bjh review

Closing the survivorship gap in children and adolescents with Hodgkin lymphoma

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Summary

The treatment of Hodgkin lymphoma (HL) is one of early success. However, disease-free survival (DFS) does not reflect latent organ injury and its impact on health status and well-being beyond 5 years. In fact, we are at a crossroads, in terms of needing individualized approaches to maintain DFS, while minimizing late effects and preserving health-related quality of life (HRQoL). Premature morbidity and mortality translate to a high societal cost associated with the potential number of productive life years ahead in this population who are young at diagnosis. The discordance between short-term lymphoma-free survival and long-term health and HRQoL creates a "survivorship gap" which can be characterized for individuals and for subgroups of patients. The current review delineates contributors to compromised outcomes and health status in child and adolescent (paediatric) HL and frames the survivorship gap in terms of primary and secondary prevention. Primary prevention aims to titrate therapy. Secondary prevention entails strategies to intervene against late effects. Bridging the survivorship gap will be attained with enhanced knowledge of and attention to biology of the tumour and microenvironment, host genetic factors, HRQoL and sub-populations with disparate outcomes.

Keywords: pediatric Hodgkin lymphoma, survivorship gap.

Epidemiology of HL in children and AYA

Hodgkin Lymphoma (HL) is a disease with the first modal peak at 20–34 years of age. In the United States (US) 1100 children and adolescents <20 years of age are diagnosed with HL each year. The overall efficacy of conventional therapy is such that, in 2016, there were an estimated 210 974 individuals living with HL in the US (Surveillance, Epidemiology, and End Results (SEER) Program, 2019), many of whom were initially treated in their childhood. While primary therapy results in a 5-year disease-free survival (DFS) of 80–85% across all patients, children have significantly better HL-specific survival than adolescent and young adults (AYA), and older adults (Kahn & Kelly, 2018). In addition, there appear to be demographic populations who have not benefited from the overall gains with conventional therapy. Population and single-centre studies in the US suggest that children and adolescents of black race, Hispanic ethnicity and lower socio-economic status (SES) are more likely than white children to be uninsured or have public insurance, more likely to present with advanced stage disease and less likely to receive radiation therapy (RT). Importantly, in population studies non-white race is associated with higher relapse rates and worse overall survival (OS) (Metzger *et al*, 2008; Grubb *et al*, 2016; Keegan *et al*, 2016). Of note, while lymphoma-free survival is more equitable among children enrolled on therapeutic clinical trials, disparities in OS persist (Kahn *et al*, 2017). While nodular sclerosing (NS) histology is the prevalent form of HL in children and adolescents, mixed cellularity (MC) disease is more common in younger children (Bazzeh *et al*, 2010).

The population gaps in OS need to be addressed by adequate representation of minorities in clinical trials in order to enable an understanding of whether the disparities stem from differences in biology of the disease, differences in toxicity or from disparate access to salvage therapies, including haematopoietic stem cell transplantation (HSCT).

Premature morbidity and mortality in HL

Long-term HL survivors commonly experience treatment-related morbidity affecting thyroid, pulmonary, gonadal, cerebrovascular and cardiovascular (CV) function (van Leeuwen

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et al, 2000; Oeffinger *et al*, 2006; Geenen *et al*, 2007; Swerdlow *et al*, 2007) (Fig 1). In addition, curative therapy has been associated with an excess risk of developing second malignant neoplasms (SMN) (Aleman *et al*, 2003; Bhatia *et al*, 2003; Castellino *et al*, 2011). These late treatment sequelae negatively impact survivors' health status (Hudson *et al*, 2003) and predispose them to premature death. Contributors to the life-long burden of morbidity in young HL patients include: acute toxicity and impaired health-related quality of life (HRQoL) during and following treatment; latent effects of initial or relapse therapies; and financial hardship during therapy, which follows into the survivorship period for decades (Linendoll *et al*, 2016; Parsons & Kumar, 2019).

