14. **Hodgkin's Lymphoma (HL)**

Introduction

In 2000, 176 cases of Hodgkin's lymphoma were diagnosed in Sweden corresponding to less than 0.4 per cent of all new malignant tumour diagnoses [10]. The age distribution is unusual since there are two age peaks, the first in patients in their 20s, and the second in their 70s. Until the 1960s, Hodgkin's lymphoma was considered to be incurable, but advances in radiotherapy and chemotherapy have made cure possible in a large number of cases, particularly among young patients.

Population based studies in Sweden show an overall survival above 90 per cent in early and intermediate stages and about 75 per cent in advanced stages for patients younger than 60 years [3,24]. For patients above the age of 60 years the overall survival is nearly 50 per cent [18]. Very few other population-based studies are reported. A register study from EUROCARE database comprising over 7 000 patients with HL diagnosed in Europe 1985–89, reported 72 per cent (range 45 to 76 per cent) age-standardized 5-year relative survival rates and a progressive decline in relative survival with increasing age [11]. For the same period of time the National Cancer Data Base in USA reported 83 per cent 5-year overall survival in more than 14 000 patients with HL, also with a decreasing survival with increased age [33]. But in this study only 18 per cent of the patients were above 60 years of age compared with 33 per cent in Sweden [10].

Radiotherapy and chemotherapy, alone or in combination, are curative treatment methods. The choice of therapy depends on the stage of the disease, the presence or absence of various prognostic factors and attempts to avoid long-term effects of treatment. Generally, a division into early and advanced stage disease is recognized (Cotswold

stage I–II vs III–IV)[1]. Many study groups subdivide patients with early stages into favorable and unfavourable (or intermediate stage) subgroups. The criteria for adverse prognostic factors are not entirely uniform between different study groups especially concerning early stages (Table 1). For the advanced stages, the International Prognostic Factor Project analyzed data on more than 5 000 patients from 25 centers and found a prognostic score (IPS), which has been widely recognized [27]. The IPS includes seven adverse factors: ≥45 years, male sex, anemia, decreased serum albumin, stage IV, leukocytosis and lymphopenia. Recently the predictive power of IPS for advanced HL was assessed in unfavorable early stage patients but showed only modest predictive ability [22].

Table 1 *Adverse prognostic factors in early stages recognized by three different study groups.*

GHSG	EORTC	NCI Canada
Large mediastinal mass (mediastinal-thoracic ratio ≥ 0.33)	Large mediastinal mass (mediastinal-thoracic ratio ≥0.35)	Histology: MC or LD
Elevated erythrocyte sedimentation rate (≥ 50 mm without or ≥30 mm with B-symptoms)	Elevated erythrocyte sedimentation rate (≥50 mm without or ≥30 mm with B-symptoms)	Elevated erythrocyte sedimentation rate
≥3 lymph nodes regions involved	≥4 lymph nodes regions involved	≥4 lymph nodes regions involved
Extranodal involvement	Age ≥50 yrs	Age >40 yrs

[1] The Cotswold Staging Classification:
Stage I=Involvement of single lymph node region or lymphoid structure (eg. spleen, thymus, Waldeyer's ring).
Stage II=Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site, hilar lymph nodes are lateralized).
The number of anatomical sites should be indicated by a suffix (eg, II_3).
Stage III=Involvement of lymph node regions or structures on both sides of the diaphragm
III_1: with or without splenic hilar, coeliac, or portal nodes
III_2: with paraaortic, iliac, mesenteric nodes.
Stage IV=Involvement of extranodal site(s) beyond that designated "E"
A=No symptoms.
B=Fever, drenching sweats, weight loss.
X=Bulky disease (>1/3 widening of mediastinum, >10 cm maximum dimension of nodal mass).
E=Involvement of extra lymphatic tissue, contiguous or proximal to know nodal site.
A single extralymphatic site as the only site of disease is classified IE.

Summary of the earlier report, SBU 129/2

The synthesis of the literature on radiotherapy for Hodgkin's lymphoma was based on 104 scientific articles, including two meta-analysis, 22 randomized studies, five prospective studies, and 58 retrospective studies.

Conclusions

- The literature review clearly showed that radiotherapy was a cornerstone in treatment for localized Hodgkin's lymphoma. At early stages, long-term survival was 80 per cent to 90 per cent when treatment was tailored to known prognostic factors.
- There was a tendency toward increased use of chemotherapy as additional treatment, however, no evidence that it increased survival.
- To further improve survival following radiotherapy, attempts were made to reduce long-term toxicity by better defining the patient groups who required lower radiation volumes, and delivering a dose that was as low as possible to avoid secondary solid tumours or delayed cardiopulmonary or gastrointestinal side effects, while not jeopardizing therapeutic results.
- In advanced disease, radiotherapy may be needed as a complement to chemotherapy to effectively control bulky disease.
- For recurrent disease, radiotherapy may be considered as relapse treatment or additional therapy in conjunction with high-dose chemotherapy.

Discussion

In the previous report (SBU-report 129/2, 1996) it was stated that radiotherapy was a cornerstone of treatment for localized HL with a long-term survival of 80–90 per cent when treatment was tailored to known prognostic factors.

Since then increasingly more reports about the long-term effects have questioned that statement.

Although most young patients are cured from HL they do not have the same life expectancy as the ordinary population. Several investigations have shown that with long-term follow-up the cumulative Hodgkin's

lymphoma specific mortality levels off over time but the treatment-related mortality especially second malignancies and cardiac diseases continue to rise and now begin to exceed the mortality due to HL [44].

Clinical trials nowadays are tailored after known prognostic factors. Current clinical studies are evaluating the use of chemotherapy together with smaller radiation fields and/or lower radiation doses, chemotherapy without radiation therapy, fewer courses of chemotherapy and alternating chemotherapy combinations but many of these studies are ongoing or the results are not yet published in full articles or the follow-up time is too short to be properly evaluated. Furthermore, freedom from relapse is no longer the most important endpoint of clinical trials. Efforts and studies strive to reduce morbidities of all kinds without compromising the excellent survival results.

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	–	2/5 068	–	**2/5 068**
C	8/5 749	11/2 341	3/291	**22/8 381**
P	–	5/930	–	**5/930**
R	14/20 587	25/2 646	19/750	**58/23 983**
L	6	1	–	**7**
O	6	4	–	**10**
Total	**34/26 336**	**48/10 985**	**22/1 041**	**104/38 362**

Assessment of new literature

Search method and selection

The assessment of literature cover the time period from 1994 to October 2001, studies on children are not included. Literature search was performed in Medline with use of the MeSH terms “Hodgkin disease” in combination with “radiotherapy“ as subheading with limitation to meta-analysis, randomized controlled studies and controlled studies. In addition also prospective studies and in some cases retrospective studies with essential

information identified through search in Medline or by scrutinizing reference lists have been reviewed. Furthermore, conference proceedings of recently closed but not published randomized trials are for information included in the reference list and in Overviews 2, 3 and 4. Search was also performed in the Cochrane Library.

