Pediatric Hodgkin Lymphoma

15

Georgina W. Hall, Cindy Schwartz, Stephen Daw, and Louis S. Constine

Contents

G. W. Hall (✉)
Pediatric and Adolescent Haematology/Oncology Unit, Children's Hospital, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford, UK
e-mail: georgina.hall@paediatrics.ox.ac.uk

C. Schwartz
Division of Pediatric Hematology Oncology and BMT, Medical College of WI, Milwaukee, WI, USA
e-mail: cschwartz@mcw.edu

S. Daw
Children and Young People's Cancer Services, Division of Paediatrics, University College Hospital, London, UK
e-mail: stephendaw@nhs.net

L. S. Constine
Department of Radiation Oncology and Pediatrics, University of Rochester Medical Center, Rochester, NY, USA
e-mail: louis_constine@urmc.rochester.edu

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15.1 Introduction

15.1.1 Comparison of Pediatric/Adolescent Vs. Adult HL

Pediatric/young adult Hodgkin lymphoma (HL) is one of the few childhood malignancies that shares aspects of its biology and natural history with an adult cancer. Historically, children were thought to have a worse prognosis than adults due to antiquated treatment approaches that were initially designed to mitigate toxicities in children. It is now clear that effective therapy provides similar or even superior outcomes in children/young adults. A comparison of the demographics of clinical presentations of pediatric/adolescent HL compared with adult HL is presented in Table 15.1. The first of the bimodal incidence peaks in HL occurs in teenagers and young adults (15–25-year age group). HL represents less than 5% of malignancies in children under the age of 15 years. In contrast, it represents 16–20% of malignancies in adolescents, making it the most common malignancy of this age group.

Childhood HL is biologically indistinguishable from HL of young and middle-aged adults other than the relative incidence of specific disease histologies (Table 15.1). Mixed cellularity (MC) and nodular lymphocyte predominant (nLP) HL are the common types of HL in the preadolescent child; adolescents and young adults are most frequently (85%) afflicted with nodular sclerosing (NS) HL [3]. Only a third of children will have advanced disease; approximately 25% will have B symptoms. The incidence of HL with adverse features increases with age. Although there were no discernable differences in clinical presentation, response to therapy, or long-term outcome for adolescents (16–21 years) vs. young adults (22–45 years) treated similarly for HL [4], the treatment of children/adolescents and adults has diverged over the years primarily due to concerns about the late adverse effects of therapy.

15.1.2 Classical Pediatric Hodgkin Lymphoma (PHL)

15.1.2.1 Overall Strategies

The adverse consequences of therapy have driven the pediatric treatment paradigm of care. Clinical trials for pediatric and adolescent HL have been designed to both reduce long-term organ injury and increase efficacy. Pediatric oncologists responded first to developmental issues in the young child and later to the long-

Table 15.1 Demographic and clinical characteristics at presentation of pediatric HL (modified from Refs. [1, 2])

	Childhood HL	AYA HL	Adult HL
Age range (years)	≤14	15–35	≥35
Prevalence of HL cases (%)	10–12	50	
Gender Male/female	2–3:1	1:1–1.3:1	
Histology Nodular sclerosis (%) Mixed cellularity (%) Lymphocyte depleted (%) NLPHL (%)	40–45 30–45 0–3 8–20	65–80 10–25 1–5 2–8	
EBV associated	27–54% Risk factors: male, younger age, mixed cellularity histology, economically disadvantaged countries	20–25%	34–40%
Other risk factors	Lower SES increasing family size	Higher SES, smaller family size, early birth order	
Stage at presentation	30–35% with stage III or IV disease, 25% with B symptoms	40% with stage III or IV disease, 30–40% with B symptoms	
Relative survival rates at 5 years	94% (<20 years)	90% (<50 years)	

AYA adolescents and young adults, *IPS* International Prognostic Score, *SES* socioeconomic status

term treatment consequences in all young survivors in the design of treatment approaches. Recognition of musculoskeletal hypoplasia in young children with HL treated with high-dose radiation such as shortened sitting height, thin necks, and narrow shoulders and chest [5–8] precipitated the development of pediatric-specific regimens for HL. Combined-modality treatments, even for low-stage disease, allowed for the reduction of radiation dose [9] and field size, thus sparing normal structures (Fig. 15.1). This strategy for care was extended to older children and adolescents when hypothyroidism [11, 12], secondary cancers, and valvular and atherosclerotic heart disease [13, 14] were also found to be attributable to high-dose radiation.

Low-dose radiation of 15–25 Gy has been the standard in childhood and adolescent HL for decades. This reduced the potential for long-term risk without adversely impacting event-free survival. A convergence of treatment approaches for adults and children/adolescents may be emerging as recent adult trials have begun to address these issues and reduce radiation doses. With overall survival over 90%, the quality of survival becomes paramount.

Early response to therapy was recognized [15, 16] as highly predictive of outcome. In Europe and the United States, response-based, risk-adapted approach to treating HL [17] allows therapy to be tailored to each individual, within the context of clinical trials. Dose-dense regimens [17] used are similar to those used by adult groups [18, 19], but the pediatric algorithms use the enhanced efficacy to support reduction of therapy.

