Integration of Pediatric Hodgkin Lymphoma Treatment and Late Effects Guidelines: Seeing the Forest Beyond the Trees

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ABSTRACT

The successful integration of clinical trials into pediatric oncology has led to steady improvement in the 5-year survival rate for children diagnosed with Hodgkin lymphoma (HL). It is estimated that >95% of children newly diagnosed with HL will become long-term survivors. Despite these successes, survival can come at a cost. Historically, long-term survivors of HL have a high risk of late-occurring adverse health effects and increased risk of nonrelapse mortality compared with the general population. The recognition of late-occurring events paired with the decades of life remaining for children cured of HL have made paramount the need to develop effective treatments that minimize the risk of late toxicity. Toward this goal, multiple, dose-intense, risk- and response-based regimens that use lower cumulative doses of chemotherapy and radiation have been developed. Appropriate frontline treatment selection requires a level of familiarity with the efficacy, acute toxicity, convenience, and late effects of treatments that may be impractical for providers who infrequently treat children with HL. There is an increasing need for guideline developers to begin to merge considerations from both frontline treatment and survivorship guidelines into practical documents that integrate potential long-term health risks. Herein, we take the first steps toward doing so by aligning cumulative treatment exposures, anticipated risks of late toxicity, and suggested surveillance recommendations for NCCN-endorsed Pediatric HL Guidelines. Future studies that integrate simulation modeling will strengthen this integrated approach and allow for opportunities to incorporate regimen-specific risks, health-related quality of life, and cost-effectiveness into decision tools to optimize HL therapy.

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In the United States, approximately 1 in 78,500 children aged 0 to 19 years is diagnosed with Hodgkin lymphoma (HL) annually, accounting for an estimated 1,050 incident patients per year.¹ Although the annual incidence per million population is <5 in children aged <10 years, it is 32.5 in adolescents aged 15 to 19 years, making HL the most common malignancy occurring in this age group.¹ Recognition that radiation alone could effectively treat HL resulted in cures even at the turn of the 20th century.^{2,3} Subsequently, the 5-year survival rate for children aged <20 years at diagnosis has steadily improved, now exceeding 95% (Figure 1).¹ Despite these successes, survival comes at the cost of increased late morbidity^{4–7} and mortality compared with the general population.^{7,8}

Progress Over Time and Divergence of Pediatric From Adult Regimens

Successful pediatric HL clinical trials have improved survival rates and reduced short- and long-term toxicity, resulting in an increasing number of long-term survivors. Although overall survival rates with contemporary therapy in children and adolescents are exceptional, subgroups experience suboptimal initial disease-free survival.⁹ Although historical definitions of risk have varied, 5-year disease-free survival rates generally range from 80% to 97% for low-risk disease and from 77% to 90% for high-risk disease.⁹ Stages IIB with bulk (pediatric), IIIB, and IVB disease have been uniformly considered as requiring high-risk treatment, whereas stage IIIA disease has been variably classified as either intermediate- or high-risk in pediatric trials, as have stages IIB and IVA disease in adult trials. Over time, risk stratification has evolved beyond its early dependence on Ann Arbor stage alone to now include bulky and extranodal lesions as higher-risk disease characteristics; however, both have been inconsistently included in high-risk groups in clinical trials.¹⁰

Risk-stratified treatment approaches, partially motivated by dose-dependent associations between specific treatment exposures and late morbidity and mortality,⁷ have reduced treatment-related organ toxicity and subsequent neoplasms in survivors of pediatric HL.¹⁰ For

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Figure 1. Overall survival rates for pediatric Hodgkin lymphoma by decade.¹

example, recognition that young women exposed to mantle radiation were at high risk of subsequent breast cancer motivated the tailoring of radiotherapy, with respect to both overall use and tissue volume exposed.^{6,11} In response, some adult regimens have used chemotherapy-only approaches to avoid radiation, whereas pediatric protocols have relied on combined-modality therapy incorporating involved-field, low-dose radiation to simultaneously reduce the risk of late cardiac events.¹²⁻¹⁴ Recognition that high cumulative alkylating agent doses and gonadal radiation adversely affect both male and female reproductive function,¹⁵⁻¹⁷ and knowledge of the particularly deleterious effects of procarbazine in male patients,¹⁸⁻²⁰ prompted the development of alternative regimens that preserve cure rates without compromising fertility for most patients.²¹ These objectives have been achieved through several key changes.

