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Adolescent and young adult Hodgkin lymphoma: Raising the bar through collaborative science and multidisciplinary care

Justine M. Kahn¹ and Kara M. Kelly²

¹Division of Pediatric Hematology/Oncology/Stem Cell Transplantation, Columbia University, Medical Center, New York, NY, USA

²Roswell Park Comprehensive Cancer Center, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, USA

Abstract

Hodgkin lymphoma (HL) is one of the most common cancers in the adolescent and young adult (AYA) population (15 – 39 years). Despite continued improvements in HL outcomes, AYAs have not exhibited survival gains to the same extent as other age groups. At present, details about tumor biology, optimal therapeutic approaches, supportive care needs, and long-term toxicities in AYAs with HL remain understudied. Herein, we summarize the current state of the AYA population with HL, specifically focusing on how collaborations across the pediatric and medical oncology divide, coupled with multidisciplinary patient care can further optimize outcomes for this group of patients.

Keywords

Hodgkin lymphoma; AYA; clinical trials; survivorship; research

Introduction

Improving the quality of cancer care and the long-term survivorship of adolescents and young adults (AYAs) diagnosed with Hodgkin lymphoma (HL) between 15 and 39 years is a high priority area. In 2005, the National Cancer Institute partnered with the Lance Armstrong foundation to form an AYA Oncology Progress Review Group (AYAO-PRG) focused on addressing the unique care needs of the AYA cancer population.¹ This formal recognition of AYAs as a distinct group with specific care and survivorship needs marked the beginning of a new war on cancer.

Epidemiology

Hodgkin lymphoma affects approximately 4,960 men, 4,100 women, and accounts for 1,190 deaths annually in the United States (U.S.). Incidence of HL follows a bimodal age -

Corresponding Author: Kara M. Kelly, MD, Roswell Park Comprehensive Cancer Center, Elm and Carlton Streets, Buffalo, New York, 14263, P: 716-845-2333 | F: 716-845-8003 | kara.kelly@roswellpark.org.

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distribution, peaking first during young adulthood, and again after 50 years of age. The age-specific incidence of AYA HL is 3.7/100,000 in males and 3.6/100,000 in females. This is in contrast to incidence in patients <15 years (Table 1).² Peak incidence generally occurs between 18 and 34 years, but rates vary by race and ethnicity. Incidence rates in non-Hispanic white 15 – 19 year olds are between 3.4 and 3.7/100,000 vs. 1.9–2.2/100,000 in non-Hispanic black patients.³ This difference converges by 35 – 39 years.⁴ Population-based analyses suggest that place of birth is associated with HL incidence in Hispanic and Asian/Pacific Islanders from 20 – 39 years; those born in the U.S. have higher rates of HL compared with their foreign-born counterparts.⁵ The association of HL risk with familial lymphoma is suggested based on observed concordance in primary relatives of AYA patients.⁶ Crump et al. reported a 7-fold increased risk of HL in offspring with an affected parent, and an 11-fold increased risk in patients <37 years with an affected sibling.⁷ Hodgkin lymphoma is more common in patients with congenital or acquired immune-system dysfunction, including ataxia telangiectasia and acquired immune deficiency syndrome, which has recently exhibited a resurgence in the U.S. AYA population.⁸

Today, 5-year relative survival exceeds 85%–90% in most patients with HL. This success is attributed in part to: (1) research identifying clinical predictors of poor outcome, (2) expanded use of risk-adapted, multimodal therapy, and (3) well-designed therapeutic trials. While progress has been made in HL treatment over the last four decades, not all age-groups have benefitted equally (Figure 1).⁹ Survival rates, cancer-related quality-of-life, and long-term treatment-related morbidities have not improved in AYAs to the same extent as in other age groups.¹⁰ Proposed hypotheses for these gaps include: age-related differences in disease and host biology, diagnosis delays, lower rates of clinical trial enrollment, treatment at facilities without young adult experience, and higher loss-to-follow up after therapy.¹¹

