## Section 13

# NON-HODGKIN'S LYMPHOMAS (NHL)

### Summary and Conclusions

This synthesis of the literature on radiotherapy for non-Hodgkin's lymphomas is based on 158 scientific articles, including 16 randomized studies, 18 prospective studies, and 90 retrospective studies. These studies involve 14 137 patients.

- 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 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 of the eye.
- It is important to identify groups and subgroups in whom radiotherapy alone is sufficient, ie, the risk for distant recurrence is small. MALT lymphoma belongs to this group.
- Radiotherapy is often valuable in palliative situations.

### Introduction

In Sweden, 1 349 cases of non-Hodgkin's lymphomas, excluding chronic lymphatic leukemia, were diagnosed in 1992, corresponding to 3.4% of all newly diagnosed malignant tumors. NHL mainly affects older age groups, and two thirds of the patients are over age 60 years at onset, the median age of newly diagnosed cases is 70 to 74 years (II). In 1992, 733 deaths were attributed to NHL in Sweden (III).

*Histologically*, NHL comprises a very heterogeneous group of tumors with large variations in morphology and clinical course. The malignant cell originates from lymphatic cells at various stages of development.

Several different histopathological classifications are in use, making it difficult to compare and evaluate different studies, although a "Working Formulation" has been developed to facilitate translation among the various classifications (1). However, the Working Formulation inadequately defines the various subgroups, and a proposed new classification, so-called REAL classification, was recently presented (2).

Sweden has hitherto used the Kiel classification[1] (XXV) which separates NHL into high-grade and low-grade malignancies. The present report also uses this classification system.

*Staging*, is rather similar to Hodgkin's lymphoma.[2]

[1] Updated Kiel Classification for non-Hodgkin's lymphomas, (1988) with additions:

| B-cell Lymphomas | T-cell Lymphomas |
|---|---|
| **Low-Grade Malignant Lymphomas** | |
| Lymphocytic<br>chronic lymphocytic leukemia<br>prolymphocyte leukemia hairy cell leukemia | Lymphocytic<br>chronic lymphatic leukemia<br>prolymphocyte leukemia |
| Lymphoplasmocytic/-cytoid (Immunocytoma) | Small cell, cribriform |
| Plasmocytic | Mucosis fungoides, Sézary's syndrome |
| Centroblastic-centrocytic follicular ± diffuse<br>diffuse | Lymphoepitheloid (Lennert's lymphoma) |
| Centrocytic (mantle cells) | Angioimmunoblastic (AILD, LgX) |
| Monocytoid | T-zone lymphoma Pleomorpha, small cell (HTLV − I ±) |
| **High-Grade Malignant Lymphomas** | |
| Centroblastic (HTLV − I ±) | Pleomorpha, mid-sized or large cell |
| Immunoblastic Burkitt's lymphoma | Immunoblastic (HTLV − I ×) |
| Large cell anaplastic (Ki − I +) | Large cell anaplastic (Ki − I +) |
| Lymphoblastic | Lymphoblastic |
| Unusual types | Unusual types |

[2] Staging of non-Hodgkin's lymphoma (Ann Arbor Classification):
Stage I = Involvement of a single lymph node region or lymphoid structure such as, eg, spleen, thymus, or Waldeyer's ring.
Stage II = Involvement of two or more lymph node regions on the same side of the diaphragm (mediastinum is one region, hilus of lung is considered a separate region).
Stage III = Involvement of lymph node regions on both sides of the diaphragm.
Stage IV = Involvement of extranodal site(s), with exception of conditions classified as "E".
Additions:
A = No general symptoms.
B = Symptoms such as fever, night sweats, and/or weight loss.
E = Involvement of a single extranodal site in conjunction to disease in a lymph node region.
CS = Clinical stage, PS = Pathological stage

Pathological staging (PS) means that the patient has undergone staging laparotomy. The definition of bulky disease varies, but most authors suggest tumors >5 cm, although definitions of >7 cm and >10 cm also exist. Bulky presentation usually represents a prognostically unfavorable factor in studies which have addressed this issue (3–7).

The extent, localization, and histology of the disease, and the patient's age and general condition determine the choice of therapy. Since lymphoma cells are highly radiosensitive, radiotherapy offers an important method for treating NHL. A broad spectrum of disease manifestations are suitable for radiotherapy alone or in combination with curative chemotherapy. Radiotherapy may also be used in certain palliative situations. The natural progression of the disease varies according to low-grade or high-grade malignant NHL: Hence, the two main groups are addressed separately here.

## Treatment, General

Which treatment is most suitable for localized NHL is a controversial issue. Radiotherapy has been the traditional approach. Since effective chemotherapy has been developed for treating advanced disease, combined radio- and chemotherapy, or chemotherapy alone have been introduced as alternatives to radiotherapy at early stages. Chemotherapy has been motivated by the presence of subclinical spread in a large share of patients with apparent local disease.

Most studies include patients at both stages I and II, making it difficult to judge the value of radiotherapy since the prognostic implications of both stages differ (5, 8–13). The prognosis for patients at stage II does not differ substantially from that at stages III and IV (14–15).

As with Hodgkin's disease, well-defined radiation volumes are often used for non-Hodgkin's lymphomas.[3]

## Low-grade malignant non-Hodgkin's lymphomas

Low-grade malignant NHL, which comprises nearly two thirds of nodal NHL based on the Kiel classification (XXV) is often characterized by a relatively slow course with a median survival of 7 to 9 years (16, 17). Relapse occurs at a steady rate of approximately 15% annually for many years (18). Curative treatment for generalized disease has yet to be confirmed. Transformation to high-grade lymphoma occurs frequently, reported in 45% of cases, whether or not patients receive treatment (19), and appears in up to 70% of autopsies (20). Spontaneous regression, of longer or shorter duration, also occurs (21).

