Radiotherapy and Oncology 134 (2019) 89–95

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Treatment patterns and disease outcomes for pediatric patients with refractory or recurrent Hodgkin lymphoma treated with curative-intent salvage radiotherapy

Christopher L. Tinkle [a,*], Noelle L. Williams [b], Huiyun Wu [c], Jianrong Wu [d], Sue C. Kaste [e,f,g], Barry L. Shulkin [e,f], Aimee C. Talleur [h], Jamie E. Flerlage [g], Melissa M. Hudson [g], Monika L. Metzger [g], Matthew J. Krasin [a]

[a] Department of Radiation Oncology, St. Jude Children's Hospital, Memphis; [b] Department of Radiation Oncology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia; [c] Department of Biostatistics, St. Jude Children's Research Hospital, Memphis; [d] Department of Biostatistics, University of Kentucky, Lexington, United States; [e] Department of Diagnostic Imaging, St. Jude Children's Research Hospital; [f] Department of Radiology, University of Tennessee Health Science Center; [g] Department of Oncology; and [h] Department of Bone Marrow Transplantation and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, United States

ARTICLE INFO

Article history:
Received 11 December 2018
Received in revised form 14 January 2019
Accepted 20 January 2019
Available online 5 February 2019

Keywords:
Hodgkin lymphoma
Pediatric
Recurrent
Relapsed
Radiation therapy
Local failure

ABSTRACT

Background and purpose: The use of radiotherapy (RT) for pediatric patients with Hodgkin lymphoma (HL) experiencing disease progression or recurrence (15%) is controversial. We report treatment patterns and outcomes for pediatric patients with refractory/recurrent HL (rrHL) treated with curative-intent RT.
Materials and methods: Forty-six patients with rrHL treated with salvage RT at our institution were identified. All received risk-adapted, response-based frontline therapy and were retrieved with cytoreductive regimens followed by RT to failure sites, with or without autologous hematopoietic cell transplantation (AHCT). Cumulative incidence (CIN) of local failure (LF) and survival were estimated after salvage RT and regression models determined predictors of LF after salvage RT.
Results: RT was administered as part of frontline therapy in 70% of patients, omitted for early response assessment in 13%, or deferred for primary progression in 17%. AHCT was omitted in 20% of patients. Median initial and salvage dose/site were 25.5 Gy and 30.6 Gy, respectively. Eight patients experienced progression. Two died without progression (median follow-up from salvage RT = 3.8 years). The 5-year CIN of LF after salvage RT was 17.7% (95% confidence interval [CI], 8.2–30.2%). The 5-year freedom from subsequent treatment failure and overall survival (OS) was 80.1% (95% CI, 69.2–92.6%) and 88.5% (95% CI, 79.5–98.6%), respectively. Inadequate response to salvage systemic therapy ($p = 0.048$) and male sex ($p = 0.049$) were significantly associated with LF after salvage RT.
Conclusion: rrHL is responsive to salvage RT, with low LF rates after moderate doses. OS is excellent, despite refractory disease. Initial salvage therapy response predicts subsequent LF.
Published by Elsevier B.V. Radiotherapy and Oncology 134 (2019) 89–95

Despite excellent prospects for long-term survival, 15% of children and young adults with Hodgkin lymphoma (HL) experience primary disease progression or recurrence [1,2]. Due to the success of upfront therapy, there are limited opportunities for investigating prospective salvage-therapy programs and to individualize second-line treatment. Various salvage treatments have been employed, yet contemporary pediatric approaches generally use second-line systemic therapy with novel agents and/or combinations followed by high-dose chemotherapy and autologous hematopoietic cell transplantation (AHCT). The addition of brentuximab vedotin (BV) as maintenance therapy after transplant has also been explored, based on encouraging results in adults [3–9]. Radiotherapy (RT) is often employed in salvage regimens.