Biology of Tumor and Host

Our ability to characterize the unique biologic profile of HL in AYAs is hindered by a paucity of banked biospecimens from patients in this age group. According to the Cooperative Human Tissue Network, 57% of the expected number of biologic specimens are banked for AYAs with cancer.¹² Differences HL histologic subtypes have been reported across the age spectrum.^{13,14} Approximately 45% of children <15 years have nodular sclerosing (NS) histology vs. 80% of AYAs; mixed cellularity (MC) histology is more common in younger patients vs. AYAs (~35% vs. 15%), and nodular lymphocyte predominant HL is less common in AYAs vs. older patients. Prior exposure to Epstein-Barr virus (EBV) confers an increased risk of developing HL and is associated with MC histology. In AYAs, EBV-negative, NS HL has been identified as a heritable disease associated with immune-related genotypes.¹⁵

Advances in our understanding of HL biology are developing largely through retrospective analyses;^{16–18} there have been no prospective studies validating predictive HL biomarkers. In adults, the validated clinical index for risk stratification is the International Prognostic Score, however new questions about the scope of its utility in the current era are emerging.¹⁹ Gene expression profiling identified a 23-gene signature predictive of survival in adults with advanced stage HL²⁰ however preliminary evidence suggests that this profile is not

predictive in younger patients.²¹ New insights into the role of EBV in suppressing expression of inhibitory cytokines may provide important information about its role in HL pathogenesis. This work may be particularly important in the AYA population, where EBV positivity and history of infectious mononucleosis have been linked to higher risk of HL.²² Prospective studies examining biologic and histopathologic differences between AYAs and other age groups with HL should be incorporated into future clinical trials.

Treatment

Optimal treatment for AYAs with HL remains a subject of debate. Current management of both pediatric and adult HL involves treatment with chemotherapy alone or in combination with radiotherapy (RT), followed by restaging with PET/CT²³ to assess treatment response. Determination of subsequent chemotherapy and/or RT is based on this interim response evaluation.²⁴ No prospective studies of efficacy or toxicity in AYAs treated with pediatric versus adult regimens have been reported, however some secondary analyses have been conducted (Table 2).

The National Comprehensive Cancer Network (NCCN) defines treatment options for adult patients with chemotherapy regimens including doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) 4 – 6, with or without RT, or the lesser-used Stanford V (doxorubicin, vinblastine, nitrogen mustard, etoposide, vincristine, bleomycin, and prednisone), with recommendations based on risk group (Table 3).²⁵ Although included in the NCCN guidelines, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine (escBEACOPP), is rarely used as first-line therapy in the U.S. Use of 30 Gy RT in patients with mediastinal bulk is standard in most adult HL regimens, however it is often omitted in AYAs with non-bulky disease.

A series of studies have examined outcomes of AYAs treated for HL on adult clinical trials (Table 2). In one retrospective analysis, patients 15–17 years treated for advanced HL on adult regimens had worse 5- and 20-year overall survival (OS) (81% and 68%) compared to similar aged patients receiving pediatric-style therapy.²⁶ In an analysis of AYAs from adult protocols in Germany,²⁷ 6-year progression-free survival (PFS) and OS estimates were 80% and 94% for patients 15–20 years. In patients 21–45 years, PFS and OS were 80% and 91%, respectively. On multivariable analyses, age was significantly associated with OS, and second malignancies were more common in older patients. Analysis of survival in 259 younger AYAs (16–21 years) and 890 older AYAs (22–45 years) treated from 1981–2004 on adult regimens²⁸ revealed no age-related difference in 10-year PFS (89% vs. 89%) or OS (77%, younger vs. 80%, older, $p=0.67$). In contrast, a recent analysis by Henderson et al,²⁹ reported that 17 – 21 year-olds treated on the Eastern Cooperative Oncology Group Intergroup trial E2496 had worse failure-free survival (FFS) and OS than 22 – 44 year olds on the same trial (FFS: 68% vs. 76%; OS: 89% vs. 93%; $p<0.0001$). Additionally, patients 17–21 years with stage III/IV disease on E2496 also had significantly worse 5-year FFS and OS than age and stage-matched counterparts treated on Children's Oncology Group (COG) study AHOD0031, (5-year FFS 68% vs. 81%; OS, 89% vs. 97%, $p<0.0001$). When analyses were restricted to the COG cohort only, no survival difference was observed between younger and older patients.