### Localized disease: stages I–II

Relatively few patients (10% to 20%) with low-grade malignant NHL have localized disease (9, 16, 17).

#### *Radiotherapy*

A review of 8 studies of radiotherapy for stage I (nearly all patients are classified by clinical stage) reported relapse-free, 10-year survival ranging from 47% to 80% (4, 6, 10, 22–26). The survival curves tend to plateau after 5 to 7 years at stage I, supporting the hypothesis that it may be possible to cure this relatively rare presentation of disease (10, 16, 22, 24, 25). Nevertheless, other studies have noted that relapse occurs later (26), even as late as after 15 years (19). The local recurrence rates following radiotherapy are reported to range between 2% and 5% (6, 10, 23, 24).

Four studies of stage II reported relapse-free, 10-year survival between 35% and 50% (23–25, 27).

Radiation volume varies by study. Involved field (IF) has been used in most studies. Few randomized studies exist. A randomized study at Stanford, including only 20 patients, found no difference in relapse-free and overall survival when comparing IF with TNI (23). A randomized EORTC study noted no difference in therapeutic results between IF versus TNI given prior to chemotherapy at stage II (28).

#### *Combination radio- and chemotherapy*

The role of chemotherapy in local, low-grade malignant NHL is unclear.

Six randomized studies compared radiotherapy alone with radiotherapy followed by chemotherapy (12, 26, 28–31). Two studies found significantly longer relapse-free survival with combination therapy (12, 29), and one study found a marginal extension (28) while the remaining three studies revealed no differences among the treatment groups. Overall survival was similar for both treatment arms in all studies.

Four retrospective reports (4, 24, 27, 32)—one study alternated chemotherapy with radiotherapy (27)—observed similar results.

Relapse-free survival for combined treatment was better in two reports (27, 32) while the other two found no differences. These studies also showed that overall survival was similar in both treatment arms.

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[3] Definition of irradiation volumes = target:
IF = Involved Field: irradiation of the involved site(s).
EF = Extended Field: irradiation of tumor site and the adjacent areas with no known disease involvement.
TNI = Total Nodal Irradiation: combination of mantle and inverse Y treatment.
TLC = Total Central Lymphatic Irradiation: TNI plus irradiation of the total abdomen and Waldeyer's ring.
TBI = Total Body Irradiation.
TSEBI = Total Skin Electron Beam Irradiation.
RTSEI = Rotational Total Skin Electron Irradiation: irradiation of the total skin surface.

### Advanced disease: stages III and IV

Most patients with low-grade malignant NHL have generalized disease on diagnosis, mainly due to bone marrow involvement (9).

The optimum treatment strategy for advanced disease is highly controversial. Two different treatment strategies exist; (a) no initial treatment except watchful waiting and, if needed, palliative, single-drug chemotherapy or IF radiotherapy, and (b) second-line treatment with extensive irradiation, aggressive chemotherapy, or combination therapy (17). A randomized study from NCI showed no difference in 5-year survival (75%) between primary watchful waiting and combination therapy with aggressive chemotherapy and extensive irradiation (33).

#### *Radiotherapy*

In the absence of curative chemotherapy for low-grade malignant NHL, very comprehensive radiotherapy has been attempted in advanced disease, however, with discouraging results (9). A study from four different centers in the United States reported a 15-year relapse-free survival of 40% following 20 Gy to 30 Gy TLC (total central lymphatic irradiation) at stage III (34). A Stanford study also reported a 15-year, relapse-free survival of 40% following 35 Gy to 50 Gy TNI, or 1.5 Gy total body irradiation plus a boost to 20–30 Gy at stage III (35). This suggests that extensive irradiation can lead to lasting freedom from disease in this patient group, mainly when disease involvement appears in less than five locations and is not bulky, but these comprise only about 10% of all patients at stage III (9).

Stanford has also reported 40% survival after 15 years without therapy in selected patients at stages III and IV (21). These patients were also compared retrospectively with corresponding patients who participated in various intervention studies, but no differences in survival were observed (36). Substantially shorter survival was found in other US studies; (median under 5 years) (37), and a median survival of 6 years in untreated patients has been reported from England (38). These patient studies are less selective, which may possibly account for the discrepancy compared to the Stanford figures.

#### *Combination radio- and chemotherapy*

A randomized study from Stanford (stages III and IV) with more than 15-years of followup showed no difference between chemotherapy alone or in combination with TNI/total body irradiation. Median survival was 10 years. After 20 years, 20% were still alive, half without disease (19). A randomized Mexican study (stages III and IV) found that combination therapy yielded significantly longer relapse-free and overall survival. After 7 years, 70% in the combination therapy arm versus 30% in the chemotherapy arm were relapse-free (39).

A prospective study from MD Anderson which alternated chemotherapy with radiotherapy in patients at stage III showed that approximately 60% were relapse-free after 7 years with a reduced risk of relapse after 4 to 5 years, suggesting that some patients could be cured (40), although these results should be interpreted with caution due to the prolonged natural course of the disease (18).

*For localized disease, the literature review shows:*

- that in most cases (>90%), radiotherapy leads to local control;
- that radiotherapy is standard treatment for low-grade malignant NHL stage I, and provides long-term survival in about 50% of cases, and in an even greater proportion of younger patients (22, 26, 32, 41);
- that involved field is the recommended radiation volume at stage I, with the exception of controlled trials (23, 42), currently nothing suggests that more comprehensive radiotherapy or the addition of chemotherapy would improve the results (16, 41–43);
- that radiotherapy is not recommended in stage II, or in the presence of general symptoms suggestive of subclinical disease extension, when there is a high risk for relapse (26).

