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Tailored strategies for radiation therapy in classical Hodgkin's lymphoma

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Abstract

Radiotherapeutic advances have contributed to the evolution of Hodgkin's lymphoma (HL) treatment paradigms. A reduction in radiation therapy (RT) field size and dose has the potential to significantly impact the therapeutic ratio by diminishing late toxicities while maintaining curability. Substantial progress in risk stratification has contributed to the development of tailored RT strategies which address both field design as well as dose. Technologic improvements have also enhanced the ability to adapt the RT technique to the individual patient. The refinement of the RT approach and its incorporation into current combined modality strategies in adult classical HL is the subject of ongoing investigation and is critically reviewed.

Keywords

Hodgkin's lymphoma; Involved-field radiation therapy; Late effects; Radiation

1. Introduction

Before the development of effective chemotherapy for Hodgkin's lymphoma (HL) such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), the dependence on radiation therapy (RT) for cure resulted in large treatment fields and delivery of high radiation doses to expansive areas of normal tissue. Although this approach was potentially curative, the incidence of late effects was substantial, contributing

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to mortality rates that were significantly elevated compared to the normal population [1]. The core late problems with RT, namely second solid malignancies and cardiovascular disease, can be separated from those of chemotherapy, which include hematologic malignancies, pulmonary problems and heart failure related respectively to alkylating agents, bleomycin, and anthracyclines.

The availability of effective chemotherapy has markedly changed the approach to RT for classical HL [2-5]. Progress in staging and response assessment through metabolic imaging [6,7] also has the potential to substantially impact the RT approach [8]. RT design and delivery differ drastically from earlier approaches, with the use of smaller radiation fields, lower radiation doses, and superior technology for planning and delivery [9,10]. Improved diagnostic imaging has allowed better identification of the appropriate targets, thus increasing the precision of RT and reducing radiation to surrounding normal tissue.

Because most patients with classical HL are now cured, how to minimize treatment toxicity without compromising efficacy and how to select patients for an intensified or deescalated approach are leading areas of research. Coupled with the reduction in radiation field size have been efforts to reduce the radiation dose, if not eliminate RT altogether. Recent developments in the integration of radiation into HL treatment paradigms are herein reviewed. The evolutions in radiation technique, field, and dose and in the risk-adapted selection of patients for RT are considered, with a focus on state-of-the art management of classical HL in adults.

2. Radiation treatment field design

Following chemotherapy, RT is employed as consolidation in early stage HL, more variably in advanced-stage bulky HL, or after incomplete response. Infrequently, RT is utilized as a single modality in very carefully selected cases of classical HL, such as a late, isolated, low-volume relapse after treatment with chemotherapy alone. RT is also utilized in the setting of stem cell transplantation for relapsed or progressive lymphoma, particularly as consolidation for residual bulky disease or for disease that had relapsed locally prior to the transplant.

2.1. Standard field sizes

The prudent design of RT fields is contingent upon the precise definition of involved disease. Proper delineation of RT fields is uniquely dependent on the anatomy of the region of interest and its lymph node distribution, the potential for microscopic disease extension into both the involved and regional areas, as well as the normal structures at risk for toxicity. The initial stage contributes to field design. For example, field design for early-stage disease in adults generally encompasses all initially involved sites, whereas in advanced disease RT is directed to residual disease after chemotherapy or bulky sites. As discussed in Section 4, the integration of metabolic imaging into standard staging has enhanced the ability to define disease extent for RT planning.

Extended-field radiation treatment (EFRT), which delivers RT to not only involved but also uninvolved lymph node regions, is now rarely used for HL. The effectiveness of chemotherapy to address microscopic disease has permitted reduction in the radiation

delivered both in terms of field size and dose, generally without compromise of outcome[5,11]. Involved-field radiation therapy (IFRT), in which the RT field is limited to the clinically involved lymph node group(s), is now considered standard-of-care in the context of combined-modality therapy [12]. The pre-chemotherapy extent of disease is used for the design of RT fields but takes into account the anatomic displacement of normal structures which may return to their original position following the shrinkage of lymph nodes after chemotherapy. In the mediastinum, the post-chemotherapy transverse extent of disease is used to delineate the RT field. In this case, enlarged mediastinal lymph nodes may become smaller allowing normal lung tissue to re-expand in the medial direction. In an effort to spare normal tissue, the post-chemotherapy volume is used to dictate the transverse extent of the RT field [12].

IFRT is the standard in the context of combined-modality treatment regardless of risk category. For instance, in the EORTC-GELA H8U trial randomizing patients with unfavorable HL to 4 cycles of MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine) plus 36–40 Gray (Gy) IFRT or 36–40 Gy subtotal nodal irradiation (STNI), no difference was detected with the reduced field size [5]. In the German Hodgkin's Study Group (GHSG) HD8 study, patients with unfavorable features were randomized between 2 cycles of COPP/ABVD (cyclophosphamide, vincristine, procarbazine, prednisone, ABVD) and 30 Gy EFRT (+10 Gy for bulky disease) versus 2 cycles of COPP/ABVD and 30 Gy IFRT (+10 Gy for bulky disease), without significant differences in outcome [13].

