Radiation Therapy Across Pediatric Hodgkin Lymphoma Research Group Protocols: A Report From the Staging, Evaluation, and Response Criteria Harmonization (SEARCH) for Childhood, Adolescent, and Young Adult Hodgkin Lymphoma (CAYAHL) Group

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Radiation therapy (RT) technology and utilization has considerably evolved over the last 50 years in the management of pediatric Hodgkin lymphoma (HL). In response to significant late effects from RT in survivors of HL, clinical trials in the United States and Europe have evaluated ways to maintain high cure rates while reducing late toxicities from treatment. Numerous differences exist with respect to the RT guidelines embedded within therapeutic protocols across cooperative groups, but greater agreement is observed in the indications for RT, doses, volumes, and the incorporation of modern treatment modalities. This report provides an overview of RT delivery in pediatric HL protocols in the United States and Europe and examines areas of consensus on the utilization and delivery of RT in pediatric HL.
Introduction

Radiation therapy (RT) has played a central role in the management of Hodgkin lymphoma (HL) for more than 50 years. Palliative RT was replaced with large fields delivered with curative treatment intent during the 1950s and 1960s. Over time, combined modality therapy (CMT) with chemotherapy followed by consolidative RT has increased cure rates while often using less intensive chemotherapy regimens and smaller RT fields at lower doses. The 10-year overall survival now exceeds 85% with CMT for pediatric patients with HL. Efforts continue to improve cure rates in the highest-risk patients, but the goal of contemporary HL therapy is now largely focused on reducing the late adverse effects of treatment using risk- and response-adapted therapies without compromising outcomes.

Substantial heterogeneity exists between national and international clinical trial protocols for pediatric and adult HL regarding optimal RT utilization. This contributes to disparate recommendations regarding indications for RT, sites requiring RT, field design, dose, permissible modalities, and motion management strategies. The Staging, Evaluation, and Response Criteria Harmonization for Childhood, Adolescent, and Young Adult Hodgkin Lymphoma initiative was formed in 2011 to promote collaboration among an international group of pediatric HL investigators who actively participate in cooperative group clinical trials. The aim of this team is to develop a unified framework to approach staging, response assessment, and treatment efficacy across pediatric HL clinical trial groups to enhance the design and execution of clinical trials. In this report, our purpose is to review and detail critical aspects of RT delivery that should be considered by pediatric, medical, and radiation oncologists interested in developing future HL trials.

Should Radiation Therapy Be Given to All Patients, Slow Early and Partial Responders to Chemotherapy, Patients With Bulky Disease, or None at All?

Historically, RT utilization was not a research question because all children and adults received RT either alone or combined with chemotherapy. Contemporary studies where all patients received RT were generally limited to stage I/II patients for whom the prechemotherapy extent of disease could be encompassed within reasonable RT fields. Of note, some trials from earlier eras included higher-risk patients with stage III/IV disease who were treated with much larger fields. In these trials, the study questions generally focused on treatment intensity, but all patients received combined modality therapy. For example, Hudson et al compared the efficacy of lower doses of involved-field RT (IFRT) of 15.5 Gy for patients with a complete response (CR) after chemotherapy compared with 25.5 Gy after a partial response (PR).

The optimization of treatment intensity in HL necessitates a standardized and reproducible method of assessing treatment response. Definitions of response, however, vary according to the timepoint(s) of evaluation and the anatomic and metabolic criteria employed, and they diverge across individual clinical trials and national and international research consortia. Interim response has been used to identify rapid early responders who may potentially receive less intensive therapy without compromising outcomes, whereas slow responders may benefit from treatment intensification.
tomography (CT) for response assessment, but over time, functional imaging has been increasingly used (Gallium or fluorodeoxyglucose [FDG] positron emission tomography [PET]).

Some more recent studies have even relied solely on metabolic response by functional imaging to assess response (NCT03907488, NCT03755804).

Over time, more intensive chemotherapy regimens were implemented to mitigate the need for large RT fields, particularly in patients with advanced disease. Successive trials demonstrated the increasing effectiveness of chemotherapy in improving relapse-free survival. Despite these advances, however, selected patients still relapsed, and identification of high-risk patients who may benefit from treatment intensification is an important need. For example, patients with bulky disease and less than CR were identified to have a higher risk of relapse with chemotherapy alone in multiple reports. Ongoing reevaluation of the value of using RT in such high-risk patients, including those with bulky disease, is warranted.

Several pediatric trials evaluated the benefit of RT in patients with a CR to chemotherapy and included both randomized and nonrandomized evaluations of omitting RT in complete responders with early stage unfavorable, early stage favorable, and advanced disease. The definition of CR varied across protocols, and later trials incorporated the use of functional imaging in addition to CT imaging. Although the investigational arm of these trials omitted RT in complete responders, patients with an incomplete response or PR still received RT. An example of this paradigm was the CCG 5942 study, in which patients with early favorable, early unfavorable, and advanced stage HL received risk-based chemotherapy followed by CT-based response assessment. Complete responders were randomized between consolidative RT and no further therapy. The results from this group of studies have been mixed, with some demonstrating that RT can be safely omitted without compromising progression-free survival in selected patients, but others indicated a significant progression-free survival benefit in patients who received consolidative RT. The interpretation and comparison of results from these trials are complicated by the different risk groups included, variable definitions of response, and systemic therapies used.

Adaptive trials using interim response assessment have included the assignment of rapid early responders (who continue to have a CR at the end of chemotherapy) to CMT or chemotherapy-alone regimens. In the St. Jude–Stanford–Dana Farber trial, low-risk patients received 2 cycles of vincristine, doxorubicin, methotrexate, and prednisone (VAMP) chemotherapy. Patients with a CR by both PET and CT received 2 additional cycles of VAMP and no RT, and partial responders received 2 more cycles of VAMP followed by RT. In the AHOD 0031 trial, patients were treated with 2 cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) chemotherapy followed by a CT-based response assessment, and responders then received 2 more cycles of ABVE-PC chemotherapy. After 4 cycles, complete responders by CT and functional imaging were randomized between consolidative RT and no further therapy.
Adaptive trials where the chemotherapy regimen was adjusted based on response to therapy were also applied, wherein only sites with inadequate or incomplete response to systemic therapy were irradiated.\textsuperscript{12,14,16,17} For example, in the AHOD 0831 study, all patients were evaluated by PET/CT for response after 2 cycles of ABVE-PC chemotherapy. Any sites of disease that had not completely responded after 2 cycles were considered slow early responding sites. After completion of chemotherapy, all sites with either bulky disease at presentation or slow early response received consolidative RT.\textsuperscript{16}

**Which Sites Should Receive Radiation: All Involved Sites or Only High-Risk Sites (Bulky, Slow, or Partial Responses)?**

RT was historically administered to all sites of disease at diagnosis in pediatric and adult patients with all stages of disease. Today, this approach is essentially limited to only patients with stage I/II disease, as in the AHOD 0431 study, in which patients with stage IA/IIA disease with <3 sites of initial involvement with a PR to 3 cycles of doxorubicin, vincristine, prednisone, and cyclophosphamide received IFRT to initially involved sites. This approach has been avoided in contemporary studies of high-risk patients with stage III/IV disease to limit the use of extensive RT fields and their subsequent late effects.\textsuperscript{2,6–9,12,14,17,19,21} In the POG 9425 study, patients received regional RT fields, such as the mantle and paraortic fields with or without the pelvis if disease was within any of these nodal basins. These volumes effectively translated into subtotal lymphoid irradiation (STLI) or total lymphoid irradiation in patients with stage III/IV disease.\textsuperscript{8}

Alternatively, RT can be selectively administered only to sites presumed to be at a higher risk of relapse. This may include sites of bulky disease and sites of either slow response or PR. The rationale for this approach is that chemotherapy alone may eradicate nonbulky disease or sites in rapid early and CR, whereas unfavorable sites may benefit from treatment intensification, including consolidative RT. This tailored RT approach can lead to a significant reduction in the volume of normal tissues irradiated, particularly in patients with advanced stage disease. Irradiation of only high-risk sites may improve the therapeutic ratio by minimizing late toxicities through the selective avoidance of RT in patients with more favorable responses. Table 1 summarizes the inclusion criteria, treatment arms, RT indications, and accrual status of past and current pediatric HL trials.

Bulky disease is frequently identified as a high-risk feature and has been irradiated in several trials,\textsuperscript{15,16} although no significant difference was observed in patterns of relapse between bulky and nonbulky sites of disease in the AHOD 0031 study.\textsuperscript{22} In addition, patients with a PR by CT or PET/CT after chemotherapy or slow early responders based on interim PET/CT are also at increased risk of relapse.\textsuperscript{12,13,17,18} To improve outcomes, high-risk sites have also been irradiated.\textsuperscript{16} For example, the AHOD 1331 study randomized patients with advanced stage disease between ABVE-PC and the adceptris, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide regimen, where bleomycin was substituted for the anti-CD30 monoclonal antibody brentuximab vedotin. All patients with bulky and PET-positive disease (Deauville 4,5) after 2 cycles were to receive RT to these sites after completion of systemic therapy. In the ongoing S1826 trial, the only sites irradiated are sites...
of residual disease after completion of systemic therapy by both PET and CT (>2.5 cm; NCT03907488).

Consensus Statement #1.

With advances in systemic therapy, it is clear that not all patients require the same intensity of therapy. Recent adaptive trial designs have treated patients at highest risk for relapse with targeted RT fields. The selection of treatment modality and regimen should be based on curative potential, balanced with the risk of late effects, to improve survival and quality of life. Limiting the use of RT to sites with an inadequate response to chemotherapy may contribute to a reduction in late effects without compromising relapse-free survival.