*For advanced disease, the literature review shows:*

- that two studies of limited tumors at stage III reported greatly prolonged remission after extensive radiotherapy (34, 35) or combination therapy (40). However, only a small number of patients are appropriate for such extensive irradiation (44);
- that two randomized studies compared chemotherapy and combination therapy (at stages III–IV) and arrived at different results (19, 39);
- that the value of adjuvant radiotherapy in advanced disease has not been confirmed;
- that radiotherapy has little impact on advanced, low-grade malignant NHL, but TBI may be considered; see this section.

### High-grade malignant non-Hodgkin's lymphoma

High-grade malignant NHL often (40%) debuts with extranodal manifestations (8, 22, 45). The clinical course is more rapid with a median survival of approximately 1 year (16). In contrast to low-grade malignant NHL, some patients with high-grade malignant NHL can be cured. Relapse occurs relatively quickly, usually within 2 years after completed treatment (21).

### Localized disease—stages I and II

At diagnosis, high-grade malignant NHL is more localized (25% to 40%) than low-grade (9, 44), with 10% to 15% of cases reported to be at stage I (46).

*Radiotherapy*

Three small studies of pathologically staged patients show that 80% to 90% were relapse-free after 5 years (9, 47, 48). A review of 10 studies of clinically staged patients shows that relapse-free survival after 5 years varies between 40% to 75% (4, 6, 10, 22, 25, 32, 46, 49–51).

At stage II, 35% to 40% of pathologically-staged patients were relapse-free after 5 years (9, 47, 48). A review of 7 studies of clinically staged patients showed a variation in relapse-free, 5-year survival between 0% to 35% (4, 12, 13, 25, 32, 49, 52). In three of these studies all patients had relapsed within 5 years (12, 32, 52).

High-grade malignant NHL requires higher doses than low-grade malignant NHL, especially with bulky disease. One study reported 18% local recurrence if the dose was less than 40 Gy and 5% local recurrence at higher doses (49). An EORTC report noted 30% local recurrence at a dose $<45$ Gy and 13% local recurrence was observed at a dose $>45$ Gy (28), and a British study found 100% local control at a dose $>45$ Gy (13). Local relapse of 3% to 10% was reported after radiotherapy alone (13, 30, 46, 50, 51, 53).

*Chemotherapy*

Three small uncontrolled studies reported that 80% to 95% were relapse-free 5 years after chemotherapy alone at stages I and II (32, 54, 55).

*Radiotherapy followed by adjuvant chemotherapy*

Six randomized studies compared radiotherapy with radiotherapy followed by various chemotherapy combinations, excluding (in all but one study) doxorubicin (5, 12, 28–31). Three of these studies showed improved disease-free, 5-year survival with combination therapy (12, 29, 30). One study demonstrated that overall survival clearly improved (12) while another showed the benefits to be marginal (30). Three studies showed no differences among the treatment arms (5, 28, 31). The EORTC study showed very high frequency of relapse in patients at stage II regardless of treatment arm, 90% had relapsed within 4 years, resulting in discontinuation of the study (28).

The same comparisons were made in two uncontrolled studies which included doxorubicin in chemotherapy (32, 49). One study showed longer freedom from relapse (32), but no improvement in overall survival, while the other study noted no differences.

*Chemotherapy followed by radiotherapy*

Earlier studies delivered irradiation first followed by adjuvant chemotherapy, but after noting that relapses often affected areas beyond the irradiated area during or shortly after completed radiotherapy, the sequence was reversed. Hence, later studies started off with chemotherapy, consolidating it with irradiation (11, 49, 56, 57).

Good therapeutic results have been achieved in prospective but nonrandomized studies where chemotherapy (usually CHOP or variants thereof) constituted primary therapy, followed by adjuvant irradiation. Six studies reported complete remission in 79% to 99% of patients, relapse-free, 5-year survival of 62% to 100%, and overall survival ranging from 65% to 94% (4, 53, 54, 56, 58, 59). Three nonrandomized studies compared chemotherapy and combination therapy without noting any differences in therapeutic results (53, 54, 58). One study observed more local recurrence in chemotherapy patients than in those receiving combination therapy; 18% versus 6% (54). A study from Milan found 87% in complete remission after chemotherapy and another 11% achieved complete remission after complementary irradiation (56). No randomized studies have been reported, although such studies (ECOG and SWOG) are under way (60).

It has been suggested that the number of chemotherapy cycles can be reduced if radiotherapy is given afterward (17), and this has been tested with excellent results (61).

*Alternating chemotherapy and radiotherapy*

Alternating chemotherapy and radiotherapy has been tried in an attempt to prevent chemo- and radioresistance. Four reports on alternating chemotherapy and radiotherapy—where most patients presented unfavorable prognostic factors such bulky disease or general symptoms—showed encouraging results, with 90% in complete remission, approximately 80% relapse-free after 5 years, and an overall 5-year survival of about 70% (11, 57, 62–64). In the Stanford study, no patient had relapsed within 5 years. The Manchester study compared its results of alternating treatment with earlier radiotherapy followed by chemotherapy, but observed no significant differences (57). It is necessary to test this treatment sequence in the context of large controlled studies.

Local recurrence ranging from 2% to 7% in irradiated areas was reported following combination therapy (11, 51, 56, 62, 64).

## Advanced disease: stages III–IV

*Chemotherapy*

Presumably, 30% to 50% can be cured by chemotherapy (65).

*Combination radio- and chemotherapy*

A randomized study at Stanford comparing chemotherapy and combination therapy shows no difference between the therapy arms, neither in terms of freedom from recur-

rence nor overall survival after 10 years (9). A large randomized multicenter study from Germany tested the value of adjuvant radiotherapy following chemotherapy, but the followup time is yet too short to draw conclusions (66).