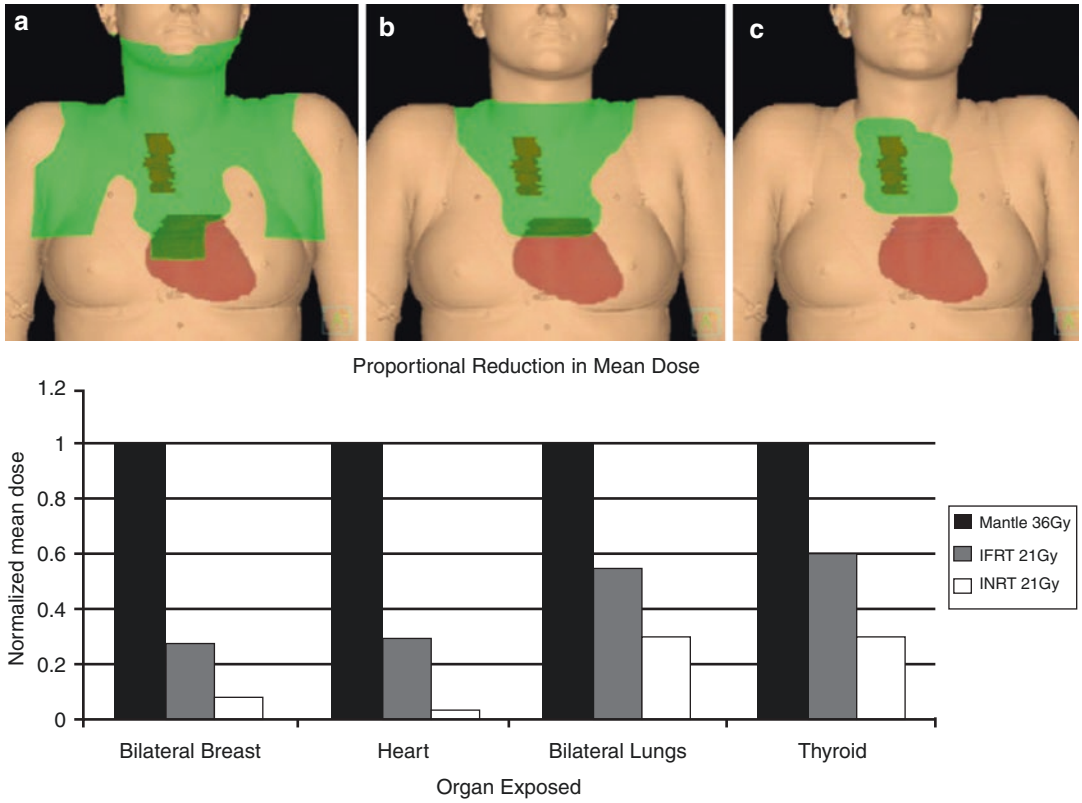

Fig. 15.1 CT-based planning images depicting a historic mantle RT, compared to standard involved field radiation treatment (IFRT) and involved-node RT (INRT) for a patient with stage I disease involving the mediastinum. The postchemotherapy volume of initially involved paratracheal nodes is depicted in dark red and the cardiac silhouette is also evident. (**a**–**c**) Demonstration of the reduction in dose to breast, lung, heart, and thyroid for the female patient shown in (**a**) from Mantle 36Gy to IFRT 21Gy to INRT 21Gy. From Hodgson et al. [10]

Table 15.2 Risk groups employed by selected pediatric study groups [20]

Study group	Risk features (RF)	Low risk	Intermediate/early unfavorable risk	High risk
Children's Oncology Group [21, 22]		IA/IIA no bulk/no LMA	All others IIB, IIIA IVA	IIIB, IVB
EuroNet-PHL-C1, C2 [23]		IA/B[a] IIA[a]	IIA, IIB (no E), IIIA (no E)	IIEB IIIEA/ IIIB IV
St. Jude/Stanford/ Dana-Farber	Categorized as favorable or unfavorable risk by IPS	IA/IIA no bulk	IA/IIA (RF), I IB IIIA IIII	IIB, IIIB, IV.

[a]No bulk, ESR < 30 mm/h

15.1.2.2 Low-Risk (Early Favorable) Disease

Although there have been differing definitions of low-risk disease (Table 15.2), risk-adapted approaches aim to define a cohort of patients that is curable with minimal therapy. Treatment group allocation, risk stratification, and response assessment vary according to each study group (Table 15.2), but all treatment groups define low risk based on stage and bulky disease. Children and adolescents with NLPHL are increasingly being treated with surgery alone or using low-dose regimens separate from those used for the treatment of classical HL.

In the decade following the introduction of MOPP, secondary leukemia and sterility emerged as significant concerns [24–27]. During the 1980s, alkylator exposure and leukemia risk were reduced by alternating MOPP and ABVD [28, 29]. The goal was to avoid reaching thresholds of toxicity for any specific agent. The Pediatric Oncology Group (POG) compared four cycles of MOPP/ABVD plus 25.5 Gy to six cycles of chemotherapy alone without detecting differences in efficacy [15]. However, the profound sensitivity of the testes to procarbazine continued to cause sterility in boys, even with only two cycles of procarbazine-containing chemotherapy [30]. Although early attempts to avoid procarbazine were unsuccessful [31], more recent regimens have achieved this goal [17].

ABVD is used routinely in adults [32], but also has not been standard of care in children. Successful regimens have been devised by the German Paediatric Oncology Hodgkin's Group (GPOH) [33] using OEPA (vincristine, etoposide, prednisone, and doxorubicin) in males (Table 15.3), by the French Society of Pediatric Oncology [36] using EBVP (etoposide, bleomycin, vincristine, prednisone), by Donaldson et al. [42] using VAMP (vincristine, doxorubicin, methotrexate, and prednisone), and by the Children's Oncology Group (COG) using ABVE (doxorubicin, bleomycin, vincristine, etoposide) [43] and ABV-PC [41] all avoiding the use of procarbazine. With these approaches, EFS of 88–92% can be achieved without significant radiation or alkylator toxicity. Patients treated on these newer regimens receive less than 200 mg/m^2 of doxorubicin plus or minus 20–25 Gy of involved-field radiation.

The traditional approach of most pediatric HL treatment groups has been to use combined-modality therapy. Currently, these study groups are involved in evaluating methods to define low-risk patients who may be cured without radiotherapy, i.e., with chemotherapy alone. However, patients with early-stage HL treated with chemotherapy alone most frequently relapse in the initially involved lymph node(s) [44]. Therefore, an effort has also been made to reduce the radiation field size by including only the initially involved lymph node(s)—so-called involved node-radiation (INRT) [45]. The complexity of defining the field for INRT has led to the development of an alternative approach termed "involved-site radiation therapy" (ISRT) [46–48]. This is a modification of IFRT, recommended for patients who when optimal pre-chemotherapy imaging (PET-CT in a position similar to what will be used at the time of radiation therapy) is not available that would be necessary for INRT treatment planning. Because the delineation of the area of