Target Volumes and Principles of Field Design

Recognizing the potential advantages and toxicity costs of CMT, RT fields decreased in size over time, from total and STLI to extended-field RT to IFRT. Historically, IFRT used 2-dimensional planning techniques and bony anatomic landmarks to develop standardized RT fields that would completely encompass involved nodal regions. A 2001 survey of international lymphoma radiation oncology experts, however, reported large variations in the field borders and dose prescriptions used between physicians. In response, Yahalom and Mauch published standardized IFRT guidelines to be used in therapeutic trials and clinical practice. Modern RT treatment planning now employs 3-dimensional target volumes and organs at risk (OARs) delineated using CT simulation and based on International Commission on Radiation Units and Measurements Reports 62 and 83. The Euronet PHL-C1 study was one of the first to define target volumes using gross tumor volume and clinical target volume (CTV) nomenclature to create “modified IFRT” fields (NCT00433459). IFRT has now given way to even more limited target delineation. Involved-node radiation therapy (INRT), proposed by the European Organisation for Research and Treatment of Cancer (EORTC), delineates the CTV to encompass only lymph nodes containing macroscopic lymphoma at diagnosis based on anatomic and functional imaging (CT and PET/CT) while excluding uninvolved nodes and normal tissues. INRT requires prechemotherapy CT and PET/CT to be obtained in the RT treatment position and that coregistration of this imaging be performed with the CT simulation for RT treatment planning. This is particularly challenging to achieve in routine clinical practice.

Involved-site RT (ISRT) is conceptually similar to INRT but permits some uncertainty in interpreting diagnostic imaging for CTV definition. The key difference between ISRT and INRT lies in the quality and accuracy of prechemotherapy imaging and the concordance of patient positioning and image registration to the treatment planning CT. First, ISRT allows physicians to use their own clinical judgment when considering potential dose to an adjacent OAR, such that the CTV can be tailored to spare nearby critical structures such as the heart. Second, additional margins are permitted to allow for uncertainties regarding the anatomic location of involved nodes in delineating the CTV. In cases where pre-treatment imaging was not performed in the RT treatment position, the pretreatment PET was not coregistered with CT, the CT was performed without intravenous contrast, or patient
positioning, motion, or slice thickness were suboptimal, the ISRT CTV may include nodal tissue adjacent to involved nodes to account for small spatial differences in the location of initially involved nodes. Although INRT was originally conceived for treatment of early stage disease, ISRT is potentially applicable to patients with all stages. ISRT was applied in the recently completed AHOD 1331 trial, which included only patients with high-risk disease. ISRT has effectively replaced IFRT in clinical practice, with most physicians using modern target volume delineation.

Ongoing trials have further reduced target volumes compared with ISRT/INRT to treat only gross residual disease with small margins based on CT or PET/CT. Historically, such smaller volumes may have been used as a boost after treatment of a larger field to lower prescription doses. In the current St. Jude studies, however, these reduced volumes are being used for the entire course of RT. Figure 1 depicts an example of representative target volumes for extended-field RT, IFRT, ISRT, and gross residual disease alone. Table 2 describes the target volumes being used in the currently active or soon-to-be-accruing Children’s Oncology Group (COG) studies.

Consensus Statement #2:

ISRT and INRT are considered standard of care for HL RT and have replaced extended fields in contemporary clinical trials. Response-adapted paradigms are a useful clinical trial construct to help identify patients who benefit from RT and intensify/de-intensify therapy based on response. Contemporary trials have applied RT to all sites of initial disease, bulky and slow responding sites, or only PET-positive disease after chemotherapy. Further study is needed to determine whether ISRT volumes can be safely reduced to treat smaller volumes, such as gross residual disease alone. Given that RT volumes may be significantly larger in patients with stage III/IV disease, different approaches may be needed in patients with early and advanced stage disease.

Functional Imaging, Simulation, and Treatment Positioning

Functional imaging using PET in HL is essential for both accurate staging and high-quality RT treatment planning. The addition of PET/CT in pretreatment staging results in different staging in 10% to 30% of patients with HL compared with contrast-enhanced CT alone by increasing the diagnostic sensitivity for questionable findings and identifying additional sites of involvement that were not observed on CT. Failure to obtain a PET/CT scan before starting chemotherapy was associated with a higher risk of relapse in patients with early stage HL. In addition, areas of increased uptake assist in target volume delineation and can be correlated with outcomes using midtreatment and postchemotherapy imaging. The anatomic precision of PET, however, should not be over-stated. The precise delineation of disease within an enlarged nodal volume should not necessarily be restricted only to FDG avid regions. Abnormalities on CT compatible with disease involvement should be included in the CTV, even in the absence of increased FDG avidity. Oncologists should be cognizant of potential non-HL sources of FDG uptake in normal tissues, including brown fat, tonsillar tissues, and normal thymic uptake, and should seek to distinguish these findings.
from disease. The assistance of colleagues in radiology and other specialties can be critical in this effort.

High-quality prechemotherapy imaging is critical to delineate appropriate RT target volumes. Given the propensity for neck and thorax involvement in HL, imaging studies of these regions should always be performed. Contrast-enhanced CT and PET/CT imaging are strongly advised in all cases unless clear contraindications exist. Pretreatment PET/CT should ideally be performed in the treatment position with the participation of the radiation oncologist. Inadequate pretreatment imaging may lead to incorrect over- or undertreatment of the patient and can potentially lead to unnecessary irradiation of uninvolved tissues. Because neck RT is typically performed with a neutrally positioned or extended neck, it is recommended that lymphoma patients with PET/CT imaging have their neck similarly positioned to improve image fusion. Similarly, if the axilla is not involved, it would be beneficial to have the patient undergo PET/CT imaging with the arms at their sides to assist in image fusion (Fig. 2).

In addition to pretreatment imaging, simulation also comprises an important and sometimes underemphasized element in the delivery of high-conformal RT. Patient positioning should be individualized to ensure reproducibility, enable accurate delineation of target volumes, and provide clinicians with the best avenue to minimize dose to OARs. The use of intravenous contrast is recommended when practical to aid in the delineation of target volumes and certain OARs, such as the left anterior descending artery. For patients treated to the cervical neck, comfortable chin extension and use of mask immobilization may help to reduce oral cavity and salivary gland dose and minimize planning target volume expansions. Patients with mediastinal disease and either no or limited neck disease who will receive intensity modulated radiation therapy (IMRT) may benefit from positioning the arms overhead to minimize collateral radiation to the arms. Comfortable and reproducible positioning may be improved using customized VacLok devices over a wing board. Patients with axillary disease may be treated with either arms up or akimbo positioning. Akimbo positioning may be more comfortable, particularly in older patients, and may be more reproducible for cases treated with proton therapy (PT). This position, however, may be less favorable in patients treated with rotational gantries using IMRT or PT due to collision concerns. Ultimately, simulation should emphasize patient comfort and setup reproducibility and be individualized. The right answer in each clinical case may vary between centers.

Consensus Statement #3:

Functional imaging is a central pillar of contemporary HL therapy in developed countries, and clinicians are strongly encouraged to obtain pretreatment, interim, and posttreatment imaging to adequately assess response. Where there is no routine access to PET/CT, caution should be taken when applying the results of PET-directed therapy trials in clinical practice.

Radiation Therapy Techniques and Modalities

The RT techniques and modalities allowed in recent HL clinical trials are reported in Table 2. Historical trials used 2-dimensional planning and anatomic-based fields to cover targeted nodal volumes based on bony anatomy. CT-based 3-dimensional volumetric planning is
now the standard of care, and more advanced techniques, including IMRT and PT, are increasingly used. The use of IMRT is permitted in AHOD 0831 and EORTC H11, and both PT and IMRT are allowed on AHOD 1331, HLHR13, and EuroNet-PHL-C2.

Three-dimensional conformal RT (CRT) enables greater dose deposition in the target and reduces the dose to non-target normal tissues by improving the precision of target volume delineation and enabling the evaluation of target coverage and OAR sparing with a dose-volume histogram. In most cases, 3-dimensional CRT is typically administered with parallel opposed anteroposterior/posteroanterior fields, leaving portions of OARs that are in field to receive the prescription dose. IMRT and volumetric modulated arc therapy enable greater sparing of OARs adjacent to the target volume from receiving higher doses at the expense of increasing the normal tissue volumes receiving low-to-intermediate doses. This low-dose bath is of concern because it may increase the risk of radiation-induced secondary malignant neoplasms (SMNs). The magnitude of risk posed by this low-dose exposure remains uncertain until mature follow-up data become available.\textsuperscript{34,35} Table 3 is adapted from Tseng et al and summarizes the RT dose-response relationships for different toxicities observed in survivors of HL for SMNs, cardiovascular, pulmonary, and endocrine late effects.\textsuperscript{36}

PT eliminates RT dose deposition beyond the target due to its unique dose distribution pattern, known as the Bragg peak. As a result, PT can deliver highly conformal doses to the CTV, as with IMRT, while providing greater sparing of normal tissues and reducing the total integral dose delivered to the patient. In a review of 14 published studies comparing 3-dimensional CRT, IMRT/volumetric modulated arc therapy and PT dosimetry for patients with lymphoma, IMRT was found to reduce the RT dose to the heart and esophagus at the expense of higher thyroid and breast doses compared with 3-dimensional CRT. PT significantly reduced the dose to the heart, thyroid, breast, lung, esophagus, and total body compared with both 3-dimensional CRT and IMRT.\textsuperscript{36} The benefit from OAR sparing is greatest in patients with long anticipated survival, because the risk of radiation-induced cardiovascular disease, SMNs, and other effects increases over time. As a result, patients with HL who are younger or have a significant reduction in dose to nearby OARs are expected to have the greatest potential benefit from PT.