So-called "iceberg radiotherapy" (30 Gy to disease sites initially >5 cm or sites with remaining disease after 3 chemotherapy cycles) is described in EORTC studies, and remission in 9% of the patients went from partial to complete remission following this type of radiotherapy (67).

Consolidated radiotherapy of 35 Gy IF was also used following chemotherapy in a German study, and 6% of the patients went from partial to complete remission following radiotherapy (68), the dose had been increased to 35 Gy after an earlier study found 18% local recurrence following 25 Gy (69).

An analysis of relapse sites has shown that two thirds of relapse occurs at sites not earlier involved, hence, adjuvant irradiation is of minor importance (3).

*Special indications for radiotherapy*

Patients with high-grade malignant NHL and bone marrow involvement, disease in the testes or in the facial sinuses, and all patients with lymphoblastic lymphoma are at high risk for lymphoma in the central nervous system (CNS). CNS prophylaxis using methotrexate therapy and/or CNS irradiation (normally 24 Gy) is therefore recommended (9, 70). Some authors are skeptical (71) or negative (72) toward CNS prophylaxis in cases of testicular lymphoma.

*Regarding localized disease, the literature review shows:*

- long-term survival after radiotherapy alone is reported in slightly over 50% of patients with high-grade malignant NHL at stage I;
- that there are reports of primary chemotherapy for localized high-grade malignant NHL, and many authors recommend chemotherapy already at stage I (32, 44, 73);
- that the frequency of relapse at stage II is significantly greater than at stage I, regardless of whether the patient is clinically or pathologically staged, and chemotherapy is unanimously recommended (28, 42, 44, 73);
- that some studies, both randomized and retrospective, suggest that relapse-free survival is extended with combination therapy (radiotherapy followed by chemotherapy), although overall survival is unaffected (41);
- that the value of adjuvant chemotherapy has not been clearly demonstrated. Often, chemotherapy has been less than optimal since doxorubicin has not been included;
- that combination therapy (chemotherapy followed by radiotherapy) has not been tested in randomized studies, but the results of retrospective comparisons of combination therapy are no different from chemotherapy alone, and the value of adjuvant radiotherapy at stages I and II remains to be demonstrated (42, 73).

*Regarding advanced disease, the literature review shows:*

- that advanced high-grade malignant NHL should be treated with chemotherapy (17);
- that adjuvant radiotherapy has not been shown to be of value (3, 9, 74);
- that consolidated radiotherapy may increase the number of complete remissions;
- that radiotherapy as a means of CNS prophylaxis is recommended for special indications.

**Total Body Irradiation (TBI)**

Total body irradiation means that the entire body is irradiated with 0.1 to 0.15 Gy/fraction 2 to 3 times per week, achieving a final dose of 1.5 to 3.0 Gy.

Following total body irradiation for high-grade malignant NHL at stages III–IV, a review of six studies published from 1978 through 1989 including 128 patients found that all patients relapsed within 5 years, except in one study which showed that 10% were relapse-free. Five-year survival was 13% (41). TBI has no value in treating high-grade malignant NHL (75, 76).

In 156 patients with low-grade malignant NHL the review shows that approximately 25% were relapse-free after 5 years, and 15% after 10 years. 60% of the patients were alive after 5 years and approximately 35% after 10 years (41). Similar results were achieved with chemotherapy for low-grade malignant NHL (16, 36, 76). Two randomized studies confirmed that the therapeutic results of TBI and chemotherapy do not differ (77, 78).

In choosing treatment modalities, consideration should be given to acute and delayed complications, radiation therapy resources, and costs. The two controlled studies found fewer infections among those receiving TBI compared to chemotherapy, but some patients were affected by permanent cytopenia following TBI, which may complicate later chemotherapy (77, 78). A randomized EORTC study showed no advantages with TBI compared to chemotherapy, neither regarding survival nor life quality (15). Some patients have developed acute myeloid leukemia or myelodysplastic syndrome (at doses >2.0 Gy) after TBI (76, 77). TBI cannot cure NHL, but may be considered as a potential treatment for advanced low-grade malignant NHL (76).

Experiments which combined TBI with total body hyperthermia, which is assumed to reduce the degree of thrombocytopenia, have been reported in isolated patients (79).

Total body irradiation in conjunction with bone marrow transplantation in NHL patients is not discussed here, but is addressed in Section 17.

## Special disease sites

### *Primary CNS lymphoma*

Primary CNS lymphoma is rare although the frequency is increasing generally, with a particularly high incidence noted among immunosuppressed individuals. Primary CNS lymphoma comprises 2% of all brain tumors and 2% of all NHL (17).

CNS lymphoma is radiosensitive, but intracranial recurrence is common, and median survival is only 12 to 18 months following radiotherapy (17, 80–82), compared to 1 to 5 months median survival after surgery alone (83). Five-year survival following radiotherapy is reported at 3% to 7% (80, 82, 83).

Lymphoma cells were reported in the cerebrospinal fluid (CSF) in 10% of patients on diagnosis (83). Opinions diverge on whether the entire craniospinal canal should be irradiated, several groups recommend it if CSF analysis reveals lymphoma cells (84, 85), while others suggest that it leads to complications in later chemotherapy (81). Orbital involvement has been reported in up to 25% of cases during the course of the disease (82), and therefore the posterior orbit should be included in the target volume (84, 86).

The dose-response relationship reveals a 5-year survival of 33% to 42% at doses >50 Gy, which is clearly superior to the 0% to 13% at doses <50 Gy (83, 87). Despite 40 Gy to the total brain, with a boost to 60 Gy in the tumor region, one prospective study reports intracranial recurrence at 60%, of which 88% occurred within the 60 Gy region (80).

