9 Principles of Radiation Therapy for Hodgkin Lymphoma

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Abbreviations

3DCRT	Three-dimensional conformal radiotherapy
ABVD	Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine
AP-PA	Opposed anterior and posterior fields
ASCT	Autologous stem cell transplantation
ASH	American Society of Hematology
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, procarbazine, prednisone
BV	Brentuximab vedotin
CR	Complete response
CT	Computed tomography
CTV	Clinical target volume
CVRT	Consolidation volume radiation therapy
DIBH	Deep-Inspiration Breath Hold
EBVP	Epirubicin, bleomycin, vinblastine, dacarbazine
EFS	Event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
FFTF	Freedom from treatment failure
GELA	Groupe d'Études des Lymphomes Adultes
GHSG	German Hodgkin Study Group
HL	Hodgkin lymphoma
IFRT	Involved-field radiation therapy
IMRT	Intensity-modulated radiation therapy
INRT	Involved-node radiation therapy
ISHL11	International Symposium on Hodgkin Lymphoma 2018 meeting
ISRT	Involved-site radiation therapy
LPHL	Lymphocyte-predominant HL
MOP-BAP	Mechlorethamine, vincristine, prednisone, bleomycin, doxorubicin, procarbazine
MOPP	Mustargen, vincristine, procarbazine, prednisone
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tumor dimension

NCCN	National Comprehensive Cancer Network
OS	Overall survival
PET	Positron emission tomography
PTV	Planning target volume
RT	Radiation therapy
STLI	Subtotal lymphoid irradiation
TLI	Total lymphoid irradiation
TSH	Thyroid-stimulating hormone

9.1 Principles of Radiation Therapy of Hodgkin Lymphoma

Radiation therapy (RT) is a major component of the successful treatment of Hodgkin lymphoma (HL). For decades, RT was used alone to cure the majority of patients with HL, and it is still the most effective single agent in the oncologic armamentarium for this disease [1]. RT alone remains the treatment of choice for patients with early-stage lymphocyte-predominant HL (LPHL) and for selected patients with classic HL who have contraindications to chemotherapy [2].Currently, most patients with HL are treated with combined-modality programs in which RT is given as consolidation after chemotherapy. As the role of RT has transformed over the years from a single modality into a component of combined-modality therapy, the classic principles of RT fields, dose, and technique have fundamentally changed.

The following principles guide the current strategy of using RT in HL:

1. RT as part of a combined-modality program is radically different from the large-field, high-dose RT that was used as a single modality in the past. Both the volume treated and the dose required are significantly reduced following chemotherapy as compared to when RT was used alone. In addition, the planning and delivery of RT has improved substantially over the last two decades and continues to improve.
2. Adding RT to chemotherapy improves disease control and allows the administration of shorter and less toxic chemotherapy regimens for all stages of HL. In early-stage HL, multiple randomized studies have shown that the omission of RT results in inferior progression-free survival even after chemo-intensification.
3. Modern RT for HL treats only involved sites to reduced doses and is both better tolerated and associated with significantly lower risk for long-term morbidities than the large-field, high-dose RT used as a single modality in the past [3].

9.2 The Evolution of Radiotherapy for HL

RT has been used in the management of HL since shortly after the discovery of X-rays [4, 5]. Initially, it was used for local palliation, but careful study by pioneers in the field including Rene Gilbert and Vera Peters demonstrated that more aggressive treatment with higher doses and larger fields resulted in the cure of many patients, especially those who presented with limited disease [6, 7]. At Stanford, Henry Kaplan, advantaged by access to the medical linear accelerator, refined the RT concepts and together with Saul Rosenberg advocated strongly for the curative potential of RT [8]. RT as a single modality remained the standard therapy for patients until effective chemotherapy was developed in the second half of the twentieth century. The success of chemotherapy along with the awareness of adverse late events linked to RT initially led to a decrease in its use, but the eventual realization that its judicious application in lower doses and to more tailored fields could enhance curability and allow a meaningful decrease in chemotherapy doses led to the development of combined-modality programs.

The RT of modern combined-modality therapy programs includes the use of very limited treatment volumes and the employment of advanced techniques that improve conformity and dose homogeneity. In contrast to RT fields of the past, which were based upon bony landmarks, these field reductions require detailed clinical information to delineate the target accurately. Both pre- and post-chemotherapy imaging are

essential to define the tumor volume and the integration of computed tomography (CT), and positron emission tomography (PET)/CT treatment planning further improves accurate RT volume design. A margin of safety to address subclinical disease and random and systematic positioning error is still necessary in treatment setup, but techniques to minimize inaccuracies in treatment planning and delivery continue to develop.

The current recommended RT volume is involved-site radiation therapy (ISRT), which uses pre- and post-chemotherapy CT imaging to tailor the radiation volumes to include only the initially involved lymph node sites and residual CT abnormalities. ISRT represents a significant reduction from the previous customary involved-field RT, which was based on bony landmarks visualized on 2D imaging. Involved-node radiation therapy (INRT) is an even more restricted form of ISRT and is recommended only when detailed pre-chemotherapy imaging in the treatment position is available [9]. The volumes for ISRT and INRT were designed to be smaller than the classic IFRT fields that encompassed the entire predefined anatomical regions. Recommendations for ISRT and INRT design have been established, and INRT has already been incorporated in combined-modality clinical trials in the European Organisation for the Research and Treatment of Cancer (EORTC) and the German Hodgkin Study Group (GHSG) [10]. Recommendations for ISRT design have recently been established by the International Lymphoma Radiation Oncology Group (ILROG), and ISRT has been incorporated into pediatric and adult guidelines and clinical trials in North America and Europe [2, 11, 12].

9.3 Indications for Radiation Therapy in HL

It is important to distinguish between classic HL and nodular lymphocyte-predominant HL (LPHL). The management of each entity is different. Most patients with stage I–II LPHL may be treated with radiation alone with curative intent, whereas combined-modality therapy is the standard approach for the majority of patients with classic HL.

9.3.1 Lymphocyte-Predominant HL

Over 75% of patients with LPHL present with stage IA or IIA disease. In this setting, the disease is commonly limited to one peripheral site (neck, axilla, or groin), and involvement of the mediastinum is extremely rare. The National Comprehensive Cancer Network (NCCN) guidelines [2], the German Hodgkin Lymphoma Study Group (GHSG), and the European Organisation for Research and Treatment of Cancer (EORTC) currently recommend limited radiation (IFRT or ISRT) as the treatment of choice for early-stage LPHL. Since the mediastinum is rarely involved, it does not need to be prophylactically treated, thus avoiding the site most responsible for radiation-related short- and long-term side effects. In a recent retrospective study of 131 patients with stage IA disease, 98% of patients obtained a complete response (CR), 98% after extended-field RT alone, 100% after involved-field RT alone, and 95% after combined-modality therapy [13]. With a median follow-up of 43 months, only 5% of patients relapsed and only three patients died. Toxicity of treatment was generally mild and was the greatest in association with combined-modality therapy. Two other studies from the Peter MacCallum in Australia and the Dana-Farber Cancer Institute in Boston supported the adequacy of limited-field RT for LPHL and suggested a reduced risk of second tumors compared to extended-field RT [14, 15].

Although there has not been a prospective study comparing extended-field RT, which was commonly used in the past, and IFRT/ISRT, retrospective data suggest that the more limited fields are adequate [15, 16]. The radiation dose recommended is 30–36 Gy, with the higher dose reserved for bulky sites.

9.3.2 Classic Hodgkin: Stage I–II

Over the last two decades, the treatment of stage I–II classic HL has changed markedly. Combined-modality therapy consisting of short-course chemotherapy, most often ABVD, followed by reduced-dose IFRT/ISRT carefully directed only to the involved lymph node(s) has replaced RT

alone as the treatment of choice. Combined modality is the standard treatment for favorable and unfavorable presentations of stage I–II disease in Europe, including the EORTC and GHSG. In the United States, chemotherapy followed by ISRT is the preferred treatment recommended by the NCCN guidelines [2]. Several randomized studies have demonstrated that excellent results in stage I–II HL may be obtained with combined-modality treatment that includes only IFRT and that more extensive fields of total or subtotal lymphoid irradiation (STLI and TLI) are not required [17].

The strategy to reduce the number of chemotherapy cycles and/or the radiation dose was tested by two large-scale randomized noninferiority studies conducted by the GHSG. In the HD10 study, 1370 patients with early *favorable* HL were randomly assigned in a 2 × 2 factorial design to receive either four or two cycles of ABVD followed by 30 or 20 Gy IFRT. The 8-year freedom from treatment failure (FFTF) and overall survival (OS) for all patients were 87% and 95%, respectively. Most importantly, there were no significant differences between patients receiving the minimal treatment of ABVD x two cycles followed by IFRT of only 20 Gy and patients receiving more chemotherapy and/or more RT [18]. Patients with unfavorable early-stage HL were randomized on the GHSG HD11 to receive either four cycles of ABVD or four cycles of baseline BEACOPP, followed by IFRT of either 30 or 20 Gy. Five-year FFTF and OS for all patients were 85% and 94.5%, respectively. There was no difference in FFTF when BEACOPP × 4 cycles was followed by either 30 or 20 Gy, and similar excellent results were obtained with ABVD × 4 cycles and IFRT of 30 Gy. Patients who received ABVD×4 cycles and only 20 Gy had a FFTF that was lower by 4.7%, but OS was similar in all treatment groups [19]. Finally, the EORTC H9U study investigated three different chemo regimens all followed by consolidative 30–40 Gy IFRT. The results showed that ABVD × 4 cycles and BEACOPP × 4 cycles were not inferior to ABVD × 6 cycles with 5-year EFS of 86%, 89%, and 90%, thus leading to the conclusion that ABVD × 4 cycles followed by IFRT yields high disease control in early unfavorable HL [20]. These large trials of the GHSG and the EORTC have established combined-modality therapy with reduced-field RT as the treatment of choice for patients with stage I–II disease.

