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The Role of Radiation Therapy in Patients With Relapsed or Refractory Hodgkin Lymphoma: Guidelines From the International Lymphoma Radiation Oncology Group

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The Role of Radiation Therapy in Patients with Relapsed/Refractory Hodgkin Lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group

Short title: Relapsed/Refractory HL ILROG Guidelines

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Short title: Relapsed/Refractory HL ILROG Guidelines

ABSTRACT

Relapsed and refractory Hodgkin lymphoma (HL) challenges clinicians to devise treatment strategies that are effective and safe. This problem is particularly prominent in an era when de-escalation trials are designed to minimize therapeutic toxicities in both early and advanced stage disease. Radiation therapy is the single most effective treatment modality for HL, and its integration into salvage regimens, or its independent use in select patients, must be understood in order to maximize our success in treating these patients. The complexity of treating relapsed/refractory HL derives from the spectrum of primary treatment approaches currently in use that creates heterogeneity in both treatment exposure and the potential toxicities of salvage therapy. Patients can have relapsed or refractory disease after limited or aggressive primary therapy (with or without radiation therapy), at early or delayed time points, with limited or extensive disease volumes, and with varying degrees of residual morbidity from primary therapy. Their response to salvage systemic therapy can be partial or complete, and the use of consolidative stem cell transplant is variably applied. New biologics and immunotherapeutic approaches have broadened but also complicated salvage treatment approaches. Through all of this, radiation therapy remains an integral component of treatment for many patients but it must be used effectively and judiciously. The purpose of this review is to describe the different treatment scenarios and provide guidance for radiation dose, volume, and timing in patients with relapsed or refractory HL.

Introduction

Hodgkin lymphoma (HL) is a curable malignancy in most patients, and remarkable progress has been made in defining standard treatment approaches. Over several decades, treatment strategies have evolved from radiation therapy (RT) alone, to combined-modality therapy (CMT), to chemotherapy alone in select situations [1-7]. Early (or interim) 18-F fluorodeoxyglucose (FDG) positron emission tomography (PET) has become integral in the contemporary era of risk-adapted therapy [8,9]. Trials such as the United Kingdom RAPID trial and the EORTC-LYSA-FIL H10 have assessed whether RT could be omitted in patients with early (after 2 or 3 chemotherapy cycles) response but with a decrement in progression-free survival [3,10]. New approaches with biologically targeted agents such as brentuximab vedotin (BV), an antibody-drug conjugate, and check-point inhibitors promise to further diminish the number of patients who are incurable [11-14]. However, in early stage disease, rates of relapse remain in the 5-10% range [1,15] and even higher after treatment with chemotherapy alone [2,3]; in advanced disease, relapse rates can be as high as 30-40% [4,16,17]. Refractory HL occurs in
~10% of patients, defying initial treatment approaches [18]. Patients with relapsed HL who are salvaged with high dose chemotherapy and hematopoietic stem cell rescue have an approximately 50% potential for cure [19,20]. Patients with refractory HL have a poor prognosis, and for those who relapse after autologous stem cell transplant the prognosis is dismal, affirming the importance

of the initial salvage regimen being successful [21,22].
The general approach to biopsy-proven relapsed/refractory HL is to determine if patients are transplant-eligible. For those who are, the sequence of therapy is to deliver a salvage regimen, mobilize and store autologous hematopoietic cells, and then consolidate the response to salvage with high-dose chemotherapy and autologous hematopoietic stem cell rescue. Patients with high-risk features (such as early relapse or extranodal relapse) are considered for post-transplantation BV. The optimal incorporation of RT into this framework could improve disease control in many patients.
In this critical review, we propose guidelines for the appropriate integration of RT in the treatment approaches for relapsed and recurrent HL with consideration for radiation dose, volume, and timing. The need for such radiation-specific treatment definition is supported by the variance in the use of RT for primary HL [23]. Because nodular lymphocyte predominant HL (nLPHL) is distinct from classic HL in terms of its natural history and treatment considerations, guideline recommendations for relapsed and recurrent classic HL are not necessarily applicable and thus nLPHL is discussed separately.

Methods

The steering committee of the International Lymphoma Radiation Oncology Group (ILROG) recognized the critical need for guidelines for the use of RT in patients with relapsed and recurrent HL. Scenarios in which RT might be considered were systematically discerned and the relevant treatment variables, including dose, volume, and timing, were listed for each scenario. This compendium was circulated amongst the committee and responses were collated by the project leader (LSC). Discordances were minimal in terms of the settings where RT was considered of value, and slight variations in timing, dose, and volume were harmonized. Collation of the recommendations was circulated and evidence to support the recommendations solicited from all members of the project group. When evidence was lacking, then consensus was the basis of the recommendation.

Definitions of refractory and relapsed HL

Refractory HL is defined as biopsy proven residual disease, after chemotherapy with or without RT. Relapsed HL is defined as biopsy-proven new disease after an initial complete response (CR) to treatment; this can be in a site of prior disease or in a new site. Biopsy documentation is mandatory with rare exceptions. Evidence of progression is either by an increase in PET-avidity or disease volume compared to previous scans in patients who were considered to have achieved CR. Biopsy documentation of relapse is mandatory with rare exceptions [24]. In the determination of PET response, the Deauville scoring system is used [25] though variations still exist on definition of a complete metabolic response (CMR) since clinical studies have used either Deauville ≥ 3 or >4 to define PET positivity. The working definition for these guidelines is that Deauville 4 or 5 denotes an inadequate response, although some patients with Deauville 4 PET avidity after chemotherapy will be effectively consolidated with RT [26].
The dominant principle is that pathological confirmation of relapsed or refractory disease is required prior to initiation of salvage therapy. Because initial imaging after primary therapy is often performed at three months, identification of disease (biopsy proven) within this interval is accepted as representing refractory rather than relapsed HL. Figure 1 A, B are examples of

patients with similar presentations who did or did not have pathologic confirmation of relapse.

ILROG guidelines for the incorporation of RT will include consideration of both refractory and relapsed HL, optimal treatment volume, RT dose, and RT timing relative to SCT if used. When RT is used either immediately before or after SCT, it is termed "peri-transplant RT." The use of prognostic factors (such as the interval between primary therapy and relapsed disease) will also be considered. The use of RT for transplant ineligible patients, for nodular lymphocyte predominant HL, and the use of total body irradiation (TBI) in conditioning regimens, will also be discussed.

Rationale for Considering RT as a Component of Salvage Therapy for Patients with Relapsed or Refractory HL

Strategies to manage and prevail over relapsed and refractory disease continue to evolve, but primarily include combinations of high dose salvage chemotherapy and stem cell transplantation (SCT) [27,28]. RT has long been demonstrated to be a powerful agent in the local control of HL [29,30]. It may be effective as salvage therapy even when used alone or with standard dose chemotherapy without autologous stem cell transplantation (ASCT), in selected cases [26,31]. The capacity for RT to enhance local disease control in sites of relapsed or refractory HL has been well established [29,32,33]. Although concerns about the toxicities of RT will always be relevant to decision-making, it must be recognized that patients with relapsed or refractory HL have a significantly increased risk for death from HL compared to patients with de novo disease, and their additional options for cure are very limited. This must be considered when assessing the possible risks associated with RT.

A critical observation supporting the rationale for RT is that patients frequently relapse or progress in sites of disease prior to high-dose chemotherapy, and the risk of local relapse after high-dose chemotherapy is significantly lower in patients who receive RT as a component of the therapy for relapsed/refractory disease [34]. In a study at the University of Rochester of patients who underwent SCT for relapsed or refractory HL, those who did not receive post-SCT involved field radiation therapy (IFRT) relapsed most commonly in sites of previous disease (31%) or previous and new sites (46%) vs. new sites only (15%). For patients who did receive IFRT, relapses were rarely in a previous site alone (1 patient) or in previous and new sites (19%) vs. new sites alone (44%) [35]. These data and multiple other studies (Table 1) support the incorporation of RT as a component of salvage therapy. In fact, this is increasingly relevant since current treatment approaches for early stage HL, as well as advanced stage disease, are moving in the direction of chemotherapy only [3,4].

High dose salvage chemotherapy (HDT) (with or without RT) supported with ASCT is the most effective salvage strategy for patients with progression after primary therapy, and approximately 50% of patients are curable [19,20]. Predictors of outcome for the success of ASCT are based on retrospective data and include remission duration <12 months, B symptoms, extranodal sites, bulk disease, advanced stage (III/IV) disease, anemia, and gene expression [36- 42]. Obtaining a pre-ASCT complete metabolic response (CMR) on PET is a powerful predictor of outcome [43-48]. In a recent Memorial Sloan Kettering study, patients who achieved a CMR from conventional dose salvage chemotherapy had an EFS of >80% compared with 26% in patients without a CMR [49]. The use of RT prior to transplant may increase the number of patients achieving a CMR and thereby improve their ultimate outcome.

Table 1 summarizes retrospective studies on patients with relapsed or refractory HL undergoing HDT/ASCT with reported outcomes for patients according to whether or not they received peri-transplant RT. Most studies demonstrate an advantage in local control with the inclusion of RT, and some also support superior progression-free survival and even overall survival. These studies vary in the timing of RT (pre-transplant versus post-transplant), radiation volume, and dose. However, the findings should be cautiously interpreted since they are retrospective and thus susceptible to selection biases that can either favor RT (patients with fewer sites or lower stages), or disadvantage RT (patients with bulk or disseminated disease, poor response to salvage therapy).