2.2. Involved-node radiation therapy

Patients with early stage HL treated with chemotherapy alone have an elevated risk for relapse in the initially involved lymph nodes [14,15]. Given the desire to reduce treatment field size, the EORTC-GELA recently introduced the concept of involved node radiation (INRT) which includes treatment of only the initially involved macroscopic disease [16]. For INRT, it is essential to use all available clinical information, including pre- and post-chemotherapy imaging with CT and ¹⁸F-FDG PET scan to define the treatment field according to the original extent of disease. Per EORTC-GELA guidelines, the clinical target volume should include only the site of originally involved lymph nodes identified prior to chemotherapy [16]. Controversy exists regarding the optimal margins in INRT field design, with groups using different definitions[17–19]. The appropriate design of INRT fields is an open question, with U.S. and European protocols having variable designations of the radiation field that INRT should encompass [16,18,19]. Therefore, it is important to delineate the INRT field according to the specific protocol being followed.

To utilize INRT, the appropriate imaging studies and other relevant staging studies must be performed prior to chemotherapy initiation. In a study of early stage HL, for instance, 36% of patients had suspicious lymph nodes on ¹⁸F-FDG PET that were occult on CT [8]. Therefore, when using an INRT approach, pre-chemotherapy evaluation with PET is required to help delineate the extent of disease [8].

Studies demonstrating the feasibility of INRT are still limited with short follow-up and small numbers, although early clinical data are emerging. Paumier et al. recently reported on 50

HL patients who received INRT per EORTC-GELA guidelines [20]. Nearly all had early stage disease and received 6 cycles of ABVD. With a median follow-up of 53 months, 4 relapses (2 in-field) were identified. The EORTC-GELA is now investigating INRT in early favorable and early unfavorable HL [21].

Providing further insight into the potential role for reduced treatment field size, Campbell et al. analyzed the outcomes of 325 patients with limited-stage HL treated with combined-modality therapy between 1989 and 2005 [18]. EFRT was used until 2006 (39% of patients); IFRT was used between 1996 and 2001 (30% of patients); and treatment fields which were described as INRT were used from 2001 onward (31% of patients). The INRT fields were designed using a margin of 5 cm and delivered using conventional treatment planning. Ninety-five percent of patients received two chemotherapy cycles. After a median follow-up of 80 months, twelve relapses were identified: four after EFRT (3%), five after IFRT (5%), and three after INRT (3%) ($P = 0.9$) [18]. Although no marginal recurrences were identified after INRT, the margins for INRT used in this study were tantamount to a reduced IFRT field. INRT as defined by the EORTC-GELA and GHSG uses significantly smaller margins [16,19]. INRT as defined by the EORTC-GELA encompasses the initially involved volume with a margin for uncertainty. Conformal radiotherapy is also routinely used in the application of INRT as defined by the EORTC-GELA.

Clinical outcome data with the application of smaller margins are not yet mature, although we believe that the initial clinical results appear promising. Successful incorporation of INRT suggests that RT field size may indeed be reduced without compromising loco-regional control although the longer-term efficacy remains to be defined. In addition, one must also consider that a “negative” PET scan, whether at baseline or after chemotherapy completion, does not necessarily signify absence of disease [22]. The limit of resolution of ^{18}F -FDG PET is a tumor deposit of approximately 0.5–1 cm which represents an estimated 10^8 – 10^9 cells [22], meaning that millions of viable cancer cells may escape radiographic detection and hence, escape being radiated with an INRT technique.

Because the relative efficacy of INRT on long-term tumor control is largely unknown, the goal of reducing the toxicities of RT must be balanced against the resultant potential loss of efficacy. This is of particular relevance to a population of patients who are largely curable with standard therapy. Until further clinical data are obtained, INRT is best performed on a protocol where the radiation field definition is standardized in the context of the risk category and chemotherapy regimen.

3. Radiation dose

Variables such as tumor size, disease extent, systemic therapy, clinical risk factors, and technical factors contribute to the prescription radiation dose. Recently, in a landmark, practice-changing study, GHSG HD10 investigators reported equivalent 5-year local control and overall survival rates for patients with stage IA or IIA favorable HL receiving 2 or 4 cycles of ABVD with 20 Gy or 30 Gy IFRT [23] (Fig. 1). The GHSG HD10 criteria for early stage, “favorable” HL are specifically delineated (involving the size of a mediastinal mass, number of nodal sites, presence of extranodal disease, and erythrocyte sedimentation

rate). The criteria differ slightly from EORTC and NCIC (National Cancer Institute of Canada) definitions of early favorable and early unfavorable disease [24]. It is important that patients receiving reduced-intensity treatment per the HD10 paradigm meet all of the study-specific criteria for risk categorization.