Since local control is difficult to achieve with radiotherapy, hyperfractionated radiotherapy (65 Gy/54 fractions) was attempted in a small pilot study. The study was terminated due to severe toxicity (88).

Attempts to improve results with combined radiotherapy and chemotherapy have been reported in eight small pilot studies using different types of chemotherapy drugs prior to or following radiotherapy (41, 84, 89–93). Five of these studies reported a longer median survival (20+ to 60 months) with combination therapy than with radiotherapy alone (41, 84, 89–91). However, one of the studies reported considerable delayed toxicity, with dementia and ataxia in 10% of patients (90).

*The literature review shows:*

- that the traditional role of radiotherapy for CNS lymphoma has been reevaluated due to the high frequency of local recurrence;
- that some authors recommend initial chemotherapy followed by radiotherapy;
- that other authors believe it is premature to recommend combination therapy, ie, radiotherapy and chemotherapy (93).
- that radiotherapy increases median survival, but it is doubtful whether radiotherapy or combined radiotherapy and chemotherapy provide any other substantial curative or palliative effects in this diagnostic group, in whom the prognosis is very poor.

### *Orbital lymphoma*

Primary orbital lymphoma is rare, <1% of all NHL, and most are low-grade malignancies. Intraocular lymphoma, often with vitreous body involvement, frequently spreads to the CNS and should be distinguished from the more common conjunctival and retrobulbaral lymphomas (94).

A review of nine studies including 266 patients (of whom two thirds had low-grade malignancies) showed that radiotherapy led to local control in 90% to 100%. Distant recurrence appeared in 20%, often in the other eye (94). A large British study observed that survival after radiotherapy for low-grade malignant orbital lymphoma was identical to an age-matched normal population, while only 25% of patients with high-grade malignant orbital lymphoma were alive after 10 years. All mortality was a result of generalized lymphoma (95).

Opinions differ concerning optimal dose. Some recommend 24 Gy to 35 Gy, since higher doses do not improve therapeutic results but yield only greater side effects (96, 97). Others recommend 30 Gy to 35 Gy for low-grade malignant NHL and 36 Gy to 40 Gy for high-grade malignant NHL (94, 95). Lens shields should be used to reduce the risk for cataracts.

Chemotherapy is reported to be ineffective against vitreous body or retinal lymphomas (86).

*The literature review shows:*

- that radiotherapy is standard treatment for low-grade malignant orbital lymphoma and leads to local control in 90% to 100% of cases (94, 95);
- that due to the high risk for generalization, high-grade malignant orbital lymphoma should be treated with chemotherapy in addition to radiotherapy (94).

### *Testicular lymphoma*

Primary testicular lymphoma is rare and comprises approximately 5% of testicular tumors and 1% to 2% of all NHL (72, 98). Bilateral involvement is reported in nearly 20% of the cases (71, 98, 99). The course of the disease frequently involves the nasopharynx and oropharynx including Waldeyer's ring, the skin, lungs, and CNS (71, 98–100).

The prognosis is poor. A literature review including documentation on more than 500 patients treated through the 1970s reported 5-year survival at 12% (71). A recurrence rate of 50% to 100% was reported after radiotherapy for localized testicular lymphoma (6, 71, 72, 99). Patients relapse quickly, often within 10 months (72, 100, 101).

A prospective study from Vancouver used short-term, initial chemotherapy followed by radiotherapy to the scrotum at stage I (to prevent recurrence in the other testicle where chemotherapy drugs have poor penetration) and also at stage II to the pelvis and para-aortal lymph regions, and 93% were disease-free after 5 years compared to 50% in historical controls with radiotherapy alone (72).

*The literature review shows:*

- that the literature reflects full agreement that chemotherapy should be given initially (6, 71, 72, 98, 99, 101, 102);
- that due to the high risk of recurrence in the other testicle, irradiation of the scrotum is recommended (71, 72, 98, 101, 102);
- that risk is high for recurrence in the CNS, but some authors doubt whether CNS prophylaxis should be given (71), while others say it is unnecessary when chemotherapy is given (72).

### *MALT lymphoma (Mucosa-Associated Lymphoid Tissue)*

A large percentage of extranodal NHL appears in mucosa associated lymphoid tissue (MALT), now considered to be a separate unit. It includes lymphoma in the gastrointestinal tract, salivary glands, lungs, thyroid, and Waldeyer's ring. Lymphomas at these sites often remain localized for prolonged periods during the course of disease and respond favorably to local therapy (103, 104).

One report shows that the risk for distant recurrence is less with MALT lymphoma (20%) than with nodal (40%) and other extranodal NHL (50%). At 10-year followup of radiotherapy, 80% of the patients who had received a diagnosis of localized MALT lymphoma without bulky presentation were still alive. 23% had experienced relapse, 13% of whom experienced isolated distant recurrence (105).

### *Lymphomas in the gastrointestinal tract*

The gastrointestinal tract is the most common extranodal site, and approximately half of all extranodal NHL originates here. With these lymphomas, particularly stomach lymphoma, one finds a high rate of subclinical involvement of Waldeyer's ring (106).

*Stomach lymphoma.* Primary stomach lymphoma comprises 20% of extranodal NHL and approximately 5% of all stomach malignancies (106). MALT-type lymphomas reportedly comprise 30% to 50 % (107–110).

Optimal treatment has been a subject of lively debate for years. Some advocate surgery alone, others radiotherapy alone, yet others surgery plus radiotherapy or chemotherapy ± radiotherapy as an alternative to surgery. Numerous publications are available, often retrospective analyses with different histopathological compositions and substantial variations in treatment, making it impossible to compare therapy types.

