11) t(10;14)(q24;q11) t(7;19)(q35;p13) t(8;14)(q24;q11) t(1;7)(p34;q34)	TCRάδ-*TAL1* TCRάδ-*RHOMB2* TCRάδ-*RHOMB1* TCRάδ-*HOX11* TCRβ-*LYL1* TCRάδ-*MYC* TCRάδ-*MYC* TCRβ-*LCK*
Precursor B lymphoblastic (pB-LBL)	B-cell precursors	Cutaneous masses and isolated lymph node masses		

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76.2.2 Clinical Features

The various subgroups of childhood NHLs have different clinical behaviour and are also characterised by the occurrence in different parts of the body (Table 76.1).

Most frequent involved sites are mediastinum (mainly lymphoblastic precursor T-NHL), abdomen (mainly Burkitt and Burkitt-like lymphoma) (Fig. 76.1) and cervical lymph nodes (mainly lymphoblastic precursor B-NHL). Less frequent sites are Waldeyer's ring, skin or bone and rarely the CNS (Fig. 76.2). Even though patients may appear to have local disease, there is often submicroscopic dissemination in certain histologic subtypes to the bone marrow and the CNS and some patients, particularly with Burkitt's disease or mediastinal T-NHL may have a rapid and aggressive course

76.2.3 Diagnostic Work Up and Staging

To establish the diagnosis of suspected NHL in children, the least invasive procedure should be preferred so that the risk of general anesthesia may be avoided. Before surgery is considered examination of blood and bone marrow and in case of pleural effusion/ascites puncture (preferably under local anesthesia) with cytologic and immunophenotypic analysis should be done.

Only if the diagnosis cannot be established with these simple methods a diagnostic biopsy should be performed. Complete resection should be done only, if possible and without any risk or functional loss for the patient. These principles are particularly important in patients with high tumor burdens, resulting in significant respiratory distress, vena cava compression, pericardial tamponade and metabolic disturbances (Fig. 76.3). Particularly in certain patients with mediastinal NHL and significant airway narrowing all diagnostic and especially invasive diagnostic procedures should be postponed after a prediagnostic cytoreductive therapy with prednisone up to 48 h until clinical stabilisation. Under no circumstances should a critically large mediastinal tumor with clinical symptoms of respiratory distress be treated surgically. Caution should be also given to the tumor lysis syndrome in patients with high tumor burdens even before the start of cytoreductive treatment.

Further staging evaluation must be done quickly since most children with NHL have rapidly growing tumors that may cause life-threatening situations. It includes physical examination, complete blood count, bone marrow and spinal fluid aspiration, analysis of electrolytes, LDH, renal and liver function tests and imaging with X-ray, ultrasonography, magnetic resonance, computerized tomography and skeletal scintigraphy.

The most widely used clinical staging system was developed at the St. Jude Children's Research Hospital in Memphis, USA (Table 76.2).

For patients with Burkitt-NHL, the St. Jude staging system has been adapted by the French Society of Pediatric Oncology (SFOP) to a system which stratifies the patients to different treatment arms tailored to their risk and cumulative tumor burden (Table 76.3).

