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Full Length Article

The role of radiotherapy in patients with refractory Hodgkin's lymphoma after treatment with brentuximab vedotin and/or immune checkpoint inhibitors

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ABSTRACT

Background: Approximately 10%–30% of patients with Hodgkin's lymphoma (HL) experience relapse or refractory (R/R) disease after first-line standard therapy. Brentuximab vedotin (BV) and immune checkpoint inhibitors (ICIs) have important roles in the salvage treatment of R/R HL. However, subsequent treatment for HL refractory to BV and/or ICI treatment is challenging.

Methods: We retrospectively analyzed patients in two institutions who had R/R HL, experienced BV or ICI treatment failure, and received radiotherapy (RT) thereafter. The overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) were analyzed.

Results: Overall, 19 patients were enrolled. First-line systemic therapy comprised doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD, 84.2%); AVD plus ICIs (10.5%); and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP, 5.3%). After first-line therapy, 15 (78.9%) and four patients (21.1%) had refractory disease and relapsed, respectively. After R/R HL diagnosis, six (31.6%), two (10.5%), and 11 (57.9%) patients received BV and ICIs concurrently, BV monotherapy, and ICI monotherapy, respectively. All patients received intensity-modulated RT ($n = 12$, 63.2%) or volumetric modulated arc therapy (VMAT; $n = 7$, 36.8%). The ORR as well as the complete response (CR) rate was 100%; the median DOR to RT was 17.2 months (range, 7.9–46.7 months). Two patients showed progression outside the radiation field; one patient had extensive in-field, out-of-field, nodal, and extranodal relapse. With a median follow-up time of 16.2 months (range, 9.2–23.2 months), the 1-year PFS and OS were 84.4% and 100%, respectively. PFS was associated with extranodal involvement ($P = 0.019$) and gross tumor volume ($P = 0.044$). All patients tolerated RT well without adverse events of grade ≥ 3.

Conclusion: RT is effective and safe for treating HL refractory to BV or ICIs and has the potential to be part of a comprehensive strategy for HL.

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1. Introduction

Hodgkin's lymphoma (HL) is an unusual B-cell neoplasm that occurs mainly in young adults. The number of new cases of HL worldwide in 2020 was estimated to be 83,087.[1] Over the past few years, first-line therapy tailored to risk and response has significantly improved cure rates and long-term survival associated with HL.[2] Although 90% of the affected patients can be cured with the standard doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen, the remaining have been reported to be resistant to standard treatment and need salvage therapeutic strategies.[3,4] Efforts have been made to improve the efficacy of salvage treatments, including chemotherapy followed by autologous hematopoietic cell transplantation (AHCT) or the addition of novel agents.[5,6]

Brentuximab vedotin (BV) and immune checkpoint inhibitors (ICIs) have revolutionized the treatment paradigm for patients with refractory or relapsed (R/R) disease, resulting in response rates higher than 50%.[4,7-14] These new agents have been subsequently included in earlier lines of therapy, including pre-AHCT salvage, post-AHCT consolidation, and first-line treatments.[15-22] This change in practice means that patients with single- or double-refractory (refractory to BV and/or ICIs) disease are becoming a common clinical problem.[6] Consequently, there is a strong need to identify additional effective salvage options that can provide long-term disease control with acceptable toxicity.

Radiotherapy (RT) was the original mainstay of treatment for patients who had early-stage disease with a favorable prognosis in the 1960s.[23] However, extended-field and high-dose RT have been reported to be associated with the development of cardiovascular disease and secondary solid tumors.[24-26] The German Hodgkin Study Group's trials HD10 and HD11 allowed the radiation field and dose to be reduced, leading to the widespread use of the combined approaches in patients with early-stage HL and a favorable prognosis.[3,27] More recently, three randomized controlled trials (RAPID, H10, and HD16) were designed to demonstrate that chemotherapy alone was not inferior in combined modality treatment, but failed.[28-30] This impressive evidence suggests that RT may have value as a noncross-resistant therapy to improve the cure rate of patients with R/R disease. Therefore, this retrospective study was aimed to evaluate the preliminary findings of RT application in patients with HL who were refractory to treatment with BV and/or ICIs.