Abbreviations: RT, radiotherapy; HL, Hodgkin lymphoma; rrHL, refractory/recurrent Hodgkin lymphoma; AHCT, autologous hematopoietic cell transplantation; CIN, cumulative incidence; LF, local failure; CI, confidence interval; FFSTF, freedom from subsequent treatment failure; OS, overall survival; TLI, total lymphoid irradiation; IFRT, involved-field radiotherapy; ISRT, involved-site radiotherapy; IRB, Institutional Review Board; MIED, methotrexate, iosfamide, etoposide, and dexamethasone; VG, vinorelbine and gemcitabine; OEPA, vincristine, etoposide, prednisone, and doxorubicin; COPDAC, cyclophosphamide; BV, brentuximab vedotin; COPDAC, cyclophosphamide, vincristine (Oncovin), prednisone, and dacarbazine; BEAM, carmustine, etoposide, cytarabine, and melphalan; TBI, total body irradiation; CR, complete response; PR, partial response; HR, hazard ratio; PD-1, programmed death 1; PTV, planning target volume; 95% IDL, 95% isodose line.

* Corresponding author at: Department of Radiation Oncology, St. Jude Children's Research Hospital, 262 Danny Thomas Place, MS 210, Memphis, TN 38105, United States.
E-mail address: christopher.tinkle@stjude.org (C.L. Tinkle).

https://doi.org/10.1016/j.radonc.2019.01.026
0167-8140/Published by Elsevier B.V.

The impact of curative-intent RT in refractory or recurrent Hodgkin lymphoma (rrHL) remains controversial.

Concerns regarding rrHL salvage RT include impact of local tumor control on survival considering potentially compounded toxicity, along with questions regarding optimal radiation field, dose, and sequencing in relation to AHCT. Factors supporting salvage RT include lack of RT cross-resistance in many chemotherapy-refractory patients [10–14] and predominantly nodal recurrence at initial disease sites [15–17]. Nodal failure has influenced RT field design; for example, total lymphoid irradiation (TLI) has been employed as "quasi-systemic therapy" to treat nodal-restricted recurrent disease in radiation-naïve patients before they undergo AHCT [18]. However, data increasingly suggest that some "low-risk" relapse patients, can be treated effectively with standard frontline chemotherapy regimens and limited RT, typically involved-field RT (IFRT) or involved-site RT (ISRT), alone [5,19–22]. Primary progressive disease, time to relapse, and chemoresistance appear to be the most consistent prognostic factors associated with survival after frontline treatment failure. How these factors influence local tumor control is less clearly established [5,23,22,24–26,20,27,28].

We reviewed our experience with pediatric and young adult patients with rrHL who were treated with curative-intent RT as a component of salvage therapy in order to assess local tumor control outcomes and identify prognostic factors. We limited analysis to patients treated with homogeneous initial and relapse therapies at our institution, including primary therapy of risk-stratified, response-adapted chemoradiotherapy and retrieval therapy of intense cytoreductive systemic regimens and RT with or without AHCT.

Materials and methods

From March 2000 to December 2015, 357 patients with newly diagnosed HL were treated at our institution. Seventy-six experienced frontline treatment failure due to progressive or recurrent disease. Thirty patients were excluded because they received frontline or salvage therapy elsewhere (Supplementary Fig. 1). Our Institutional Review Board (IRB) approved the study. Frontline therapy, follow-up, and treatment failure assessment have been detailed previously [20,29–31] (Supplementary Methods and Table 1).

Salvage therapy

Salvage regimens were based on physician recommendations and influenced by initial therapy course and intensity, timing and site(s) of treatment failure, and patient status. Most patients were retrieved with high-dose methotrexate, ifosfamide, etoposide, and dexamethasone (MIED) (n = 17) or with vinorelbine and gemcitabine with or without ifosfamide (VG) (n = 18). In cases of localized late treatment failure after initial treatment with chemotherapy only, patients received Stanford V chemotherapy (n = 6), whereas regimens of vincristine, etoposide, prednisone, and doxorubicin (OEPA), cyclophosphamide, vincristine, prednisone, and dacarbazine (COPDAC) (n = 2), and bendamustine and BV (n = 2) were used in patients treated recently. For high-risk patients who responded to the first or subsequent courses of salvage chemotherapy, AHCT with high-dose chemotherapy conditioning followed. Transplant-conditioning regimens consisted of carmustine, etoposide, cytarabine, and melphalan (BEAM) (n = 31) or busulfan/melphalan (n = 2). One patient in whom synchronous recurrent HL and myeloid sarcoma were diagnosed at first relapse underwent total body irradiation (TBI) followed by cyclophosphamide treatment. Typically, salvage RT was administered to sites involved at time of treatment failure in patients who received upfront RT or to all sites of initial disease in patients where upfront RT was omitted. Salvage RT followed AHCT or retrieval chemotherapy in high- and low-risk patients, respectively. Photon irradiation was delivered to all patients at diagnosis and/or progression. A dose of 30.6 Gy was delivered unless prior normal-tissue exposure or size of the salvage RT field limited safe delivery. RT delivery techniques evolved over time from simple field arrangements encompassing complete nodal station(s) to conformal RT, including IMRT, restricted to sites of nodal progression.

