REGULAR ARTICLE

blood advances

Patterns of progression after immune checkpoint inhibitors for Hodgkin lymphoma: implications for radiation therapy

Jessica F. Burlile,[1] Kelsey M. Frechette,[1] William G. Breen,[1] Steven R. Hwang,[2] Alexandra S. Higgins,[2] Adrienne N. Nedved,[3] William S. Harmsen,[4] Sydney D. Pulsipher,[4] Thomas E. Witzig,[2] Ivana N. Micallef,[2] Bradford S. Hoppe,[5] Thomas M. Habermann,[2] Gita Thanarajasingam,[2] Patrick B. Johnston,[2] David J. Inwards,[2] N. Nora Bennani,[2] Jennifer L. Peterson,[5] Bradley J. Stish,[1] William G. Rule,[6] Stephen M. Ansell,[2] and Scott C. Lester[1]

[1]Department of Radiation Oncology and [2]Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN; [3]Department of Pharmacy, Mayo Clinic, Rochester, MN; [4]Department of Biostatistics and Health Sciences Research, Mayo Clinic, Rochester, MN; [5]Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL; and [6]Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ

Key Points

- The cumulative incidence of local-only progression for patients with pre-ICI limited disease was 34%.
- Patients with limited disease may benefit from consolidative RT, as the potential for preventing relapse could be as high as 1 in 3.

Immune checkpoint inhibitors (ICIs) have demonstrated remarkable response rates in relapsed or refractory Hodgkin lymphoma (HL). Still, most patients eventually progress. Patterns of progression after ICIs are not well described and are essential to defining the role of local therapies in combination with ICIs. We identified patients who received ICIs for HL between 2013 and 2022. Fludeoxyglucose-18 positron emission tomography (FDG-PET) before initiating ICI and at progression on/after ICI were reviewed, and areas of active HL were recorded. An exploratory analysis of treatable progression included patients with ≤5 sites of disease on pre-ICI FDG-PET and progression only at pre-ICI sites. Ninety patients were identified; 69 had complete records, and of these, 32 (52%) had relapsed at ICI initiation, 17 (25%) were refractory, and 16 (23%) received ICI as first-line therapy. Forty-five of 69 patients had ≤5 sites of disease (limited) on pre-ICI FDG-PET. Patients with >5 sites of disease had a higher risk of progression, and every site of disease >5 sites conferred an additional 1.2x higher chance of progression. At a median follow-up of 4.0 years, 41 of 69 patients had progressed on/after ICIs (cumulative incidence 66.4%), and of these, 22 of 41 patients progressed only at pre-ICI sites (cumulative incidence 39.4%). In an exploratory analysis, the cumulative incidence of a treatable progression among 45 patients with limited disease was 34%. The cumulative incidence of any progression among this cohort was 58.9%. More than one-third of patients with limited disease before ICIs experienced progression only at pre-ICI sites of disease. These patients could be candidates for radiation during or after ICIs.

Introduction

Hodgkin lymphoma (HL) is sensitive to chemotherapy and radiation therapy (RT) and is often cured using these modalities.[1] However, about 10% of patients will relapse or harbor refractory disease and will require escalation to high-dose chemotherapy (HDC) and stem cell rescue, with or without brentuximab consolidation.[1] About 50% of people who undergo autologous stem cell transplant (ASCT) will

Submitted 27 August 2023; accepted 18 December 2023; prepublished online on *Blood Advances* First Edition 5 January 2024; final version published online 1 March 2024. https://doi.org/10.1182/bloodadvances.2023011533.

Original data are available upon reasonable request from the corresponding author, Jessica. F. Burlile (burlile.jessica@mayo.edu).

The full-text version of this article contains a data supplement.

sustain durable disease control,[1] but relapse after ASCT is typically considered incurable. This is a devastating event for a young population, as over half of the patients who undergo transplant for HL are between the ages of 15 and 34 years.[2] Treatment for relapsed or refractory HL after ASCT includes allogeneic stem cell transplant, brentuximab vedotin and other CD30 antibodies, immune checkpoint inhibitors (ICIs) targeting programmed death signaling, and investigational agents such as histone deacetylase inhibitors, Janus kinase 2 inhibitors, and chimeric antigen receptor (CAR) T-cell therapy.[3] Of these, ICIs have shown promising results, and for relapsed and refractory disease, the addition of nivolumab results in durable disease control for some patients, with a median progression-free survival (PFS) of 14.7 months in the CheckMate 205 trial.[4]

However, despite these advances, most patients with relapsed or refractory disease do progress after ICIs, and additional therapeutic options are urgently needed.[5] Although the response kinetics of relapsed or refractory HL have been described, the patterns of progression and predictors for this type of progression remain poorly understood. Identifying these parameters will help identify opportunities for synergistic therapies to be deployed in conjunction with ICIs. Specifically, for patients with fewer areas of disease and a pattern of local progression, consolidative local therapies such as RT could be used. The goal would be to increase the durability of response to ICIs, potentially eliminate the need for indefinite ICIs, and possibly cure a subset of patients. Patients with more extensive disease or those with a pattern of progression predominantly at new sites would be more likely to benefit from systemic intensification in the context of clinical trials, including consideration of adoptive T-cell therapy.