2. Materials and methodss

2.1. Patient inclusion

Two institutional databases (Fujian Medical University Union Hospital and Sun Yat-sen University Cancer Center) were retrospectively reviewed to identify HL patients treated with RT between November 2018 and February 2022. The inclusion criteria for this study were (1) a histologically confirmed diagnosis of classical HL; (2) treatment with BV and/or ICIs; (3) subsequent disease refractory to treatment with BV and/or ICIs. (4) hypermetabolic residual lesions detected on positron emission tomography/computed tomography (PET/CT) after BV or ICIs. Initial and salvage treatment data before BV/ICI administration were collected from electronic data sources, including chemotherapy regimens, use of RT, response to the initial therapy, AHCT, and the outcome of the last treatment before treatment with BV/ICIs. In addition to the clinical factors mentioned above, disease volume and sites at the time of disease discovery as being refractory to BV and/or ICI treatment were collected. Finally, information about RT was collected, including dose, response, survival data, treatment failure pattern, and toxicity.

Treatment responses were evaluated using PET/CT according to the 2014 Lugano Criteria.[31] Adverse events were assessed using the Common Terminology Criteria for Adverse Events version 5.0.

2.2. Radiotherapy

Patients were immobilized in the supine position with a thermoplastic mask for the head-neck-shoulder region or the body. Three-dimensional CT simulation was performed using 5-mm slices with contrast enhancement. Localization images were uploaded to the VARIAN Eclipse Treatment Planning System, version 15.6. Involved-site radiation therapy was administered according to the guidelines of the International Lymphoma Radiation Oncology Group. The post-BV and/or post-ICI gross tumor volume (GTV) was defined as hypermetabolic residual lesions detected on PET/CT. Adjacent nodal diseases that responded to treatment with BV and/or ICIs were included in the clinical target volume (CTV), provided their inclusion was not associated with marked toxicity. A 5-mm left–right and anterior–posterior expansion and 5- to 10-mm superior–inferior expansion of the GTV and CTV were used to obtain the corresponding planning gross target volume (PGTV) and planning target volume (PTV), respectively. The organs at risk included the parotid glands, spinal cord, lungs, heart, esophagus, and female breasts.

2.3. Statistical methods

The overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) were analyzed. ORR was defined as the proportion of patients with either a complete response (CR) or a partial response (PR) following treatment. DOR was defined as the duration of time from the initial objective response to progression. PFS was defined as the time from the treatment to disease progression or death. OS was defined as the time from the treatment to death due to any reason.

Continuous variables are summarized in the form of median and range values, and categorical variables are summarized in the form of frequencies and percentages. Survival analysis was performed using the Kaplan–Meier method with 95% confidence interval (CI) estimates. Univariate analysis was performed using the log-rank test. A two-sided *P*-value of < 0.05 was considered significant. Data were analyzed with SPSS (version 23.0) and R (version 3.5.3) software.

3. Results

3.1. Patient characteristics

Between November 2018 and February 2022, 19 patients were enrolled in this study. The patients' baseline characteristics are listed in Table 1. The median patient age was 23 (range, 10–60) years. The ratio of male-to-female patients was 10∶9. The HL types noted among the patients were as follows: 13 patients had nodular sclerosis classic HL, three patients had mixed-cellularity classic HL, and three patients had lymphocyte-rich classic HL. At the time of initial staging, 9, 5, and 5 patients were in stages II, III, and IV of the disease according to the Ann Arbor staging system, respectively. Ten patients (52.6%) were diagnosed with extranodal disease. Stage before RT was the same as the initial stage.