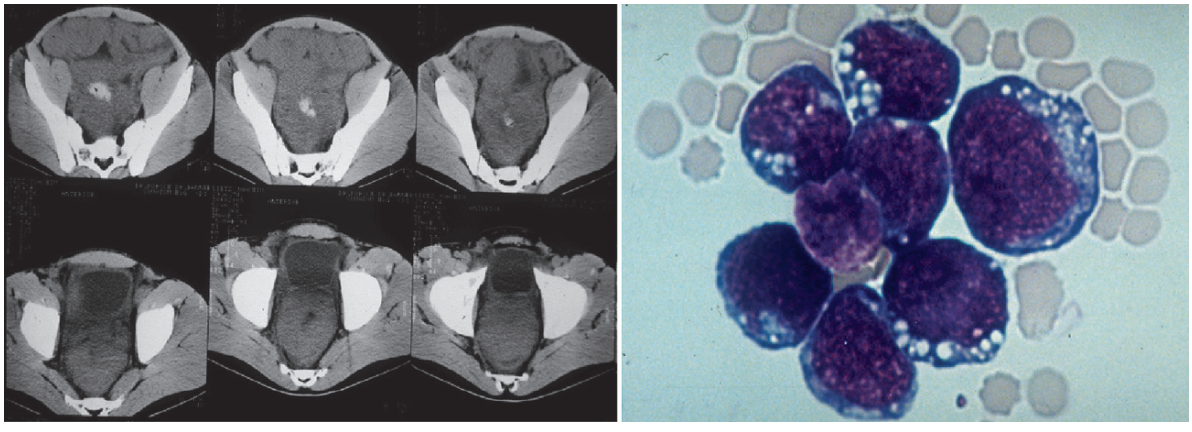


Fig. 76.1 Five year old boy, who had clinical examination because of abdominal pain and distention. Ultrasonography and MRI showed massive thickening of the bowel walls with some small areas of ascites between. Fine needle aspiration showed typical L-3 lymphoblasts with intensively basophilic cytoplasm and distinctive cytoplasmic vacuoles. Immunophenotyping and molecular studies confirmed the diagnosis of Burkitt lymphoma

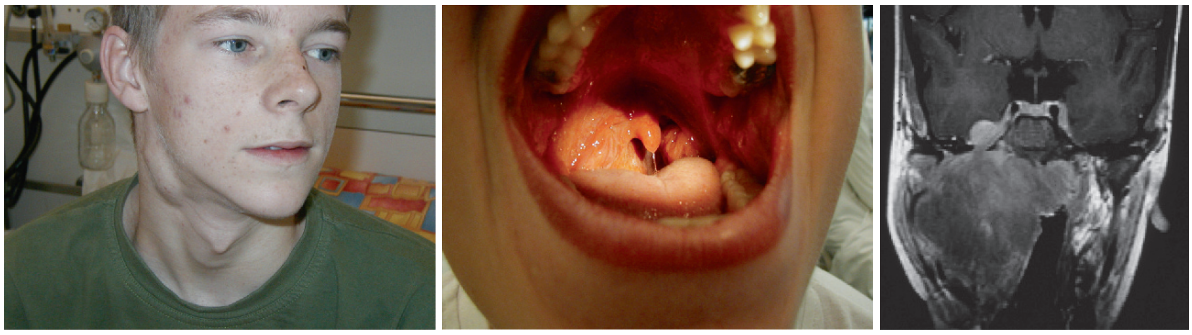
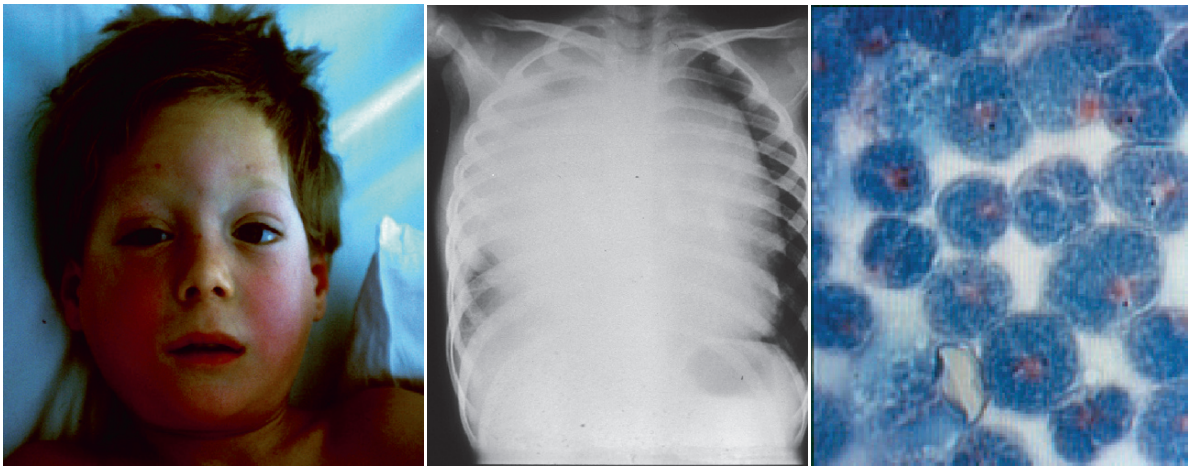


Fig. 76.2 Fifteen year old boy, complaining about difficulties in swallowing. Physical examination revealed right cervical lymphadenopathy with massive involvement of the Waldeyer's ring. MRI showed that the tumor mass infiltrated through the base of the skull with involvement of the CNS. Since CNS fluid and bone marrow aspiration were non-diagnostic, biopsy of the cervical lymph node under local anesthesia was done, demonstrating diffuse large B cell lymphoma