Pediatric therapy uses a risk-adapted, response-based approach with dose-intensive regimens such as ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide)³⁰ or OEPA/COPDac (vincristine, etoposide, prednisone, doxorubicin, cyclophosphamide, dacarbazine), with or without involved field (IFRT) or involved site (ISRT) RT for higher-risk patients (Table 3).³¹ In pediatric protocols, IFRT or ISRT are reserved for advanced stage disease and for cases with sub-optimal response to up-front chemotherapy. This response-based approach has allowed for omission of RT in a significant number of good-responders.^{31,32} Standard RT dosing in pediatric studies ranges from 15 – 25Gy.

Secondary analyses of pediatric cooperative group studies have provided some information on outcomes of AYAs treated for HL in the pediatric treatment setting. For the most part, these analyses have not demonstrated survival differences across age groups.³³ Combined data from the German Hodgkin Study Group (GHSG) HD9³⁴/HD12³⁵ and CCG 59704³⁶ trials revealed no survival difference between children and AYAs.³⁷ In high-risk patients receiving a BEACOPP-based regimen on Children's Cancer Group (CCG) 59704, event-free survival (EFS) was 93% and OS was 97%. In patients 16 – 21 years, 5-year EFS was 88–93% and OS neared 100%.³⁶ In a separate analysis from two Pediatric Oncology Group (POG) HL trials, no survival difference was observed between patients <14 years vs. 15–21 years.³²

Across pediatric and adult oncology, risk stratification, treatment paradigms, and response criteria have developed in parallel as a result of long-standing differences in clinical practice between disciplines. Thus, despite multiple secondary analyses, debates about optimal up-front chemotherapy or appropriate use of RT in AYAs with HL remain unresolved. New efforts to harmonize response criteria and risk stratification are underway, which will allow for direct comparison of outcomes across future trials.^{38,39} The recent NCI Trials Planning Consensus included a call for AYA-specific clinical trials.^{18,40} Collaborations between the COG and the North American cooperative research groups are in the early stages of developing common treatment protocols in select groups of AYAs with HL.

Adult and pediatric therapy varies for relapsed HL; limited data are available on AYA outcomes in this setting. An analysis from the Center for International Blood and Marrow Transplantation examined outcomes of AYAs after autologous hematopoietic cell transplantation (autoHCT) for HL. Five years post-autoHCT, OS was 91% (95% confidence interval [95%CI] 88%–93%), relapse rate was 8% (95%CI 6% – 10%) and non-relapse mortality was 7% (95%CI 5%–9%). Predictors of overall mortality after autoHCT included a Karnofsky score < 90, higher number of chemotherapeutics received prior to transplantation, and receipt of total body irradiation.⁴¹

Targeted therapy offers to improve outcomes while reducing long-term treatment related toxicities. Phase 2 trials of checkpoint inhibitors, specifically nivolumab⁴² and pembrolizumab⁴³ have shown outstanding efficacy in adults with relapsed/refractory HL leading to their Food and Drug Administration (FDA) approval for these indications.⁴⁴ The anti-CD30 antibody-drug conjugate brentuximab vedotin (Bv) has shown efficacy in adults in both relapsed and up-front settings.^{45,46} The combination of Bv with gemcitabine

demonstrated high complete response rates in patients up to age 30 years with relapsed/refractory HL.^{47,48}

Ongoing studies include a Phase 2 study investigating Bv in place of vincristine in the OEPA/COPDac regimen (NCT01920932) and a Phase 3 study in patients up to 21 years comparing five cycles of ABVE-PC to AVEPC with Bv for intermediate and high-risk HL (NCT02166463).