The majority of the patients (n = 16, 84.2%) received ABVD as their frontline therapy, two patients (10.5%) received doxorubicin, vinblastine, and dacarbazine plus ICIs, and one patient (5.3%) received bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). Four patients (21.1%) received first-line consolidation RT. After first-line therapy, 15 patients (78.9%) were found to have refractory disease, and four patients (21.1%) relapsed with a median DOR of 22.3 months. Of the patients who were diagnosed with R/R disease, 6 (31.6%), 2 (10.5%), and 11 (57.9%) patients received BV and ICIs concurrently, BV monotherapy, and ICI monotherapy, respectively. The median numbers of BV and ICI cycles were 2 (range, 2–6 cycles) and 6 (range, 2–22 cycles), respectively.

Table 1
Clinical characteristics of the 19 patients with refractory Hodgkin's lymphoma after treatment with BV and/or ICIs.

Characteristics	No. (%)
All	19 (100)
Sex	
Male	9 (47.4)
Female	10 (52.6)
Age, years	
≤23	11 (57.9)
> 23	8 (42.1)
Stage at the initial diagnosis	
II	9 (47.3)
III	5 (26.3)
IV	5 (26.3)
Extranodal involvement at baseline	
Yes	10 (52.6)
No	9 (47.4)
Involved regions at baseline	
1–2	2 (10.5)
3–4	8 (42.2)
≥ 5	9 (47.3)
Histologic subtype	
Nodular sclerosis	13 (68.4)
Lymphocyte rich	3 (15.8)
Mixed cellularity	3 (15.8)
First-line regimen	
ABVD	16 (84.2)
AVD + ICI	2 (10.5)
BEACOPP	1 (5.3)
Initial radiotherapy	
Yes	4 (21.1)
No	15 (78.9)
Response to first-line therapy	
Refractory disease	15 (78.9)
Relapse	4 (21.1)
Salvage treatment with BV or ICIs	
BV	2 (10.5)
ICIs	11 (57.9)
BV and ICIs	6 (31.6)

Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; AVD, adriamycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone; BV, brentuximab vedotin; ICIs, immune checkpoint inhibitors.

The most commonly used ICIs included tislelizumab and sintilimab. Response to BV included PR (50%), stable disease (SD, 12.5%) and progression disease (PD, 37.5%), respectively. Response to ICIs included PR (58.8%), SD (11.8%) and PD (29.4%), respectively. Two patients received AHCT after BV or ICIs; however, they still showed disease progression.

3.2. RT target and dosimetry analysis

All patients received intensity-modulated RT (IMRT; $n = 12$, 63.2%) or volumetric modulated arc therapy (VMAT; $n = 7$, 36.8%). The median time from RT to the beginning of BV or ICI treatment was 5.1 months (range, 2.0–19.5 months). PET-guided RT was applied to all patients, and the median maximum standard unit value (SUV_{max}) was 6.0 (range, 2.5–10.3). The median GTV and CTV were 53.9 and 365.5 mL, respectively (Table 2). The prescribed median dose was 26 Gy for the PTV with a simultaneous integrated boost of 36 Gy for residual disease (PGTV) in daily fractions of 2–3 Gy.

The dose-volume statistics for the critical normal tissues are shown in Table 3. The mean dose to the lungs and lung irradiated by 20 Gy or more (V_{20}) were 9.4 Gy and 14.4%, respectively. The mean dose to the heart was 6.4 Gy, indicating good cardiac protection. The median maximum dose to the spinal cord was 21.5 Gy. The mean doses to the left and right parotid glands, thyroid gland, esophagus, and left and right breasts were 0.8, 12.0, 7.4, and 3.4 Gy, respectively.

Table 2
Radiation target and dosimetry parameters in the 19 patients.

