

Background and Rationale for Radiotherapy in Early-Stage Hodgkin Lymphoma

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2.1 Introduction

The curative role of radiation therapy for patients with HL was first established in 1950 by Dr. Vera Peters in Toronto (Peters 1950), based on the concept of contiguous spread of HL. Based on her results and the results of other pioneers, notably Dr. Henry Kaplan at Stanford, extended-field radiotherapy was established as a curative treatment for stage I, II, and some cases of stage III disease, as detailed in Chap. 1. For a number of years, radiotherapy was the only known curative treatment for HL.

With the introduction in 1964 by Dr. Vincent DeVita at the National Cancer Institute of combination chemotherapy with mechlorethamine, vincristine, procarbazine, and prednisone (the MOPP regimen), cures could be achieved even in patients with advanced disease (DeVita, Jr. et al. 1970). The MOPP regimen also proved effective in the treatment of recurrences after extended-field radiotherapy for stage I–III disease (Horwich et al. 1997). Randomized trials were then carried out, testing if the addition of chemotherapy to radiotherapy up front could improve outcome compared to radiotherapy alone with chemotherapy reserved for recurrences. Meta-analysis of these trials showed that the risk of recurrence was significantly reduced by the addition of chemotherapy up front, but that OS was not influenced, at least in the short term (10–15 years) (Specht et al. 1998).

The need for the extended radiation fields when effective chemotherapy salvage of recurrences was available was also tested in a number of randomized trials. Meta-analysis of these trials showed that the risk of recurrence was significantly reduced by the use of

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Table 2.1 Definition of favourable and unfavourable (intermediate) early-stage Hodgkin lymphoma

	GSHG	EORTC	Stanford	NCIC
Risk factors	(a) Large mediastinal mass (b) Extranodal disease (c) ESR ≥ 50 without B-symptoms or ≥ 30 with B-symptoms (d) ≥ 3 nodal areas	(a) Large mediastinal mass (b) Age ≥ 50 years (c) ESR ≥ 50 without B-symptoms or ≥ 30 with B-symptoms (d) ≥ 4 nodal areas	(a) B-symptoms (b) Large mediastinal mass	(a) Histology other than LP/NS (b) Age ≥ 40 years (c) ESR ≥ 50 (d) ≥ 3 nodal areas
Favourable	CS I-II without risk factors	CS I-II (supra-diaphragmatic) without risk factors	CS I-II without risk factors	CS I-II without risk factors
Unfavourable	CS I or CS IIA with ≥ 1 risk factors CS IIB with (c) or (d) but without (a) and (b) (which are included in advanced disease)	CS I-II (supra-diaphragmatic) with ≥ 1 risk factors	CS I-II with ≥ 1 risk factors	CS I-II with ≥ 1 risk factors

GSHG: German Hodgkin Lymphoma Study Group; EORTC: European Organization for Research and Treatment of Cancer; NCIC: National Cancer Institute of Canada; ESR: erythrocyte sedimentation rate; LP: lymphocyte predominance; NS: nodular sclerosis; CS: clinical stage

more extensive radiotherapy, but that overall survival was not influenced (Specht et al. 1998). Hence, in the setting of effective chemotherapy, the extended radiation fields were no longer needed.

During the era when MOPP was the standard systemic therapy for HL, radiation therapy alone was routinely given for patients with pathologically confirmed early-stage disease, sparing these patients from the toxicity of MOPP chemotherapy. In 1973, Dr. Gianni Bonadonna in Milan introduced the combination chemotherapy regimen consisting of adriamycin, bleomycin, vinblastine, and dacarbazine (the ABVD regimen) (Bonadonna et al. 1975). This regimen proved more effective and less toxic than MOPP (Canellos et al. 1992; Duggan et al. 2003; Somers et al. 1994). Gradually, combined modality therapy became the standard treatment for early-stage HL. This change was initially based solely on the superiority of combined modality treatment with regard to recurrence-free survival. However, very long-term follow-up of randomized trials has also shown a significant OS benefit of combined modality therapy over radiation therapy for patients with early-stage disease (Ferme et al. 2007; Specht 2003). This superiority seems to be based on the adverse influence of the long-term toxicity of intensive therapy for recurrences (Franklin et al. 2005; Specht 2003).

Issues around the radiation therapy component of combined modality therapy include the optimal radiation

dose, radiation field size, and treatment technique, and whether it can be eliminated in selected patients based on initial clinical characteristics or response to systemic therapy. Over the years, trials have been designed and conducted to address these questions.

In the design of most clinical trials for early-stage HL, patients are frequently classified into favorable versus unfavorable groups according to the presence or absence of prognostic factors. The classification criteria can vary from group to group, but disease bulk, number of sites of disease, constitutional symptoms, and/or sedimentation rates are among factors that are typically used. Summarized in Table 2.1 are definitions of favorable and unfavorable-prognosis early-stage HL as defined by several major groups active in HL trials. A clear understanding of specific selection criteria for inclusion in various clinical trials will allow a better appreciation of the applicability of the trial results to individual patients.

2.2 Combined Modality Therapy for Early-Stage Hodgkin Lymphoma

As part of combined modality therapy, the optimal radiation doses and field sizes have been explored by a number of trials. Specifically, in an effort to reduce

toxicity, investigators have addressed the question of radiation dose de-escalation and radiation field-size reduction in the context of combined modality therapy.