Table 15.3 Treatment results for early, favorable pediatric HL

Group or institution	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy). field	Survival (%)		Follow-up interval (years)	References
					Overall	DFS, EFS, or RFS		
Combined-modality trials								
US CCG 5942	294	IA/B, IIA	4 COPP/ABV	21, IF	100	97	3 10	[34, 35]
SFOP MDH-90	171	I – II	4 VBVP, good responders	20, IF	97.5	91	5	[36]
	27	I – II	4 VBVP 1–2 OPPA, poor responders	20, IF		78	5	
GPOH-HD95	326,224	I, IIA IIB, IIIA	2 OEPA or 2 OPPA above + COPP	CR: No RT PR: 20 IF (10–15 Gy boost)	99 97	94 88	5	[37, 38]
GPOH-HD2002	195,139	IA, 1B, IIA, IE, IIB,IIAE, IIIA	2 OEPA or 2 OPPA Above +2 COPP or 2 COPDAC	20 ± 10–15 IF	99.5 98.5	92 88	5	[39, 40]
Chemotherapy alone								
US CCG 5942	106	CS IA/B, IIA	4 COPP/ABV	CR: None	100	91	3	[34]
Response based RT *AHOD0431 [D,E]* *St. Jude consortium[C]*	278 88	IA, IIA IA, IIA	4 AV-PC 4 VAMP	21 IF if PR 25.5 IF/ none if Early CR	99 100	80 89	4 5	[41]

ABVD Adriamycin, bleomycin, vinblastine, and dacarbazine, *AEIOP* Italian Association of Hematology and Pediatric Oncology, *CCG* Children's Cancer Group, *ChlVPP* chlorambucil, vinblastine, procarbazine, and prednisolone, *COPP* cyclophosphamide, vincristine (Oncovin), prednisone, and procarbazine, *COPP/ABV* cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone, Adriamycin, bleomycin, and vinblastine, *CR* complete response, *CS* clinical stage, *EF* extended field, *EFS* event-free survival, *HD* Hodgkin's disease, *IF* involved field, *MDH* multicenter trial, *MH* multicenter Hodgkin's trial, *MOPP* nitrogen mustard, vincristine (Oncovin), procarbazine, and prednisone, *M/T* mediastinal/thoracic ratio, *OEPA* vincristine (Oncovin), etoposide, prednisone, and Adriamycin, *OPA* vincristine (Oncovin), prednisone, and Adriamycin, *OPPA* vincristine (Oncovin), procarbazine, prednisolone, and Adriamycin, *PR* partial response, *PS* pathologic stage, *R* regional, *RFS* relapse-free survival, *RT* radiotherapy, *SFOP* French Society of Pediatric Oncology, *VAMP* vinblastine, Adriamycin, methotrexate, and prednisone, *VBVP* vinblastine, bleomycin, etoposide (VP-16), and prednisone, *AVPC* doxorubicin, vincristine, prednisone, etoposide
Mediastinal thoracic ratio < 0.33, lymph node <6 cm

involvement is less precise, a somewhat larger treatment volume is treated than with INRT, but less than traditionally used with IFRT. Other radiation techniques that are contemporary and reduce the treatment volume include intensity-modulated radiation therapy, deep inspiration breath holding (to reduce the volumes of the lung and heart that might be exposed), and protons [49].

Nachman et al. showed an increased relapse rate in patients who did not receive radiation despite achieving CR at the end of chemotherapy [34, 35]. Late-response evaluation may not have identified the optimal cohort for reduction of radiation. Early response may better define the profoundly chemotherapy-sensitive patient who does not need radiation. Based on the

excellent outcomes of low-risk HL patients achieving CR after two cycles of chemotherapy [15], recent trials in the COG, the St. Jude/DFCI/Stanford Consortium, and the EuroNet PHL group [50, 51], have examined early response to determine who does or does not require radiation post-chemotherapy.

The prognostic importance of early chemotherapy response rather than end of chemotherapy response has led to the use of early response assessment (after 6–9 weeks) to titrate individual therapy and dose-dense regimens to maximize the early response rates. The St. Jude/DFCI/Stanford Consortium has reported 2-year EFS of 90.8% in early-responding, low-risk patients with either classical or nodular lymphocyte-predominant HL treated with 4 cycles of VAMP without radiation [51]. The most recent COG study (AHOD0431) found that early assessment by PET after one cycle is a predictor of recurrence [41, 52]. The current EuroNet PHL-C1 classical HL trial is evaluating PET activity after two intensive cycles of OEPA (cumulative dose of anthracycline is 160 mg/m^2) to predict who does not require radiotherapy [53]. All such reductions in treatment may increase the risk of relapse; hence, adverse outcomes such as the need for high-dose salvage therapy (e.g., stem cell transplant or high-dose radiation) must be closely monitored.

15.1.2.3 Intermediate- and High-Risk (Advanced, Unfavorable) Disease

For children with advanced-stage disease, improving efficacy while limiting long-term toxicity is even more challenging. The approach in pediatric HL has been to increase the number of agents so as to limit cumulative doses of individual agents. Regimens used in the 1980–1990s alternated MOPP/ABVD [29, 54] or used the hybrid COPP/ABV [34] to avoid the cumulative doses of doxorubicin (300–400 mg/m^2) and bleomycin (120–160 mg/m^2) associated with six to eight cycles of the four-drug ABVD regimen [28, 32].

Minimalistic dose regimens in combined-modality protocols, such as VEPA (Table 15.4), that eliminated traditional alkylating agents were not successful and resulted in a 70 and 49% 5-year EFS for stage III and IV HD, respectively [61].

It has been known for decades that outcome in HL is optimized by chemotherapeutic dose intensity. Only recently has this knowledge been considered a clue to improving outcome [62–64]. ABVE-PC was developed by the COG (by adding prednisolone and cyclophosphamide to ABVE) for the treatment of advanced HL and dose density was increased by the use of 3-week cycles [17]. This regimen is similar to dose-dense regimens such as Stanford V and BEACOPP, developed simultaneously in the adult groups [18, 19]. BEACOPP and escalated BEACOPP are dose-intensive regimens with improved efficacy compared to COPP/ABVD. Instead of further cumulative dose escalation, the COG and EuroNet PHL take advantage of dose-dense delivery to limit cumulative cytotoxic therapy. Such dose-intensive regimens also limit the cumulative dose of agents delivered to the early responders. The GPOH-HD/EuroNet PHL group has substituted dacarbazine for procarbazine, resulting in excellent long-term results [40].