Characteristics	Value
Target delineation with PET, No. (%)	19 (100.0)
RT technique, No. (%)	
IMRT	12 (63.2)
VMAT	7 (36.8)
Sites of RT, No. (%)	
Cervical/axillary/infraclavicular	11 (57.9)
Mediastinal	15 (78.9)
GTV, mL	
Median (range)	53.9 (5.4–238.0)
CTV volume, mL	
Median (range)	365.5 (102.0–843.8)
Dose to GTV, Gy	
Median (range)	36 (25.5–56.0)
Dose to CTV, Gy	
Median (range)	26.4 (20.0–30.0)
Number of fractions	
Median (range)	17 (10–25)

Abbreviations: CTV, clinical target volume; GTV, gross target volume; IMRT, intensity modulated radiation therapy; PET, positron emission tomography; RT, radiotherapy; VMAT, volumetric modulated arc therapy.

Table 3
Dose-volume statistics for serial normal critical structures.

Characteristics	Median (range)
Spinal cord, maximum dose, Gy	21.5 (7.6–40.7)
Heart, mean dose, Gy	6.4 (0.3–15.4)
Lung	
V_{20}, %	14.4 (0.2–31.4)
Mean dose, Gy	9.4 (3.1–15.7)
Parotid glands, mean dose, Gy	0.8 (0.8–0.8)
Thyroid gland, mean dose, Gy	12.0 (0.7–25.1)
Esophagus, mean dose, Gy	7.4 (0.3–14.8)
Breast, mean dose, Gy	3.4 (2.9–13.4)

Abbreviation: V_{20}, percentage of lung volume irradiated with 20 Gy or higher.

3.3. Response to RT and survival

Overall response and CR to RT were achieved in 16 patients (100%), who were assessed using PET/CT (Fig. 1). No patient died during the follow-up period. With a median follow-up time of 16.2 months (range, 9.2–23.2 months) for all patients, the 1-year OS, local control (LC), and PFS rates were 100%, 100%, and 84.4%, respectively (Fig. 2). The median DOR to RT was 17.2 months (range, 7.9–46.7 months). In the explorative analysis, PFS was associated with extranodal involvement ($P = 0.019$) and GTV ($P = 0.044$, Fig. 2). Concurrent application of BV and ICIs or monotherapy was not related to PFS ($P = 0.74$).

3.4. Failure pattern and toxicity

Three patients had relapse at 9, 11, and 15 months after RT, respectively. Of those patients, two experienced out-of-field relapse, and one had extensive in-field and out-of-field nodal relapse (Fig. 3). One of three replased patients received repeated irradiation at the involved sites after treatment failure. All patients tolerated RT well without any grade ≥ 3 adverse events (Table 4). Radiation-related adverse events included leukocytopenia in three patients (grade 1: one patient, grade 2: two patients), oral mucositis in four patients (grade 1: three patients, grade 2: one patient), and radiation dermatitis, asymptomatic pneumonia, and fatigue in one patient (grade 1).

4. Discussion

Refractory disease after treatment with BV or ICIs has been an emerging phenomenon in the treatment of HL. Because of the rarity and heterogeneity of HL, optimizing the combination and sequence of local

