OVERVIEW ARTICLE

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A Systematic Overview of Radiation Therapy Effects in Non-Hodgkin's Lymphoma

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A systematic review of radiation therapy trials in several tumour types was performed by The Swedish Council of Technology Assessment in Health Care (SBU). The procedures for evaluation of the scientific literature are described separately (Acta Oncol 2003; 42: 357–365). This synthesis of the literature on radiation therapy for non-Hodgkin's lymphoma (NHL) is based on data from seven randomized trials. Moreover, data from 17 prospective studies, 22 retrospective studies and 27 other articles were used. In total, 73 scientific articles are included, involving 13 305 patients. The results were compared with those of a similar overview from 1996 including 14 137 patients. The conclusions reached can be summarized as follows:

Indolent lymphomas

- Data indicate that one-third to one-half of patients with indolent lymphoma in stage I are cured by radiotherapy (follow-up more than 15 years).
- Addition of chemotherapy to radiotherapy does not indicate any improvement in overall outcome.
- Optimal radiation dose is not defined and extended field is not superior to involved field.

Aggressive localized lymphomas

- Data indicate that half of the patients in stage I are cured by radiotherapy alone.
- 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.
- Conflicting data have been published on the value of radiotherapy towards bulky disease and no firm conclusions can be drawn.
- Optimal dose for radiation alone or after chemotherapy has not been established.

Total body irradiation (TBI)

The value of TBI for treatment of NHL has not been proven.

- There is no proof that fractionated TBI in conjunction with high-dose chemotherapy is superior to chemotherapy regimens alone.

Primary CNS lymphomas

- Data show that radiotherapy induces a response of short duration and is associated with major neurotoxicity, especially in elderly patients.
- High-dose methotrexate therapy seems to lead to longer survival than radiotherapy alone. No randomized trials have been performed.
- There is fairly good support for primary chemotherapy including high-dose methotrexate followed by radiotherapy in patients below 60 years.
- 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-resistant 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.
- There are sparse data supporting radiotherapy alone in localized indolent lymphomas in salivary glands.

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 non-myeloablative 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.

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

NHL comprises a very heterogeneous group of tumours and the classification systems are in a continuous evolution. In the previous report (SBU 129/2, 1996) the Kiel classification was used. In 1994 the REAL classification (Revised European–American Classification of Lymphoid Neoplasms) was presented (2). 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 (3). 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 according to Hiddemann et al. (4) has been used (Table 1).

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

In 1993 the International Non-Hodgkin's Lymphoma Prognostic Factors Project analysed data on more than 2000 patients from 16 institutions and presented the so-called International Prognostic Index (IPI) (Table 3). The number of IPI factors effectively predict prognosis and is now used for almost all subtypes of NHL (5), 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 NHL 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 also included 7 articles of later date.

Conclusions

- Non-Hodgkin's lymphomas are highly radiosensitive, and local recurrence following radiotherapy is unusual.
- Radiotherapy probably cures approximately 50% 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 (mucosa associated lymphoid tissue) belongs to this group.
- Radiotherapy is often valuable in palliative situations.

Discussion

In stage I, limited radiotherapy leads to local control in over 90% of the patients with both indolent and aggressive lymphomas, with a long-term survival of about 50%. 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, for example 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

Abbreviations: M=meta analysis; C=controlled clinical trial; P=prospective trial; R=retrospective study; L=literature review; and O=other studies.

ASSESSMENT OF NEW LITERATURE

This report deals separately with nodal and extranodal NHL. New publications that confirm conclusions from previous report or provide new information are included.