First, the availability of granulocyte colony-stimulating factor facilitated the adoption of dose-dense, collectively myelosuppressive regimens incorporating additional agents while simultaneously allowing for the reduction of cumulative doses of individual agents within regimens.^{22,23} For example, the incorporation of etoposide into pediatric regimens enhanced antitumor efficacy while reducing cumulative alkylating agent doses.²²⁻²⁶ Together, these approaches allowed the containment of cumulative doxorubicin-equivalent doses of anthracyclines^{27,28} to ≤ 250 mg/m² and cyclophosphamide-equivalent doses of alkylating agents¹⁷ to ≤ 7 g/m².^{21,29,30} Such changes come with potential tradeoffs. For example, frequent scheduling and higher doses of etoposide have been associated with an increased risk of subsequent leukemia,^{31,32} although with contemporary pediatric HL regimens this risk is exceedingly low.^{10,33} In

addition, in adolescents with HL aged 17 to 21 years, treatment using an adult versus a pediatric approach resulted in approximately 10% fewer patients receiving radiation but an approximately 10% reduction in progression-free survival.³⁴ Although this effect may be multifactorial, the implications of additional relapsed therapy must be considered.

Improved CT imaging and the emergence of FDG-PET as a biomarker of chemotherapy response, combined with the aforementioned progress in qualifying baseline disease risk, led to the current risk-based, response-adapted treatment approach that has facilitated the reduction and elimination of consolidative radiation exposure for those achieving rapid resolution of disease activity.^{22,23} For individuals less responsive to chemotherapy, improvements in image-guided treatment and the transition from extended-field (eg, mantle) to involved-field radiation, and more recently involved-site or involved-node radiation, significantly reduced doses to normal tissues³⁵ and contributed to clear reductions in posttreatment morbidity and premature mortality,^{36,37} most notably regarding subsequent neoplasms.³⁸

Need for Guidelines in Treatment of De Novo Pediatric HL

Although successful cooperative group HL trials have yielded several efficacious treatment strategies, heterogeneity in risk stratification and response criteria has made it challenging to identify a “single-best” approach in pediatric patients.¹⁰ Now more than ever, balancing cure and long-term toxicity, risks and benefits of long-term surveillance, and increasing recognition of the importance of the quality and not just the quantity of life-years has challenged treatment decision-making. Thus, the development of the pediatric-specific NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for HL is a timely, much-needed step to facilitate progress toward personalized treatment.³⁹

Comparisons between cumulative exposures for regimens endorsed by both the pediatric and adult classic HL NCCN Guidelines can be found in Tables 1-3. Differences in cumulative exposures are largely determined by disease risk stratification at diagnosis, early response to therapy, number of treatment cycles, and need for consolidative radiation as defined by the protocol (eg, radiation to large mediastinal adenopathy regardless of response when treating high-risk disease using doxorubicin/bleomycin/vincristine/etoposide/prednisone/cyclophosphamide (ABVE-PC). Because a limited number of cycles are required to cure low-risk HL, the cumulative dose differences and thus the coinciding late health risks are minimal between endorsed regimens in low-risk individuals who achieve an

adequate early response to therapy. However, differences emerge for those who do and do not require additional consolidative chemotherapy or radiation. For example, when treating low-risk HL using doxorubicin/vincristine/prednisone/cyclophosphamide (AVPC) or vincristine/etoposide/prednisone/doxorubicin (OEPA), a higher risk of late effects is directly related to organ-specific radiation exposure in those achieving inadequate early responses to therapy because no additional consolidative chemotherapy is used. However, when beginning with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD), selection of the additional consolidative regimen can significantly impact the cumulative anthracycline exposure (100–300 mg/m²) regardless of the need for radiation based on response.