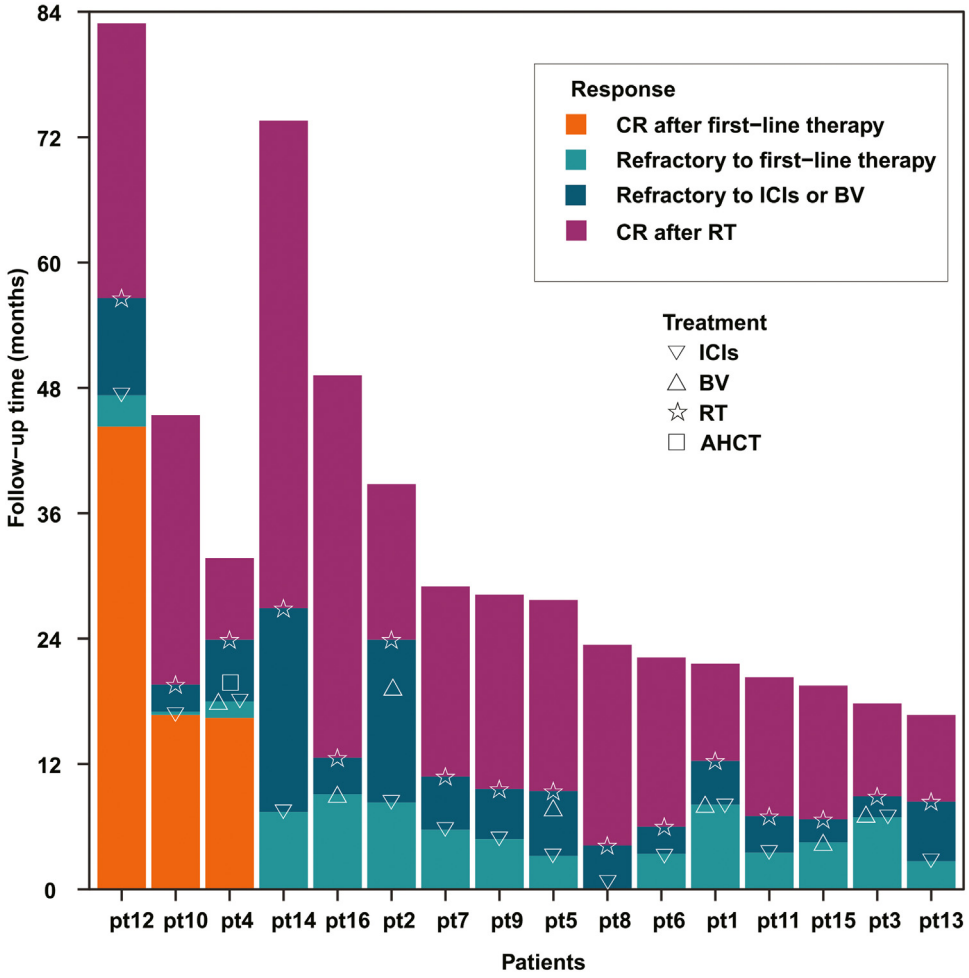

Fig. 1. Treatment and response of 16 evaluable patients diagnosed with refractory or relapsed Hodgkin's lymphoma. The length of each bar represents the follow-up time from the initial diagnosis of each patient with Hodgkin's lymphoma; each symbol indicates the initiation of different treatments, including ICIs, BV, and RT; and each color shows the response to these treatments. AHCT, autologous hematopoietic cell transplantation; BV, brentuximab vedotin; CR, complete response; ICIs, immune checkpoint inhibitors; pt, patient; RT, radiotherapy.

Table 4
Incidence of RT-related toxicities.

Toxicities	No. (%)
Leukocytopenia	
Grade 1	1 (5.3)
Grade 2	2 (10.5)
Oral mucositis	
Grade 1	3 (15.8)
Grade 2	1 (5.3)
Radiation dermatitis	
Grade 1	1 (5.3)
Asymptomatic pneumonia	
Grade 1	1 (5.3)
Fatigue	
Grade 1	1 (5.3)

Abbreviation: RT, radioterapy.

and systemic treatments for these patients remains challenging. To our knowledge, this is the first study to demonstrate that RT was effective and safe for HL refractory to BV or ICI treatment. Patients with extra-nodal involvement or GTV ≥ 54 mL had a significantly lower PFS than did patients without extra-nodal involvement or GTV < 54 ml. These findings highlight the importance of seeking out the optimal combination of RT and subsequent novel therapies for the prevention of disease progression.