Beyond hematologic malignancy, RT has been used successfully in the oligometastatic setting for multiple epithelial cancers. This has resulted in superior rates of local control, leading to improved overall survival for patients with limited disease.[6] Within the context of HL, patients with limited-volume disease before starting ICIs may also benefit from consolidative RT. For this group of patients, we postulate that comprehensive radiation may prevent or delay progression. With this paradigm in mind, we aim to investigate patterns of disease progression on or after ICI therapy for patients with HL. In an exploratory analysis, we identify a group that may benefit most from consolidative RT: those with limited disease pre-ICIs who progress exclusively locally.

Methods

This retrospective review was approved by the Mayo Clinic Institutional Review Board. All patients gave authorization for their medical data to be used for retrospective research.

Through a cancer center pharmacy search, we identified patients who received an ICI for HL between 2013 and 2022 at 1 institution. The pre-ICI Fludeoxyglucose-18 positron emission tomography (FDG-PET) and FDG-PET at progression on or after ICI were reviewed, with all sites of involvement and progression documented. We defined 14 discrete sites of disease. Eleven of the 13 lymph node regions defined by Ann Arbor staging were included; epitrochlear and popliteal were excluded because these were not completely captured on all FDG-PET scans. Sites soft tissue, bone or bone marrow, and parenchymal were added because many patients had disease present at these sites, yet they are not adequately captured within the lymph node regions of Ann Arbor staging. Multiple sites of distinct disease within these 3 categories were counted as separate sites (eg, a pelvic bone metastasis and a cervical vertebral metastasis are counted as 2 sites, not 1). Therefore, the 14 sites were: (1) Waldeyer's ring, (2) cervical and/or supraclavicular, (3) infraclavicular, (4) axillary and/or internal mammary, (5) hilar, (6) mediastinal, (7) para-aortic, (8) spleen, (9) mesenteric, (10) iliac, (11) inguinal or femoral, (12) soft tissue, (13) bone or bone marrow, and (14) parenchymal. These sites are listed in table form in supplemental Table 1.

We defined a treatable progression event as pre-ICI limited disease: (1) ≤5 sites on pre-ICI FDG-PET and (2) progression at only pre-ICI sites (ie, exclusively local relapse). These 5 sites of disease could be located anywhere in the body if it was considered reasonable to treat all 5 sites of disease during a single radiation treatment course. Patients who recurred at new sites or who had more than 5 initial sites on pre-ICI FDG-PET were excluded from this designation. This 5-site description of limited disease was chosen based on clinical experience of radio-encompasability and the fact that other oligometastatic publications,[6] as well as recent HL studies, have used a similar number of sites when investigating consolidative radiation.[7,8] In addition, it is worth noting that a traditional mantle radiation field would include (1) cervical and supraclavicular, (2) infraclavicular, (3) axillary, (4) hilar, and (5) mediastinal sites. Similarly, it would be reasonable to radiate 5 sites of disease, even if on opposite sides of the diaphragm, using involved field or involved node radiation techniques.

Clinical judgment was used when it came to categorizing patients into the limited or nonlimited disease category. For example, several patients had widespread bony disease, which was recorded as nonlimited even though only 1 site (bone) was involved. In contrast, patients with adjacent sites of disease within 5 cm, for example, tumors in the ipsilateral supraclavicular and infraclavicular sites, which could be encompassed within a single planning target volume, were considered 1 site instead of multiple sites of disease. This scenario was rare but did apply to 2 patients. The supplemental Materials, section 1.2, provides example cases.

Sites of disease on pre-ICI FDG-PET were also recorded for patients who did not progress after ICI, to analyze predictors and patterns of progression.

Descriptive statistics were generated for the group of 69 patients with complete records. Univariate Cox models for PFS were performed for the entire cohort of 69 patients to identify any characteristics that may be associated with progression. Death was a competing risk for this analysis. Cumulative incidence of a treatable progression as well as univariate Cox models for treatable PFS were run on both the complete cohort and the subset of patients with limited disease (≤5 sites). For this analysis, both a nontreatable progression (development of distant disease) and death were competing risks.