General Indications for and Timing of RT in the Relapsed/Refractory Setting in Patients Eligible for HCT and ASCT

Patients with limited volume relapsed/refractory disease should be considered for RT as a component of the salvage approach. Limited volumes are those that can be irradiated with acceptable predicted morbidities. In patients with more disseminated relapses, or with multi- focal progression, RT to select sites may be useful where local disease control has been a dominant clinical problem. More specifically, patients who might benefit from RT include those have persistent FDG-avid disease after conventional dose salvage chemotherapy or after SCT, and/or have primary refractory disease with a distribution that allows for RT administration with acceptable risks for morbidity [43,50-52]. Additionally, RT is appropriate to address involvement at sites where local control is especially critical, such as disease compressing the
spinal cord or nerve roots, obstructing the superior vena cava, airways, ureters, or lymphatics with problematic lymphedema (Table 2).

As shown in Table 1, the timing of the peri-transplant RT for relapsed and refractory disease in reported series is variable and controversial.

Advantages of pre-SCT RT include:

1. Enhancement of maximal cytoreduction in order to achieve a state of minimal residual disease prior to transplant in patients with relapsed/refractory disease only partially responsive to salvage chemotherapy [51,53]. Transplant success has been clearly associated with achieving a PET “negative” status [43-48].
2. If RT is administered (“sandwiched”) after the standard dose salvage therapy (e.g. ifosfamide/carboplatin/etoposide, or gemcitabine/vinorelbine/doxorubicin, or gemcitabine/dexamethasone/cisplatin, or BV-based regimens)[54], the RT volume can be adapted to the post-chemotherapy tumor; RT then is administered prior to the ultimate high-dose chemotherapy and stem cell transplantation as well as the post- transplant consolidative immunotherapy.
3. Since the optimal sequencing of post-SCT RT and post-SCT immunotherapy is unknown, pre-SCT RT obviates such concerns for patients who are candidates for post-SCT immunotherapy due to having residual post-SCT disease.

Disadvantages of pre-SCT RT include:

1. The modest delay in initiating the conditioning regimen that may allow for progression in sites not being irradiated. However, it should be recognized that this would be uncommon. The pre-SCT RT is actually a component of the salvage/cytoreduction

regimen so, in fact, it is not a delay. Moreover, it can be given in an accelerated schedule.
2. An increase in the risk for peri-transplant toxicity such as pneumonitis, sinusoidal obstructive syndrome, dermatitis, mucositis, and enteritis [53,55-57]. Most of these toxicities can be avoided with modern ISRT design and delivery, and proper supportive care.
Advantages of post-SCT RT include:

1. The overall response to systemic therapy is fully defined so that the RT volume and dose can be adapted and potentially limited.
2. Since the disease burden is less, RT may have an increased likelihood of sterilizing residual microscopic disease, allowing for an increased effectiveness of the chosen RT dose.
Disadvantage of post-SCT RT:

1. Patients who have prolonged recoveries from their SCT may have an inordinate delay or a lack of interest for receiving post-SCT RT. This delay might compromise the effectiveness of RT.

PET/CT imaging to assess response after standard-dose salvage ("re-induction of response") prior to ISRT (if given pre-transplant) or after SCT (if given post-transplant) is recommended since the results could affect the choice of RT dose and volume. For patients who receive pre-SCT RT, it should be initiated as soon as possible after the most recent course of chemotherapy. The conditioning regimen should then begin immediately after RT (when
given pre-transplant) in order to minimize the time interval during which sites of relapse might manifest, and also the duration of neutropenia that might occur. Stem cell harvest should precede any salvage RT.
A schema representing an approach to treating relapsed/refractory HL is seen in Figure

2. Table 3 is a summary for all of the upcoming disease scenarios. Other guidelines for treatment exist [National Comprehensive Cancer Network (www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf), British Society of Hematology, American Society for Blood and Marrow Transplantation, Lymphoma Study Association] [27,58,59], but do not explicitly examine the role of RT. Thus, specific areas of discordance are nebulous and these ILROG guidelines are intended to fill that gap.

Normal Tissue Dose Constraints

Since the primary goal for patients with relapsed and refractory HL is to effect cure or long-term palliation, the risk for treatment-related toxicities of aggressive salvage therapy programs are relatively less important than for patients with primary HL. Radiation dose and volume are thus determined with recognition of this dilemma, and this is particularly an issue for patients who whose disease sites are being re-irradiated. The dominant toxicities that impact decision-making when combining RT and chemotherapy in the salvage setting are pneumonitis, [55,56] cardiac injury, secondary malignancies, and hematologic compromise with associated risks for infection [57]. The potential for these morbidities is dependent on a spectrum of risk factors that include previous treatment exposures and co-morbid medical conditions. The risk of toxicity, particularly cardiac and

subsequent malignancies, may be substantially lower with modern RT techniques [31,50,60,61]. When determining RT dose and volume, typical dose constraints remain as a goal, such as limiting the bilateral lungs V20 to <30%, V5 to <55%, and mean lung dose to <13.5 Gy, and the cumulative mean heart dose to <20Gy [56]. In all scenarios that follow in these guidelines, dose ranges for the radiation target are suggested, with the higher doses preferable if the toxicity profile is acceptable. Following the transplant, subsequent follow-up and surveillance for normal tissue toxicities are the same as for other patients with HL and based on their treatment exposures.

Radiation Treatment Technique

Radiation treatment technique is standard as that used for patients with primary HL. We recommend CT simulation with the use of intravenous contrast for head and neck, mediastinal sites, and infradiaphragmatic sites, and fusion with diagnostic PET-CT for target delineation. Deep inspiration breath hold can minimize dose to cardiac and pulmonary structures. The ISRT guidelines for the treatment of HL should be followed [31].

REFRACTORY HL

Salvage RT in the setting of primary refractory HL: if CR after salvage chemotherapy (Deauville 1-3) (Figure 3)

In patients who are refractory to primary chemotherapy but are complete responders to salvage chemotherapy, available evidence supports proceeding with ASCT. In this situation, RT is an appropriate adjuvant for patients with a limited number of refractory disease sites (where all of the relapsed disease sites can be irradiated), or a site adjacent to a critical structure (Table 2) where a local relapse could have devastating consequences. Bulk disease at relapse may also be an indication for RT [62], and can be targeted even with all sites of relapse cannot be safely irradiated. RT would not be recommended for most patients who are refractory in multiple non-bulky or extra-nodal (extensive bony, hepatic or pulmonary) disease sites (e.g. too extensive to be encompassed within a tolerable RT field), and who achieve a CR to salvage chemotherapy. For patients who have previously been irradiated and have refractory disease in this location, RT is generally not appropriate unless dose constraints are acceptable. These considerations also apply to patients who will be irradiated after their SCT. A strategy appropriate for irradiating patients with multiple (including bulky) sites is administering RT pre- SCT to areas of disease involvement. This approach can be followed by total lymphoid RT [51], though is rare in contemporary practice.

The RT volume in this scenario would mirror the above indications for RT assuming that the toxicity profile is considered acceptable. Thus, all initial sites of disease (at first diagnosis) are appropriately irradiated if the disease was localized (e.g. Stage I and contiguous Stage II) at diagnosis and within this volume at relapse [63]. If concerns for toxicity exist, then only refractory sites are irradiated unless the previously involved but chemotherapy-responsive disease sites are in close proximity to the refractory site and inclusion does not lead to excess toxicity. For bulky disease presentations (e.g. >5 cm in greatest dimension), then this site is irradiated, with adjacent sites if considered safe. Extranodal sites are considered in a parallel manner; if adjacent, and radiation exposure is considered safe, then they can be included.

The RT dose is dependent on disease response. For patients who achieve a CR after salvage chemotherapy, then 30 Gy is an appropriate choice. For patients who have a CMR but residual identifiable disease on CT (e.g. >2.5 cm), a slightly increased dose of 36 Gy is appropriate, if safe. If a site is Deauville 3 rather than Deauville 1-2, or in a critical location, 36 Gy is also considered. For

patients who have previously been irradiated, and a meaningful dose (at least 18 Gy) cannot be administered that meets typical toxicity dose constraints, then RT should be avoided. For the rare patient with disseminated nodal disease who will receive TLI as part of the salvage program, patients might receive 18 Gy (1.8 Gy daily or bid over 1-2 weeks) to areas of refractory disease followed by 18 Gy TLI with similar fractionation as pioneered at Memorial Sloan Kettering [51] and which has a long term safety record [64].

Salvage RT in the setting of primary refractory HL: if PR after salvage chemotherapy (Deauville 4) (Figure 4)

For patients who have not achieved a CR to initial salvage chemotherapy, additional high dose chemotherapy regimens or biologics are indicated with the goal of achieving CR. However, patients with a PR to salvage chemotherapy may also sometimes proceed to ASCT. In this situation, similar approaches exist as for patients who have achieved a CR with the exception of RT timing and dose. Thus, if the PR sites are disseminated and non-bulky, then RT is generally not recommended although an aggressive pre-SCT RT approach is sometimes used with extended RT volumes. If the PR sites are localized or limited in number, or adjacent to critical structures, then RT is recommended usually pre-SCT as a component of cytoreduction.