Sequential randomized clinical trials in HL have led to steady improvements in disease-related survival and continued reductions in therapy-related toxicities. Historically, AYAs enroll on clinical trials at much lower rates than children and older adults.^{49,50} Lack of clinical trial enrollment prohibits trialing novel therapies in a population that could greatly benefit from their use. Though the clinical trials culture is robust in pediatric oncology, incorporation of new agents has lagged in pediatric populations due to requirements for initial data from adult trials. New efforts to include adolescents in early phase trials by the FDA will hopefully provide younger AYAs access to investigational agents. Minimizing excess exposure to cytotoxic chemotherapy and omitting RT when possible are top priorities, as these patients are expected to survive >50 years after diagnosis. Ability to refine AYA HL therapy will come with a clearer understanding of HL biology in this age group, as well as with formal hypothesis testing through prospective clinical trials of novel agents.⁵¹

Access-to-care

Insurance

Historically, AYAs represent a population with the lowest percentage of health insurance compared to other age groups in the U.S.⁵² Public or no insurance has been associated with a higher likelihood of late stage disease at presentation⁵² and worse cancer-specific survival.^{53–55} In AYAs with HL, public or no insurance is associated with worse HL-specific survival, independent of disease stage.⁵⁶ In AYA survivors⁵⁷, health insurance rates have been observed to decrease over time after diagnosis, particularly for older AYAs and those with less education.⁵⁸ More than two thirds of uninsured AYA survivors reported having no personal provider or routine medical care.^{58,59} Considering the long-term risks associated with HL therapy, this remediable barrier to adequate follow-up care deserves attention.

Racial, ethnic and socioeconomic disparities in HL outcomes

Race, ethnicity and socioeconomic status (SES) have been shown to impact long-term outcomes in AYAs with HL. A SEER-based study of 40-year survival trends and outcomes by race and ethnicity in children and AYAs with HL found that black AYAs had worse survival than white AYAs (White: 91.1% [95%CI 89.7 – 92.3]; Black: 80.5% [95%CI: 75.5–84.6]) in the most recent evaluable time period (2007–2012).⁶⁰ Proposed reasons for disparities often relate to systems-level factors influencing access-to-care in the community oncology setting (e.g. fewer choices regarding treatment location, low clinical trial enrollment, higher loss to follow up).⁶¹ Population-based analyses have demonstrated that in AYAs with early-stage HL, residing in a low-SES neighborhood is significantly associated with worse survival.⁵⁶ This may partly relate to their receiving sub-optimal therapy. In HL,

use of combined-modality therapy has led to substantial improvements in survival over time and is commonly recommended for patients with both limited and advanced-stage disease. A study by Keegan et al found that black and Hispanic patients were more likely to receive chemotherapy alone (vs. chemotherapy + RT) than non-Hispanic white patients.⁵⁶ Not receiving RT was an independent predictor of higher mortality in AYAs.

Location of care

There is some debate about the optimal treatment setting for AYAs with HL.^{62–64} In a population-based cohort of 1,094 AYAs treated for newly-diagnosed HL at NCI-designated Comprehensive Cancer Centers (NCI-CCC)/COG centers vs. community hospitals in California, a 2.2-fold higher risk of mortality for 30–39 vs. 1–29 year olds ($p<0.001$) was observed among those treated at community hospitals.⁶⁵ Survival differences by age were not significant when comparing patients only treated at NCI-CCC/COG centers. Reasons for these findings are difficult to parse out, however some hypotheses relate to the presence of more robust supportive care (including psychosocial) teams at larger medical centers.

Survivorship and long-term treatment sequelae

Psychosocial impact of HL

The psychosocial impacts of a cancer diagnosis and treatment during young adulthood are significant and long-lasting.⁶⁶ In a survey-based assessment of AYAs with leukemia and lymphoma, more than one third of AYAs with hematologic malignancies experienced clinically meaningful anxiety, depression, or post-traumatic stress during and after completion of therapy.⁶⁷ Young adult HL survivors reported issues with physical functioning and vitality, as well as with finances.^{68,69} A report from the Childhood Cancer Survivor Study (CCSS) identified that depressive symptomatology was significantly associated with exposure to intensive chemotherapy in HL survivors.⁷⁰ Validated tools to address the psychosocial distress of AYAs during and after cancer therapy are lacking. A recent meta-analysis of psychological interventions found that available interventions for children and adults with cancer were inadequate to address the psychosocial needs of AYAs.⁷¹