Recently, trials utilizing results of interim PET scans that were performed after two or three cycles of ABVD to identify possible patients who may be treated with chemotherapy alone have been reported [21–23]. In the UK RAPID trial, researchers tested a chemotherapy-alone treatment program for patients with favorable stage I–II HL who had a negative PET, defined strictly as Deauville 1–2 only, after three cycles of ABVD. They found that ABVD × 3 cycles was inferior to combined-modality therapy in a per-protocol analysis in which randomized groups were analyzed as treated; progression-free survival was significantly better for patients who received consolidative RT (HR 2.36 in favor of IFRT, $p = 0.02$) [23]. Most recently, in data presented at the International Symposium on Hodgkin Lymphoma 2018 meeting (ISHL11) in Cologne, Germany, additional analysis of the UK RAPID study found that as maximum tumor diameter (MTD) increased, so did the risk of relapse, specifically in patients who did not receive RT. For patients with an MTD < 5 cm, 5-year event-free survival was 93.6% where as it was 79.3% in patients with an MTD ≥ 5 cm (HR 1.23 [95% CI: 1.01–1.48], $p = 0.04$) [24]. Similarly, a chemotherapy-alone approach has been proven inferior by the EORTC H10 trials for patients with favorable and unfavorable stage I–II HL. In the EORTC H10F and H10U trials, the ABVD-alone arms for patients who were PET-negative (Deauville <3) after ABVD × 2 cycles were terminated early due to an excess number of events when radiation therapy was not incorporated into the therapy even though RT omission was compensated for by an intensification in the number of cycles of ABVD [22]. In the final analysis of the favorable subset of H10, ABVD with INRT resulted in a 5-year PFS of 99.0%, while ABVD alone resulted in a 5-year PFS of only 87.1%. Similarly, in the unfavorable subset, noninferiority also could not be demonstrated with chemotherapy alone as the 5-year PFS was 92.1% in the combined-modality arm and 89.6% in the

chemotherapy-alone arm. Thus, H10 concluded that combined modality with ABVD and INRT remained the standard of care for patients with either favorable or unfavorable stage I–II HL [25].

Most recently, the GHSG presented the results of HD16 at the ISHL11 and the American Society of Hematology (ASH) 2018 meetings. Patients with early-stage favorable HL were randomized to either a standard arm of ABVD × 2 cycles followed by 20 Gy IFRT versus an experimental arm of no further therapy if they were PET-negative, defined as Deauville 1–2, at the end of two cycles of ABVD. The initial analysis, which included Deauville 1–3 patients, showed the omission of RT resulted in inferior outcomes for these favorable-risk patients with a 5-year estimated PFS of 93.4% in the combined-modality arm and 86.1% in the chemotherapy-alone arm. The difference of −7.3% [95% CI: −13.0%, −1.6%] could not exclude the prespecified non-inferiority margin of 3.01%, and thus, combined modality with ABVD × 2 cycles followed by 20 Gy of radiation remains the standard of care for patients with early-stage favorable HL [26].

Finally, the UK RATHL trial, though advertised as a trial for advanced-stage HL, actually was comprised of approximately 50% of patients with stage II disease [27]. This included patients with B symptoms, large mediastinal adenopathy, or >2 sites of disease. Patients with a negative interim PET (Deauville <4) were treated with ABVD or ABVD/AVD chemotherapy alone, without RT. The 3-year PFS was a respectable 90.0%, and the authors conclude that this is acceptable. However, patients on the H10U trial who were treated with just four cycles of ABVD followed by consolidative RT had a 3-year PFS of 95% (Table 9.1).

Thus, we have learned from GHSG HD8 that reducing the irradiated volume from the extended-field RT that was used in the era before adequate systemic therapy to involved-field RT does not result in inferior outcomes. We have also learned from GHSG HD10 and HD11 that combined modality with reduced dose and reduced-volume RT after systemic therapy results in excellent outcomes for patients with early-stage HL. Finally, we may conclude from the UK RAPID, EORTC H10, and GHSG HD11 trials that the omission of RT results in inferior outcomes and combined modality remains the standard of care. This conclusion has been further bolstered by a recent systematic review, in which combined-modality treatment was found to improve tumor control and overall survival in patients with early-stage

Table 9.1 Summary of trials for stage I–II Hodgkin lymphoma in the PET era (Courtesy of Dr. Richard Hoppe, Stanford University, United States of America)

Study	Definition of PET negative	Total chemo	PFS (%) (years)	PFS diff	OS	Notes
NCIC CTG HD.6 [28]	CT CR/cru	CR/cru ABVD × 4	95 (5)		94 (12)	Excludes B sx, bulk
		PR ABVD × 6 (5)	81.0 (5)			
RAPID [23] (per protocol)	*D* < 3	ABVD × 3	97.1 (3)	6.3	97.1 (3)	Excludes B sx, bulk
		ABVD × 3 + RT	90.8 (3)			
EORTC/GELA/FIL H10F [25]	*D* < 3	ABVD × 4	87.1 (5)	11.9	100 (5)	EORTC favorable
		ABVD × 3 + RT	99.0 (5)		99.6 (5)	
EORTC/GELA/FIL H10U [25]	*D* < 3	ABVD × 6	89.6 (5)	2.5	98.3 (5)	EORTC unfavorable
		ABVD × 4 + RT	92.1 (5)		96.7 (5)	
GHSG HD16 [26]	*D* < 3	ABVD × 2 + RT	93.4 (5)	7.3	98.1 (5)	GHSG favorable
		ABVD × 2	86.1 (5)		98.4 (5)	
Israeli [29]	*D* < 4	ABVD × 2–4 + RT	98.5 (5)	9.9		
		ABVD × 4–6	88.6 (5)			
CALGB/Alliance 50604 [30]	D < 4	ABVD × 4	92.0 (3)			Non-randomized
RATHL [27]	D < 4	A(B)VD × 6	90.0 (3)			B sx, bulk, > sites

Hodgkin lymphoma [31, 32]. We acknowledge there may be select early-stage HL patients for whom a chemotherapy-alone approach may be preferred. A commonly cited example is a young woman who would likely receive a large volume of radiation to breast tissue due to her anatomy or localization of disease in the mediastinum and axillae. It is our recommendation that these patients are discussed in a multidisciplinary conference prior to the start of treatment and that patients are made aware of all possible treatment options so that their preferences may be considered.

9.3.3 Stage III–IV HL

Although the role of consolidative RT after induction chemotherapy in stages III–IV remains controversial, RT is often added in patients who present with bulky disease or who do not have a clear complete remission after chemotherapy [33]. The results of prospective studies testing the concept have been conflicting. A meta-analysis of several randomized studies demonstrated that the addition of radiotherapy to chemotherapy reduces the rate of relapse but did not show survival benefit for combined modality compared to chemotherapy alone [34]. Unfortunately, nearly all studies that addressed the question of adding RT in stage III–IV disease were conducted in the pre-PET era. With interim PET imaging, it is possible that a more selective use of RT would prove its benefit.

For historical context, we will briefly discuss three main pre-PET era studies. The EORTC 20884 trial was a randomized study that evaluated the role of IFRT in patients with stage III–IV Hodgkin disease who obtained a CR after MOPP/ABV chemotherapy [35]. Patients received six or eight cycles of MOPP/ABV (number of cycles depended upon the response). Patients who did not achieve a CR (40%) based upon CT imaging only were not randomized but were all assigned to receive IFRT. Among the 333 randomized patients, the 5-year overall survival rates were 91% (no RT). Among the partial responders after six cycles of MOPP/ABV, the addition of IFRT yielded overall survival and event-free survival rates that were similar to those obtained among patients who achieved a CR to chemotherapy. This suggests a key role for consolidative RT in stages III–IV when patients fail to achieve a complete response to chemotherapy. Unfortunately, MOPP/ABV is toxic and has been abandoned for use in North America. A more modern randomized study evaluated the role of consolidation RT after CR to chemotherapy used ABVD × 6 cycles, which is the most common regimen currently used for advanced-stage HL. This trial was conducted at the Tata Medical Center in India. It included patients of all stages, but nearly half were stages III–IV. A subgroup analysis of these patients showed a statistically significant improvement of both 8-year event-free survival (EFS) and 8-year overall survival with added RT compared to ABVD alone (EFS 78 vs. 59%; $p < 0.03$ and OS 100 vs. 80%; $p < 0.006$) [36]. Finally, a secondary analysis of the UKLG LY09 study evaluated the effect of consolidation RT following different chemotherapy regimens in advanced-stage patients. Although more patients with bulky disease and partial response were in the RT group, PFS and overall survival were significantly better for 43% of the patients who received RT in this study. Subgroup and multivariate analysis confirmed this benefit from additional RT [37].

The first study to incorporate PET imaging in an attempt to define the more selective use of RT was the GHSG HD15 trial. In this trial, patients with advanced disease were treated with different schedules of BEACOPP chemotherapy. Following completion of chemotherapy, patients with residual disease greater than 2.5 cm underwent PET imaging. If the PET scan was negative, patients received no further therapy. If the PET scan was positive, the patients received 30 Gy of consolidative RT. Although the group with a positive PET scan had a worse PFS than the PET-negative group (86.2% vs. 92.6%), the results in the PET-positive group were actually quite good for this subset of poor-prognosis patients, supporting the use of RT for patients in PR by PET following completion of chemotherapy [38]. Another recent trial evaluated the role of RT

among stage IIB–IVB patients who had interim and end-of-treatment PET-negative disease [39]. The GITIL/FIL HD 0607 trial randomized patients who had nodal disease >5 cm to receive no further treatment or consolidative RT to the initially bulky sites following ABVD × 6 cycles. With a median follow-up of 3.6 years, there was no significant difference in PFS (93% vs. 97% at 3 years, $p < 0.3$) or OS (99% vs. 100%, $p < 0.08$). The RT question was not addressed for patients who failed to achieve a complete metabolic response following the completion of chemotherapy. Finally, the US Intergroup trial S0816 treated patients with chemotherapy alone, including chemotherapy escalation for patients who had an interim-positive PET [40]. Among patients who had an end-of-treatment positive PET, the 2-year PFS was only 30.6%. Although no RT was utilized for these patients, an analysis was completed assuming patients who met the GHSG HD15 criteria were irradiated [41]. Assuming a modest 50% local control for RT, this would have boosted the likely PFS from 30.6% to 42.8%. Assuming a more likely 80% local control for RT, this would have boosted the 2-year PFS to 50.2%.