2.2.1 Radiation Dose and Fractionation

In the era of treating HL with radiotherapy alone, 40 Gy was for a long time considered the tumoricidal dose based on the original publication by Henry Kaplan (Kaplan 1966). Later analyses indicated that tumor control was achieved at lower doses and was dependent on tumor size at the time of irradiation (Mendenhall et al. 1999; Schewe et al. 1988; Vijayakumar and Myrianthopoulos 1992). A re-analysis of the available dose–response data from patients treated with radiotherapy alone showed no positive dose–response relationship at doses above 32.5 Gy, and because of the wide confidence limits of the estimates no appropriate dose levels for various tumor burdens could be estimated (Brincker and Bentzen 1994). Moreover, the available data did not show a major importance of overall treatment time in the range from 4 up to 6–7 weeks. The capacity of the lymphoma cells to repair sublethal damage appeared to be small suggesting that dose per fraction is not very important for the dose needed to obtain tumor control. Hence, choice of fractionation does not seem to be critical, and schedules with a low degree of damage to the normal tissues should therefore be selected. The randomized HD4 study by the German Hodgkin Study Group (GHSg) documented that for subclinical involvement 30 Gy was equally effective as 40 Gy (Duhmke et al. 2001).

The appropriate radiation dose after chemotherapy in early-stage HL was examined in two trials for patients with favorable-prognosis disease and in one trial for patients with unfavorable-prognosis disease.

The European Organization for Research and Treatment of Cancer (EORTC) H9F trial was a three-arm trial in which all patients received six cycles of epirubicin, bleomycin, vinblastine, and prednisone (EBVP) (Thomas et al. 2007). After a complete response, patients were randomized to receive no further treatment, 36 Gy, or 20 Gy of involved-field irradiation (IFRT). Patients with a partial response all received 36 Gy of IFRT with or without a 4 Gy boost. As will be discussed in a later section, the chemotherapy-alone

arm was closed early due to lower than expected event-free survival. In an interim analysis of 783 enrolled patients, at a median follow-up of 33 months, the 4-year event-free survival (EFS) of patients randomized to receive 36 Gy versus 20 Gy was not significantly different (87% versus 84%) (Thomas et al. 2007).

The GHSg HD10 trial on patients with low-risk early-stage disease also explored the use of lower doses of radiation therapy as part of combined modality therapy (Eich et al. 2005). The design was a 2×2 randomization in which patients were randomized to four versus two cycles of ABVD, followed by 30 Gy versus 20 Gy of IFRT. With respect to the arms evaluating radiation doses, in the most recent interim analysis that included 1,370 patients, at a median follow-up of 41 months, the freedom from treatment failure were comparable between the two arms (94% versus 93%).

For patients with unfavorable early-stage HL, the use of lower doses of radiation therapy is being addressed by the GHSg HD11 trial (Klimm et al. 2005). Patients were randomized to ABVD versus cyclophosphamide, doxorubicin, etoposide, procarbazine, prednisolone, vincristine, and bleomycin (BEACOPP), followed by 30 Gy versus 20 Gy of IFRT radiation therapy. In the most recent interim analysis that included 1,570 patients, at a median follow-up of 3 years, there was no significant difference between the 30 and 20 Gy arms (90% versus 87%).

However, all of these trials have median follow-up time of less than 5 years, and peer-reviewed published results are not yet available. Additional follow-up is therefore needed to establish the safety of 20 Gy of radiation treatment.

2.2.2 Radiation Field Size

Among patients with favorable-prognosis early-stage HL, no randomized trials have been conducted comparing extended-field (EFRT) versus IFRT after chemotherapy. However, IFRT was adopted as the standard arm in a number of recent European trials, including EORTC H7F, H8F, H9F, and GHSg HD10. In patients with unfavorable-prognosis disease, three trials have compared EFRT versus IFRT as part of combined modality therapy, although the results should be applicable to patients with favorable-prognosis disease as well.

In the EORTC H8U trial, two of the three arms compared four cycles of MOPP/ABV followed by either EFRT or IFRT (Ferme et al. 2007). The 5-year EFS rates were 88% and 87%, respectively, at a median follow-up of 92 months.

In the GHSG HD8 trial, 1,204 patients with CS I–II HL with adverse factors were randomized to receive two cycles of cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) and ABVD followed by EFRT or IFRT (Engert et al. 2003). At a median follow-up time of 54 months, the 5-year freedom from treatment failure rates of the two arms were 86% and 84%, respectively ($p=0.56$), and the 5-year overall survival rates were 91% and 92%, respectively ($p=0.24$).

In an Italian trial by Bonnadonna et al., 136 patients with CS I unfavorable and CS IIA favorable and unfavorable HL received four cycles of ABVD followed by either subtotal nodal irradiation or IFRT (Bonnadonna et al. 2004). At a median follow-up of 116 months, the 12-year freedom from progression of the two arms were 93% and 94%, respectively, and the 12-year overall survival were 96% and 94%, respectively.

The definition of IFRT was never quite clear, and the term was interpreted in different ways in different studies. Many radiation oncologists used the lymph node region diagram employed in the Ann Arbor staging classification (Kaplan and Rosenberg 1966). However, this diagram was never intended for definition of radiation fields. Commonly accepted guidelines stated that IFRT is treatment of a whole region, not individual lymph nodes (Yahalom et al. 2007; Yahalom and Mauch 2002).

The concept and guidelines for IFRT were developed for use with conventional two-dimensional (2D) treatment planning. With this treatment a considerable volume of tissue which never contained lymphoma was irradiated. However, the evidence detailed above consistently indicates that, in the scenario of combined modality treatment with efficient chemotherapy, irradiation of uninvolved lymph nodes and other tissues is not necessary. This is supported by analyses of sites of relapse in early-stage patients who were for some reason treated with chemotherapy alone (Shahidi et al. 2006). Moreover, reductions in the IFRT fields to encompass only the initially involved lymph nodes with a maximum margin of 5 cm have been shown to be safe (Campbell et al. 2008). In this study, among the 102 patients treated with chemotherapy followed by reduced

IFRT, at a median follow-up of 50 months, there were three relapses, all of which were at distant sites.