The optimal dose for bulky or otherwise unfavorable disease remains unclear, and a dose threshold has been more difficult to define. These tumors are often treated with combined-modality therapy incorporating higher doses of IFRT (30–40 Gy) depending on response and tumor bulk. Recent trials have evaluated whether the radiation dose can be safely reduced in subgroups of patients with unfavorable HL. In the GHSG HD11 trial, for instance, patients with early-stage, unfavorable HL were randomized to ABVD $\times$ 4 cycles or baseline BEACOPP $\times$ 4 cycles, followed by 20 Gy or 30 Gy IFRT. Inferiority of 20 Gy as compared to 30 Gy could not be excluded when combined with ABVD, whereas 20 Gy was not inferior when combined with BEACOPP [25].

Ongoing studies are also evaluating how to integrate PET to guide therapy in the era of treatment de-escalation. In the GHSG HD17 trial [26], patients with early unfavorable HL will receive escalated BEACOPP $\times$ 2 cycles and ABVD $\times$ 2 cycles followed by randomization based on the end-of-chemotherapy PET response: IFRT or INRT if PET positive and IFRT or observation if PET negative. As discussed in Section 6.2, a major research focus in HL is how to utilize not only the post-chemotherapy response, but the early response on interim PET to guide the radiation decision.

4. Radiation planning and advanced radiation treatment techniques

Further tailoring of the radiation field for HL has been facilitated by metabolic imaging, as well as by advances in conformal therapy.

4.1. Metabolic imaging to define the radiation field

There has been substantial technological progress with conformal RT techniques such as intensity-modulated radiotherapy (IMRT) and stereotactic approaches. IMRT allows the radiation dose to tightly conform to a three-dimensional tumor shape by modulating the intensity of multiple radiation beams to achieve the desired dose distribution. Three-dimensional tumor volumes are routinely developed using CT scan treatment planning. While CT provides anatomic definition, it has limitations. Small volume nodal disease, which can significantly impact RT field design, can be missed. Following chemotherapy, residual masses which may represent scar tissue can also be difficult to interpret without functional imaging. ^{18}F -FDG PET provides complementary information and can aid in delineating anatomic areas at risk. Therefore, PET has been integrated into RT planning and contributes functional information to the design of the tumor volume. Although the CT abnormality is traditionally used to define the RT volume even if PET negative, the addition of PET can potentially alter the volume should additional suspected sites be identified [9,27].

Multiple studies have now demonstrated that PET/CT treatment planning can affect tumor-volume definition and management in lymphoma patients [8,9,27–30]. For example, in a

study of 30 patients with early stage HL who received a staging PET/CT and chemoradiation, integration of PET information into IFRT planning would have increased the treated volume in seven patients and decreased it in two [27]. Girinsky et al. also co-registered pretreatment CT and PET scans performed in the treatment position with a post-chemotherapy CT simulation planning scan; PET helped to delineate lymph nodes that were otherwise undetectable on CT scan in 36% of patients [8]. In a prospective multi-center study of 137 early stage HL patients, RT was cancelled in 4.8% and the treatment plan was modified in 13% based on information from pre-radiotherapy PET. Overall, the concordance in treatment strategy with or without pre-radiotherapy PET was 82% [30]. Because PET/CT for radiation planning may at times result in an increase in treatment volume, PET for fusion in RT planning must be cautiously applied as concerns for late effects are paramount.

4.2. Conformal therapy

Conformal radiation allows delivery of a more targeted dose using three-dimensional imaging information and beam arrangements. Three-dimensional conformal radiation (3D-CRT) and IMRT are types of conformal radiation and are used to deliver tightly conformal doses to the tumor volume [31]. Steep dose gradients are achieved to spare normal structures especially for patients at particular risk for treatment complications. For example, conformal therapy delivered to an anterior mediastinal mass may reduce the dose of radiation to the spine and much of the heart and lung tissue located behind the mass [31-33,9,34-36]. The role of IMRT has been limited in HL due to the low doses required, the need to identify target lymph nodes with certainty, and limitations in the dosimetric advantage of IMRT when treating a large field. IMRT may result in a dosimetric advantage in select HL cases, particularly when applying the IFRT or INRT approach. A significant reduction in the mean dose delivered to the coronary arteries, heart, and lungs has been demonstrated by using IMRT in combination with breath-hold technique [33]. The dose reduction to normal structures was most significant for treatment of masses in the upper mediastinum.