One randomized trial was excluded: Aviles 1998: Too low quality in radiotherapy, presentation and probably in follow-up.

Overview of new studies

Early stages (stage I–II without adverse prognostic factors) and Intermediate stages (stage I–II with adverse prognostic factors)

Radiotherapy alone; evaluating radiation field size or dose

Overview 1 (after the list of references)

Radiotherapy versus chemotherapy

Two randomized studies have earlier compared radiotherapy with MOPP chemotherapy and come to different conclusions (see previous report, SBU-report 129/2, 1996). However, these studies are not relevant today because the use of staging laparotomy and suboptimal chemotherapy. NCI in Canada is performing a randomized trial in patients below 40 years of age with favourable prognosis comparing subtotal nodal irradiation, STNI, including splenic irradiation with 4–6 cycles of ABVD (see Overview 2) alone. No published results are available yet, (see Addendum after the text).

Radiotherapy alone versus chemotherapy plus radiotherapy

Overview 2 (after the list of references)

One meta-analysis, including older studies (1967–88) [59] and two recent, randomized trials [19,51] are reported and the results are consistent. Two trials are not finally reported yet and it will take many years to get the mature results for these studies [52,58]. One prospective randomized trial is ongoing in UK and still open for accrual, (see Addendum after the text).

Chemotherapy plus radiotherapy versus chemotherapy alone

SBU-report 129/2, 1996, one study reported better relapse-free survival with combined modality treatment, but no difference in overall survival. No new trial has been reported but four new studies are underway (MSKCC in New York, NCI Canada/ECOG, GHSG HD13 and, CALGB), (see Addendum after the text).

Radiation volume or dose after chemotherapy

Overview 3 (after the list of references)

There are a few randomized trials reported which have evaluated if the addition of chemotherapy to radiotherapy would admit a reduction of radiation volume or dose. Some recent trials concerning the same question are only reported in abstracts. There are also two German trials (GHSG HD10 and HD11) underway testing 20 vs 30 Gy involved field in early and intermediate stages after two or four chemotherapy courses.

The question if radiotherapy is needed at all is not addressed in these trials. But there is an ongoing EORTC H9-F trial, which compares three dose levels, 36, 20 and 0 Gy to involved fields in patients in complete remission after six chemotherapy cycles, (see Addendum after the text)

The literature shows that:

- More extensive radiotherapy fields substantially reduce recurrence rate but overall survival is not significantly affected.
- The addition of chemotherapy to radiotherapy reduces recurrence rate but overall survival is not significantly affected.
- The optimal dose is not definitely defined. For subclinical disease 30 Gy is sufficient and 30–32 Gy might be the optimal dose for tumour control. After chemotherapy the radiation dose can be reduced to 20 Gy to non-bulky sites.
- In early stages extended radiotherapy could be replaced by reduced irradiation after or integrated with chemotherapy.
- The current approach with brief chemotherapy followed by limited radiotherapy is now supported by five randomized trials. However, they are only published as abstracts yet.

- The question if radiotherapy is needed at all in early stages (and intermediate stages) is not yet answered in controlled studies.

Early and intermediate stages.

	1 = High	*2 = Moderate*	*3 = Low*	*Total*
M	1/3 888	–	–	**1/3 888**
C	1/258	2/671	3/405	**6/1 334**
R	–	1/169	–	**1/169**
O	–	1	–	**1**
Total	**2/4 146**	**4/840**	**3/405**	**9/5 391**

Advanced stages: stage III and IV

The therapy of choice in advanced disease is combination chemotherapy and 60–90 per cent of patients achieve complete remission. Approximately one third of these patients relapse with 80 per cent of the recurrences within three years and 40–50 per cent of the patients become long-term survivors (reviewed and evaluated in SBU-report, "Chemotherapy for Cancer", 155/2, 2001). Recently data from 25 centers on about 5 000 patients with advanced Hodgkin's disease treated in the 1980s with combination chemotherapy with or without radiotherapy have been collected and evaluated. This International prognostic factors project on advanced Hodgkin's disease has developed a seven-factor prognostic scoring system where each adverse factor reduced freedom from progression rate by 8 per cent. After five years the freedom from progression was 84 per cent with no adverse prognostic factor present and 42 per cent with five or more factors. The prognostic score was also predictive of overall survival. The 5-year overall survival ranged between 90 and 56 per cent [27].

Advanced stages

Overview 4 (after the list of references)

The role of additional radiotherapy in advanced stages after chemotherapy is uncertain and controversial (see also previous reports; SBU-report 129/2, 1996 and SBU-report 155/2, 2001). It has been widely adopted without demonstration of which, if any, subsets of patients will have improved survival [1].

Further randomized trial exploring the value of additional radiotherapy after chemotherapy in advanced stages is underway in Germany (HD12), (see Addendum after the text).

Conversion of partial to complete remission by additional radiotherapy

In a SWOG (Southwest Oncology Group) study the complete remission rate increased from 61 per cent after chemotherapy to 80 per cent after additional low dose radiotherapy (IF 20 Gy) [20]. In a Swedish population-based study the complete remission rate improved from 72 per cent after 8 chemotherapy cycles to 91 per cent after additional radiotherapy with 40 Gy to areas with residual disease [3]. In an EORTC/GPMC (European Organization for the Research and Treatment of Cancer/Groupe Pierre-et-Marie-Curie) study patients in partial remission after a full course of chemotherapy received involved field radiotherapy 30/40 Gy and 72 per cent of the patients converted to complete remission [53] and in an Italian randomized trial 14 of 15 partial responders achieved complete remission by additional radiotherapy [6].

These studies may suggest a role for radiation in patients with residual disease after completed chemotherapy, but the studies are not controlled. Furthermore, in HL it is very difficult to define PR with certainty, as there are no sensitive means to distinguish between active residual disease and fibrotic remnants. So patients classified as partial responders might be complete responders with residual abnormalities without active disease, which may continue to regress over long periods of time. In the future the positron emission tomography (PET) may be a useful tool to diagnose the persistence of viable tumours in patients with residual masses [65].

