15. **Non-Hodgkin's Lymphoma (NHL)**

Introduction

In Sweden, 1 342 cases of non-Hodgkin's lymphoma's (NHL), excluding chronic lymphatic leukemia were diagnosed in 2000, corresponding to 3 per cent of all new malignant tumour diagnoses [9]. NHL is generally a disease of older adults and increases in incidence with advancing age and somewhat more than 50 per cent of the patients are above 70 years at diagnosis (from Cancer incidence in Sweden 1995–99).

NHL comprises a very heterogeneous group of tumours and the classification systems are in a continuous evolution. In the previous report (SBU-report 129/2, 1996) the Kiel classification was used. In 1994 the REAL classification (Revised European-American Classification of Lymphoid Neoplasms) was presented [27]. This classification considers not only morphological and biological observations but also immunological and genetic findings as well as clinical observations to identify specific disease. Recently a modification of the REAL classification, the WHO (World Health Organization) classification, has been introduced [28]. In the studies below with long follow-up periods older classification systems were used. However, in this report a clinical grouping in indolent and aggressive lymphomas[1] according to Hiddemann et al has been used [29].

Treatment strategies depend upon the subtype of the disease, localization and stage. The Cotswold[2] staging classification is widely used for staging of NHL.

In 1993 the International Non-Hodgkin's Lymphoma Prognostic Factors Project analyzed data on more than 2 000 patients from 16 institutions and presented the so-called International Prognostic Index (IPI)[3].

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[1] [2] [3] The footnotes are explained on the following pages.

Proposed Clinical Schema for Malignancies of the Lymphoid System:

B-Cell Lineage	T-Cell Lineage
I. Indolent lymphomas (low risk)	*I. Indolent lymphomas (low risk)*
Chronic lympocytic leukaemia/small lymphocytic lymphoma* Lympoplasmacytic lymphoma/immuno-cytoma**/Waldenstrom's macroglobulinemia Hairy cell leukaemia Splenic marginal zone lymphoma Marginal zone B-cell lymphoma – Extranodal (MALT-B-cell lymphoma) – Nodal (monocytoid) Follicle center lymphoma/follicular, (small cell)-grade I Follicle center lymphoma/follicular, (mixed small and large cell)-grade II	Large granular lymphocytic leukaemia, T and NK cell types*** Mycosis fungoides/Sézary syndrome Smoldering and chronic adult T-cell leukaemia/lymphoma (HTLV1**)***
II. Aggressive lymphomas (intermediate risk)	*II. Aggressive lymphomas (intermediate risk)*
Prolymphocytic leukaemia*** Plasmacytoma/multiple myeloma Mantle cell lymphoma Follicle center lymphoma/follicular, (large cell)-grade III Diffuse large B-cell lymphoma (includes immunoblastic & diffuse large & centroblastic lymphoma) Primary mediastinal (thymic)large B-cell lymphoma High-grade B-cell lymphoma, Burkitt-like***	Prolymphocytic leukaemia*** Peripheral T-cell lymphoma, unspecified*** Angioimmunoblastic lymphoma*** Angiocentric lymphoma*** Intestinal T-cell lymphoma*** Anaplastic large cell lymphoma (T- and null cell type)
III. Very aggressive lymphomas (high risk)	*III. Very aggressive lymphomas (high risk)*
Precursor B-lymphoblastic lymphoma/leukaemia Burkitt's lympoma/B-cell acute leukaemia Plasma cell leukaemia	Precursor B-lymphoblastic lymphoma/leukaemia Adult T-cell lymphoma/leukaemia
IV. Hodgkin's disease	

*   Includes B-CLL with plasmacellular differentiation (equivalent to lymhoplasma-cytoid lymphoma of the KIEL system).
** Note that the term was changed in the REAL clissification from lymphoplasmacytoid to lymphoplasmacytic lymphoma to avoid confusion with the Kiel term lympho-plasmacytoid which represents B-CLL with plasmacellular differentiation
*** Provisional clinical grouping

Stage I=   Involvement of single lymph node region or lymphoid structure
(eg. spleen, thymus, Waldeyer's ring).

Stage II=   Involvement of two or more lymph node regions on the same side of the
diaphragm (the mediastinum is a single site, hilar lymph nodes are lateralized).
The number of anatomical sites should be indicated by a suffix (eg, II$_3$).

Stage III= Involvement of lymph node regions or structures on both sides of the
diaphragm
III$_1$: with or without splenic hilar, coeliac, or portal nodes
III$_2$: with paraaortic, iliac, mesenteric nodes.

Stage IV= Involvement of extranodal site(s) beyond that designated "E"

A=   No symptoms.

B=   Fever, drenching sweats, weight loss.

X=   Bulky disease (>1/3 widening of mediastinum, >10 cm maximum dimension
of nodal mass).

E=   Involvement of extra lymphatic tissue, contiguous or proximal to know nodal site.
A single extralymphatic site as the only site of disease is classified IE.

3) The International Prognostic Index (IPI)

Patients of all ages	*Patients ≤60 years of age*
Age (≤60 years vs >60 years)	LDH (≤normal vs >normal)
LDH (≤normal vs >normal)	Performance status (0–1 vs 2–4)
Performance status (0–1 vs 2–4)	Stage (I/II vs III/IV)
Stage (I/II vs III/IV)	
Extranodal involvement (≤1 site vs >1 site)	

The number of IPI factors effectively predict prognosis and is now used
for almost all subtypes of NHL [64], but it is sparsely used in the
publications reviewed in this report.

Summary of the earlier report, SBU 129/2

The synthesis of the literature on radiotherapy for non-Hodgkin's lym-
phoma was based on 158 scientific articles, including 16 randomized studies,
18 prospective studies, and 90 retrospective studies. These studies involved
14 137 patients. The report covered the literature until 1993 and it also
included seven articles of later date.

Conclusions

- Non-Hodgkin's lymphomas are highly radiosensitive, and local recurrence following radiotherapy is unusual.

- Radiotherapy probably cures approximately 50 per cent of both low-grade and high-grade malignant NHL at stage I. Involved field treatment is apparently sufficient, however, higher doses are required for high-grade malignant lymphomas.

- Chemotherapy is recommended for stage II. Consolidation radiotherapy after chemotherapy may increase the number of complete remissions. The value of adjuvant radiotherapy has not been confirmed.

- Radiotherapy plays a limited role at stages III and IV.

- Radiotherapy is clearly indicated for extranodal localized disease in the skin and in the orbit.