IMRT may be best applied in HL patients at potentially higher risk for complications following RT. These patients may include those who are referred for IFRT before or after stem cell transplantation, particularly if they have received prior radiation or have a higher risk for radiation pneumonitis. In a patient who has received prior radiation, IMRT may allow reirradiation of relapsed or refractory disease given the proximity of previously irradiated normal structures. In selected patients with bulky mediastinal disease or bleomycin toxicity, IMRT may also have the benefit of sparing the heart and lung [31]. Conformal RT has particular utility in these clinical scenarios; however one must consider the potential tradeoffs when a lower dose is delivered to a larger volume, as is often the case with IMRT as compared to conventional RT [32,36].

Interest in proton radiotherapy in HL, particularly for mediastinal masses, has also been growing [37]. In a dosimetric comparison of conventional radiation, IMRT, and three-dimensional proton RT for patients with disease in the upper mediastinum but not in or below the hila, proton RT significantly reduced the dose to the breast, lung, and total body [38]. Proton therapy for HL is still under investigation. Ultimately, each clinical scenario

should be analyzed independently to determine the optimal treatment approach given the patient's tumor volume, normal structures at risk, age and co-morbidities.

5. Reducing complications of radiation treatment

A brief overview of late treatment effects is presented as it may relate to HL patients. The toxicities of RT are influenced by the irradiated volume, dose administered, and technique, as well as by the extent and type of prior chemotherapy, patient age, and end-organ function. Much of the data used to estimate risks of RT are derived from studies in which radiation alone was used and delivered with extended fields to higher dose. As discussed, field size, dose, and technology has significantly changed. Therefore, the nature of late effects is unknown in the setting of modern radiation delivery. Some data (although not all) suggest a reduction in toxicities with more modern radiotherapy practices [39–41]. Thus, the risks and benefits of RT must be considered in the context of newer radiation techniques.

Mediastinal RT is common for HL and may cause acute and late pulmonary complications. Bleomycin can increase the risk of acute pulmonary pneumonitis and late pulmonary fibrosis in patients receiving pulmonary RT [42–44]. With modern combined-modality therapy, asymptomatic pulmonary compromise can be seen after completion of therapy that may improve or resolve over time [45]. An increased risk of cardiovascular complications has been reported in recipients of mediastinal RT [46–50]. Cardiac dysfunction may also occur after anthracyclines, particularly after doxorubicin [51–53]. The dose to the heart can now be calculated using advanced techniques, and can be constrained using conformal techniques in order to minimize the risk of cardiac injury. However, the impact of low-dose RT to the heart may not become apparent until larger cohorts of survivors treated with low-dose, combined-modality regimens have longer follow-up.

Long-term survivors of HL are at increased risk of secondary solid tumors and non-Hodgkin's lymphoma, with a general latency period of 10 or more years following treatment [54–58]. There is evidence to suggest that a dose–response relationship between RT and the risk of secondary malignancies exists [60]. Multiple studies have now suggested that lower RT dose should translate into a reduction in late effects when used judiciously [39,40,59–61]. It has also been demonstrated that a reduction in the volume of normal tissue treated can translate into a reduction in late effects [59]. This is particularly important since the majority of late effects data is derived from a period of time when EFRT alone was the primary curative treatment for HL. EFRT field design encompassed all lymph node regions including uninvolved sites, and thus included substantial volumes of normal tissue which were in turn exposed to full-dose RT. For example, breast tissue exposure was most significant when the axillae were irradiated in a typical mantle field as opposed to the mediastinal and hilar region. Prophylactic axillary radiation is no longer routinely performed and therefore, the volume of breast tissue exposed using IFRT or INRT is significantly reduced (Figs. 2 and 3) [62]. With newer CT-based planning, normal structures can be contoured as avoidance structures and thereby shielded. Thus a combination of reduced volumes and modern radiotherapy techniques suggests a long-term reduction in late effects is feasible. This is particularly important when developing chemoradiation paradigms meant to maximize cure while avoiding late toxicities.

6. Whether and in which patients to radiate

Given the concerns about the toxicities of RT, the necessity of RT in limited-stage as well as advanced HL remains a matter of debate. Expert opinions in this regard can be sharply divided, especially in the approach to early stage, nonbulky disease [63,64].

6.1. Combined-modality therapy versus chemotherapy alone

We believe that full-course chemotherapy alone has become an acceptable alternative to the combined-modality treatment of limited-stage HL. In prospective studies of modern chemotherapy versus chemoradiation, a statistically significant overall survival disadvantage with RT omission has not been convincingly demonstrated [15,65,66]. A randomized study purporting a survival benefit to RT [67] after 6 cycles of ABVD had numerous limitations, including short-term follow-up and heterogeneity in stage (45% stage III/IV), disease bulk (15% bulky), mediastinal involvement (72% uninvolved), age (46% under age 15 years) and histology (11% lymphocyte-predominant and mostly mixed cellularity).