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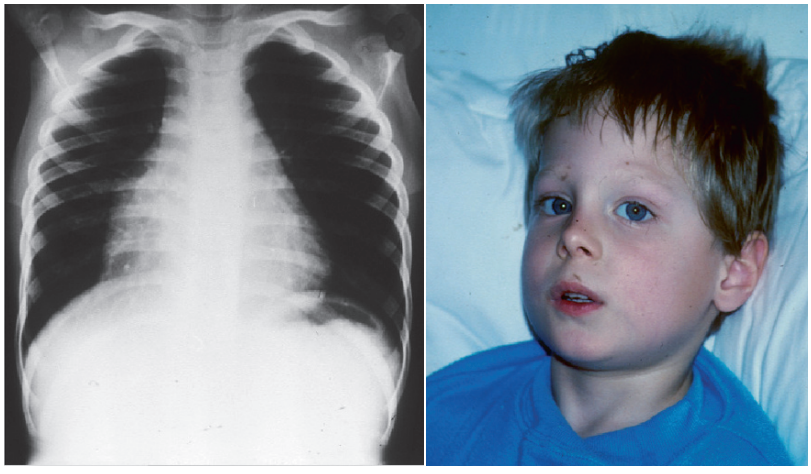

day 8

Fig. 76.3 Four year old boy with swelling and plethora of the face, cervical lymphadenopathy and respiratory distress in lying position. Chest X-ray showed a huge mediastinal tumor with pleural effusion on the right side. Pleural fluid aspiration in upright position with a thin needle using local anesthesia revealed convoluted lymphoblasts of T-cell type, positively stained with the acid phosphatase reaction and confirmed by immunophenotyping. After initiation of prednisolone there was a rapid tumor response with regression of the existing superior vena cava syndrome. Further treatment with a T-NHL/ALL-polychemotherapy protocol led to a complete and permanent remission

Table 76.2 St. Jude Children's Research Hospital staging system for non-Hodgkin lymphoma (Murphy et al. 1980)

Stage I
A single tumor (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen
Stage II
A single tumor (extranodal) with regional node involvement
Two or more nodal areas on the same side of the diaphragm
Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm
A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected
Stage III
Two single tumors (extranodal) on opposite sides of the diaphragm
Two or more nodal areas above and below the diaphragm
All primary intrathoracic tumors (mediastina, pleural, thymic)
All extensive primary intraabdominal disease
All paraspinal or epidural tumors, regardless of other tumor site(s)
Stage IV
Any of the above with initial CNS and/or bone marrow involvement

Table 76.3 Risk stratification of B-cell non-Hodgkin lymphomas (SFOP) (Patte et al. 2001)

Group	Extent of Tumor
A	Resected stage I and abdominal stage II
B	Unresected stage I, non abdominal stage II, any stage III or IV, B-ALL-CNS negative (with < 70% blasts in BM)
C	CNS involvement or B-ALL with at least 70% blasts in the bone marrow

SFOP, French Society of Pediatric Oncology.

The stratification system utilizes the clinical stage assigned according to the St. Jude staging system.

Table 76.4 Staging system according to different risk groups in B-cell non- Hodgkin lymphomas used by the BFM- group (Seidemann et al. 2001)

Risk group 1:	Initial complete resection of the lymphoma manifestation
Risk group 2:	No or incomplete resection of lymphoma manifestation and one of the following criteria: only extraabdominal sites or abdominal sites and LDH less than 500 U/L
Risk group 3:	No or incomplete resection of abdominal lymphoma and LDH > 500 U/L, all patients with bone marrow involvement or/and CNS disease, or/and multifocal bone involvement

A similar staging system according to the different risk groups in Burkitt-NHL patients is being used by the BFM group (Table 76.4).

76.2.4 Treatment and Results

Nowadays clinical trials are available for all childhood NHL-types and participation in these studies is strongly recommended which guarantees treatment by an experienced multidisciplinary team of specialists. Chemotherapy is the mainstay of treatment. It is the same in lymphoblastic NHL of precursor B- and T-lineage as in precursor B- and T-ALL as the distinction between lymphoblastic NHL and ALL is largely arbitrary and simply based on the percentage of blasts in the bone marrow aspirate. CNS therapy is included in these regimes particularly for children with lymphoblastic and Burkitt-NHL, whereas the addition of radiotherapy does not have any benefit on survival except in rare cases (e.g. oncologic emergency).