Primary surgery can identify the spread of disease and avoid the risk for perforation and hemorrhaging from radiotherapy and/or chemotherapy (106). However, the reported risks are small (45, 108), and surgery does not always prevent these complications (109). With modern diagnostic methods (endoscopy and computerized tomography), surgical exploration is unnecessary (108). Removing the stomach in these, often elderly, patients involves some morbidity and may create disorders such as dumping syndrome and malabsorption, which can be avoided by limiting treatment to chemotherapy and/or radiotherapy.

Many authors recommend primary surgery, and seven studies showed that 5-year survival following surgery at stage I was 37% to 87% and at stage II 38% to 61%, figures which do not differ from the results of radiotherapy alone without surgery (108). Recent publications report no improvement in therapeutic results in patients who receive primary surgery (108, 110, 111).

Consensus was achieved at the Lugano Workshop in 1993 that stomach lymphoma can be successfully treated without resection, but that surgery can be required if complications appear (112). No randomized studies are available.

Postoperative radiotherapy of 20 Gy to 25 Gy delivered to the whole abdomen, with possibly a 15 Gy boost to the tumor region or 40 Gy to the epigastrium, is used most frequently, and a substantial reduction in the frequency of relapse is reported compared to historical controls without radiotherapy (106). Other studies, however, have not arrived at similar results (113). Recurrence in 15% to 20% is reported following radiotherapy (6, 107). Recurrence in 8% was noted with adjuvant radiotherapy following radical surgery. Dosage exceeding 20 Gy to 25 Gy did not improve the results, and nothing suggested that radiotherapy to the whole abdomen was necessary (114). A large population-based study found that radiotherapy included in primary treatment reduced the frequency of relapse (110). No randomized studies are available.

Following alternating chemotherapy and radiotherapy without surgery, local control was reported in 82% of cases, 5-year relapse-free survival in 62%, and overall 5-year survival in 73% (111). Another study observed similar 5-year survival after radical surgery alone, and that adjuvant radiotherapy did not improve the results (113).

Regardless of treatment, one report found MALT lymphoma to have a clearly better prognosis than other stomach lymphomas (109), but analysis in a population-based Danish study showed that this correlated to the more limited nature of MALT lymphoma (110).

It was recently suggested that Helicobacter pylori may be an etiological factor behind the development of low-grade malignant MALT stomach lymphoma (115), and that elimination of the bacteria also leads to regression of

lymphoma (116). Continued followup and further study is needed to verify this. If confirmed, it would represent a major therapeutic breakthrough.

*The literature review shows:*

- that treatment recommendations vary widely in the literature;
- that attempting initial antibiotic treatment is recommended for low-grade malignant MALT lymphoma (116);
- that for superficial involvement, some studies recommend resection alone (106, 107), and for larger tumors, radical surgery alone (113) or followed by adjuvant radiotherapy (107, 114) or adjuvant chemotherapy (106);
- that different studies claim primary surgery is unnecessary (108, 110–112). Rather, radiotherapy is recommended for limited tumors, and combination therapy for more extensive involvement (106, 108), or combination therapy throughout, (111), or chemotherapy alone (32);
- that the value of postoperative, adjuvant radiotherapy, and chemotherapy has not been confirmed;
- that chemotherapy should be used for generalized disease;

  that there is a major need for controlled studies to identify optimal treatment.

*Small bowel lymphoma*

Small bowel lymphoma constitutes nearly 20% of extranodal NHL and 25% of all small bowel malignancies (106). The risk is increased if malabsorption and immunological dysfunctions are present. Involvement of the ileum is most common, but duodenum involvement is uncommon (106, 110). MALT lymphoma is reported in 25% of cases (109). The prognosis for small bowel lymphoma is reportedly worse than for stomach lymphoma (106), but small bowel lymphoma is often more advanced on diagnosis and more frequently a high-grade malignancy (45, 110, 112). A British study, however, found no difference in prognosis (109).

Surgery is generally the primary treatment, but frequently the disease is multifocal and characterized by extensive intra-abdominal diffusion, making radical resection impossible (106). The consensus at the Lugano Workshop was that diagnostic laparotomy and resection should be performed (112). Radiotherapy has been reported to increase relapse-free survival (106), but a large population study did not find that radiotherapy reduced the frequency of relapse (110). A 25% relapse frequency has been reported following postoperative radiotherapy for localized small bowel lymphoma (114).

*The literature review shows:*

- that primary surgery is recommended for localized small bowel lymphoma (112);
- that if radical surgery can be performed, some recommend adjuvant radiotherapy, and otherwise postoperative chemotherapy (114), while others always recommend chemotherapy following resection (110);
- that chemotherapy should be used for advanced disease (110).

*Colorectal lymphomas*

These comprise nearly 5% of extranodal NHL and $< 1\%$ of colorectal malignancies. The most common sites are the cecum and rectum (106).

Normally, treatment is surgery followed by radiotherapy (106, 117). A report involving few patients showed 15% recurrence after radical surgery and adjuvant radiotherapy (114).

*Lymphoma in Waldeyer's ring*

Lymphoma in Waldeyer's ring is the second most common extranodal localization following the gastrointestinal tract, and comprises 15% of all extranodal NHL. Tonsil involvement is reported in at least half of the cases (118, 119). A much higher incidence of Waldeyer's lymphoma is reported in Europe than in the United States (15, 118). During the course of the disease recurrence often appears in the gastrointestinal tract (105, 118, 120, 121). Some studies (122), but not all (28), report involvement of Waldeyer's ring to be a prognostically unfavorable factor.