Modern sophisticated techniques, including better imaging, three-dimensional (3D) treatment planning, and highly conformal treatment delivery, have opened up the possibilities to further reduce the irradiated volume in patients with early-stage HL. The EORTC-GELA Lymphoma Group (GELA: Groupe d'Etudes des Lymphomes de l'Adulte) pioneered the concept of involved-node radiotherapy (INRT), using modern 3D conformal techniques and imaging, preferably including positron emission tomography with 2-[^{18}F]fluor-2-deoxyglucose (FDG-PET) (Girinsky et al. 2006). The specifications are in accordance with the ICRU 50/62 recommendations, although no guidelines exist taking into account the post-chemotherapy planning of a pre-chemotherapy volume (ICRU 1993). With INRT the clinical target volume (CTV) includes only the volume of tissue which contained the initially involved lymph nodes. Due to the uncertainty of the exact localization on the post-chemotherapy planning CT scan of the involved nodes on the pre-chemotherapy staging CT scans, the whole area on the relevant CT slices are included in the target definition (Girinsky et al. 2008). The corresponding planning target volume (PTV) takes into account organ movement and set-up variations, which may vary in different anatomical sites, but in general a 1 cm isotropic margin is considered sufficient. For patients in complete remission (CR) or complete remission unconfirmed (CRu) after chemotherapy, no further radiotherapy is added. For patients in partial remission (PR) after chemotherapy, a boost to the residual lymphoma mass is added. Response criteria based on CT scans are employed (Cheson et al. 1999; Lister et al. 1989), as newer response criteria based on FDG-PET scans have not been validated for treatment planning (Cheson et al. 2007). The introduction of INRT represents a drastic reduction in the irradiated volume in patients with early-stage HL. No randomized trials have compared this approach with IFRT or EFRT. However, the GHSG is planning in its HD17 study in patients with early favorable disease to randomize between INRT and IFRT (Eich et al. 2008). The INRT concept is employed in the current EORTC-GELA-IIL (IIL: Intergruppo Italiano Linfomi) H10 trial, and it is also employed for routine treatment outside of protocol in most of the participating centers. Analyses of relapse frequency and localization will be extremely important for the validation of the INRT concept.

2.2.3 Association of Radiation Dose/Field Size and Late Toxicity

Complications of radiation therapy for HL will be discussed in a separate chapter. However, it is important to recognize that because of the long latency to late effects after radiation therapy for HL, most of the data on late effects, including risks of second malignancy and cardiac disease, are based on patients treated during a time period when higher radiation doses, larger treatment fields, and less conformal techniques were used, as compared to patients treated in the modern era.

Several case–control studies have shown a clear radiation dose–response relationship on the risk of breast cancer after HL. In a large international case–control study on breast cancer after HL that included 105 cases of breast cancer and 266 matched controls, radiation dose to the area of the breast where the tumor developed in the case (and a comparable area in matched controls) was estimated for each case–control set (Travis et al. 2003). Breast cancer risk increased significantly with increasing radiation dose to reach eightfold for the highest category (median dose 42 Gy) compared to the lowest dose group (< 4 Gy) (p -trend for dose < 0.001). A significant radiation dose–response relationship was similarly demonstrated in a Dutch study that included women from the international investigation (van Leeuwen et al. 2003). The Childhood Cancer Survivor Study group recently published a case–control study on 120 cases of breast cancer (65% were in survivors of HL) matched to 464 controls by age at initial cancer and time since initial cancer (Inskip et al. 2009). Again, a significant linear radiation dose–response was observed (p -trend < 0.0001), with an estimated relative risk of breast cancer of 6.4 at 20 Gy and 11.8 at 40 Gy.

In an international investigation by Travis et al., lung cancer risk increased with increasing radiation dose to the area of the lung in which cancer developed (p -trend with dose < 0.001), with the relative risk becoming significantly increased after doses of 30 Gy or higher (Travis et al. 2002). These findings support the notion that radiation dose reduction will likely result in lower second malignancy risks.

Hodgson et al. used a validated radiobiological model that takes into account cell initiation, inactivation, and proliferation after varying doses of radiation therapy to quantify the excess risk of radiation-induced second malignancy after various radiation treatment

fields and doses (Hodgson et al. 2007). The risks were estimated in 37 patients with mediastinal HL treated with IFRT to 35 Gy, and hypothetical mantle radiation therapy to 35 Gy, and IFRT to 20 Gy. The estimated relative risks of cancers of the breast and lung after “historical” treatment with mantle radiation therapy to 35 Gy were in agreement with those found in epidemiological studies. With the modern treatment of IFRT to 35 Gy, the 20-year excess relative risks of breast and lung cancer were estimated to be reduced by 63% and 21%, respectively. With potential future treatment of IFRT to 20 Gy, there were further reductions in the excess relative risks by 77% and 57%, respectively.

A significant dose–response relationship for cardiovascular complications after radiation therapy for HL has also been demonstrated. Hancock et al. showed that cardiac mortality after HL was significantly increased after doses of higher than 30 Gy to the mediastinum, but the increase was not significant after 30 Gy or lower (Hancock et al. 1993). Subsequent reports from the same group on results of a prospective cardiac screening study in asymptomatic long-term HL survivors showed an increased risk of valvular disease, diastolic dysfunction, and coronary disease, although the median dose to the mediastinum in this screened cohort was 44 Gy (Heidenreich et al. 2003; Heidenreich et al. 2005; Heidenreich et al. 2007).