Bulky mediastinum/bulky disease

Overview 4 (after the list of references)

The mediastinum is involved in 70 per cent of the cases of HL, and in one-third of these cases the involvement is considered bulky or large (mediastinal-thoracic ratio ≥0.33) and very large when this ratio is greater than 0.45.

Bulky mediastinum/bulky disease has generally been considered as an adverse prognostic factor with a high relapse frequency when treated with either radiotherapy or chemotherapy alone. Based on limited data

consolidating radiotherapy to patients with bulky mediastinal adenopathy is usually recommended [1] and reviewed in SBU-report 129/2, 1996. However, it is difficult to find any clear evidence for a survival benefit by this treatment.

In the international study of prognostic score in advanced HL the presence of a mediastinal mass did not appear to have a strong prognostic effect except in the small subgroup with very large masses [27].

Longer remission duration but no better survival were observed in a SWOG trial with 20 Gy involved field adjuvant radiotherapy for patients in complete remission after chemotherapy with bulky disease in advanced stages [20].

In a meta-analysis no better disease control with additional radiotherapy was noted after chemotherapy in patients with bulky disease in intermediate and advanced stages [37].

In a GELA (Group d'etudes des Lymphomes de l'adulte) trial the disease-free survival and overall survival for patients with bulky disease were the same for consolidation with either chemotherapy or radiotherapy [7,21].

In uncontrolled series the prognostic importance of bulky disease could not be proven after combined modality treatment [3,22,25,38]. This might indicate that radiotherapy should be used in conjunction with chemotherapy in treatment of bulky disease but no randomized proof exists.

The literature shows that:

- There is no evidence for survival benefit of additional radiotherapy in advanced stages.
- Trials that compared additional radiotherapy with additional chemotherapy did not show any advantage of irradiation in terms of survival and in a meta-analysis the survival was significantly better without radiotherapy.
- There are reports that additional radiotherapy after a full course of chemotherapy resulting in partial remission could lead to increased complete remission rate. But there may be doubts if many partial remissions really represent active disease. There is no scientific proof that irradiation in these cases leads to any survival benefit.

- Radiotherapy after chemotherapy for sites with initial tumour bulk is questionable. No survival benefit or better disease control has been reported with radiotherapy. On the other hand the prognostic importance of bulky disease was lost after combined modality treatment in uncontrolled series, which might indicate an effect of radiotherapy. Only one small randomized trial exists which showed no difference between radiotherapy and chemotherapy as consolidation after complete remission in bulky disease.
- With the recognition that adjuvant irradiation poses an added hazard for second tumours its use should be restricted.

Advanced stages.

	1 = High	**2 = Moderate**	**3 = Low**	**Total**
M	1/1 740	–	–	**1/1 740**
C	–	3/418	4/727	**7/1 145**
P	1/712	2/267	–	**3/979**
R	1/4 695	2/362	–	**3/5 057**
L	1	–	–	**1**
O	1/44	–	–	**1/44**
Total	**5/7 191**	**7/1 047**	**4/727**	**16/8 965**

Radiation as salvage therapy

This subject was reviewed in SBU-report 129/2, 1996. Since then only a small number of patients treated with radiation as salvage therapy following chemotherapy failure has been reported [47,48,64]. But this approach may be considered in selected patients with favourable factors such as limited nodal recurrence after a long disease-free interval and without previous large field radiotherapy. Comparisons with other salvage methods do not exist.

The literature shows that:

- Radiotherapy as salvage treatment might be an alternative in late limited nodal recurrence after initial chemotherapy although no controlled trials exist but only reports on small patient materials.

Radiation as salvage therapy.

	1 = High	2 = Moderate	3 = Low	Total
R	–	1/52	2/21	**3/73**
Total	**–**	**1/52**	**2/21**	**3/73**

Radiotherapy in conjunction with high-dose chemotherapy and stem cell support

Patients with induction failure or early relapse (within 12 months) after chemotherapy have a poor prognosis. These patients are often treated with high-dose chemotherapy (HDCT) and stem cell support. The value of this therapy is difficult to interpret because of patient selection and the paucity of large randomized trials with long follow-up, reviewed in SBU-report 155/2, 2001.

Irradiation to involved fields is widely used in the USA either before or after high dose therapy and sometimes TNI; (total nodal irradiation) or TBI; (total body irradiation) either as a single dose or in a fractionated manner. Sometimes accelerated fractionation is used [41]. Radiotherapy to involved fields (often meaning mantle or inverted Y) with or without TNI/TBI incorporated into the induction chemotherapy prior to or following HDCT is reported in small uncontrolled retrospective series with a heterogeneous applications of radiotherapy [41,42,43, 49,50,55]. Some data point to better local disease control with involved field radiotherapy but there is no evidence that this translates into longer survival.

Furthermore it is difficult to distinguish between the contribution of the radiotherapy and the effect of chemotherapy for the outcome in these series.

In a report from Toronto, treatment related mortality (TRM) was noted in one third of the patients with thoracic radiotherapy prior to HDCT in contrast to none in patients with radiotherapy to extra-thoracic areas. The mortality was mainly due to pulmonary toxicity. The authors recommended the use of radiotherapy after HDCT to decrease TRM [61].

At Stanford University they now prefer to give radiotherapy after HDCT and to smaller volumes due to unacceptable toxicity from irradiation before HDCT [31].

The value of radiotherapy in conjunction with HDCT is not established by randomized trials but one prospective randomized trial from Rochester in USA is underway [15].

The literature shows that:

- Radiotherapy in conjunction with high-dose chemotherapy and stem cell support may increase the local disease control but there is no evidence of improved survival.
- Radiotherapy especially thoracic prior to high-dose chemotherapy may contribute to high treatment related mortality.

Radiotherapy in conjunction with high-dose chemotherapy and stem cell support.

	1 = High	2 = Moderate	3 = Low	Total
R	–	4/224	4/196	**8/420**
O	1	–	–	**1**
Total	**1**	**4/224**	**4/196**	**9/420**

Radiation technique and quality assurance studies

Some of the late effects we observe today are the result of treatment techniques that are no longer in use. Dose variations in the past may have led to excessive normal tissue injury as well as inadequate disease control. Many modifications in the current practice depend on the observed complications of past treatment.

Well-designed quality-assurance programs ought to clarify in what way different practices affect both the normal tissues and the disease control. Quality control in radiotherapy for Hodgkin's disease became a major focus of attention in the 1990s.

Many discrepancies that might influence the outcome were found in a patterns of care study from USA surveying data concerning planning

from 61 radiotherapy institutions to assess compliance to guidelines in the late 1980s. Surprisingly, only 80 per cent of the centers used treatment with daily AP/PA fields, hardly no in vivo dosimetry was used. Furthermore, 70 per cent did not use dose compensation, more than half of the institutions did not use immobilization the patients and 30 per cent did not calculate a gap between the upper and lower fields [32].