- It is important to identify groups and subgroups in which radiotherapy alone is sufficient, i.e., the risk for distant recurrence is small. MALT lymphoma belongs to this group.

- Radiotherapy is often valuable in palliative situations.

Discussion

In stage I, limited radiotherapy leads to local control in over 90 per cent of the patients with both indolent and aggressive lymphomas, with a long-term survival of about 50 per cent. In indolent lymphomas no studies showed improved results with the addition of chemotherapy, while some studies suggested an extended relapse-free survival with the addition of chemotherapy in aggressive lymphomas. Combination chemotherapy was dominant for treatment of aggressive lymphomas of more advanced stages. Consolidation radiotherapy might increase the number of complete remissions but no effect on survival was proven. Consequently irradiation had little value in advanced stages. Radiotherapy had a well-documented place in certain extranodal lymphomas e.g., indolent orbital and localized thyroid lymphomas as well as for cutaneous lymphomas in special situations. Radiotherapy could also be an important tool in palliative situations.

Literature

The articles on which the conclusions in the SBU 129/2 report were based were classified and graded as follows (number of studies/number of patients).

	1 = High	2 = Moderate	3 = Low	Total
M	–	–	–	**–**
C	4/1 119	10/824	2/118	**16/2 061**
P	7/333	10/446	1/47	**18/826**
R	17/5 323	43/2 300	30/1 284	**90/8 907**
L	24/2 312	3	–	**27/2 312**
O	3/6	4/25	–	**7/31**
Total	**55/9 093**	**70/3 595**	**33//1 449**	**158/14 137**

Assessment of new literature

The present report deals separately with nodal and extranodal non-Hodgkin's lymphomas. New publications that confirm conclusions from previous report or give new information are included. Sections concerning total body irradiation in conjunction with high-dose chemotherapy and radioimmunotherapy have been added.

The assessment of literature covers the time period from 1994 to 2001, studies on children are not included. Literature search was performed in Medline with use of the search term "lymphoma, non-Hodgkin/radiotherapy" with limitation to meta-analysis, randomized controlled studies and prospective controlled studies. No meta-analysis were found and very few randomized studies, why prospective studies identified through a search in Medline have also been reviewed. However, even prospective studies are few and therefore reviews and some retrospective studies with essential information also have been included, identified through Medline and by scrutinizing reference lists. Furthermore, a few conference proceedings of recently closed but not published studies are included.

Reasons for exclusion of randomized trials

Glick 1995: Abstract 1995 and presented at ASCO, but no publication has followed.

Shchepotin 1996: Three-armed study with few patients and suboptimal radiotherapy and chemotherapy.

Overview of new studies

Nodal non-Hodgkin's lymphomas

Indolent non-Hodgkin's lymphomas

The indolent lymphomas (previously usually designated low-grade malignant) are quite rare before the age of 30, primarily affecting older patients in the sixth through eighth decades. These lymphomas often follow an indolent course with a long survival. Transformation to aggressive lymphoma frequently occurs and spontaneous regression, of longer or shorter duration may also occur. Most commonly they involve the lymph nodes and are usually of follicular subtype, but they also have a predilection for certain extranodal sites, particularly those associated with mucosa (see below).

Localized disease: stage I–II

Few patients with indolent lymphoma present with localized disease (10–20 per cent). Indolent lymphomas are very radiosensitive and radiotherapy has been the mainstay for patients with localized indolent lymphomas.

Radiotherapy alone

Long-term follow-up data i.e. ≥15 years after radiotherapy are now emerging in retrospective series. One study reports 33 per cent progression-free survival for patients in stage I at 15 years [55]. Another study reports 40 per cent relapse free survival at 15 years for patients in stage I and II with very few relapses 10 years after radiotherapy [43]. British National Lymphoma Investigation, BNLI, has performed a retrospective analysis on patients in stage I/I$_E$ and report a complete remission rate of 98 per cent after 35 Gy and a relapse rate at 10 years of 51 per cent with most of the recurrences occurring within five years [69]. From Florida a 49 per cent freedom from relapse at 20 years is reported for patients in stage I and II, the majority of relapses occurred within five years but some recurrences were seen between five and ten years [32].

Interestingly a report on 26 patients in complete remission after the surgical biopsy was not treated at all but only followed. After a median follow-up of 4.6 years 50 per cent of the patients had not relapsed and

7/13 recurrences were distant relapses [62]. However, patients with this presentation are very rare and no controlled randomized trial comparing radiotherapy with wait and see policy in this situation has been performed.

The optimal radiation dose for indolent lymphomas has not been determined in any prospective randomized study but since 1997 BNLI performs a randomized trial comparing 24 Gy with 40–45 Gy in stage I. A German prospective multicenter study recommends 36–44 Gy to involved lymph nodes [63]. In a retrospective analysis from Florida no local recurrences occurred after 30 Gy, suggesting that most indolent lymphomas are adequately treated with 30 Gy [32]. How the doses were specified was not given, so different modes of specifications may partly explain the different recommendations.

Involved field, IF, treatment is for the most part advocated and used but the definition of IF may vary somewhat among different centers.

Because most recurrences occur outside the irradiated area a German prospective multicenter study has used extended field (EF) mostly meaning mantle and paraaortic fields or even more comprehensive radiotherapy with total central lymphatic irradiation (TCL) meaning irradiation of Waldeyer's ring, mantle field and the whole abdomen for patients in stage I and II. The median follow-up was 68 months and the relapse rate at seven years was 26 per cent in stage I and 44 per cent in stage II [63]. Results of TCL to about 100 patients in limited stage III are published and one of these reports suggests a possible increase of second malignancies [16].

Two randomized trials were reported in previous report (SBU-report 129/2, 1996) which compared involved field with total nodal irradiation (TNI) and no difference in therapeutic results were found since then, no further controlled trials have been published.

Radiotherapy alone versus radiotherapy plus chemotherapy
Earlier randomized trials have failed to demonstrate that the addition of chemotherapy after radiotherapy is superior to radiation alone (SBU-report 129/2, 1996), which was confirmed in a randomized British trial starting in the mid-1970s, with a minimum of 11 year follow-up, showing that the addition of chemotherapy (chlorambucil) after radiotherapy gave no

benefit in outcome [33]. A later analysis of the same data but on some-what fewer patients report 15 years relapse-free survival of 55 per cent for patients in stage I and 29 per cent for patients in stage II and the local recurrence rate after radiotherapy was 2 per cent [17].

The literature shows that:

• One third to one half of patients with indolent lymphoma in stage I seem to be cured by radiotherapy (follow-up more than 15 years).