The evidence leaves little doubt that omission of RT may be associated with a greater risk of relapse [15,68,69]. The reader is referred to a recent meta-analysis in this regard, which included unconfounded trials of combined-modality therapy versus chemotherapy alone in early stage HL [69]. Outcomes with RT omission are partly contingent upon the adequacy of the preceding chemotherapy. In the EORTC-GELA H9-F study for early favorable HL investigating reduction or omission of IFRT following complete remission to EBVP (epirubicin, bleomycin, vinblastine, prednisone), no differences were seen between 20 and 36 Gy radiation on interim analysis [68] (Table 1). However, the no-RT arm was closed due to excess relapse [68]. The 4-year failure-free survival was only 69% with EBVP alone despite patients having achieved complete remission, suggesting that the excess treatment failures may have been due to ineffective chemotherapy. Because escalated BEACOPP can be more effective (albeit more toxic) than ABVD [70,71], the failure-free survival in limited-stage patients treated with escalated BEACOPP without RT may prove to be greater than in patients treated with ABVD alone. This, however, remains to be seen.

Supporting the omission of RT in selected cases is the randomized study conducted at the Memorial Sloan-Kettering [65], comparing ABVD $\times$ 6 cycles followed by RT versus ABVD $\times$ 6 alone for nonbulky, mostly limited-stage disease (Table 1). No significant difference in 5-year freedom-from-progression (FFP) was observed. However, the study was only powered to detect a 20% difference. Although there was a tendency toward better 5-year overall survival in the RT arm, longer follow-up would be required to capture the late effects of RT coupled with their potentially adverse impact on survival.

Also supporting consideration of omission of RT is the NCIC-ECOG HD6 trial [15,72] (Table 1), where patients with nonbulky, stage IA–IIA HL were randomized to 4 to 6 cycles of ABVD alone, versus to a strategy that involved RT (typically ABVD $\times$ 2 followed by STNI). With 11-year median follow-up, there was a tendency toward improved 12-year freedom from progression in the RT arm ($P = 0.05$), but a statistically significantly inferior overall survival as compared to the no-RT arm [72]. The subgroup of patients with poorer-risk disease had significantly improved disease control but inferior overall survival

compared to patients treated with chemotherapy alone, while patients with favorable risk features had no difference in disease control or overall survival. Inferior overall survival in the RT arm was attributed to deaths from causes other than lymphoma or early toxicity. These findings from the HD6 study exemplify the need for extended follow-up when assessing the relative impact of chemotherapy and chemoradiation. However, it is crucial to note that the HD6 trial utilized much more extensive RT than would be delivered today, such that the outcomes of chemotherapy versus chemoradiation with modern, smaller radiation field sizes and doses remain to be determined.

Omission of radiation did not adversely affect cure rates in the majority of patients on the HD6 trial. In patients treated with ABVD alone, the 5-year FFP was significantly better in those who had achieved CR or unconfirmed CR on CT after 2 cycles of ABVD (95% at 5 years, versus 81% in those who did not; $P = 0.007$) [15]. This importantly suggests that the subset of patients who do not achieve an early chemotherapeutic response may stand to benefit the most from consolidative RT.

Of note, patients with bulky disease were excluded from these randomized studies of chemotherapy alone. Although combined-modality therapy remains the standard for patients with bulky, limited-stage HL, the role and necessity of modern RT in this subgroup has not been adequately evaluated. In a randomized study of bulky, early stage HL, which included an arm of ABVD for 6 cycles and a combined-modality arm involving ABVD with mantle-field RT, a significant tumor-control and overall survival advantage to combined-modality therapy was seen on mature follow-up [73]. In a small randomized study of consolidative RT versus observation in patients with bulky (> 5 cm) HL and post-chemotherapy, PET-negative residual masses, an event-free survival advantage to RT was reported on unadjusted analysis [74]; however, this study had numerous limitations including short follow-up, nonstandard chemotherapy, mixture of stages, and no reporting of overall survival. One must consider long-term toxicities of combined modality therapy as it relates to the potential for radiation to enhance long-term disease control and survival. We believe that factors such as age, female gender, family history of malignancy such as breast cancer, and smoking history should be considered when having a balanced discussion of the risks versus benefits of RT in such scenarios.

In advanced-stage HL, the role of RT is less defined [75–78]. A comprehensive review of this topic is beyond the scope of this article. However, studies have variably supported and refuted the integration of radiation into the treatment of advanced HL. For example, a recently reported retrospective study suggested both a progression-free and overall survival advantage to consolidative RT for advanced HL, despite the presence of more adverse prognostic features in the radiated patients [78]. On the other hand, an older meta-analysis found that adding RT to chemotherapy was associated with improved tumor control, but similar overall survival presumably due to late toxicities, whereas the parallel design of RT replacing additional chemotherapy yielded similar tumor control but decreased overall survival [76]. Thus considerable variability remains in clinical practice as to whether RT is added to chemotherapy.