In summary, the data from the EORTC 20884 and GITIL/FIL HD 0607 suggest a limited role for RT among patients who achieve a complete response to chemotherapy. In contrast, the EORTC 20884, GHSG HD15, and special analysis of the US Intergroup S0816 trial all suggest that patients who fail to achieve a CR to chemotherapy are very likely to be benefited by the incorporation of RT. Some patients may benefit simply from consolidative RT at the conclusion of chemotherapy, while others may benefit from its inclusion in an overall salvage treatment program.

9.3.4 RT in Salvage Programs for Refractory and Relapsed HL

High-dose therapy supported by autologous stem cell transplantation (ASCT) has become a standard salvage treatment for patients with HL who relapse or remain refractory to primary therapy. Many of these patients have not received prior RT or have relapsed at sites outside the original radiation field. These patients could benefit from integrating RT into the salvage regimen.

Poen and colleagues from Stanford analyzed the efficacy and toxicity of adding cytoreductive or consolidative RT to 24 of 100 patients receiving high-dose therapy [42]. When involved sites were irradiated in conjunction with transplantation, no in-field failures occurred. While only a trend in favor of IFRT could be shown for the entire group of transplanted patients, analysis restricted to patients who had no prior RT or those with relapse stages I–III demonstrated significant improvement in freedom from relapse. Fatal toxicity in this series was not influenced significantly by IFRT. Similar improvements in outcomes by the addition of RT have been demonstrated in multiple other series including studies from the University of Rochester [43] and the University of Torino [44]. At MSKCC, a program that integrated RT into the high-dose regimen for salvage therapy was developed and included accelerated hyperfractionated irradiation (twice daily fractions of 1.8 Gy each) to start after the completion of reinduction chemotherapy and stem cell collection and prior to the high-dose chemotherapy and stem cell transplantation [45–47]. Patients who had not been previously irradiated received involved-field RT (18 Gy in 5 days) to sites of initially bulky (>5 cm) disease and/or residual clinical abnormalities, followed by total lymphoid irradiation (TLI) of 18 Gy (1.8 Gy per fraction, bid.) during an additional 5 days. Patients who had prior RT received only involved-field RT (when feasible) to a maximal dose of 36 Gy. A recent report detailed the outcomes of 186 patients treated from 1985 to 2008. The 10-year OS and EFS were 56% [48]. The authors concluded that this was a safe and effective salvage strategy. A report on the quality of life and treatment-related complications of this program disclosed only a small number of late complications [49].

ILROG has published consensus guidelines regarding best practice for inclusion of RT in salvage treatment programs for Hodgkin lymphoma [50]. This report details the patient variables that

affect selection of salvage treatment, including intensity of prior therapy, extent of relapse, whether disease is chemorefractory, and how radiation can best be incorporated into effective salvage therapy.

9.4 Radiation Fields and Volumes: Principles and Design

In the past, radiation-field design attempted to include multiple involved and uninvolved lymph node sites. The large fields known as *mantle*, *inverted Y*, and *TLI* were synonymous with the radiation treatment of HL. These fields are no longer in use.

IFRT encompasses a significantly smaller volume and was incorporated into many clinical trials of the past two decades. Extending this concept further, even more limited radiation volumes termed involved-node radiation therapy (INRT) and involved-site radiation therapy (ISRT) have been introduced into combined-modality programs and endorsed by guideline groups as the new standard RT volumes for HL [9, 10]. Even when radiation is used as primary management for LPHL, the treatment volumes should be limited to the involved site or to the involved sites and immediately adjacent the lymph nodes.

The terminologies that define radiation volumes may be confusing and create difficulties in comparing treatment programs. However, general definitions and guidelines are now available and should be followed [9]. The following are definitions of types of radiation fields and volumes that have been used in HL.

9.4.1 Extended-Field Radiation Therapy

This field includes the involved lymph node group *plus* the adjacent clinically uninvolved region(s). For extranodal disease, it includes the involved organ plus the clinically uninvolved lymph node region. It was common during the era of treatment with RT alone to treat large fields encompassing multiple lymph node regions, both involved and uninvolved. The field design that includes all of the supradiaphragmatic lymph node regions was referred to as the *mantle* field. The field that includes all lymph node sites below the diaphragm (with or without the spleen and called after its shape) is the *inverted Y*. When all the major lymph node regions above and below the diaphragm were irradiated, this was referred to as *total lymphoid irradiation* (Fig. 9.1). If the pelvic nodes were not included, this was referred to as *subtotal nodal irradiation*. Extended fields are rarely used in modern treatment of HL.

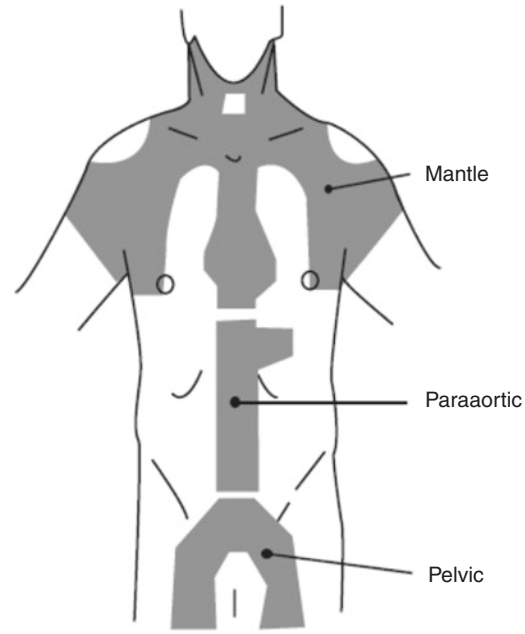


Fig. 9.1 Illustration of extended RT fields used in the past

9.4.2 Involved-Field Radiation Therapy

These fields are limited to the clinically involved lymph node *regions* [51]. It was influenced by lymphoid regions that were defined in the Ann Arbor staging system for Hodgkin's disease [52]. For extranodal sites, the field includes the organ alone (if no evidence for lymph node

involvement). IFRT was commonly employed in clinical trials during the past two decades, but fields have now become even smaller as 3D cross-sectional imaging has become widely available. The new volumes based on CT-based simulation are *involved-node radiation therapy (INRT)* and *involved-site radiation therapy (ISRT).*

9.4.3 Involved-Site Radiation Therapy (ISRT): The New Standard Volume for HL

The International Lymphoma Radiation Oncology Group (ILROG) now recommends the use of ISRT to treat HL [9]. ISRT has already been adopted as the standard volume by several organizations including the NCCN [2]. In the majority of cases, assuming the same clinical presentation and response, ISRT is smaller than IFRT and more precise as treatment volumes are determined by modern cross-sectional imaging such as CT and PET-CT rather than by standard bony landmarks of the involved location as seen on 2D imaging. The concept of ISRT was developed as an extension of the INRT concept that was conceived earlier [10]. In comparison to INRT, ISRT allows for more flexibility and use of clinical judgment when the strict criteria for INRT pre-chemotherapy imaging cannot be met. Indeed, in the majority of practices, pre-resection or pre-chemotherapy precise imaging is not available in the radiation treatment position. ISRT accounts for this deficiency. INRT is fundamentally a more optimal case of ISRT when accurate pre-chemotherapy imaging allows for tighter margins around the original volumes. Finally, unlike IFRT, which uses predetermined anatomical regional "borders" determined by bony landmarks that are easy to visualize during conventional 2D simulation, which has now been replaced by CT or PET/CT simulation, ISRT and INRT incorporate the current concepts of volume determination as outlined in the ICRU Report 83 [53]. The modern RT treatment volumes are based on defining a gross tumor volume (GTV), a clinical target volume (CTV), and a planning target volume (PTV). The PTV is then used to define beam coverage.

9.4.3.1 ISRT When RT Is the Primary Treatment

RT as single modality in HL is relevant for stage I–II lymphocyte-predominant Hodgkin lymphoma (LPHL). It may also be relevant in selected cases of early-stage classic HL in patients who are not candidates for primary chemotherapy due to serious comorbidities. In most clinical situations that require RT as the primary modality, the GTV should be readily visualized during simulation. In this situation, the clinical target volume (CTV) should be more generous since microscopic or subclinical disease is more likely to be present without chemotherapy.

9.4.3.2 ISRT When RT Is Part of Combined-Modality Treatment

RT is often part of the treatment program for early-stage classic HL following adequate systemic chemotherapy. RT improves freedom from treatment failure and progression-free survival even in patients with a negative interim PET [22, 23, 26,] and allows for a reduced number of chemotherapy cycles [18]. In a recent systematic review, combined-modality treatment was found to improve tumor control and overall survival in patients with early-stage Hodgkin lymphoma [29]. In select patients with advanced-stage disease, localized RT may be used for residual sites of lymphoma after full course of chemotherapy [39]. The GTV may be markedly affected by prior systemic chemotherapy, and it is therefore particularly important to review the pre-chemotherapy imaging and to define the pre-chemotherapy volume on the

simulation CT study as "pre-chemotherapy GTV" as well as the post-chemotherapy remaining CT and/or PET abnormality as "post-chemotherapy" GTV.

9.4.4 Involved-Node Radiation Therapy (INRT): A Special Case of ISRT

INRT was originally developed and implemented by the EORTC to replace IFRT in prospective randomized studies (EORTC/GELA/IIL H10). It mandated accurate PET/CT information prior to chemotherapy and in a position similar the subsequent post-chemotherapy radiation therapy treatment position. The INRT technique reduces the treated volume to a minimum, but in order to be safe, optimal imaging both before and after chemotherapy is needed [9, 38]. INRT represents a special case of ISRT, where pre-chemotherapy imaging is ideal for post-chemotherapy treatment planning (Fig. 9.2). PET/CT up front for staging purposes is mandatory as it has been demonstrated that PET/CT is the most accurate imaging method for determining disease extent in HL [39]. In order to enable image fusion of the pre-chemotherapy and the post-chemotherapy planning images, the pre-chemotherapy PET/CT scan should be acquired with the patient in the treatment position and using the same breathing instructions that will be used later for RT. Ideally, the patient should be scanned on a flat couch top, with the use of appropriate immobilization devices and using markers at skin positions which are visible in the imaging. During or following the completion of chemotherapy, a response assessment using PET/CT or contrast-enhanced CT should be performed. A planning CT scan is acquired with the patient in the same position as in the pre-chemotherapy CT scan. This highly conformal treatment technique has been shown to be safe, provided strict adherence to the principles above is maintained [54–56].