• The optimal dose is still not defined.

• There is no proof that extended radiotherapy is superior to involved field.

• There is no evidence that the addition of chemotherapy to radio-therapy will improve the overall outcome.

Indolent non-Hodgkin's lymphomas localized disease: stage I–II.

	1 = High	2 = Moderate	3 = Low	Total
C	–	–	2/148	**2/148**
P	–	1/100	1/26	**2/126**
R	1/208	2/249	2/61	**5/518**
Total	**1/208**	**3/349**	**5/235**	**9/792**

Advanced disease: stages III–IV

The majority of patients with indolent lymphomas present with advanced disease mainly due to bone marrow involvement. The optimal treatment strategy is still controversial. Radiotherapy plays a very limited role in advanced stages as concluded in the previous report (SBU-report 129/2, 1996). Since then reports of significance concerning radiotherapy in advanced stages have not been published. However, in a retrospective study, low dose radiation (4 Gy in 2 fractions) proved efficient with long-lasting effects (more than 50 per cent freedom from local progression at 2 years) [23].

Aggressive non-Hodgkin's lymphomas

Aggressive NHL (previously designated high-grade malignant) comprise a diverse group of diseases with varying presentations, natural histories and responses to therapy. They can occur at any age but they are in general diseases of middle-aged and older adults.

Localized disease: stage I–II

About one third of aggressive NHL present as localized disease and many of them with extranodal location. Until the 1980s the majority of patients with early-stage aggressive lymphoma were treated with radiotherapy alone. The literature review in the previous report (SBU-report 129/2, 1996) showed that somewhat more than 50 per cent of patients in stage I are cured. The relapse-free 5-year survival of similarly treated clinical stage II patients ranged between 0–35 per cent and chemotherapy was unanimously recommended. Combination therapy (chemotherapy followed by radiotherapy) was then not tested in randomized trials, but the results from retrospective comparisons of combination therapy were not different from chemotherapy alone, and the value of additional radiotherapy in localized disease remained to be demonstrated.

Radiotherapy alone

BNLI has performed a retrospective analysis on patients in stage I/I$_E$ and reported a complete remission rate of 84 per cent after 40 Gy and a relapse rate at 10 years of 32 per cent with no relapse occurring after five years [69]. In a Swedish retrospective study on patients in stage I/I$_E$ the complete remission rate was 92 per cent after a median radiation dose of 44 Gy. Twentynine percent of the patients relapsed after a median follow-up of five years, 4 per cent within the radiation field. The 5-year survival was comparable for nodal and extranodal lymphomas [54].

The optimal radiation dose for aggressive lymphomas has not been determined in any prospective randomized study but since 1997 BNLI has been performing a randomized trial comparing 30 Gy with 40–45 Gy for patients in stage I treated with radiotherapy alone.

A prospective study from Texas with combined modality treatment found significantly better local control with doses ≥40 Gy than with lower doses [22].

Radiotherapy versus chemotherapy plus radiotherapy
No randomized trial has been published since previous report.

In a Swedish non-randomized study from three institutions the relapse rate was higher in the radiotherapy group compared with the combined modality therapy group for patients in stage I/I$_E$ (29 per cent vs 15 per cent, p=0.05) [54]. The median radiation dose was 44 Gy. In another non-randomized study from four institutions in the Netherlands and Belgium significantly better progression-free survival at 10 years for patients in stage I/I$_E$ was shown for combined modality therapy compared with radiotherapy alone (83 per cent vs 47 per cent). The median radiation dose was 40 Gy. In the radiotherapy group approximately 75 per cent had their first recurrence either at nodal sites on the other side of the diaphragm or at extranodal sites [68]. A Japanese retrospective survey from 25 institutions on almost 800 patients in stage I/I$_E$-II/II$_E$ showed significantly better 5-years event-free survival for patients treated with chemotherapy (mainly CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone) followed by radiotherapy to involved field (median dose 42 Gy) compared with radiotherapy alone (63 per cent vs 47 per cent). According to the international prognostic index (IPI) 5-years event-free survival was 76 per cent for patients with 0–1 risk factor, 61 per cent for patients with two risk factors, and 26 per cent with three or more risk factors. In this report only about 25 per cent of the patients had only nodal manifestations but event-free survival was identical for nodal and extranodal involvement [53].

The optimal radiation dose after chemotherapy has not been determined. A retrospective study from Florida recommended 30 Gy for patients with nonbulky tumour (≤6 cm) if complete remission was achieved by chemotherapy, otherwise 40–45 Gy was recommended after chemotherapy [32].

Chemotherapy plus radiotherapy versus chemotherapy alone
A randomized trial performed by SWOG (Southwest Oncology Group) has shown that combined modality therapy with three cycles of CHOP followed by involved field radiotherapy (40–55 Gy) is significantly superior to eight cycles CHOP with respect to both progression-free (77 per cent vs 64 per cent) and overall survival (82 per cent vs 72 per cent) at five

years for patients in stage I/I$_E$ including bulky disease and nonbulky stage II/II$_E$. Furthermore, life-threatening toxicity (mostly grade 4 neutropenia or decreased left ventricular ejection fraction) was less common (although not significant, p=0.06) in the combined treatment group than in patients who received eight cycles of CHOP [47]. This trial began in 1988, and although the international prognostic index (IPI) was not published until 1993, the authors have retrospectively analysed the clinical characteristics of the 401 patients according to stage-modified IPI. Most of the patients (72 per cent) were considered to be in the low risk group. Patients with 0–1 risk factors had an estimated 5-year progression free survival of 77 per cent, for patients with two risk factors 60 per cent, and only 34 per cent for patients with three risk factors. With longer follow-up, median eight years, the actuarial curves for failure free survival and overall survival of the two treatment groups are overlapping, due to increased late relapses and deaths in the combined therapy group [47a].

Chemotherapy plus radiotherapy

Some uncontrolled studies have been published on the efficacy of combined modality therapy with anthracykline based-chemotherapy. A prospective study from Texas with combined modality treatment reported after a minimum follow-up of five years a relapse-free survival of 81 per cent in stage I and 59 per cent in stage II [22]. In a French prospective study with alternating chemotherapy and radiotherapy in stages I–II the 5-year disease-free survival was 77 per cent for patients in stage I and 67 per cent in stage II [50]. In an Italian cooperative study with a 6-week chemotherapy regimen followed by locoregional radiotherapy (36 Gy) the 4-year relapse-free survival for stage I and II were 80 per cent and 78 per cent respectively [20].