Patients with diffuse large B-cell lymphomas (DLBCL), mediastinal large B-cell lymphomas and anaplastic large cell lymphomas (ALCL) are mainly treated on protocols either designed for Burkitt lymphoma or similar protocols with similarly good results. Overall more than 75% of children with NHL can be now cured with modern intensive polychemotherapy protocols and due to advances in supportive care to reduce the life-threatening complications of NHL and of therapy.

76.3 Hodgkin Lymphoma (HL)

76.3.1 Classification and Pathology

Two major subtypes of HL are differentiated according to the WHO classification:

Nodular lymphocyte predominant Hodgkin lymphoma (NLP HL) and classical Hodgkin lymphoma (cHL) subdivided in four histologic categories:

Lymphocyte-rich
Nodular sclerosis
Mixed cellularity
Lymphocyte depleted

In the cHL subtypes multinucleated Reed-Sternberg cells and their mononucleated variant Hodgkin cells are characteristic findings, expressing CD 30 antigen. Molecular studies have shown HL to be of B-cell origin. Only 0, 1–10% of the total cell population in HL are malignant cells, whereas the majority of the tumor consists of inflammatory cells (histiocytes, plasma

cells, eosinophils, lymphocytes, neutrophils etc.) and fibrosis. This peculiar histologic pattern has been attributed to the secretion of different cytokines by the tumor.

76.3.2 Clinical Features

Most patients present with painless cervical or supraclavicular enlarged lymph nodes which feel rubbery and firm at palpation. Differential diagnosis should include inflammatory conditions, especially with indolent course like atypical mycobacteriosis and toxoplasmosis, but also NHL, metastatic solid tumors (e.g. soft tissue sarcoma, neuroblastoma, nasopharyngeal carcinoma), histiocytoses and benign malformations. More than 60% of the patients with HL have also mediastinal involvement, sometimes causing symptoms of bronchial compression or superior vena cava syndrome (Fig. 76.4). Axillary or inguinal lymphadenopathy is less frequent at initial presentation. Unexplained fever, weight loss of more than 10% within last 6 months and night sweats are considered as "B"-symptoms. Pruritus is another systemic symptom, sometimes leading to enormous scratching (Fig. 76.4).

76.3.3 Diagnostic Work Up and Staging

After diagnosis has been established by excisional biopsy, careful assessment of all lymph node regions by clinical examination and ultrasonography is essential. In addition complete blood count, analysis of electrolytes, LDH, renal and hepatic function tests should be done. The erythrocyte sedimentation rate, serum