An experimental dosimetry study from 23 centers in Australia and New Zealand has shown a wide variation in the dose delivered within a mantle field and within the centers surveyed [2]. In a study aimed to measure the mantle planning in Australia and New Zealand a chest X-ray was sent to radiation oncologists asking them to mark the lung blocks on the X-ray. In 44 replies the mediastinal coverage was judged inadequate in at least 50 per cent of the cases [5]. The GHSG (German Hodgkin study group) conducted a randomized multicenter study between 1988 and 1993 with different radiation doses in patients with early-stage HL treated with radiotherapy only [17]. A panel of four experienced chairpersons from different radiation therapy departments prospectively reviewed the planning and verification films, the radiotherapy reports charts, the technique and the dosimetry. If at least three out of four panelists voted for protocol violations (PV), about one-third of the patient's radiotherapy were assigned as PV, mainly inadequate treatment volume or dose, protracted treatment time or technical inadequacies. Nineteen per cent of the patients with PV relapsed compared to 11 per cent without PV. Freedom from treatment failure at five years was 82 per cent in patients treated without PV compared with 70 per cent in patients with PV ($p < 0.04$).

In a randomized SWOG trial, studying the value of adjuvant radiotherapy in patients in complete remission after chemotherapy, a quality assurance review of the radiotherapy was performed. In 17 per cent of the patients there was considered to be major protocol violations. Forty-four per cent of these patients relapsed compared to only 10 per cent of the patients who had received radiotherapy according to protocol. But other patient characteristics of the two groups were not given [20]. The Quality control program of the radiation therapy in the EORTC H8 multicenter study in early stages revealed a 14 per cent major deviation related to the treated volumes and 40 per cent related to the dose [28].

The literature shows that:

- Even recent reports demonstrate to that the problems of technical accuracy are still a major factor in the irradiation of large volumes in HL.
- Awareness of the wide variations in radiotherapy practice is essential in evaluating the value of irradiation and the overall treatment outcome.
- Furthermore, the mostly very sparse information about the radiation technique and how the doses are specified in articles concerning radiotherapy in lymphomas makes it problematic to interpret and compare the results of radiotherapy from different centers and studies.

Radiation technique and quality assurance studies.

	1 = High	**2 = Moderate**	**3 = Low**	**Total**
C	–	2/623	–	**2/623**
R	2/436	–	–	**2/436**
O	2	–	–	**2**
Total	**4/436**	**2/623**	**–**	**6/1 059**

Long-term sequelae

Fifteen years after diagnosis the mortality from causes other than HL begin to exceed deaths from HL. These causes of death are mostly treatment related and increase steadily after 15 years. However, the absolute excess risk of death during each five-year follow-up interval is less for patients treated in more recent years (1980–1995) than in the prior treatment era (1962–1980) in a report from the Stanford University [29]. From the Netherlands a 20 years cumulative risk of dying from HL of 33 per cent and from all other causes 20 per cent is reported [62].

Secondary malignancies

The 20-year cumulative risk of developing a secondary malignancy after treatment for HL is 15–20 per cent, which means a nearly fourfold excess as compared with the risk expected in the general population. The relative risk of a second malignancy after treatment for HL ranges from 2.2 to 6.4 in reports from Canada, Stanford, United Kingdom and the Netherlands [8,26,60,62].

Myelodysplastic syndrome (MDS)/Acute non-lymphatic leukemia (ANLL)

ANLL has mostly been related to alkylating agents especially MOPP-therapy. A decreasing risk for ANLL is reported for patients treated in the 1980's when the use of MOPP diminished compared with patients treated in the 1970's [62]. Radiotherapy alone does not increase the risk of leukemia [60,62]. There are different opinions as to whether combined modality treatment with addition of radiotherapy to chemotherapy confers a higher risk over chemotherapy alone [1]. Recently topoisomerase II inhibitors especially etoposide with known leukemogenic effect has been introduced in the therapy arsenal often together with radiotherapy. What that means for the future we do not know yet.

After high-dose chemotherapy with autografting for HL and NHL an actuarial incidence of 4–18 per cent for MDS/ANLL is observed with 5–15 years follow-up [4]. Radiotherapy is often incorporated in the induction treatment of these patients especially in USA. It is unclear whether MDS/ANLL is related to the initial therapy, treatments in conjunction with HDCT, or a result of cumulative effects of all these exposures [4]. Retrospective data to evaluate risk factors for therapy-related MDS/ANLL in these patients has been collected. Multivariate analysis revealed an association between pretransplant radiation and the risk of MDS/ANLL, but failed to show any association with pretransplant chemotherapy or conditioning regimens with exception of patients who had got etoposide for stem-cell mobilization. These patients had a 12-fold increased risk of developing ANLL [35].

Secondary non Hodgkin-lymphoma (NHL)

The relationship of secondary NHL after therapy for HL is poorly understood. The risk for developing secondary NHL is independent of the initial therapy with similar risks for primary radiotherapy, combined modality treatment, and chemotherapy alone in some series [26,60] but in another report combined modality treatment lead to a higher risk [62]. It has been speculated that in some cases NHL may represent a natural evolution and in other cases that the immunological deficiency or perturbation related to HL and/or the treatment may cause the development of NHL [1].

Secondary solid tumours

Secondary solid tumours have a much longer latent period than secondary leukemias and NHL. Radiotherapy is considered to have the major carcinogenic role in the development of solid cancers after treatment for HL [1]. The highest risk for developing secondary solid tumours has been observed among patients, who had received primary combined treatment modality followed by more treatment courses for recurrences [62]. The long-term risks of secondary tumours are dependent on age at treatment. It has been observed that the relative risk of secondary solid tumours of many types is greatly increased with younger age at first treatment but also there is a decline of the relative risk, as the young patients grow older (>20 years follow-up) [63]. For adult and older patients no plateau or decline in the relative risk of secondary solid tumours after long follow-up has been observed [60].

- Lung cancer
  Lung cancer is the most common type of secondary cancer after treatment for HL. A twofold to eightfold excess risk of lung cancer compared with the risk in the general population is observed five or more years after HL treatment and no peak is reached [60]. There is general agreement of an excess risk after irradiation but not on the contribution of chemotherapy [60,63]. Smoking history, particularly continued smoking, after treatment of HL markedly increases the risk [1].

