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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.[1] 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.[2,3]

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.[4,5] Of note, some trials from earlier eras included higher-risk patients with stage III/IV disease who were treated with much larger fields.[6–9] 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).[7]

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.[10,11] 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.[6,12,13] Earlier studies employed computed

tomography (CT) for response assessment, but over time, functional imaging has been increasingly used (Gallium or fluorodeoxyglucose [FDG] positron emission tomography [PET]).[10] 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.[12,14–16] 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,[2,12,17] early stage favorable,[2,9,12,13,18] and advanced disease.[2,6,12,14,19] 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,[6,9,12–14,18,19] but others indicated a significant progression-free survival benefit in patients who received consolidative RT.[2,6,20] The interpretation and comparison of results from these trials are complicated by the different risk groups included,[6,17,18] 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.[13,17] 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.[13] 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.[17]

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.[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.[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.[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.[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,[15,16] although no significant difference was observed in patterns of relapse between bulky and nonbulky sites of disease in the AHOD 0031 study.[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.[12,13,17,18] To improve outcomes, high-risk sites have also been irradiated.[16] For example, the AHOD 1331 study randomized patients with advanced stage disease between ABVE-PC and the adcetris, 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.[23]

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.[24,25] 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.[26] 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.[26–28] 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.[29] 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.[30,31] Failure to obtain a PET/CT scan before starting chemotherapy was associated with a higher risk of relapse in patients with early stage HL.[32] 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.[27] 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[33] 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.[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.[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.[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.[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.[41] Favorable event-free survival, however, has been reported in several retrospective studies in adult and pediatric patients with HL.[42–46] To

date, grade 3 pneumonitis was rare after IMRT and PT.[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.[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.[50,51] DIBH also conferred lower estimated lifetime excess risks of cardiovascular disease and secondary lung, breast, and thyroid cancers.[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.[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.[54] In AHOD 0031, 244 patients (14.3%) relapsed, and 94% of recurrences had some component of in-field failure after 21 Gy.[22] 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 mechlorethamine, doxorubicin hydrochloride, vinblastine, vincristine, bleomycin, etoposide, and prednisone (Stanford V).[55] 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.[41] 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.[56]

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.[57] 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.[36] 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.[58,59]

Consensus Statement #6:

Athough 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.[60] 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.

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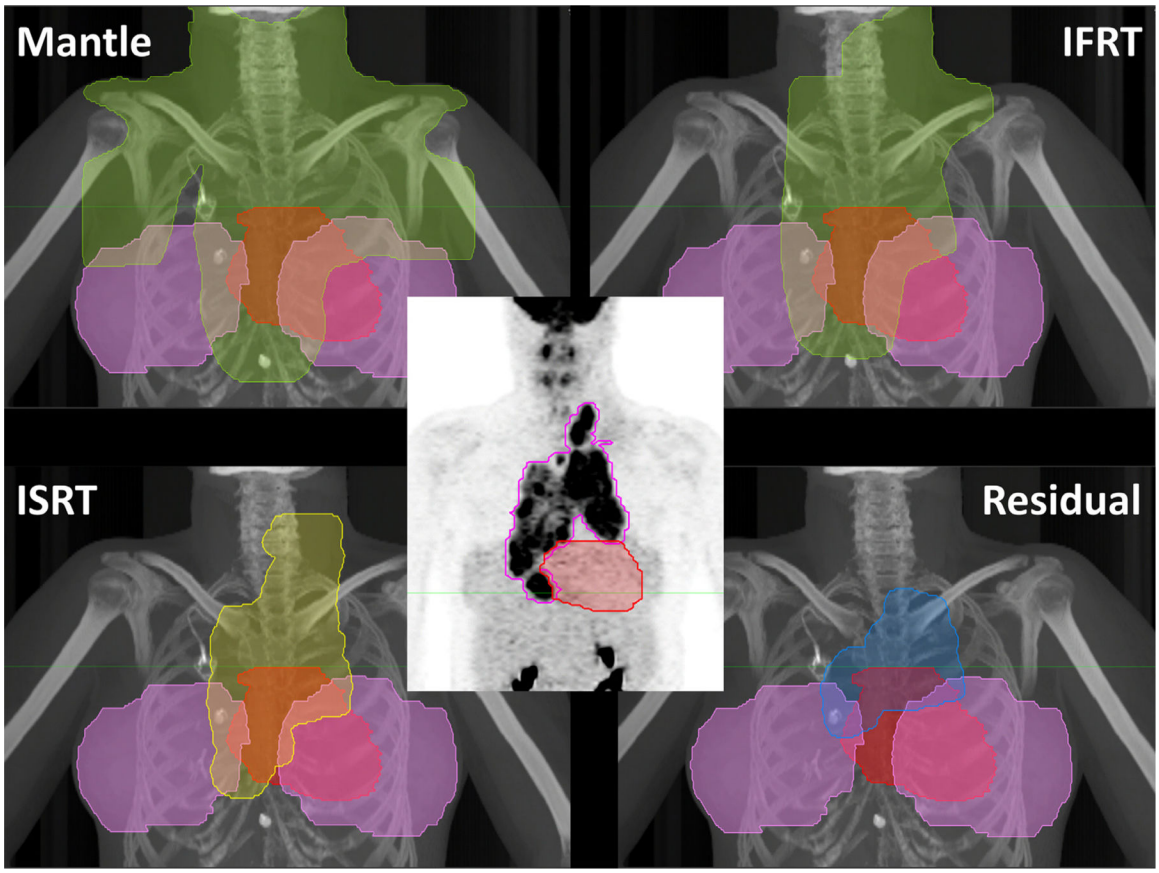