Results

We identified 90 patients who received an ICI for HL between 2013 and 2022. Twenty-one patients were excluded from this analysis because of incomplete or inaccessible outside medical records, incomplete FDG-PET scan data, or concurrent cancer

diagnoses, which confounded PET-CT interpretation. Sixty-nine patients were included in this patterns of progression analysis. Thirty-six (52%) patients received ICI after having achieved remission earlier in their disease course and were classified as relapsed. Refractory disease was seen in 17 patients (25%), and 16 patients received an ICI as first-line therapy (23%). Median time to progression was 4.0 years (interquartile range, 1.9-5.3 years).

Nivolumab was the most frequently prescribed ICI (78%), and pembrolizumab was the second most common (17%). More than half of patients received ICI monotherapy: 56% of the relapsed group and 36% of the nonrelapsed group. ICI monotherapy was the most frequently prescribed regimen in both groups. Combination ICIs such as ipilimumab and nivolumab, or ICIs in combination with brentuximab or cytotoxic chemotherapy, were also used. (supplemental Table 2) The median number of pre-ICI FDG-PET sites was 4 (interquartile range, 2-7; range, 1-12), and 50 patients (72.5%) had previously undergone HDC/ASCT. All but 2 of the relapsed or refractory cohorts had previously undergone ASCT.

The median number of previous treatments before ICI (including systemic therapies, HDC/ASCT, and nonpalliative radiation courses) was 4 (range, 0-16). Nearly half of patients (30 of 69, 43%) had received radiation at some point in their treatment course leading up to ICI. Of the 30 patients, 17 had received more than 1 course of radiation or had more than 1 site treated, for a total of 57 radiated sites (see supplemental Table 3 for more details). The median number of treatments before ICI for this group was 6.5. Most sites of disease (39 of 57, 68%) remained controlled at the time of ICI initiation. Twenty-one percent (12 of 57) definitely showed disease persistence or recurrence, and 6 sites (12%) could not be evaluated because of incomplete records. Therefore, 39 of 51, or 76% of evaluable sites, were controlled at the time of ICI initiation.

Most patients were less than 50 years of age (69.6%), and most had nodular sclerosis HL (85.5%). All stages of HL were represented: 63.7% had either stage III or IV disease at initial HL diagnosis (Table 1). Nearly 20% of patients (8 of 41) who progressed had discontinued ICIs because of immune-related adverse events, and overall, 16% of patients (11 of 69) discontinued ICIs because of immune-related adverse events.

Survival among the entire cohort

Of the 69 patients, 45 (65.2%) had ≤5 sites of disease on pre-ICI FDG-PET. Twenty-four were alive without progression at the time of analysis. Four had died without progression, 18 had died with progression, and 23 had progressed but were alive (Table 2). Among the 45 patients with ≤5 sites of disease, at the last follow-up, 20 were alive without progression, 4 had died without progression, 10 had died with progression, and 14 were alive with progression.

Of the 17 patients with refractory disease at the time of ICI initiation, 11 (65%) experienced progression after ICI. In contrast, 25 of the 36 patients (69%) with relapsed disease at the time of ICI initiation experienced progression after ICI (Table 3).

However, the pre-ICI relapsed group harbored more patients with a treatable progression after ICIs (exclusively local progression at ≤5 sites). Twenty-two percent (22%) or 2 of 11 total patients who were pre-ICI refractory, compared with 36% or 9 of 25 total patients who relapsed, experienced a treatable progression.

Table 1. Patient characteristics

		N	%
Age at ICI initiation	Median age	40.1 y	
	<50	48	69.6
	50-59.9	7	10.1
	60-69.9	6	8.7
	70-79.9	5	7.2
	≥80	3	4.3
Sex	Female	33	47.8
	Male	36	52.2
Histology	Nodular sclerosing	59	85.5
	Mixed cellularity	3	4.3
	Classical NOS	6	8.7
	Lymphocyte rich	1	1.4
Bulky	Yes	21	30.4
	No	47	68.1
	Unknown	1	1.4
Extranodal disease	Yes	29	42.0
	No	40	58.0
Stage at diagnosis	I	2	2.9
	II	23	33.3
	III	15	21.7
	IV	29	42.0
Pre-ICI disease	Relapsed	36	52.2
	Refractory	17	24.6
	First diagnosis	16	23.2
Previous ASCT	Yes	50	72.5
	No	19	27.5
Previous radiation	Yes	30	43.5
	No	39	56.5
ICIs used	Nivolumab	54	78.3
	Pembrolizumab	12	17.4
	Other	3	4.3
Number of disease sites at ICI initiation	≤5 sites	45	65.2
	>5 sites	24	34.8
Number of therapies before ICIs	Mean	4.4 therapies	
	Q1, Q3	1, 6	
	Range	0-16	

NOS, not otherwise specified.