Similarly, the differences in late health risks become more apparent between the various intermediate- and high-risk regimens (Tables 1–3). For example, in the high-risk regimens, the cumulative doxorubicin exposure with 6 cycles of ABVD is 300 mg/m² compared with 250 mg/m² with 5 cycles of ABVE-PC and 160 mg/m² with 6 total cycles of OEPA + cyclophosphamide/vincristine/prednisone/dacarbazine (OEPA-COPDAC). In contrast, lower exposure to anthracyclines in the ABVE-PC and OEPA-COPDAC regimens comes at the expense of higher alkylating agent exposure that can be avoided with ABVD. In addition, 6 cycles of ABVD affords an intentional omission of radiation, whereas high-risk pediatric regimens use PET-only, response-adapted radiation in the absence of large mediastinal adenopathy (ie, with ABVE-PC), allowing for an omission of radiation in a large percentage of patients, highlighting the tradeoffs to consider when choosing the best regimen for individual patients.

Although the tolerability of acute adverse events (eg, reduced nausea/emesis, neuropathy, myelosuppression, and related fever and neutropenia) and the efficacy and convenience of outpatient biweekly delivery favor ABVD for adult oncology practices, the potential for late cardiotoxicity in children and adolescents due to higher cumulative doses of doxorubicin, magnified by concurrent chest-directed radiation with historical modalities and doses, has led to a historical divergence from this approach in pediatric oncology practices.¹⁰ In this regard, pediatric regimens have distinct advantages in young patients; however, they have also introduced new exposures with unique acute and late toxicity risk profiles (eg, epipodophyllotoxins and risk of subsequent leukemia). In addition, they require consecutive day infusions, which are potentially challenging for working caregivers and adolescents/adults. As delineated in the NCCN Guidelines,³⁹ it is critical to weigh the risks and benefits of both the acute and late toxicity profiles of each treatment regimen for each patient.

Rigor in Guideline Development and Evaluation of Late Effects Screening

It is important to reiterate that many late effects will not become clinically apparent until decades after cancer treatment. In adolescent and young adult populations transitioning from pediatric to adult practices, this latency raises concern regarding continuing screening and recognition of adverse health events, potentially leading to poorer outcomes. Awareness and anticipation of potential cancer treatment-related late effects by survivors and providers are essential to facilitate timely interventions to prevent or decrease the burden of health complications and optimize quality of life. Clinical practice guidelines exist to inform screening in childhood cancer survivors.^{40,41} In North America, the Children's Oncology Group guidelines are frequently used and combine evidence linking therapeutic exposures to specific late effects, with screening recommendations aligning the magnitude of risk with screening intensity.⁴¹

In the general medical community, increasing awareness regarding the adverse effects of intensive lifelong screening⁴² has led to “value-based” consideration of the tradeoffs between the benefits, harms, and costs of screening strategies.⁴² High-value strategies provide a quantifiable benefit that clearly justifies the harms and associated costs, whereas low-value strategies result in disproportionately small health benefits relative to the harms and costs incurred.⁴² Value and intensity are not the same,^{42,43} however, and although more intensive screening may provide greater benefit in lives extended, it can result in higher levels of false-positive results, diagnostic workups, overdiagnosis, costs, and patient anxiety that may not be justified by the incremental increase in benefit.^{42,44,45} For example, although data support screening for survivors of childhood cancer at high risk of breast cancer due to chest radiation,⁴⁶ the false-positive rates in women at average risk in the general population are not insignificant.^{47,48} Optimizing value therefore requires finding the intermediate level of intensity that best balances benefits with harms and costs.⁴²

There are inherent challenges to conducting research optimizing value-based screening in survivors of childhood cancer, including the long latency to many late effects, the large numbers needed to detect a significant effect, the evolution of treatment approaches, and the lack of clinical equipoise.⁴⁹ Screening intensity has thus historically relied on expert opinion to determine the appropriateness of recommendations. To overcome these challenges, researchers have used simulation modeling to evaluate the clinical effectiveness and cost-effectiveness of endorsed strategies.^{46,49–51} Despite being limited in scope (radiation-related breast cancer,^{46,52,53} colorectal cancer,⁵⁴ anthracycline-related cardiomyopathy^{49–51}), these efforts have facilitated the refinement and often