Patients with disease extending into the inferior mediastinum may also comprise a subgroup that derives a greater potential benefit from PT due to a greater reduction in heart dose.\textsuperscript{37–40} PT may improve sparing of many OARs, but the delivery can be quite challenging due to setup uncertainties and changes in external anatomy and tissues within the chest. Due to the complexity of PT treatment, COG requires institutions to demonstrate accuracy and proficiency of delivery using the Imaging and Radiation Oncology Core thoracic phantom before patients are permitted to receive PT on clinical trials.

To date, outcomes and follow-up for patients treated with either IMRT or PT remain too short to demonstrate a significant reduction in late toxicities compared with 2- and 3-dimensional CRT. The absence of data demonstrating that these dosimetric benefits translate into a clinical benefit is not unexpected because many serious adverse effects occur 10 years or longer after completion of therapy.\textsuperscript{41} Favorable event-free survival, however, has been reported in several retrospective studies in adult and pediatric patients with HL.\textsuperscript{42–46} To
date, grade 3 pneumonitis was rare after IMRT and PT.\textsuperscript{42,43,47,48} Long-term follow-up of toxicity is needed from these advanced photon and PT data sets. In addition, toxicity will be significantly affected by target site, technique, and target volume delineation parameters, which need to be accounted for in the interpretation of these data.

**Motion Management**

Four-dimensional CT is recommended for thoracic and abdominal primary tumor sites where target volume and/or normal organs move with respiration. Respiratory motion management is advised to ensure appropriate coverage when target volumes move with breathing. Motion management strategies include the use of an internal target volume to account for tumor excursion during all phases of the breathing cycle, abdominal compression, or gated delivery. Regardless of the strategy used, we recommend including the entire lungs in the treatment planning CT for all chest wall and thoracic tumors to enable accurate pulmonary dose measurements.

Deep-inspiration breath hold (DIBH) is an important technique in modern RT planning and delivery and has been reported in pediatric patients.\textsuperscript{49} In general, this technique results in reduced lung dose compared with free-breathing delivery and may shift the heart inferiorly, which can potentially reduce the heart dose in selected patients receiving RT to the mediastinum. Reports from Petersen et al and Charpentier et al both demonstrated that DIBH was associated with lower mean heart doses, heart V20, and lung V20 in patients treated with both 3-dimensional CRT and IMRT.\textsuperscript{50,51} DIBH also conferred lower estimated lifetime excess risks of cardiovascular disease and secondary lung, breast, and thyroid cancers.\textsuperscript{52} Although 4-dimensional CT and DIBH are increasingly incorporated into clinical practice, few outcomes have been reported. DIBH may be particularly helpful in patients with superior mediastinal disease by increasing the separation between the heart and the inferior extent of disease. The magnitude of benefit may be less in patients with lower mediastinal disease if the CTV moves in concert with the heart. In all clinical scenarios, the volume of the irradiated lung is typically reduced with DIBH. Lymphoma radiation oncologists are strongly encouraged to consider DIBH in appropriate patients where OAR dosing may be improved with this technique.

**Consensus Statement #4:**

Pre- and posttreatment imaging (where appropriate) should be fused to the RT treatment planning study to aid in target volume delineation. The selection of CT simulation positioning, immobilization devices, motion management, and treatment modality are all essential to optimizing the efficacy of RT, improving conformality, and minimizing dose to OARs. Lymphoma radiation oncologists should leverage advanced RT technologies and motion management strategies where appropriate, including DIBH.

**Patterns of Failure and Radiation Therapy Dose**

Based on the experience derived from decades of clinical trials, the standard consolidative RT dose for patients with primary disease after induction chemotherapy is 20 to 30 Gy in adults and 20 to 25.5 Gy in children.\textsuperscript{17,53} These doses are based on clinical trials where most
patients were irradiated and the predominant site of failure was within the RT field. On 2 prospective clinical trials in the St. Jude Children’s Research Hospital consortium from 1990 to 2000, of 195 pediatric patients treated with either VAMP or VAMP/cyclophosphamide, vincristine, and prednisone (COP) followed by IFRT to 15 to 25.5 Gy, 27 patients relapsed and 81% recurred in field. In AHOD 0031, 244 patients (14.3%) relapsed, and 94% of recurrences had some component of in-field failure after 21 Gy. In contrast, in adult patients with stage I to II and bulky mediastinal disease who received 36 Gy (n = 264) on the Intergroup E2496 trial, in-field relapses represented 61% of all relapses after doxorubicin hydrochloride, bleomycin sulfate, vinblastine sulfate, and dacarbazine (ABVD) and 52% of all relapses after mechloretamine, doxorubicin hydrochloride, vinblastine, vincristine, bleomycin, etoposide, and prednisone (Stanford V). Although relapse patterns are also affected by systemic therapy intensity, these studies suggest that doses of 15 to 25.5 Gy lead to higher rates of in-field relapse compared with doses akin to 36 Gy.

Although newer trials are identifying patients with favorable outcomes for whom RT may be eliminated, these adaptive trials are also identifying patients at a higher risk of relapse. Such patients may benefit from higher-than-standard RT doses. In AHOD 1331 and Euronet-PHL-1 and 2, pediatric patients with residual FDG-avid disease receive doses of 30 Gy rather than 20 to 21 Gy (Table 4). In EORTC H11, adult patients with FDG-avid disease after chemotherapy receive 36 Gy rather than 30 Gy.

**Consensus Statement #5:**

The optimal RT dose intensity as part of CMT is dependent on disease stage/risk status, the chemotherapy regimen, and response to therapy. Historically, pediatric and adult patients received doses of approximately 20 and 30 to 36 Gy, respectively. Selection of RT dose outside of clinical trials should be consistent with both the selected treatment paradigm and response assessment. Future pediatric trials that focus on reducing the number of patients receiving RT should consider the use of higher doses, such as 30 Gy in selected higher-risk patients. Patients with incomplete response after chemotherapy may benefit from treatment intensification, including but not limited to a higher dose RT of >30 Gy to selected sites.

**Normal Tissue Toxicity**

Although cure rates for HL generally exceed 85%, long-term survivors are at high risk of developing late adverse effects due to their chemotherapy and RT. Castellino et al reported that 5-year survivors of pediatric HL in the Childhood Cancer Survivors Study (CCSS) diagnosed between 1970 and 1986 had a substantial excess absolute risk (EAR) of morbidity and mortality compared with the general population, including an EAR of 23.9 for SMNs and 13.1 for cardiovascular disease per 10,000 person-years. The SMNs with the greatest EAR compared with the general population were for hematopoietic (6.8), sarcoma (5.6), breast (4.4), and gastrointestinal (4.4) malignancies per 10,000 person-years. The 30-year cumulative incidence of grade 3 + cardiovascular and pulmonary complications were 11.1% (95% confidence interval, 8.5%–13.8%) and 5.1% (95% confidence interval, 3.3%–6.9%), respectively.
The CCSS is a great resource for identifying factors associated with late toxicity from the treatment of pediatric patients. Most patients with HL in the CCSS were treated with outdated treatment fields and doses (eg, STLI to doses of 40 Gy), which makes it difficult to extrapolate their outcomes to modern radiation field designs, techniques, and doses. Zhou et al compared the normal tissue dose received by 50 patients with HL in the CCSS who were diagnosed between 1970 and 1986 with 191 patients treated on AHOD0031 and AHOD0831 who were diagnosed between 2002 and 2012. In the more contemporary patients with HL treated on COG studies, mean heart dose decreased by 22.9 Gy (68.6%) and 17.6 Gy (56.8%) in patients with early and advanced stage disease, respectively. Similarly, mean breast dose also decreased by 15.5 Gy (83.5%) and 11.6 Gy (70%) in patients with early and advanced stage disease, respectively. Significant reductions in lung and thyroid dose were also observed in COG patients compared with CCSS participants. Reductions in the total prescribed RT dose and changes in field volumes served as major contributors to the observed differences. This suggests that patients treated with RT in the present day receive significantly lower doses to the heart, lungs, breast, and thyroid and are therefore unlikely to develop the same degree of treatment-related late toxicities compared with CCSS patients.

Table 3 summarizes published manuscripts reporting on risk factors for SMNs, cardiovascular morbidity, and other late effects as a function of RT dose. Importantly, many of the published outcomes were derived from the now antiquated extended-field RT and STLI fields. Patients treated to these fields often received RT to the stomach and pancreas to high doses, leading to significantly increased risk of diabetes and SMNs of the pancreas and stomach. In addition, the RT doses delivered to the heart significantly increased the risk of valvular disease, congestive heart failure, and early cardiac death. Treatment with modern ISRT fields to 30 Gy using IMRT or PT is expected to substantially reduce these risks.

**Consensus Statement #6:**

Although there is insufficient long-term follow-up data to demonstrate reductions in late effects from IMRT and PT in HL, robust outcomes data have demonstrated that dose responses exist for cardiovascular disease/death, lung and thyroid dysfunction, SMNs, and numerous other late effects across multiple disease sites. Late effects are the leading causes of death in HL survivors, and lymphoma radiation oncologists should pursue all strategies to reduce late morbidity and mortality through a reduction in RT use where appropriate, minimizing radiation to high-risk tissues, and use of advanced RT modalities and novel technologies. Strategies to prospectively collect patient outcomes, dosimetry, and late effects and quantify the impact of modern RT on HL morbidity and survival should be pursued within cooperative groups and compared across trials.