Table 2. Survival outcomes

	Outcome		
	Alive	Died	Total
No progression	24	4	28
Progression	23	18	41
Total	47	22	69

Table 3. Type of progression stratified by pre-ICI disease state

	Local	Distant	Local and distant	Total progression	No progression	Total
Initial diagnosis	4	–	1	5	11	16
Relapsed	11	1	13	25	11	36
Refractory	5	–	6	11	6	17
Total	20	1	20	41	28	69

Risk of progression among the entire cohort

Patients with >5 sites of disease were 2.2 times more likely to progress than those with ≤5 sites of disease (95% confidence interval [CI], 1.18-4.08; $P = .013$). Every site of disease over 5 sites conferred an additional 1.2 times higher chance of progression (95% CI, 1.05-1.29; $P = .003$). Of note, 30% of patients had disease only above or only below the diaphragm at the time of ICI initiation; this cohort did not have a lower risk of progression compared with patients with disease on both sides of the diaphragm.

Male patients were less likely to progress compared with female patients (hazard ratio, 0.49; 95% CI, 0.26-0.91; $P = .024$), and the number of previous lines of therapy was not associated with progression. Of the patients who progressed, 22 of 41 (53.7%) progressed only at pre-ICI sites of disease. Among all patients at 4 years, the cumulative incidence of any progression was 66.4% (95% CI, 55.3-79.1), and the cumulative incidence of progression at only pre-ICI sites of disease was 39.4% (95% CI, 28.7-53.9). Death was a competing risk for each analysis, and progression at a new or distant site was a competing risk for cumulative incidence of progression only at pre-ICI sites of disease (Figure 1).

Risk of progression among patients with limited disease

The 45 patients with ≤5 sites of disease were then analyzed as a separate cohort. The cumulative incidence of a treatable progression among patients with ≤5 sites of disease was 34.0% (95% CI, 21.8-53.1). Distant progression and death were competing risks. In contrast, the cumulative incidence of any progression (local, distant, or both; with death as a competing risk) for the cohort of 45 patients with limited disease was 58.9% at 4.2 years (95% CI, 45.0-77.1; Figure 2). There were neither patient nor disease characteristics that were associated with a statistically significantly higher risk of treatable progression (pre-ICI limited disease [≤5 sites] and exclusively local relapse).

Patients treated with upfront ICIs

Sixteen patients were treated with ICIs as first line therapy. Most had limited disease, and most did not progress on or after ICIs. Nine of 11 patients who did not progress and 3 of 5 patients who did progress had limited disease (≤5 sites). All stages of disease were represented, but patients were mostly late stage. Eighty percent of patients with limited disease progressed exclusively locally (4 of 5 of those who progressed), and none received radiation with ICIs.

Patterns of progression are summarized in Table 3.

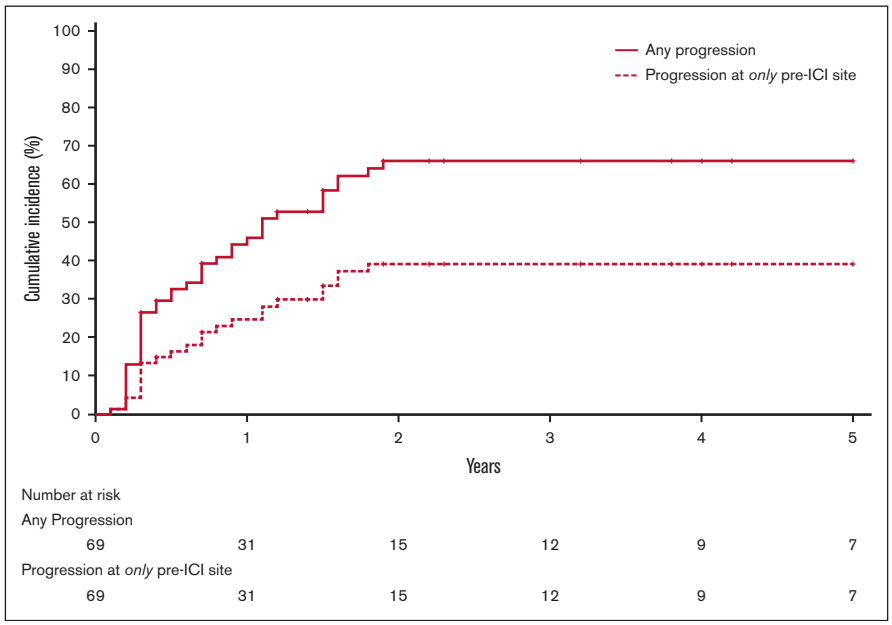

Figure 1. Cumulative incidence of any progression (solid line) or progression at only a pre-ICI site (dashed line) among the complete cohort, regardless of number of sites of disease before ICIs (n = 69). Cumulative incidence of any progression at median follow-up of 4.0 years was 66.4%, and cumulative incidence of progression only at pre-ICI sites of disease was 39.4%. Death was a competing risk for both arms. Distant progression, or new sites of disease, was also a competing risk for cumulative incidence of progression at only pre-ICI site.