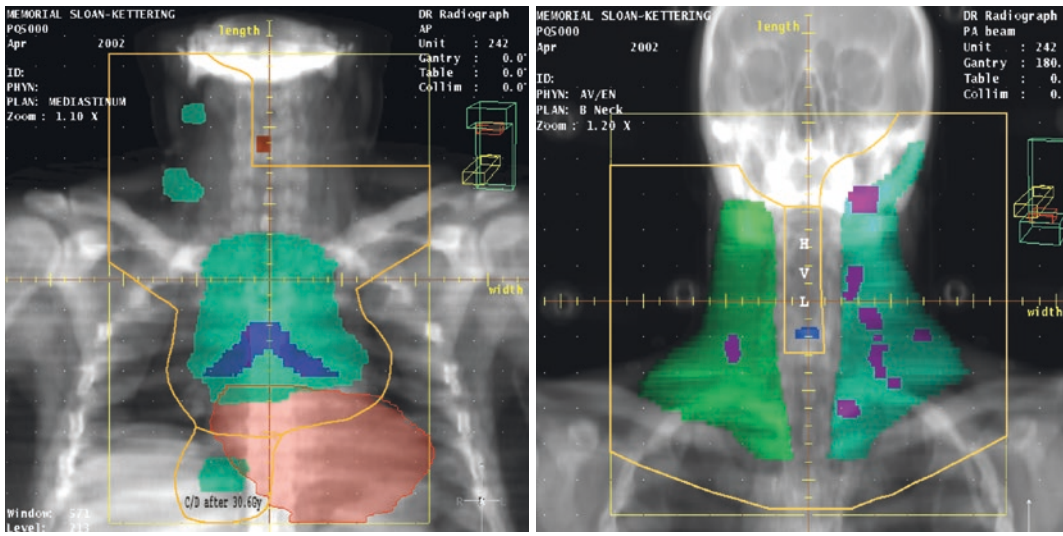


Fig. 9.2 Involved-node radiation therapy. Single lymph node in the left lower neck prior to chemotherapy (left) and following chemotherapy (right). The border of the field encompasses the original volume of the node and not of the whole unilateral neck (as in IFRT approach) (Courtesy of Dr. Theodore Girinsky, Institute Goustave-Roussy, France)

9.4.5 Volume Definitions for Planning ISRT and INRT

These principles apply regardless if RT is used as primary treatment or as part of combined modality and are relevant to both involved-site radiation therapy (ISRT) and involved-node radiation therapy (INRT). The only difference between ISRT and INRT is the quality and accuracy of the pre-chemotherapy imaging, which determines the margins needed to allow for uncertainties in the contouring of the clinical target volume (CTV).

9.4.5.1 Volume of Interest Acquisition

Planning RT for lymphoma is based on obtaining a three-dimensional (3D) simulation study using either a CT simulator, a PET/CT simulator, or an MRI simulator. If PET and/or CT information has been obtained separately or prior to simulation, it is possible to transfer the data either manually or electronically into the simulation CT data. Ideally, any imaging studies that provide planning information should be obtained in the treatment position and using the planned immobilization devices.

9.4.5.2 Determination of Gross Tumor Volume (GTV)

Pre-chemotherapy (or Presurgery) GTV

Any abnormalities on imaging studies obtained prior to any intervention that might have affected lymphoma volume should be outlined on the simulation study, as these volumes should (in most situations) be included in the CTV.

No Chemotherapy or Post-chemotherapy GTV

The primary imaging of untreated lesions or post-chemotherapy residual GTV should be outlined on the simulation study and is always part of the CTV.

9.4.5.3 Determination of Clinical Target Volume (CTV)

CTV encompasses in principle the original (prior to any intervention) GTV. Yet, normal structures such as the large vessels, lungs, kidneys, and muscles that were clearly uninvolved should be excluded from the CTV based on clinical judgment. In outlining the CTV, the following points should be considered:

(a) Quality and accuracy of imaging and transfer of volumes to simulation images.
(b) Concerns of changes in volume since imaging.
(c) Patterns of spread.
(d) Potential subclinical involvement.
(e) Adjacent organs constraints.

If separate nodal volumes are involved, they can potentially be encompassed in the same CTV. However, if the involved nodes are >5 cm apart, they can be treated with separate volumes using the CTV-to-PTV expansion guidelines as outlined further.

9.4.5.4 Determination of Internal Target Volume (ITV)

ITV is defined in the ICRU Report 62 [54] as the CTV plus a margin that accounts for uncertainties in size, shape, and position of the CTV within the patient. The ITV is mostly relevant when the target is moving with respiration, most commonly in the chest and upper abdomen. The optimal way to manage respiratory motion is to use 4D-CT simulation to understand target movement and to generate accurate ITV margins or to use breath-hold techniques. Alternatively, the ITV may be determined by fluoroscopy or estimated by an experienced clinician. In the chest or upper abdomen, margins of 1.5–2 cm in the superior-inferior direction may be necessary. In sites such as the neck, which are well immobilized and unlikely to change shape or position during or in between treatments, outlining the ITV is not required.

9.4.5.5 Determination of Planning Target Volume (PTV)

PTV is the volume that considers the CTV (or ITV, when relevant) and also accounts for setup uncertainties in patient positioning and alignment of the beams during treatment planning and through all treatment sessions. The practice of determining the PTV varies across institutions.

The clinician and/or treatment planner adds the PTV and applies standard margins that depend on estimated setup variations that are a function of immobilization device, body site, and patient cooperation. While standard patient setup has historically been done based on skin marks and weekly portal films, daily image-guided RT (IGRT) has allowed for reduction in PTV margins. The smaller margins are a function of more certainty with setup, which can ultimately help reduce the radiation dose to the normal structures. IGRT can include daily orthogonal KV images or cone beam CT scan (KV or MV). In general, PTV expansions can range from 0.3 to 1.0 cm depending on the location and use of IGRT.

9.4.6 Determination of Organs at Risk (OAR)

The OARs are normal structures that, if irradiated, could result in significant morbidity including acute toxicity, such as pneumonitis and esophagitis, and late toxicity, such as hypothyroidism, cardiac toxicity, and second cancers. OARs may influence treatment planning or the prescribed dose. They should be outlined on the simulation study. Dose-volume histograms (DVH) and normal tissue complication probability (NTCP) should be calculated by the planner and the plan vetted by the clinician in consideration of this information. Of note, the general principle with regard to OARs in HL should always be ALARA—as low as reasonably achievable—and should depend on the disease distribution, planned treatment volume, and total dose.

9.4.6.1 Lung

A major concern for patients with HL and mediastinal disease who receive RT is pneumonitis with grade 3 pneumonitis rates as high as 7% reported by the MD Anderson Cancer Center (MDACC) following IMRT. This is especially true if given as part of second-line therapy and transplant. The MDACC group evaluated factors predictive of grade 1–3 pneumonitis (14% overall) and found the risk of radiation pneumonitis increases with mean lung dose >13.5 Gy, $V_{20} > 30\%$, $V_{15} > 35\%$, $V_{10} > 40\%$, and $V_5 > 55\%$. Of note, the strongest predictor was V_5 with $V_5 > 55\%$ associated with a risk of pneumonitis of almost 35% [57].

9.4.6.2 Heart

Multiple studies have explored the relationship of heart dose and cardiac toxicity and death among HL survivors. Cardiac toxicity may be due to pericarditis, arrhythmia, coronary artery disease, valvular disease, and cardiomyopathy/congestive heart failure. Dosimetric factors have been identified that have been associated with increased risk of cardiac toxicity. Van Nimwegen et al. reported on a cohort of HL survivors from the Netherlands and found a mean heart dose correlated well with coronary heart disease, demonstrating an excess relative risk of 7.4% per Gy mean heart dose [58]. A statistically significant increased risk of coronary heart disease was demonstrated among patients getting a mean heart dose as low as 5–14 Gy (RR 2.31) compared with a mean heart dose of 0 Gy. This risk was even higher for mean heart dose of 15 Gy or higher (RR 2.83 for 15–19 Gy, 2.9 for 20–24 Gy, and 3.35 for 25–34 Gy).

A recent analysis of 24,214 5-year survivors of childhood cancer in the Childhood Cancer Survivor Study provided substantial insights into the relationships between radiation and risk of long-term cardiac disease. Mean heart doses >10 Gy were associated with increasing cardiac disease risk in a dose-response manner. Volumes of the heart receiving radiation also were correlated with cardiac risk; children receiving a V_5 of >50% had a 1.6-fold increased risk of late cardiac disease. Those receiving at least 20 Gy to any part of the heart also were at increased risk. Current recommendations are to keep the mean heart dose as low as possible with stricter goals to try and keep the mean heart dose <15 Gy in adults and <10 Gy in pediatrics whenever possible. Rarely, should mean heart doses greater than 20 Gy be used, unless patients are being treated definitively in the salvage setting [59].

While mean heart dose may be appropriate for radiation evaluation for IFRT, it is unclear whether it is as important when more conformal techniques

are being used, which can redistribute the dose [60]. Recent studies have demonstrated radiation dose relationships with specific cardiac substructures. For example, Van Niwmegen demonstrated a relationship between heart failure and mean dose to the left ventricle [56]. Among patients treated with anthracyclines, the 25-year cumulative risk of heart failure was 11.2% for mean LV dose <15 Gy, 15.9% for 16–20 Gy, and 32.9% for greater than or equal to 21 Gy. Another study by Cutter et al. demonstrated 30-year cumulative risks of valvular heart disease of 3%, 6.4%, 9.3%, and 12.4% for mean valvular dose of <30, 31–35, 36–40, and >40 Gy [61]. Based on this data, we would recommend keeping the mean valve dose <30 Gy, mean left ventricle dose <15 Gy, and ideally <5 Gy.