Table 1

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 lymphocytic leukaemia/small lymphocytic lymphoma[1]	Large granular lymphocytic leukaemia, T- and NK-cell types[3]
Lymphoplasmacytic lymphoma/immunocytoma[2]/ Waldenstrom's macroglobulinaemia	Mycosis fungoides/Sézary syndrome
Hairy cell leukaemia	Smouldering and chronic adult T-cell leukaemia/ lymphoma (HTLV1[2])[3]
Splenic marginal zone lymphoma	
Marginal zone B-cell lymphoma	
Extranodal (MALT-B-cell lymphoma)	
Nodal (monocytoid)	
Follicle centre lymphoma/follicular (small cell)—grade I	
Follicle centre lymphoma/follicular (mixed small and large cell)—grade II	
II. Aggressive lymphomas (intermediate risk)	II. Aggressive lymphomas (intermediate risk)
Prolymphocytic leukaemia[3]	Prolymphocytic leukaemia[3]
Plasmacytoma/multiple myeloma	Peripheral T-cell lymphoma, unspecified[3]
Mantle cell lymphoma	Angioimmunoblastic lymphoma[3]
Follicle centre lymphoma/follicular (large cell)—grade III	Angiocentric lymphoma[3]
Diffuse large B-cell lymphoma (includes immunoblastic and diffuse large and centroblastic lymphoma)	Intestinal T-cell lymphoma[3]
Primary mediastinal (thymic) large B-cell lymphoma	Anaplastic large cell lymphoma (T- and null cell type)
High-grade B-cell lymphoma, Burkitt-like[3]	
III. Very aggressive lymphomas (high risk)	III. Very aggressive lymphomas (high risk)
Precursor B-lymphoblastic lymphoma/leukaemia	Precursor T-lymphoblastic lymphoma/ leukaemia
Burkitt's lymphoma/B-cell acute leukaemia	Adult T-cell lymphoma/leukaemia
Plasma cell leukaemia	
IV. Hodgkin's lymphoma	

[1]Includes B-CLL with plasmacellular differentiation (equivalent to lymphoplasmacytoid lymphoma of the KIEL system).
[2]Note that the term was changed in the REAL classification from lymphoplasmacytoid to lymphoplasmacytic lymphoma to avoid confusion with the Kiel term lymphoplasmacytoid, which represents B-CLL with plasmacellular differentiation.
[3]Provisional clinical grouping.

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. A literature search was performed in Medline with use of the search term 'lymphoma, non-Hodgkin/radiotherapy' with limitation to meta-analyses, randomized controlled studies and prospective controlled studies. No meta-analyses were found and very few randomized studies, hence 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 have also been included, identified through Medline and by scrutinizing reference lists. Furthermore, a few conference proceedings of recently closed but unpublished studies are included.

Reasons for exclusion of randomized trials

- Glick et al. 1995: Abstract presented at ASCO 1995 (6), but no publication has followed.
- Shchepotin et al. 1996 (7): Three-armed study with few patients and suboptimal radiotherapy and chemotherapy.

OVERVIEW OF NEW STUDIES

Nodal non-Hodkin'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%). Indolent lymphomas are very radiosensitive and radiotherapy

Table 2

The Cotswold Staging Classification

Stage I = Involvement of single lymph node region or lymphoid structure (e.g. 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 (e.g. 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 known nodal site. A single extralymphatic site as the only site of disease is classified I_E

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% progression-free survival for patients in stage I at 15 years (8). Another study reports 40% relapse-free survival at 15 years for patients in stages I and II with very few relapses 10 years after radiotherapy (9). The 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% after 35 Gy and a relapse rate at 10 years of 51% with most of the recurrences occurring within 5 years (10). From Florida a 49% freedom from relapse at 20 years is reported for patients in stages I and II, the majority of relapses occurring within 5 years but some recurrences were seen between 5 and 10 years (11).

Interestingly, in a report on 26 patients in complete remission after the surgical biopsy no further treatment was given. After a median follow-up of 4.6 years, 50% of the patients had not relapsed and 7/13 recurrences were distant relapses (12). 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 the BNLI has performed a randomized trial comparing 24 Gy with 40–45 Gy in stage I. A German prospective multicentre study recommends 36–44 Gy for involved lymph nodes (13). In a retrospective analysis from Florida no local recurrences occurred after 30 Gy, suggesting that most indolent lymphomas are adequately treated with 30 Gy (11). 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 centres.

Because most recurrences occur outside the irradiated area, a German prospective multicentre study has used extended field (EF), mostly meaning mantle and para-aortic fields, or even more comprehensive radiotherapy with total central lymphatic (TCL) irradiation, meaning irradiation of Waldeyer's ring, mantle field and the whole abdomen for patients in stages I and II. The median follow-up was 68 months and the relapse rate at 7 years was 26% in stage I and 44% in stage II (13). Results of TCL irradiation of about 100 patients in limited stage III are published and one of these reports suggests a possible increase of second malignancies (14).