The RT volume is considered similarly to patients who have a CMR to salvage chemotherapy. The PR site alone can be treated, or that site with adjacent CR sites, using differential dosing (such as a simultaneous integrated or sequential boost). The combination of ISRT to post-chemotherapy salvage residual disease sites, immediately followed by TLI (or other extended fields) prior to SCT is of proven effectiveness for some patients who have disseminated nodal disease [51].

The RT dose is generally increased to 36-40 Gy for chemotherapy refractory disease. An acceptable strategy is to irradiate the responding (i.e. CR) adjacent sites to 30-36 Gy and boost the PR sites to 36-40 Gy. For patients who have been previously irradiated, then the aforementioned dose constraints are a guide. For patients who will be treated pre-SCT, an accelerated ISRT followed by TLI may be considered [51]. Alternately, once per day RT can be used.

Salvage RT in the setting of persistent refractory HL (Deauville 5)

For patients with persistent refractory (or progressive) HL, then alternate salvage chemotherapy and biologics including brentuximab vedotin and anti-PD1 check-point inhibitors may be administered. RT is rarely considered appropriate for patients with disseminated refractory sites unless large volume pre-SCT RT is chosen when further systemic therapy is inappropriate and RT is considered the most effective palliative approach.

For limited refractory situations, RT is beneficial and considerations are similar to the CR and PR scenario except: (1) considerations for pre-SCT RT are even more powerful, (2) the radiation dose can be escalated to 40-45 Gy to areas of refractory disease, (3) an integrated boost approach and interim PET re-staging is more likely to be considered in which the sites of responding disease receive a lower dose than the sites of refractory disease.

RELAPSED HL

Salvage RT in the setting of initial stage IA-IIA HL treated without RT:

Patients with initial stage IA-IIA disease who achieve CR after primary treatment with chemotherapy alone but then recur are appropriately considered for salvage RT as a component of a strategy that includes ASCT, or with conventional chemotherapy followed by ISRT without SCT [26]. Generally these include patients who have achieved a CMR to salvage chemotherapy and do not have sizeable residual CT abnormalities [65]. However, even patients with residual PET avidity after salvage chemotherapy whose Deauville scores have not actually increased might have prolonged disease-free survival with RT in the absence of ASCT [26]. RT as an independent treatment approach in general would only be considered for patients who are unsuitable for systemic therapy since long-term control is achieved in fewer patients than when a combined approach is used. However, the capacity for RT alone to salvage patients who were initially treated solely with chemotherapy certainly does exist and remains a consideration for such patients [29,33]. RT should be strongly recommended as a component of salvage therapy unless multiple sites (beyond what can be encompassed with predicted tissue tolerance) are involved and the volume would be thereby be expansive and exceed what is considered tolerance for the patient under consideration due to co-morbid and chemotherapy-associated normal tissue limitations [33,66]. Currently, alternatives to high-dose salvage with SCT that include check-point inhibitors such as pembrolizumab or nivolumab combined with ISRT are being tested in patients with limited previously unirradiated site relapse [11].

The RT volume includes all sites of initial disease if considered tolerable, certainly in patients with CS I-II disease and those who have relapsed within 6-12 months, using ISRT principles [31]. The volume may include all sites of initial disease even if the relapse is delayed but the treatment toxicities are considered to be acceptable. Alternately, for patients with a delayed relapse, just the initial bulk or relapsed sites can be irradiated if the risks of a more comprehensive volume are considered to have an adverse toxicity profile.

The RT dose is 30-36 Gy following a CR to salvage chemotherapy, and 36-40 Gy following a PR to salvage therapy. Again, as for patients with refractory disease, an integrated boost can be considered in which all initial sites are irradiated to 30 Gy and the resistant sites are irradiated to 36-40 Gy.

RT as a sole treatment strategy should, in general, only be considered in patients who are not candidates for CMT, since RT alone is less likely to be curative (see above discussion). Recognizing the limitations of RT as an independent approach, the profile of the relapse parameters is important when considering the patient for RT alone. These include the following: chemotherapy was minimal (e.g. 3-4 cycles ABVD), the relapse was delayed, the disease volume was localized (e.g. $\leq$3 contiguous sites), non-bulky, nodal, and without B
symptomatology. Such patients are essentially treated as if they have de novo HL, with doses ranging from 30-40 Gy. The minimal treatment volume is ISRT, but extended fields such as mantle, spleen/para-aortics +/- pelvis or combinations may be considered since RT is being used as the primary and sole treatment modality [29,33].

All other situations of relapsed HL (Figure 5)

Patients initially treated for advanced stage or unfavorable early stage disease are more likely to

have received full course chemotherapy. In this regard, the morbidities attendant to their chemotherapy exposure might impact the salvage approach and the role of RT. In general, patients who recur with disseminated disease are unlikely to be favorable candidates for adjuvant RT. Conversely, patients who initially had advanced disease but who recur in a limited number of sites might benefit from RT to those sites if the toxicity profile is reasonable. Other situations in which RT might be appropriate include patients who recur with bulk disease that is targetable, particularly if the response to salvage chemotherapy is modest and if toxicity constraints do not preclude RT exposure. Patients who recur in critical locations (Table 2) might benefit from RT since a relapse in those sites would be morbid.

Volume of RT: As implied above, sites of relapsed disease are appropriate targets, and can include contiguous previously involved sites particularly if the relapse is rapid (<6-12 months).

Dose of RT: If the sites of relapsed disease completely respond to salvage therapy, then 30-36 Gy is recommended. If sites only partially respond to salvage therapy, then 36-40 Gy is considered. The strategy of treating adjacent but responsive disease sites to 30 Gy and boosting partially responding sites is sensible.

RT as a sole treatment strategy: For patients who relapse with local and limited volume disease, relapse after limited chemotherapy alone, or are not candidates for systemic therapy, then RT alone is a consideration. In this situation, radiation doses of 36-40 Gy are recommended if safe.

Transplant ineligible

Some patients are transplant ineligible due to co-medical morbidities such as impaired cardiopulmonary function, advanced age, or having failed to adequately respond to salvage therapy. Approaches for the management of this group of patients is personalized and based on their co-morbid conditions, previous chemotherapy and RT exposures, response to salvage therapy including chemotherapy and biologics, and future alternative options.

If CR to salvage therapy: For patients who initially had limited stage HL, then all initial sites of disease should be targeted with RT if the toxicity profile is acceptable. Otherwise, just sites of relapsed HL are irradiated, particularly if the relapse is delayed. The recommendation is to treat ISRT volumes to doses of 30-36 Gy. Integrated or sequential boosts (e.g. lower doses to adjacent but non-relapsed sites, higher doses to relapsed or bulk sites) are useful in this situation.

If PR to salvage therapy: These patients will often be treated with brentuximab or PD1 inhibitors for variable intervals [26], and ultimately become candidates for SCT (further discussed below in "Impact of new therapy"). Considerations for RT volume and dose are similar to the CR situation except that the decision making can be more nuanced in terms of the inclusiveness of the fields (i.e. treating all initially involved sites and increasing RT dose to the
partially responding sites). The peak doses might rarely exceed 40 Gy for patients with relapsed bulk disease that only partially responds to salvage therapy.

If no salvage chemotherapy: These patients, by definition, have overt and active disease. As for patients who only partially respond to salvage therapy, the RT volume and dose are tailored to the particular patient's tolerance to RT with the goal of treating at risk sites to progressively higher RT doses depending on the distribution of disease sites, normal tissue toxicity constraints based on previous exposures, and the goals of therapy (i.e. curative or palliative).

Other considerations

Refractory/relapsed nLPHL: It is critical that these patients be biopsied in order to define whether they have relapsed HL, progressive transformation of germinal centers, or transformation to an aggressive non-Hodgkin lymphoma [67]. Decision making depends on all the previously noted issues for classic HL including whether the disease is refractory or relapsed, the time to relapse, the distribution of initial and relapsed disease, previous RT and chemotherapy exposures, and the response to salvage chemotherapy if administered. An important difference in this population is that patients will more likely have been treated for their primary nLPHL with RT alone if they initially had stage I or II disease. Moreover, it must be recognized that the morbidities of aggressive salvage therapy for relapsed disease can sometimes outweigh its advantages. In addition, biologic agents such as rituximab can be very effective for salvage, though are inadequate as a sole treatment approach. Recommendations for these patients include approaches that can range from localized RT, combined chemotherapy (often with rituximab) and RT, or even SCT if the patient has previously received moderate systemic therapy with or without RT. For patients who are asymptomatic, observation may also be the most appropriate strategy. For patients who have limited-stage relapse, particularly at delayed intervals, then salvage chemotherapy combined with adjuvant RT, RT alone, or even observation, are often most appropriate. Radiation doses range from 30- 40 Gy depending on previous chemotherapy and radiation exposures, and normal tissue constraints.