Despite 5-year DFS rates approaching 95%, the risk of all-cause mortality with historic therapy remains higher than the age-matched population. The Childhood Cancer Survivor study (CCSS) reported OS of 74·1% [95% confidence interval (CI) 71·8–76.6] at 30 years for paediatric HL survivors treated between 1970 and 1986 and surviving at least 5 years (Castellino *et al*, 2011). The majority of this cohort was treated with extended field RT, with some receiving combination chemotherapy and staging splenectomy. The standard mortality ratio differed by sex, and was 6·3 (95% CI: 5·6–7·1) for males and 12·0 (95% CI: 10·4–13·8) for females. The excess adverse risk (EAR) for overall death was estimated at 95·5 per 10 000 person-years (95% CI: 86·1–105·5). The EAR per 10 000 person-years for the leading causes of death was 38·3 for HL, 23·9 for SMN, and 13·1 for CV disease (Castellino *et al*, 2011). With changes in radiation doses and in field size, the 15-year cumulative incidence of at least one grade 3–5 condition was significantly lower for survivors diagnosed in 1990–1999 (the expansion cohort of CCSS) compared with those diagnosed with HL in 1970–1979 (17·7% vs. 26·4%; $P < 0·0001$) (Gibson *et al*, 2018). Thus, it appears that reductions in therapy have already translated into reduced all-cause and cause-specific mortality attributed to SMN and CV disease (Armstrong *et al*, 2016).

The German HL Late Effects Research Project captured detailed outcomes in 2548 survivors of childhood HL

