Radiotherapy for Hodgkin Lymphoma
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The major goal of developing this book is to optimize radiotherapy for Hodgkin lymphoma by providing clinicians who treat patients with this disease with a comprehensive account of the background for radiotherapy for Hodgkin lymphoma, the rationale for radiotherapy in a modern combined modality setting, and the data that document its contribution to the best outcome for patients. Special emphasis is given to the changes in volume and dose that have evolved over the past 2 decades, and the use of modern advanced technologies in imaging and radiotherapy planning and delivery in order to accurately target involved sites and protect adjacent organs.

Radiotherapy was the first curative treatment modality for this previously lethal disease, and the achievements of the pioneers of curative radiotherapy for Hodgkin lymphoma represented some of the earliest success stories of the non-surgical treatment of cancer. With the advent of effective multiagent chemotherapy regimens, the role of radiotherapy changed. Radiotherapy now became part of multimodality treatment. Moreover, the long-term toxicity of the very extensive radiation fields of the past became apparent. This led to a virtual scare of radiotherapy in certain circles, and efforts were made to replace combined modality treatment with chemotherapy alone, almost no matter how intensive, with surprisingly little regard for the long-term toxicity of chemotherapy itself.

Recent evidence on the consequences of omitting radiotherapy altogether in the treatment of Hodgkin lymphoma demonstrates that such a strategy is not yielding the best possible results with regard to cure. In early-stage disease, the interim analysis of the large H10 trial of the EORTC/GELA/IIL demonstrates that in patients who were rendered PET-negative after two cycles of ABVD, the substitution of radiotherapy with more chemotherapy in favorable and unfavorable patients results in significantly higher relapse rates than standard treatment with less chemotherapy followed by involved node radiotherapy (INRT). In advanced disease, where many regarded radiotherapy as of no additional value, the recent analysis of the British LY09 trial demonstrates that the omission of radiotherapy seemed to be to the detriment of the chance of cure also in these patients. Finally, the concept of mini-chemotherapy with mini-radiotherapy has been shown to yield excellent results in patients with favorable and unfavorable early-stage disease, as demonstrated by the final analyses of the German Hodgkin Study Group HD10 and HD11 trials.

Radiotherapy remains the most effective single modality for the treatment of Hodgkin lymphoma. The modern application of this treatment modality, with lower doses and with very much reduced volumes, has proved effective and reduced the toxicity of this treatment tremendously. Highly advanced technologies within imaging, e.g., PET/CT-scanning, image co-registration, four-dimensional scanning and
motion compensation, and within treatment planning and delivery, e.g., intensity-modulated radiotherapy, arc-therapy, image-guidance and motion gating or tracking, have revolutionized radiotherapy. These techniques allow highly conformal radiotherapy, sparing large volumes of normal tissues while maintaining target coverage. Such techniques can and should be employed in the treatment of Hodgkin lymphoma. We and others have developed these techniques, which are employed in the treatment of Hodgkin lymphoma in several large institutions on both sides of the Atlantic. It is our sincere hope that this book will aid radiation oncologists worldwide in implementing modern highly conformal radiotherapy in the multimodality treatment of Hodgkin lymphoma to the benefit of present and future patients.

This book could not have been written without the generous help of many colleagues who have contributed their knowledge and expertise to the different chapters of this book, and we wish to express our sincere gratitude for their contribution and support.

Finally, we want to dedicate this book to our spouses, Henrik and Judith, who have been most patient throughout and given us support and encouragement when we needed it most.

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1.1 Introduction

In December, 1895, Wilhelm Conrad Röntgen first published his discovery of X-rays in a short communication to the Medical Physics Society of Würzburg, Germany, entitled “Über eine neue Art von Strahlen” (“On a New Type of Rays”) (Röntgen 1895; Lederman 1981; Dubois and Ash 1995). The biologic effects of the new rays were soon discovered, and they were almost immediately used in dermatology and to treat superficial cancers.