ABVE-PC is the backbone for all COG trials. This dose-dense approach allows for the elimination of procarbazine and the limitation of the doxorubicin and etoposide dose. The first such study (POG 9425) resulted in 5-year EFS of 84% and 5-year overall survival (OS) of 95% for advanced HL. Early responders (after three cycles of ABVE-PC) on this study proceeded directly to receive 21 Gy regional RT. Others received two more cycles (total five ABVE-PC in 15 weeks) prior to 21 Gy RT This backbone was used in AHOD0031 to evaluate a response-based vs. standard approach to therapy for intermediate-risk disease and to study augmentation of therapy for high-risk patients with a slow early response to therapy [65].

Low-dose, involved-site radiation remains a relevant modality of therapy in high-risk disease. The multicenter trial GPOH-HD95 used OPPA/COPP for girls and OEPA/COPP for boys with radiation dose determined by end of chemotherapy response. For the intermediate- and higher-risk groups (TG2 and TG4), outcome was

Table 15.4 Treatment results for advanced, unfavorable pediatric Hodgkin lymphoma

Group of institution	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy), field	Survival, %		Follow-up interval (year)	Reference
					Overall	DFS. EFS. or RFS		
Combined-modality trials								
Germany, Austria HD-95 (2001) (2013)	280	II_EB, III_EA/B, IIIB, IVA/B	2 OEPA/OPPA + 4 COPP	PR:20–35, IF CR: No RT	97	84	3 10	[37] [38]
HD-2002	239	IIBE, IIIAE, IIIB, IV	2 OEPA, 4 COPDAC	20 ± 10–15 Gy IF RT	95	87	5	[40]
AHOD 0031	380	Not I/IIA no bulk, III, IVB	RER:ABVE-PC × 4	21GY IF RT	97.8	87.9		[55]
	382 151		RER: ABVE-PC × 4 SER: ABVE-PC × 4	No RT 21GY IF RT	95.3	84.3 75.2		
	153		SER: ABVE-PC × 4 add DECA × 2	21GY IF RT		79.3		[56]
AHOD 0831	145				95.9	80.2		
	77	III, IVB	RER: 5 ABVE-PC	21 GY to residual or bulky disease				
	68		SER: Add Iifos/vinor × 2	21GY IF RT				[57]
CCG 59704	99				97	94		
		IIB, IIIB, IV	BEACOPP × 4 RER (F): BEACOPP × 4	No				[16]
			RER (M): ABVD × 4 SER: BEACOPP × 4	21 GY 21 GY				[34] [35]
St. Jude's, Stanford, DFCI (2004)	159	CS IB/IIB or Bulky>6 cm	6 VAMP/COP	15 IF if CR	93	76	5	[58]
		CS III/IV		25.5 IF if PR				
COG—P9425 (2009)	216	CS IB, IIB, $IIIA_2$, IIIB, IV	RER: 3 ABVE-PC SER: 5 ABVE-PC	21 IF	95	86	5	[17]
		IIA/IIIA1 "bulk"		21 IF		84		
Chemotherapy alone UKCCSG (2002)	67	CS IV	6–8 ChlVPP	None[a]	80.8	55.2	5	[59]

(continued)

Table 15.4 (continued)

Group of institution	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy), field	Survival, %		Follow-up interval (year)	Reference
					Overall	DFS. EFS. or RFS		
US CCG (2002)	394	CS I/II[b], CS IIB, CS III	6 COPP/ABV	None	100	83	3	[34]
	141	CS IV	COPP/ABV, CHOP, AraC/VP-16	None	94	81	3	
US POG (1997) *Response-based RT* AHOD0031 (2010)	81 1712	CS IIB, III2A, IIIB, IV All except: IA, IIA non-bulk IIIB, IVB	4 MOPP/4 ABVD Standard arm; 21 IF/4 ABVE-PC	None Randomized: RER: ± RT SER: ± 2 DECA	96 98	79 85	5 4 [60]	[16]

ABVD Adriamycin, bleomycin, vinblastine, and dacarbazine, *ABVE-PC* Adriamycin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide, *AEIOP* Italian Association of Hematology and Pediatric Oncology, *AraC* cytosine arabinoside, *CAPTe* cyclophosphamide, Adriamycin, prednisone, and teniposide, *CCG* Children's Cancer Group, *CCOPP* vincristine (Oncovin), procarbazine, and prednisone, *ChlVPP* chlorambucil, vinblastine, procarbazine, and prednisolone, *CHOP* cyclophosphamide, hydroxydaunomycin, vincristine (Oncovin), and prednisone, *COMP* cyclophosphamide, vincristine (Oncovin), methotrexate, and prednisolone, *COPP* cyclophosphamide, vincristine (Oncovin), prednisone, and procarbazine, *COPP/ABV* cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone, Adriamycin, bleomycin, and vinblastine, *CR* complete response, *CS* clinical stage, *CVPP* cyclophosphamide, vinblastine, procarbazine, and prednisone, *DFS* disease-free survival, *EF* extended field, *EFS* event-free survival, *HD* Hodgkin's disease, *IF* involved field, *MDH* multicenter trial, *MH* multicenter Hodgkin's trial, *MOPP* nitrogen mustard, vincristine (Oncovin), procarbazine, and prednisone, *NR* no response, *OEPA* vincristine (Oncovin), etoposide, prednisone, and Adriamycin, *OPA* vincristine (Oncovin), prednisone, and Adriamycin, *OPPA* vincristine (Oncovin), procarbazine, prednisolone, and Adriamycin, *POG* Pediatric Oncology Group, *PR* partial response, *PS* pathologic stage, *R* regional, *RFS* relapse-free survival, *RT* radiotherapy, *SFOP* French Society of Pediatric Oncology, *TLI* total lymphoid irradiation, *UKCCSG* United Kingdom Children's Cancer Study Group, *VAMP* vinblastine, doxorubicin, methotrexate, and prednisone, *VEEP* vincristine, etoposide, epirubicin, and prednisolone, *VEPA* vinblastine, etoposide, prednisone, and Adriamycin, *DECA* dexamethasone, etoposide, cisplatin, cytarabine

[a]Presence of adverse features = (t)hila, >4 nodal sites, bulk

[b]12 patients received 20–35 Gy, IF; 2 received whole lung irradiation

significantly better for those receiving radiation therapy (TG2, 0.78 vs. 0.92; TG 2 + 3, 0.79 vs. 0.91) [33, 38]. The Children's Cancer Group also noted improved outcome for patients treated with radiation, despite CR at the end of chemotherapy [34, 35]. Kelly et al. [66] reported excellent results using a modified approach to BEACOPP that reduced doses of chemotherapy for girls and for boys with a rapid response. Nonetheless, this regimen is not being used currently because cumulative doses of chemotherapy remain high.