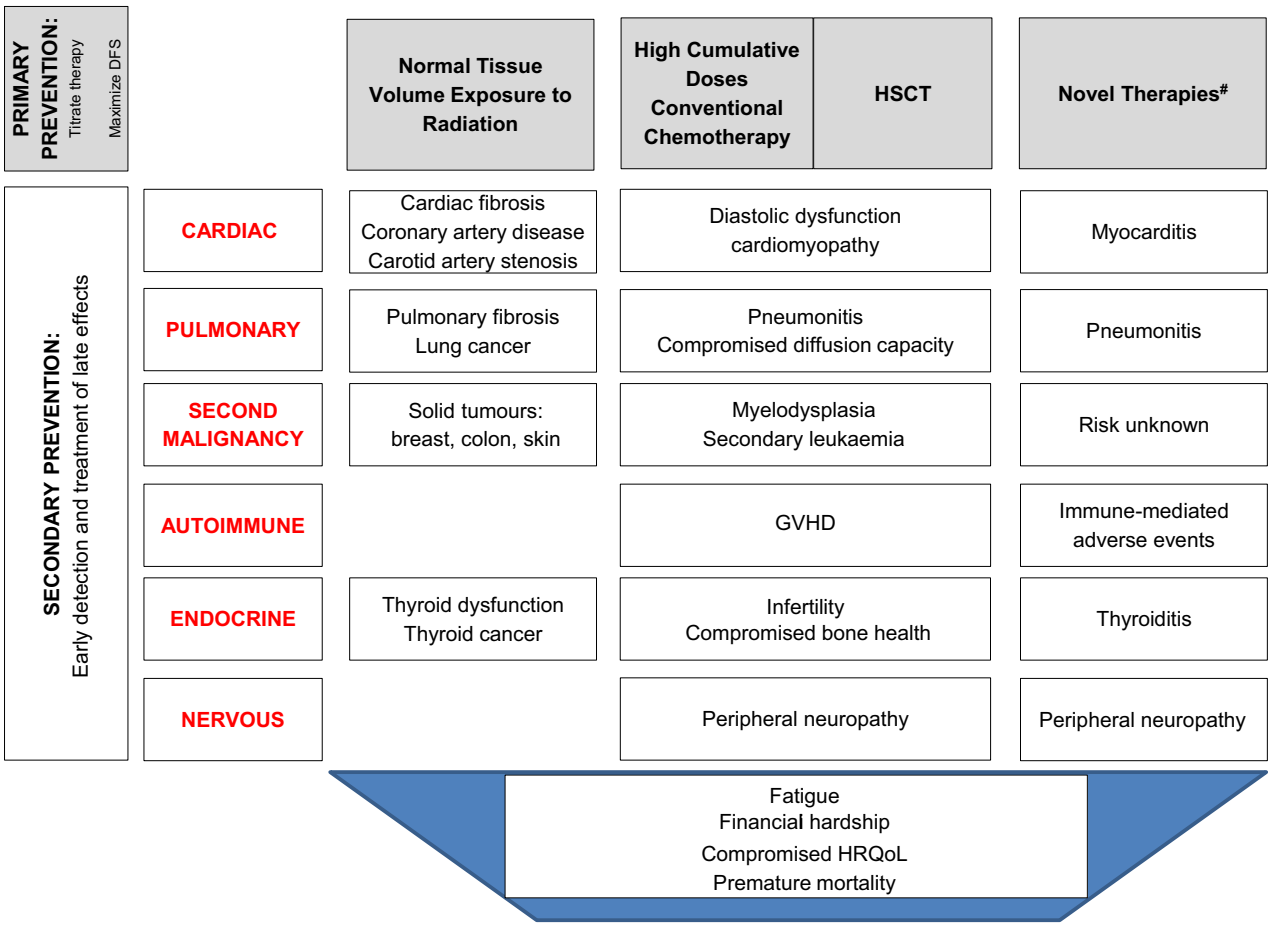

Fig 1. Modifiable off target effects amenable to primary or secondary prevention in survivors of paediatric Hodgkin lymphoma. #Novel therapies: Brentuxzimab vedotin, Checkpoint inhibitors, CD30 Chimeric Antigen Receptor T cells. DFS, disease-free survival; GVHD, graft-versus-host disease; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation.

between 1970 and 2002. While many of the overall late effects mirror those self-reported by CCSS participants, this study was able to validate cardiac outcomes (Schellong *et al*, 2010) and characterize sequential improvements in the risk of male fertility with decreased utilization of procarbazine. In the St. Jude Life Cohort, where participants underwent a detailed standardized CV assessment, the cumulative incidence of HL survivors experiencing at least one grade 3–5 CV condition was 45·5% at 50 years, compared with 15·7% in community controls (Bhakta *et al*, 2016). Myocardial infarction and structural heart defects were prevalent contributors to the excess burden in survivors and were associated with high cardiac radiation dose (≥35 Gy), reflecting the treatment era of extended field approaches. Survivors of childhood HL, particularly those with neurological, cardiac and pulmonary chronic conditions, are at risk for impaired fitness and diminished HRQoL (Wogksch *et al*, 2019). Long term survivorship studies to date have been unable to sort out the added burden of salvage therapy, specifically autologous HSCT, underlying late effects and premature mortality.

Data from historic cohorts inform us that high cumulative doses of chemotherapy and extended field RT were the drivers of compromised long-term survivorship (Fig 1, Table I). Since the late 1990s, efforts have focused on finding the efficacy-toxicity balance toward narrowing the survivorship gap. While epidemiological data from long-term survivors of HL has characterized the range and dose associations of conventional chemotherapy and RT to latent organ toxicity, the changes in therapy since 1997 and the promise of replacement of conventional therapy with novel agents remains to be realised because follow-up is short. Recognition of the cost of cure has informed primary and secondary approaches to improve the long-term trajectory of health in children and adolescents with HL. Internationally, the goals for paediatric HL trials have been to improve or maintain excellent disease control while reducing treatment burden.