- Breast cancer
  Breast cancer is the most common secondary malignancy in women after therapy for HL. The risk is high for patients irradiated between the time of puberty and the age of 30 years but little or no elevated risk for women irradiated after 30 years of age. The median time to presentation of secondary breast cancer is about 15 years (range 4–20) after treatment [13]. Although the incidence increases with time after therapy the relative risk diminishes after 20 years [63]. The increased risk is confined to patients treated with radiotherapy alone [60]. No case of male breast cancer has been reported after irradiation for HL. These tumours appear within or at the edge of the treatment fields [12].

- Other secondary solid tumours
  The relative risk of developing other solid tumours is also increased. A significantly increased risk of cancers in stomach, colon, tongue, mouth, pharynx, liver and soft tissue was only found in patients who had received combined modality therapy. Cancer in small intestine, bone and melanoma occurred solely in patients treated with radiotherapy (with or without chemotherapy) and thyroid cancer risk was significantly increased only in radiotherapy-treated groups [60].

Cardiac complications

Cardiovascular complications after radiotherapy of mediastinum, mainly mantle therapy, constitute the second most frequent cause of treatment-related mortality in HL patients. Cardiac deaths have been responsible for about one quarter of the mortality from causes other than HL and constitute nearly 5 per cent of the deaths in the entire HL population [29,56]. The relative risk of cardiac death is elevated during the initial 5 years after treatment with a slowly continuing increase in patients followed more than 20 years. Young age at the time of irradiation increased the risk for both myocardial infarction and other cardiac deaths. With modern techniques, with additional cardiac shielding, the cardiac morbidity has decreased but the incidence of myocardial infarction has not changed [26]. In one study no increased risk for cardiac death was found for doses 30 Gy or less but this has not been reported in any other study [26].

- Myocardial infarction
  Myocardial infarctions constitute more than two thirds of the cardiac mortality observed in irradiated HL patients at Stanford [29]. In a study from Switzerland a high relative risk for myocardial infarction and sudden death was found in males with risk factors for cardiovascular disease but not for females or males without risk factors [23]. Another study with increased risk for fatal myocardial infarction also found that all the deceased patients had at least one risk factor for cardiovascular disease [34]. Despite low mean fraction dose and moderate total dose a high incidence of ischemic cardiac deaths was observed in a report

from the Netherlands [56] but in a report from Canada no increased risk for death of myocardial infarction was found [8].

- Other cardiac deaths
  Radiation damage to the pericardium, the myocardium and heart valves frequently follows mantle irradiation. These complications were often seen after radiotherapy in the 1960's and early 1970's. However, the risk of cardiac deaths from causes other than myocardial infarction has markedly diminished with modern radiation technique [26].

The literature shows that:

- With long-term follow-up the mortality from causes other than HL begins to exceed deaths from HL. Mostly this excess risk of death is attributed to secondary malignancy and cardiac deaths especially myocardial infarction.
- The 20-year cumulative risk of developing a secondary malignancy after treatment for HL is 15–20 per cent, almost a fourfold excess as compared with the risk expected in the general population.
- The risk of leukemia is not increased by radiotherapy alone. Different opinions exist whether combined modality treatment with radiotherapy and chemotherapy confers a higher risk than chemotherapy alone.
- Development of NHL after treatment of HL may be multifactorial but is poorly understood. The role of radiotherapy is unclear.
- Secondary solid tumours have a long latent period, median time over 10 years. Radiotherapy is considered to have the major carcinogenic role in the development of solid cancers after treatment for HL. The relative risk of secondary solid tumours of many types is greatly increased with younger age at treatment.
- Cardiovascular disease is the second most frequent cause of treatment-related mortality in HL patients and myocardial infarctions constitute more than two-thirds. Mediastinal irradiation, mainly mantle therapy, is clearly associated with these late-effects.

- Changes in treatment introduced during the last decades seem to have reduced the risk of death from secondary cancers and cardiovascular disease, although several additional years of follow-up will be required to confirm these data.
- An important issue is the dose effect in radiotherapy. Is there any safe dose, especially in combined modality therapy programs, so that the risk for secondary tumours or cardiac disease will not be increased?
- It might be that not only the given therapy is responsible for the secondary malignancies but also that the immune defect in HL-patients predispose the development of another malignancies. No comparative studies exist with other cured cancer patient groups concerning the frequency of secondary malignancies.

Long-term sequelae.

	1 = High	2 = Moderate	3 = Low	Total
R	9/11 857	1/258	–	**10/12 115**
L	3	–	–	**3**
O	1	–	–	**1**
Total	**13/11 857**	**1/258**	**–**	**14/12 115**

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	2/5 628	–	–	**2/5 628**
C	1/258	5/1 089	6/663	**12/2 010**
P	1/712	2/267	–	**3/979**
R	12/16 988	11/1 414	6/217	**29/18 619**
L	4	–	–	**4**
O	7/44	1	–	**8/44**
Total	**27/23 630**	**19/2 770**	**12/880**	**58/27 280**

Conclusions and Comments

- Solid scientific documentation shows that more than 80 per cent in early stages and 60–70 per cent in advanced stages of younger patients with Hodgkin's lymphoma are now cured by the development of radiotherapy and combination chemotherapy. ([27]R1, [37]M1, [44]L1, [59]M1).

- Long-term follow-up reveals that after 15 to 20 years the mortality from HL in early and intermediate stages is exceeded by other death causes, mostly secondary malignancies and cardiac deaths especially myocardial infarction. ([8]R1, [26]R1, [29]R1, [44]L1, [60]R1, [62]R1, [63]R1).

- Convincing data show that radiotherapy plays a major role in the development of solid cancers and cardiovascular disease, but no randomized trials have been performed. ([1]L1, [13]L1, [26]R1, [29]R1, [56]R2, [60]R1, [62]R1, [63]R1).

During the last decade increasing awareness of fatal long-term sequelae has fundamentally changed treatment strategies in early and intermediate stages. A thorough long-term follow-up is essential to evaluate the effects of the modifications of the therapy.

- In early stages extended field irradiation is now replaced by brief chemotherapy followed by limited radiotherapy to decrease late sequelae. This approach is strongly supported by early reports from randomized trials. Final results cannot be fully evaluated in many years. ([40]C3, [45]C3, [46]C3, [52]C3).

The optimal radiation dose and volume after chemotherapy are not defined or if irradiation is needed at all. Several studies are underway.

- In intermediate stages two recently reported randomized trials indicate that combined modality therapy is preferable and that involved field could substitute extended field irradiation. It is still too early to draw any firm conclusions. ([6]C3, [57]C3).