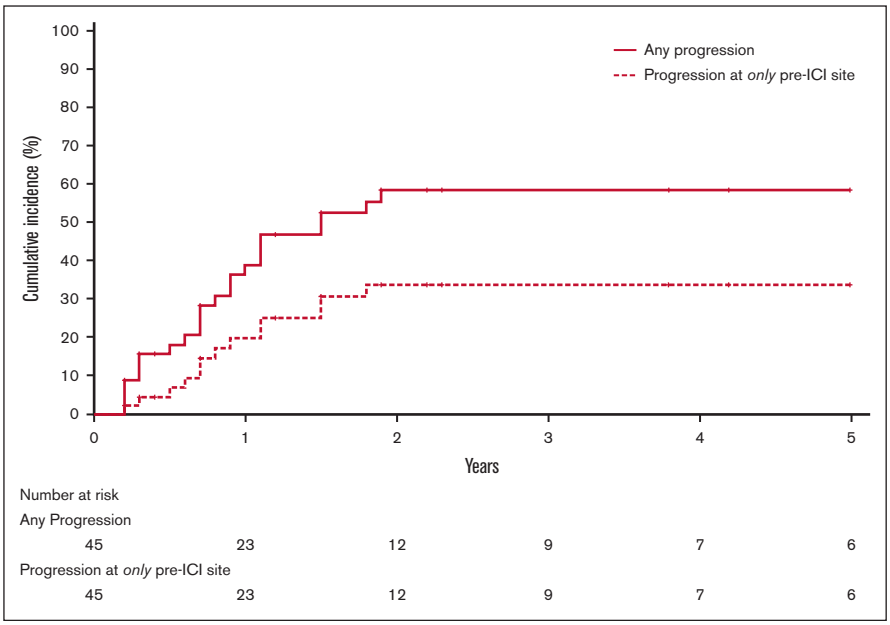

Figure 2. Cumulative incidence of any progression (solid line) or progression at only a pre-ICI site (dashed line) for the subset of patients (n = 45) with limited disease (≤5 sites pre-ICI). Cumulative incidence of any progression at median follow-up of 4.0 years was 58.9% among this cohort, and cumulative incidence of progression only at pre-ICI sites of disease was 34%. Death was a competing risk for both arms. Distant progression, or new sites of disease, were competing risks for patients in the progression at only pre-ICI site arm.

Discussion

ICIs represent a significant advancement for many patients with HL, but patterns of progression after ICI treatment are not well described. The average patient undergoing ASCT for relapsed or refractory HL is in their early 30s.[9] Relapse after transplant approaches 50%, and this number is higher for primary refractory HL, larger number of prior regimens, less than complete remission to salvage treatment on FDG-PET, duration of first remission <12 months, poorer performance status, and extranodal involvement.[10,11] Treatment options after relapse are limited, and before the advent of ICIs, they were restricted to extended-line chemotherapy regimens (single-agent or multiagent), allogeneic transplantation, brentuximab vedotin, or radiation alone.[12] These therapies historically resulted in only limited durations of disease control, which represented a devastating situation for these young patients.

An early phase 2 study of brentuximab vedotin after relapse followingASCT reported a median PFS of 5.6 months and an overall survival of 22.4 months, despite a high overall response rate of 75%.[13] Post-ASCT relapse treatment with single-agent chemotherapy regimens (gemcitabine, bendamustine) generally results in a PFS of 7 months or less,[12,14] and although multiagent chemotherapy regimens may produce better outcomes, there are limited data in the posttransplant setting. Second transplants are offered in select cases as well: 3-year PFS was 36% after a second ASCT in 1 small study,[15] and 5-year PFS was 20% in a study of allogeneic transplants (median time to relapse was 6 months).[16] When nivolumab was shown to be a viable option for patients who had relapsed or were refractory to ASCT, with a reported 86% PFS at ~6 months, this represented a major shift in the treatment of relapsed or refractory HL.[17] The Checkmate 205 study (nivolumab) then reported a median duration of response of 16.6 months, superior to other salvage treatment options.[4] Similarly, the Keynote-087 study reported an identical duration of response (16.6 months) and similar PFS (13.7 months) for patients receiving single-agent pembrolizumab.[18] Because of these studies and others, combination ICI therapies have also been investigated, and studies such as SWOG S1826 have shown promising results of nivolumab in combination with chemotherapy.[19] Of note, several patients in the presently reported cohort did receive combination doxorubicin, vinblastine, and dacarbazine, and nivolumab. None of these patients relapsed.