**Conclusions**

RT remains an integral component in the management of many patients with HL, and the decision to use CMT should rest on appropriate patient selection and consideration of clinical benefits relative to toxicities. Based on results from several trials published within the last 7 years, better identification of patients who will benefit from RT has led to an
increasing number of patients who may defer RT and its potential effects. Modern RT fields, modalities, and delivery techniques have substantially reduced RT exposure to uninvolved normal tissues, which is expected to further reduce late toxicities from RT. We encourage HL investigators to continue to provide sophisticated guidance on RT delivery in future clinical trials to ensure the most appropriate and effective use of RT.

References

1. Kaplan HS, Rosenberg SA. The management of Hodgkin’s disease. Cancer 1975;36:796–803. [PubMed: 1157037]
2. Wolden SL, Chen L, Kelly KM, et al. Long-term results of CCG 5942: A randomized comparison of chemotherapy with and without radiotherapy for children with Hodgkin’s lymphoma—A report from the Children’s Oncology Group. J Clin Oncol 2012;30:3174–3180. [PubMed: 22649136]
3. Jhawar SR, Rivera-Núñez Z, Drachtman R, Cole PD, Hoppe BS, Parikh RR. Association of combined modality therapy vs chemotherapy alone with overall survival in early-stage pediatric Hodgkin lymphoma. JAMA Oncol 2019;5:689–695. [PubMed: 30605220]
4. Tebbi CK, Mendenhall N, London WB, et al. Treatment of stage I, IIA, IIA1 pediatric Hodgkin disease with doxorubicin, bleomycin, vincristine and etoposide (DBVE) and radiation: A Pediatric Oncology Group (POG) study. Pediatr Blood Cancer 2006;46:198–202. [PubMed: 16136581]
5. Donaldson SS, Link MP, Weinstein HJ, et al. Final results of a prospective clinical trial with VAMP and low-dose involved-field radiation for children with low-risk Hodgkin’s disease. J Clin Oncol 2007;25:332–337. [PubMed: 1723049]
6. Friedmann AM, Hudson MM, Weinstein HJ, et al. Treatment of unfavorable childhood Hodgkin’s disease with VEPA and low-dose, involved-field radiation. J Clin Oncol 2002;20:3088–3094. [PubMed: 1218022]
7. Hudson MM, Krasin M, Link MP, et al. Risk-adapted, combined-modality therapy with VAMP/COP and response-based, involved-field radiation for unfavorable pediatric Hodgkin’s disease. J Clin Oncol 2004;22:4541–4550. [PubMed: 15542805]
8. Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: The results of P9425. Blood 2009;114:2051–2059. Erratum in: Blood 2010;116:605. [PubMed: 19584400]
9. Mauz-Körholz C, Hasenclever D, Dörffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin’s lymphoma: The GPOH-HD-2002 study. J Clin Oncol 2010;28:3680–3686. [PubMed: 20625128]
10. Roberts KB, Younes A, Hodgson DC, et al. ACR Appropriateness Criteria® Hodgkin lymphoma-unfavorable clinical stage I and II. Am J Clin Oncol 2016;39:384–395. [PubMed: 27299425]
11. Mauz-Körholz C, Metzger ML, Kelly KM, et al. Pediatric Hodgkin lymphoma. J Clin Oncol 2015;33:2975–2985. [PubMed: 26304892]
12. Dörffel W, Rühl U, Lüders H, et al. Treatment of children and adolescents with Hodgkin lymphoma without radiotherapy for patients in complete remission after chemotherapy: Final results of the multinational trial GPOH-HD95. J Clin Oncol 2013;31:1562–1568. [PubMed: 23509321]
13. Metzger ML, Weinstein HJ, Hudson MM, et al. Association between radiotherapy vs no radiotherapy based on early response to VAMP chemotherapy and survival among children with favorable-risk Hodgkin lymphoma. JAMA 2012;307:2609–2616. [PubMed: 22735430]
14. Kelly KM, Sposto R, Hutchinson R, et al. BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: A report from the Children’s Oncology Group. Blood 2011;117:2596–2603. [PubMed: 21079154]
15. Charpentier AM, Friedman DL, Wolden S, et al. Predictive factor analysis of response-adapted radiation therapy for chemotherapy-sensitive pediatric Hodgkin lymphoma: Analysis of the
16. Kelly KM, Cole PD, Pei Q, et al. Response-adapted therapy for the treatment of children with newly diagnosed high risk Hodgkin lymphoma (AHOD0831): A report from the Children’s Oncology Group Br J Haematol 2019;187:39–48. [PubMed: 31180135]

17. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk Hodgkin lymphoma: A report from the Children’s Oncology Group Study AHOD0031. J Clin Oncol 2014;32:3651–3658. [PubMed: 25311218]

18. Keller FG, Castellino SM, Chen L, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: A report from the Children’s Oncology Group. Cancer 2018;124:3210–3219. [PubMed: 29738613]

19. Weiner MA, Leventhal B, Brecher ML, et al. Randomized study of intensive MOPP-ABVD with or without low-dose total-nodal radiation therapy in the treatment of stages IIB, IIIA2, IIIB, and IV Hodgkin’s disease in pediatric patients: A Pediatric Oncology Group study. J Clin Oncol 1997;15:2769–2779. [PubMed: 9256118]

20. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin’s lymphoma. N Engl J Med 2015;372:1598–1607. [PubMed: 25901426]

21. Kung FH, Schwartz CL, Ferree CR, et al. POG 8625: A randomized trial comparing chemotherapy with chemoradiotherapy for children and adolescents with Stages I, IIA, IIIA1 Hodgkin Disease: A report from the Children’s Oncology Group. J Pediatr Hematol Oncol 2006;28:362–368. [PubMed: 16794504]

22. Dharmarajan KV, Friedman DL, Schwartz CL, et al. Patterns of relapse from a phase 3 study of response-based therapy for intermediate-risk Hodgkin lymphoma (AHOD0031): A report from the Children’s Oncology Group. Int J Radiat Oncol Biol Phys 2015;92:60–66. [PubMed: 25542311]

23. Yahalom J, Mauch P. The involved field is back: Issues in delineating the radiation field in Hodgkin’s disease. Ann Oncol 2002;13:79–83. [PubMed: 12078908]

24. International Commision on Radiation Units & Measurements. Prescribing, recording and reporting photon beam therapy, report 62) Bethesda, MD: International Commision on Radiation Units & Measurements; 1999.

25. Grégoire V, Mackie TR. State of the art on dose prescription, reporting and recording in intensity-modulated radiation therapy (ICRU report no. 83). Cancer Radiother 2011;15:555–559. [PubMed: 21802333]

26. Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: Field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys 2014;89:854–862. [PubMed: 23790512]

27. Hodgson DC, Dieckmann K, Terezakis S, Constine L. International Lymphoma Radiation Oncology Group. Implementation of contemporary radiation therapy planning concepts for pediatric Hodgkin lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group. Pract Radiat Oncol 2015;5:85–92. [PubMed: 25413415]

28. Wirth A, Mikhaeel NG, Aleman BMP, et al. Involved site radiation therapy in adult lymphomas: An overview of International Lymphoma Radiation Oncology Group guidelines. Int J Radiat Oncol Biol Phys 2020;107:909–933. [PubMed: 32272184]

29. Mikhaeel NG, Milgrom SA, Terezakis S, et al. The optimal use of imaging in radiation therapy for lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys 2019;104:501–512. [PubMed: 30763664]

30. Hutchings M, Loft A, Hansen M, et al. Position emission tomography with or without computed tomography in the primary staging of Hodgkin’s lymphoma. Haematologica 2006;91:482–489. [PubMed: 16585015]