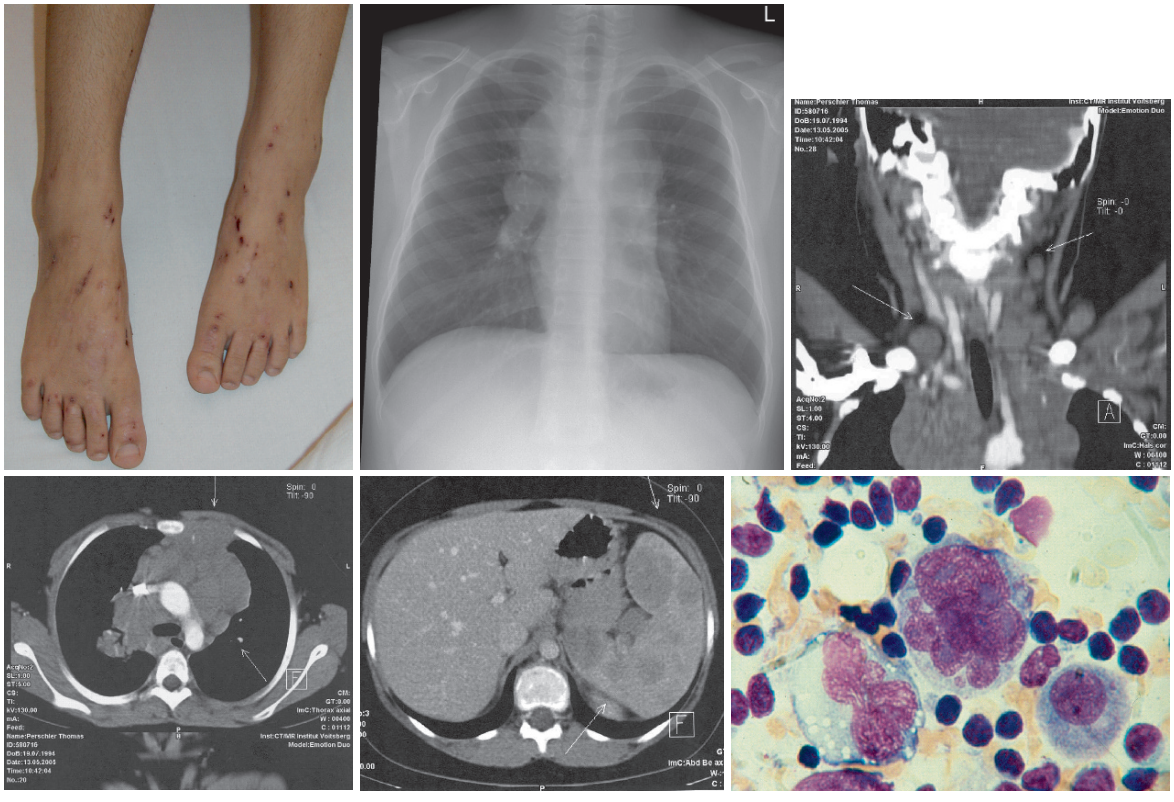

Fig. 76.4 The 12 year old boy had extensive dermatologic work-up because of itching and scratching. Chest X-ray revealed polycyclic bilateral enlargement of hilar lymph nodes. CT showed left cervical and right supraclavicular lymph node enlargement, a bulky mediastinal mass with anterior chest wall infiltration and a single left lung nodule as well as splenic involvement. Touch preparation smear of the excised supraclavicular lymph node showed typical Reed-Sternberg and Hodgkin cells

copper and ferritin may be elevated as well as C-reactive protein, which can be used in follow-up evaluation. CT of the chest provides further information about the mediastinal lymph nodes as well as lungs, chest wall and pericardium. To evaluate the abdominal and pelvic lymph nodes and for diagnosis of splenic and hepatic involvement MRI may provide better information in children with the advantage of no radiation side effects. Positron emission tomography (PET) is being used as a promising new diagnostic tool for staging HL in adults; however prospective trials evaluating PET in pediatric HL are still awaiting. Since HL spreads along contiguous lymph nodes staging is based on the natural course of the disease (Table 76.5). Substage classification A means "asymptomatic" disease, substage B fever, night sweats and weight loss of more than 10% over the last 6 months and substage E extralymphatic disease. Bone marrow aspiration with biopsy should be reserved for patients with clinical stage III or IV or patients with B-symptoms, technetium-99 bone scan for patients with suspected skeletal metastases.

In the era when HL patients were only treated and cured with mainly radiotherapy, it was important to detect also minimal disease, so that exploratory laparatomy and splenectomy was the recommended staging procedure. Today, the success of diverse non-cross-resistant chemotherapy cycles in conjunction with the refinement in diagnostic imaging led to the abandonment of surgical staging. Laparotomy or better laparoscopic surgery is now reserved for females, who need transposition of the ovaries outside the irradiation field in case of pelvic irradiation.

Table 76.5 Staging classification for Hodgkin lymphoma (Carbone et al. 1971)

Stage I	Involvement of a single lymph node (I) or of a single extralymphatic organ or site (I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (II_E)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (III_S) or by localized involvement of an extralymphatic organ or site(III_E) or both (III_{SE})
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement

76.3.4 Treatment and Results

Radiotherapy still is a fundamental part of current treatment protocols, however due to improvement of non-cross-resistant multiagent chemotherapy now can be reduced in dose and field. Chemotherapy mostly are derivates from the MOPP combination designed by Devita and ABVD regimen developed by Bonadonna given in alternating cycles according to the stage of disease. In some patients with favourable clinical presentation in early stage it is now investigated if the administration of risk-adapted multiagent chemotherapy alone can completely avoid involved – field radiation with the intention of sparing their late effects without impairing the results. Most current multicenter trials include central reviewing of all imaging studies by the study center in order to give a tailored risk-adapted treatment plan with precisely prescribed radiation fields and dosages in conjunction with the stage adapted chemotherapy. This has allowed not only for a more homogenous treatment stratification as well as comparison between the groups but also for further improvement of the already excellent treatment results in all treatment groups possibly also decreasing the acute and late side effects of treatment.

Further Reading

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