Recent trials in both the COG and in Europe addressed early-response-directed approaches to limit the need for radiation. AHOD0031 for intermediate-risk HL used the dose-dense ABVE-PC regimen to support and evaluate the concept of an early-response-based algorithm [60]. This study showed that rapid early response (RER) could identify a cohort comprising 45% of patients who did not benefit from radiation. However, in a subset analysis from this study of patients with anemia and bulky limited-stage disease, the EFS was 89.3% for rapid early responder or complete remission patients who received IFRT, compared with 77.9% for patients who did not receive IFRT ($P = 0.019$) [67]. For patients who had a slow early response (SER), a marginal benefit from augmented chemotherapy was observed. The high-risk study (AHOD-0831) limited radiation fields for rapid early responders while augmenting therapy for slow early responders; outcomes were similar to POG9425 but used less radiation for RER and less doxorubicin for SER [E].

Adult patients with high risk randomized to ABVD vs. brentuximab with AVD have been reported to have a reduced risk of progression, death, or non-complete response [68], resulting in approval in the United States for this indication. However, it is not clear that this approach has an advantage in the setting of pediatric regimens that have had greater efficacy than ABVC. COG has a randomized, ongoing study comparing standard ABVE-PC to ABrVE-PC (Harker-Murray et al.), and the St. Jude Consortium is similarly evaluating the use of brentuximab with their backbone therapy.

15.1.2.4 Future Considerations in Classical Pediatric and Adolescent HL

Progress has been made in the treatment of children with HL with all stages of disease and risk factors, but several issues remain to be resolved. Response to chemotherapy may define both the total amount of chemotherapy required and the need for radiotherapy (RT). For early-stage patients, the balance between chemotherapy dose and radiation exposure continues to be explored. Restriction of RT to initially involved lymph nodes (involved-node irradiation or involved-site irradiation) rather than chains (or regions) of nodes may affect the balance of risk. For high-risk disease, dose-dense chemotherapy improves efficacy and supports tailoring of therapy to the patient's response. RT is clearly effective in enhancing the local control of PHL, but has a dose-dependent toxicity profile favoring a limited volume/dose approach. Ongoing studies are needed to assess the role of RT for initial bulky disease, to residual postchemotherapy disease (particularly if it is PET negative), and to involved organs. Carefully designed and sequential evidence-based studies are needed to continue to improve efficacy while limiting toxicity.

15.1.3 Nodular Lymphocyte-Predominant HL (NLPHL)

An indolent, peripheral, NHL-like disease, NLPHL was recognized in the early 1990s as a clinicopathologically distinct form of HL [69]. Unlike classical HL, NLPHL is a CD20-positive, CD30- and CD15-negative, B cell lymphoma that is not associated with EBV genomic integration. There is a distinct male predominance (ratio 2–3:1) with nearly 90% of pediatric patients having early-stage disease (IA/IIA). A higher percentage (10–20%) of children have NLPHL [3] compared to adults (3–8%) [70], and although >50% of pediatric and adolescent cases are under the age of 14 years [71], the incidence peaks between 14 and 18 years. Peripheral lymphadenopathy is the most common presentation involving the axilla, cervical, and

inguinal regions, often present for months or years. Rarely is advanced or central disease seen.

Adults with early-stage NLPHL are treated with involved-field radiotherapy, standard cHL therapy, or combined-modality therapy. Children have, until 2005 and the start of NLPHL-specific clinical trials, received standard pediatric cHL therapy with combined-modality chemoradiotherapy [72], which is excessively toxic.

Morbidity, even mortality, secondary to repeated courses of intensive therapy to eradicate this indolent, usually nonfatal disease has resulted in a drive to reduce the intensity of therapy to avoid late effects [71].

Children with fully resected early-stage nLPHD have been cured without the need for any chemoradiotherapy [73–76], but the specific situations in which this strategy is appropriate are currently under investigation. Two nonrandomized clinical trials, EuroNetPHL-LP1 and COG's AHOD03P1, have looked at reducing the toxicity of upfront therapy for early-stage disease (stage I and II) [73, 74]. As salvage therapy is effective for late or even multiple relapses which generally recur at the original site of disease with no stage upgrade, OS is expected to remain near to 100% [77]. The EuroNetPHL-LP1 used surgical resection alone or low-dose anthracycline-free CVP chemotherapy for non-resectable disease, and COG's AHOD03P1 used AVPC (equivalent to CHOP) with selective radiotherapy. Excellent EFS rates of 60–75% with no or low-dose chemotherapy have been obtained and only 10% of COG patients received RT, maintaining 100% OS [78].

Because of transformation rates of approximately 5% to aggressive B-NHL [79] in adults, usually diffuse large B cell lymphoma [80], concerns regarding reduced therapy that could potentially allow persistence of the CD20 clone and increased transformation rates remain. In theory, the addition of rituximab would help to specifically eradicate the CD20 clone and reduce transformation rates. However, transformation rates in children are not known but appear extremely low.

Rituximab has been studied in adults for use in this and all other CD20-positive lymphomas [81]. The pediatric community have traditionally been wary about using rituximab in young children because of impact on immune status/memory. As early-stage NLPHL is viewed as a highly curable disease with minimal chemotherapy or surgery alone, the use of rituximab has been reserved for treating more aggressive, advanced, or relapsed disease. Assessing the impact of adjuvant rituximab therapy on EFS and transformation rates in children within a randomized clinical trial has been the unattainable aim of clinicians for well over a decade. The reluctance of the pediatric community to use rituximab in this and other CD20+ lymphomas is abating.

Current proposed clinical trials using low-dose NHL-like therapy including anti-CD20 therapy are focused on the natural history, establishing risk categories, variant histologies, and transformation rates, with biological substudies looking at specific molecular characteristics.

15.1.4 Recurrence, Relapse, and Salvage in PHL

15.1.4.1 Introduction

Relapsed and refractory classical Hodgkin lymphoma (HL) remains a clinical and therapeutic challenge. Approximately 10% of patients with early-stage and up to 30% with advanced-stage disease relapse after first-line chemotherapy.