There are also data to support current attempts to reduce radiation treatment field size in limiting complications. In the GHSG HD8 trial, patients on the extended-field arm were significantly more likely to experience acute side effects including leukopenia, thrombocytopenia, nausea, gastrointestinal toxicity, and pharyngeal toxicity (Engert et al. 2003). A higher risk of second malignancy was also observed in the extended-field arm compared with the involved-field arm (4.5% versus 2.8%), although the difference was not statistically significant. A subsequent analysis of 89 patients age 60 or older on this trial showed that elderly patients had a significantly inferior outcome when treated with EFRT as compared with IFRT, both in terms of freedom from treatment failure (58% versus 70%, $p = 0.034$) and overall survival (59% versus 81%, $p = 0.008$) (Klimm et al. 2007). In an Italian trial, at a median follow-up of almost 10 years, three cases of second malignancies were reported, all of which were in the EFRT arm (Bonadonna et al. 2004). In a meta-analysis by Franklin et al. on second malignancy risk after HL, the second malignancy risk after

EFRT versus IFRT was compared (Franklin et al. 2006). There was a trend of increased risk of second malignancy with EFRT with an odds ratio of 1.54 ($p=0.09$). In addition, the risk of breast cancer was higher with EFRT, with an odds ratio of 3.25 ($p=0.040$). A recent cohort study from the Netherlands on 1,122 female 5-year survivors of HL also showed a lower breast cancer risk with smaller radiation volume (De Bruin et al. 2009). In their multivariate Cox regression analyses, in which time-to-event was taken into account, women treated with mantle field irradiation (including the axillary, mediastinal, and neck nodes) had an almost threefold increased risk of breast cancer compared with those treated with mediastinal irradiation alone.

A larger radiation treatment field has also been shown to be associated with increased risk of cardiac complications. Hull et al. reported on the risk of cardiac disease in 415 HL survivors (Hull et al. 2003). The only treatment-related risk factor for the development of coronary artery disease on multivariable analysis was a matched mantle and subdiaphragmatic field as opposed to a mantle field alone or subdiaphragmatic field alone (hazard ratio, 7.8, $p=0.04$).

2.3 Can Radiation Therapy Be Safely Eliminated in Early-Stage Hodgkin Lymphoma?

As trials are being conducted evaluating reducing radiation dose and field size in combined modality therapy for early-stage HL, investigators have explored the

option of eliminating radiation therapy and treating patients with early-stage disease with chemotherapy alone.

2.3.1 Trials Comparing Combined Modality Therapy Versus Chemotherapy Alone

Recently, a meta-analysis of trials testing this important question has been performed by the Cochrane Haematological Malignancies Group (Herbst et al. 2010). Randomized controlled trials comparing chemotherapy alone with identical chemotherapy combined with radiotherapy in newly diagnosed patients with HL of all ages in clinical stage (CS) I or II were included (Aviles and Delgado 1998; Bloomfield et al. 1982; Eghbali et al. 2005; Noordijk et al. 2005; Pavlovsky et al. 1988; Straus et al. 2004). These trials are summarized in Table 2.2. Trials with less than 80% of patients in CS I or II (Laskar et al. 2004; Nachman et al. 2002; O'Dwyer et al. 1985; Picardi et al. 2007), and trials where the number of chemotherapy cycles varied between treatment arms (Kung et al. 2006; Meyer et al. 2005), were not included in the main analysis, but they were included in supplementary sensitivity analyses. These trials are summarized in Table 2.3. These trials varied in the study design, patient population, types of chemotherapy, and radiation fields employed. The findings and the limitations of each of the trials are discussed below.

Aviles and Delgado from the National Medical Centre, Mexico, randomized 307 patients with

Table 2.2 Randomized controlled trials comparing chemotherapy alone with identical chemotherapy combined with radiotherapy in newly diagnosed patients with Hodgkin lymphoma of all ages in clinical stage (CS) I or II

Trial	Patient population	No. patients	Treatment arms	Median follow-up	Results
Aviles et al.	CS I–II supradiaphragmatic, bulky disease	99	6×ABVD	11.4 years	DFS (12 years) 48%, OS (12 years) 59%
		102	6×ABVD+MFRT		DFS (12 years) 76%, OS (12 years) 88%
Bloomfield et al.	“Poor prognosis” PS I or II	18	6×CVPP	1.8 years	Complete remission 61%
		19	6×CVPP+IFRT		Complete remission 95%
Eghbali et al.	CS I–II without risk factors (see Table 2.1,	130	6×EBVP	4.3 years	EFS (5 years) 69%, OS (5 years) 97%
Noordijk et al.	EORTC criteria), in CR after 6×EBVP	448	6×EBVP+IFRT (20 or 36 Gy)		EFS (5 years) 87%, OS (5 years) 99%

Table 2.2 (continued)

Trial	Patient population	No. patients	Treatment arms	Median follow-up	Results
Pavlovsky et al.	CS I–II	142	6×CVPP	4 years	DFS (7 years) 62%, OS (7 years) 82%
		135	3×CVPP+IFRT (30 Gy)+3×CVPP		DFS (7 years) 71%, OS (7 years) 89%
Straus et al.	CS I–II and CS IIIA (13% of pts.), no bulky disease	76	6×ABVD	5.6 years	FFP (5 years) 81%, OS (5 years) 90%
		76	6×ABVD+IFRT or modified EFRT (36 Gy)		FFP (5 years) 86%, OS (5 years) 97%