Two randomized trials were reported previously (SBU report 129/2), comparing involved field with total nodal irradiation (TNI), and no differences 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), which was

Table 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)	

confirmed in a randomized British trial starting in the mid-1970s, with a minimum of 11 years follow-up, showing that the addition of chemotherapy (chlorambucil) after radiotherapy gave no benefit in outcome (15). A later analysis of the same data but on fewer patients reports 15 years relapse-free survival of 55% for patients in stage I and 29% for patients in stage II and the local recurrence rate after radiotherapy was 2% (16).

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 radiotherapy 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: stage III–IV. The majority of patients with indolent lymphomas present with advanced disease mainly due to bone marrow involvement. The role of chemotherapy was evaluated in SBU report 155/2, 2001 (17). Radiotherapy plays a very limited role in advanced stages as concluded in the previous report (SBU 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 two fractions) proved efficient with long-lasting effects (more than 50% freedom from local progression at 2 years) (18).

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 129/2) showed that more than 50% of patients in stage I are cured. The relapse-free 5-year survival of similarly treated clinical stage II patients ranged between 0 and 35% and chemotherapy was unanimously recommended. Combination therapy (chemotherapy followed by radiotherapy) was not then 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. The BNLI has performed a retrospective analysis of patients in stage I/I_E and reported a complete remission rate of 84% after 40 Gy and a relapse rate at 10 years of 32% with no relapse occurring after 5 years (10). In a Swedish retrospective study of patients in stage I/I_E the complete remission rate was 92% after a median radiation dose of 44 Gy. Twenty-nine per cent of the patients relapsed after a median follow-up of 5 years, 4% within the radiation field. The 5-year survival was comparable for nodal and extranodal lymphomas (19).

The optimal radiation dose for aggressive lymphomas has not been determined in any prospective randomized study but since 1997 the 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 (20).

Radiotherapy versus chemotherapy plus radiotherapy. No randomized trial has been published since the 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% vs. 15%, $p = 0.05$) (19). 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% vs. 47%). The median radiation dose was 40 Gy. In the radiotherapy group approximately 75% had their first recurrence either at nodal sites on the other side of the diaphragm or at extranodal sites (21). A Japanese retrospective survey from 25 institutions on almost 800 patients in stage I/I_E–II/II_E showed significantly better 5-year 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% vs. 47%). According to the IPI, 5-year event-free survival was 76% for patients with 0–1 risk factor, 61% for patients with 2 risk factors, and 26% with 3 or more risk factors. In this report only about 25% of the patients had only nodal manifestations but event-free survival was identical for nodal and extranodal involvement (22).

The optimal radiation dose after chemotherapy has not been determined. A retrospective study from Florida recommended 30 Gy for patients with non-bulky tumour (≤ 6 cm) if complete remission was achieved by chemotherapy, otherwise 40–45 Gy was recommended after chemotherapy (11).

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 of CHOP with respect to both progression-free (77% vs. 64%) and overall survival (82% vs. 72%) at 5 years for patients in stage I/I_E including bulky disease and non-bulky 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 (23). This trial began in 1988, and although the 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%) 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%, for patients with 2 risk factors 60%, and only 34% for patients with 3 risk factors. With longer follow-up, median 8 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 (24).

Chemotherapy plus radiotherapy. Some uncontrolled studies have been published on the efficacy of combined modality therapy with anthracycline-based chemotherapy. A prospective study from Texas with combined modality treatment reported after a minimum follow-up of 5 years a relapse-free survival of 81% in stage I and 59% in stage II (20). In a French prospective study with alternating chemotherapy and radiotherapy in stage I–II the 5-year disease-free survival was 77% for patients in stage I and 67% in stage II (25). In an Italian co-operative study with a 6-week chemotherapy regimen followed by locoregional radiotherapy (36 Gy), the 4-year relapse-free survival for stages I and II was 80% and 78%, respectively (26).

The literature shows that:

- About half of patients (47–65%) with aggressive NHL 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 combined modality treatment the 5-year progression-free survival ranges between 74 and 83% in stage I and 59 and 78% in stage II.
- The 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 NHL 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: stage III–IV. In advanced stages of aggressive NHL combination chemotherapy is the therapy of choice (evaluated in the SBU 155/2 report, 2001) (27), and radiotherapy plays only a minor role, if any, 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. However, despite radiotherapy, bulky disease seems to remain an unfavourable factor. In a prospective study with combined modality treatment in stage I–II, bulky disease (≥ 10 cm) proved to be the only unfavourable prognostic factor (25). The adverse prognostic value of tumour bulk (> 6 cm) was also confirmed in a large retrospective survey from Japan where 70% of the patients had received combined modality therapy (22). Similar results were seen in a retrospective series from Florida (11).