Cure can still be achieved in a substantial proportion of patients with recurrent disease, but there is no uniform approach to salvage therapy. The optimal salvage treatment has not been defined in children and adolescents as there are no randomized trials defining the "best" salvage chemotherapy regimen or comparing standard-dose chemotherapy (SDCT) vs. high-dose chemotherapy and autologous stem cell transplant (HDCT/ASCT), which is often considered the standard of care in adult practice. Pediatric practice adopts a more individualized risk-stratified and response-adapted approach to salvage treatment with both non-transplant (SDCT plus radiotherapy) and transplant (SDCT plus HDCT/ASCT) salvage.

At the point of relapse, a full disease reassessment including histologic confirmation is mandatory and then an analysis of pre-salvage risk factors is undertaken. All patients have a common starting point with re-induction SDCT and this is followed by consolidation treatment. The choice of consolidation treatment is guided by

risk stratification based on prognostic factors as well as an assessment of chemosensitivity which is commonly done after two cycles of SDCT and includes FDG-PET response. Achieving a complete metabolic remission on FDG-PET prior to consolidation has been shown to be highly prognostic in the relapse setting and is considered to be a major goal of re-induction SDCT [82]. Consolidation after SDCT will be radiotherapy only in "low-risk" relapse or HDCT/ASCT in "standard-risk" relapse, and these two strategies will be appropriate for the vast majority of relapse/progressive HL. A small number of patients are refractory to SDCT and do not achieve a CR with two or more lines of SDCT and these are "high-risk" patients [82]. Consolidation in these high-risk patients may be either conventional HDCT/ASCT possibly with post-HDCT consolidation RT or maintenance-targeted therapy such as brentuximab vedotin, or alternative experimental approaches may be applied including novel agents such as checkpoint inhibitors or allogeneic transplantation.

15.1.4.2 Standard-Dose Salvage Chemotherapy Regimens

After recurrence is noted, the first step is reinduction with a SDCT salvage regimen. There is no "best" chemotherapy regimen at salvage, and there are no randomized studies comparing standard-dose chemotherapy regimens. The choice of regimen should take account of primary therapy, use of non-cross-resistant drugs, and cumulative drug toxicities. The aim of salvage therapy is to obtain cytoreduction and to demonstrate chemosensitivity which is done most accurately now with FDG-PET as first-line treatment. It also facilitates collection of peripheral stem cells for ASCT. Salvage regimes can be divided into intensive conventional regimens[1] (mini-BEAM), cisplatin-based regimens[2] (ESHAP, DHAP [ESHAP, DHAP, APPE, DECAL]), ifosfamide-based regimens[3](EPIC, IEP, ICE, IV), or others[4] (GV, IGEV). The COG uses IV as its standard regimen because of efficacy and with the intent of avoiding etoposide-induced secondary malignancy after stem cell transplantation [83]. In Europe, alternating IEP/ABVD was used in the EuroNet-PHL-R1 trial but more recently the IGEV regimen has been widely adopted. The decision to continue salvage therapy with RT consolidation vs. HDCT/ASCT is based on assessment of predictive factors.

15.1.4.3 Prognostic Factors at Relapse in Pediatric HL: Standard-Dose Chemoradiotherapy Vs. High-Dose Chemotherapy/ Stem Cell Transplantation

Prognostic factors at relapse may be used to allocate patients to a risk-stratified salvage approach. This is in contrast to adult practice where consolidation with HDCT/ASCT is considered standard of care. There are currently no universally accepted prognostic criteria in children (or adults) defining individualized salvage treatment plans. Factors which are prognostically important include time to relapse, prior treatment in first line, stage/disease burden at relapse, and response to salvage chemotherapy. In children, low-risk patients may be salvaged with RT consolidation only, while standard-risk patients are salvaged with HDCT. The cut point between low- and standard-risk patients is not universally defined. In Europe, low-risk patients salvaged with SDCT plus RT only include those with early relapse after up to 4 cycles of chemotherapy and late relapse after up to 6 cycles with *all* of the following: nodal relapse, no prior RT (or relapse only outside prior RT fields), consolidation RT that has acceptable toxicity (i.e., no excessive RT fields), and chemotherapy-responsive disease. All other patients have intensification with HDCT/ASCT.

[1] Mini-BEAM; BCNU, etoposide, cytarabine, melphalan

[2] *ESHAP,* etoposide, methylprednisolone, cytarabine, cisplatin; *DHAP,* dexamethasone, cytarabine, cisplatin; *APPE,* cytarabine, cisplatin, prednisone, etoposide; *DECAL,* cytarabine, cisplatin, prednisone, etoposide, asparaginase

[3] *EPIC,* etoposide, vincristine epirubicin, prednisolone; *IEP,* ifosfamide, etoposide, prednisolone; *ICE,* ifosfamide, carboplatin, etoposide; *IV,* ifosfamide, vinorelbine

[4] *GV* gemcitabine, vinorelbine; *IGEV,* ifosfamide, gemcitabine, vinorelbine, prednisolone

Time to relapse from end of first-line treatment is the most important pretreatment risk factor and highly significant for OS and EFS in pediatric studies [84–86] and dominated all other prognostic factors in multivariate analysis of the ST-HD-86 trial, the largest prospective pediatric relapse trial published to date [87], with DFS of 41, 55, and 86% for those with refractory disease, early relapse, and late relapse, respectively. This study showed that salvage can be risk adapted because subgroups with markedly better or worse prognosis can be defined. Stage IV and extranodal disease were also associated with lower OS.

A recent French experience [88] found the only relevant prognostic factors to be time to relapse and chemoresistance with primary progressive HL having an EFS <40% compared with approximately 80% in late relapse and chemosensitivity (CR or PR >70%) to salvage associated with a DFS of 77% vs. 10% with poor response ($p < 0.0001$). Chemosensitivity to SDCT and disease status at transplantation are also predictive of outcome. In one study, 5-year FFS was 35% for patients with chemosensitive disease vs. 9% with chemoresistant disease [84]. Another group found 68% OS and 59% FFS at 5 years in chemosensitive patients vs. 18% and 0% in chemoresistant patients [85]. Several particularly adverse factors have been noted. Chemoresistant patients had 5-year FFS of 0% with HDCT/ASCT [85]. Adolescents with B symptoms at recurrence had poor OS even after HDCT/ASCT (11-year OS 27% with B symptoms vs. 60% without) [89]. No difference in OS or FFS between age subgroups or in comparison with adult cohorts has been reported by several studies [84, 85, 90]. Of note, many of these studies did not incorporate FDG-PET response assessment which is now well recognized as the most important prognostic factor, which may overcome the significance of some factors as is the case in first-line treatment [91].