CS: clinical stage; PS: pathological stage; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; CVPP: cyclophosphamide, vinblastine, procarbazine, prednisone; EBVP: epirubicine, bleomycin, vinblastine, prednisone; MFRT: mantle field radiotherapy; IFRT: involved-field radiotherapy; EFRT: extended-field radiotherapy; DFS: disease-free survival; EFS: event-free survival; FFP: freedom from disease progression; OS: overall survival

Table 2.3 Randomized controlled trials comparing chemotherapy alone with chemotherapy combined with radiotherapy in newly diagnosed early-stage Hodgkin lymphoma. Trials with less than 80% of patients in CS I or II, and trials where the number of chemotherapy cycles varied between treatment arms

Trial	Patient population	No. patients	Treatment arms	Median follow-up	Results
Laskar et al.	All stages included, in CR after 6×ABVD. Here are only CS-I-II included	44	6×ABVD	5.3 years	EFS (8 years) 94%, OS (8 years) 98%
		55	6×ABVD+IFRT		EFS (8 years) 97%, OS (8 years) 100%
Nachman et al.	Children with any stage in CR after chemotherapy. Here are only CS I-II included	173	4×COPP/ABV (no adverse factors)	Not reported	EFS (3 years) 91%, OS (3 years) 100%
		189	6×COPP/ABV (adverse factors) 4×COPP/ABV+IFRT (21 Gy) (no adverse factors) 6×COPP/ABV+IFRT (21 Gy) (adverse factors)		EFS (3 years) 83%, OS (3 years) 100% EFS (3 years) 97%, OS (3 years) 100% EFS (3 years) 87%, OS (3 years) 95%
O'Dwyer et al.	CS IB–IIIA	17	6×MOPP	6 years	Four relapsed, two died
		16	EFRT+6×MOPP		Three relapsed, three died
Picardi et al.	CS I–IV with bulky disease (≥5 cm) with residual PET mass after chemotherapy	80	6×VEBEP	3.3 years	EFS (5 years) 86%, OS (5 years) 100%
		80	6×VEBEP+IFRT (32 Gy)		EFS (5 years) 96%, OS (5 years) 100%
Kung et al.	PS I–IIIA, children	78	6×MOPP/ABVD	8.3 years	EFS (8 years) 83%, OS (8 years) 94%
		81	4×MOPP/ABVD+IFRT (25.5 Gy)		EFS (8 years) 91%, OS (8 years) 97%
Meyer et al.	CS I–IIA, without bulk (≤10 cm), unfavorable (see Table 2.1, NCIC criteria)	137	4–6×ABVD	4.2 years	FFP (5 years) 88%, OS (5 years) 95%
		139	2×ABVD+STNI (35 Gy)		FFP (5 years) 95%, OS (5 years) 92%

CR: complete remission; CS: clinical stage; PS: pathological stage; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; COPP: cyclophosphamide, vincristine, procarbazine, prednisone; MOPP: mechlorethamine, vincristine, procarbazine, prednisone; VEBEP: etoposide, epirubicine, bleomycin, cyclophosphamide, prednisone; IFRT: involved-field radiotherapy; EFRT: extended-field radiotherapy; STNI: subtotal nodal radiotherapy; EFS: event-free survival; FFP: freedom from disease progression; OS: overall survival

supradiaphragmatic stage I or II disease in a three-arm study to either six cycles of ABVD, or to mantle field radiotherapy (MFRT) alone, or to MFRT to 35–38 Gy preceded and followed by three cycles of ABVD (Aviles and Delgado 1998). Only the first and last of the three arms of the study are relevant here. With a median follow-up of 11.4 years the estimated 12-year disease-free survival (DFS) of patients treated with combined modality was 76% compared with 48% for patients treated with chemotherapy alone ($p < 0.01$). The corresponding figures for overall survival (OS) were 88% and 59%, respectively ($p < 0.01$).

Bloomfield et al. from the Cancer and Leukemia Group B reported on a small study in progress (Bloomfield et al. 1982). A total of 37 patients were randomized to either six cycles of cyclophosphamide, vinblastine, procarbazine, and prednisone (CVPP), or to six cycles of CVPP and involved-field radiotherapy (IFRT). Complete response rate was superior with combined modality treatment (95% versus 61%, $p = 0.04$), but with a median follow-up of only 22 months from diagnosis there was no survival difference. Unfortunately, no further published data from this trial have appeared.

In the EORTC-H9F trial, CS I–II, favorable-prognosis patients were randomized after a complete response to six cycles of EBVP to the following three arms: IFRT to 36 Gy, IFRT to 20 Gy, or no further treatment (Eghbali et al. 2005; Noordijk et al. 2005). The chemotherapy alone was closed due to higher than expected number of relapses. The main criticism of this study is the inadequate chemotherapy employed. However, this study was restricted to selected patients with favorable features, and the EBVP regimen was chosen since its efficacy in combination with involved-field radiation therapy had been proven in the earlier EORTC H7F trial.

Pavlovsky et al. from the Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA) randomized 277 patients with CS I–II HL to receive six monthly cycles of CVPP followed by IFRT to 30 Gy, versus six cycles of CVPP alone (Pavlovsky et al. 1988). At 84 months, the DFS of the combined modality therapy arm was significantly higher than that of the chemotherapy-alone arm (71% versus 62%, $p = 0.01$). On subgroup analysis, the difference between the two arms were highly significant among patients with unfavorable features (age > 45 , > 2 sites, or bulky disease), with DFS of 75% in the combined modality

therapy arm versus 34% in the chemotherapy-alone arm ($p = 0.001$). Among favorable patients, the difference in DFS was not significant (77% versus 70%). The main limitation of this study is the inferior chemotherapy regimen used, which likely explained the poor treatment outcome especially for the unfavorable patients treated with chemotherapy alone. In addition, 45% of patients in this trial were children aged under 16. The results therefore may not be entirely applicable to the adult population.