This study constitutes a critical step toward understanding the role of RT in patients with poor response to BV or ICIs. RT was a radical treatment for patients with early-stage HL in the 1960s.[23] Subsequently, the effectiveness of RT for improving PFS has been well established for newly diagnosed early-stage HL by multiple randomized controlled trials. The additional benefit of RT has been found to be substantial across the subgroups examined, regardless of subgroups stratified according to the risk and early response to chemotherapy.[3,27] However, considering potential late organ dysfunction and the risk of second primary malignancies among young adults, the question of whether novel targeted agents or more intensive regimens may compensate for the role of RT remains. No matter how effective it is in terms of LC, RT in diffuse large B-cell lymphoma (DLBCL) provides no survival benefit if distant failure outweighs the risk of local failure. In contrast to DLBCL, HL is highly sensitive to chemotherapy, and in most cases (> 80%), relapsed disease after ABVD affected the originally involved areas in patients with HL. Henceforth, it is logical to use RT in selecting patients to ensure optimal results and avoid significant morbidity.

While 90% of the patients with HL can be cured by standard first-line treatment, 10%–30% of patients show relapse or refractory disease after the standard first-line treatment.[4,7] Younger patients tend to be healthier, and therefore, can often tolerate higher-intensity chemotherapy and AHCT. Thus, AHCT was reported to afford a better prognosis and adopted as the standard treatment for R/R patients, according