Table 1
Patient and treatment characteristics.

Characteristic		N	% or Median (Range)
Age @ initial diagnosis		46	16.5 y (4.7–22.0 y)
Sex	Male	23	50.0%
	Female	23	50.0%
Race	White	33	72%
	Black	11	24%
	Other	2	4%
Histology	Nodular sclerosing	33	72%
	Classical, other	11	24%
	NLP	2	4%
Ann Arbor stage	I	4	8%
	II	21	46%
	III	10	22%
	IV	11	24%
B symptoms	No	23	50%
	Yes	23	50%
Extranodal disease	No	26	57%
	Yes	20	43%
Initial failure type	Progressive disease	10	22%
	Early relapse	18	39%
	Late relapse	18	39%
Initial failure site	Lymph node	32	70%
	Extranodal	2	4%
	Both	12	26%
New failure site	No	38	83%
	Yes	8	17%
Time to 1st relapse		36	10.7 mo (1.2–42.7 mo)
Salvage transplant	No	9	20%
	Yes	37	80%
Frontline RT	No	6	13%
	Yes	32	70%
	Deferred	8	17%
RT dose/site	Frontline		25.5 Gy (8–30.6 Gy)
	Salvage		30.6 Gy (12–43.2 Gy)
Re-RT to any site	No	18	39%
	Yes	28	61%
	Cumulative Re-RT Dose/site		56.1 Gy (41.1–68.7 Gy)

NLP, nodular lymphocyte predominant.

Response assessment

Adequate responses to initial salvage therapy included complete response (CR) (defined as reduction of ≥75% in tumor size on a CT scan [using the product of two largest tumor dimensions on an axial plane to determine size] and negative gallium or PET scans) and partial response (PR) (defined as 50%–74% reduction in tumor size on CT scan, regardless of PET avidity). Inadequate response was defined as response not meeting these criteria. No patient who experienced CR had a positive PET scan.

Statistical analysis

Treatment failure was defined as development of new lesions; >25% increase in size of existing lesions, based on bi-dimensional measurements on CT; or abnormal uptake on gallium or PET scans. Progressive disease was defined as treatment failure within

3 months of initial therapy completion, early relapse as treatment failure from 3 to 12 months after initial therapy completion, and late relapse as treatment failure more than 12 months after initial therapy completion [20]. Freedom from subsequent treatment failure (FFSTF) was defined as time from start of salvage RT to disease progression or death, whichever occurred first. Overall survival (OS) was defined as time from start of salvage RT to death. Patients without an event were censored at last follow-up date or the last date they were known to be free of an event. FFSTF and OS were estimated using the Kaplan–Meier method, presented with 95% confidence intervals (CIs), and compared using the log-rank test. CINs of LF from the end of salvage RT, with other events considered as competing risk, were estimated by the method of Kalbfleisch and Prentice ([32]) and compared using the Gray test. To identify predictors of LF after salvage RT, cumulative-incidence regression analysis was used. Significance was determined by the Wald test and results were summarized by the hazard ratio (HR). All analyses were performed in SAS software (version 9.1, SAS Institute, Inc., Cary, NC).