Table 1. Cumulative Exposures and Late-Effects Risk in NCCN-Recommended Low-Risk Pediatric HL Regimens

	AVPC (×3)		OEPA (×2)		ABVD (×2) ^a			
	AER ^b	IER ^b + RT	AER ^b	IER ^b + RT	AER ^b + ABVD (×1–2)	AER ^b + AVD (×4)	AER ^b ± ABVD (×1) + RT	IER ^b + ABVD (×2) + RT
Exposures (mg/m ²)								
Doxorubicin	150	150	160	160	150–200	300	100–150	200
Bleomycin (IU/m ²)	—	—	—	—	60–80	40	40–60	80
Vincristine	8.4	8.4	9	9	—	—	—	—
Etoposide	—	—	1,250	1,250	—	—	—	—
Prednisone	840	840	1,800	1,800	—	—	—	—
Cyclophosphamide	3,600	3,600	—	—	—	—	—	—
Dacarbazine	—	—	—	—	2,250–3,000	4,500	1,500–2,250	3,000
Vinblastine	—	—	—	—	36–48	72	24–36	48
Radiation (Gy)	—	21	—	20–35	—	—	20–30	30
Late-Risk Profiles^c								
Infertility	Low	Low High ^d	Low	Low High ^d	Low	Low	Low High ^d	Low High ^d
Neuropathy	Low	Low	Low	Low	Low	Low	Low	Low
Avascular necrosis	Low	Low	Low	Low	Low	Low	Low	Low
Pulmonary toxicity	Low	Low	Low	Low	Low	Low	Low	Low
Thyroid dysfunction	Low	Low High ^e	Low	Low High ^e	Low	Low	Low High ^e	Low High ^e
Cardiomyopathy	Int	Int High ^f	Int	Int High ^f	Int	High	Int High ^f	Int High ^f
SN	Low	High ^g	Low	High ^g	Low	Low	High ^g	High ^g
Recommended Surveillance⁴⁰								
Pulmonary toxicity	None vs at entry into LTFU and as clinically indicated (if bleomycin or chest RT)							
Hypothyroidism	None vs yearly ^e							
Cardiomyopathy	Every 2 (high-risk) to 5 (intermediate-risk) y							
Breast SN	None vs yearly beginning at age 25 y and 8 y after RT ^h							
Colorectal SN	None vs every 5 y, beginning at age 30 y and 5 y after RT ⁱ							
Thyroid SN	None vs yearly ^e							
Skin SN	None vs yearly ^g							

Abbreviations: ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; AER, adequate early response; AVD, doxorubicin/vinblastine/dacarbazine; AVPC, doxorubicin/vincristine/prednisone/cyclophosphamide; BEACOPP, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone; HL, Hodgkin lymphoma; IER, inadequate early response; Int, intermediate; LTFU, long-term follow-up; RT, radiation therapy; SN, subsequent neoplasm.

^aRanges reflect strategies outlined in the NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma, Version 2.2021 (age ≥18 years; available at NCCN.org).

^bResponse assessments based upon FDG-PET/CT, PET/MRI, and/or contrast-enhanced diagnostic CT or MRI of original sites of disease as per primary study methodology.

^cRisk reflects published guideline stratification for infertility⁶¹ and cardiomyopathy.⁶² Neuropathy, avascular necrosis, and pulmonary toxicity were considered low if incidence in clinical trials was <5% and intermediate if ≥5%.^{23,25,31,63–65} Thyroid dysfunction risk was considered high if mean thyroid RT dose was >10 Gy and otherwise was considered low.⁶⁶ SN risk was considered high depending on dose and volume of RT and otherwise was considered low.

^dIf ≥4 Gy to testes or ≥15 Gy to both ovaries.⁶¹

^eIf mean thyroid RT dose was >10 Gy.⁶⁷

^fIf ≥15 Gy chest RT.⁶²

^gDepending on RT dose and volume.⁴⁰

^hAny breast RT.^{40,68}

ⁱAny abdomen/pelvis RT.^{40,69}

the deintensification of recommended screening frequencies.^{46,49–51} Notably, they have paved the way for much-needed efforts to evaluate existing screening

recommendations across a broader set of health outcomes and to assess multilevel interventions seeking to reduce the burden of morbidity in survivors.