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 to both disease-free and overall survival (28). 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 (29).

Total body irradiation (TBI)

Total body irradiation means that the entire body is irradiated with 0.1 to 0.15 Gy/fraction 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 stage I–II were treated by

radiotherapy with TBI to 1.5 Gy followed by involved field to 40 Gy. Twenty-four patients achieved complete remission after TBI, and after a median follow-up of 53 months, 19 patients remained alive and disease free (30). 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 stage 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 (31).

A major concern is that TBI may increase the risk of secondary leukaemia. In a retrospective cohort study on 61 patients with mostly indolent NHL initially treated with TBI with a median follow-up of about 9 years, five cases of ANLL/MDS (acute non-lymphocytic leukaemia, myelodysplastic syndrome) were observed in patients who subsequently had received either alkylating agents alone or combined modality treatment. The cumulative 15-year risk of leukaemia was 17% and the relative risk 117. A previous case-control study by the same authors on leukaemia following NHL treated by similar chemotherapy regimens but without TBI has shown a 2- to 13-fold relative risk for the various regimens (32).

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 4 weeks between each of them. Seventy-five 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% but had a median survival of 78 months (33).

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 155/2 (17, 27) 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 (34). A review of retrospective or registry data found that the combination of fTBI and cytostatic drugs was not superior to chemotherapy regimens alone in aggressive NHL (35). 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 in both indolent and aggressive NHL (36).

In a report in 1999 from the European Bone Marrow Transplantation (EBMT) Lymphoma Registry on about 5 000 transplanted patients from 131 centres the actuarial risk for ANLL/MDS at 5 years post-transplant was 3% for patients with NHL, and a multivariate analysis demonstrated fTBI as a risk factor. However, these risks for ANLL/MDS may not exceed those for a similar group of patients after standard treatment and a further survey is under way (37).

The literature shows that:

- The benefit of radiotherapy for bulky disease has not been definitely confirmed.
- The value of TBI for treatment of NHL 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 extranodal non-Hodgkin's lymphomas

Primary extranodal 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 extranodal NHL presents as localized disease and has 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 anatomical extent of the disease. Special consideration must be taken in

organs for which curative doses of radiation compromise 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 increasing incidence not only in immunocompromised patients but also in immunocompetent patients and the rate of increase is greater than for NHL at other sites (38, 39). However, in a Danish population-based study no increased incidence of non-AIDS-related primary CNS lymphoma was found (40). The prognosis is dismal.

The previous report (SBU 129/2) concluded that the traditional role of radiotherapy for CNS lymphoma has been re-evaluated 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 (41).

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 (42). 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 overall or disease-free survival has not been reached. This may suggest a positive effect of the other drugs (vincristine, procarbazine and high-dose cytarabine) (43). Less favourable results were seen when the Nordic Lymphoma Group evaluated combination chemotherapy (44).

Only one randomized trial has been reported. A British multicentre trial compared radiation alone with radiation followed by chemotherapy (CHOP). No benefit from additional CHOP was observed (45). This result was not surprising because 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 was probably 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 in 1980–1995 with more than 1 000 immunocompetent patients with PCNSL, 676 patients were analysed 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 analysed because of the heterogeneity of chemotherapy regimens and therapy sequence (46).

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% (43, 47, 48) in comparison to median survival of 17–21 months and 5-year survival of 26–27% reported with radiotherapy alone in recent retrospective series (49, 50). 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 (43). Long-term follow-up has revealed that after 1 year nearly 80% of the survivors over the age of 60 at diagnosis had developed progressive leukoencephalopathy, and almost 100% within 4 years of treatment. Only 30% of younger patients had similar symptoms after a 7.5-year latency (47, 51). 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 (51). It is likely that the neurotoxicity is a sequelae of whole-brain radiation exacerbated by the toxicity of methotrexate and cytarabine (39).