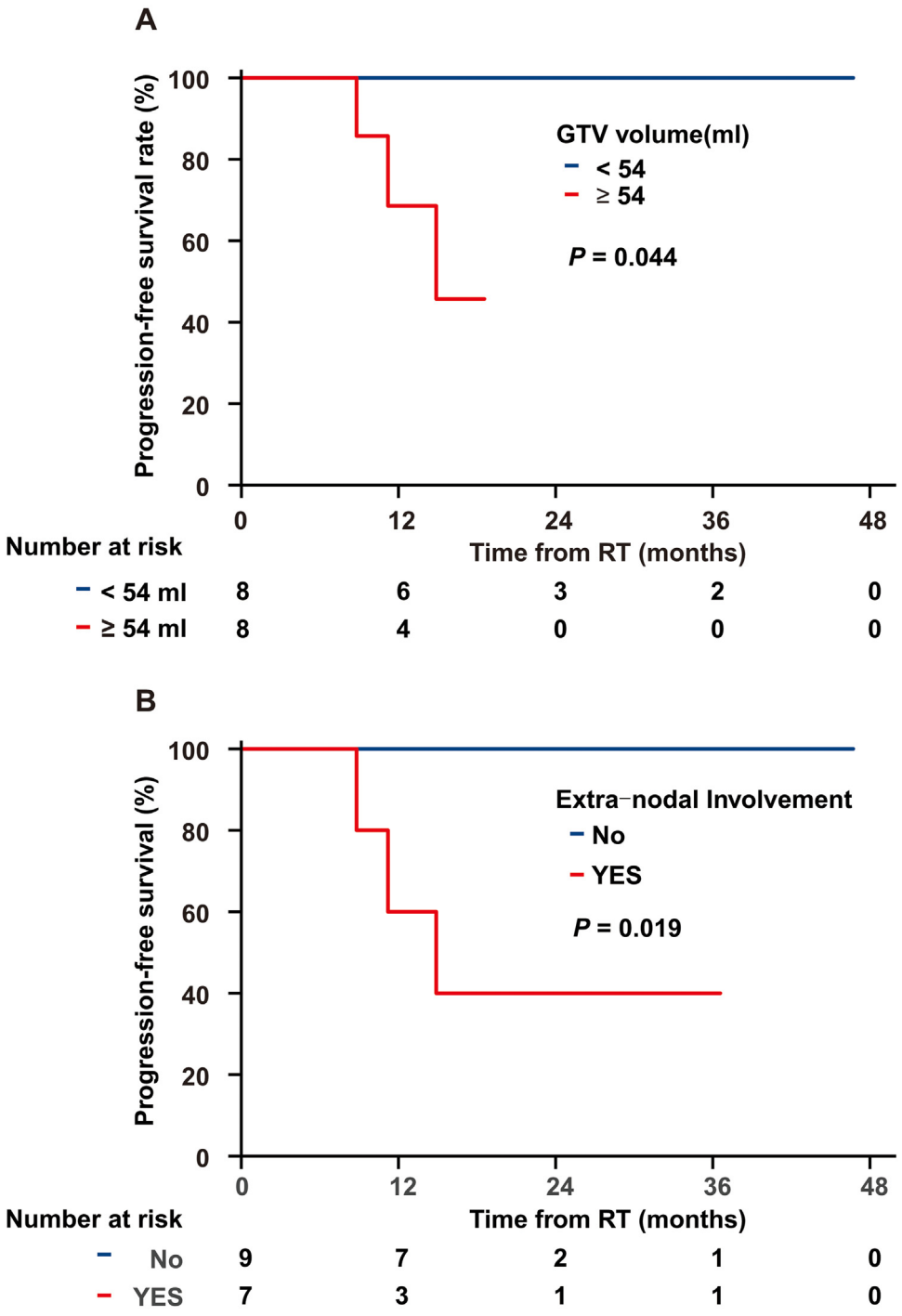

Fig. 2. Progression-free survival rate of 16 evaluable patients diagnosed with refractory or relapsed Hodgkin's lymphoma, stratified by extranodal involvement and GTV. Progression-free survival was worse when patients had extranodal involvement (A) and GTV ≥ 54 ml (B). GTV, gross target volume; RT, radiotherapy.

to the guidelines.[32,33] Patients with R/R HL who were ineligible for transplantation, including those with disease refractory to AHCT, have dismal outcomes with salvage chemotherapy. BV and ICIs have revolutionized the treatment paradigm for these patients, leading to response rates ranging from 50% to 93% and CR rates between 12% and 81%. However, the higher response rate with a single agent did not translate into a long-term survival benefit. More recently, although a 95% CR rate was achieved with pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin (pembro-GVD) for R/R disease in a phase 2 study, 95% of patients still received subsequent AHCT.[34] Logically, for patients with a high risk of widespread systemic relapse (high risk of out-of-field relapse), the ultimate goal of using novel agents and RT is achieving a favorable CR rate before AHCT. On the other hand, for patients with a low risk of systemic relapse, BV and/or ICIs plus RT may be the optimal therapeutic combinations. The extension of the disease may have some impact on the response to radiotherapy and the duration of remission. In our study, all 19 patients achieved CR after RT, so the relationship between stage and response could not be performed.

This retrospective study had some limitations. RT was not randomly assigned, and there is a chance that the selection bias may have affected the results. In clinical practice, patients with localized residual disease are most likely to receive RT. However, our results provide important