Primary prevention to close the survivorship gap

Refining frontline conventional therapy

Reduction of the burden of treatment in HL survivors begins with continued refinement in primary therapy approaches. Therapy for children with lymphocyte-predominant histology HL has diverged from therapy for NS and MC disease, with the recognition that this is a biologically different disease (Appel *et al*, 2016; Marks *et al*, 2018). A comprehensive review in 2015 summarized contemporary paediatric treatment approaches for *de novo* HL (Kelly, 2015). Five-year DFS in paediatric HL ranged from 79·8% to 97% for low risk HL (Landman-Parker *et al*, 2000; Mauz-Korholz *et al*, 2010; Metzger *et al*, 2012; Tebbi *et al*, 2012; Wolden *et al*, 2012; Keller *et al*, 2018) to 77 to 90 % for high risk disease (Schwartz *et al*, 2009; Mauz-Korholz *et al*, 2010; Kelly *et al*, 2011; Wolden *et al*, 2012; Friedman *et al*, 2014; Kelly *et al*, 2019) in completed trials. With the goal of lowering cumulative doses of anthracyclines to a doxorubicin equivalent dose of ≤250 mg/m^2 and alkylating agents to <7 g/m^2 (cyclophosphamide equivalent dose) (Green *et al*, 2010), contemporary paediatric chemotherapy regimens have diverged from the conventional adult approaches of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) and BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, prednisone, procarbazine) by using combination chemotherapy with non-cross-resistant agents [adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide (ABVE-PC) or vincristine, etoposide, prednisone, adriamycin/cyclophosphamide vincristine, prednisone, dacarbazine (OEPA/COPDac)] (Mauz-Korholz *et al*, 2010; Friedman *et al*, 2014). The delivery of dose dense therapy in Children's Oncology Group (COG) regimens is facilitated by supportive care including granulocyte colony-stimulating factor (GCSF) and accepted myelosuppression in paediatric settings. These studies demonstrate anti-lymphoma efficacy with lower cumulative doses of alkylating agents and anthracyclines (Table II) than are customary with adult treatment regimens (Kelly, 2015). Furthermore, risk-based response adapted approaches, facilitated by interim imaging in recent paediatric trials have decreased RT delivery (Friedman *et al*, 2014; Keller *et al*, 2018; Kelly *et al*, 2019).

Although the risk for some late toxicities varies by gender, with male patients being at higher risk for infertility associated with alkylator-based therapy and female patients at greater risk for the development of breast cancer within the RT field (Armstrong *et al*, 2007; Castellino *et al*, 2011), few paediatric trials have investigated regimens that tailored treatment by gender (Kelly *et al*, 2011). With the procarbazine-free regimen OEPA/COPDac, boys had comparable DFS to girls who received the standard OPPA-COPP regimen in the GPOH-HD-2002 trial (Korholz *et al*, 2004; Mauz-Korholz *et al*, 2010). Substitution of RT with alkylator therapy in girls with high risk HL was associated with comparable outcomes as boys in the COG trial C59704 (Kelly *et al*, 2011).

The continued dependence on consolidative involved-field RT toward maintaining 5-year DFS in paediatric HL has been critiqued. In the pre-positron emission tomography (PET) era trials in adult HL (Johnson *et al*, 2010; Borchmann *et al*, 2011; Gordon *et al*, 2013) found a significant benefit to the use of RT as part of initial therapy. More recently, the GITIL/FIL HD 0607 trial found no significant benefit to RT among patients with nodal masses ≥5 cm who had a negative PET scan after two and four cycles of ABVD (Casasnovas *et al*, 2019), and adult HL protocols incorporating escalated dose BEACOPP have reported 5-year progression-free survival (PFS) rates >85% with limited or no routine use of RT (Borchmann *et al*, 2018). These findings suggest that PET-computed tomography (CT) may be utilized to tailor or avoid RT for the majority of HL patients

Table I. Primary and secondary prevention strategies to close survivorship gaps in paediatric Hodgkin lymphoma.