It is clear that for those patients who progress after ASCT, ICIs represent a paradigm-changing therapy, although the median event-free interval is still between 1 and 2 years.[4] In addition, immune-related adverse events remain a problem, and 16% of patients in this retrospective review discontinued ICIs secondary to toxicity. By analyzing patterns of progression after ICIs, our aim was to identify a subgroup of patients who may benefit from early intervention with additional local therapy. We hypothesize that this subgroup may be those patients with ≤5 sites of disease before starting ICIs. At our institution, over one-third of patients with limited disease progressed only at these pre-ICI sites of disease (cumulative incidence: 34%). This indicates that a sizable proportion of patients with limited HL may benefit from local therapy such as radiation, which could lead to a prolongation of PFS after ICIs. Extrapolating from oligometastatic data emerging from the study of epithelial cancers, it may be possible to provide long-lasting remission and even longer overall survival for select patients.[6]

Patients with >5 sites of disease at ICI initiation are more likely to progress, but 8 of 24 (25%) of these patients did progress exclusively locally, and the cumulative incidence of progression at pre-ICI sites among all patients in our study was 39.4%, a sizable minority. If amenable to safe RT treatments, treating more than 5 sites of disease certainly could be feasible, and the number of patients who could benefit from consolidative RT increases.

The International Lymphoma Radiation Oncology Group, in their guidelines addressing the use of radiation in relapsed or refractory HL, suggests that patients with limited-volume disease should be considered for salvage RT.[1] Past research has shown that radiation provides excellent local control, and modern techniques of radiation delivery (namely improved image guidance allowing decreased volumes and better sparing of organs at risk) appear safe and as effective as older, more extensive techniques.[20-24] The use of RT in relapsed and refractory settings similarly provides superior local control.[1,7,25,26]

The addition of RT to ICIs has shown great promise in the upfront setting: new data report exceedingly high rates of PFS (100% at 3 years) when a combination of chemotherapy, ICI, and consolidative radiation is used.[27] Rates of toxicity remained low with this combination treatment. Very little has been published regarding the combination of radiation and ICI treatment for patients with relapsed or refractory HL, but small retrospective studies are encouraging, demonstrating that radiation can be effective in bridging to stem cell transplant or providing disease control on its own.[28,29] In 1 small series of a dozen patients, 92% achieved a complete response 18 months after radiation delivery.[28] The patients who had previously received irradiation in our study represent a heterogeneous group with pretreated and likely more treatment-resistant HL (median number of lines of treatment before ICI was 6.5). Yet at least 68% of these irradiated sites remained controlled at the time of ICI initiation.

In these patterns of progression analysis, we must note several limitations. The number of patients included in this study was rather small, and the group was heterogenous. Most patients received ICIs for relapsed or refractory disease (77%), but some received ICIs as a primary, upfront treatment. Many patients had received previous radiation treatments (but none received radiation between starting ICIs and progression after ICIs), the details of which were not available for every patient. In addition, patients with more heavily pretreated diseases likely harbor different disease biology and may respond differently to both ICI and radiation. This has not been adequately explored in the literature and was not accounted for in our study. Anti–CD-30 CAR T-cell therapy is also under investigation for relapsed or refractory HL, and it remains to be seen how this new therapy will fit in with current and future treatment paradigms.[30,31] It is not clear how ICIs, consolidative radiation, and CAR T-cell therapy would be optimally sequenced or combined.

Outcomes with ICIs such as nivolumab appear to be excellent in both the upfront and salvage settings; however, the data we present here, in which a significant portion of patients experience local-only failure, indicate that there may be a role for local therapy with RT. These opportunities may exist both in the upfront as well as salvage settings. Several phase 2 prospective clinical trials have begun to investigate consolidative radiation in combination with ICIs for relapsed or refractory HL: 1 specifically investigating the abscopal effect,[32] 1 combining involved site radiation with pembrolizumab,[33] and a third using radiation in lieu of ASCT for low-risk patients.[7] We await the results of these ICI trials and turn a keen eye toward CAR T-cell therapy, where consolidative radiotherapy may also provide prolonged relapse-free survival in those patients who do not achieve complete remission.

In this series of patients who were treated with ICIs for HL, over half progressed exclusively locally. Among those with limited pre-ICI disease (5 or fewer sites), the cumulative incidence of an exclusively local progression was 34%. These findings indicate that there is a large proportion of patients with HL who (1) relapse locally and (2) would likely benefit from the excellent local control that RT can safely provide. It is possible that HL may harbor a unique oligometastatic paradigm, and that thoughtful consolidative treatment of all sites of disease may lead to better local disease control, lower rates of distant spread, improved quality of life through longer treatment-free intervals, and even improved survival.