Results

Baseline patient and treatment characteristics

Table 1 lists the patient (n = 46) and treatment characteristics. The median age was 16.5 years (range, 4.7–22.0 years) at initial diagnosis and 17.5 years (range, 6.0–23.9 years) at first treatment failure. Advanced disease presentation was observed in 32 patients (70%) and nodular sclerosing histologic variant in 33 patients (72%) at initial diagnosis. Disease progression less than 3 months post-primary therapy occurred in 10 patients (22%), and relapse occurred in 36 (78%). The median time to first recurrence after completion of primary therapy was 10.7 months (range, 1.2–42.7 months). Lymph nodes were a component of initial failure in 44 patients (96%). Failure in a site distinct from the involved sites at diagnosis was documented in eight patients (17%). Frontline consolidative RT to a median dose of 25.5 Gy was delivered to 32 patients (70%), was deferred in eight patients (17%) because of progressive disease, and was omitted in six patients (13%) based on protocol-defined response criteria. Of the patients who received frontline RT, IFRT was employed in the majority of cases (88%). While IFRT was most commonly used at salvage, a large proportion of patients were treated with ISRT (42%). Likewise, conformal RT through the use of IMRT was used more frequently at the time of salvage therapy (3% at frontline and 22% at salvage). The median salvage RT was 30.6 Gy, with a range of 12–43.2 Gy.

Response to frontline and salvage regimens

Table 2 summarizes frontline and salvage therapies employed, as well as types of primary disease failure, responses to salvage therapies, and overall disease outcomes. When frontline RT was omitted based on a favorable response to chemotherapy (n = 6), two patients experienced early relapse and four late relapse, all of which were nodal. Four of these six patients experienced recurrence in at least one site distinct from initial disease site(s). All of these patients had adequate response to salvage chemotherapy and subsequently received salvage RT to a median 30.6 Gy (range, 25.5–30.6 Gy) to sites of recurrent disease without AHCT. Two patients progressed after salvage RT; one entirely within the previously irradiated site and the other within the prior RT site plus a new, distant nodal site. These two patients were then treated with re-induction chemotherapy and AHCT followed by RT to sites of second recurrence (30.6 Gy to sites previously unirradiated and 25.5 Gy to sites previously treated). They had no evidence of disease at last follow-up at 1.1 and 3.3 years post treatment, respectively.

Of the 32 patients treated with primary chemoradiation, two experienced progressive disease within 3 months of primary chemoradiation, 16 experienced early relapse, and 14 experienced late relapse. All patients with adequate response to salvage chemotherapy underwent AHCT followed by salvage RT, except for three patients who were considered low risk for recurrence and whose salvage therapy was chemoradiation only. These three patients have experienced long-term disease control after being treated with salvage chemotherapy followed by mantle-field irradiation to 25.5 Gy and are at least 5 years post-salvage therapy. Fig. 1 shows a patient treated with frontline dose-reduced chemotherapy and response-based RT followed by salvage chemotherapy, AHCT, and consolidative ISRT.

Of the 10 patients with primary progressive disease, six experienced disease progression while receiving frontline chemotherapy, two experienced progression while receiving frontline RT, and two experienced progression within 3 months of frontline chemoradiation completion. Seven of these patients experienced CR to initial salvage therapy and underwent AHCT followed by consolidative RT. All remain alive with no evidence of disease, except for one patient who died of respiratory failure attributed to transplant complications.

Disease control, survival outcomes, and long-term toxicity

With a median follow-up from end of salvage RT of 3.8 years (range, 0.3–13.7 years), eight patients experienced subsequent disease progression. Failure patterns after salvage RT included local failures (n = 4), defined as being within salvage radiation field, and synchronous local and distant failures (n = 4). Median time to subsequent disease progression post-salvage RT was 6.7 months (range, 0.4–32.9 months). Five-year CIN of LF post-salvage RT was 17.7% (95% CI, 8.2%–30.2%) (Fig. 2A). Analysis of LF after salvage RT by response to first salvage chemotherapy demonstrated a 5-year CIN of LF of 12.4% (95% CI, 4.5%–25.1%) for patients with adequate

Table 2
Response to frontline and salvage regimens by patient (indicated in parentheses).

Frontline Therapy		Frontline Failure	First Salvage Therapy				Outcome
CT	RT	Type	CT	RT	Transplant	Response to CT	
VAMP (6) VAMP/COP (8) Stanford V (28) OEPA/COPDac (2) Other (2)	IFRT (28) ISRT (4) None (14)	Progression (10) Early Relapse (18) Late Relapse (18)	MIED (17) Gem/Vin (18) Stanford V (6) OEPA/COPDac (2) Benda/Brentux (2) Other (1)	IFRT (22) ISRT (15) TBI/ISRT (1) None (8)	Yes (34) No (12)	CR/PR (38) SD/PD (8)	AWOD: CR1 (3) CR2 (33) CR3 (4) DOD (4) DWOD (2)

CT, chemotherapy; RT, radiation therapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CR1–3, complete remission 1–3; AWOD, alive without disease; DOD, died of disease; DWOD, died without disease. Please see text for chemotherapy regimens and RT fields.