In a Memorial Sloan Kettering Cancer Center trial, patients with non-bulky CS IA–IIB and CS IIIA were randomized to six cycles of ABVD with or without radiation therapy (Straus et al. 2004). The target accrual was 90 patients per arm. After 152 patients were accrued at 10 years, the trial was closed due to slow accrual. No significant differences in freedom from progression (FFP) (86% versus 81%) and overall survival (97% versus 90%) were found at a median follow-up of 60 months. Seven of the eight relapses in the chemotherapy-alone arm were in initially involved nodal sites. This trial, however, was underpowered to determine if the two treatment approaches are truly equivalent. Furthermore, care should be taken in the interpretation of long-term toxicity data when they become available since the majority of patients randomized to receive radiation therapy were treated with EFRT.

The meta-analysis of these five unconfounded trials in (almost exclusively) early-stage HL showed not only a highly significant advantage for combined modality treatment with regard to tumor control, but the meta-analysis also showed a highly significant ($p < 0.00001$) advantage with regard to OS with a hazard ratio of 0.40 (95% confidence interval 0.27–0.59) (Herbst et al. 2010). The meta-analysis of OS is shown in Fig. 2.1.

The remaining six trials testing chemotherapy alone versus combined modality either included more than 20% of patients with advanced disease or they were confounded in the sense that more cycles of chemotherapy were given in the chemotherapy-only arm than in the combined modality arm, see Table 2.3.

Laskar et al. reported results of a randomized trial from Tata Memorial Hospital in India comparing six cycles of ABVD with or without IFRT (Laskar et al. 2004). Only patients who achieved a complete response to the chemotherapy were randomized. Patients of all stages were included, and 55% had CS I–II disease.

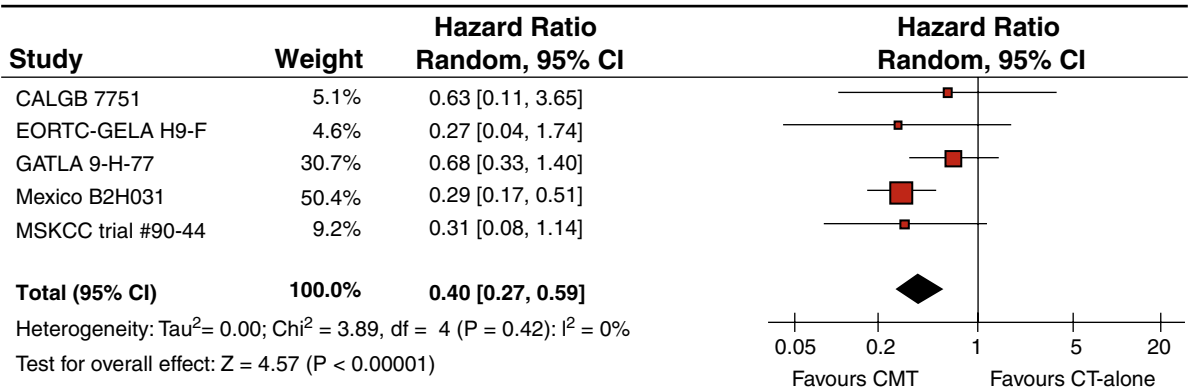


Fig. 2.1 Meta-analysis of overall survival (OS) in patients with early-stage Hodgkin lymphoma who were treated with chemotherapy alone (CT) or chemotherapy and radiotherapy (CMT). Solid squares represent effect estimates for the single trials, the size of the squares represent the weight of the individual studies

in the meta-analysis. Horizontal lines indicate the 95% confidence intervals (CI). The width of the diamond shows the 95% confidence interval for the pooled hazard ratios. (Reprinted with permission from Herbst et al. 2010)

Significant differences in 6-year EFS (88% versus 76%, $p=0.01$) and OS (100% versus 89%, $p=0.002$) were observed, favoring the combined modality therapy arm. However, no significant difference was found in stages I and II with regard to neither EFS nor OS, whereas, surprisingly, significant differences were found for stages III and IV. This study is limited by the high proportion of pediatric patients, with 46% age under 15. Also, the generalizability of the results to cases seen in the western world is unclear, as 71% of cases were of mixed cellularity histology, reflecting the high proportion of Epstein Barr Virus-related cases in developing countries.

The Children's Cancer Group (CCG) conducted a randomized trial on patients under the age of 21 comparing low-dose IFRT and noradiation therapy after a complete response to chemotherapy (Nachman et al. 2002). Sixty-eight percent had CS I–II disease. Patients were stratified into three risk groups based on clinical stage and presence of adverse factors. On an as-treated analysis, the 3-year EFS of the chemotherapy-alone arm was 85%, which was significantly lower than that of the combined modality therapy arm of 93% ($p=0.0024$). The randomization was stopped on the recommendation of the Data Monitoring Committee because of a significantly higher number of relapses on the no-radiation therapy arm. Of note, among the 34 relapses with known sites of relapse in the chemotherapy-alone arm, 29 were exclusively in the original sites of disease, three were in both previously involved and new sites, and only two were exclusively in new sites. However, as in the

previous study, the relevance of the results of this pediatric trial to adult patients is not clear. Moreover, the follow-up is relatively short in this study.