15.1.4.4 Role of Radiotherapy in Relapsed Hodgkin Lymphoma

Radiotherapy has an important role in salvage, but must be individualized based on previous radiation exposure, in or out of field recurrence, stage at recurrence, and the toxicities of total treatment burden [92]. Increasing numbers of patients are RT naïve at relapse as the use of RT is increasingly restricted in first-line treatment and RT fields are also becoming highly restricted in some first-line trials to FDG-PET-positive residua. Therefore, at relapse many patients have never received RT, and some other patients may relapse in prior disease sites that have never received RT because they received focal targeted RT only. Salvage with RT alone is generally not recommended, but integration of RT in salvage is relevant in two contexts:

1. As consolidation treatment in low-risk group patients after SDCT.
2. In selected patients as consolidation after HDCT/ASCT

15.1.4.5 High-Dose Chemotherapy and Autologous Stem Cell Transplant

COG protocols have studied HDCT/ASCT and immunomodulatory therapy in all patients except the lowest-risk group (late relapse without bulky disease or B symptom in those initially treated for IA/IIA disease with minimal systemic therapy) [93]. In Europe, HDCT/ASCT has a recognized role in salvage for those with higher-risk features, namely, all primary progressive HL and early relapse after 6 cycles of first-line chemotherapy, all relapse with poor response to reinduction, and finally those patients in whom RT consolidation is either not feasible (advanced-stage relapse) or too toxic (extensive RT fields required or re-irradiation of prior irradiated sites). Patients without high-risk features and who achieve a complete FDG-PET-defined response after two cycles of SDCT may receive only consolidation SDCT plus RT.

There are no studies that define the most effective HDCT. BEAM and CVB (cyclophosphamide, etoposide, carmustine) are commonly used. TBI-containing regimens confer no benefit and are associated with increased toxicity and late effects. Transplant-related mortality is down to 0–2% in some series. A higher TRM rate has been associated with history of atopy, thoracic irradiation, multiple chemotherapy regimens, and multiple relapses.

Series with HDCT/ASCT in pediatric and adolescent patients are small and report EFS rates of 31–67% [84, 85, 90, 94]; outcome for children is similar to adults with HDCT/ASCT [84, 90]. Studies that evaluate survival benefit rather than event-free survival after disease recurrence often rely on transplant after second or later recurrence to achieve good OS [85, 95]. Patients with primary progressive disease and those resistant to salvage regimens remain a huge challenge. SDCT with radiotherapy will not afford a chance of cure, but even HDCT/ASCT is inadequate therapy for most such patients. New approaches to such patients, such as use of post-HDCT consolidation maintenance-targeted treatment, were tested in the Aethera trial with up to 16 cycles of brentuximab vedotin or post-HDCT radiotherapy which is also an option to minimize further relapse. Allogeneic SCT or immunomodulatory therapy may prove beneficial [93].

Long-term follow-up is required post-HDCT for detection of late relapse and development of second cancers, which have been reported at a rate of 5–10% at 5 years and substantially higher at 20 years or more in some series. Thirty-eight percent of deaths occurred 4–12 years after ASCT; 85% of relapses occur within 2 years of ASCT [86].

15.1.4.6 High-Dose Chemotherapy and Allogeneic Stem Cell Transplantation

The role of allogeneic transplant in relapsed HL remains unknown. The poor outcome with HDCT/ASCT in chemotherapy poor responders to salvage and those who remain FDG-PET positive after salvage has resulted in exploration of alloSCT. Allogeneic transplantation is not recommended as the initial transplant approach outside of a clinical trial setting [96] due to the high non-relapse mortality (NRM) rate, mainly caused by graft vs. host disease and infection. Reduced intensity conditioning (RIC) ameliorates the NRM while maintaining theoretical graft vs. lymphoma effect. Allogeneic-SCT may be an option for relapse post-HDCT/ASCT and for patients with refractory advanced-stage HL and chemoresistant disease at salvage.

Children and adolescents allografted for HL had an OS of 45% and PFS of 30% at 5 years [97]. All were heavily pretreated, almost half with HDCT/ASCT. Those with chemosensitive disease and good performance status achieved 3-year OS of 83% and PFS of 60%. NRM was 21 ± 4% in both the RIC and myeloablative conditioning groups. RIC was associated with a significantly higher relapse risk compared to myeloablative conditioning. Graft vs. host disease did not affect relapse rate.

Although studies based on registry data are useful, prospective trials are required to gain a better understanding of the role of allogeneic transplantation. The indications, optimal time point, conditioning regimen, and GVHD prophylaxis still need to be better defined. With the advent of newer immunotherapy agents, including checkpoint inhibitors, the role of alloSCT globally in HL is under review and the numbers of such transplants are declining globally.

15.1.4.7 Brentuximab Vedotin and Checkpoint Inhibitors

In recent years there have been two early-phase pediatric trials investigating novel agents in children. The first is the phase I/II pediatric trial (ClinicalTrials.gov number NCT01492088) investigating single-agent brentuximab vedotin in R/R HL and anaplastic large cell lymphoma [98]. The recommended phase II dose was 1.8 mg/kg as in adults and the ORR was 47% (CR rate 33%, PR rate 12%) in HL patients and toxicity was manageable. This compares with the pivotal phase II study in adults where the ORR was 75% (CR rate 34%) [99]. The second is the ongoing risk-stratified and response-adapted phase II salvage trial in first R/R HL of nivolumab plus brentuximab vedotin followed by bendamustine plus brentuximab vedotin in poor initial responders in first R/R HL in children and young adults (Checkmate 744 trial, AHOD1721; NCT02927769) [100]. The preliminary results of this study are recently presented showing 64% of patients achieved a CMR after brentuximab vedotin plus nivolumab. Of those inadequate responders that switched to second-line brentuximab vedotin plus bendamustine, all achieved a CMR after 2 cycles of this intensification.

The overall CMR rate with either first or second salvage in this trial was 86%, demonstrating that only a small number of patients cannot achieve a CMR pre-HDCT with these combinations.