31. Rigacci L, Vitolo U, Nasi L, et al. Positron emission tomography in the staging of patients with Hodgkin’s lymphoma: A prospective multicentric study by the Intergruppo Italiano Linfomi. Ann Hematol 2007;86:897–903. [PubMed: 17701410]
32. Figura N, Flampouri S, Mendenhall NP, et al. Importance of baseline PET/CT imaging on radiation field design and relapse rates in patients with Hodgkin lymphoma. Adv Radiat Oncol 2017;2:197–203. [PubMed: 28740932]
33. Castellino RA, Blank N, Hoppe RT, Cho C. Hodgkin disease: Contributions of chest CT in the initial staging evaluation. Radiology 1986;160:603–605. [PubMed: 3737899]
34. Cella L, Conson M, Pressello MC, et al. Hodgkin’s lymphoma emerging radiation treatment techniques: Trade-offs between late radio-induced toxicities and secondary malignant neoplasms. Radiat Oncol 2013;8:22. [PubMed: 23360559]
35. Weber DC, Johanson S, Peguret N, Cozzi L, Olsen DR. Predicted risk of radiation-induced cancers after involved field and involved node radiotherapy with or without intensity modulation for early-stage Hodgkin lymphoma in female patients. Int J Radiat Oncol Biol Phys 2011;81:490–497. [PubMed: 20800383]
36. Tseng YD, Cutter DJ, Plastaras JP, et al. Evidence-based review on the use of proton therapy in lymphoma from the Particle Therapy Cooperative Group (PTCOG) lymphoma subcommittee. Int J Radiat Oncol Biol Phys 2017;99:825–842. [PubMed: 28943076]
37. Dabaja BS, Hoppe BS, Plastaras JP, et al. Proton therapy for adults with mediastinal lymphomas: The International Lymphoma Radiation Oncology Group guidelines. Blood 2018;132:1635–1646. Erratum in: Blood 2019;133:1384–1385. [PubMed: 30108066]
38. Everett AS, Hoppe BS, Louis D, et al. Comparison of techniques for involved-site radiation therapy in patients with lower mediastinal lymphoma. Pract Radiat Oncol 2019;9:426–434. [PubMed: 31128302]
39. Ntentas G, Dedeckova K, Andrilik M, et al. Clinical intensity modulated proton therapy for Hodgkin lymphoma: Which patients benefit the most? Pract Radiat Oncol 2019;9:179–187. [PubMed: 30708133]
40. Tseng YD, Pankuch M, Mohindra P, et al. Selection of mediastinal lymphoma patients for proton therapy within the Proton Collaborative Group Registry: Concordance with the ILROG guidelines. Am J Clin Oncol 2021;44:269–274. [PubMed: 33852456]
41. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572–1582. [PubMed: 17035650]
42. Paumier A, Khodari W, Beaudre A, et al. Intensity-modulated radiotherapy and involved-node concept in patients with Hodgkin lymphoma: Experience of the Gustave-Roussy Institute. Cancer Radiother 2011;15:709–715. [PubMed: 22116023]
43. Filippi AR, Ciammella P, Piva C, et al. Involved-site image-guided intensity modulated versus 3D conformal radiation therapy in early stage supradiaphragmatic Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2014;89:370–375. [PubMed: 24613810]
44. Hoppe BS, Tsai H, Larson G, et al. Proton therapy patterns-of-care and early outcomes for Hodgkin lymphoma: Results from the Proton Collaborative Group Registry. Acta Oncol 2016;55:1378–1380. [PubMed: 27579554]
45. Wray J, Flampouri S, Slayton W, et al. Proton therapy for pediatric Hodgkin lymphoma. Pediatr Blood Cancer 2016;63:1522–1526. [PubMed: 27149120]
46. Hoppe BS, Hill-Kayser CE, Tseng YD, et al. Consolidative proton therapy after chemotherapy for patients with Hodgkin lymphoma. Ann Oncol 2017;28:2179–2184. [PubMed: 28911093]
47. Pinnix CC, Smith GL, Milgrom S, et al. Predictors of radiation pneumonitis in patients receiving intensity modulated radiation therapy for Hodgkin and non-Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2015;92:175–182. [PubMed: 25863764]
48. Nanda R, Flampouri S, Mendenhall NP, et al. Pulmonary toxicity following proton therapy for thoracic lymphoma. Int J Radiat Oncol Biol Phys 2017;99:494–497. [PubMed: 28872001]
49. Lundgaard AY, Hjalgrim LL, Rechner LA, et al. TEDDI: Radiotherapy delivery in deep inspiration for pediatric patients - A NOPHO feasibility study. Radiat Oncol 2018;13:56. [PubMed: 29587881]
50. Petersen PM, Aznar MC, Berthelsen AK, et al. Prospective phase II trial of image-guided radiotherapy in Hodgkin lymphoma: Benefit of deep inspiration breath-hold. Acta Oncol 2015;54:60–66. [PubMed: 25025999]
51. Charpentier AM, Conrad T, Sykes J, et al. Active breathing control for patients receiving mediastinal radiation therapy for lymphoma: Impact on normal tissue dose. Pract Radiat Oncol 2014;4:174–180. [PubMed: 24766684]

52. Aznar MC, Maraldo MV, Schut DA, et al. Minimizing late effects for patients with mediastinal Hodgkin lymphoma: Deep inspiration breath-hold, IMRT, or both? Int J Radiat Oncol Biol Phys 2015;92:169–174. [PubMed: 25754634]

53. Eich HT, Diehl V, Gørgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin’s lymphoma: Final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol 2010;28:4199–4206. [PubMed: 20713848]

54. Krasin MJ, Rai SN, Kun LE, et al. Patterns of treatment failure in pediatric and young adult patients with Hodgkin’s disease: Local disease control with combined-modality therapy. J Clin Oncol 2005;23:8406–8413. [PubMed: 16293871]

55. Advani RH, Hong F, Fisher RI, et al. Randomized phase III trial comparing ABVD plus radiotherapy with the Stanford V regimen in patients with stages I or II locally extensive, bulky mediastinal Hodgkin lymphoma: A subset analysis of the North American Intergroup E2496 trial. J Clin Oncol 2015;33:1936–1942. [PubMed: 25897153]

56. Castellino SM, Geiger AM, Mertens AC, et al. Morbidity and mortality in long-term survivors of Hodgkin lymphoma: A report from the Childhood Cancer Survivor Study. Blood 2011;117:1806–1816. [PubMed: 21037086]

57. Zhou R, Ng A, Constine LS, et al. A comparative evaluation of normal tissue doses for patients receiving radiation therapy for Hodgkin lymphoma on the Childhood Cancer Survivor Study and recent Children’s Oncology Group trials. Int J Radiat Oncol Biol Phys 2016;95:707–711. [PubMed: 27020112]

58. Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2012;84:449–455. [PubMed: 22386373]

59. Bates JE, Howell RM, Liu Q, et al. Therapy-related cardiac risk in childhood cancer survivors: An analysis of the Childhood Cancer Survivor Study. J Clin Oncol 2019;37:1090–1101. [PubMed: 30860946]

60. Bates JE, Parikh RR, Mendenhall NP, et al. Long-term outcomes in 10-year survivors of early-stage Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2020;107:522–529. [PubMed: 32173399]

61. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, Van’t Veer MB, Bartelink H, van Leeuwen FE. Long-term cause-specific mortality of patients treated for Hodgkin’s disease. J Clin Oncol 2003;21:3431–3439. [PubMed: 12885835]

62. Schaapveld M, Aleman BM, van Eggermond AM, et al. Second cancer risk up to 40 years after treatment for Hodgkin lymphoma. N Engl J Med 2015;373:2499–2511. [PubMed: 26699166]

63. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290:465–475. [PubMed: 12876089]

64. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin’s disease. J Natl Cancer Inst 2002;94:182–192. [PubMed: 11830608]

65. Gilbert ES, Stovall M, Gospodarowicz M, et al. Lung cancer after treatment for Hodgkin lymphoma. JAMA 2013;310:2573–2579. [PubMed: 24088832]

66. Morton LM, Gilbert ES, Stovall M, et al. Risk of esophageal cancer following radiotherapy for Hodgkin lymphoma. Haematologica 2014;99:e193–e196. [PubMed: 25271315]

67. Morton LM, Dores GM, Curtis RE, et al. Stomach cancer risk after treatment for Hodgkin lymphoma. J Clin Oncol 2013;31:3369–3377. [PubMed: 23980092]

68. Dores GM, Curtis RE, van Leeuwen FE, et al. Pancreatic cancer risk after treatment of Hodgkin lymphoma. Ann Oncol 2014;25:2073–2079. [PubMed: 25155241]

69. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin’s disease. JAMA 1993;270:1949–1955. [PubMed: 8411552]

70. van Nimwegen FA, Schaapveld M, Janus CP, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med 2015;175:1007–1017. [PubMed: 25915855]
71. van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol 2016;34:235–243. [PubMed: 26573075]

72. Cutter DJ, Schaapveld M, Darby SC, et al. Risk of valvular heart disease after treatment for Hodgkin lymphoma. J Natl Cancer Inst 2015;107 djv008. [PubMed: 25713164]

73. van Nimwegen FA, Ntentas G, Darby SC, et al. Risk of heart failure in survivors of Hodgkin lymphoma: Effects of cardiac exposure to radiation and anthracyclines. Blood 2017;129:2257–2265. [PubMed: 28143884]

74. Bowers DC, McNeil DE, Liu Y, et al. Stroke as a late treatment effect of Hodgkin’s disease: A report from the Childhood Cancer Survivor Study. J Clin Oncol 2005;23:6508–6515. [PubMed: 16170160]

75. De Bruin ML, Dorresteijn LD, van’t Veer MB, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. J Natl Cancer Inst 2009;101:928–937. [PubMed: 19535773]

76. Ng AK, Li S, Neuberg D, et al. A prospective study of pulmonary function in Hodgkin’s lymphoma patients. Ann Oncol 2008;19:1754–1758. [PubMed: 18467315]

77. van Nimwegen FA, Schaapveld M, Janus CP, et al. Risk of diabetes mellitus in long-term survivors of Hodgkin lymphoma. J Clin Oncol 2014;32:3257–3263. [PubMed: 25154821]

78. Cella L, Liuazzi R, Conson M, D’Avino V, Salvatore M, Pacelli R. Development of multivariate NTCP models for radiation-induced hypothyroidism: A comparative analysis. Radiat Oncol 2012;7:224. [PubMed: 23270411]

79. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin’s lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol 2005;23:4634–4642. [PubMed: 15837968]

80. Huynh-Le MP, Walker AJ, Kominers SD, Paz-Priel I, Wharam MD, Terezakis SA. Patterns of failure after involved field radiation therapy for pediatric and young adult Hodgkin lymphoma. Pediatr Blood Cancer 2014;61:1210–1214. [PubMed: 24523203]
Fig. 1.
Representative field borders/dose distribution for a representative patient with Hodgkin lymphoma and mediastinal involvement (delineated in the center with pink contours) receiving treatment with Mantle field, involved-field and involved-site radiation therapy (yellow) and to residual disease (blue) alone after chemotherapy. The heart (red) and female breast (pink) are also illustrated.
Fig. 2.
Computed tomography (CT) simulation fusion with CT component from baseline positron emission tomography/CT scan where patient simulation setup is different from staging scan (arms up vs down), illustrating the difficulty with target volume delineation in the axilla, supraclavicular, and cervical regions.
## Table 1