Second cancers related to radiation therapy

Patients treated for HL are at risk for subsequent malignant neoplasms (SMNs) primarily related to RT, including breast, thyroid, and oropharyngeal cancers.^{72,73} In a large cohort of patients from the CCSS, the 30-year cumulative incidence of second cancers was 9.3%, with HL patients accounting for 33% of the SMNs.⁷⁴ The risk of subsequent breast cancer after thoracic RT is over 24-fold the expected incidence in healthy controls. Among childhood cancer survivors, approximately 30% of patients receiving 10 Gy chest RT develop breast cancer by 50 years.⁷⁵ In a genome wide association study to identify loci of genetic susceptibility to breast cancer development after RT, the interaction of certain germline variants with ionizing radiation conferred a higher risk of RT-associated breast cancer in some patients.⁷⁶ In another study using GWAS, a genetic locus at 6q21 was associated with higher risk for RT-associated SMNs in patients treated as adolescents.⁷⁷ This susceptibility locus was not associated with SMNs in patients treated as adults.

Cardiac sequelae

A significant burden of morbidity and late mortality after HL therapy is related to cardiac toxicity from anthracyclines and thoracic RT.^{78,79} The relative risk of coronary artery disease, congestive heart failure, valve dysfunction, pericardial disease, and sudden cardiac death is significantly increased in survivors of HL who receive RT compared to the general population. Risk factors for RT-induced cardiotoxicity include total dose >30–35 Gy, larger field, presence of tumor near the heart, younger age at treatment, and anthracycline exposure.⁸⁰ Cardiovascular complications account for approximately 25% of mortality in patients treated for HL, with myocardial infarction being the most common cardiac event. The estimated incidence of RT-induced cardiac disease 10-years post-therapy is between 10 and 30%. Up to 88% of HL-survivors harbor asymptomatic cardiac abnormalities by 10 years. Radiation doses correlate with cardiovascular disease in HL patients 25 years after therapy. In one study, 20 – 25 Gy was associated with 5–6% cumulative incidence, while 36 Gy was associated with 21% cumulative incidence of cardiovascular disease. By age 50 years, the cumulative incidence of HL survivors experiencing at least one grade 3–5 toxicity was 45.5% vs. 15.7% in controls.^{81,82} Recent efforts to reduce RT doses and narrow radiation fields are at the forefront of research. For AYAs who receive RT, studies suggest that long-term follow up with echocardiogram is paramount to early detection and prevention of potential cardiac events later on.

Fertility

Fertility preservation and reproductive health are significant concerns for AYAs with HL.⁸³ The effect of cancer therapy on reproductive function depends on patient age at treatment, the extent of exposure to gonadotoxic chemotherapy or direct radiation, as well as on individual patient characteristics.⁸³ Female survivors of HL are at risk for both acute ovarian failure (AOF) and early menopause (premature ovarian failure [POF]). Among 3,390 childhood cancer survivors, 215 women (6.3%) <40 years developed AOF; increased risk was associated with HL and older age at diagnosis.⁸⁴ On multivariable analyses, exposure to procarbazine at any age, and to cyclophosphamide between 13–20 years were independent risk factors for AOF. In a separate cohort study of cancer survivors, the cumulative incidence of POF was significantly higher in survivors vs. sibling controls (8% vs. 0.8%; risk ratio: 13.21; $p<0.05$). Increasing doses of alkylating agents and diagnosis of HL were associated with higher risk.⁸⁵ In one study of women <40 years with HL, 51.4% had continuous amenorrhea after 3.2 years after eight cycles of dose-escalated BEACOPP, but not after standard BEACOPP.⁸⁶ On multivariable analyses, amenorrhea was significantly associated with advanced stage, age >30 years during therapy, and with not taking oral contraceptives during treatment. In contrast to the risks associated with escalated BEACOPP, the risk of POF with the ABVD regimen is reportedly less than 10%.⁸⁷ No prospective studies have examined fertility risk in AYAs with HL, however, an active COG ancillary study (NCT01793233) is prospectively assessing ovarian reserve in AYAs up to 29 years with newly diagnosed lymphoma.