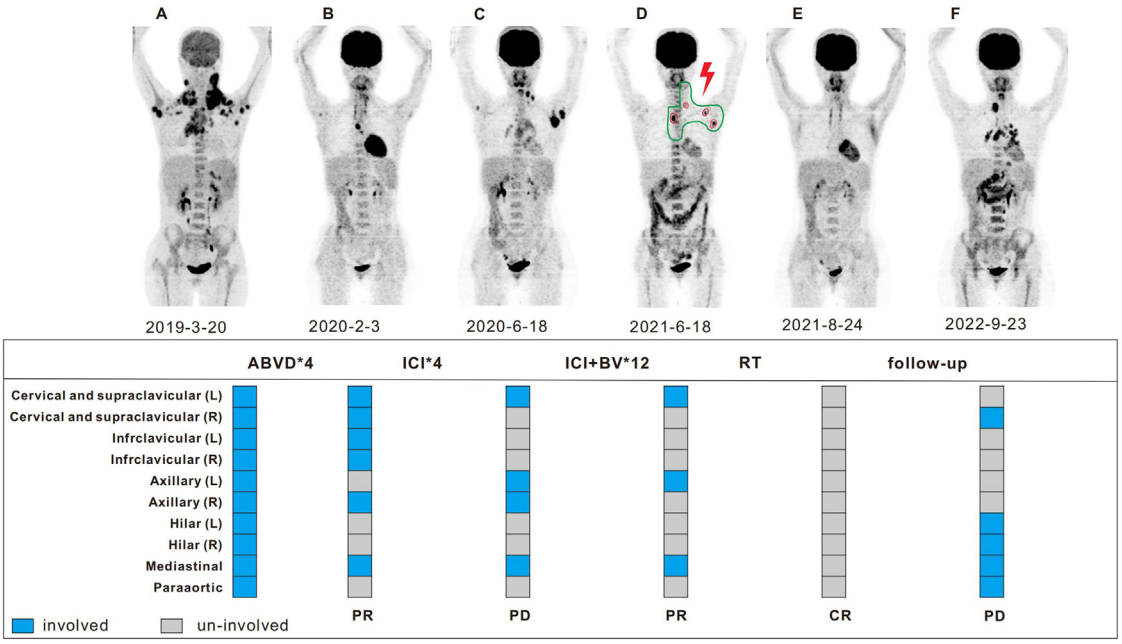

Fig. 3. A 23-year-old female patient was diagnosed with Hodgkin's lymphoma, stage IV. (A) The initially involved sites included bilateral cervical, supraclavicular, infraclavicular, axillary, hilar, mediastinal, splenic hilus, paraaortic, sternal, and vertebral sites. (B) PET after ABVD revealed residual lesions in cervical, supraclavicular, infraclavicular, mediastinal, and axillary regions. The disease was refractory to ABVD; the patient then received ICIs followed by BV. (C) PET after treatment with ICIs and BV showed cervical, supraclavicular, and axillary hypermetabolic lesions. (D, E) Subsequently, RT was administered and a complete metabolic response was achieved (20 Gy to the CTV and 30 Gy to the GTV). (F) PET performed 14 months after RT showed extensive progression at the paraortic, hilar, mediastinal, and supraclavicular sites. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BV, brentuximab vedotin; CTV, clinical target volume; GTV, gross target volume; ICI, immune checkpoint inhibitors; L, left; PET, positron emission tomography; R, right; RT, radiotherapy.

information on individualized treatment in single- or double-refractory HL patients, especially in view of the challenges in conducting randomized trials to evaluate the role of RT. The local control rate of RT in this study was similar to that in some earlier studies, regardless of the total dose and fractions used. Owing to the small sample size treated with hypofractionated RT and a short follow-up time, a long follow-up will be necessary to assess late toxicity with RT over time. We believe that additional work is required to optimize the RT dose, combination, and sequence of RT and systemic treatment in different risk groups.

5. Conclusions

In conclusion, this study demonstrated that RT was effective and safe for the management of HL refractory to BV or ICIs. Our results provide potential evidence to support the use of RT as part of a comprehensive strategy to cure HL.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics statement

The study was conducted in compliance with the principles of the Declaration of Helsinki, and approved by the institutional review boards of Fujian Medical University Union Hospital and Sun Yat-sen University Cancer Center (approval number: 2022WSJK019), which waived the requirement for signed informed consent because of the retrospective nature of the study.

Consent for publication

The patient whose medical images are presented in this manuscript provided consent for publication of her medical images for the manuscript. Only de-identified data and images are used in this manuscript.

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Data availability

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Author contributions

Y.Y., Y.Z., and T.L conducted the research conception and design and provided administrative support. R.Z., H.S., Y.Q., G.S., T.T., S.C., C.H., S.L., J.C., H.F., J.L., J.S., T.L., Y.Z., and Y.Y. provided the study material or patients. R.Z., H.S., Y.Q., G.S., T.T., S.C., C.H., S.L., and J.C. collected and assembled the data. R.Z., Y.Y., Y.Z., J.C., and T.L. analyzed and interpreted the data. All of the authors participated in the manuscript drawing and final approval.

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