The literature shows that:

- As 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 in prospective and retrospective series has 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	–	4/138	1/31	5/169
R	–	–	2/111	2/111
L	4/676	–	–	4/676
O	2	–	–	2
Total	6/676	4/138	4/195	14/1 009

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 129/2) 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 (52), which makes randomized trials almost impossible.

The conclusions from the previous literature review (SBU 129/2) are on the whole unchanged, that is full agreement that chemotherapy should be given initially (after orchiectomy), irradiation to the 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.

The International Extranodal Lymphoma Study Group (IELSG) has recently conducted a retrospective study on 373 men with primary testicular diffuse large B-cell lymphoma from 23 centres to evaluate patterns of presentation, treatment and outcomes (53). The median age of the patients was 66 years, and 57% of the patients presented with stage I, and 22% with stage II. The majority of patients (75%) were treated with combination chemotherapy, 34% had received prophylactic scrotal irradiation, but only 18% had received prophylactic intrathecal chemotherapy. The median survival for patients with stage I–II was 5.8 years with an actuarial 10-year overall survival of 27%. 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%. 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%.

IELSG is now performing a prospective study to assess the efficacy of prophylactic scrotal radiotherapy 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 (52). 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 (mucosa associated lymphoid tissue) lymphomas. 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% of all NHL (54, 55). Typically, MALT lymphomas arise from lymphoid tissue that has been acquired as the result of a chronic inflammatory, often autoimmune, disorders (56). 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 (3).

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 in 1993 (57). 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 (58).

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% have spread to the gastric lymph nodes or beyond at the time of diagnosis (56, 59, 60). Gastric MALT lymphomas are in most cases preceded by *Helicobacter pylori*-associated chronic gastritis. Eradication of *H. pylori* by antibiotic and anti-acid therapy leads to regres-

sion of the lymphoma in approximately 75% of the cases (56). However, relapse following antibiotics is not uncommon. Only long-term prospective studies can assess the value of eradication of *H. pylori* (61).

The classical approach for management of gastric lymphomas has been primary surgery (54). However, treatment recommendations vary widely in the literature and prospective randomized clinical trials have not been preformed. An international survey was performed in 1996–1997 including 19 centres in Europe, the United States and Japan. All centres 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 centres preferred surgery sometimes combined with radiotherapy or chemotherapy. In two centres 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 (62). Radiotherapy alone may be one approach to treat MALT lymphomas refractory to antibiotic therapy. In a small prospective study from the Memorial Sloan Kettering Cancer Centre (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 (63).

A German prospective multicentre study performed in 1992–1996 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 (64). 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 (65, 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 multicentre study was performed in 1993–1996. 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 radiotherapy as well. The 2-year overall survival for indolent lymphomas ranged between 89% and 96%. For high-grade lymphomas, patients with complete resection or microscopic tumour residuals had significantly better overall survival (88% for stage I_E and 83% for stage II_E) than those with macroscopic residues (53%). 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 (67).

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 towards stomach-conserving therapy with radiotherapy and/or chemotherapy.
- The roles of radiotherapy and chemotherapy in gastric lymphomas have still to be defined.

MALT lymphomas

	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 (approximately 80%) 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% (68, 69).

No randomized trials concerning therapy exist. In a retrospective analysis with most patients treated with radiotherapy the cause-specific survival at 5 years was significantly better for MALT lymphomas; 90% compared with 55% if no evidence of MALT lymphoma existed and nearly all of these patients had aggressive lymphomas. These results indicate that radiotherapy could be a satisfactory treatment in indolent lymphomas (70). 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 (68).

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 the tongue. The therapy results vary greatly depending on histology and anatomical site (71).

Lymphoma in Waldeyer's ring (tonsil, base of the tongue and nasopharynx). Head and neck lymphomas occur predominantly in Waldeyer's ring. About 70% 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. There is often a relationship to gastrointestinal involvement (71).

One prospective randomized study has been published on NHL in Waldeyer's ring. Three hundred and sixteen 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 (FFS) and overall survival (OS) at 5 years were significantly better in the combined modality group compared with either radiotherapy alone or chemotherapy alone (FFS, 83% vs. 48% vs. 43%; OS, 90% vs. 58% vs. 56%) (72). In this study radiotherapy was given before chemotherapy but in reviews chemotherapy before radiotherapy is advocated (69, 71, 73).