Other more common late effects of HL therapy include pulmonary toxicity associated with bleomycin, and thyroid dysfunction. Risk factors for lung toxicity include older age, cumulative bleomycin dose, concomitant lung RT, and prior lung disease. Use of growth

factors may increase the incidence of pulmonary toxicity in adults;⁸⁸ data in AYAs is not available. Hypothyroidism after cervical RT is also frequently observed. In a cohort of over 10,000 children and adolescents in the British Childhood Cancer Survivor Study, 19.9% of HL survivors developed hypothyroidism, especially if RT was administered. Increasing dose of RT, older age at diagnosis and female sex were independently associated with higher risk for hypothyroidism.⁸⁹

Just as standard treatment guidelines for AYA HL have not been established, long-term follow up guidelines for this age group vary widely between COG and the National Comprehensive Cancer Network (NCCN). In a study comparing post-therapy screening recommendations for AYAs with HL, Barthel et al noted significant variation between COG Long-Term Follow-Up Guidelines, NCCN Guidelines for Age-Related Recommendations: AYA Oncology, and NCCN Guidelines for Treatment of Cancer by Site.⁹⁰ Efforts to develop age-specific follow-up guidelines and survivorship programs for AYAs with HL should be considered a high-priority. Given excellent outcomes with both pediatric and adult-type regimens, questions about optimal therapy for AYAs should consider the late-effects of proposed treatments when planning.

Moving the field forward for AYAs with HL

The AYA cancer population has been systematically under-studied, both in clinical trials and in the community oncology setting. The paucity of standardized treatment and follow-up guidelines has resulted in wide variation in care for AYAs with HL. This is particularly the case in the community, where an estimated 70% – 80% of AYAs receive HL therapy. Unanswered questions about healthcare access and delivery, as well as about long-term survival in AYAs with HL have provided us with priority areas to improve cancer care and optimize outcomes in this population. These include: (1) Development of AYA-specific biobanks to examine age-related differences in the biology of disease control, host immune response and susceptibility to late toxicities, (2) development of quality assessment measures with targeted interventions to provide evidence-based psychosocial support and treatment, (3) establishment of dedicated social work and supportive care teams to guide financial planning, health insurance coverage, and access to multidisciplinary provider networks, and (4) collaboration between pediatric and adult cooperative groups – with expanded trials access for AYAs, particularly those treated in the community oncology setting.

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Abbreviations

HL	Hodgkin lymphoma
AYA	Adolescent and young adult

EFS	Event-free survival
OS	Overall survival
FFS	Failure-free survival
FFTF	Freedom from treatment failure
PFS	Progression-free survival
ABVE-PC	Doxorubicin, bleomycin, vinblastine, etoposide, prednisone, and cyclophosphamide
DECA	Dexamethasone, etoposide, cisplatin, and cytarabine
Stanford V	Doxorubicin, vinblastine, nitrogen mustard, etoposide, vincristine, bleomycin, and prednisone.
OEPA/OPPA	Vincristine, etoposide, prednisone, doxorubicin/vincristine, prednisone, procarbazine, doxorubicin
COPDac	Cyclophosphamide, vincristine, prednisone, dacarbazine
COPP	Cyclophosphamide, vincristine, procarbazine, and prednisone
ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine
MOPP	Mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, dacarbazine
IMEP	Ifosfamide, methotrexate, etoposide
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine
SEER	Surveillance Epidemiology and End Results program

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Figure 1.
Relative survival by time and age in patients with Hodgkin lymphoma, 1988-2013, *SEER Database*.
Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov)
SEER*Stat Database: Mortality - All COD, Aggregated With State, Total U.S. (1969-2014)
<Katrina/Rita Population Adjustment>, National Cancer Institute, DCCPS, Surveillance
Research Program, released December 2016. Underlying mortality data provided by NCHS
(www.cdc.gov/nchs). Accessed December 15, 2017.