The literature shows that:

- About half of patients (47–65 per cent) with aggressive non-Hodgkin's lymphoma in stage I are cured by radiotherapy alone.

- Randomized and non-randomized studies favour combined modality treatment with chemotherapy followed by radiotherapy instead of radiotherapy or chemotherapy alone in localized disease. With com-

bined modality treatment the 5-year progression-free survival ranges between 74–83 per cent in stage I and 59–78 per cent in stage II.

• The international prognostic index (IPI) is a better prognostic instrument than the traditional staging.

• The optimal radiation dose either for radiation alone or after chemotherapy has not been established.

Aggressive non-Hodgkin's lymphomas localized disease: stage I–II.

	1 = High	2 = Moderate	3 = Low	Total
C	1/401	–	–	**1/401**
P	–	3/326	–	**3/326**
R	3/1 243	2/509	–	**5/1 752**
Total	**4/1 644**	**5/835**	**–**	**9/2 479**

Advanced disease: stages III–IV

In advanced stages of aggressive non-Hodgkin's lymphoma combination chemotherapy is the therapy of choice and radiotherapy plays only a minor if any role in the management of these patients.

Bulky disease has in many studies proved to be an adverse prognostic factor and consolidating radiotherapy is often recommended to reduce the incidence of local recurrence and improve survival. But despite radiotherapy bulky disease seems to remain an unfavourable factor. In a prospective study with combined modality treatment in stages I–II, bulky disease (≥10 cm) proved to be the only unfavourable prognostic factor [50]. The adverse prognostic value of tumour bulk (>6 cm) was also confirmed in a large retrospective survey from Japan where 70 per cent of the patients had received combined modality therapy [53]. Similar results were seen in a retrospective series from Florida [32].

Only one randomized trial has been published where patients with aggressive lymphoma in stage IV with initially bulky disease (≥10 cm) in complete remission after chemotherapy were randomized to involved field radiotherapy (40–50 Gy) or observation. The combined modality

therapy was significant superior to chemotherapy alone with respect both to disease free and overall survival [6]. But few patients were included and the statistical methods used were poor so the result must be interpreted with caution. However, these results were recently confirmed by a retrospective Italian study. Overall survival was significantly superior after consolidation radiotherapy in patients with advanced aggressive NHL and initially bulky disease in complete remission after chemotherapy compared to no radiotherapy [19].

Total body irradiation (TBI)

Total body irradiation means that the entire body is irradiated with 0.1 to 0.15 Gy/fractions two to five times per week, achieving a final dose of 1.5–3.0 Gy.

In a French pilot study 26 previously untreated patients with indolent lymphoma in stages I–II were treated by radiotherapy with TBI to 1.5 Gy followed by involved field to 40 Gy. Twentyfour patients achieved complete remission after TBI, and after a median follow-up of 53 months, 19 patients remained alive and disease-free [58]. These results initiated an EORTC (European Organization for Research and Treatment of Cancer) trial comparing radiotherapy to involved fields with TBI plus involved fields in indolent lymphomas in stages I–II. How these low doses could control the disease is difficult to understand but there are experimental data suggesting that the efficacy might be explained by immune enhancement, induction of apoptosis and hypersensitivity to low radiation doses [60].

A major concern is that TBI may increase the risk of secondary leukemia. In a retrospective cohort study on 61 patients with mostly indolent NHL initially treated with TBI with a median follow-up of about nine years, five cases of ANLL/MDS (acute non-lymphocytic leukemia, myelodysplastic syndrome) were observed in patients who subsequently had received either alkylating agents alone or combined modality treatment. The cumulative 15-year risk of leukemia was 17 per cent and the relative risk 117. A previous case control study by the same authors on leukemia following NHL treated by similar chemotherapy regimens but without TBI has shown a twofold to 13-fold relative risk for the various regimens [67].

As most patients with advanced indolent NHL will eventually relapse and be treated with chemotherapy the approach with initial TBI seems very hazardous. Recently a small retrospective study with TBI or total abdominal-pelvic irradiation (TAI) in heavily pretreated patients with advanced indolent lymphomas was presented. Two daily fractions of 0.75–0.8 Gy were given to a total dose of 20 Gy for TAI and 15 Gy for TBI, which consisted of two successive half-body irradiations with four weeks between each of them. Seventyfive per cent of the TBI patients achieved complete remission and median survival was 43 months. The TAI patients who were not so heavily pretreated achieved complete remission in 77 per cent but had a median survival of 78 months [44].

Fractionated TBI (fTBI) in conjunction with high-dose chemotherapy (HDCT) and stem cell rescue

Fractionated TBI to 12 Gy is widely used in combination with high doses of various cytostatic drugs as conditioning therapy followed by stem cell rescue in patients with relapsed or refractory lymphoma. (HDCT in these situations has been reviewed and evaluated in SBU-report no 155/2, 2001 and its value is not unequivocally proven).

A British study with HDCT and fTBI in patients with indolent lymphomas showed prolonged freedom from recurrence but no survival advantage in comparison with a historical control group with conventional treatment. Twelve per cent of the high-dose treated patients developed secondary ANLL/MDS and the lack of survival advantage was probably due to therapy-related deaths from ANLL/MDS [4]. A review on retrospective or registry data found that the combination of fTBI and cytostatic drugs was not superior to chemotherapy regimens alone in aggressive non-Hodgkin's lymphoma [49]. The conclusion in another very comprehensive review on conditioning regimens in HDCT was the lack of convincing evidence that TBI-containing regimens were better than chemotherapy alone both in indolent and aggressive NHL [5].

In a report 1999 from the European Bone Marrow Transplantation (EBMT) Lymphoma Registry on about 5 000 transplanted patients from 131 centers the actuarial risk for ANLL/MDS at five years post-transplant was 3 per cent for patients with NHL and a multivariate analysis demonstrated fTBI as a risk factor. But these risks for ANLL/MDS may not

exceed those for a similar group of patients after standard treatment and a further survey is underway [48].

The literature shows that:

- Benefit of radiotherapy for bulky disease has not been definitely confirmed.

- The value of total body irradiation for treatment of non-Hodgkin's lymphoma has not been proven.

- Fractionated TBI in conjunction with high-dose chemotherapy has not been demonstrated to be superior to chemotherapy regimens alone.

Bulky disease and total body irradiation (TBI).