In Chicago, in 1902, Pusey published what appears to be the first documented case of radiotherapy of Hodgkin’s disease (Pusey 1902). Figure 1.1 shows a 4-year-old boy with the diagnosis of Hodgkin’s disease. The enlarged glands on the right side of the neck had been removed surgically, and in September, 1901, the boy was referred to Pusey “for exposure of the glands on the left side of the neck.” “There was a mass of glands on the left side as large as a fist. Under x-ray exposures the swelling rapidly subsided, and in 2 months the glands were reduced to the size of an almond.” In 1903, Senn, also from Chicago, published in more detail his cases of “that strange disease known as pseudoleucæmia, or Hodgkin’s disease” (Senn 1903); the first case is shown in Fig. 1.2. This patient was “forty-three years of age, a saloon keeper and farmer by occupation. The glandular affection dates back a year, having commenced in the cervical region almost simultaneously on both sides, and involves now very extensively the glands of these localities as well as of the axillary and inguinal regions. The increased respiratory movements and dullness over the anterior mediastinum indicate the extension of the disease to the bronchial and mediastinal glands. Spleen considerably enlarged.” The treatment started on March 29, 1902, and the patient “received thirty-four treatments as
Fig. 1.1 A case of Hodgkin’s disease that was treated in 1901 by W. A. Pusey, Professor of Dermatology in the Medical Department of the University of Illinois. (a) The patient on September 11, before the start of radiotherapy. (b) The condition on January 8, 1902, after the patient was treated intermittently from November 1901. This seems to be the first documented case of radiotherapy for Hodgkin’s disease (from Pusey 1902).

Fig. 1.2 A case of pseudoleucæmia, or Hodgkin’s disease, that was treated in 1902 by N. Senn, Professor of Surgery, Rush Medical College, Chicago. (a) The patient before radiotherapy. (b) April 24, 1902, at the end of radiotherapy (from Senn 1903).
follows: right side of neck one minute, left side of neck one minute, neck from before backward one minute, neck from behind forward one minute, each axilla one minute, each groin one minute, spleen one minute. Daily sittings for the first ten days; 60 volts 8 ampères were used each day; distance of tube from surface twelve inches, a medium vacuum tube being used.” At the end of treatment on April 24 “all of the glands subjected to the x ray treatment have nearly disappeared.” Senn concluded that “the eminent success attained … by the use of the x ray can leave no further doubt of the curative effect of the Röntgen therapy in the treatment of pseudoleucæmia.”

The optimism created by these early reports of almost miraculous responses to X-rays was soon tempered by the reports of almost inevitable recurrences (Coley 1915; Desjardins and Ford 1923; Minot 1926). For the next 40–50 years radiotherapy came to be regarded as a palliative treatment.

### 1.2 Radiotherapy as a Curative Treatment Modality

Technical advances gradually allowed larger and deeper volumes to be irradiated with better control of dosage. Some radiotherapists began to use extended field radiation therapy for patients with Hodgkin’s disease with doses as high as possible. The pioneer of this concept was René Gilbert from Geneva, Switzerland, who reported that prolonged remission could be achieved with this method (Gilbert 1925; Gilbert and Babaïantz 1931).

Vera Peters in Toronto (see Fig. 1.3) in 1950 presented the first definitive evidence that patients with early stage Hodgkin’s disease could be cured with radiotherapy (Peters 1950; Peters and Middlemiss 1958). Eric Easson from Manchester, UK, in 1963 confirmed, with somewhat more convincing statistical methods, that localized Hodgkin’s disease (i.e., lymphadenopathy confined to one or two contiguous anatomical sites) was probably curable with radical radiotherapy (Easson and Russell 1963; Easson 1966). These results were achieved with kilovolt radiation, and doses of more than 20–27 Gy could seldom be given.

The development at Stanford of the linear accelerator enabled Henry Kaplan in 1956 to start treating patients with Hodgkin’s disease with high-dose (30–40 Gy), extended field radiotherapy including all major lymph node regions, the so-called total lymphoid radiotherapy (Rosenberg and Kaplan 1970), see Fig. 1.4. Figure 1.5 shows Henry Kaplan and Saul Rosenberg at their weekly Hodgkin’s disease staging conferences at Stanford. In 1962, he published his first results with this technique in patients with localized disease (Kaplan 1962), demonstrating dramatic improvements in survival compared with patients treated palliatively. Analyses after longer follow-up of the results of radical radiotherapy with megavolt equipment (linear accelerators) compared with palliative radiotherapy and radical radiotherapy with kilovolt equipment demonstrated the highly significant improvement in the prognosis for these previously incurable patients (Kaplan 1966), see Fig. 1.6. Total or subtotal lymphoid irradiation with megavolt equipment became the standard treatment for early-stage Hodgkin’s disease on both sides of the Atlantic.
1.3 Radiotherapy as Part of Combined Modality Treatment