Table 2. Cumulative Exposures and Late-Effects Risk in NCCN-Recommended Intermediate-Risk Pediatric HL Regimens

	ABVE-PC (×4)		OEPA (×2) + COPDAC (×2)		ABVD (×2) ^a					
	AER ^b	IER ^b + RT	AER ^b	IER ^b + RT	AER ^b + ABVD (×2)	AER ^b + AVD (×4)	IER ^b + BEACOPP (×4)	IER ^b + BEACOPP (×4) + RT		
Exposures (mg/m ²)										
Doxorubicin	200	200	160	160	200	300	240	240		
Bleomycin (IU/m ²)	60	60	—	—	80	40	80	80		
Vincristine	11.2	11.2	15	15	—	—	5.6	5.6		
Etoposide	1,500	1,500	1,250	1,250	—	—	2,400	2,400		
Prednisone	1,120	1,120	3,000	3,000	—	—	2,240	2,240		
Cyclophosphamide	3,200	3,200	2,000	2,000	—	—	5,000	5,000		
Dacarbazine	—	—	1,500	1,500	3,000	4,500	1,500	1,500		
Vinblastine	—	—	—	—	48	72	24	24		
Procarbazine	—	—	—	—	—	—	2,800	2,800		
Radiation (Gy)	—	21	—	20–35	—	—	—	30		
Late-Risk Profiles ^c										
Infertility	Low	Low High ^d	Low	Low High ^d	Low	Low	High (M)	Int (F)	High (M)	Int (F) High (F) ^d
Neuropathy	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Avascular necrosis	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Pulmonary toxicity	Low	Low	Low	Low	Low	Low	Int	Int	Int	Int
Thyroid dysfunction	Low	Low High ^e	Low	Low High ^e	Low	Low	Low	Low	Low	High ^e
Cardiomyopathy	Int	Int High ^f	Int	Int High ^f	Int	High	Int	Int	Int	High ^f
SN	Low	High ^g	Low	High ^g	Low	Low	Low	Low	Low	High ^g
Recommended Surveillance ⁴⁰										
Pulmonary toxicity	None vs at entry into LTFU and as clinically indicated (if bleomycin or chest RT)									
Hypothyroidism	None vs yearly ^e									
Cardiomyopathy	Every 2 (high-risk) to 5 (intermediate-risk) y									
Breast SN	None vs yearly beginning at age 25 y <u>and</u> 8 y after RT ^h									
Colorectal SN	None vs every 5 y, beginning at age 30 y <u>and</u> 5 years after RT ⁱ									
Thyroid SN	None vs yearly ^e									
Skin SN	None vs yearly ^g									

Abbreviations: ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; ABVE-PC, doxorubicin/bleomycin/vincristine/etoposide/prednisone/cyclophosphamide; AER, adequate early response; AVD, doxorubicin/vinblastine/dacarbazine; BEACOPP, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone; COPDAC, cyclophosphamide/vincristine/prednisone/dacarbazine; F, female; HL, Hodgkin lymphoma; IER, inadequate early response; Int, intermediate; LTFU, long-term follow-up; M, male; OEPA, vincristine/etoposide/prednisone/doxorubicin; RT, radiation therapy; SN, subsequent neoplasm.

^aRanges reflect strategies outlined in the NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma, Version 2.2021 (age ≥18 years; available at NCCN.org).

^bResponse assessments based upon FDG-PET/CT, PET/MRI, and/or contrast-enhanced diagnostic CT or MRI of original sites of disease as per primary study methodology.

^cRisk reflects published guideline stratification for infertility⁶¹ and cardiomyopathy.⁶² Neuropathy, avascular necrosis, and pulmonary toxicity were considered low if

incidence on clinical trials was <5% and intermediate if ≥5%.^{23,25,31,63–65} Thyroid dysfunction risk was considered high if mean thyroid RT dose was >10 Gy and otherwise was considered low.⁶⁶ SN risk was considered high depending on dose and volume of RT and otherwise was considered low.