	1 = High	2 = Moderate	3 = Low	Total
C	–	–	1/88	**1/88**
P	–	1/96	1/26	**2/122**
R	3/5 884	3/440	1/34	**7/6 358**
L	3	–	–	**3**
Total	**6/5 884**	**4/536**	**3/148**	**13/6 568**

Primary extra nodal non-Hodgkin's lymphomas

Primary extra nodal lymphomas can arise in almost every organ and the frequency of each entity is low and thus randomized trials are nearly impossible to perform and the available literature may not reflect the optimal therapeutic approach. Frequently extra nodal NHL present as localized disease and have the potential to be cured by local treatment. Generally the principles of therapy for primary extranodal lymphomas are similar to those of localized nodal lymphomas and they are often included in studies on nodal lymphomas (see above). Indolent localized lymphomas are mostly treated with radiotherapy alone and aggressive lymphomas with chemotherapy followed by radiotherapy. Exceptions to that approach are sometimes made due to certain known traits of aggressiveness and/or anatomic extent of the disease. Special consideration must be taken in organs for which curative doses of radiation compromize function, such as lung and kidney.

Primary CNS lymphomas (PCNSL)

Primary CNS lymphoma is usually an aggressive B-cell-lymphoma arising in the brain tissue as a single or multifocal brain tumour, often involving the leptomenginges, sometimes also intraocular structures and rarely the spinal cord parenchyma. It is a rare tumour, despite rising incidence not only in immunocompromized patients but also in immunocompetent patients and the rate of increase is greater than for NHL at other sites [12,45]. However, in a Danish population-based study no increased incidence of non-AIDS related primary CNS lymphoma was found [34]. The prognosis is dismal.

The previous report (SBU-report 129/2, 1996) concluded that the traditional role of radiotherapy for CNS lymphoma has been reevaluated due to the high frequency of local recurrence. The median survival was only 12 to 18 months after radiotherapy and some authors recommended combined modality treatment with initial chemotherapy followed by radiotherapy while others believed it was too early to recommend this combination.

In an attempt to diminish the local recurrence rate a pilot study with accelerated radiation therapy (50 Gy/25 fractions/13 days) in Toronto was discontinued due to toxicity and no improved outcome [37].

The introduction of chemotherapy has prolonged survival. High-dose methotrexate (HD MTX) is the most effective drug in PCNSL. In a review study, the addition of other drugs at conventional doses has not improved the outcome compared to high-dose methotrexate alone [18]. However, in a prospective study with combined modality treatment with multiagent chemotherapy including high-dose methotrexate very long survival was achieved. The median overall survival was 60 (1–77) months for all the patients, and for patients below 60 years with a median follow-up of 50 months the median OS or DFS have not been reached. This may suggest a positive effect of the other drugs (vincristine, procarbazine and high-dose cytarabine) [2].

Only one randomized trial has been reported. A British multicenter trial compared radiation alone with radiation followed by chemotherapy (CHOP). No benefit from additional CHOP was observed

[46]. This result was not surprising since CHOP therapy is not optimal in CNS lymphoma because the drugs in this regimen have a poor blood-brain barrier penetration. Furthermore, the chemotherapy was given after irradiation when the blood-brain barrier probably was restored. Few patients were included in the trial, and there was imbalance between the two arms with respect to age and neurological performance status, which are known prognostic factors.

In a review of 50 series published, 1980–95 with more than 1 000 immuno-competent patients with PCNSL, 676 patients could be analyzed with respect to prognostic factors and therapeutic outcome from different treatment modalities. Multivariate analysis confirmed the independent favourable prognostic value of age below 60 years, whole brain radiation of >40 Gy, HD MTX therapy and intrathecal chemotherapy. The addition of spinal irradiation failed to improve survival. Patients treated with combined modality therapy had significantly longer survival than those treated with either radiotherapy or chemotherapy alone. The impact on survival of whole brain radiotherapy and the dose to tumour bed in these patients could not be analyzed because of the heterogeneity of chemotherapy regimens and therapy sequence [57].

Prospective studies with chemotherapy including high dose methotrexate followed by radiotherapy have shown median survival of 33–60 months and 5-year survival of 22–40 per cent [1,2,52] in comparison to median survival of 17–21 months and 5-year survival of 26–27 per cent reported with radiotherapy alone in recent retrospective series [13,36]. All studies comprise few patients.

A major concern is the development of severe neurotoxicity with neurological impairment and/or dementia early after combined modality treatment especially in elderly patients [2]. Long-term follow-up has revealed that after one year nearly 80 per cent of the survivors over the age of 60 at diagnosis, had developed progressive leukoencephalopathy, and almost 100 per cent within four years of treatment. Only 30 per cent of younger patients had similar symptoms after a 7.5-year latency [1,14]. Therefore, one author recommends that patients above 60 years who achieve a complete remission with chemotherapy should not receive radiation but should be observed closely [14]. It is likely that the

neurotoxicity is a sequelae of whole-brain radiation exacerbated by the toxicity of methotrexate and cytarabine [45].

The literature shows that:

- Since radiotherapy alone induces response of short duration and appears to predispose to major neurotoxicity its role is questionable and remains to be determined.

- High-dose methotrexate therapy alone leads to longer survival than radiotherapy alone.

- The results of combined modality therapy are difficult to interpret because of different inclusion criteria, heterogeneity of drug regimens and radiotherapy schedules and the paucity of randomized trials.

- Young patients with a good performance status have a significant chance of long-term survival (even with radiation therapy only).

- To minimize the risk of neurotoxicity of combined modality treatment it has been proposed to treat patients who obtain a complete remission, with chemotherapy alone, and delay radiotherapy for relapses or persistent disease. But the efficacy of this strategy is not proven because only a few prospective trials with few patients have assessed the impact on survival and toxicity.

- Until well-established standard therapy is defined, younger patients are recommended to receive primary chemotherapy including high-dose methotrexate followed by radiotherapy. This approach has in prospective and retrospective series shown improved survival compared with radiotherapy alone. For patients above 60 years one report recommends deferring radiotherapy until relapse.

Primary CNS lymphomas

	1 = High	2 = Moderate	3 = Low	Total
C	–	–	1/53	**1/53**
P	–	3/108	1/31	**4/139**
R	–	–	2/111	**2/111**
L	4/676	–	–	**4/676**
O	2	–	–	**2**
Total	**6/676**	**3/108**	**4/195**	**13/979**

Orbital lymphomas

Primary orbital lymphomas include adnexal involvement in retrobulbar tissues, conjunctivae, eyelids and lacrimal glands. They are generally indolent lymphomas, often of MALT-type see below. No publications have changed the conclusions from the previous report (SBU-report 129/2, 1996) that radiotherapy to a low dose is the standard treatment for localized indolent orbital NHL. Intraocular lymphomas are not included here because they frequently spread to CNS or are a manifestation of primary CNS lymphoma and should subsequently be treated as PCNSL.