Lymphoma in salivary glands. The majority of the lymphomas in salivary glands are located in the parotid, are 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-year survival of 90–95%. Radiotherapy alone was considered the therapy of choice (74).

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 haemophagocytic 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 poor, with 5-year survival of only 12–15% after radiotherapy alone (71, 73). Neither randomized trials nor prospective studies concerning optimal therapy exist. Some retrospective analyses suggest that combination of chemotherapy and radiation may offer the best chance of long-term disease-free and overall survival (75, 76), while others do not find any significant improvement in the prognosis with combined modality (77, 78). 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 (69, 71, 73).

The literature shows that:

- For aggressive lymphomas in Waldeyer's ring with limited disease combined modality with chemotherapy and radiotherapy is the current recommendation.
- 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-cell lymphomas. Nothing essential changes earlier recommendations, that is radiotherapy for progressive or refractory mycosis fungoides and for B-cell lymphomas 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. Radiolabelled monoclonal antibodies against antigen on the surface of B lymphocytes are used to carry the radioactivity to the disease sites where they emits continuous, exponentially decreasing, low-dose irradiation. Usually iodine 131 or yttrium 90 labelled antibodies are used to target the CD20 antigen, which more than 90% of

B-cell NHL express, but other monoclonal antibodies have also 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 uses repetitive infusions of low non-myeloablative doses of radiolabelled antibodies, and the alternative is high myeloablative doses of radioactivity in conjunction with autologous haematopoietic stem cell rescue. Studies with low-dose strategy have shown objective responses in 65–80% of the patients, complete remission in 20–50% of the patients, with a median response duration of 12 months. The high-dose strategy has demonstrated objective responses in 85% of the patients, complete remission in up to 79% of the patients, and a median response duration of more than 24 months (79, 80). 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% for patients with indolent lymphomas and 20% for those with aggressive lymphomas. Reversible cardiopulmonary toxicity was dose limiting in this setting (81).

Only one randomized clinical trial with RIT has been performed. One hundred and forty-three patients with relapsed/refractory indolent or transformed NHL were randomized between Zevalin (ibritumomab tiuxetan: anti-CD20 monoclonal antibody conjugated with yttrium 90) radioimmunotherapy and rituximab (anti-CD20 monoclonal antibody) immunotherapy. The overall response rate was 80% in the Zevalin arm vs. 56% in the rituximab arm ($p = 0.002$) with a 30% vs. 16% complete remission, respectively (82).

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 non-myeloablative 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
M	–	–	–	–
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 indicate that one-third to one-half of patients with indolent lymphoma in stage I are cured by radiotherapy (follow-up more than 15 years) ((8)R3, (9)R2, (10)R1, (11)R2, (15)C3).
- Addition of chemotherapy to radiotherapy does not suggest any improvement in overall outcome ((15)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 the SBU 129/2 report are still valid.

Aggressive localized lymphomas

- Data indicate that one-half of patients in stage I are cured by radiotherapy alone ((10) R1, (19) 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 (19) R1, (20) P2, (21) R2, (22) R1, (23) C1, (25) P2, (26) P2, con (24) C3).

– Conflicting data have been published on the value of radiotherapy towards bulky disease and no firm conclusions can be drawn (pro (28) C3, (29) R2, con (11) R2, (22) R1, (25) P2).

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

Total body irradiation (TBI)

The value of TBI for treatment of NHL has not been proven.

– There is no proof that fractionated TBI in conjunction with high-dose chemotherapy is superior to chemotherapy regimens alone ((34) R1, (35) L1, (36) L1).

Primary CNS lymphomas

– Data show that radiotherapy induces response of short duration and is associated with major neurotoxicity, especially in elderly patients ((41) P2, (42) L2, (43) P2, (46) L1, (47) P3, (49) R3, (50) R3).
– High-dose methotrexate therapy seems to lead to longer survival than radiotherapy alone. No randomized trials have been performed ((42) L1, (43) P2, (47) P3, (48) P2).
– There is fairly good support for primary chemotherapy including high-dose methotrexate followed by radiotherapy in patients below 60 years ((42) L1, (43) P2, (46) L1, (47) P3).
– 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-resistant 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 ((69) L1, (71) L1, (72) C2, (73) L1).
– There are sparse data supporting radiotherapy alone in localized indolent lymphomas in the salivary gland ((74) 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 non-myeloablative 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 ((82) C2).

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