Contemporary pediatric Hodgkin lymphoma clinical trials

| Trial             | Cooperative group | Inclusion criteria                                                                 | Accrual status | Treatment arms/indications for RT                                                                 | Percentage treated with RT |
|-------------------|-------------------|-------------------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------------------------------|---------------------------|
| AHOD 0031        | COG               | Stage I-IB; I-IIA; III-IVA; III-IVAE with or without bulk; IA/IIA with bulk          | Completed      | All received 4 cycles ABVE-PC  
  • RER & CR: Randomized to ± IFRT  
  • SER: Randomized to ± DECA × 2 augmented therapy and all received IFRT.  
  RER: >60% reduction in PPD for all target lesions.  
  SER: <60% reduction in PPD for all target lesions.  
  CR: >80% reduction in PPD and negative gallium or FDG-PET scan (less than mediastinal background blood pool).  | 67.5%            |
| AHOD 0431        | COG               | Stage I/IIA (no bulk) LPHD not allowed.                                             | Closed         | All received 3 cycles of doxorubicin, vincristine, prednisone, and cyclophosphamide.  
  • If < PR: Off-protocol therapy  
  • If PR: IFRT  
  • If CR: Observation (Off-protocol therapy for high-risk relapse; IV, DECA, and IFRT for low-risk relapse).  
  CR: Anatomic reduction >80% in PPD and FDG-PET-negative result.  | 43.5%            |
| HOD05             | SJCRH             | Stage IB; IIIA; and I-IIA with any of the following:  
  Bulky LMA, E lesions, or ≥3 nodal sites                                           | Closed         | All receive 12 weeks Stanford V → ERA (after 8 weeks of chemotherapy)-adapted RT.  
  • If CR and nonbulky: 15 Gy in 1.5 Gy/fx  
  • If PR and/or mediastinal bulk: 25.5 Gy in 1.5 Gy/fx  
  ERA defined by PET negative and > (CR) anatomic response or <75% (PR) anatomic response regardless of PET.  | ~100%            |
| HOD08             | SJCRH             | Stage IA or IIA and nonbulky mediastinal (<33% mediastinal to thoracic ratio on CXR) and <3 LN regions and no E lesion | Closed         | All receive 8 weeks Stanford V, followed by ERA-adapted RT.  
  25.5 Gy in 1.5Gy/fx RT to a site with <75% anatomic response or PET+, but omitted for >75% response and PET−.  | NR              |
| HLHR13            | SJCRH             | Stage IIB, IIIB, IVA, or IVB; LPHD not allowed                                      | Closed         | ERA driven by metabolic and anatomic response.  
  • 2 cycles AEPA—→ERA—→4 cycles.  
  CAPDac—→ERA-adapted RT.  
  RT given if ERA is Deauville 4–5 or anatomic response <75% from baseline.  | NR              |
| AHOD 0831        | COG               | Stage IIIB-IVB                                                                     | Closed         | All receive 2 cycles ABVE-PC.  
  • If CR: 2 cycles ABVE-PC—→Risk-adapted RT.  
  • If PR/SD: 2 cycles Ifos/Vino—→2 cycles.  
  ABVE-PC—→Risk-adapted RT.  
  • If PD: Off-protocol therapy.  
  CR: Deauville 1 or 2  
  PR: Deauville 3, 4, 5 with >50% decrease in PPD.  | 76.2%            |
| AHOD 1331        | COG               | Stage IIB with Bulk; IIIB; IVA; IVB                                                | Open           | Randomized to 5 cycles ABVE-PC versus Bv-AVEPC—→ERA-adapted ISRT.  
  RER: Deauville 1, 2, or 3.  
  SER: Deauville 4, 5.  
  CR: Deauville 1, 2.  
  PR: Deauville 3, 4, 5 at the end of treatment.  | NR              |
| Euronet-PHL-C1   | EuroNet           | All stages/risk categories; LPHD not allowed                                       |                | All receive 2 cycles OPEA—→ERA.  
  TG1: RT unless CMR on ERA.  
  TG2: 2 cycles COPDAC versus COPP—→RT unless CMR on ERA.  
  TG3: 4 cycles COPDAC versus COPP—→RT unless CMR on ERA.  
  ERA is defined by PET only (±) where adequate response = no initially involved PET+ areas remain positive.  | 33.3%            |
| Trial            | Cooperative group | Inclusion criteria                                      | Accrual status | Treatment arms/indications for RT                                                                 | Percentage treated with RT |
|------------------|-------------------|--------------------------------------------------------|----------------|-----------------------------------------------------------------------------------------------|---------------------------|
| Euronet-PHL-C2   | EuroNet           | All stages/risk categories, LPHD not allowed           | Open           | - All receive 2 cycles OEPA → ERATL-1: PET→1 cycle COPDac-28 or PET→19.8 Gy RT to initial sites TL-2 and TL-3: Randomized to 2 (TL2)-4 (TL3) cycles COPDac-28 versus DECOPDac-21 → LRA if IR at ERA.  
  - ERA PET-: No RT.  
  - ERA PET+, COPDac-28: 19.8 Gy RT to initial sites ±10 Gy boost to LRA PET+ sites.  
  - ERA PET+, DECOPDac-21: LRA PET+: Observation.  
  - ERA PET+, DECOPDac-21, LRA PET +: 28.8 Gy to LRA PET+ sites. | NR                      |
| cHOD17 SJCRH     |                   | All stages/risk categories, LPHD not allowed           | Open           | - Low and intermediate risk receive 2 cycles BEABOVP → ERA.  
  - Low Risk: ±ERA-adapted RT. → Observation.  
  - Intermediate Risk: 1 cycle BEABOV ± P → ±ERA-adapted RT.  
  - High-risk: AEPA → ERA → 4 cycles CADac ± P → ±ERA-adapted RT.  
  ERA driven by metabolic response only RT given when ERA is Deauville 4 or 5. | NR                      |

Abbreviations: ABVE-PC = doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; AEPA = adetris, etoposide, prednisone, adriamycin; BEABOV±P = bendamustine substitution for mechlorethamine in the original Stanford V backbone with or without prednisone; BEVEPC = adetris, doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide; CAPDac, cyclophosphamide, adetris, dacarbazine; CMR = complete metabolic response; COG = Children’s Oncology Group; COPDAC = cyclophosphamide, oncovin, prednisone, dacarbazine; COPP = cyclophosphamide, oncovin, prednisone, procarbazine; CR = complete response; CXR = chest x-ray; DECA = dexamethasone, etoposide, cisplatin, and cytarabine; DECOPDAC = dacarbazine, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone; ERA = early response assessment; FDG = fluorodeoxyglucose; fx = fraction; Ifos/Vino = ifosfamide, vinorelbine; IFRT = involved-field radiation therapy; IR = inadequate response; ISRT = involved-site radiation therapy; IV = intravenous; LMA = large mediastinal adenopathy; LN = lymph node; LPHD = lymphocyte predominant Hodgkin lymphoma; LRA = late response assessment; NR = not yet reported; OEPA = oncovin, etoposide, prednisone, adriamycin; PD = progressive disease; PET = positron emission tomography; PPD = product of perpendicular diameter of target lesions; PR = partial response; RER = rapid early responding; RT = radiation therapy; SD = stable disease; SER = slow early responding; SJCRH = St. Jude Children’s Research Hospital; Stanford V = chemotherapy regimen consisting of mechlorethamine, doxorubicin hydrochloride, vinblastine, vincristine, bleomycin, etoposide and prednisone; TG = treatment group; TL = treatment level.
## Table 2

Radiation therapy fields, target volumes and administration on contemporary clinical trials

| Trial         | Field design | GTV                                           | CTV                                           | Modality allowed                                                                 | 4-dimensional CT used | Dose            |
|---------------|--------------|-----------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------|-----------------------|-----------------|
| AHOD 0031     | IFRT         | Any lymph node measuring >1.5 cm in a single axis on CT | Anatomic compartment defined in the protocol for IFRT based on sites of initial involvement | AP/PA (except certain sites; eg, inguinal nodes)                                 | No                    | 21 Gy/14 fx     |
| AHOD 0431     | IFRT         | Any lymph node measuring >1.5 cm in a single axis on CT | Anatomic compartment defined in the protocol for IFRT based on sites of initial involvement | AP/PA (except certain sites; eg, inguinal nodes) IMRT not allowed                 | No                    | 21 Gy/14 fx     |
| HOD05 HOD08   | Tailored-field | Initially involved nodal site                  | - GTV +2 cm margin with additional margin to account for patient and beam effects, respecting pushing borders and anatomic barriers to disease spread - Patients with mixed response will have treatment fields modified to limit the volume treated after 15 Gy to only sites with <CR with a 2 cm margin and bulky LMA, regardless of response | AP/PA; 3-dimensional conformal RT; use of compensating filters and wedging to homogenize dose across the treatment field encouraged | No                    | CR: 15 Gy/10 fx PR or bulky LMA: 25.5 Gy/17 fx >75% PPD response, PET−: None <75% PPD reduction, PET +/-: 25.5 Gy/17 fx |
| HLHR13        | ISRT         | Postchemotherapy lymph nodes in PR            | GTV +1 cm (anatomically constrained)          | 3-dimensional conformal RT; IMRT                                                | Yes                   | >75% PPD response, PET−: None <75% PPD reduction, PET +/-: 25.5 Gy/17 fx |
| cHOD17        | Modified ISRT | Postchemotherapy lymph nodes in PR            | GTV +0.5 cm (anatomically constrained)         | IMPT                                                                            | Yes                   | Deauville 1–3: None Deauville 4–5: 25.5 Gy/17 fx |
| AHOD 0831     | Modified IFRT | 1. Initial bulk, postchemotherapy residual 2. Macronodular splenic disease, entire spleen is considered GTV 3. Postchemotherapy residual non-bulky disease with PET2 SER 4. Postchemotherapy residual non-bulky disease measuring ≥2.5 cm in axial diameter at completion of chemotherapy in patients with PET2 SER even if site was PET negative | Postchemotherapy nodal and/or involving parenchyma, regardless of size and response, within the anatomic compartment that encompasses GTV | AP/PA; 3-dimensional conformal RT; IMRT | Yes                   | 21 Gy/14 fx     |
| AHOD 1331     | ISRT         | GTV: Imaging abnormalities persistent after all chemotherapy that conform to prechemotherapy nodal and non-nodal tissues involved before treatment that meet the criteria for requiring RT (LMA or SRL). GTV-PET+: area of imaging abnormality that remains PET5+ (Deauville ≥5) | Initially involved lymph nodes/tissues, accounting for response to chemotherapy. • Typically, entire nodal fossa/level that contained initially abnormal node(s) will be contoured as CTV. In general, margin of 1.5 cm above/below involving nodes is recommended | AP/PA; IMRT; proton | Yes                   | 21 Gy/14 fx     |
### Target volumes