Low relapse risk; 8% to 17% after radiotherapy alone is reported by some authors (6, 123) and substantially more (35% to 85%) in other studies (121, 123). This large variation is probably due to the small number of patients studied and the substantial variation in treatment.

A small, uncontrolled study showed clearly better relapse-free survival for chemotherapy compared to radiotherapy (123).

A small uncontrolled study of combined radiotherapy and chemotherapy showed clearly better relapse-free survival for combination therapy using short-term chemotherapy and low-dose irradiation compared to high-dose radiotherapy alone, but no difference in overall survival, although less sequela in the form of mouth dryness for combination therapy. The radiotherapy arm of the study found all recurrence located below the diaphragm (124). Another two small, uncontrolled studies showed more favorable therapeutic results with combination therapy than with radiotherapy alone (120, 125).

*The literature review shows:*

- that low-grade malignant Waldeyer's lymphoma at stage I can be irradiated (119, 126);
- that most publications recommend combination radiotherapy and chemotherapy (119–122, 124–126).

*Thyroid lymphoma*

Primary thyroid lymphoma is unusual and constitutes approximately 2% of extranodal NHL, and approximately 5% of all thyroid tumors. It affects especially elderly women (127, 128). Most reports include relatively few patients, who have been collected over many years and who received varying treatments, making evaluation difficult. No randomized studies compare radiotherapy with other treatments.

Traditionally, radiotherapy has achieved good results for localized thyroid lymphoma. A small, retrospective Swedish study showed that 5-year survival (75%) for irradiated patients was the same as in an age-matched normal population (129). A larger British study, however, found only 40% 5-year survival, but many patients had received less than 40 Gy, and local relapse was 80% among these patients (130). A 5-year, relapse-free survival of 70% to 90% was reported in stage I, however, the recurrence rate was clearly higher in stage II (128, 131–133).

Three studies of combination radio- and chemotherapy showed relapse-free, 5-year survival of 70% to 80% (132, 134, 135). In one study, nonrandomized comparisons showed longer relapse-free survival for combination therapy than for radiotherapy (134), but another study found no difference between these two forms of treatment (132).

A literature review of over 200 patients with localized thyroid lymphoma treated by radiotherapy, chemotherapy, or combination therapy showed a total recurrence rate of 30%. Distant recurrence was 30% following radiotherapy compared to 5% following combination therapy. If radiotherapy at stage I included the mediastinum, the recurrence rate dropped to 15% (127).

*The literature review shows:*

- that 5-year survival following radiotherapy for localized thyroid lymphoma is reported to be about 50% (128, 130, 131, 134), and 70% to 90% for stage I only (128, 131–133);
- that following combination therapy, 5-year survival is about 70% to 80% (132, 134, 135);
- that, in general, radiotherapy is recommended for stage I mainly if the disease is not bulky. The dose should be no less than 40 Gy, and the upper mediastinum should be included;
- that stages II-IV should be treated by primary chemotherapy, and if complete remission is not achieved or if the disease is bulky, it should be followed by radiotherapy (128, 135) or combination therapy if the patient's condition permits (131, 133, 134);
- that two authors recommend combination therapy even at stage I (127, 135).

*Skin lymphoma*

Special staging is used for skin lymphoma[4] (136). Mycosis fungoides and Sézary syndrome are T-cell lymphomas, which initially appear at or during early stages, and are limited to the skin. Approximately 20 new cases of mycosis fungoides are diagnosed annually in Sweden.

*Radiotherapy.* These lymphomas are highly radiosensitive, and radiotherapy of the entire skin surface has been used since the 1950s. TSEBI (Total Skin Electron Beam Irradiation) delivers high-energy electron therapy to the entire skin surface; but at a limited depth, thereby preventing general toxicity. Radiotherapy plays an important role in treating mycosis fungoides but is not suitable for Sézary syndrome due to side effects (137).

Several different methods have been described. A Stanford study used a six-field method with the patient standing, 30 Gy to 36 Gy were given during 8 to 10 weeks with a 1-week break after 18 Gy to 20 Gy. The eyes were shielded and "shadowed" areas such as the perineum and the soles of the feet received extra treatment. Patients with thick plaque or tumors received an initial boost of 15 Gy (137). In nearly 200 patients who were treated at Stanford as described above, complete remission was achieved in

[4] National Cutaneous T-cell Lymphoma Workshop Staging Classification:

| T | Skin | N | Lymph nodes | M | Visceral organs* |
|---|---|---|---|---|---|
| T1 | Limited plaques (< 10% BSA)** | N0 | No adenopathy; histology negative | M0 | No involvement |
| T2 | Generalized plaques | N1 | Adenopathy; histology negative | M1 | Visceral involvement |
| T3 | Cutaneous tumors | N2 | No adenopathy; histology positive | | |
| T4 | Generalized erythroderma | N3 | Adenopathy; histology positive | | |

Stage

I Limited (IA) or generalized plaques (IB) without adenopathy or histologic involvement of lymph nodes or viscera (T1N0M0 or T2N0M0)

II Limited or generalized plaques with adenopathy (IIA) or cutaneous tumors with or without adenopathy (IIB); without histologic involvement of lymph nodes or viscera (T1–T2N1M0. T2N0–1M0).

III Generalized erythroderma with or without adenopathy; without histologic involement of lymph nodes or viscera (T4N0–1M0)

IV Histologic involvement of lymph nodes (IVA) or viscera (IVB) with any skin lesion and with or without adenopathy (T1–4N2–3M0 for IVA; T1–4N0–3M1 for IVB)

* Blood involvement should be recorded as absent (B0) or present (B1) but is not currently used to determine final stage.