Testicular lymphomas

Testicular lymphoma is a rare disease with an incidence of 0.26 per 100 000 men [25] which make randomized trials almost impossible.

The conclusions from the previous literature review (SBU-report 129/2, 1996) are on the whole unchanged i.e. full agreement that chemotherapy should be given initially (after orchiectomy), irradiation to scrotum was recommended due to high risk of recurrence in the other testicle, and a high risk of recurrence in the CNS but no consensus of the value of CNS prophylaxis.

Recently the International Extranodal Lymphoma Study Group (IELSG) has conducted a retrospective study on 373 men with primary testicular diffuse large B-cell lymphoma from 23 centers to evaluate patterns of presentation, treatment, and outcomes [76]. The median age of the patients was 66 years, and 57 per cent of the patients presented with stage I, and 22 per cent with stage II. The majority of patients (75 per cent) were treated with combination chemotherapy, 34 per cent had

received prophylactic scrotal irradiation, but only 18 per cent had received prophylactic intrathecal chemotherapy. The median survival for patients with stages I–II was 5.8 years with an actuarial 10-year overall survival of 27 per cent. Prophylactic scrotal irradiation was associated with a better progression-free and overall survival. Without scrotal irradiation the long-term recurrence risk in the contralateral testis was 40 per cent. Prophylactic intrathecal chemotherapy was associated with a better progression-free survival. CNS recurrences occurred up to 10 years after diagnosis and the actuarial 10-year risk was 35 per cent.

IELSG is now performing a prospective study to assess the efficacy of prophylactic scrotal RT and intrathecal chemotherapy in addition to CHOP chemotherapy. However, many CNS failures occur in brain parenchyma rather than in meninges and intrathecal chemotherapy is unlikely to prevent these CNS failures [25]. Prophylactic cranial irradiation might prevent relapses in brain parenchyma but there are few published data regarding the benefit of prophylactic whole brain radiation and no ongoing studies.

MALT lymphomas (Mucosa Associated Lymphoid Tissue)

MALT lymphomas recapitulate the features of MALT (Peyer's patches) rather than those of lymph nodes. They arise in numerous extranodal sites (gastrointestinal tract, orbital structures including lacrimal glands and conjunctivae, salivary glands, Waldeyer's ring, larynx, thyroid, thymus, breast, lung, liver, kidney, bladder and dura) and account for about 7 per cent of all NHL [61,65]. Typically, MALT lymphomas arise from lymphoid tissue that has been acquired as the result of a chronic inflammatory, often autoimmune disorders [31]. They tend to remain localized for a long time and are therefore treated with regional therapy. The outcome and prognosis for MALT lymphomas are more favourable than for other extranodal lymphomas. Non-gastrointestinal locations represent about half of the MALT lymphomas [28].

Lymphomas in the gastrointestinal tract

The gastrointestinal tract is the most common site of extranodal lymphomas. A special staging system was designed for these lymphomas at the Lugano Workshop 1993 (59). The optimal treatment of gastrointestinal lymphomas is a very controversial issue and depends on the histological

type and the stage of the disease. In advanced stages of aggressive lymphomas chemotherapy is the therapy of choice [74].

Stomach lymphoma

MALT lymphomas constitute the majority of indolent lymphomas of the stomach and may undergo transformation to aggressive lymphoma. Usually gastric MALT lymphomas present with stage I_E but approximately 20 per cent have spread to the gastric lymph nodes or beyond at the time of diagnosis [30,31,40]. Gastric MALT lymphomas are in most cases preceded by Helicobacter pylori-associated (HP) chronic gastritis. Eradication of H pylori by antibiotic and anti-acid therapy leads to regression of the lymphoma in approximately 75 per cent of the cases [31]. However, relapse following antibiotics is not uncommon. Only long-term prospective studies can answer the value eradication of H pylori [51].

The classical approach for management of gastric lymphomas has been primary surgery [61]. However, treatment recommendations vary widely in the literature and prospective randomized clinical trials have not been preformed. An international survey was performed 1996–97 including 19 centers in Europe, United States and Japan. All centers initially used H. pylori eradication in localized indolent MALT-NHL as monotherapy. Retreatment after failure varied considerably, radiotherapy alone was the most common choice followed by chemotherapy alone, but some centers preferred surgery sometimes combined with radiotherapy or chemotherapy. In two centers patients were entered in randomized trials with gastric resection versus radiotherapy or chemotherapy. When H pylori eradication was not suitable due to histology or stage the preferred treatment also showed great variation [15]. Radiotherapy alone may be one approach to treat MALT lymphomas refractory to antibiotic therapy. In a small prospective study from Memorial Sloan Kettering Cancer Center (MSKCC) 29 patients with localized indolent MALT lymphoma without prior evidence of H pylori or persistent lymphoma after antibiotic therapy were irradiated with a low dose (median 30 Gy). All patients obtained a biopsy-confirmed complete remission [72].

A German prospective multicenter study performed 1992–96 on primary lymphoma of the stomach found no difference in event free or overall survival between gastric resection and treatment with comprehensive

radiotherapy and/or chemotherapy in stage I or II [70]. In a following study, ongoing, the radiotherapy target volumes are reduced and H pylori eradication is part of the protocol.

Small prospective studies with chemotherapy alone or combined with radiotherapy in primary resectable aggressive gastric lymphomas have also been performed [26,66] but definitive conclusions are difficult to draw because the series included few patients and they mixed chemotherapy and radiotherapy.

On the other hand there are still advocates for primary gastric resection. A German-Austrian prospective multicenter study was performed 1993–96. Non-responders to H pylori eradication and patients with indolent stage II_E underwent gastric resection and depending on the residual tumour status and risk factors the patients received either radiotherapy or no further treatment. Patients with high-grade lymphoma stage I_E/II_E received chemotherapy after surgery and in case of incomplete resection also radiotherapy. The 2-year overall survival for indolent lymphomas ranged between 89 to 96 per cent. For high-grade lymphomas, patients with complete resection or microscopic tumour residuals had significantly better overall survival (88 per cent for stage I_E and 83 per cent for stage II_E) than those with macroscopic residues (53 per cent). The authors claim that, except for H pylori-positive indolent lymphoma stage I_E and locally advanced high-grade lymphomas, resection remains the therapy of choice. However, they also propose a randomized trial comparing surgery with conservative treatment [21].