Total body irradiation as a component of a conditioning regimen: TBI-based conditioning regimens for non-allogeneic transplant programs are very rarely appropriate compared with chemotherapy-based regimens because of the attendant transplant-associated morbidities and mortality associated with the TBI-based regimens [68]. Such uncommon exceptions include situations in which refractory or relapsed disease is in multiple extranodal or bone marrow sites, and the patient is or has been only partially responsive to all systemic salvage approaches. In this situation, a TBI-based regimen can be considered after extensive counseling regarding the treatment-associated risks. Moreover, RT to sites of relapsed or refractory disease (with fractionated doses of 18-24 Gy, though rarely even higher) immediately prior to TBI (usually 12 Gy in 1.5 Gy fractions) may be considered.

Palliative RT: Palliative RT is certainly an important approach for patients with relapsed HL who do not have systemic options, are inappropriate for more aggressive RT approaches, or who need time to recover from previous treatment approaches while they are en route to additional systemic therapies (see below) [63].

Relapse after SCT: These patients can be consided for allogeneic SCT using radiation doses and volumes similar to those for patients with relapsed disease. They will more commonly be treated with targeted agents and immunotherapies as discussed below.

Impact of new therapy (targeted agents, immunotherapies)

Novel therapies are changing the landscape of treatment approaches for relapsed and refractory HL. However, patients who are radiation-naive and have localized stage I-II relapses in sites of initial disease should have RT as a component of therapy. This reflects the fact that RT is an effective agent for the local control of HL, and should be integrated into salvage therapy prior to a point when the frequency and bulk of disease relapses mitigate any potential for RT contributing meaningfully to disease control. Emerging systemic approaches include brentuximab vedotin [11,12,14,69], immune checkpoint inhibitors [13], adoptive cell therapy, monoclonal antibodies,

vaccines and cytokines, as well as novel targeted agents. The impact of agents such as brentuximab vedotin and anti-PD1 check-point inhibition has been profound (supported by results from KEYNOTE-013, KEYNOTE-087, CheckMate 205 trials [22,70]), but their effectiveness for durable disease control is unknown. Unfortunately, the enthusiasm for novel approaches can translate into a reluctance to include RT as a component of salvage therapy, even when a solitary site of disease is dominating the clinical picture. RT should be used to enhance the potential for local disease control prior to exhaustively exposing the patient to successive systemic agents with their associated toxicities. The limitations of brentuximab vedotin in terms of durable disease control are increasingly understood while such data for the anti-PD1 mAbs are still emerging.

Concerns relating to the combined toxicities of novel agents and RT must be considered in the decision-making process given the paucity of data addressing this issue. Recognizing this, the concurrent use of radiation and biologics may be inadvisable. Pulmonary tolerance to the combined approaches remains to be fully elucidated but is a potentially fatal toxicity of anti-PD- 1/PD-L1 monoclonal antibodies [71]. Evidence-based recommendations for integrating RT and biologics are sparse and the role of radiation either prior to or directly after check-point inhibitors remains investigational.

CONCLUSION

Dramatic success in the curability of HL has resulted from our increased understanding and adeptness in mining the utility of both chemotherapy and RT. As a corollary, the ability to convert biological insights into new therapeutics has broadened our therapeutic armamentarium for both primary and relapsed HL. Decades of experience with RT for HL have validated its effectiveness in locally controlling HL. The recent challenge is to further improve long-term outcomes by avoiding the late toxicities that occurred in patients treated with historic approaches. Modern principles and techniques for RT have dramatically decreased the RT volumes and doses and consequently also the estimated risks of late toxicities. This should lead to better usage of RT also in the relapsed/refractory setting. We should identify which patients require RT in the primary and relapsed/refractory setting to improve their disease control and outcomes. We need to rationally integrate our treatment approaches as we strive to create increasingly personalized approaches to the treatment of Hodgkin lymphoma.

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Figure Legends

Figure 1. Biopsy to confirm relapsed/refractory HL. A: 23 y.o. male stage IIEX HL with Deauville 5 imaging abnormalities in the mediastinum after 6 ABVD (adriamycin, bleomycin, vinblastine, dacarbazine); he underwent biopsy that showed tumor necrosis but no viable HL. B: 27 y.o. male with stage IVX HL with Deauville 4 imaging abnormalities in the mediastinum after 6 ABVD; he underwent biopsy that showed viable HL. Axial images with ISRT contouring demonstrate areas that ultimately were irradiated.

Figure 2. An approach to treating relapsed and refractory HL. Clinical factors may warrant intervention. Partial response by CT criteria is sufficient for consideration of ASCT although a PET-guided approach is recommended. In selected cases observation may be appropriate, e.g. in those relapsing > 5 years from primary therapy; observe if ASCT contra-indicated. Those with minimal response or stable disease may be considered appropriate candidates for allogenic SCT; further attempts at cytoreduction are recommended if ASCT is being contemplated.
Allogenic HSCT may be favored for those requiring > 2 lines of salvage therapy to achieve a response, or in those with < CMR. Modified from the NCCN guidelines at www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf

Figure 3. Refractory HL then CR to salvage chemotherapy. 39 y.o. female with stage II classical HL with bilateral neck, bulky mediastinal, and left pericardial nodal involvement.. A: PET-CT at initial diagnosis (left panel), and restaging PET-CT after 6 cycles of ABVD showing a Deauville 2 response. B: Follow up PET-CT 2.5 months after completion of ABVD showing FDG-avid relapsed disease (left panel), and restaging PET-CT after 3 cycles of brentuximab/bendamustine showing a complete response. C: Sample Beam's eye view showing planning target volume (magenta) in relation to organs-at-risk (left panel), and sample axial images of planning CT showing planning target volume (magenta) and isodose distribution of IMRT plan. D: Dose volume histograms, and lung, heart, and left ventricle metrics. She is currently without evidence of disease 6 months post-treatment

Figure 4. Refractory HL then PR to salvage chemotherapy. 25 y.o. female presented with stage IIIB classical HL, with bilateral neck, bulky mediastinal, bilateral hilar, and upper abdominal nodal involvement. A: Bilateral neck, bulky mediastinal, bilateral hilar, and upper abdominal nodal involvement. She received ABVD x 6 with PR but persistent PET avidity in the mediastinum and left neck. She had a continued PR after ICE x 3 with continued PET avidity in the left SVC and mediastinum (DS4). PET-CT 30 days after high dose BEAM and ASCT showed MCR. B. Beam's eye view showing the 30.6 Gy planning target volume (magenta) and 37.4 Gy boost planning target volume (blue) in relation to organs-at-risk (left panel). Representative axial slices from the planning CT showing the planning target volumes (magenta and blue color- wash) and isodose lines of the IMRT plan (right panels). C: Dose volume histogram (top panel) and lung, heart and left ventricle metrics (bottom panel). She is now without evidence of disease, 2 years after RT.

Figure 5. Relapsed, then refractory HL. 37 y.o. patient with CSIIB bulky mediastinal classic HL treated with ABVDx6 with CMR. Patient was on protocol and randomized to not receive RT. Patient was in CR for 1.5 years. A: PET-CT scan with and without inspiration. Bone marrow biopsy in 2011 with no evidence of disease. B: Continued CR on follow-up until April 2014 when CT scan showed PD in the mediastinal residue CT volume. PET-CT showed avidity in the mediastinum. Mediastinal biopsy in April 2014 showed classical HL. C: Planned salvage therapy included IGEV (ifosfamide, gemcitabine, vinorelbine) x 4 followed by ASCT. PET after 2 IGEV showed partial response (PR). D: PET-CT after 4 IGEV showed progression (increase in size and metabolic activity). E: RT in October 2014 VMAT (SIB) consisted of 30 Gy/20 fractions to larger volumes, and 40 Gy/20 fractions to PET+ sites after 4 IGEV. F: Post-RT CT scan: very good PR and patient proceeded to FEAM (fotemustine, etoposide, cytarabine, melphalan) ASCT in December 2014. PET evaluation 4 weeks after ASCT showed CMR.

Table 1. Retrospective studies on patients with relapsed or refractory HL undergoing HDT/ASCT

	No. Pts	RT Timing	RT Field	RT Dose	Results
Poen *(IJROBP 1996)*	24 IFRT/76 no IFRT	18 Pre-Tx, 6 Post-Tx	• Bulk > 5 cm • Encompassed w/in standard RT field • Disease refractory to cytoreductive CT • Persistent disease	Median 30 Gy (range, 12.5-45 Gy)	• 30 Gy provided LC in >90% of cases • Pts with stage I-III disease at relapse and w/o prior local treatment had greatest benefit from IFRT • In stage I-III: 3 yr FFR : 100% IFRT, 67% no IFRT; 3 yr OS: 85% IFRT, 60% no IFRT
Wendland *(AJCO 2006)*	21 IFRT/ 44 no IFRT	1 Pre-and Post-TX, 5 Pre-Tx, 15 Post-Tx	IFRT	Median 28.8 Gy (range, 21-43.2 Gy)	• IFRT pts more likely to have bulky disease at initial diagnosis (*P*=0.05). • 5 yr OS: 73% IFRT, 56% no IFRT • PFS similar in both IFRT and no IFRT groups (*P*=0.83) • 22 no IFRT pts and 5 IFRT pts died
Kahn *(IJROBP 2011)*	46 IFRT/ 46 no IFRT	38 Pre-Tx, 8 Post-Tx	Encompassed at-risk sites	Median 30 Gy (range, 21-45 Gy)	• 10/46 IFRT pts relapsed or progressed after SCT compared with 17/46 control pts • Toxicity risk is significant, particularly when bulsulfan-based conditioning is combined w/IFRT
Biswas *(Radiother Oncol 2012)*	32 RT/ 30 no RT	30 Post-Tx	12 mediastinal/mantle IFRT, 8 para-aortic (PA)-pelvic or inguinal region IFRT	Median 30.6 Gy (range 6.0–44.2 Gy)	• Estimated 3-year OS (p = 0.05) and DSS (p = 0.08) were 69.6% and 82.1% with IFRT and 40% and 57.6% without IFRT on univariate analysis. • B-symptoms were adverse on univariate (p = 0.007) and