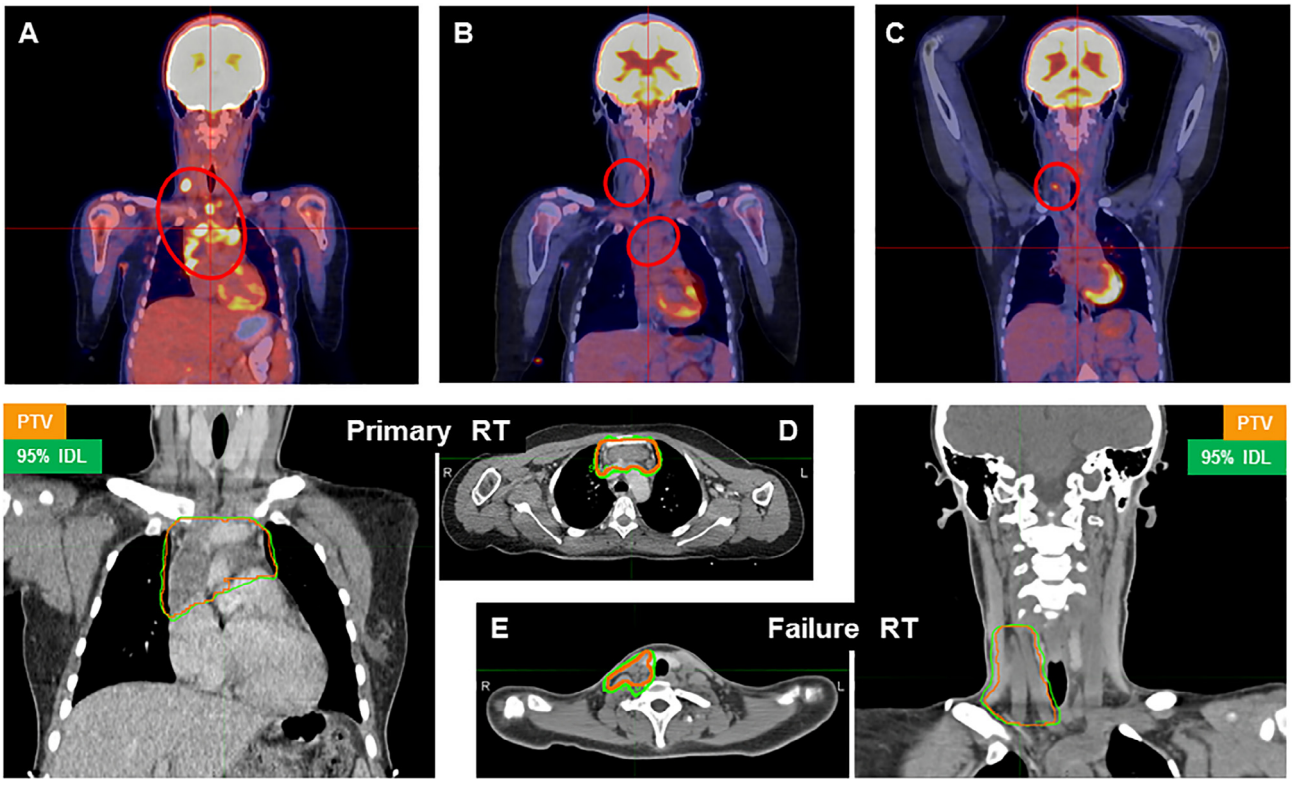

Fig. 1. Example case. (A) Baseline PET/CT of a 15-year old with stage IIA Hodgkin lymphoma of the right cervical and mediastinal lymph nodes. (B) Complete metabolic response to both sites after reduced Stanford V chemotherapy. (C) Abnormal FDG uptake in the right cervical region 3 months after initial therapy. (D) Given partial anatomic response on CT after primary chemotherapy, she received involved-site radiation therapy (ISRT) to the mediastinum to 25.5 Gy. (E) After salvage chemotherapy and allogeneic hematopoietic cell transplant, she received ISRT to the right cervical region to 30.6 Gy. She has completed adjuvant brentuximab vedotin therapy and is currently without evidence of disease. PTV, planning target volume; 95% IDL, isodose line.