Fig. 1.

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.

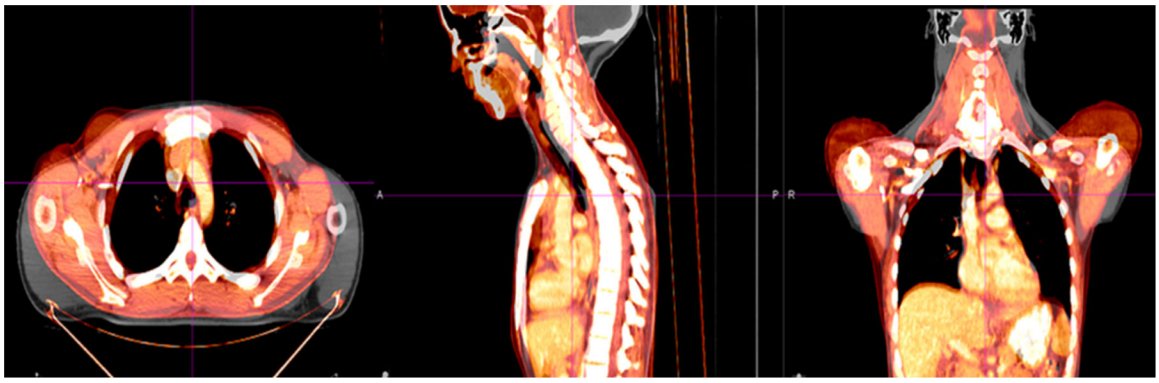

Fig. 2.

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-IIB; I-IIAE; III-IVA; III-IVAE with/without bulk; IA/IIA with bulk	Completed	All received 4 cycles ABVE-PC • RER & CR: Randomized to ± IFRT • RER and PR: 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 IA/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. PR: Anatomic reduction >50% in PPD of measurable disease regardless of FDG-PET response.	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 OEPA→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 = adcetris, etoposide, prednisone, adriamycin; BEABOV±P = bendamustine substitution for mechlorethamine in the original Stanford V backbone with or without prednisone; Bv-AVEPC = adcetris, doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide; CAPDac, cyclophosphamide, adcetris, 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/prednisolone; 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	Target volumes		Modality allowed	4-dimensional CT used	Dose
		GTV	CTV			
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 defined 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 ≥3)	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 If PR with persistent PET5+ disease, small volume boost of 9 Gy/6 fx added

Trial	Field design	Target volumes		Modality allowed	4-dimensional CT used	Dose
		GTV	CTV			
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: 10.8/6 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: 28.8Gy/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.