			3 both mantle and PA IFRT 4 cervical/axillary region IFRT 1 IFRT to femur 4 info unavailable		multivariate (p = 0.01) analysis. • HL pts who received IFRT following ASCT had improved local control in areas of previously relapsed disease (p = 0.03). • OS and DSS showed marginal benefit at 3 years.
Goda *(IJROBP 2012)*	34 RT alone/ 22 RT+CT	Post-Transplant progression or relapse	42 IFRT, 14 EFRT	Median 35 Gy (range, 8-40.3 Gy)	• Median OS 40.8 months • 1 yr PFS was higher in pts in whom all diseased sites were irradiated (49%) compared with those in whom only the symptomatic site was treated (22%, *P*=.07).
Eroglu *(AJCO 2015)*	20 IFRT/25 no IFRT	16 Pre-Tx, 5 Post-Tx	IFRT	Median 30 Gy (range, 25-44 Gy)	• Early stage: 5 yr OS 81% IFRT, 48% no IFRT • Advanced stage: no difference
Milgrom *(Cancer 2016)*	22 RT/ 167 no RT	1 Pre-Tx, 21 Post-Tx	7 Med 11 Med/neck 3 Med/neck/axilla 1 Neck only	Median 36 Gy (range, 25.2-41.4 Gy)	• 7 disease relapses (3 distant) • 1 pt w/ grade 3 pancytopenia • Primary refractory or PET pos: 4 yr local control 81% with RT, 49% no RT
Levis *(CLML 2017)*	21 IFRT/ 52 no IFRT	6 Pre-Tx, 15 Post-Tx	IFRT	Median 30 Gy (range, 25.2-43.2 Gy)	• 19/21 pts responded to IFRT (15 CR, 4 PR) • Overall no difference • Pts with stage I or II disease at time of relapse and PET+ before ASCT: 3 yr PFS 68% IFRT, 50% no RT; 5 yr OS 92% IFRT, 62% no RT

Rimner (*IJROBP 2017*)	186 IFRT + TLI	186 Pre-Tx	IFRT + TLI	IFRT (18-20 Gy) followed by TLI (15-18 Gy)	• 5yr/10yr OS: 68%/56% • 5yr/10yr EFS: 62%/56% • 5yr/10-yr CI of HL-related deaths: 21%/29% • 8 pts had grade ≥3 cardiac toxicity with 3 deaths. • 10 pts developed second malignancies, 5 of whom died. • Accelerated IFRT followed by TLI and HDT is effective and safe salvage strategy for pts w/ excellent long-term OS, EFS, and DSS. CR to SC is most important prognostic factor.
Wilke (IJROBP, 2017)	80 HDCT+AHCT	48 Pre-Tx, 32 Post-Tx	26 Mediastinum 14 Head/neck 4 Axilla 4 Abdomen/pelvic	30.6 Gy (range, 16-44 Gy)	• At median follow-up of 25 months, 2 yr OS and PFS were 96% and 52%, respectively. • Consolidative RT was found to significantly improve the 2-year PFS (67% vs 42%, P<.01) without a significant change in OS (100% vs 93%, PZ.15). • The improvement seen on 2-year PFS with consolidative RT remained significant on multivariate analysis (HR 4.64, 95% CI 1.98-10.88). • Minimal toxicity was observed among pts receiving RT.

Abbreviations: RT, radiation therapy; Tx, transplant; bid, twice-daily; IFRT, involved-field radiation therapy; OS, overall survival; LC, local control; CR, complete response; PR, partial response; DFS, disease-free survival; TLI, total lymphoid irradiation; CI, cumulative incidence; SC, salvage chemotherapy; CI, cumulative incidence; FFP, freedom from progression; EFS, event free survival; DSS, disease specific survival; HDT, high dose therapy; HL, Hodgkin lymphoma; HDCT, high dose chemotherapy; AHCT, autologous hematopoietic cell transplantation

Table 2. General Indications for Radiotherapy as Part of Salvage in Patients with Relapsed/Refractory Hodgkin Lymphoma

1. Localized relapse
2. Disseminated relapse but with sites including:
    A) Bulky disease (≥ 5 cm)
    B) Persistent FDG-avid disease after salvage chemotherapy or after SCT
    C) Critical for local control, e.g.
        (i) Spinal cord compression (vertebral involvement)
        (ii) Nerve root compression
        (iii) Superior vena cava compression
        (iv) Airway compression
        (v) Lymphedema
        (vi) Hydronephrosis

Table 3: Treatment Summaries

Refractory HL: Salvage RT if CR after salvage chemotherapy (Deauville 1-3)	
Timing	Immediately prior to SCT 4-12 weeks following ASCT, pending hematological recovery and resolution of acute side effects
Dose	CR (anatomic and DS 1-2) after salvage chemotherapy: 30 Gy CMR but residual disease that is >2.5 cm: can escalate dose to 36 Gy if safe If site is Deauville 3 or in a critical location: can escalate dose to 36 Gy if safe If previously irradiated, typical dose constraints should be considered, i.e. bilateral lungs V20 to <30%, V5 to <55%, mean lung dose <13.5 Gy and the cumulative mean heart dose to <20Gy. If a meaningful dose (at least 18 Gy) cannot be administered that meets these dose constraints, then RT should be avoided. If disseminated nodal disease treated with extended field RT: 30-36 Gy to involved sites if the toxicity profile is acceptable
Volume	All initial sites of disease are irradiated if safely encompassable. If toxicity concerns exist, then only refractory sites are irradiated unless the remaining but responsive initial disease sites are close to the refractory site(s) and their inclusion does not exacerbate toxicity. Can consider RT to extranodal sites if RT exposure is considered safe.
Refractory HL: Salvage RT if PR after salvage chemotherapy (Deauville 4)	
Timing	For patients with metabolic or anatomic PR, then RT pre-SCT to achieve minimal residual disease.
Dose	Irradiate CR adjacent sites to 30-36 Gy and boost PR sites to 36-40 Gy For treatment pre-SCT, accelerated ISRT (18-20 Gy over 5 days with twice/day fractionation) followed by TLI (15-18 Gy over 5 days with twice/day fractionation) has proven efficacy. Alternately, once daily fractions of 1.5-1.8 Gy can be used.
Volume	Similar to patients who have a CR to salvage chemotherapy. PR site alone can be treated, or also including adjacent CR sites using differential dosing (simultaneous integrated boost, etc.) if the toxicity profile is acceptable. ISRT to post-chemotherapy salvage residual sites immediately followed by TLI prior to SCT is of proven effectiveness for some patients who have disseminated nodal disease.
Refractory HL: Salvage RT for persistent refractory (or progressive) HL (Deauville 5)	
Dose	For patients with persistent refractory (or progressive) HL, then alternate salvage chemotherapy and biologics including Brentuximab Vedotin and anti-PD1 check-point inhibitors may be administered.

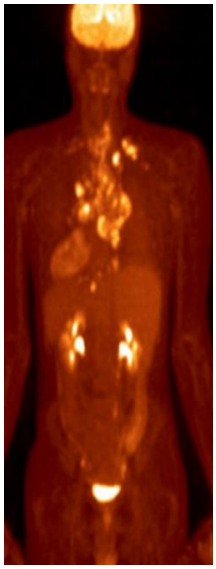
	RT is inadvisable for patients with disseminated refractory sites, due to the toxicity profile, unless extended field pre-SCT RT is determined to be the most likely approach to engender a CMR. Otherwise, RT is similar to the above CR and PR scenarios except: (1) considerations for pre-SCT RT are even more powerful (2) the RT dose can be escalated to 40-45 Gy to areas of refractory disease (3) an integrated (simultaneous) boost approach is more likely to be considered in which the sites of responding disease receive a lower dose than the sites of refractory disease.
Relapsed HL: Salvage RT if initial stage IA-IIA HL treated without RT	
Timing	Similar to the refractory setting in which the arguments for pre-SCT vs. post-SCT RT apply. Patients treated with conventional chemotherapy followed by ISRT (and no SCT) should receive RT 2-4 weeks after chemotherapy.
Dose	CR to salvage chemotherapy: 30-36 Gy PR to salvage chemotherapy: 36-40 Gy An integrated (simultaneous) boost can be considered in which all initial sites are irradiated to 30 Gy and the resistant sites are irradiated to 36-40 Gy.
Volume	Includes all sites of initial disease if considered tolerable and patient has relapsed within 6-12 months using ISRT principles. Also includes all sites of initial disease if the relapse is delayed and RT toxicities are acceptable. Alternately, if a delayed relapse, just the relapsed sites can be irradiated if the risks of a more comprehensive volume are considered to have an adverse toxicity profile.
RT only	Should only be considered in patients who are not candidates for combined modality therapy. Doses ranging from 30-40 Gy for patients whose chemotherapy was minimal (e.g. 3-4 cycles ABVD), the relapse was delayed, the disease volume was localized (e.g. $\leq$3 contiguous sites), non-bulky, nodal, and without B symptomatology. The minimal treatment volume is ISRT, but extended fields such as mantle, spleen/para-aortics +/- pelvis or combinations may be considered since RT is being used as the primary and sole treatment modality.
Relapsed HL: All other situations	
Timing	If administered after the SCT, then RT is initiated when acute SCT morbidities and hematologic parameters have recovered, usually within 4 to12 weeks. For patients who remain PET avid despite salvage chemotherapy and biologics, but who are still planned to undergo SCT, then pre-SCT RT is considered (either ISRT or rarely ISRT+TLI).
Dose	CR to salvage chemotherapy: 30-36 Gy