In diffuse large cell gastric lymphomas a prospective randomized trial comparing chemotherapy with chemotherapy plus irradiation is ongoing (IELSG 4).

The literature shows that:
- Optimal management of gastrointestinal lymphomas is still a very controversial issue and has not been established in prospective randomized clinical trials. The treatment recommendations vary widely in the literature.

- For indolent gastric MALT lymphomas there is a general agreement that eradication of H pylori is the first therapeutic option. Whether the disappearance of H pylori definitely cures the patients is not known.

- Primary surgery for gastric lymphomas has been the classical approach but there is now an increasing trend toward stomach-conserving therapy with radiotherapy and/or chemotherapy.

- The roles of radiotherapy and chemotherapy in gastric lymphomas have still to be defined.

MALT lymphomas (Mucosa Associated Lymphoid Tissue).

	1 = High	2 = Moderate	3 = Low	Total
P	3/455	–	2/41	**5/496**
L	3	–	–	**3**
O	6/22	–	–	**6/22**
Total	**12/477**	**–**	**2/41**	**14/518**

Thyroid lymphomas

The majority (~80 per cent) of thyroid lymphomas present with stage I or II disease. Thyroid lymphoma occurs more frequently in women than in men and is commonly associated with Hashimoto's thyroiditis. The predominant histology is diffuse large B-cell lymphoma but indolent malignant lymphoma of MALT type occur in about 25 per cent [3,24].

No randomized trials concerning therapy exist. In a retrospective analysis with most patients treated with radiotherapy the cause specific survival at five years was significantly better for MALT lymphomas; 90 per cent compared with 55 per cent if no evidence of MALT lymphoma existed and nearly all these patients had aggressive lymphomas. These results indicate that radiotherapy could be a satisfactory treatment in indolent lymphomas [35]. Patients with aggressive lymphoma managed with radiotherapy alone have a high frequency of relapse mostly outside the treated field. A review of retrospective data from different institutions supports the use of combined modality treatment in these patients [3].

The literature shows that:

- Radiotherapy alone is considered appropriate therapy for patients with indolent thyroid lymphomas in stage I.

- The recommended therapy for localized aggressive thyroid lymphomas is combined treatment modality with chemotherapy followed by radiation.

Head and neck lymphomas

The head and neck area is the second most common site of extranodal presentation of NHL of different entities. The tonsils are the most common site followed by nasopharynx, oral cavity, salivary glands, paranasal sinuses and the base of tongue. The therapy results vary greatly depending on histology and anatomic site [75].

Lymphoma in Waldeyer's ring (tonsil, base of the tongue and nasopharynx)
Predominantly, head and neck lymphomas occur in Waldeyer's ring. About 70 per cent of primary tonsil NHL are of the diffuse large B-cell type, MALT-lymphomas are uncommon but other indolent lymphomas such as follicular lymphomas are quite common. Often there is a relationship to gastrointestinal involvement [75].

One prospective randomized study has been published on NHL in Waldeyer's ring. Threehundredsixteen patients with aggressive lymphoma in stage I were randomized between radiotherapy alone, chemotherapy alone (CHOP or CHOP like) and radiotherapy followed by chemotherapy. Failure-free and overall survival at 5 years were significantly better in the combined modality group compared with either radiotherapy alone or chemotherapy alone (FFS, 83 per cent vs 48 per cent vs 43 per cent; OS, 90 per cent vs 58 per cent vs 56 per cent) [7]. In this study radiotherapy was given before chemotherapy but in reviews chemotherapy before radiotherapy is advocated [24,73,75].

Lymphoma in salivary glands
The majority of the lymphomas in salivary glands are located in the parotid, mostly of indolent histology and often associated with Sjögren's syndrome [73]. A small randomized trial of 39 patients with stage I or II

indolent lymphoma of the parotid glands compared radiotherapy alone with radiotherapy followed by adjuvant chemotherapy (COP: cyclophosphamide, vincristine, prednisone). No significant difference was found between the treatment groups with an overall 5-years survival of 90–95 per cent. Radiotherapy alone was considered the therapy of choice [8].

Lymphoma in the nasal cavity and paranasal sinuses

Both B-and T-cell lymphomas occur in this site. These lymphomas appear to be rare in Western countries, where they usually show a B-cell phenotype. They are relatively common in Asian countries and most of them have a T/NK-cell phenotype. They frequently spread to the central nervous system and hemophagocytic syndrome is a common clinical complication. This category of lymphoma has been referred to in the past as lethal midline granuloma and, more recently, as angiocentric T/NK-cell nasal lymphoma. Indolent lymphomas are rare. The treatment results have been dismal, with 5-year survival of only 12–15 per cent after radiotherapy alone [73,75]. Neither randomized trials nor prospective studies concerning optimal therapy exist. Some retrospective analysis suggest that combination of chemotherapy and radiation may offer the best chance of long-term disease free and overall survival [38,42], while others do not find any significant improvement of the prognosis with combined modality [10,39]. However, the studies showed that immunophenotype, stage, local extensions and IPI-factors are very important prognostic factors for the choice of therapy. In reviews combined modality is recommended [24,73,75].

The literature shows that:

- For aggressive lymphomas in Waldeyer's ring with limited disease combined modality with chemotherapy and radiotherapy is the current recommendation in the literature.

- For localized indolent lymphomas in salivary glands radiotherapy alone is recommended.

- For lymphomas in the nasal cavity and paranasal sinuses the current practice is combined modality with chemotherapy and radiotherapy.

Head and neck lymphomas.

	1 = High	2 = Moderate	3 = Low	Total
C	–	1/316	1/39	**2/355**
R	1/175	3/283	–	**4/458**
L	3	–	–	**3**
Total	**4/175**	**4/599**	**1/39**	**9/813**

Cutaneous lymphomas

Several retrospective series often comprising few patients have been published since 1994 on both primary cutaneous B-and T-cells lymphomas. Nothing essential that change earlier recommendations i.e. radiotherapy for progressive or refractory mycosis fungoides and for B-cells lymphoma with limited distribution (if not radically excised).