Authorship

Contribution: J.F.B. performed data curation (extensively updating database), investigation (image review), and visualization, wrote the original draft, and reviewed and edited the manuscript; K.M.F. curated data (updating database), wrote the original draft, and reviewed and edited the manuscript; W.G.B. conceptualized, performed investigation and methodology, supervised, wrote the original draft, and reviewed and edited the manuscript; B.S.H. performed methodology, supervised, and reviewed and edited the manuscript; S.R.H., A.S.H., and A.N.N. curated data (original database) and reviewed and edited the manuscript; W.S.H. and S.D.P. conducted formal analysis and performed visualization; T.E.W., I.N.M., T.M.H., G.T., P.B.J., D.J.I., J.L.P., B.J.S., and W.G.R. supervised and reviewed and edited the manuscript; N.N.B., S.M.A., and S.C.L. conceptualized, performed methodology, supervised, and reviewed and edited the manuscript; and all authors confirm that they have full access to all data and each author takes responsibility for the results presented here.

Conflict-of-interest disclosure: W.G.B. reports consulting for and being on a scientific advisory board of GE Healthcare. T.M.H. reports being on the data monitoring committees of Seagen, Tess Therapeutics, and Eli Lilly & Co; being on scientific advisory boards of Eli Lilly & Co, MorphoSys, Incyte, BeiGene, and Loxo Oncology; receiving research support from Genentech and Sorrento; and all payments were made to the institution. B.S.H. reports being a scientific advisory consultant for Merck via Children's Oncology Group for study AHOD1822, and all payments were made to the institution. B.J.S. reports research funding from Varian, and all payments were made to the institution. N.N.B. is a previous member of advisory boards for Daichii Sankyo Inc, Kyowa Kirin, Vividon Therapeutics, Kymera, Secura Bio, Affimed GmbH, and Astellas Pharma, US, and all payments were made to the institution. G.T. discloses participation in advisory boards for Seattle Genetics and Novartis; all funds have been routed to a research fund (no personal remuneration). The remaining authors declare no competing financial interests.

ORCID profiles: J.F.B., 0000-0001-8653-1045; S.R.H., 0000-0002-6536-1291; S.D.P., 0000-0002-3193-4565; T.E.W., 0000-0002-4215-6500; B.S.H., 0000-0002-2312-5418; N.N.B., 0000-0001-8358-5953; J.L.P., 0000-0001-7458-1504.

Correspondence: Jessica F. Burlile, Department of Radiation Oncology, Mayo Clinic, 200 1st St SW, Rochester, MN 55905; email: burlile.jessica@mayo.edu.