9.4.6.3 Thyroid

While hypothyroidism is a common late toxicity, it can be easily managed with thyroid supplementation medication. Cella et al. demonstrated a dose volume effect with 11.5% of patients with hypothyroidism with a $V_{30} < 63\%$ vs. 71% for patients with V_{30} greater than or equal to 63% [62].

9.4.6.4 Second Cancers

The primary cause of death among long-term survivors of HL is second cancers. The most common among survivors are breast cancer, thyroid cancer, sarcomas (bone and soft tissue), and lung cancer. Risk modeling has identified linear dose risks for all these cancers, except for thyroid cancer.

Breast cancer is the most concerning second cancer among female survivors receiving radiation. While smaller treatment fields have greatly reduced the risk of second breast cancers, consideration of breast dose is important in minimizing the risk for all patients. Travis et al. demonstrated that radiation doses >4 Gy were associated with increased risk of secondary breast cancer with increasing dose further increasing the risk. In fact, the relative risk was 1.8 and 4.1 for breast dose of 4–6.9 and 7–23.1 Gy, respectively [63]. Therefore, it is important to keep the mean breast dose as low as possible and try to minimize the breast V_4 to as low as possible.

Lung cancer is an aggressive second cancer that will often result in death for a HL survivor. Fortunately, the risk can greatly be mitigated for nonsmokers. However, among smokers, this risk is increased significantly with the addition of lung irradiation. Travis et al. demonstrated among HL survivors that lung dose of >5 Gy had a relative risk of 5.9 compared with lung dose <5 Gy for developing a second lung cancer [64]. Similar to concerns of pneumonitis, lung V_5 should be evaluated with attempts to keep as low as possible.

Secondary sarcomas have also been found to increase with higher radiation doses to the body. Tukenova et al. demonstrated increased risk (12.5) for dying from a secondary sarcoma when the calculated integral dose was >150 J [65].

Thyroid cancers do not have a linear dose-risk relationship with radiation. Bhatti et al. demonstrated a relative risk increase in secondary thyroid cancers of 8.5 with doses of 5–10 Gy, 10.6 for 10–15 Gy, 13.8 with 15–20 Gy, and 14.6 for 20–25 Gy, with relative risks then declining with doses >25 Gy [66].

9.4.7 Consolidation Volume Radiation Therapy (CVRT)

As systemic therapies continue to improve, further reductions in RT volumes may be possible. Currently, there are ongoing studies looking at modifications in systemic therapy to include brentuximab vedotin (BV) and/or checkpoint inhibitors, such as pembrolizumab and nivolumab [67, 68]. One recent reported study from Memorial Sloan Kettering Cancer Center (MSKCC) demonstrated a favorable response to BV-AVD × 4 cycles followed by ISRT [69]. Consolidation volume radiation therapy (CVRT), which treats only residual CT abnormalities in patients who achieve a CR by PET, is currently being tested after BV-AVD × 4 cycles [70].

9.5 Dose Considerations and Recommendations

Although doses in the range of 40–44 Gy were at one time recommended for the definitive treatment of HL, these recommendations have been modified over time, both in the context of

combined-modality therapy for cHL and the treatment of patients with LPHL. The radiation dose is typically delivered in 1.8–2.0 Gy fractions. If significant portions of lung or heart are included, the dose per fraction can be reduced to 1.5 Gy. The available data indicate that the choice of fractionation is not critical for tumor control and that a schedule with minimal risk of damage to normal structures should be selected.

The GHSG evaluated dose in patients with stage IA–IIB disease without risk factors in a randomized trial of 40 Gy extended-field radiation alone vs. 30 Gy extended-field radiation with a boost of 10 Gy to the involved site of disease [71, 72]. There was no significant difference in outcome between the two arms of the study indicating that 30 Gy is sufficient for clinically uninvolved areas when RT is used alone. The optimum dose for clinically involved sites of disease with RT alone has not been tested in a randomized trial.

More relevant to current practice is the determination of the adequate radiation dose after treatment with chemotherapy. In many early studies, radiation doses were kept at approximately 40 Gy even after achieving a CR to chemotherapy; others reduced the dose in advanced disease when combined with five cycles of chemotherapy to 20–24 Gy with excellent overall results [73]. Studies of combined modality in advanced stage also used reduced doses of RT for patients who achieved a CR to chemotherapy and higher doses (approximately 30 Gy) for patients in PR. The pediatric groups addressing the concern of radiation effects on skeletal and muscular development also effectively reduced the dose of RT after combination chemotherapy to 21–24 Gy [74]. However, recent reports have demonstrated that >90% of all relapses occur in field, suggesting higher doses may be appropriate for pediatrics in certain cases [75].

Several recent studies addressed the adequacy of low-dose IFRT following chemotherapy. A study conducted by the EORTC/GELA [76] randomized patients with favorable early-stage HL to 36, 20, or no IFRT after achieving a CR to six cycles of EBVP. Because an excessive number of relapses occurred in the no-RT arm, this arm was closed early. There was no difference in EFS at 4 years between patients receiving IFRT 36 Gy (87%) vs. 20 Gy (84%). A GHSG randomized study (HD 10) addressed the radiation dose question after short-course chemotherapy [18]. Patients with favorable stages I–II were randomized to receive either four or only two cycles of ABVD followed by IFRT of 30 or 20 Gy. At a median follow-up of 7 years, there was no difference in FFTF among the four arms. FFTF at 5 years was 93.4% in patients treated with 30 Gy (91.0–95.2%) and 92.9% in those receiving 20 Gy (90.4–94.8%). These results, taken together with the better tolerability and the lack of inferiority in secondary efficacy endpoints, led to the conclusion that 20 Gy IFRT, when combined with even only two cycles of ABVD, is equally effective to 30 Gy IFRT in this very favorable group of patients [15]. The GHSG HD11 study targeted patients with unfavorable early stage and randomized them to either ABVD × 4 cycles or BEACOPP × 4 cycles; either program was followed by either 20 or 30 Gy to the involved field. Five-year FFTF and OS for all patients were 85% and 94.5%, respectively. There was no difference in FFTF when BEACOP × 4 cycles was followed by either 30 or 20 Gy, and similar excellent results were obtained with ABVD × 4 cycles and IFRT of 30 Gy. Patients who received ABVD × 4 cycles and only 20 Gy had FFTF that was lower by 4%. OS was similar in all treatment groups [19]. These results suggest that 30 Gy should remain the standard IFRT dose following ABVD in unfavorable early-stage HL [77].

For patients with early-stage LPHL, no advantage has been shown for doses over 30–35 Gy [15].

For patients with residual lymphoma after chemotherapy, the residual mass may represent a more refractory disease, and increasing the dose to the CTV to 36–40 Gy should be considered.

9.5.1 The Significance of Reducing the Radiation Dose

Recent studies clearly indicate that the risk of secondary solid tumor induction is radiation dose related. This was carefully analyzed for secondary breast and lung cancers as well as for other tumors [63, 64, 78, 79]. While it will take more years of careful follow-up of patients in randomized studies to display the full magnitude of risk tapering by current reduction of radiation volume and dose,

recent data suggest that this likely to be the case. In a Duke University study, two groups of patients with early-stage HL were treated with different radiation approaches over the same period. One group received RT alone, given to extended fields with a median dose of 38 Gy; the second group received chemotherapy followed by involved-field low-dose (median of 25 Gy) RT. While 12 patients developed second tumors in the first group and 8 of them died, no second tumors were detected in the second group. The median follow-up was 11.7 and 8.1 years, respectively [80]. Similar observations with an even longer follow-up were made by the Yale group [81]. In a study that used data-based radiobiological modeling to predict the radiation-induced second cancer risk, lowering the dose from 35 to 20 Gy and reducing the extended field to IFRT reduced lung cancer risk and breast cancer risk by 57% and 77%, respectively [82].

Finally, a study by a French Collaborative Lymphoma group (GOELAM) randomized patients with favorable stage I–II HL to receive a conservative RT dose of 40 Gy to involved sites and 30 Gy to adjacent site control arm or in the "experimental arm" to receive only 36 Gy and 24 Gy to the adjacent sites after ABVD × 3 cycles [83]. Surprisingly, the 10-year incidence of severe or fatal complications was nil in the experimental arm but reached 15.5% in the control arm ($p < 0.003$) and 11.1% in the historical controls that received the higher dose. The 10-year FFTF and overall survival rates were similar for the 89 patients in the experimental arm (88.6% and 97.8%, respectively), for the 99 patients in the conservative arm (92.6% and 95%, respectively), and for the 202 patients in the historical control group (91.9% and 92.9%, respectively).

9.5.2 Dose Recommendations

Radiation alone (as primary treatment for LPHL) using ISRT

- Clinically involved and adjacent uninvolved nodes: 30–36 Gy.

Radiation alone (as primary treatment for cHL [uncommon])

- Clinically involved sites: 36 Gy at a minimum.
- Clinically uninvolved sites: 30 Gy.

Radiation following chemotherapy in a combined-modality program

- Patients in CR after chemotherapy: 20–30 Gy.
  - For pediatric or adolescent patients: 15–24 Gy.
  - In some programs of short chemotherapy for bulky or advanced-stage disease (e.g., Stanford V), the recommended RT dose is 30–36 Gy.
- Patients in PR after chemotherapy: 30–40 Gy.

9.6 New Aspects of Radiation Volume Definition and Treatment Delivery

The abandonment of large-field irradiation for most patients with HL permits the use of more conformal RT volumes and introduction of other innovative RT techniques. The change in the lymphoma RT paradigm coincided with substantial improvement in imaging and treatment planning technology that has revolutionized the field of RT. The integration of fast high-resolution computerized tomography into the simulation and planning systems of radiation oncology has changed how treatment volumes and relationship to normal critical structures are determined and planned. In the recent past, tumor volume determinations were made with fluoroscopy-based simulators that produced often poor-quality imaging requiring wide "safety margins" that detracted from accuracy and sparing of critical organs. Most modern simulators are in fact high-resolution CT scanners with software programs that allow accurate conformal treatment planning and provide detailed information on the dose volume delivered to normal structures within the treatment field and the homogeneity of dose delivered to the target. More recently, these simulators have been integrated with a PET scanner that provides additional tumor volume information for consideration during radiation planning.