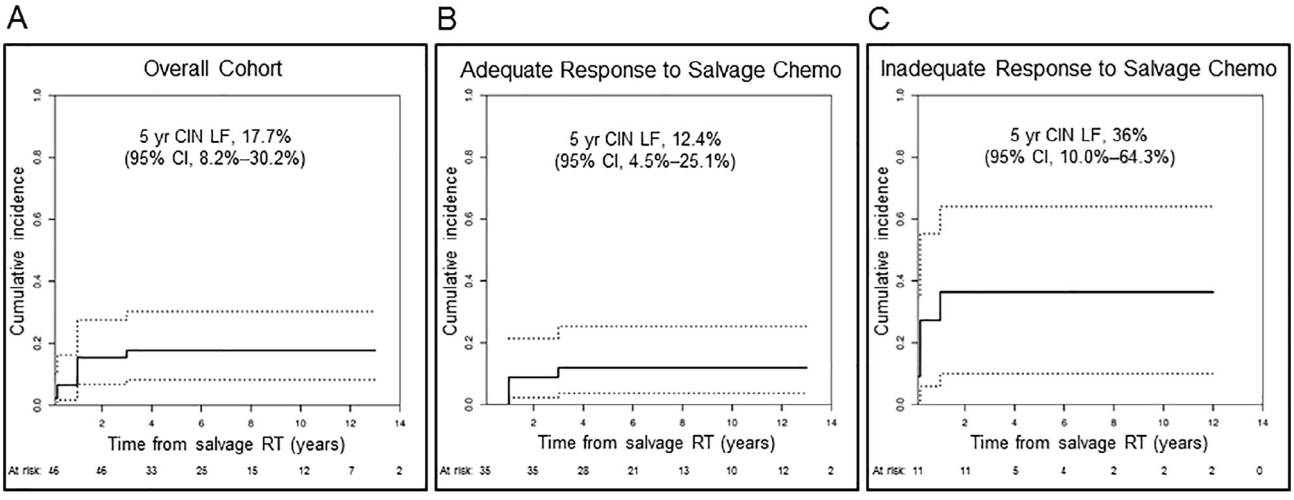

Fig. 2. Cumulative incidence (CIN) and 5-year estimates of local failure (LF) after salvage irradiation for the overall cohort (A), for patients with adequate response to salvage chemotherapy (B), and patients with inadequate response to salvage chemotherapy (C). Patients with inadequate response experienced significantly higher LF rate (Gray's test, $p = 0.0475$). CI = confidence interval.

response to salvage chemotherapy, compared to 35% (95% CI, 10.0%–64.3%) for patients with an inadequate response ($p = 0.0475$) (Fig. 2B and C).

Cumulative-incidence regression analysis of predictors of LF post-salvage RT revealed inadequate response to first salvage chemotherapy ($p = 0.048$) and male sex ($p = 0.049$) were significantly associated with risk of LF (Table 3). However, additional variables, including the clinical variable of age; disease characteristics of primary risk category and primary disease failure type; and treatment factors of salvage RT dose, repeat RT, and receipt of AHCT, were not significantly associated with LF post-salvage RT.

The five-year estimate of FFTF for all patients was 80.1% (95% CI, 69.2%–92.6%) (Fig. 3A). The five-year estimate of OS was 88.5% (95% CI, 79.5%–98.6%) (Fig. 3B). The cause of death was either HL

Table 3
Cumulative incidence regression analysis of associations between clinical variables and local failure.

Variable	HR	95% CI for HR	*P*-value
Age (continuous)	0.92	0.82–1.03	0.18
Sex (female vs. male)	7.84	1.01–60.90	**0.049**
Primary risk category	1.04	0.45–2.37	0.93
Response to 1st salvage chemotherapy (inadequate vs. adequate)	0.25	0.065–0.98	**0.048**
Salvage RT dose: <30.6 vs. ≥30.6 Gy	3.87	0.72–20.70	0.11
Repeat RT (no vs. yes)	0.38	0.094–1.57	0.18
Autologous transplant (no vs. yes)	0.64	0.12–3.40	0.61
Primary progression vs. other	2.35	0.58–9.60	0.23
Early relapse vs. other	0.99	0.24–4.05	0.99
Late relapse vs. other	0.46	0.099–2.13	0.32

HR, hazard ratio; CI, confidence interval.
A two-sided significance level of P < 0.05 was considered statistically significant (bold).