** BSA, body surface area.

98% at T1 (limited plaque), 71% at T2 (generalized plaque) and 36% at T3 (tumors). After 10 years, 50% at T1 and 20% at T2 were relapse-free. Relapse occurred within 5 years (137). Survival was similar with radiotherapy as with local skin treatment using a chemotherapy drug (mustin) at T1 and T2 (136). Other studies reported 33% to 44% 5-year, relapse-free survival at T1 and T2 (138, 139). One study of an eight-field method reports 90% relapse at T1 and T2. No differences were noted for doses above or below 20 Gy (140).

TSEBI is complex, time-demanding, and probably does not provide an adequate dose to the entire skin surface due to problems associated with field borders. A simplified method, where the patient stands on a rotating platform (single field rotational skin electron irradiation = RTSEI), has been developed in Montreal. Treatment results are comparable to other TSEBI methods (141). Another simplified method, with the patient supine during treatment, is advantageous for elderly, critically ill patients, and also reportedly yields results similar to "classic" TSEBI (142).

Aimed at altering the natural course of the disease, a study in Philadelphia tested TSEBI combined with a moderate dose of TNI to prevent diffusion to the lymph nodes. Nonrandomized comparison with TSEBI showed longer disease-free intervals, but not longer overall survival. This is attributed to the high frequency of secondary malignancies and patient selection in the more extensive radiotherapy group (143). A pilot study combined TSEBI with TBI (1.5 Gy), but did not achieve better results than with TSEBI alone (144).

*Combination radiotherapy and chemotherapy*. TSEBI followed by 6 months of chemotherapy in T3 patients did not reduce the rate of recurrence in the skin; all had relapsed within 2 years, although with plaque (ie, downstaging compared to initial tumor status) (145). A randomized study between TSEBI plus concurrent chemotherapy and local skin treatment with mustin found, at early stages, no difference in the rates of remission or relapse-free survival in either arm of the study (146). A pilot study of TSEBI combined with retinoid did not show better results than radiotherapy alone (147).

B-cell lymphoma also occurs primarily in the skin. This is the third most common extranodal manifestation. Several authors have recently reported that these lymphomas have a favorable course with little tendency toward extracutaneous diffusion, hence, local therapy is appropriate (148).

One study reported 13% extracutaneous relapse following IF irradiation (148). Another three studies recommended radiotherapy (149–151), while yet another study found irradiation insufficient for high-grade malignant NHL in the skin (152).

*The literature review shows:*

- that radiotherapy (TSEBI) for mycosis fungoides is recommended for: progression or refractory disease with local skin treatment with chemotherapy drugs at T1, rapid progression at T2, or initially at T3 and then with a boost to the tumor sites (153);
- that radiotherapy can, to a high degree, induce complete remission in early stages with relatively prolonged freedom from disease, but most patients will relapse and experience progressive disease (136, 143);
- that radiotherapy combined with chemotherapy or retinoid therapy does not provide better treatment results;
- that IF radiotherapy is recommended for cutaneous B-cell lymphoma with limited diffusion (148–151).

*AIDS lymphoma*

Malignant lymphoma is the most common malignant disease among patients with immunodeficiency syndrome, and the frequency of NHL is 60 times higher among AIDS patients than among the population at large (17). NHL appears in 5% to 10% of AIDS patients (154). Extranodal disease is common, involving mainly the CNS (17). Radiotherapy of the CNS can provide complete remission, but long-term survival is rare (17, 155). Most patients die within 3 months after treatment (156).

It has also been claimed that CNS lymphoma in AIDS patients is less radiosensitive than CNS lymphoma in nonimmunosuppressed patients (157). The potential for long-term survival is determined more by the progression of the underlying immunodeficiency syndrome than by the lymphoma (17).

*Palliative radiotherapy*

Patients who have relapsed and/or cannot be cured frequently experience localized problems which may be relieved by radiotherapy, eg, urethral obstruction, massive edema in the legs due to enlarged nodal areas in the abdomen, severe pain due to spinal cord involvement, or discomfort from enlarged nodes in the neck, axilla, or abdomen (9).

In chemotherapy-resistant patients, half-body irradiation using a single dose of 5 Gy to 6 Gy is reported to provide subjective relief in 80% of patients, and even objective disease regression, mainly concerning low-grade malignant NHL (158).

*Radiotherapy methods*

Generally, several well-defined radiation volumes are used for NHL (see footnote under General Treatment). Radiotherapy for skin lymphoma (TSEBI) is highly resource demanding, using a complex six- to eight-field method, requiring advanced radiotherapy equipment and precision dosimetry. TNI, TLC, and TBI are also complex, resource-intensive therapies.

NHL recurrence usually appears in distant lymph node regions or extranodally, in contrast to Hodgkin's disease where 80% of recurrence appears in the immediate lymph node regions (43). Therefore, in contrast to Hodgkin's disease, lower target volumes are sufficient for NHL.

A Toronto report claims that 20 Gy is sufficient for low-grade malignant NHL and that 30 Gy to 35 Gy are required for optimal control of high-grade malignant NHL, especially if disease is bulky (10). EORTC claims that 25 Gy to 30 Gy are required to achieve satisfactory local control of low-grade malignant NHL (15). Other reports suggest higher doses >40 Gy (43) for high-grade malignant NHL, especially if the disease is bulky (4, 43). A British study found a dose-response association of 100% local control at 45 Gy or more for high-grade malignant NHL (13).

Local control has been reported with doses varying from single-dose 8 Gy to 10 Gy to multiple 0.1 Gy to 0.15 Gy, 2 to 3 times per week up to a total of approximately 1.5 Gy (for total body irradiation). Standard treatment is 1.8 to 2.0 Gy per fraction 5 times per week (43).

### Literature

*The articles that appear in the reference list 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 |

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