| Trial          | Field design | GTV | CTV | Modality allowed | 4-dimensional CT used | Dose      |
|----------------|--------------|-----|-----|-------------------|-----------------------|-----------|
| Euronet-PHL-C1 | Modified IFRT| PTV1: All initially involved lymph node before chemotherapy + safety margin of 1–2 cm taking into account the area of involvement | PTV2: Includes all lymph nodes with poor response after 2 cycles of chemotherapy with a 1–2 cm safety margin | 3-dimensional conformal RT | Yes       | PTV1: 19.8 Gy/11 fx  
                   |              |     |     |                   | PTV2: 10.86 fx           |           |
| Euronet-PHL-C2 | ISRT/INRT    | Standard arm: LRA PET+ node(s) > 1 cm (GTV boost). Experimental arm: LRA PET+ >1cm or LRA PET+ EN sites (eg, bone, liver, lung) | Standard arm (ISRT): Prechemotherapy nodal GTV + 5 mm, boost if required to postchemotherapy GTV + 5 mm. ERA PET+ EN sites (eg, bone, liver, lung) + 5–30 mm depending on site Experimental arm: Nodal GTV + 5 mm; EN sites (eg, bone, liver, lung) + 5–30 mm depending on site | 3-dimensional conformal RT (opposed fields preferred); IMRT/arc/proton therapy allowed at discretion of treating oncologist. | No        | Standard arm:  19.8 Gy/11 fx; Boost 10 Gy/5 fx  
                   |              |     |     |                   | Experimental arm: 28.8 Gy/16 fx |           |

**Abbreviations:** AP/PA = anteroposterior/posteroanterior; CR = complete response; CT = computed tomography; CTV = clinical target volume; EN = extranodal; fx = fraction; GTV = gross tumor volume; IFRT = involved-field radiation therapy; IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiation therapy; ISRT = involved-site radiation therapy; LMA = large mediastinal adenopathy; PET = positron emission tomography; PET2 = Deauville score on interim PET/CT after 2 cycles of chemotherapy; PET5 = Deauville score on PET/CT after 5 cycles of chemotherapy; PPD = product of perpendicular diameter of target lesions; PR = partial response; PTV = planning target volume; RT = radiation therapy; SER = slow early responding; SRL = slow-responding lesion.

* Excluding selected regions of initial nonbulky disease with rapid early responding to chemotherapy.
Table 3  
Summary of literature describing risk of secondary cancers, cardiovascular disease, pulmonary toxicity, and endocrinopathies among Hodgkin lymphoma survivors treated with radiation  

| Literature | Cohort and treatment period | Outcome | Reference group | Risk (95% confidence interval) | Evidence of linear relationship or cumulative incidence |
|------------|-----------------------------|---------|-----------------|-------------------------------|-----------------------------------------------|
| **Secondary cancers** | | | | | |
| Aleman et al., 2003 | Netherlands (hospital based) N = 1261, Median 26 y (all <41), Treated 1966–1987 | Fatal second solid tumors | General population | RT alone: SMR 5.4 (3.4–8.2) RT and CT: SMR 4.4 (2.0–8.3) Salvage Rx: SMR 8.3 (6.1–11.2) | |
| Castellino et al., 2011 | USA (CCSS patients with HL) N = 2742, Median 14 y (2–20), Treated 1970–1979 | Fatal second malignant neoplasms | No RT | <30 Gy \( \stackrel{\text{a}}{=} \) HR 1.9 (0.4–8.7) ≥30 Gy \( \stackrel{\text{a}}{=} \) HR 7.4 (1.8–30.3) | |
| Schaapveld et al., 2015 | Netherlands (hospital-based) N = 3905, Treated 1965–2000 | Incidence of second solid cancers | General population; no RT | SIR 4.2 (3.9–4.5) AER 100.5 (91.3–110.2) HR for Mantle RT 2.6 (1.8–3.6) 30-year cumulative incidence = 28.5% (26.4–30.5) | |
| Travis et al., 2003 | International population-based N = 3817 (105 cases and 266 controls), Median 22 y (all ≥10), Treated 1965–1994 | Incidence of breast cancer | 0–3.9 Gy \( \stackrel{\text{a}}{=} \) | 4.0–6.9 Gy: RR 1.8 (0–4.5) 7.0–23.1 Gy: RR 4.1 (1.4–12.3) 23.2–27.9 Gy: RR 2.0 (0.7–5.9) 28.0–37.1 Gy: RR 6.8 (2.3–22.3) 37.2–40.4 Gy: RR 4.0 (1.3–13.4) 40.5–61.3 Gy: RR 8.0 (2.6–26.4) [≥4 Gy: RR 3.2 (1.4–8.2)] ERR/Gy = 0.15 (0.04–0.73) | |
| Travis et al., 2002 and Gilbert et al., 2003 | International population-based N = 19,846 (227 cases and 455 controls), Median 50 y (9–81), Treated 1965–1994 | Incidence of lung cancer | <5 Gy \( \stackrel{\text{a}}{=} \) | >0.4–9 Gy: RR 1.3 (0.3–4.9) 5.0–14.9 Gy: RR 4.1 (0.7–22) 15.0–29.9 Gy: RR 2.5 (0.1–16.1) 30.0–39.9 Gy: RR 8.6 (2.9–30) ≥40 Gy: RR 7.2 (2.2–28) [≥5 Gy: RR 5.9 (2.7–13.5)] ERR/Gy = 0.15 (0.06–0.39) | |
| Morton et al., 2014 | International population registry N = 19,882 (36 cases and 71 controls), Median 34 y, Treated 1943–1992 | Incidence of esophageal cancer | <30 Gy and no RT \( \stackrel{\text{a}}{=} \) | 50 Gy: RR 4.3 (1.5–15.3) ERR/Gy = 0.38 (0.04–8.17) \( P_{\text{trend}} < .001 \) | |
| Morton et al., 2013 | International population registry N = 19,882 (89 cases and 91 controls), Median 30 y (11–83), Treated 1943–2003 | Incidence of stomach cancer | 0 Gy \( \stackrel{\text{a}}{=} \) | 0.1–0.9 Gy: RR 1.3 (0.4–4.4) 1.0–4.9 Gy: RR 1.0 (0.3–3.5) 5.0–24.9 Gy: RR 0.5 (0.1–2.7) 25.0–34.9 Gy: RR 4.6 (1.2–20.5) 35.0–39.9 Gy: RR 8.2 (2.6–29.7) ≥40 Gy: RR 4.2 (1.2–15.6) [≥25 Gy vs <25 Gy: RR 5.8 (3.0–12.3)] ERR/Gy = 0.09 (0.04–0.21), \( P_{\text{trend}} < .001 \) | |
| Literature            | Cohort and treatment period                                                                 | Outcome                               | Reference group | Risk (95% confidence interval)                              | Evidence of linear relationship or cumulative incidence |
|-----------------------|---------------------------------------------------------------------------------------------|---------------------------------------|-----------------|-------------------------------------------------------------|---------------------------------------------------------|
| Dores et al., 2014    | International population registry N = 19,882 (36 cases and 70 controls) Median 47 y (12–76) | Incidence of pancreatic cancer       | <10 Gy          | ≥10 Gy: RR 4.3 (1.7–15)                                      | ERR/Gy 0.098 (0.015–0.42)                               |
|                       | Treated 1943–2003                                                                          |                                       |                 |                                                             | $ P_{0.005}^a $                                          |
| Hancock et al., 1999  | USA (Stanford) N = 2232 (88 deaths) Average 29 y (2–82) Treated 1960–1990                  | Cardiac death                         | General population | 0–30 Gy: SMR 2.6 (0.4–8.7)                                 |                                                        |
| Aleman et al., 2003   | Netherlands (hospital based) N = 1261 (45 deaths) Median 26 y (all <41) Treated 1965–1987  | Cardiovascular death                  | General population | >30 Gy: SMR 3.5 (2.7–4.3)                                 |                                                        |
| Van Nimwegen et al., 2015 | Netherlands (hospital based) N = 2524 (1713 events) Median 27 y Treated 1965–1995        | Incidence of any cardiac event        | No RT           | >0–29 Gy: HR 2.3 (1.3–3.8)                                 | ERR/Gy 0.074 (0.013–0.148), $ P_{0.001}^a $                                          |
|                       | (325 cases and 1204 controls) Median 32 y (all <51) Treated 1965–1995                    |                                       |                 | 30–35 Gy: HR 3.1 (2.3–4.2)                                 |                                                        |
|                       | (352 cases and 1205 controls) Median 32 y (all <51) Treated 1965–1995                    |                                       |                 | ≥36 Gy: HR 3.8 (3.0–5.0)                                   |                                                        |
| Van Nimwegen et al., 2016 | Netherlands (hospital based) N = 2617 (352 cases and 1204 controls) Median 32 y (all <51) Treated 1965–1995 | Incidence of myocardial infarction/angina | No RT | >0–5 Gy: RR 1.14 (0.62–2.10)                               |                                                        |
|                       | (313 cases and 1203 controls) Median 32 y (all <51) Treated 1965–1995                    |                                       |                 | 5–14 Gy: RR 2.14 (1.28–3.58)                               |                                                        |
|                       | (313 cases and 1203 controls) Median 32 y (all <51) Treated 1965–1995                    |                                       |                 | 15–19 Gy: RR 2.76 (2.10–3.59)                              |                                                        |
|                       | (313 cases and 1203 controls) Median 32 y (all <51) Treated 1965–1995                    |                                       |                 | 20–24 Gy: RR 2.79 (2.3–3.49)                               |                                                        |
|                       | (313 cases and 1203 controls) Median 32 y (all <51) Treated 1965–1995                    |                                       |                 | 25–34 Gy: RR 3.21 (2.52–4.09)                              |                                                        |
|                       | (313 cases and 1203 controls) Median 32 y (all <51) Treated 1965–1995                    |                                       |                 | 35–45 Gy: RR 2.54 (0.96–6.69)                              |                                                        |
| Cutter et al., 2015   | Netherlands (hospital based) N = 1852 (89 cases and 200 controls) Median 27 y Treated 1965–1995 | Incidence of valvular heart disease   | No RT           | ≥30 Gy: RR 1.4 (0.5–3.8)                                   |                                                        |
|                       | All <41 y                                                                            |                                       |                 | 31–35 Gy: RR 3.1 (1.7–5.6)                                 |                                                        |
|                       | (91 cases and 278 controls) Median 28 y (all <51) Treated 1965–1995                    |                                       |                 | 36–40 Gy: RR 3.4 (3.9–7.7)                                 |                                                        |
|                       | (91 cases and 278 controls) Median 28 y (all <51) Treated 1965–1995                    |                                       |                 | >40 Gy: RR 11.8 (4.9–28.5)                                 |                                                        |
|                       | (91 cases and 278 controls) Median 28 y (all <51) Treated 1965–1995                    |                                       |                 | $ P_{0.001}^a $ (nonlinearity)                             |                                                        |
| Van Nimwegen et al., 2017 | Netherlands (hospital based) N = 2617 (313 cases and 1203 controls) Median 32 y (all <51) Treated 1965–1995 | Incidence of congestive heart failure | No RT           | 1–15 Gy: RR 1.27 (0.86–1.89)                               |                                                        |
|                       | (313 cases and 1203 controls) Median 32 y (all <51) Treated 1965–1995                    |                                       |                 | 16–20 Gy: RR 1.65 (0.98–2.77)                              |                                                        |
|                       | (313 cases and 1203 controls) Median 32 y (all <51) Treated 1965–1995                    |                                       |                 | 21–25 Gy: RR 3.84 (1.97–7.47)                              |                                                        |
|                       | (313 cases and 1203 controls) Median 32 y (all <51) Treated 1965–1995                    |                                       |                 | ≥26 Gy: RR 4.39 (2.00–9.65)                                |                                                        |
|                       | (313 cases and 1203 controls) Median 32 y (all <51) Treated 1965–1995                    |                                       |                 | $ P_{0.001}^a $                                            |                                                        |
| Bowers et al., 2005   | United States (CCSS patients with HL) N = 1926 Median 27 y (all <51) Treated 1970–1986   | Incidence of stroke                   | Siblings        | Malignant RT: RR 5.62 (2.59–12.25)                         |                                                        |
| De Bruin et al., 2009 | Netherlands (hospital based) N = 2201 (96 cases) Median 47 y Treated 1965–1995          | Incidence of ischemic cerebrovascular disease (including transient ischemic attack) | No RT           | RT to neck/mediastinum: HR 2.5 (1.1–5.6)                   |                                                        |