	PR to salvage chemotherapy: 36-40 Gy Treat adjacent but responsive disease sites to 30 Gy and boost partially responding sites to 36-40 Gy For patients who have previously been irradiated, then dose constraints to the critical tissues (i.e. lungs, heart, kidneys) must be acceptable.
Volume	Sites of relapsed disease and inclusion of contiguous previously involved sites particularly if the relapse is rapid (<6-12 months).
RT only	For patients who relapse with local and limited volume, and are not candidates for systemic therapy, then RT alone (36-40 Gy) is considered. The radiation doses can be limited to 30 Gy if there are concerns about toxicity.
Transplant ineligible or relapse after SCT	
CR to salvage therapy	All initial sites of disease can be targeted if the toxicity profile is acceptable. Otherwise, just sites of relapsed HL are irradiated, particularly if the relapse is delayed. Treat ISRT volumes to doses of 30-36 Gy that might include integrated or sequential boosts (e.g. lower doses to adjacent but non-relapsed sites, higher doses to relapsed or bulk sites).
PR to salvage therapy	Greater attempt to treat all initially involved sites, but increased dose to partially responding sites. Peak doses might rarely exceed 40 Gy if relapsed bulk disease only partially responds to salvage therapy.
No salvage therapy	RT volume and dose are tailored to the particular patient's tolerance with the goal of treating at risk sites to progressively higher RT doses depending on the distribution of disease sites, normal tissue toxicity constraints based on previous exposures, and the goals of therapy (i.e. curative or palliative).
Refractory/relapsed nLPHL	
Timing	For patients with limited-stage relapse, particularly at delayed intervals, then limited systemic therapy, salvage chemotherapy combined with adjuvant RT, or RT alone, or observation, are all considerations.
Dose	30-40 Gy depending on previous chemotherapy and RT exposures, and normal tissue constraints.
Volume	Biopsy-proven relapsed HL, or all initial sites of disease depending on toxicity profile and influenced by the rapidity of the relapse.
Total body irradiation	
Indication	Rarely appropriate. Exceptions can include patients only partially responsive to all systemic salvage approaches and with extranodal or bone marrow disease.
Dose	RT to sites of refractory or relapsed disease (fractionated doses of 18-24 Gy, though rarely even higher) immediately prior to TBI (usually 12 Gy in 1.5 Gy fractions) can be considered.

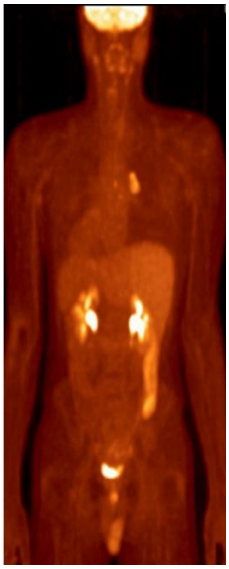
Volume	Whole body. Patients must be counseled on treatment-associated risks.
Palliative RT: When patients have relapsed HL and without systemic options	
Timing	When symptomatic, or if patients will receive additional systemic therapies but need extra recovery time from previous treatment
Volume	Symptomatic sites or those that threaten to compromise organ function.
Dose	Variable total doses and fractionation schedules are acceptable depending on goals and concerns about normal tissue toxicities

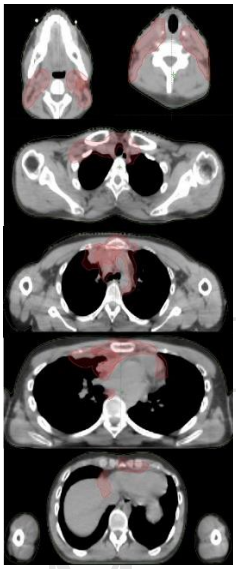
A

At diagnosis



After 6 cycles of ABVD





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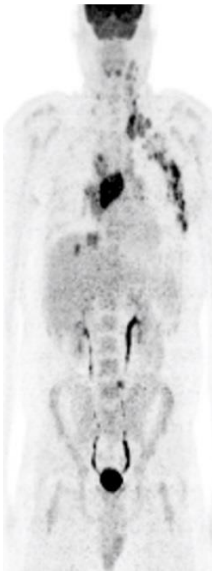
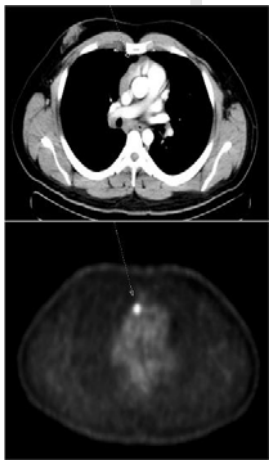
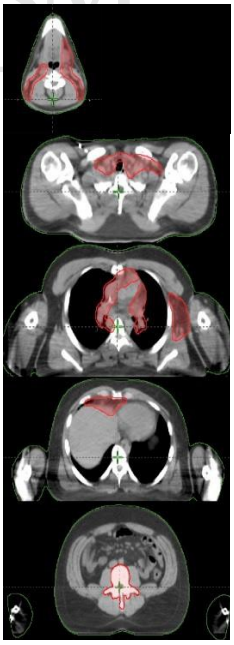
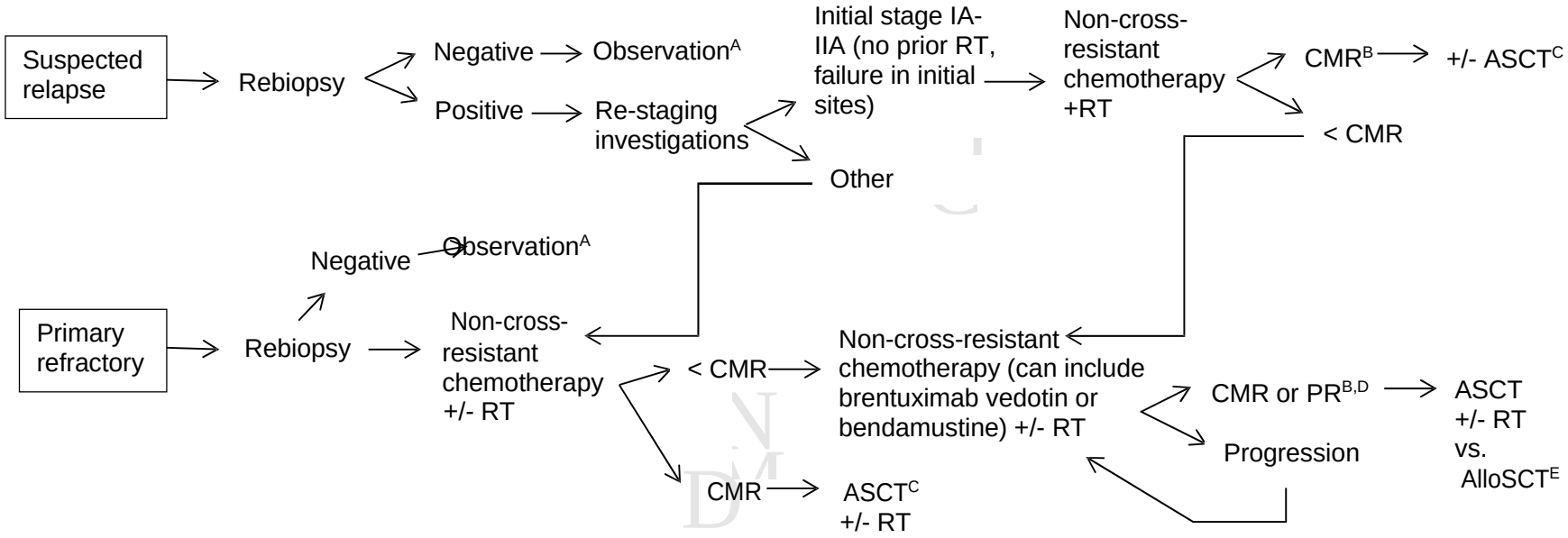
At diagnosis