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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[61]	Netherlands (hospital based) N = 1261 Median 26 y (all <41) Treated 1965–1987	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[56]	USA (CCSS patients with HL) N = 2742 Median 14 y (2–20) Treated 1970–1979	Fatal second malignant neoplasms	No RT	<30 Gy *: HR 1.9 (0.4–8.7) ≥30 Gy *: HR 7.4 (1.8–30.3)	
Schaapveld et al., 2015[62]	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[63]	International population-based N = 3817 (105 cases and 266 controls) Median 22 y (all ≤30) Treated 1965–1994	Incidence of breast cancer	0–3.9 Gy †	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[64] and Gilbert et al., 2003[65]	International population-based N = 19,046 (227 cases and 455 controls) Median 50 y (9–81) Treated 1965–1994	Incidence of lung cancer	<5 Gy †	>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[66]	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 †	≥30 Gy: RR 4.3 (1.5–15.3)	ERR/Gy = 0.38 (0.04–8.17) P_{trend} < .001 ‡
Morton et al., 2013[67]	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 †	0.1–0.9 Gy: RR 1.3 (0.4–4.1) 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*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[68]	International population registry N = 19,882 (36 cases and 70 controls) Median 47 y (12–76) Treated 1943–2003	Incidence of pancreatic cancer	<10 Gy†	≥10 Gy: RR 4.3 (1.7–15)	ERR/Gy 0.098 (0.015–0.42) P_{trend} = .005‡
Cardiovascular					
Hancock et al., 1993[69]	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) >30 Gy*: SMR 3.5 (2.7–4.3)	
Aleman et al., 2003[61]	Netherlands (hospital based) N = 1261 (45 deaths) Median 26 y (all <41) Treated 1965–1987	Cardiovascular death	General population	RT alone: SMR 7.2 (4.2–11.6) RT and CT: SMR 5.5 (2.2–11.3) Salvage Rx: SMR 5.9 (3.7–9.0)	
Van Nimwegen et al., 2015[70]	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) 30–35 Gy*: HR 3.1 (2.3–4.2) ≥36 Gy*: HR 3.8 (3.0–5.0)	Patients treated with mediastinal RT had 40-y cumulative incidence of 54.6% (51.2–57.9)
Van Nimwegen et al., 2016[71]	Netherlands (hospital based) N = 2617 (325 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) 5–14 Gy: RR 2.14 (1.28–3.58) 15–19 Gy: RR 2.76 (2.10–3.59) 20–24 Gy: RR 2.79 (2.23–3.49) 25–34 Gy: RR 3.21 (2.52–4.09) 35–45 Gy: RR 2.54 (0.96–6.69)	ERR/Gy 0.074 (0.033–0.148), P_{trend} < .001‡
Cutter et al., 2015[72]	Netherlands (hospital based) N = 1852 (89 cases and 200 controls) All <41 y Treated 1965–1995	Incidence of valvular heart disease	No RT	≤30 Gy†: RR 1.4 (0.5–3.8) 31–35 Gy: RR 3.1 (1.7–5.6) 36–40 Gy: RR 5.4 (3.9–7.7) >40 Gy: RR 11.8 (4.9–28.5) P_{trend} < .001 (nonlinearity)	
Van Nimwegen et al., 2017[73]	Netherlands (hospital based) N = 2617 (91 cases and 278 controls) Median 28 y (all <51) Treated 1965–1995	Incidence of congestive heart failure	No RT	1–15 Gy†: RR 1.27 (0.86–1.89) 16–20 Gy: RR 1.65 (0.98–2.77) 21–25 Gy: RR 3.84 (1.97–7.47) ≥26 Gy: RR 4.39 (2.00–9.65) P_{trend} < .001	
Bowers et al., 2005[74]	United States (CCSS patients with HL) N = 1926 All <21 y Treated 1970–1986	Incidence of stroke	Siblings	Mantle RT: RR 5.62 (2.59–12.25)	
De Bruin et al., 2009[75]	Netherlands (hospital based) N = 2201 (96 cases) All <51 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)	

Literature	Cohort and treatment period	Outcome	Reference group	Risk (95% confidence interval)	Evidence of linear relationship or cumulative incidence
Pulmonary toxicity					
Ng et al., 2008[76]	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					
van Nimwegen et al., 2014[77]	Netherlands (hospital based) N = 2264 <51 y 1965–1995	Diabetes	General population	≥36 Gy paraortic/spleen HR 2.3 (1.54–3.44) ≥36 Gy paraortic alone HR 1.82 (1.02–3.25)	HR/Gy mean dose to pancreatic tail 1.017 (P < .001)
Cella et al., 2013[78]	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

Treatment outcomes

Median follow-up	Trialadult/pediatric	No. of patients	Chemotherapy	Radiation therapy	Patients who relapsed, n (%)	Relapses, n (%)		
						In-field	Out of field	Both
7.6 y	**HOD90/HOD94** Pediatric[54]	195	VAMP; VAMP/CVP	IFRT (15–25.5 Gy)	27 (13.8)	14 (51.9)	5 (18.5)	8 (29.6)
6.5 y	**Intergroup E2496** Adult[55]	135	ABVD × 6–8	IFRT (36 Gy)	19 (14.1)	8 (42.1)	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** Pediatric[22]	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)[79]	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 (≤40 y)[80]	37	ABVD (adult)	IFRT (<30 Gy)	7 (18.9)	3 (43)	1 (14)	3 (43)
		37	ABVE-PC (pediatric)	IFRT (≥30 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 = Natioanl 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.