^dIf ≥4 Gy to testes or ≥15 Gy to both ovaries.⁶¹

^eIf mean thyroid RT dose was >10 Gy.⁶⁷

^fIf ≥15 Gy chest RT.⁶²

^gDepending on RT dose and volume.⁴⁰

^hAny breast RT.^{40,68}

ⁱAny abdomen/pelvis RT.^{40,69}

Table 3. Cumulative Exposures and Late-Effects Risk in NCCN-Recommended Advanced-Stage or High-Risk Pediatric HL Regimens

	ABVE-PC (×5)		OEPA (×2) + COPDAC (×4)		ABVD (×2) ^a	
	AER ^b + RT	IER ^b + RT	AER ^b	IER ^b + RT	AER ^b + ABVD (×4)	IER ^b + BEACOPP (×4)
Exposures (mg/m ²)						
Doxorubicin	250	250	160	160	300	240
Bleomycin (IU/m ²)	75	75	—	—	120	80
Vincristine	14	14	21	21	—	5.6
Etoposide	1,875	1,875	1,250	1,250	—	2,400
Prednisone	1,400	1,400	4,200	4,200	—	2,240
Cyclophosphamide	6,000	6,000	4,000	4,000	—	5,000
Dacarbazine	—	—	3,000	3,000	4,500	1,500
Vinblastine	—	—	—	—	72	24
Procarbazine	—	—	—	—	—	2,800
Radiation (Gy)	21 to LMA	21–30	—	20–35	—	—
Late Risk Profiles ^c						
Infertility	High (M)	Int (F)	High (M)	Int (F)	High (M)	Int (F)
Neuropathy	Low	Low	Low	Low	Low	Low
Avascular necrosis	Low	Low	Int	Int	Low	Low
Pulmonary toxicity	Low	Low	Low	Low	Low	Int
Thyroid dysfunction	Low	Low	Low	Low	Low	Low
		High ^e		High ^e		High ^e
Cardiomyopathy	High	High	Int	Int	High	Int
				High ^f		
SN	Low	High ^g	Low	High ^g	Low	Low
	High ^g					
Recommended Surveillance ⁴⁰						
Pulmonary toxicity	None vs at entry into LTFU and as clinically indicated (if bleomycin or chest RT)					
Hypothyroidism	None vs yearly ^e					
Cardiomyopathy	Every 2 (high-risk) to 5 (intermediate-risk) y					
Breast SN	None vs yearly beginning at age 25 y and 8 y after RT ^h					
Colorectal SN	None vs every 5 y, beginning at age 30 y and 5 y after RT ⁱ					
Thyroid SN	None vs yearly ^e					
Skin SN	None vs yearly ^g					

Abbreviations: ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; ABVE-PC, doxorubicin/bleomycin/vincristine/etoposide/prednisone/cyclophosphamide; AER, adequate early response; COPDAC, cyclophosphamide/vincristine/prednisone/dacarbazine; F, female; HL, Hodgkin lymphoma; IER, inadequate early response; Int, intermediate; LMA, large mediastinal adenopathy; LTFU, long-term follow-up; M, male; OEPA, vincristine/etoposide/prednisone/doxorubicin; RT, radiation therapy; SN, subsequent neoplasm.

^aRanges reflect strategies outlined in the NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma, Version 2.2021 (age ≥18 years; available at NCCN.org).

^bResponse assessments based upon FDG-PET/CT, PET/MRI, and/or contrast-enhanced diagnostic CT or MRI of original sites of disease as per primary study methodology.

^cRisk reflects published guideline stratification for infertility⁶¹ and cardiomyopathy.⁶² Neuropathy, avascular necrosis, and pulmonary toxicity were considered low if incidence on clinical trials was <5% and intermediate if ≥5%.^{23,25,31,63–65} Thyroid dysfunction risk was considered high if mean thyroid RT dose was >10 Gy and otherwise was considered low.⁶⁶ SN risk was considered high depending on dose and volume of RT and otherwise was considered low.