9.6.1 New Technologies

Intensity-modulated RT (IMRT), tomotherapy, and volumetric modulated arc therapy (VMAT) are advanced systems for photon delivery. These modalities redistribute the radiation to provide high-dose conformality of the target area, but with less conformality in the low-dose region. They also allow for accurately enveloping the tumor with either a homogenous radiation dose ("sculpting") or delivering higher doses to predetermined areas in the tumor volume ("painting"). In the treatment of lymphoma, there are several clinical situations where highly conformal photon techniques provide a benefit. In the mediastinum, a review article of comparison studies showed that IMRT compared with conventional 3D-conformal radiation techniques reduced the mean heart dose on average by 1.44 Gy, mean esophagus dose by 1.4 Gy, and lung V_{20} by 11% [84]. Highly conformal photon techniques can also be useful in the treatment of very large or complicated tumor volumes in the abdomen and head and neck lymphomas. IMRT also allows re-irradiation of sites prior to high-dose salvage programs that otherwise will be prohibited by normal tissue tolerance, particularly of the spinal cord (Figs. 9.3a–d and 9.4a–c).

In general, when using highly conformal photon techniques for mediastinal disease, treatment planning generally tries to avoid equally spaced beams or continuous arcs around the patient in an effort to avoid some of the low-dose bath, especially to the lungs and breasts. MD Anderson Cancer Center has described both the butterfly IMRT technique and the rainbow IMRT technique as ways to optimize the IMRT beam arrangement in mediastinal lymphoma. In the butterfly technique, three anterior and two posterior beams are used to reduce excess exposure to heart, lungs, and spinal cord. In the rainbow technique, one anterior-posterior (AP) beam and four anterior obliques at 0°, 20–30°, 40–60°, 300–320°, and 335–345° are used for patients with only anterior mediastinal disease [85, 86]. Similarly, the University of Torino evaluated optimized VMAT plans that include non-coplanar partial arcs [87, 88]. Early clinical data has begun to emerge from the use of IMRT for mediastinal lymphoma demonstrating similar disease control to 3DCRT treatment [78, 89]. While most have shown little to no pneumonitis with these techniques, MDACC did report a 15% grade 1–3 pneumonitis risk including 6.9% grade 3 rate [58].

9.6.2 Deep Inspiration Breath Hold

An additional technique that can be used to try and further minimize heart and lung dose for mediastinal lymphoma patients and can be used with 3DCRT, IMRT, or proton therapy is deep inspiration breath hold (DIBH). DIBH is a simple technique which the patient inhales deeply and holds this breath during treatment. DIBH can optimize the internal anatomy by pulling the heart caudally while allowing the disease to be irradiated to remain more superiorly by the great vessels for patients with superior mediastinal disease. This allows for more cardiac sparing for these patients. DIBH also immobilizes the disease in the mediastinum, which controls respiratory motion and eliminates the need for an ITV. Finally, it expands the total lung volume, which results in an overall decreased dose to the lungs [90].

Petersen et al. conducted a prospective phase II study of DIBH among patients with mediastinal lymphoma among 19 patients. In the study, the mean lung dose was reduced on average by 2 Gy with DIBH and mean heart dose by 1.4 Gy. Another study by Charpentier et al. reported on 47 patients undergoing DIBH, where the mean lung dose was reduced by approximately 1.5 Gy and mean heart dose reduced by 2.5 Gy [91]. While DIBH appears beneficial for disease located in the superior mediastinum, the benefit is not as obvious for patients with lower mediastinal disease that extends to the level of the heart [92]. This was seen in a study by Paumier et al. who demonstrated a mean heart dose reduction of 50% for patients with upper mediastinal disease, while it was only 8–9% and not significant for lower mediastinum. Similarly, the mean lung dose was reduced by 26% for upper mediastinal disease, but only 18% reduction for lower mediastinal disease [93] (Fig. 9.5).

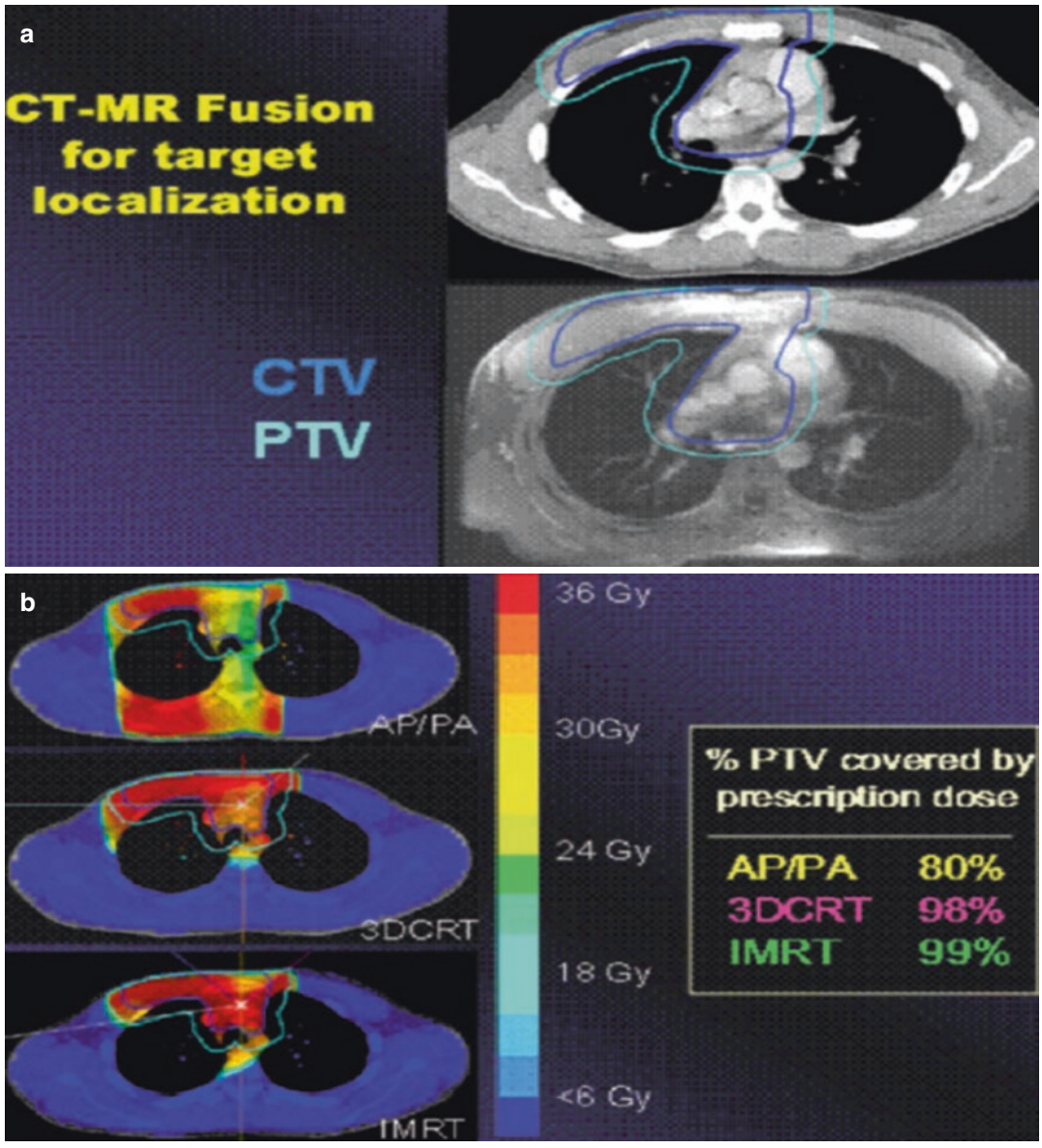
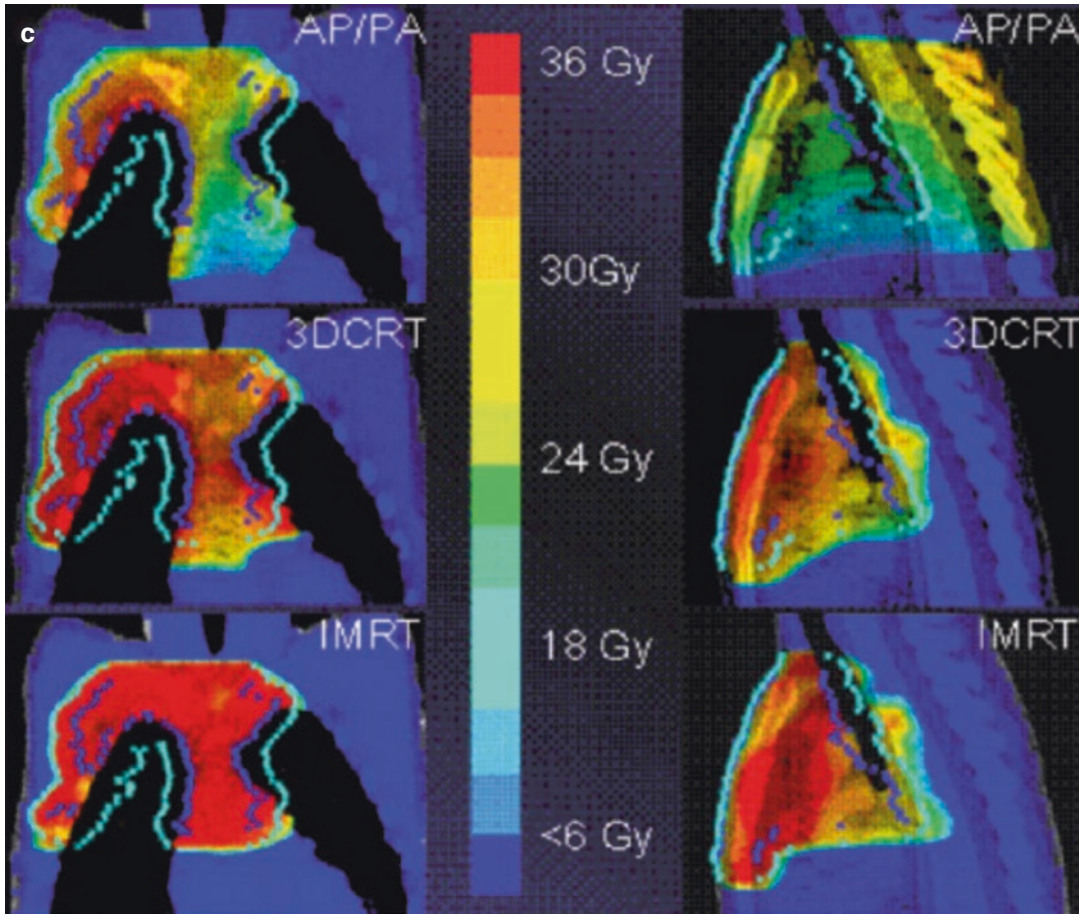