TABLE 1

Age-specific SEER incidence of Hodgkin lymphoma per 100,000 *, 2007–2011^{91–93}

AYA Age Group (Years)	Incidence	
	Male	Female
0 – 14	0.7	0.5
15 – 19	3.0	3.3
20 – 24	4.3	4.6
25 – 29	4.1	4.1
30 – 34	3.9	3.5
35 – 39	3.3	2.6
40+	3.8	2.5

* Rates are per 100,000 and are age-adjusted to the 2000 United States Std Population (19 age groups); Census P25-1130

SEER: Surveillance Epidemiology and End Results

TABLE 2

Clinical trials data suggest that differences in early outcome relate to treatment, rather than to age

Location	Regimen	Children	AYA	Adult
North America	ABVE, ABVE-PC ^{30,32}	5y – EFS: 87%	5y – EFS: 86%	
	Stanford V or ABVD ²⁹		5y – FFS (17–21y): 68%	5y – FFS (22–44y): 76%
Hungary ⁹⁴	OEPA/OPPA ± COPP		5y-EFS: 83%	
	ABVD		5y-EFS: 78%	
Canada ⁹⁵	ABVD			
	MOPP/ABVD ⁹⁶		5y-PFS: 77%	5y-PFS: 80%
	ABVD		6y-FFTF: 80%	6y-FFTF: 80%
Germany ^{97,98}	COPP/ABVD		10-FFTF: 79%	10y-FFTF: 76%
	COPP/ABVD ± IMEP			
	BEACOPP standard or escBEACOPP ³⁴			

EFS: Event-free survival; *FFS* or *FFTF*: failure-free survival or freedom from treatment failure; *ABVE-PC*: doxorubicin, bleomycin, vinblastine, etoposide, prednisone, and cyclophosphamide; *DECA*: dexamethasone, etoposide, cisplatin, and cytarabine; *Stanford V*: doxorubicin, vinblastine, nitrogen mustard, etoposide, vincristine, bleomycin, and prednisone. *OEPA/OPPA*: vincristine, etoposide, prednisone, doxorubicin/vincristine, prednisone, procarbazine, doxorubicin; *COPP*: Cyclophosphamide, vincristine, procarbazine, and prednisone; *ABVD*: Doxorubicin, bleomycin, vinblastine, dacarbazine; *MOPP*: Mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, dacarbazine; *IMEP*: Ifosfamide, methotrexate, etoposide; *BEACOPP*: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine

TABLE 3

Comparison of adults and pediatric standard treatment approaches for Hodgkin lymphoma

	Adult	Pediatric
Stage I – IIA favorable	ABVD x 2 cycles + 20Gy IFRT ABVD x 3 – 6 cycles	OEPA x 2 cycles ± response-based ISRT
Stage I – II unfavorable	ABVD x 4 – 6 cycles ± 30Gy IFRT ABVD x 4 – 6 cycles +30Gy IFRT (for bulky disease) escBEACOPP x 2 cycles + ABVD x 2 cycles + ISRT ^a	ABVE-PC x 4 cycles ± response-based ISRT OEPA x 2 cycles + COPDac x 2 cycles + response-based ISRT
Advanced stage	ABVD x 6 cycles ABVD x 6 cycles + 30 Gy IFRT (for bulky disease) escBEACOPP x 6 cycles + ISRT (in residual PET+)	ABVE-PC x 5 cycles + RT to bulky, slow-responding sites OEPA x 2 cycles + COPDac x 2 cycles + response-based ISRT

^aEscalated BEACOPP is rarely used in the up-front setting in the United States, however it is often used as front-line therapy in European protocols.

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; *Gy*: Gray; *IFRT*: involved field radiation therapy; *OEPA*: vincristine, etoposide, prednisone, doxorubicin; *BEACOPP*: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine; cyclophosphamide, vincristine, prednisone, procarbazine; *Stanford V*: doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone; *ISRT*: involved site radiation therapy; *ABVE-PC*: doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; *COPDac*: cyclophosphamide, vincristine, prednisone, dacarbazine

PET: positron emission topography