An early and very small trial carried out at the Montefiori Medical Center, New York, included only 33 patients and was never fully reported (O'Dwyer et al. 1985). Patients in stages IB–IIIA were randomized between EFRT followed by six cycles of MOPP or six cycles of MOPP alone. This trial did not indicate any difference between the two treatments, but it was of course far too small.

Picardi et al. conducted a randomized trial designed to evaluate whether radiation therapy can be safely eliminated if a complete response by PET scan is achieved after chemotherapy (Picardi et al. 2007). A total of 260 patients were included in the study. One hundred and sixty patients became PET-negative and had >75% reduction in the tumor mass at the completion of six cycles of etoposide, epirubicin, bleomycin, cyclophosphamide, and prednisone (VEBEP). These patients were randomized to 32 Gy of IFRT versus no further treatment. At a median follow-up of 40 months, there was a significant DFS benefit favoring the addition of consolidative radiation therapy (96% versus 86%, $p=0.03$), suggesting that even in carefully selected patients based on optimal functional imaging response to chemotherapy, the omission of radiation therapy is associated with a higher relapse rate.

The Pediatric Oncology Group carried out a study in children in pathological stage (PS) I–IIIA (Kung et al. 2006). A total of 159 patients were randomized to

either six cycles of MOPP/ABVD or four cycles of MOPP/ABVD followed by IFRT to 25.5 Gy. With a median follow-up time of over 8 years no significant difference was demonstrated either in EFS or OS.

In a randomized trial conducted by the National Cancer Institute of Canada (NCIC) and Eastern Cooperative Oncology Group, patients with non-bulky CS I–II disease were stratified into low-risk (LP/NS, age <40, ESR <50, and <3 sites of disease) and high-risk groups (Meyer et al. 2005). Low-risk patients were randomized to EFRT versus four to six cycles of ABVD, and high-risk patients were randomized to two cycles of ABVD followed by radiation therapy versus four to six cycles of ABVD. At a median follow-up of 4.2 years, patients treated with chemotherapy alone had a significantly inferior 5-year progression-free survival of 87% versus 93% in patients treated with either EFRT or combined modality therapy ($p=0.006$). There were no significant differences in OS. In examining the results of this trial, it needs to be taken into consideration that the “standard arm” in the low-risk group was EFRT, which had been shown to be inferior to combined modality therapy in several randomized trials even among favorable patients, and is currently no longer viewed as standard treatment. Furthermore, as in the Memorial Sloan Kettering trial, the majority of patients assigned to receive radiation therapy were treated with EFRT, which will likely have significant contribution to late effects.

In the meta-analysis mentioned previously, analyses were made including the six trials mentioned above that did not fulfill the inclusion criteria for the reasons mentioned above. These analyses confirmed the significant improvement in tumor control and OS with combined modality treatment (Herbst et al. 2010).

There are short-term non-randomized data suggesting that radiation therapy can be omitted in patients with advanced-stage HL based on PET response at the end of chemotherapy (Kobe et al. 2008). However, it is not clear whether the results are applicable to patients with early-stage HL. The results of the study by Picardi et al. mentioned above do not point in that direction (Picardi et al. 2007).

One of the key criticisms of trials that showed a significantly inferior outcome in the chemotherapy-alone arm was the inadequate chemotherapy used in some of the trials. These include the CVPP regimen used in the study from Argentina (Pavlovsky et al. 1988), the EBVP regimen used in the EORTC H9F trial (Eghbali

et al. 2005; Noordijk et al. 2005), and the VEBEP regimen used in the trial by Picardi et al. (Picardi et al. 2007). Shahidi et al. retrospectively analyzed 61 patients with supradiaphragmatic HL treated with chemotherapy alone at Royal Marsden Hospital (Shahidi et al. 2006). The majority of patients received vinblastine, epirubicin, etoposide, and prednisolone (VEEP) or chlorambucil, vinblastine, procarbazine, and prednisone (ChlVPP). At a median follow-up of 6.5 years, there were a total 24 recurrences, resulting in a 5-year relapse rate of 40%. In a Phase II study conducted by the CALGB (Straus et al. 2007), patients with non-bulky early-stage HL were treated with six cycles of adriamycin, vinblastine, and gemcitabine (AVG) chemotherapy alone without radiation therapy. At a median follow-up of only 1.1 years, 11 of 99 patients relapsed, yielding a 2-year PFS rate of only 71%.

It therefore appears that less-effective or abbreviated chemotherapy, or alternatives to ABVD designed to limit chemotherapy-related toxicity, is not acceptable when radiation therapy is omitted. Toxicities associated with full course ABVD can be non-trivial, and these include myelosuppression, peripheral neuropathy, bleomycin lung toxicity, and cardiac toxicity. Of these ABVD-related toxicities, perhaps the most serious one is cardiac toxicity. In a study conducted by Aviles et al. on 399 HL patients treated with chemotherapy alone (Aviles et al. 2005), 163 patients received ABVD chemotherapy. Survivors were closely followed by cardiac examination and testing. At a median follow-up of 11.5 years, among the 163 patients treated with ABVD alone, six patients developed congestive heart failure, 10 had myocardial infarction, and a total of seven cardiac deaths were observed. Compared to the matched general population, the risk of cardiac deaths was significantly elevated at 46-fold, representing 39 excess cardiac deaths per 10,000 person-years of follow-up. A British study on 7,033 patients with HL survivors also demonstrated the independent effect of chemotherapy on risk of cardiac mortality (Swerdlow et al. 2007), although the relative risks were less dramatically elevated. The risk of cardiac mortality was separately analyzed for patients who received chemotherapy with mediastinal irradiation and chemotherapy without mediastinal irradiation. Among patients who received ABVD without mediastinal irradiation, a significantly elevated relative risk of cardiac mortality of 7.8 was observed ($p=0.01$). The relative risks of cardiac mortality after treatment with any adriamycin-based chemotherapy with and

without mediastinal irradiation were 2.4 ($p=0.05$) and 3.2 ($p<0.001$), respectively.