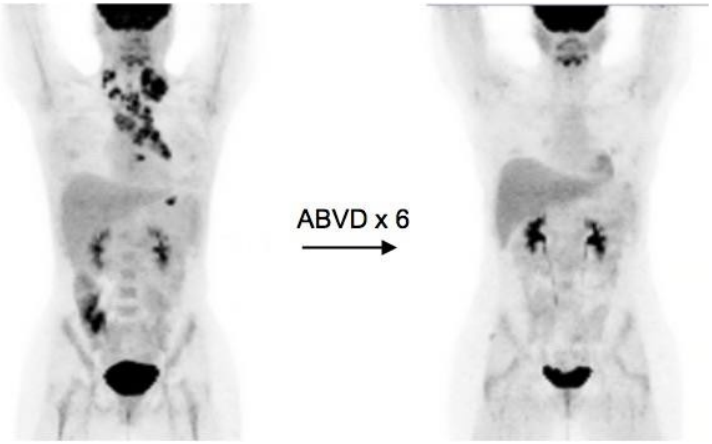
After 6x ABVD. Mediastinal node was biopsy proven refractory disease. PET-CT after salvage chemo showed CR






Suspected relapse
Rebiopsy
Negative
Observation[A]
Positive
Re-staging investigations
Initial stage IA-IIA (no prior RT, failure in initial sites)
Non-cross-resistant chemotherapy +RT
CMR[B]
+/- ASCT[C]
< CMR
Other
Primary refractory
Rebiopsy
Negative
Observation[A]
Non-cross-resistant chemotherapy +/- RT
< CMR
CMR
ASCT[C] +/- RT
Non-cross-resistant chemotherapy (can include brentuximab vedotin or bendamustine) +/- RT
CMR or PR[B,D]
ASCT +/- RT vs. AlloSCT[E]
Progression

A



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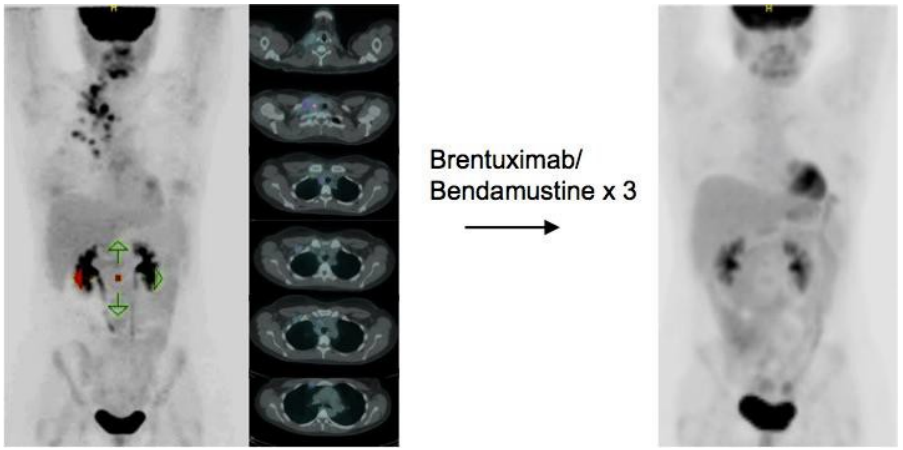

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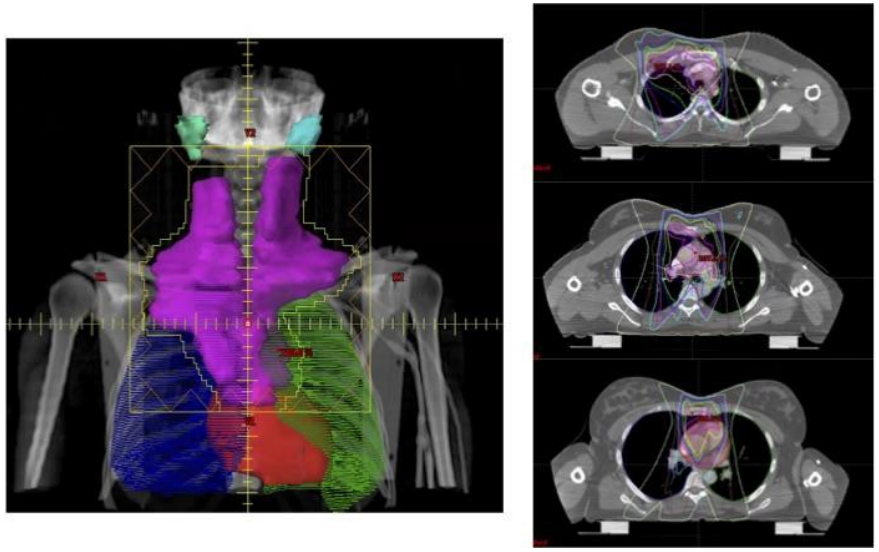
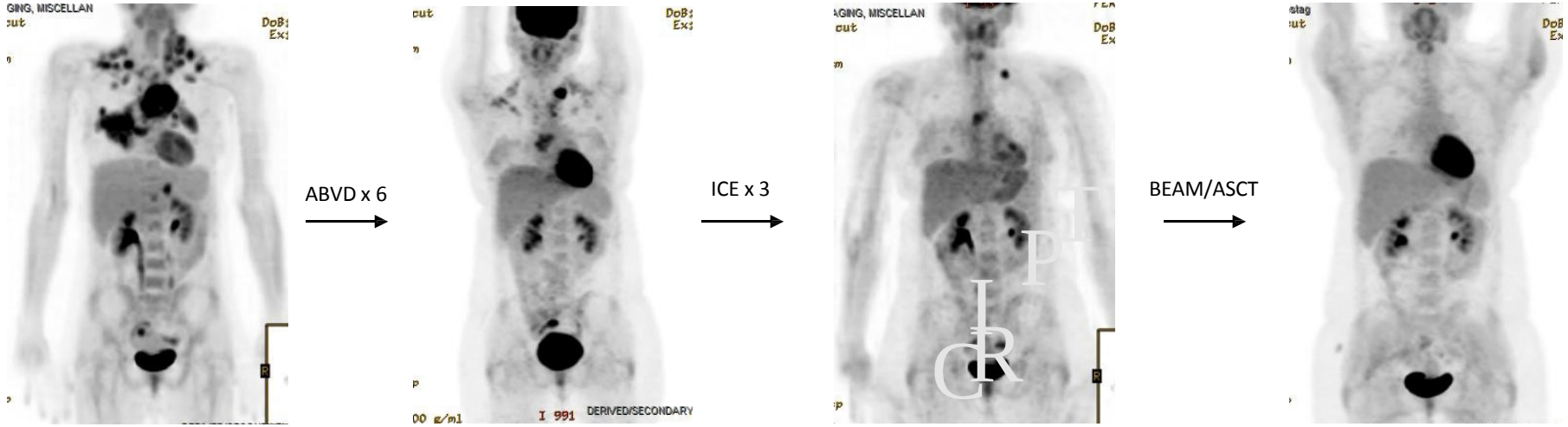


D

	Lungs	Heart	Left Ventricle
Mean dose	8.5 Gy	6.8 Gy	1.3 Gy
V20	18.7%	15.6%	
V15	23.9%	20.5%	
V5	41.3%	29.6%	

A



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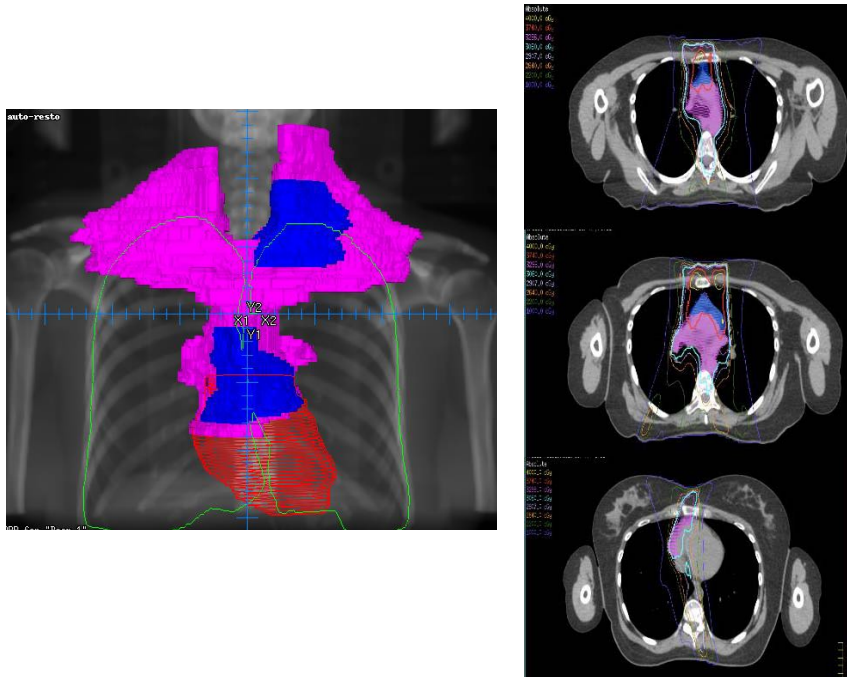