- In advanced stages there is no evidence for any survival benefit from additional radiotherapy. ([14]C3, [16]C2, [20]C2, [21]C2, [37]M1, [54]C3).
- The role of radiotherapy in case of residual tumour and bulky disease still remains controversial. (*Pro* [20]C3, *Con* [7]C3, [21]C2, [37]M1, *Ambiguous* [3]R2, [22]P1, [25]P2, [38]R2).
- There is no scientific support for improved survival with radiotherapy in conjunction with high-dose chemotherapy with stem cell support. ([41]R2, [42]R3, [43]R3, [49]R3, [50]R2, [55]R3).
- Radiotherapy as salvage treatment might be an alternative in late limited nodal recurrence after initial chemotherapy. However, the body of knowledge is small. ([47]R3, [48]R3, [64]R2).

The role of radiotherapy in the treatment of Hodgkin lymphoma is decreasing.

Addendum

Early and intermediate stages

Radiotherapy alone versus chemotherapy		
NCI-Canada/ ECOG	STNI/inverted Y vs ABVD x 4–6 favourable	open
Radiotherapy alone versus chemotherapy plus radiotherapy		
UK Lymphoma group	Mantle vs VAPEC-B x 1 + IF (30–40 Gy)	open
Chemotherapy plus radiotherapy versus chemotherapy alone		
MSKCC	ABVD x 6+ mantle /inverted Y (STNI/TNI for st IIIA) vs x ABVD x 6	recently closed no results
NCI-Canada/ ECOG	ABVD x 2 + STNI/inverted Y vs ABVD x 4–6 Unfavourable	open
GHSG HD 13	ABVD x 2 + IF 20–30 Gy vs ABVD x 4–6	open
CALGB	ABVD x 4 + IF vs ABVD x 6	soon to be started
Evaluating radiation dose after chemotherapy		
GHSG HD 10	ABVD x 2 + IF 30 Gy or 20 Gy vs ABVD x 4 + IF 30 Gy or 20 Gy	open
GHSG HD 11	ABVD x 4 + IF 30 Gy or 20 Gy vs BEACOPP base x 4 + IF 30 Gy or 20 Gy	open
EORTC H9-F	EBVP x 6 + IF 36 Gy vs EBVP x 6 + IF 20 Gy vs 6 x EBVP alone	open

Advanced stages: stage III and IV (st IIB with risk factors)

The role of additional radiotherapy		
GHSG HD 12	BEACOPP escalated x 8 + 30 Gy bulk or 0 RT vs BEACOPP escalated x 4 + BEACOPP base x 4 + 30 Gy bulk or 0 RT	open

Abbreviations:
ANLL; acute non-lymphocytic leukemia
AP/PA; anterior-posterior/ posterior- anterior (radiation fields)
CALGB; Cancer and Leukemia Group B
EF; extended field
EORTC; European Organization for the Research and Treatment of Cancer
GELA; Groupe d´etudes des Lymphomes de l´adulte
GHSG; German Hodgkin study group
GPMC; Groupe Pierre-et-Marie-Curie
HDCT; high-dose chemotherapy
HL; Hodgkin's lymphoma
IF; involved field
IPS; international prognostic score
MDS; myelodysplastic syndrome
MSKCC; Memorial Sloan Kettering Cancer Center
NHL; non-Hodgkin' lymphoma
PET; positron emission tomography
PV; protocol violations
STNI; subtotal nodal irradiation
SWOG; Southwest Oncology Group
TBI; total body irradiation
TNI; total nodal irradiation
TRM; treatment related mortality

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Excluded randomized study:
Aviles A, Delgado S. A prospective clinical trial comparing chemotherapy, radiotherapy and combined therapy in the treatment of early stage Hodgkin's disease. Clin Lab Haem 1998;20:95-9.

Overview 1 *Hodgkin's lymphoma. Radiotherapy alone: evaluating radiation field size or dose.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Specht 1998 [59] M	Reduced RT volume. **A:** more extensive RT **B:** less extensive RT	1962–82, 8 trials St IA–IIIB mostly IA, IIA A: 1 005 pts B: 969 pts
Brinker 1994 [9] O	Optimal dose for disease control	4117 radiation fields from the 1960s to the 1990s
Dühmke 1996 [17] C	Reduced radiation dose **A:** EF 40 Gy **B:** EF 30 Gy + IF 10 Gy	1988–93 St IA-IIB, A: 170 pts B: 175 pts
Mendenhall 1999 [39] R	Optimal dose for disease control TNI/STNI mostly 30–40Gy	1967–94 169 pts St I–II

EF: extended field; IF: involved field; FFTF:freedom from treatment failure; HL: Hodgkin's lymphoma; ns: no significant; OS: overall survival; pts: patient(s); PV:protocol violations; RT:radiotherapy; STNI: subtotal nodal irradiation; TF: treatment failure; TNI: total nodal irradiation; y: year(s)

Results	Conclusion/Comments
OS% TF%, at 10 y A 77 31 B 77 ns 43 p<0.00001	More extensive RT reduces recurrences but no difference in OS. Increased mortality from recurrent HL in pts receiving smaller field irradiation balanced by increased treatment related mortality with more extensive RT. **M1/3 888**
No dose-response above 32.5 Gy	32.5 Gy could be the optimal dose. Re-analysis of retrospective data. In previous SBU-report 129/2, Ref no. 94. **O2**
OS% FFTF%, at 5 y A 93 70 B 98 ns 81 p <0.03 PV 70 no PV 82 p <0.04	30 Gy is sufficient for subclinical involvement. Definition of EF is missing. PV in 1/3 of the patients. PV had prognostic significance in this study. **C2/345**
No increased tumour control for doses above 30 Gy.	30 Gy seems to be a sufficient dose. Increased rate of local failure with increasing tumour size. **R2/169**

Overview 2 *Hodgkin´s lymphoma. Radiotherapy alone vs chemotherapy + radiotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Specht 1998 [59] M	Benefit of adding CHT to RT **A:** RT + CHT **B:** RT only	1967–88, 13 trials St IA–IIIB A: 839 pts B: 856 pts
Sieber 2001 [58] C	Benefit of neo-adjuvant CHT **A:** RT **B:** ABVD x 2 + RT	1994–98 St IA–II no risk factors A: 282 pts B: 289 pts
Press 2001 [51] C	Benefit of neo-adjuvant CHT **A:** STNI **B:** CHT + STNI	1989–2000 St I–IIA no bulk A: 161 B: 165
Radford 2001 [52] C	Benefit of neo-adjuvant CHT **A:** RT **B:** VAPEC-B x 1 + RT	1989–97 St I–IIA no bulk A: 63 pts B: 62 pts
Enrici 1999 [19] C	Benefit of neo-adjuvant CHT **A:** STNI **B:** ABVD x 1 + STNI	1983–89 St I–IIA no bulk A: 37 pts B: 36 pts
Noordijk 1994, [45] 1997, [46] C	Reduced RT volume **A:** STNI **B:** EBVP x 6 + RT IF	1988-93 St I–II “favourable” A: 165 pts B: 168 pts