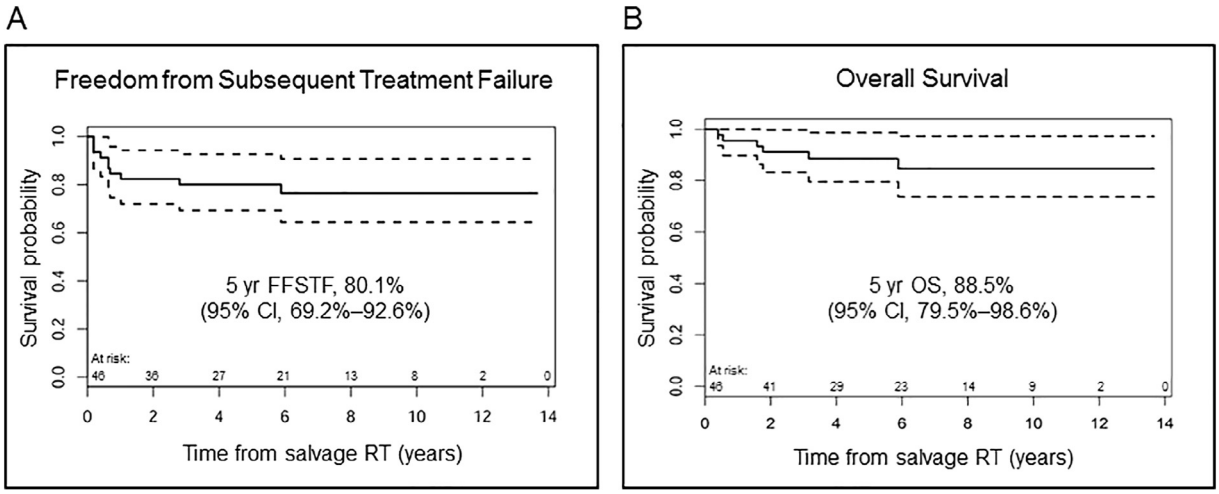

Fig. 3. Kaplan–Meier probability distributions of freedom from subsequent treatment failure (FFSTF) (A) and overall survival (OS) (B) after salvage irradiation, with 5-year estimates. CI = confidence interval.

(n = 4) or treatment-related respiratory failure (n = 2). Of those patients who succumbed to HL, the median time from initial diagnosis to death was 31.4 months (range, 14.9–47.3 months).

The most common grade 3 or higher late toxicities (>3 months from end of salvage RT) were pulmonary (8.7%), cardiac (6.5%), gastrointestinal (2.2%), and other (2.2%). Grade 2 hypothyroidism was the most common endocrine toxicity (n = 7), while four patients experienced significant pulmonary toxicity, resulting in death in two. Second malignancies developed in two patient (4.3%), both of which were considered outside the primary or salvage RT fields. One patient was found to have Burkitt lymphoma of the small intestine 6 years from salvage RT which included a modified mantle field after initial RT to a mantle field, while one patient was diagnosed with a forearm melanoma after 1 year of salvage RT also consisting of a modified mantle field after initial treatment to a mantle field.

Discussion

We examined patterns of care and treatment outcomes for 46 pediatric and young adult patients with progressive or relapsed HL treated with curative-intent salvage RT. Despite initially recalcitrant disease, we demonstrated a salvage treatment paradigm of intensive chemotherapy and moderate-dose RT limited to sites of refractory disease, with or without AHCT, provides durable local control and encouraging long-term survival outcomes. Five-year CIN of LF after salvage RT was 17.7% (95% CI, 8.2%–30.2%), whereas the FFSTF was 80.1% (95% CI, 69.2%–92.6%). Overall survival was 88.5% (95% CI, 79.5%–98.6%). While the sequencing of RT in relation to other components of therapy and the restricted targeting of regions with recurrent disease have remained a consistent part of our salvage treatment paradigm, our approach to RT has evolved to the current use of involved nodal RT with proton therapy employed in most cases.