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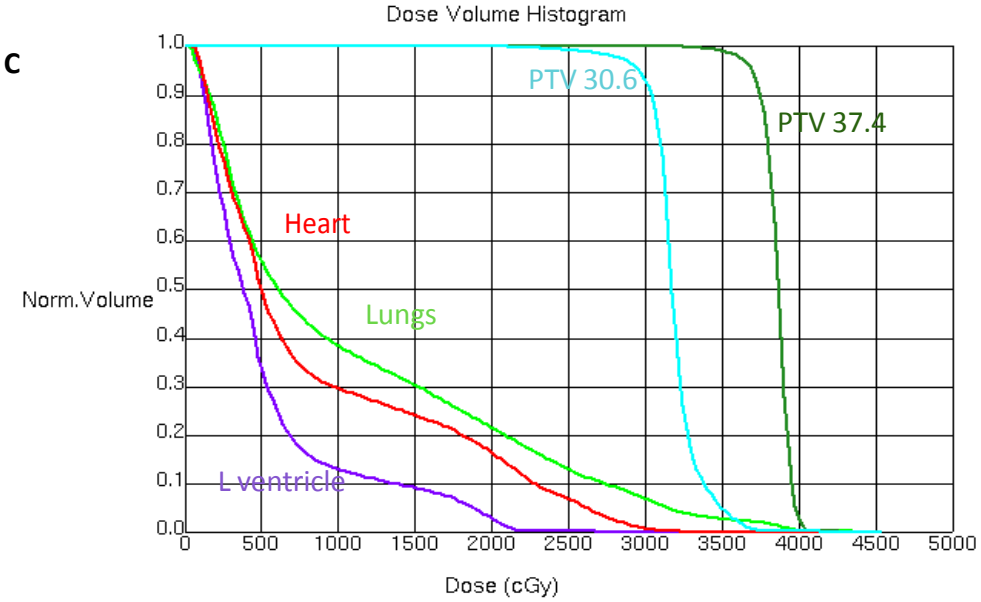
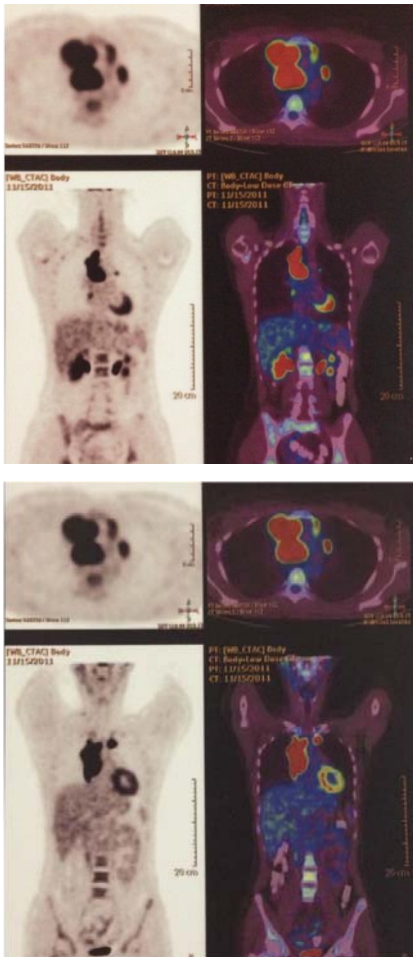
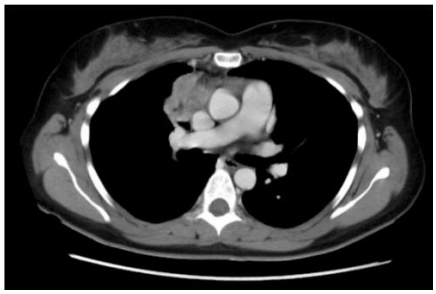


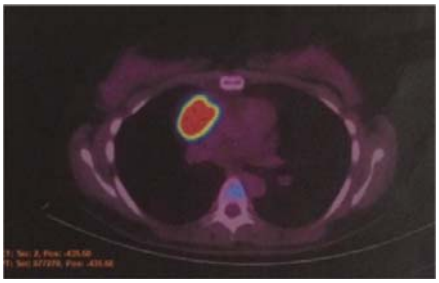
	Lungs	Heart	Left Ventricle
Mean dose	10.8 Gy	8.7 Gy	5.0 Gy
V20	22%	16%	
V15	30%	25%	
V5	55%	50%	

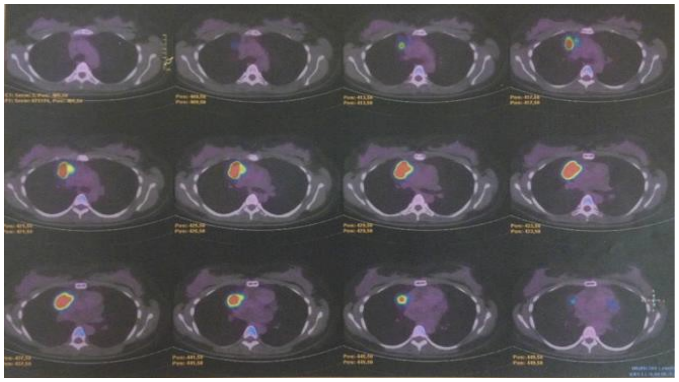
A



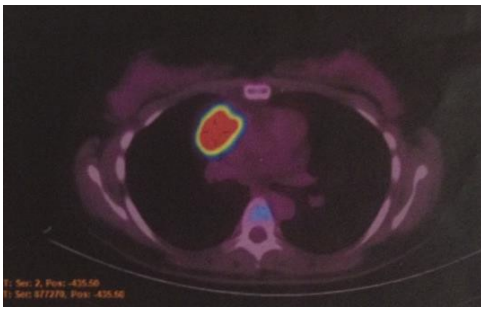
B



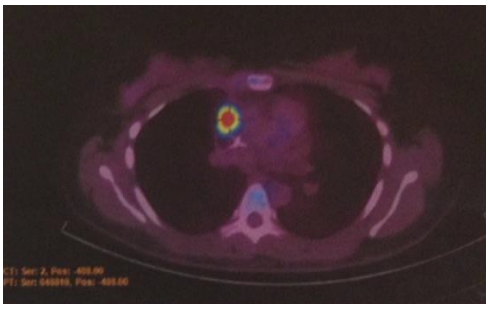




C

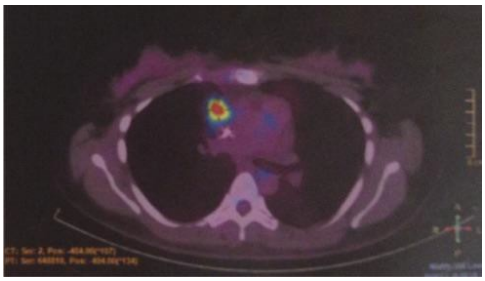


At relapse

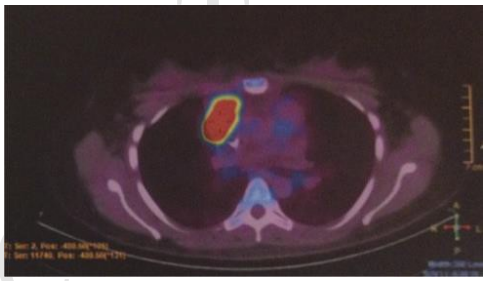


After 2 IGEV

D

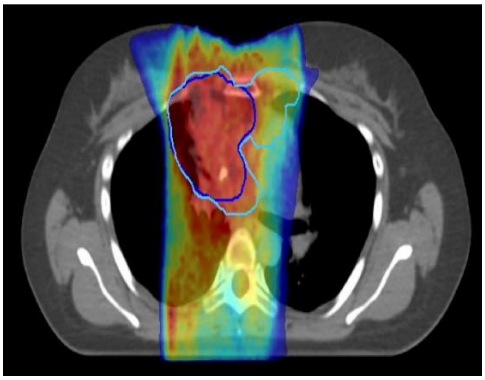


After 2 IGEV

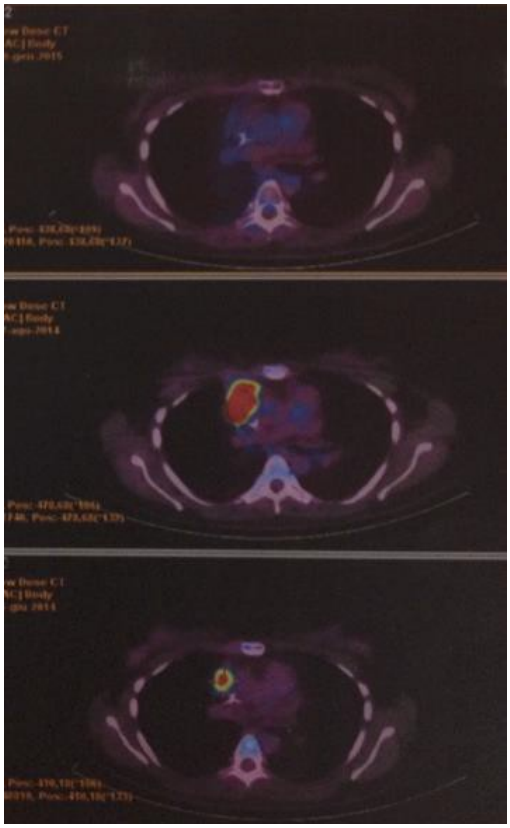


After 4 IGEV

E



F



After ASCT

After 4 IGEV

After 2 IGEV