Wherever the role of RT is questioned, consultation with a radiation oncologist early in the treatment course is encouraged in order to have an informed discussion of risks versus benefits. Whether in limited or advanced HL, clear subsets of patients do benefit from the addition of RT. However, more accurate identification of such patients is needed. Whether interim ^{18}F -FDG PET can help to distinguish these subsets of patients is the focus of ongoing trials, as next discussed.

6.2. Midtreatment metabolic imaging to guide radiation therapy

As in non-Hodgkin's lymphoma, it has been repeatedly recognized that the results of ^{18}F -FDG PET, when performed after only 2 or 3 cycles of chemotherapy, are prognostically significant in classical HL whether in the frontline [79–87] or relapsed [88,89] setting. A negative midtreatment PET has consistently been associated with favorable outcomes. Outcomes of HL patients with a positive midtreatment PET, while generally worse, have been quite variable, likely due in part to the small number of PET positive patients represented in these series. Table 2 summarizes prospective studies of midtreatment PET in newly diagnosed HL, wherein treatment was not modified on the basis of the early PET result. Such information on the quality of the early chemotherapeutic response may help shape individually tailored, risk-adapted treatments[90–92]. The reader is referred to recent critical reviews on this topic [22,93].

Concurrent with efforts to tailor RT based on early metabolic imaging are efforts to reduce chemotherapeutic toxicity in adequately responding patients, while maintaining or escalating the intensity of chemotherapy in suboptimally responding patients [90–92]. Recently, clinical trials have used end-of-chemotherapy PET to guide whether and which sites to radiate. For example, PET performed after completion of BEACOPP has been used to restrict RT to residually FDG-avid masses, with encouraging outcomes in advanced HL [94,95]. In the HD18 trial for advanced HL, patients achieving negative PET after 2 cycles of escalated BEACOPP do not receive RT [96]. As shown in Table 3, other randomized multicenter trials are investigating the omission of RT in patients having a negative PET both after 2 cycles of ABVD and after chemotherapy completion[97,98].

The effectiveness of adding RT to sites of residual PET positive disease, however, is not fully defined. As reviewed elsewhere [22,93], tumors that are resistant to chemotherapy (potentially identified by a true-positive post-therapy PET) are commonly also resistant to radiation. Although the majority of early stage HL patients with positive post-chemotherapy PET scans achieve durable remissions after RT [99], the relative impact that RT has on these outcomes is unclear, in part because of the high cure rates that such patients have regardless. RT may be the appropriate salvage approach in some such instances, but we believe it should not be assumed to be the appropriate next step in all cases. An additional consideration is that potential toxicities of RT may compromise the safety of future treatments for relapsed disease, including hematopoietic stem cell transplantation. Thus a positive post-chemotherapy PET may alternatively identify patients who stand to benefit, or who do not stand to benefit, from the addition of RT.

In early HL, several large, randomized clinical trials are evaluating de-escalation and/or escalation of therapy based on PET performed after 2 or 3 cycles of first-line chemotherapy

(Table 3) [21,100,101]. A shared approach in these trials is the omission of RT in patients who are regarded as having a negative interim PET scan. Although this approach may be valid, caution is advised, as it is not yet clear whether the excellent cure rates already achievable in such patients will be maintained with de-escalation of therapy. Indeed in the H10 trial for patients with early favorable or unfavorable HL [21], the experimental arm in which patients with negative PET after ABVD $\times$ 2 receive 1 or 2 additional cycles of ABVD without RT was closed early due to excess treatment failure. RT has since been added to this arm following ABVD completion.

How to modify the RT plan in light of potentially prognostic information gained from interim PET scanning is not yet known. It must be kept in mind that the favorable outcome typically observed in HL patients with negative interim PET scans were achieved with unabridged therapy. Because the role of interim PET in guiding lymphoma treatment is still under investigation, treatment decisions on this basis are best made in the context of clinical trials. Furthermore, the limitations of PET scanning must be considered, including the risk of false positive and false negative results, the uncertainty as to what constitutes an adequate metabolic response, and issues with the reproducibility of the read [93]. Truncation of chemotherapy due to a “negative” cycle 2 PET cannot be supported outside a study, particularly if RT is also omitted on that basis.

7. Conclusions

There is continued interest in restricting RT delivered to patients with classical HL, while at the same time maintaining or improving upon the rate of cure. However, there are ongoing debates regarding the role and appropriate modality of RT, as well as the patient population in whom RT is indicated. Conclusions from various studies of similar patient populations have often varied. The appropriateness of RT, and if appropriate then which technique and dose, is far from an all-or-none.

Ongoing efforts to minimize treatment toxicities in patients with HL must be tempered by the possibility that the curability of the disease may suffer. More accurate risk-stratification is central to the development of successful, individually tailored regimens. Approaches to risk stratification should integrate pretreatment variables, such as disease site, extent and histology, with information about the quality of the chemotherapeutic response. In order to optimize cure rates while minimizing both acute and late toxicities, further study of the tailored integration of radiation into lymphoma treatment paradigms is of great importance.