Treatments that block the interaction between programmed death-1 (PD-1) and its ligands have shown high levels of activity in adults with HL. The anti-PD-1 antibody nivolumab induced objective responses in 20 of 23 adult patients (87%) with relapsed HL [101]. Another anti-PD-1 antibody, pembrolizumab, produced an objective response rate of 65% in 31 heavily pretreated adult patients with Hodgkin lymphoma who relapsed after receiving brentuximab vedotin [102]. These agents may be used as a bridge to transplant, as post-HDCT maintenance brentuximab vedotin, or as alternatives to conventional SDCT. These novel agents when used as a single agent achieve CR rates of 19–33%, but in combination achieve higher CR rates as in the Checkmate trial [100]. An interesting combination is brentuximab vedotin plus bendamustine [103] which achieves CR rates in excess of 75% which means that most patients can achieve a CR prior to HDCT making the use of alloSCT which is often used in patients that cannot achieve a CR less appealing.

15.1.5 Late Effects

Long-term adverse sequelae of greatest concern in children treated for HL (particularly with regimens including high-dose radiation) include impairment of muscle and bone development [5] and injury to the lungs [104], heart [105], thyroid gland [11, 12], and reproductive organs [106]. Cardiovascular dysfunction, pulmonary fibrosis, and secondary malignancies significantly compromise the quality and length of life in survivors [107].

15.1.5.1 Cardiac Toxicities

High-dose (>30 Gy) radiation to the mediastinum has been associated with significant long-term effects in patients with HL. Stanford investigators reported that the actuarial risk of developing cardiac disease necessitating pericardiectomy was 4% at 17 years in a series of long-term survivors of childhood HL who had received high-dose radiation [14]. Screening echocardiogram, exercise stress test, and resting and 24-h ECG identified numerous clinically significant cardiac abnormalities in HL patients who had mediastinal irradiation at a median age of 16.5 years (range, 6.4–25 years). Significant valvular defects were detected in 42%, autonomic dysfunction in 57%, persistent tachycardia in 31%, and reduced hemodynamic response to exercise in 27% of patients [108]. With the introduction of techniques that reduce the radiation dosage to the heart, rates of radiation-associated cardiac injury have declined dramatically.

Mediastinal irradiation given for HL may further predispose patients with PHL to anthracycline-related myocardiopathy [14, 109]. Cardiac dysfunction after anthracycline therapy itself is notable, with the highest risk in those receiving high cumulative doses or in young children who may be affected by an adverse effect on cardiac myocyte growth [14, 109]. Fortunately, most pHL patients are adolescents and current pHL regimens doses are significantly lower than those used in adult ABVD regimens.

15.1.5.2 Pulmonary Toxicities

Chronic pneumonitis and pulmonary fibrosis should be rare in the current era of treatment for primary HL (Fig. 15.1). Predisposing therapies include thoracic radiation and bleomycin chemotherapy [104, 105]. The bleomycin in ABVD can cause both acute pulmonary compromise and late pulmonary fibrosis and can be augmented by the fibrosis that can be associated with pulmonary radiation. Asymptomatic pulmonary dysfunction that improves over time has been observed after contemporary combined-modality treatment.

15.1.5.3 Thyroid Toxicities

Thyroid sequelae are common after RT for PHL. Hypothyroidism, hyperthyroidism, thyroid nodules, and thyroid cancer have been observed in long-term survivors [11, 12]. Of these, hypothyroidism, particularly compensated hypothyroidism, defined as thyroid-stimulating hormone (TSH) elevation in the presence of a normal thyroxine

(T4) level, is the most common thyroid abnormality. The primary risk factor for hypothyroidism is higher cumulative radiation dosage; the influence of age remains controversial [11, 12]. As many as 78% of patients treated with radiation dosages greater than 26 Gy demonstrate thyroid dysfunction, as indicated by elevated TSH levels [11].

15.1.5.4 Secondary Malignancies

The overall cumulative risk of developing a subsequent malignancy after treatment for PHL has been reported to range from 7% to 10% at 15 years from diagnosis and rises to 16–28% by 20 years (Table 15.5) [116]; these data are based on patients treated in earlier decades. The most common secondary malignancies historically included both secondary acute myeloid leukemia (MDS/secondary AML) and solid tumors. However, leukemias are now infrequent due to changes in chemotherapy. Female breast cancer is a particular concern but is likely to be less common with current radiation doses and techniques, since it is associated with RT fields that include breast tissue (especially mantle fields) and higher radiation doses (Fig. 15.1).

15.1.6 Summary/Future Directions

Tremendous strides have been made in treating children with HL, both in terms of cure and reduction of toxicity. Devising new strategies to treat children with HL is problematic because of the overall success of current treatment regimens. However, grouping patients into different risk categories, using response-based therapy and newer imaging techniques, allows investigators to construct protocols intended to diminish therapy-induced toxicity for patients with favorable prognoses. These protocols also aim to improve efficacy of treatment for patients with intermediate and unfavorable prognoses. Unfortunately, the ability to conduct clinical trials, where the difference in survival between treatment arms is likely to be small, is compromised by the large patient numbers required to detect such differences. If a reduction in treatment toxicity is the intended goal of a new regimen, then many years of follow-up are necessary to prove efficacy. For patients with refractory, or multiple relapsed disease, phase II studies investigating the use of monoclonal anti-CD30 and anti-PD-1 antibodies alone and in combination, and with other checkpoint inhibitors, in children and adolescents are ongoing internationally. The importance of investigators working together throughout the world to share data and new treatment approaches in order to cure children with HL safely is clear.

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Table 15.5 Secondary cancers after childhood HL

Reference	Cohort size	Time period studied	Number of secondary cancers	Cumulative incidence (%) (years)	Standardized incidence ratio
Stanford [110]	694	1960–1995	59	Males, 9.7% (20 years); females, 16.8% (20 years)	Males, 10.6; females, 15.4
LESG [111]	1641	1940s to 1991	62	18% (30 years)	7.7
[112]	1136	1955–1986	162	26.4% (40 years)	
Roswell [113]	182	1960–1989	28	26.7% (30 years)	9.4
LESG [114]	1380	1955–1986	135	31.2% (30 years)	17.9
US/European [115]	5925	1935–1994	195	Solid tumors: 11.7% (25 years)	7.7
University of Rochester/Johns Hopkins/University of Florida/ St. Jude/Dana-Farber [116]	930	1960–1990	102	19% (25 years)	Males, 8.41; females, 19.93

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