^dIf ≥4 Gy to testes or ≥15 Gy to both ovaries.⁶¹

^eIf mean thyroid RT dose was >10 Gy.⁶⁷

^fIf ≥15 Gy chest RT.⁶²

^gDepending on RT dose and volume.⁴⁰

^hAny breast RT.^{40,68}

ⁱAny abdomen/pelvis RT.^{40,69}

Integration of Frontline Treatment and Late Effects Guidelines

The selection of NCCN-preferred regimens for de novo, pediatric, classic HL largely reflects efficacy and provider familiarity. However, providers, in combination with patients and caregivers, must also consider the risks of long-term health consequences when selecting the optimal regimen for individual patients. Existing literature^{4–8,55–57} and guidelines^{40,41} should be simultaneously considered before and after the selection of therapy for each patient. As previously mentioned, late effects guidelines outline potential health consequences and recommended surveillance strategies.^{40,41} However, parallel consideration of treatment selection based on efficacy, acute toxicity, convenience, and late effects requires a familiarity with both treatment and follow-up guidelines that is impractical for providers who infrequently treat children with HL. There is therefore an increasing need for guideline developers to merge considerations from both frontline treatment and survivorship guidelines into practical documents that integrate potential long-term health risks. Tables 1 to 3 represent initial steps toward this objective by characterizing NCCN-endorsed treatment regimens by cumulative exposure, risk for associated late effects, and impact on subsequent screening recommendations. We assigned risk based on published guidelines where available (ie, gonadal toxicity⁵⁸ and cardiomyopathy⁵⁹). For conditions in which dose-dependent associations with late toxicity were unavailable (eg, neuropathy, pulmonary toxicity, avascular necrosis), we relied on reported incidences from clinical trials, because these particular conditions largely represent long-term (ie, occurring during therapy and persisting long-term) rather than late-occurring conditions. Conditions occurring in approximately <5% of study patients were considered low-risk, and those occurring in 5% to 10% of patients were considered intermediate-risk. We did not identify more frequently occurring conditions to assign as high-risk.^{21,23,29,60–62} For predominantly radiation-dependent conditions (ie, thyroid dysfunction⁶³ and subsequent neoplasms),^{64–66} risk was considered high or low based on receipt or no receipt of prior radiation.

Largely because of the aforementioned successes in treatment and cure, pediatric HL represents a unique population in which to pioneer the convergence of frontline treatment and late-toxicity guidelines. Although our efforts reflect well-described associations between individual treatment exposures and specific outcomes, they represent the relative risk of events taken from individual trials and cohorts. Risk derived from clinical trial reports to date may underestimate low-grade conditions, including fatigue and neuropathy, that often go

unreported in such studies yet may still have a significant impact on functional outcomes or quality of life. It is difficult to compare the impact of “risk” for different adverse events on decision-making without better understanding patient perspectives. For example, although occurrences of treatment-related leukemia associated with HL regimens are infrequent, its devastating implications may influence some patients to accept a higher incidence of other toxicities instead. Moreover, risk of late toxicity is substantially greater for individuals who experience relapse and receive additional cytotoxic chemotherapy, new or extended-field radiation exposure, and/or hematopoietic cell transplant. It is therefore important to balance these considerations with new trial development and in the selection of endorsed frontline regimens.