Radioimmunotherapy (RIT)

Radioimmunotherapy is a new therapeutic modality with systemic radiation used in patients with relapsed/refractory NHL. Radiolabeled monoclonal antibodies against antigen on the surface of B-lymphocytes are used to carry the radioactivity to the disease sites where it emits continuous, exponentially decreasing, low-dose irradiation. Usually iodine-131 or yttrium-90 labeled antibodies are utilized targeting the CD20 antigen, which more than 90 per cent of B-cells non-Hodgkin's lymphomas express, but also other monoclonal antibodies have been used e.g., CD22. Myelosuppression is dose limiting and the optimal dose and administration schedules have not been definitely defined. Two approaches have emerged; one utilizes repetitive infusions of low nonmyeloablative doses of radiolabeled antibodies and the alternative is high myeloablative doses of radioactivity in conjunction with autologous hematopoietic stem cell rescue. Studies with low-dose strategy have shown objective responses in 65–80 per cent of the patients, complete remission in 20–50 per cent of the patients, with a median response duration of 12 months. The high-dose strategy has demonstrated objective responses in 85 per cent of the patients, complete remission in up to 79 per cent of the patients, and a median response duration of more than 24 months [11,56]. After myeloablative doses of iodine-131-anti CD20 antibody

and autologous stem-cell rescue in patients with relapsed NHL treated with a median of three prior chemotherapy regimens, 12 of 29 patients continued in unmaintained remission for more than 3 years after treatment. The progression-free survival rate at 4 years was estimated to be 51 per cent for patients with indolent lymphomas and 20 per cent for those with aggressive lymphomas. Reversible cardiopulmonary toxicity was dose limiting in this setting [41].

Only one randomized clinical trial with RIT has been performed. One hundred fortythree patients with relapsed/refractory indolent or transformed NHL were randomized between Zevalin (ibritumomab tiuxetan: anti-CD20 monoclonal antibody conjugated with ^{90}Y) radioimmunotherapy and rituximab (anti-CD20 monoclonal antibody) immunotherapy. The overall response rate was 80 per cent in the Zevalin arm vs 56 per cent in the rituximab arm (p=0.002) with a 30 per cent vs 16 per cent complete remission, respectively [71].

Comparison between different radionuclides or antibodies in clinical trials has not been performed.

The literature shows that:

- Several phase I and II studies with radioimmunotherapy have documented promising results by this new therapeutic modality with systemic radiation.

- A variety of monoclonal antibodies, radionuclides and study designs have resulted in high response rates with a number of durable complete and partial remissions with both myeloablative and nonmyeloablative approaches in patients with recurrent or refractory lymphomas. In some studies these responses have lasted longer than prior remissions from previous chemotherapy.

- One randomized clinical trial showed superior therapy results with radiolabelled antibody compared with the corresponding unlabelled antibody.

- Future studies are needed to define the role of RIT and which RIT regimen(s) will be most efficacious in the management of NHL.

Radioimmunotherapy.

	1 = High	2 = Moderate	3 = Low	Total
C	–	1/143		**1/143**
P	–	1/29	–	**1/29**
L	2	–	–	**2**
Total	**2**	**2/172**		**4/172**

Literature

The articles on which the conclusions in this report were based were classified and graded as follows (number of studies/number of patients).

	1 = High	2 = Moderate	3 = Low	Total
C	1/401	2/459	4/328	**7/1 188**
P	3/455	8/563	5/124	**16/1 142**
R	7/8 754	10/1 289	5/206	**22/10 249**
L	17/676	–	–	**17/676**
O	10/20	–	–	**10/20**
Total	**38/10 306**	**20/2 311**	**14/658**	**72/13 275**

Conclusions and Comments

Indolent lymphomas

- Data support that one third to one half of patients with indolent lymphoma in stage I are cured by radiotherapy (follow-up more than 15 years). ([32]R2, [33]C3, [43]R2, [55]R3, [69]R1).

- Addition of chemotherapy to radiotherapy does not suggest any improvement of overall outcome. ([33]C3).

Optimal radiation dose is not defined and extended field is not superior to involved field.

No new reports concerning radiotherapy in advanced stages have appeared and the statements from SBU report 129/2 1996 are still valid.

Aggressive localized lymphomas

- Data indicate that one half of patients in stage I is cured by radio-therapy alone. ([54]R1, [69]R1).

- Although randomized and non-randomized studies favour combined modality treatment with chemotherapy followed by radiotherapy instead of radiotherapy or chemotherapy alone in localized disease no firm conclusions can be drawn. (*Pro* [20]P2, [22]P2, [47]C1, [50]P2, [53]R1, [54]R1, [68]R2, *con* [47a]C3).

- Conflicting data have been published on the value of radiotherapy towards bulky disease and no firm conclusions can be drawn. (*Pro* [6]C3, [19]R2, *con* [32]R2, [50]P2, [53]R1).

Optimal dose for radiation alone or after chemotherapy has not been established.

Total body irradiation (TBI)

The value of total body irradiation for treatment of non-Hodgkin's lymphoma has not been proven.

- There is no proof that fractionated TBI in conjunction with high-dose chemotherapy is superior to chemotherapy regimens alone. ([4]R1, [5]L1, [49]L1).

Primary CNS lymphomas

- Data show that radiotherapy induces response of short duration and is associated with major neurotoxicity, especially in elderly patients. ([1]P3, [2]P2, [13]R3, [18]L1, [36]R3, [37]P2, [57]L1).

- High-dose methotrexate therapy seems to lead to longer survival than radiotherapy alone. No randomized trials are performed. ([1]P3, [2]P2, [18]L1, [52]P2).

- There is fairly good support for primary chemotherapy including high-dose methotrexate followed by radiotherapy in patients below 60 years. ([1]P3, [2]P2, [18]L1, [57]L1).

To minimize the risk of neurotoxicity of combined modality treatment it has been proposed to use chemotherapy alone and delay radiotherapy for relapse, especially in patients above 60 years or use it in chemotherapy resistent disease. Optimal chemotherapy regimen is not defined and the role of radiotherapy remains to be determined.

Head and neck lymphomas

- There is some support for combined modality treatment with chemotherapy and radiotherapy for aggressive lymphomas in Waldeyer's ring with limited disease. ([7]C2, [24]L1, [73]L1, [75]L1).

- There is sparse data supporting radiotherapy alone in localized indolent lymphomas in salivary glands. ([8]C3).

Radioimmunotherapy (RIT)

Radioimmunotherapy is a new treatment modality with systemic radiation for patients with advanced NHL, where conventional external beam radiotherapy plays only a minor role.

Several phase I and II studies with RIT have documented promising results. A variety of monoclonal antibodies, radionuclides and study designs with both myeloablative and nonmyeloablative approach have resulted in high response rates in patients with recurrent or refractory NHL.

- One randomized clinical trial is published, showing superior therapy results with radiolabelled antibody compared with the corresponding unlabelled antibody. ([71]C2).

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