2.3.2 Trials of Early PET Scans for Selecting Patients for Omission of Radiotherapy

Given the highly significant prognostic value of early PET response to chemotherapy, an intriguing question is if early PET response can be used as a tool to identify early-stage HL patients in whom radiation therapy can be omitted. The EORTC/GELA H10 trial is a randomized study designed to address this question. For patients with favorable disease, the standard arm consists of three cycles of ABVD followed by INRT while patients on the experimental arm receive two cycles of ABVD followed by PET scan. If the scan is negative, patients will receive two additional cycle of ABVD and then no further treatment. If the PET scan is positive, patients will receive two cycles of dose-escalated BEACOPP, followed by INRT. For patients with unfavorable disease, the standard arm consists of four cycles of ABVD followed by INRT while patients on the experimental arm receive two cycles of ABVD followed by PET scan. If the scan is negative, patients will receive four additional cycles of ABVD and then no further treatment. If the PET scan is positive, patients will receive two cycles of dose-escalated BEACOPP, followed by INRT. This trial is currently ongoing and results are not available.

In a British study in patients with CS IA and IIA without bulky disease, patients in complete or partial remission after three cycles of ABVD are examined with PET scan. If this scan is negative patients are randomized to IFRT or no further treatment. This trial has accrued the planned number of patients, but results will not be available for some time.

In a retrospective series by Barnes et al. (Barnes et al. 2008), 68 patients with non-bulky early-stage HL treated with anthracycline-based chemotherapy were reviewed. All patients underwent interim PET scan after two to three cycles of chemotherapy. A negative interim PET was observed in 51 patients and a positive interim PET in 17 patients. Sixty patients (88%) achieved a complete response to the chemotherapy. At a median follow-up of 32 months, six of the patients who achieved an initial complete response relapsed.

Five of the six relapses were observed in patients treated with chemotherapy alone with negative interim PET, with the relapses occurring at the initial site(s) of disease. This is a small retrospective study with short follow-up, but the results raise the concern that chemotherapy alone may not be adequate even in the setting of initially non-bulky disease and a negative interim PET. It therefore appears that at the current time, there is no available data to support the omission of radiation therapy based on PET response or early-PET response in patients with early-stage HL.

2.3.3 Patterns of Failure After Chemotherapy for Early-Stage Hodgkin Lymphoma

Detailed patterns of failure analysis of the NCIC trial, which compared EFRT alone versus chemotherapy alone in low-risk patients, and compared combined modality therapy with two cycles of ABVD followed by IFRT with chemotherapy alone, were reported by MacDonald et al. (Macdonald et al. 2007). In patients randomized to receive chemotherapy alone, 88% of the relapses were in-field and would have been included in the EFRT. Although this study did not utilize IFRT, the authors found that 71% of the relapses in the chemotherapy-alone arm would have been included in an involved-field treatment.

In the randomized trial conducted by the CCG comparing chemotherapy alone based on risk group, and chemotherapy followed by IFRT, there were 34 relapses in the chemotherapy-alone arm (Nachman et al. 2002). In 29 of the 34 (85%) relapses, they were isolated relapses at initial sites of disease, which would have been covered by the IFRT.

Pattern of relapse data were also available in the randomized trial by Picardi et al. assessing whether radiation therapy can be eliminated based on PET response at the completion of the radiation therapy (Picardi et al. 2007). In the chemotherapy-alone arm, a total of 11 relapses were observed, all of which were at initial bulky site and/or contiguous nodal region. In contrast, only two relapses were observed in the combined modality therapy arm, one of which was in-field and the other one was out-of field.

In the study from Royal Marsden hospital on 61 patients with supradiaphragmatic HL treated with

chemotherapy alone, of the 24 recurrences, 11 (45%) were in the same site, four (17%) were in new sites, and nine (38%) were in both old and new sites (Shahidi et al. 2006). The high relapse rate, including relapses at distant sites may be due to the inadequate chemotherapy, and the inclusion of patients with unfavorable factors such as large mediastinal adenopathy and B symptoms in the study.

2.4 Conclusion

Radiation therapy for early-stage HL has undergone substantial transformation over the last several decades. Its role evolved from being the sole treatment modality using large treatment fields to adjuvant local therapy directed to limited site(s) after systemic therapy. Given the well-documented patterns of relapse of the disease even after effective chemotherapy, and the failure thus far to reliably identify subgroups of early-stage patients in whom radiation therapy can be safely eliminated, radiation therapy remains an essential modality for the treatment of the disease. Continued advances in radiation therapy technology such as fusion with functional images, respiratory gating, and highly conformal techniques including IMRT and proton therapy will further improve targeting while sparing normal tissues (Ghalibafian et al. 2008; Girinsky et al. 2007; Girinsky and Ghalibafian 2007; Goodman et al. 2005; Yahalom 2005). In addition, if it is confirmed that reducing radiation field size and doses are safe and feasible as trial results become mature, further decrease in radiation-related toxicity will be anticipated. With the known toxicity of full-course chemotherapy which appears to be essential in the absence of radiation therapy, it appears that the treatment of choice for early-stage HL is abbreviated chemotherapy followed by limited radiation therapy, which will provide the best chance of cure up front while limiting acute and late effects.

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