Pediatric-specific data for rrHL are limited. Most reports have been specific to adult populations or include few younger patients. However, there is particular concern for long-term morbidity in the younger population leaving important questions regarding outcomes and optimal RT volume, dose, and sequencing with transplant. For example, use of accelerated TLI with or without IFRT as a component of salvage therapy in radiation-naïve patients has resulted in excellent survival outcomes [18]; however, this is less suitable for children, given potential for unacceptable toxicities [33]. Several retrospective studies have examined the role of salvage IFRT in the peri-transplant setting, and some reports have demonstrated PFS advantage with the addition of IFRT [34–36]. Our study has further extended these findings by providing novel data regarding treatment patterns and outcomes specific to pediatric and young adult patients within this relatively uniformly treated cohort. Moderate-dose salvage RT, with or without AHCT, has encouraging long-term local control (82.3% at 5 years). Further, of the four patients who developed synchronous local and distant progression, two experienced progression outside conventional TLI field (liver and peripheral lung).

Several groups have tried to identify factors predictive of survival outcomes in children and adults with HL that was refractory to primary therapy or with relapsed disease after initial treatment [5]. Variables identified in children and adolescents include progressive disease during frontline therapy [5] and response to initial salvage chemotherapy [20]. Results have been mirrored in adult settings ([18]). Other factors associated with poor survival in pediatric patients include extranodal disease at time of treatment failure, a mediastinal mass at time of transplant, and presence of B symptoms at relapse [23,37]. In our study, adequate response to initial salvage therapy was associated with lower risk of subsequent LF. Although several studies have shown many patients with rrHL receiving chemotherapy alone do not exhibit cross-resistance to RT [13,38], our data suggest subsequent chemosensitivity predicts enhanced response to radiation or, conversely, hint at existence of a population in which salvage RT may ultimately be omitted [39–41]. Male sex has been associated with inferior survival in adults with HL [42,43], but is not a consistent finding; in a larger pediatric study of AHCT of rrHL, female patients had significantly worse outcomes [44]. Our finding of an association between male sex and LF awaits further investigation in larger pediatric patient cohorts.

Among the 38 patients who had adequate response to initial salvage therapy in our study, nine (20%) did not undergo AHCT, but durable tumor control was established in all of them after salvage therapy. They remain alive and disease free. These findings support the notion that not all patients who experience disease relapse after frontline therapy require AHCT, particularly if their response to initial salvage therapy is adequate and time to recurrence is long [5,20,27]. Although AHCT is curative in 50% of adult patients with chemotherapy-sensitive primary disease and has been established as standard of care for patients with rrHL [3,4], a randomized trial of AHCT compared to salvage chemoradiation would be required to determine whether AHCT improves outcomes for specific patient groups in the pediatric setting [26]. Substantial limitations preclude this type of study.

Although optimal integration of novel systemic therapy options into the salvage treatment paradigm for the pediatric patient population continues to evolve, these agents are likely to influence patient selection for salvage RT and AHCT. BV is a promising agent in the salvage setting, both for patients who have progressed after undergoing AHCT or two cycles of salvage chemotherapy and are not candidates for transplant ([45]) and for patients who have completed AHCT and are at high risk for subsequent progression ([8,46]). In addition to targeted chemotherapy, immunotherapy with programmed death 1 (PD-1) blockade has shown promising response rates and acceptable safety in patients with rrHL whose disease has progressed after several lines of salvage therapy, including AHCT and BV ([47,9]).

Conclusions

This study represents one of the largest childhood cohorts of rrHL published, with a focus on salvage RT approaches in this vulnerable population and on the impact of clinical variables on local tumor control. We observed a low CIN of LF after moderate-dose salvage RT (17.7%) at 5 years, and an association with enhanced local control in patients who had adequate response to induction salvage chemotherapy. These data contribute to the growing pediatric literature highlighting the role of salvage RT and reaffirm the importance of large, risk-stratified, prospective trials specific to rrHL and patient population.

Financial disclosure

This work was supported in part by the American Lebanese Syrian Associated Charities (ALSAC) and by National Cancer Institute grant P30 CA021765 (St. Jude Cancer Center Support Grant). The funding sources did not have a role in study design, the collection, analysis or interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

Conflict of interest

None declared.

Acknowledgements

The authors would like to thank Keith A. Laycock, PhD, ELS, for scientific editing of the manuscript and Brandon Bianski for assistance with data extraction.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.01.026.

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