* ERR/Gy = 0.074 (0.013–0.148), $ P_{0.001}^a $ (nonlinearity)
### Pulmonary toxicity

| Literature       | Cohort and treatment period | Outcome                                      | Reference group | Risk (95% confidence interval)                                                                 | Evidence of linear relationship or cumulative incidence |
|------------------|-----------------------------|----------------------------------------------|-----------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| Ng et al., 2008⁶  | United States (DFCI/BWH) N = 52, Median 31 y (18–69), Treated 2001–2005 | Decline in %DLCO | N/A | MLD ≥13 Gy or V20 ≥33% = 60% persistently declined %DLCO | ERR/Gy −0.96 (−1.79 to −0.14) at 1 y after treatment |

### Endocrinopathy

| Literature       | Cohort and treatment period | Outcome                                      | Reference group | Risk (95% confidence interval)                                                                 | Evidence of linear relationship or cumulative incidence |
|------------------|-----------------------------|----------------------------------------------|-----------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| van Nimwegen et al., 2014⁷⁷ | Netherlands (hospital based) N = 2264, <51 y, 1965–1995 | Diabetes | General population | ≥36 Gy paraaortic/spleen HR 2.3 (1.54–3.44), ≥36 Gy paraaortic alone HR 1.82 (1.02–3.25) | HR/Gy mean dose to pancreatic tail 1.017 (\(P < .001\)) |
| Cella et al., 2013⁷⁸ | Italy (Naples) N = 53 (22 cases), Median age 28 y (14–70), Treated 2001–2009 | Hypothyroidism | N/A | Cumulative risk (median follow-up: 32 mo; V30 to thyroid gland ≤62.5% = 11.5% hypothyroidism, V30 to thyroid gland > 62.5% = 70.8% hypothyroidism) |

*Abbreviations: %DLCO = percentage predicted carbon monoxide-diffusing capacity; AER = absolute excess risk; CCSS = Childhood Cancer Survivor Study; CT = chemotherapy; DFCI/BWH = Dana-Farber Cancer Institute, Brigham and Women’s Hospital; ERR = excess relative risk; HL = Hodgkin lymphoma; HR = hazard ratio; MLD = mean lung dose; N/A = not available; RR = relative risk; RT = radiation therapy; Rx = prescription; SIR = standardized incidence ratio; SMR = standardized mortality ratio.

*Prescribed dose.

†Estimated dose to where late outcome occurred.

‡No evidence of departure from linearity.
## Table 4

| Median follow-up | Trial | adult/pediatric | No. of patients | Chemotherapy | Radiation therapy | Patients who relapsed, n (%) | Relapses, n (%) |
|------------------|-------|-----------------|----------------|--------------|-------------------|----------------------------|----------------|
| 7.6 y            | HOD90/HOD94 Pediatric⁵¹ | 195 | VAMP, VAMP/CVP | IFRT (15–25.5 Gy) | 27 (13.8) | 14 (51.9) | 8 (29.6) |
| 6.5 y            | Intergroup E2496 Adult⁵⁵ | 135  | ABVD × 6–8 | IFRT (36 Gy) | 19 (14.1) | 8 (42.1) | 3 (15.8) |
|                  |       | 129  | Stanford V × 12 weeks | IFRT (36 Gy) | 23 (17.8) | 7 (30.4) | 11 (47.8) | 5 (21.7) |
| 4 y              | AHOD 0031 Pediatric⁵²   | 1712 | ABVE-PC × 4 (RER, CR) | IFRT (21 Gy) | 32 (9.0) | 15 (47) | 4 (13)  | 13 (41)  |
|                  |       |      | ABVE-PC × 4 (RER, CR) | None | 51 (14.1) | NS | NS | NS |
|                  |       |      | ABVE-PC × 4 (RER, <CR) | IFRT (21 Gy) | 59 (10.3) | 24 (41) | 11 (19) | 24 (41) |
|                  |       |      | ABVE-PC × 2, ABVE-PC × 2 ±DECA (SER) | IFRT (21 Gy) | 52 (17.1) | 27 (52) | 2 (4) | 23 (44) |
|                  |       |      | Uncategorized | Uncategorized | 4 (8.7) | 2 (50) | 0 (0)  | 2 (50)  |
| 4.2 y            | NCIC/ECOG Adult (>16 y)⁵⁹ | 203  | ±ABVD × 2  | SNRT (35 Gy) | 10 (4.9) | 3 (30) | 3 (30) | 4 (40) |
|                  |       | 196  | ABVD × 6–8 | None | 23 (11.7) | 20 (87) | 0 (0) | 3 (13) |
| 4.4 y            | Hopkins Pediatric/young adult (≥ 0 y)⁶⁰ | 37  | ABVD (adult) | IFRT (<30 Gy) | 7 (18.9) | 3 (43) | 1 (14) | 3 (43) |
|                  |       | 37   | ABVE-PC (pediatric) | IFRT (>80 Gy) | 6 (16.2) | 1 (17) | 5 (83) | 0 (0) |

Abbreviations: ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; ABVE-PC = doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; CR = complete response; CVP = cyclophosphamide, vincristine, and procarbazine; DECA = dexamethasone, etoposide, cytarabine, and cisplatin; ECOG = Eastern Cooperative Oncology Group; IFRT = involved-field radiation therapy; NCIC = National Cancer Information Center; NS = not significant; RER = rapid early responding; SER = slow early responding; SNRT = subtotal nodal radiation therapy; VAMP = vinblastine, doxorubicin, methotrexate, and prednisone.