Ref 51: CHT = 3 courses of doxorubicin + vinblastine

Results			Conclusion/Comments
	OS%	**TF %, at 5 y**	Addition of CHT reduces recurrences but does not significantly affect OS. Mostly MOPP or variants were used. In some studies more extensive RT was given to pts not receiving CHT; in some studies pts with advanced stages were included. However, subgroup analysis showed similar reduction of TF. **M1/3 888**
A	79	16	
B	77 ns	33 p< 0.00001	
	OS%	**FFTF%, at 22 m**	Neoadjuvant CHT reduces the relapse frequency but no difference in survival. Abstract, short follow-up.
A	98	84	
B	98	96 p<0,05	
	OS%	**FFS% at 3 y**	Neoadjuvant CHT reduces the relapse frequency but no difference in OS. **C2/326**
A	96	81	
B	98 ns	94 p<0.001	
		FFP%, at 5 y	Brief (4 weeks) neo-adjuvant CHT gives a significant improvement of FFP. No difference in survival Abstract.
A		62	
B		93 p=0.0002	
	OS%	**RFS%, at 10 y**	Neoadjuvant CHT reduces the relapse frequency but no difference in OS. Few patients, low power. **C3/73**
A	97	73	
B	92 ns	94 p<0.01	
	OS%	**RFS%, at 6 y**	With CHT possible to reduce RT volume. RFS better with CHT, but no difference in OS. In the report (1994) short follow-up. **C3/254** In the abstract (1997) more patients and longer follow-up. **C3/–**
A	96	81	
B	98 ns	92 p=0.004	

The table continues on the next page

Overview 2 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Meerwaldt 2001 [40] C	Reduced RT volume **A:** STNI **B:** MOPP/ABV x 3 + RT IF	1993–99 St I–II "favourable" A: 272 pts B: 271 pts
Horning 1997 [30] C	Reduced RT volume and dose **A:** STNI **B:** VBM x 2 + RT IF + VBM x 4	1988–95 St I–II A: 43 pts B: 35 pts

CHT: chemotherapy; EF: extended field; IF: involved field; FFP: freedom from progression; FFS: failure free survival; FFTF:freedom from treatment failure; m: month(s); OS: overall survival; pts: patient(s); PV:protocol violations; RFS: relapse free survival; RT:radiotherapy; STNI: subtotal nodal irradiation; TF: treatment failure; TFFS: Treatment failure free survival; y: year(s) ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; EBVP: epirubicin, bleomycin, vinblastine, prednisone; MOPP: mustine, vincristine, procarbazine, prednisone; VAPEC-B: vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin; VBM: vinblastine, bleomycin, methotrexate.

Results			Conclusion/Comments
	OS%	**TFFS%, at 46 m**	With CHT possible to reduce RT volume.
A	96	77	RFS better with CHT, but no difference in OS.
B	99 ns	99 p<0.001	Abstract.
			C3/–
	OS%	**FFP%, at 5 y**	No difference in outcome. With CHT possible to reduce
A	No	92	RT volume and dose.
B	diff	87	Alteration of the inclusion criteria during the study but probably without significance. Few patients, low power.
			C3/78

Overwiew 3 *Hodgkin´s lymphoma. Radiation volume or dose after chemotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Noordijk 1994, [45] 1997, [46] C	Reduced RT volume **A:** STNI **B:** EBVP x 6 + RT IF	1988–93 St I–II "favourable" A: 165 pts B: 168 pts
Meerwaldt 2001 [40] C	Reduced RT volume **A:** STNI **B:** MOPP/ABV x 3 + RT IF	1993–99 St I–II "favourable" A: 272 pts B: 271 pts
Horning 1997 [30] C	Reduced RT volume and dose **A:** STNI **B:** VBM x 2 + RT IF + VBM x 4	1988–95 St I–II A: 43 pts B: 35 pts
Rüffer 2001 [57] C	Reduced RT volume COPP/ABVD x 2 to all **A:** RT EF **B:** RT IF	1993–98 St I–II and risk factors, St III 965 pts No of pts in the two groups, A and B, not reported.
Bonfante 2001 [6] C	Reduced RT volume and dose ABVD x 4 to all **A:** STNI **B:** RT IF	1990–96 St IA/B, IIA, IIAE incl. bulky disease A: 66 pts B: 70 pts
Loeffler 1997 [36] C	Reduced RT dose COPP/ABVD x 2 to all **A:** EF 40 Gy **B:** EF 20 Gy, bulk 40 Gy **C:** EF 30 Gy, bulk 40 Gy	St I, II with risk factors, III A HD1 1984–88 A 76 pts B 71 pts HD5 1988–93 C111 pts

CHT: chemotherapy; EF: extended field; IF: involved field; FFP: freedom from progression; FFTF:freedom from treatment failure; HD: high dose; m: month(s); OS: overall survival; pts: patient(s); PV: protocol violations; RT:radiotherapy; RT EF: radiotherapy extended field; RT IF :radiotherapy involved field; STNI: subtotal nodal irradiation; TF: treatment failure; y: year(s) ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; COPP: cyclophosphamide, vincristine, procarbazine, prednisone.

Results			Conclusion/Comments
	OS%	**RFS%, at 6 y**	With CHT possible to reduce RT volume.
A	96	81	RFS better with CHT, but no difference in OS.
B	98 ns	92 p=0.004	In the report (1994) short follow-up. **C3/254** In the abstract (1997) more patients and longer follow-up.
	OS%	**TFFS%, at 46 m**	With CHT possible to reduce RT volume.
A	96	77	RFS better with CHT, but no difference in OS.
B	99 ns	99 p<0.001	Abstract.
	OS%	**FFP%, at 5 y**	No difference in outcome. With CHT possible to reduce
A	No	92	RT volume and dose.
B	diff	87	Alteration of the inclusion criteria during the study but probably without significance. Few patients, low power. **C3/78**
	OS %	**FFTF%, at 26 m**	Reduction of RT volume possible after CHT.
A	97	94	
B	97	92 ns	Abstract, short follow-up.
	OS %	**FFP %, at 10 y**	Reduction of RT volume possible after CHT.
A	93	97	
B	94 ns	94 ns	Abstract.
	OS%	**FFTF%, at 4 y**	20 Gy is sufficient after CHT.
A	88	80	**C1/258**
B	94	79	
C	93 ns	86 ns	