Fig. 9.3 (**a**) CT-MR fusion for target localization of HL involving the mediastinum and right chest wall. *CTV* clinical treatment volume, *PTV* planning treatment volume. (**b**, **c**) Treatment plans comparing AP/PA, 3DCRT, and IMRT. *PTV* planning treatment volume, *AP/PA* opposed anterior and posterior fields, *3DCRT* three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy. (**d**) Comparison of lung complication probability of different plans



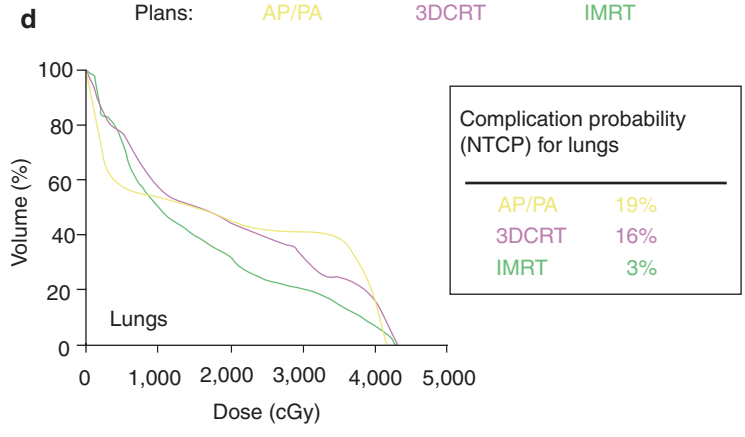


Fig. 9.3 (continued)

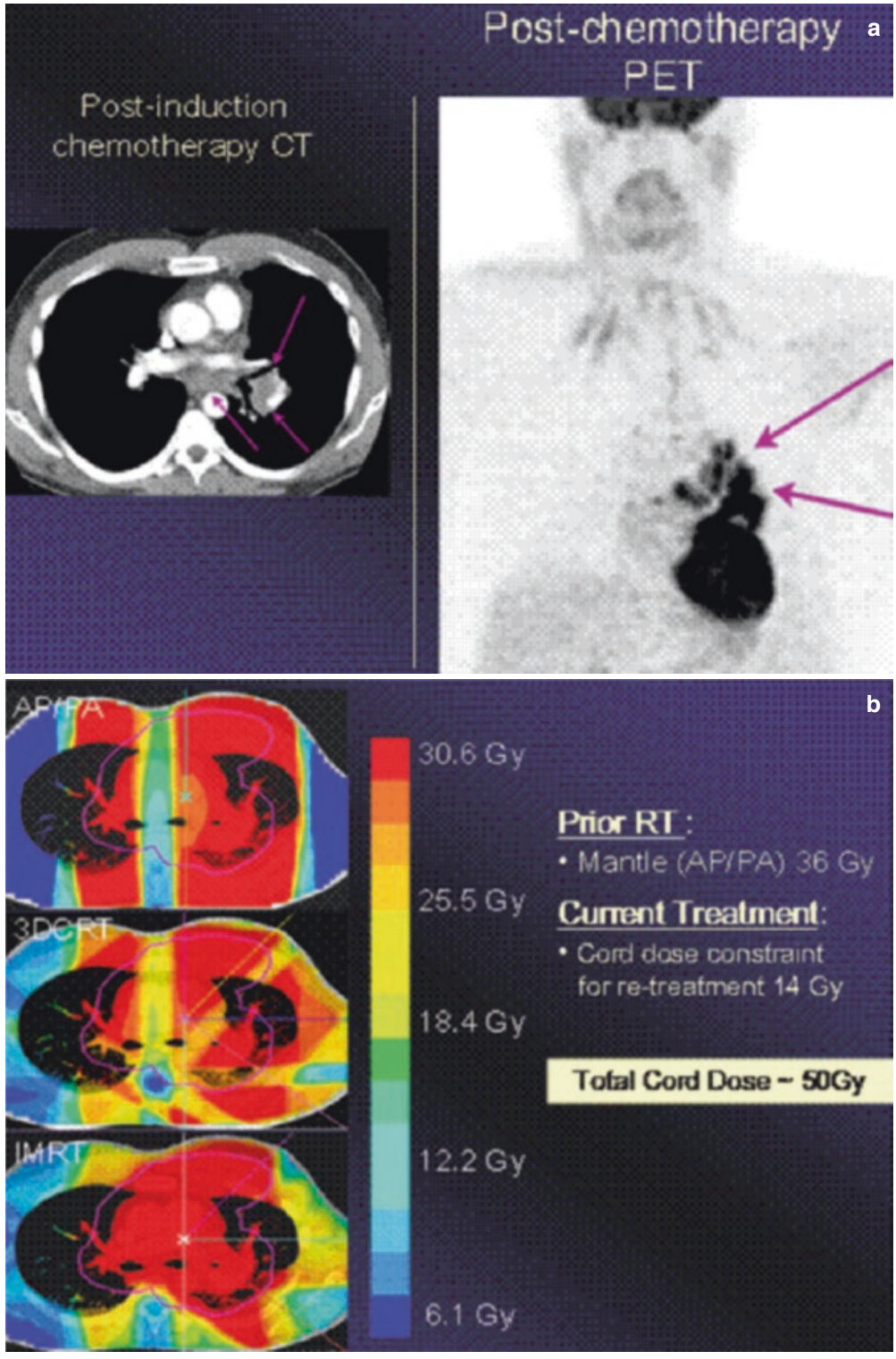
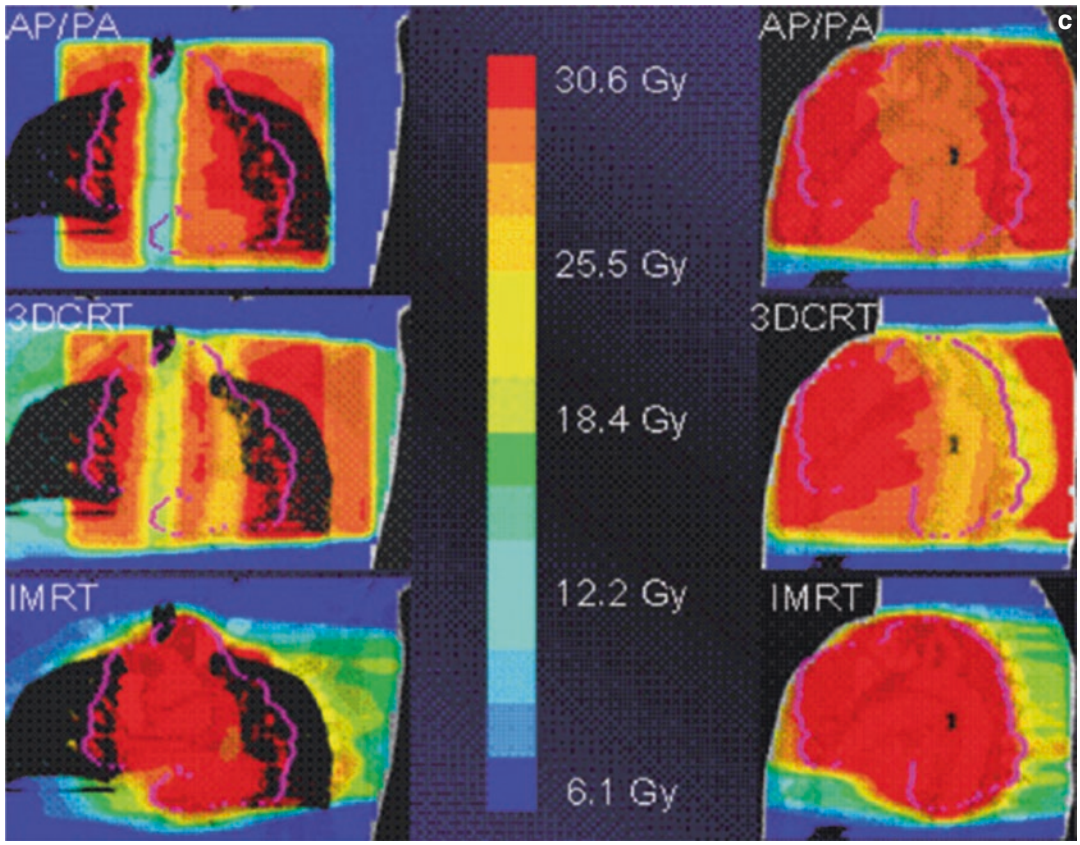


Fig. 9.4 (**a**) Use of IMRT for re-irradiation of a patient relapsing after ABVD and mantle-field irradiation to 36 Gy. (**b**, **c**) Treatment planning options for re-irradiation. *AP/PA* opposed anterior and posterior fields, *3DCRT* three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy



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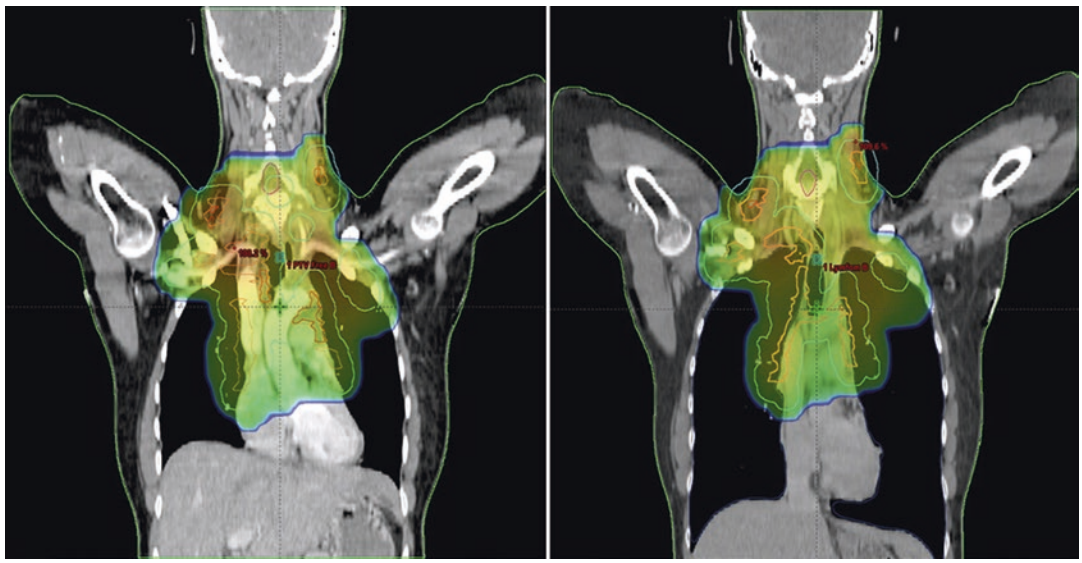

Fig. 9.5 An example case in which the use of DIBH increases total lung volume and pulls the heart caudally, thus decreasing dose to lung and heart without compromising coverage (Courtesy of Lena Specht, MD PhD, Rigshospitalet, University of Copenhagen, Denmark)

9.7 Proton Therapy

Another technical advance is the use of particle therapy (protons). Protons have the advantage of a more defined depth of penetration than photons, which eliminates the "exit dose" of photons. Proton therapy may be helpful in the mediastinum, in select cases where significant sparing of OARs including the heart, lungs, and esophagus cannot be achieved with IMRT [56]. In a review article of several dosimetric studies comparing highly conformal photon techniques with proton therapy, on average proton therapy reduced the mean heart dose by 2.24 Gy, breast by 2.45 Gy, lung by 3.28 Gy, thyroid by 2.09 Gy, and mean body dose by about 40% [76]. Patients with lower mediastinal disease may benefit more from proton therapy, due to the potential gains in reducing the radiation dose to the heart as described in the ILROG guidelines [94]. The ILROG guidelines also discuss in detail both the advantages and disadvantages of proton therapy for lymphoma and identify parameters that can help clinicians better select the appropriate modality.

While proton therapy planning and deliver is more complex than photon-based treatments, multicenter clinical outcomes have demonstrated similar disease control rates with that of IMRT or 3DCRT [95]. Furthermore, risks of pneumonitis have been extremely low [96], and there can be improved cardiac sparing [97]. Proton therapy may also be helpful in other situations including relapsed and refractory patients that require higher doses of radiation, when the disease involves the axilla, due to the ability to spare the breasts with posterior fields, and in pediatric HL, where the risk of second cancers is highest. Fig. 9.6 shows representative colorwash dose distributions for the same patient across different radiation treatment approaches.

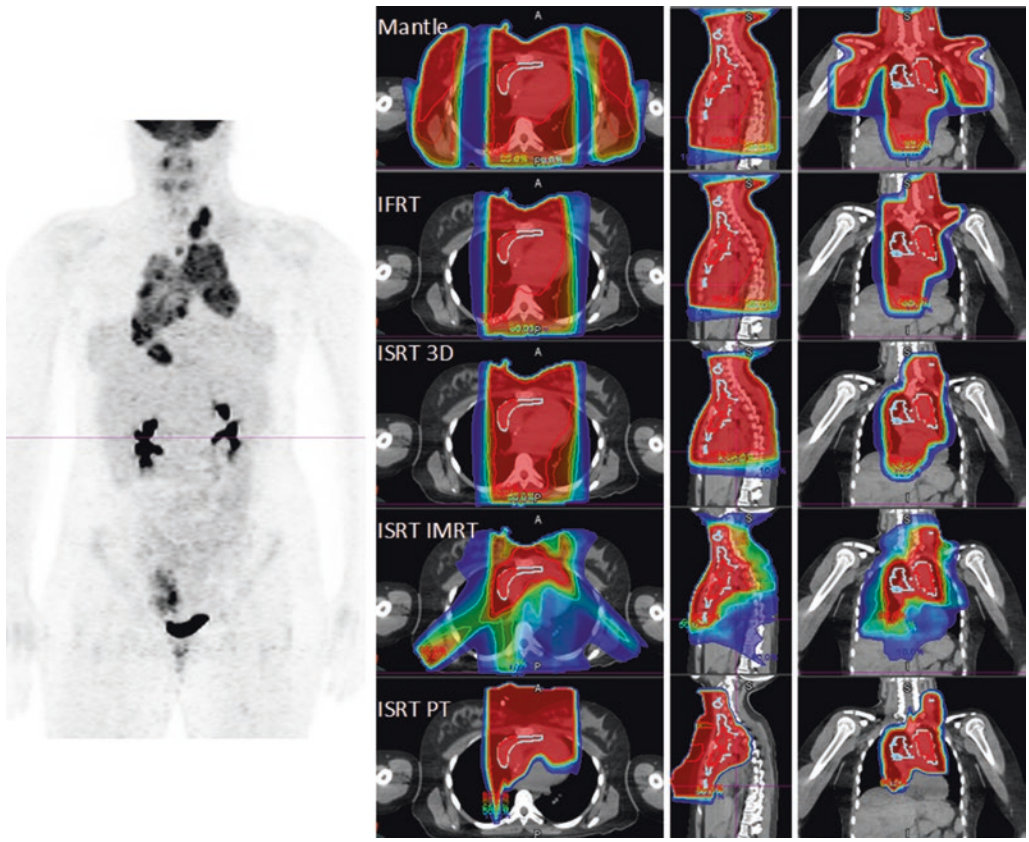

Fig. 9.6 A sample case of an 18-year-old woman with stage II HL at diagnosis with representative plans using various treatment modalities including mantle field, IFRT, ISRT using 3DCRT (ISRT 3D), ISRT using IMRT (ISRT IMRT), and ISRT using proton therapy (ISRT PT) (Courtesy of Brad Hoppe, MD MPH, University of Florida, United States of America)

9.8 Common Side Effects and Supportive Care During Radiation Therapy

The side effects of RT depend on the irradiated volume, dose administered, and technique employed. They are also influenced by the extent and type of prior chemotherapy, if any, and by the patient's age, habits, and presence of intercurrent disease. Most of the information that we use today to estimate risk of RT is derived from strategies that used radiation alone, with larger treatment volumes and higher doses. As noted previously, field sizes have been reduced and doses decreased, and other technological advances have all drastically reduced the radiation exposure to the OARs. It is thus misleading to inform patients of risks of RT using information from RT of the past as this is no longer practiced.

It is critical to remember that most of the data of long-term complications associated with RT and particularly second solid tumors and coronary heart disease were reported from databases of patients with HL treated more than 25 years ago. It is also important to note that we have very limited long-term follow-up data on patients with HL who were treated with chemotherapy alone.

9.8.1 Common Acute Side Effects

Radiation, in general, may cause fatigue, and areas of the irradiated skin may develop mild sun exposure-like dermatitis. The acute side effects of irradiating the full neck and portions of the mouth include dryness, change in taste, and pharyngitis. Patients who are treated to the neck and mediastinum may also develop mild dysphagia and esophagitis, which is self-limited. With the doses and techniques of irradiation currently employed in HL, all of these side effects are usually mild and transient. The main potential side effects of subdiaphragmatic irradiation are loss of appetite, nausea, and increased bowel frequency. Again, these reactions are usually mild and can be minimized with standard antiemetic medications.

9.8.2 Uncommon Early Side Effects

Lhermitte sign: Less than 3% of patients who have treatment that includes long lengths of the spinal cord may note an electric shock sensation radiating down the backs of both legs when the head is flexed (Lhermitte sign) 6 weeks to 3 months after mantle-field RT. Possibly secondary to transient demyelination of the spinal cord, Lhermitte sign resolves spontaneously after a few months and is not associated with late or permanent spinal cord damage. The risk is likely increased in the presence of prior neurotoxic chemotherapy such as vincristine or vinblastine.

Pneumonitis and pericarditis: During the same period, radiation pneumonitis and/or acute pericarditis may occur in <3% of patients; these side effects occur more often in those who have extensive mediastinal disease. Both inflammatory processes have become rare with modern radiation techniques.

The consideration and discussion of potential late side effects and complications of both RT and chemotherapy are of prime importance. A more complete discussion is detailed in Chap. 20.

9.8.3 Supportive Care During Treatment

It is important to prepare the patient for the potential side effects of RT, and in addition to physician-led discussion, many organizations and cancer centers also provide written patient information regarding RT for lymphomas. Since some level of xerostomia may be associated with RT that involves the upper neck and/or lower mandible and mouth, attention to dental care is advised. If dryness is a concern, it is advised to arrange for a consultation with a dental expert for overall dental evaluation and consideration of mouth guards (from scatter) and/or supplemental fluoride treatment during and after RT.

Soreness of the throat and mild-to-moderate difficulty of swallowing solid and dry food may also occur during neck irradiation, with onset at a

dose of approximately 20 Gy. These side effects are almost always mild, self-limited, and subside shortly after completion of RT. Skin care with hydrating lotion and sunscreen is advised for all patients undergoing RT. Temporary hair loss is expected in irradiated areas, and recovery is generally observed after several months.

9.8.4 Follow-Up After Treatment

We normally recommend a first post-RT follow-up visit 6 weeks after the end of treatment and obtain post-RT baseline blood count, standard biochemistry tests, as well as TSH levels (if there was neck irradiation) and lipid profile (if applicable) at that visit. Follow-up imaging studies normally commence 3 months after completion of treatment. Patients treated with radiation therapy alone for NLPHL should have a posttreatment PET scan to confirm a complete response. Other follow-up studies are included in the NCCN guidelines for HL [2].

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