With the advent of chemotherapy for Hodgkin’s disease, combining the two treatment modalities became an issue. At first, monotherapy with vinblastine in combination with extended field radiotherapy was...
History of Radiotherapy of Hodgkin’s Disease (Now Hodgkin Lymphoma)

tested by Maurice Tubiana (see Fig. 1.7) from Paris, France, in the first randomized study by the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Group (Tubiana et al. 1979), demonstrating superior relapse-free survival with adjuvant monochemotherapy. Later randomized trials testing more effective chemotherapy regimens with radiotherapy, carried out first at Stanford (Hoppe et al. 1985) and later at other centers, showed superior relapse-free survival but no significant difference in overall survival (Specht et al. 1998). However, long-term follow-up of the very extensive radiotherapy demonstrated very significant long-term sequelae (Henry-Amar 1983; van Leeuwen et al. 1994; Travis et al. 1996; Hoppe 1997). Moreover, in the setting of effective chemotherapy, the extensive radiation fields were no longer needed (Specht et al. 1998). Hence, the use of radiotherapy for the treatment of Hodgkin’s disease changed dramatically, from total or subtotal nodal radiotherapy to involved field radiotherapy including only the involved lymph node regions (Yahalom and Mauch 2002). With the advent of even more sophisticated techniques, including advanced imaging and highly conformal treatment planning and delivery, radiotherapy can be used as a highly effective and precise tool to maximize the chance of cure while minimizing toxicity in patients with Hodgkin’s disease.

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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
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

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

<table>
<thead>
<tr>
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<th>GHSG</th>
<th>EORTC</th>
<th>Stanford</th>
<th>NCIC</th>
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<tr>
<td><strong>Risk factors</strong></td>
<td>(a) Large mediastinal mass</td>
<td>(a) Large mediastinal mass</td>
<td>(a) B-symptoms</td>
<td>(a) Histology other than LP/NS</td>
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<tr>
<td></td>
<td>(b) Extranodal disease</td>
<td>(b) Age ≥ 50 years</td>
<td>(b) Large mediastinal mass</td>
<td>(b) Age ≥ 40 years</td>
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<tr>
<td></td>
<td>(c) ESR ≥ 50 without B-symptoms or ≥ 30 with B-symptoms</td>
<td>(c) ESR ≥ 50 without B-symptoms or ≥ 30 with B-symptoms</td>
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</tr>
<tr>
<td><strong>Favourable</strong></td>
<td>CS I-II without risk factors</td>
<td>CS I-II (supra-diaphragmatic) without risk factors</td>
<td>CS I-II without risk factors</td>
<td>CS I-II without risk factors</td>
</tr>
<tr>
<td><strong>Unfavourable</strong></td>
<td>CS I or CS IIA with ≥ 1 risk factors</td>
<td>CS I-II (supra-diaphragmatic) with ≥ 1 risk factors</td>
<td>CS I-II with ≥ 1 risk factors</td>
<td>CS I-II with ≥ 1 risk factors</td>
</tr>
<tr>
<td></td>
<td>CS II B with (c) or (d) but without (a) and (b) (which are included in advanced disease)</td>
<td>CS I-II with ≥ 1 risk factors</td>
<td>CS I-II with ≥ 1 risk factors</td>
<td>CS I-II with ≥ 1 risk factors</td>
</tr>
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GHSG: 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
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-[18F]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>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>No. patients</th>
<th>Treatment arms</th>
<th>Median follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aviles et al.</td>
<td>CS I–II supradiaphragmatic, bulky disease</td>
<td>99</td>
<td>6×ABVD</td>
<td>11.4 years</td>
<td>DFS (12 years) 48%, OS (12 years) 59%</td>
</tr>
<tr>
<td>Bloomfield et al.</td>
<td>“Poor prognosis” PS I or II</td>
<td>18</td>
<td>6×CVPP</td>
<td>1.8 years</td>
<td>Complete remission 61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19</td>
<td>6×CVPP + IFRT</td>
<td></td>
<td>Complete remission 95%</td>
</tr>
<tr>
<td>Eghbali et al.</td>
<td>CS I–II without risk factors (see Table 2.1, EORTC criteria), in CR after 6×EBVP</td>
<td>130</td>
<td>6×EBVP</td>
<td>4.3 years</td>
<td>EFS (5 years) 69%, OS (5 years) 97%</td>
</tr>
<tr>
<td>Noordijk et al.</td>
<td>CS I–II</td>
<td>448</td>
<td>6×EBVP + IFRT (20 or 36 Gy)</td>
<td>4.3 years</td>
<td>EFS (5 years) 87%, OS (5 years) 99%</td>
</tr>
</tbody>
</table>

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
Table 2.2 (continued)

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

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

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

CR: complete remission; CS: clinical stage; PS: pathological stage; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; COPP: cyclophosphamide, vincristine, procarbazine, prednisone; MOPP: mechloethamine, 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 I-A-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.
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...