Overwiew 4 *Hodgkin's lymphoma. Advanced stages (in the meta-analysis intermediate stages are included).*

Author Year (ref no) Design	**Aim/ Study question**	**Patient population**
Loeffler 1998 [37] M	a) Additional RT (additional design) **A:** CHT **B:** CHT + RT b) Substitute RT with CHT (parallel design) **C:** CHT_1 + CHT_2 or more cycles of CHT_1 **D:** CHT_1 + RT or CHT_2 + RT	a) 1968–88 8 studies* St I–IV (mostly IIB–IV) DC OS A: 406 434 pts B: 512 569 pts b) 1972–88 8 studies* St IIB–IV (mostly IIIB–IV) DC OS C: 420 460 pts D: 417 479 pts
Fabian 1994 [20] C Included in meta-analysis [37]	RT in CR after CHT **A:** MOP-BAP x 6 **B:** same CHT + RT IF	1978–88* St III–IV A: 143 pts (130 no more therapy) B: 135 pts (104 received RT)
Coleman 1998 [14] C	Additional RT after CT? **A:** CVPP x 6 **B:** CVPP x 12 **C:** CVPP x 6 + RT **D:** CVPP x 3 + RT + CVPP x 3	1975–1981 St IIIB–IV (some st IIA–B, IIIA) A: 70 pts B: 61 pts C: 59 pts D: 68 pts

Ref no 37: *Overall survival, OS, was evaluated in 8 studies while disease control, DC, only was evaluated in 7 of these.
Ref no 20: *Initially there was a third arm with levamisole. This was dropped 1982 due to slow pts accrual.
CHT: chemotherapy; DC; disease control; DFS: disease free survival EF: extended field; EFS: event free survival; IF: involved field; FFP: freedom from progression; FFTF:freedom from treatment failure; HD: high dose; m: month(s); OS: overall survival; pts: patient(s); PV: protocol violations; RFS: relapse free survival; RT:radiotherapy; RT IF :radiotherapy involved field; STNI: subtotal nodal irradiation; TF: treatment failure; y: year(s)

Results	Conclusion/Comments
At 10 y. a) Addition of RT improved DC with 11% p<0.0001; TF was reduced with nearly 40%. The benefit of RT was more pronounced in st I–III, in pts with mediastinal involvement (but not on bulky disease), in NS and LP. No benefit in st IV. No difference in OS. Sign. more fatal events after RT. b) No difference in DC; OS 8% better without RT p=0.045 All pts (A, B, C, D): sign. more fatal events after RT; RR=1.73, p=0.005 Sign. more leukaemia related deaths after combined treatment (CHT + RT) p=0.038.	Additional RT significantly improves disease control but not survival. More fatal events in the RT-arm. In parallel design trials, the same disease control in both arms, but sign. better OS without RT. The conclusions from this meta-analysis must be handled with caution as the studies were initiated 20 or more years ago with combinations of chemotherapy (mostly MOPP-based) and radiotherapy techniques that are considered outdated today. Furthermore the extent of the irradiation and the doses were not considered and randomization was based on remission in some studies and included all patients in other studies. In the combined modality groups, more deaths from causes other than Hodgkin's lymphoma, including leukemia were seen, but data were missing in 48% of the cases with a predominance of missing data in the combined modality group. **M1/1 740**
OS% RFS%, at 5 y A 79 66 B 86 ns 74 ns	No improvement in RFS (except for pts with nodular sclerosis and/or bulky disease) by adjuvant RT in CR after CHT. In pts who got planned therapy remission duration was sign better in RT-arm. **C2**
No difference between the four arms concerning CR, DFS, FFS or OS.	No benefit of additional RT after CHT Alterations during the study; (maintenance therapy with chlorambucil omitted, inclusion of st IIIB 1979). Low power. **C3/258**

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Overwiew 4 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Diehl 1995 [16] C Included in meta-analysis [37]	More CHT instead of RT in CR COPP/ABVD x 3 to all **A:** RT IF **B:** COPP/ABVD x 1	1984–88 St IIIB–IV 100/171 pts in CR after CHT randomized A: 51 pts B: 49 pts
Fermé 2000 [21] C	More CHT instead of RT in CR/PR MOPP /ABV x 6 + **A:** MOPP /ABV x 2 **B:** (S)TNI ABVPP x 6 + **C:** ABVPP x 2 **D:** (S)TNI	1989–1996 St IIIB–IV A: 92 pts B: 114 pts C: 116 pts D: 96 pts
Brice 2001 [7] Subgroup analysis of ref 21 above.	See ref 21 above	See ref 21, subgroup of pts with large mediastinum A + C no RT, 32 pts B + D RT, 29 pts
Raemaekers 2001 [54] C	RT in CR after CHT **A:** MOPP/ABV x 6–8 **B:** MOPP/ABV x 6–8 + RT IF	1989–2000 St III–IV 418 pts in CR A: 161 pts B: 172 pts

ABV(D)(PP): doxorubicin, bleomycin, vinblastine, and (dacarbazine)(procarbazine, prednisone), COPP: cyclophosphamide, oncovine, procarbazine and prednisone, CVPP: CCNU, vinblastine, procarbazine, prednisone, DC; disease control = time to failure, progression, no CR or relapse (death in CR censored), FFTF:freedom from treatment failure, IF:involved field, MOP-BAP: nitrogen mustard, vincristine, prednisone, bleomycin, doxorubicin, procarbazine, MOPP: nitrogen mustard, vincristine, procarbazine, prednisone, RFS; relapse free survival, RT; radiotherapy

Results				Conclusion/Comments
	% Relapse at 6 y			No difference between adjuvant RT or additional CHT as sconsolidation in complete remission after CHT. **C2**
A	25			
B	20 ns			
No diff. in FFTF and OS				
	OS%, at 5 y			Interim analysis. RT not superior to CHT for consolidation in CR/PR. **C2/418**
A	85			
B	88 ns			
C	94			
D	78 p=0.002			
	DFS%, at 5 y			
A + C no RT	74			
B + D, RT	79 ns			
	EFS%	**OS%, at 5 y**		No difference between RT and CHT for consolidation therapy in patients with large mediastinum. Subgroup analysis. Few patients. **C3/–**
A + C	84	96		
B + D	66 ns	97 ns		
	RFS%	**EFS%**	**OS%, at 5y**	RT IF does not improve treatment results in stage III–IV HL-patients in CR after CHT. Abstract. **C3/–**
A	85	82	89	
B	87 ns	79 ns	85 ns	