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Fig. 1.

This is a 20 year old woman with stage IA HL who received 2 cycles of ABVD followed by 20 Gy involved field radiation (IFRT). (A) Pre-chemotherapy CT, axial view and (B) PET scan, coronal view, demonstrating unilateral neck involvement of HL; (C) Post-chemotherapy CT, axial view and (D) Post-chemotherapy PET, coronal view, demonstrating complete response. She then received IFRT to 20 Gy per GHSG HD10 with the involved field of the unilateral neck demonstrated in panel (E); the blue contour represents the involved site of disease and includes the lymph node remnants post-chemotherapy. The

potential reduction in treatment field size using INRT is depicted in panel (F); the pink contour represents the margin placed around the involved site of disease (blue) using the EORTC-GELA guidelines.

Fig. 2.

A comparison of field size for a (A) mantle field compared to a (B) mediastinal involved field RT and (C) INRT for a mediastinal mass demonstrating a reduction in volume of tissue irradiated. The pink contour represents the involved site of disease. The purple contour noted in the INRT panel represents the margin placed around the involved site of disease that is the treated volume.

Fig. 3.

(A) Digitally reconstructed radiographs showing typical RT fields for historic mantle RT, contemporary involved-field RT (IFRT) and involved-node RT (INRT) for a patient with stage I disease involving the upper mediastinum. The post-chemotherapy volume of initially involved mediastinal nodes is shown in green. Hila are shown in blue and violet. (B) Reduction in dose to breast and lung for this female patient shown in (A). For each volume, the prescribed dose to the clinical target volume is the same. The resulting mean dose to breast and lung tissue with mantle RT is a set value = 1. The proportional reduction in normal tissue dose occurs as a result of the reduction in treated volume with IFRT and INRT.

Figure adapted with permission from Hodgson et al. [62], Fig. 1, page 236.

Table 1

Selected studies of chemotherapy versus chemoradiation for early Hodgkin's lymphoma.

Study	Cohort	Evaluable patients	Chemotherapy	Radiation	FFP	FFS or EFS	OS
NCIC-ECOG HD6 [15,72]	Nonbulky IA–IIA	203	None (if very low risk) or ABVD × 2	STNI	93% (5 y) ^a 92% (12 y) ^c	88% (5 y) ^b 80% (12 y)	94% (5 y) 87% (12 y) ^a
		196	ABVD × 4–6	None	87% (5 y) 87% (12 y)	86% (5 y) 85% (12 y)	96% (5 y) 94% (12 y)
EORTC-GELA H9-F, interim analysis [68]	Early favorable I–II, with CR only	239	EBVP × 6	IRFT 36 Gy	–	88% (4 y) ^a	98% (4 y)
		209	EBVP × 6	IFRT 20 Gy	–	85% ^a	100%
		130	EBVP × 6	None	–	69%	98%
Straus et al. [65]	Nonbulky I–II, or nonbulky IIIA (13%)	76	ABVD × 6	IFRT or modified EFRT	86% (5 y) ^d	–	97% (5 y) ^e
		76	ABVD × 6	None	81%	–	90%

Table reproduced from Kasamon YL, chapter 18: Hodgkin's Lymphoma, Table 18-3, page 241, in Ettinger DS, Donehower RC, Olsen M, Schwartz RN (eds): Current Cancer Therapeutics, 5th edition. New York, Current Medicine Group LLC, 2009, with kind permission from Springer Science and Business Media. ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CR, complete response; EBVP, epirubicin, bleomycin, vinblastine, prednisone; EFRT, extended-field radiation therapy; EFS, event-free survival; EORTC-GELA, European Organization for Research and Treatment of Cancer-Grouped'Etudes des Lymphomes de l'Adulte; FFP, freedom from progression; FFS, failure-free survival; Gy, Gray; IFRT, involved-field radiation therapy; NCIC-ECOG, National Cancer Institute of Canada-Eastern Cooperative Oncology Group; OS, overall survival; STNI, subtotal nodal irradiation.

^a Statistically significant compared with no-radiation arm.

^b $P = 0.06$.

^c $P = 0.05$.

^d $P = 0.61$. Powered to detect a 20% difference.

^e $P = 0.08$.

Table 2
Prospective studies of 18F-FDG-PET during first-line chemotherapy for Hodgkin's lymphoma.