Although they are consistent with existing guideline approaches,⁴¹ our risk estimates could be strengthened by a number of steps. First, investigations into protocol-specific late health risks reflecting combinations of exposures (eg, ABVE-PC as a collective treatment) are needed. These data, although lacking in HL trials, have been alternatively assessed in recently treated survivors of B-cell non-Hodgkin lymphoma.⁶⁷ This strategy is dependent on the availability of large datasets containing uniformly treated cohorts of patients. Second, although many late-effects studies have categorized radiation exposure by prescribed dose, it is increasingly well recognized that this is a crude indicator of organ-specific dose exposures, which are a more accurate indicator of late-toxicity risk. The Pediatric Normal Tissue Effects in the Clinic collaboration is working to create better quantitative tissue-specific dose-risk information necessary to refine guidelines for both treatment and follow-up.⁶⁸ In addition, consideration of modifiable risks factors present at diagnosis could inform treatment selections. For example, hypertension has been shown to potentiate anthracycline-mediated risk for heart failure in survivors of childhood cancer.⁶⁹ It is reasonable, therefore, to consider that given a choice between equally efficacious regimens, one may choose a lower anthracycline-containing regimen, or administration of a cardioprotective agent, for an obese patient with a strong family history of hypertension. It will also be critical to incorporate health status and health-related quality of life into future decision-making algorithms, including the modifying impact of interventions (eg, the impact of fertility preservation on how a patient weighs the risk of infertility). Equally important will be the consideration of not only tradeoffs between dichotomous exposures (eg, radiation vs no radiation) but also whether the addition of novel agents (eg, CD30-targeted therapy and PD-1 inhibitors), treatment reductions for patients who later experience relapse, and/or contemporary radiation modalities

that mitigate exposure to healthy tissue (eg, proton therapy) will result in more acceptable collective toxicity profiles.

These strategies are difficult if not impossible to prospectively evaluate in randomized clinical trials given the short duration of follow-up relative to the long latency to incident late effects. Simulation models offer one avenue for estimating an individual's risk for a given late effect and can be integrated into shared decision-making. Parsons et al⁷⁰ showed the promise of simulated algorithms to determine the risks associated with combination therapy and to understand and facilitate discussion of these late health risks at diagnosis. Integrating health utilities based on risk estimates from multiple datasets, they simulated differences in late health outcomes and quality-adjusted life expectancy between chemotherapy-only and combined-modality regimens.⁷⁰ Similarly, Bhakta et al⁷¹ simulated life expectancy and quality of life for patients treated using either ABVD or OEPA-COPDAC. Although the latter requires validation, both studies offer exciting potential for decision-making tools that will facilitate personalized HL treatment strategies and will benefit from large-scale collaborations and pooling of individual patient-level data, which are emerging as critical resources for HL and other diseases. For example, the Hodgkin Lymphoma International Study for Individual Care dataset compiles data from numerous large pediatric and adult treatment HL trials and international datasets.⁷⁰ From this pooled dataset, authors have begun to use simulation models to estimate projected life expectancy, quality-adjusted life expectancy, and cause of death for survivors of HL treated in contemporary trials.⁷² The Pediatric Cancer Data Commons is another pooled dataset under development that merges individual study data limited to pediatric HL trials.⁵⁷ Both show the capabilities of large collaborative efforts and highlight the potential for such datasets to inform future treatment guidelines.

Screening Implementation

Notably, >80% of long-term survivors of childhood cancer are no longer followed by their treating institution and instead receive follow-up care in primary care settings.⁷³ Although this transition is inevitable for all

childhood cancers, it occurs sooner in survivors of HL given that many are diagnosed in adolescence and have fewer years remaining within pediatric practices, potentially complicating surveillance adherence. Several care delivery models⁷⁴ have been used to facilitate provider and survivor awareness of and adherence to surveillance recommendations in primary care settings, in addition to providing survivorship care plans.⁷⁵ Despite recent evidence of improvement, poor adherence still impedes optimal survivorship care delivery,⁷⁶ highlighting a need to explore novel mechanisms, such as the use of motivational interviewing^{77,78} and mHealth,^{79,80} to engage long-term survivors and providers in routine survivorship care. In the interim, the implementation of models of care best fit to local resources, and open and clear communication between providers are essential to optimizing survivorship care delivery.

Summary

Collaboration through cooperative group trials and long-term follow-up cohort studies has resulted in multiple effective pediatric HL treatment options. Although all are reasonable, late-effects profiles differ between risk groups and regimen. We have integrated cumulative dose, late-effects risk, and long-term follow-up surveillance recommendations with NCCN Guidelines-endorsed pediatric treatment regimens³⁹ to facilitate shared decision-making between providers and patients. Future studies (eg, simulation models) will strengthen this integrated approach and allow opportunities to incorporate regimen-specific risks, health-related quality of life, and clinical effectiveness and cost-effectiveness into decision-making tools seeking to better personalize HL treatment selections.

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