References

1. Constine LS, Yahalom J, Ng AK, et al. The role of radiation therapy in patients with relapsed or refractory Hodgkin lymphoma: guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2018;100(5):1100-1118.
2. Hasenclever D, Diehl V, Armitage JO, et al. A prognostic score for advanced Hodgkin's disease. *N Engl J Med*. 1998;339(21):1506-1514.
3. Domingo-Domènech E, Sureda A. Treatment of Hodgkin lymphoma relapsed after autologous stem cell transplantation. *J Clin Med*. 2020;9(5):1384.
4. Armand P, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the Multicohort Single-Arm Phase II CheckMate 205 Trial. *J Clin Oncol*. 2018;36(14):1428-1439.
5. Herbaux C, Merryman R, Devine S, et al. Recommendations for managing PD-1 blockade in the context of allogeneic HCT in Hodgkin lymphoma: taming a necessary evil. *Blood*. 2018;132(1):9-16.
6. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET Phase II Randomized Trial. *J Clin Oncol*. 2020;38(25):2830-2838.
7. Harker-Murray PD, Cole PD, Hoppe BS, et al. Response-adapted therapy (tx) with nivolumab plus brentuximab vedotin (nivo + BV) without autologous hematopoietic cell transplantation (auto-HCT) in children, adolescents, and young adults (CAYA) with low-risk relapsed/refractory (R/R) classic Hodgkin lymphoma (cHL): CheckMate 744. *J Clin Oncol*. 2023;41(suppl 16):7515.
8. Hoppe BS, Daw S, Cole P, et al. Consolidative radio therapy in place of autologous stem cell transplant in patients with low-risk relapsed/refractory (R/R) classic Hodgkin lymphoma (cHL) treated with nivolumab plus brentuximab vedotin: CheckMate 744. *Int J Radiat Oncol Biol Phys*. 2023;117(2):S1-S2.
9. Myers R, Hill BT, Shaw BE, et al. Long-term outcomes among two-year survivors of autologous hematopoietic cell transplant for Hodgkin and diffuse large B-cell lymphoma. *Cancer*. 2018;124(4):816-825.
10. Sureda A, André M, Borchmann P, et al. Improving outcomes after autologous transplantation in relapsed/refractory Hodgkin lymphoma: a European expert perspective. *BMC Cancer*. 2020;20(1):1088.
11. Hahn T, McCarthy PL, Carreras J, et al. Simplified validated prognostic model for progression-free survival after autologous transplantation for Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2013;19(12):1740-1744.
12. Moskowitz AJ, Perales MA, Kewalramani T, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. *Br J Haematol*. 2009;146(2):158-163.
13. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30(18):2183-2189.
14. Venkatesh H, Di Bella N, Flynn TP, Vellek MJ, Boehm KA, Asmar L. Results of a phase II multicenter trial of single-agent gemcitabine in patients with relapsed or chemotherapy-refractory Hodgkin's lymphoma. *Clin Lymphoma*. 2004;5(2):110-115.
15. Smith SM, van Besien K, Carreras J, et al. Second autologous stem cell transplantation for relapsed lymphoma after a prior autologous transplant. *Biol Blood Marrow Transplant*. 2008;14(8):904-912.
16. Sureda A, Robinson S, Canals C, et al. Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2008;26(3):455-462.
17. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311-319.
18. Armand P, Zinzani PL, Lee HJ, et al. Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy for relapsed/refractory classical Hodgkin lymphoma. *Blood*. 2023;142(10):878-886.
19. Herrera AF, LeBlanc ML, Castellino SM, et al. SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). *J Clin Oncol*. 2023;41(suppl 17):LBA4.
20. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. *J Clin Oncol*. 2004;22(14):2835-2841.
21. Eich HT, Diehl V, Görgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol*. 2010;28(27):4199-4206.
22. Dabaja BS, Hoppe BS, Plastaras JP, et al. Proton therapy for adults with mediastinal lymphomas: the International Lymphoma Radiation Oncology Group guidelines. *Blood*. 2018;132(16):1635-1646.
23. Fermé C, Eghbali H, Meerwaldt JH, et al; EORTC-GELA H8 Trial. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med*. 2007;357(19):1916-1927.
24. Fuchs M, Goergen H, Kobe C, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: final results of the International, Randomized Phase III HD16 Trial by the German Hodgkin Study Group. *J Clin Oncol*. 2019;37(31):2835-2845.
25. Poen JC, Hoppe RT, Horning SJ. High-dose therapy and autologous bone marrow transplantation for relapsed/refractory Hodgkin's disease: the impact of involved field radiotherapy on patterns of failure and survival. *Int J Radiat Oncol Biol Phys*. 1996;36(1):3-12.

26. Josting A, Nogová L, Franklin J, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Lymphoma Study Group. *J Clin Oncol*. 2005;23(7):1522-1529.

27. Bröckelmann PJ, Bühnen I, Meissner J, et al. Nivolumab and doxorubicin, vinblastine, and dacarbazine in early-stage unfavorable Hodgkin lymphoma: final analysis of the Randomized German Hodgkin Study Group Phase II NIVAHL Trial. *J Clin Oncol*. 2023;41(6):1193-1199.

28. Lucchini E, Rusconi C, Levis M, et al. Immune checkpoint inhibitors in combination with radiotherapy as salvage treatment for relapsed/refractory classical Hodgkin lymphoma: a retrospective analysis in 12 patients. *Hematol Rep*. 2021;13(2):9080.

29. Quéro L, Gilardin L, Fumagalli I, et al. Anti-PD-1 immunotherapy in combination with sequential involved-site radiotherapy in heavily pretreated refractory Hodgkin lymphoma. *Cancer Radiother*. 2019;23(2):132-137.

30. Ramos CA, Grover NS, Beaven AW, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma. *J Clin Oncol*. 2020;38(32):3794-3804.

31. National Cancer Institute. CD30 Receptor-Activated T-cells in Treating Patients with Relapsed or Refractory CD30+ Hodgkin Lymphoma or Non-Hodgkin Lymphoma. Accessed 21 June 2023. https://www.cancer.gov/about-cancer/treatment/clinical-trials/search/v?id=NCI-2016-00789

32. Abscopal effect of radiotherapy and nivolumab in relapsed Hodgkin lymphoma after anti-PD1 therapy (AERN). ClinicalTrials.gov identifier: NCT03480334. Updated 13 September 2023. Accessed 21 June 2023. https://clinicaltrials.gov/ct2/show/NCT03480334

33. Pembrolizumab and involved site radiation therapy for early stage relapsed or primary refractory Hodgkin lymphoma. ClinicalTrials.gov identifier: NCT03179917. Updated 20 December 2023. Accessed 21 June 2023. https://clinicaltrials.gov/ct2/show/NCT03179917