Study	No.	Stage	Chemo, +/- RT	Cycles before PET	No. PET+ (%)	PPV	NPV	EFS, PET+	EFS, PET-	Median follow-up
Friedberg et al. [79]	22	I-IV; 28% III-IV	Mostly ABVD	3	5 (23%)	80%	94%	-	-	24 mo
Gallamini et al. [81]	108	IIA with RF. IIB-IV; 46% III-IV	Mostly ABVD	2	20 (19%)	90%	91%	6% (2 y)	96% (2 y)	20 mo (mean)
Hutchings et al. [82]	77	I-IV; 36% III-IV	Mostly ABVD	2	16 (21%) ^a	69%	95%	0% (2 y)	96% (2 y)	23 mo
	64			4	13 (20%)	85%	96%	19% (2 y)	96% (2 y)	23 mo
Zinzani et al. [83]	40	IIB-IV; 48% III-IV	ABVD	2	8 (20%) ^b	100%	100%	-	-	18 mo
	40			4	7 (18%) ^b	100%	100%	-	-	18 mo
Gallamini et al. [80]	260 ^c	IIA with RF. IIB-IV; 47% III-IV	Mostly ABVD	2	50 (19%) ^a	86%	95%	13% (2 y)	95% (2 y)	26 mo
Furth et al. [84]	40	I-IV; 48% III-IV	OEPA ^d	2	14 (35%)	14%	100%	86% (4 y)	100% (4 y)	46 mo
Cerci et al. [85]	104	I-IV; 58% III-IV	ABVD ^e	2	30 (29%) ^c	53%	92%	53% (3 y)	91% (3 y)	36 mo
Straus et al. [86]	88	Nonbulky I-II	AVG	2	24 (27%)	46%	84%	54% (2 y)	88% (2 y)	40 mo

Table modified from Kasamon YL [93], Table 1, page 3.

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AVG, doxorabin, vinblastine, gemcitabine; EFS, event-free survival; MRU, minimal residual uptake; NPV, negative predictive value; OEPA, vincristine, etoposide, prednisone, doxorubicin; PPV, positive predictive value; RF, risk factor(s); RT, radiation therapy.

^aMRU cases were analyzed with PET- cases.

^bMRU cases (4 after cycle 2 PET, 3 after cycle 4 PET) were analyzed separately; 1 relapsed.

^cIncludes previously reported patients [81,82].

^dPediatric study; 98% received RT.

^e59% received RT.

Table 3

Selected studies using interim PET to guide radiation in Hodgkin's lymphoma.

Study	Timing of interim PET	Treatment	Comments
Interim PET in limited-stage disease:			
RAPID trial [100], from UK NCRI ^a	After ABVD × 3	PET–, randomize to RT vs. no further therapy PET+, further ABVD + IFRT	Eligibility restricted to stage IA or IIA, nonbulky disease.
HD16 [101], from GHSG	After ABVD × 2	Standard arm: IFRT (20 Gy) regardless of PET Experimental: PET–, no further therapy Experimental: PET+, IFRT (20 Gy)	Eligibility restricted to early favorable disease.
H10 [21], from EORTC, GELA, IIL	After ABVD × 2	Standard arm: complete ABVD + INRT (30 Gy) regardless of interim PET [Experimental: PET–, complete ABVD without RT] Experimental: PET–, complete ABVD + INRT (30 Gy) Experimental: PET+, BEACOPPesc + INRT (30 Gy)	For favorable and unfavorable, including bulky, HL. Arm closed after interim analysis New arm since interim analysis
Interim PET in advanced disease:			
HD18 [96], from GHSG	After BEACOPPesc × 2	PET–, randomize to 2 vs. 6 more cycles (no RT) PET+, randomize to BEACOPPesc with vs. without rituximab	RT restricted to residual PET+ sites 2.5 cm
RATHL [102], from UK NCRI	After ABVD × 2	PET–, randomize to ABVD vs. AVD (no RT) PET+, BEACOPP-14 or BEACOPPesc	RT optional in patients with persistent PET+ disease
Interim and post-treatment PET to guide RT:			
HD0607 [98] for advanced HL, from GITIL	After ABVD × 2	PET–, complete ABVD; if still PET–, randomize to IFRT (30 Gy) vs. no RT PET+, randomize to BEACOPPesc with vs. without rituximab ^c	RT is to initially bulky and/or residual disease ^b No RT planned
HD0801 [97] for advanced HL, from IIL	After ABVD × 2	PET–, complete ABVD; if still PET–, randomize to IFRT (30 Gy) vs. no RT PET+, high-dose therapy with autologous SCT	RT is to initially bulky sites

Table modified from Y. Kasamon [93], Table 2, page 5.

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; SCT: stem cell transplantation; EORTC: European Organization for Research and Treatment of Cancer; esc: escalated; GELA: Groupe d'Etude des Lymphomes de l'Adulte; GHSG: German Hodgkin Study Group; GITIL: Gruppo Italiano Terapie Innovative Nei Linfomi; Gy, Gray; HL: Hodgkin's lymphoma; IIL: Intergruppo Italiano Linfomi; NCRI: National Cancer Research Institute; RATHL: response-adapted therapy in Hodgkin lymphoma; RT: radiation therapy.

^a Accrual completed.^b No RT if no residual mass.^c If PET– after 4 cycles of BEACOPPesc +/- rituximab.