Cause of survivorship gap	Primary prevention	Secondary prevention
Normal tissue volume exposure to RT -Thyroid dysfunction -Cardio-toxicity -Pulmonary Toxicity -SMN	**Tailor application of RT** -Utilize decision models toward shared decisions on use of RT for de novo disease based on tumour (stage, bulk) and patient factors -Imaging and biological biomarkers to determine overall and disease site-specific benefit for RT **Modify RT dose and fields** -INRT -New techniques (Breath hold, IMRT) -Proton therapy	**Guideline based†** Screening for early detection of SMN in RT field: -Breast – self-examination; mammogram; breast MRI -Colon - colonoscopy; stool guaiac -Lung – spiral CT -Skin – physical examination -Thyroid – examination; ultrasound Screening for cardio-pulmonary health: -Echocardiogram; EKG -Lipid and metabolic screening -Carotid artery exam vs. ultrasound -Coronary artery score Screening endocrine health: -TSH; Free thyroxine
High cumulative doses Alkylating agent chemotherapy Anthracycline chemotherapy **HSCT** -Cardio-toxicity -Pulmonary Toxicity -SMN -Infertility	**Personalized initial therapy** -Minimize cumulative doses based on: harmonized risk criteria; clinical predictors; host pharmacogenomics -Inclusion of, or substitution with novel agents: integral biomarkers; response adaptation -Expansion of trials of novel agents to younger adolescents **Tailor salvage regimens, use of HSCT in relapse** -Use of maintenance novel agents after HSCT **Fertility preservation** -Preservation: Sperm; testicular tissue; oocyte -GnRH analogue therapy **Supportive care** -GCSF to support delivery of dose-dense therapy -Cardio-protection (dexrazoxane) -Anticipate and manage immune-mediated adverse events	**Guideline based†** Screening for early detection of SMN: -MDS; secondary leukaemia - FBC Screening for cardio-pulmonary health: -Echocardiogram; EKG -Lipid and metabolic screening -PFT Screening endocrine health: -Sex hormones; ovarian reserve **Pharmacological management of CV risk** **Reproductive assistance** **Survivorship care/health maintenance** -Patient education -Survivorship care plans -Electronic personal health records; transition care -Diet -Exercise -Smoking avoidance/cessation -HPV vaccination
Novel therapies*	**Biologically-based selection of patients** **Inclusion of adolescent patients in clinical trials** -A priori subgroup analyses of toxicity in the younger cohort **PROs** -Early detection/management of symptom, to maximize dose delivery	**Long term follow-up** -Neuropathy -Immune function -Immune mediated-adverse events

Table I. (*Continued*)

Cause of survivorship gap	Primary prevention	Secondary prevention
Diminished HRQoL	**Systematic evaluation/PROs**	**Evaluate financial hardship**
		Enhance work/minimize productivity loss
-Fatigue	-Fatigue	
-Financial hardship	-HRQoL	-Patients
-Productivity loss	-Neuropathy	-Caregivers
	Shared decision making: patient and provider	
Population disparities	**Reduce population disparities**	**Utilize EHR and administrative data**
-Minority populations -AYA	-Facilitate equal access to clinical trials for de novo and relapsed disease -Enhance care compliance	-Identify populations at increased risk for late effects

AYA, adolescents and young adults; CT, computed tomography; CV, cardiovascular; EHR, electronic health record; EKG, electrocardiogram; FBC, full blood count; HPV, human papilloma virus; HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; IMRT, intensity-modulated radiation therapy; INRT, involved node therapy; MDS, myelodysplastic syndrome; MRI, magnetic resonance imaging; PFT, pulmonary function test; PROs, patient-reported outcomes; RT, radiation therapy; SMN, second malignant neoplasm; TSH, thyroid stimulating hormone.

*Novel Therapies include: Brentuximab vedotin; Checkpoint inhibitors; CD30 Chimeric Antigen Receptor T cells.

†Screening guidelines are not meant to be all inclusive; guideline recommendations vary for an individual based on therapy exposure, cumulative dose and individual patient risk factors or co-morbidities; survivorshipguidelines.org (Landier *et al*, 2004).

who achieve a rapid metabolic response, when chemotherapy is sufficiently intensive.

In fact, recent paediatric trials indicate the feasibility of response-adapted omission of radiation. Pending the proof of safety and efficacy of novel agents in paediatric HL, contemporary RT continues to have a curative role in settings of bulk disease or chemo-resistance, thereby sparing subsequent need and risk of salvage HSCT in chemo-insensitive patients. Importantly, serial decreases in RT field extent (from extended field to involved field, to involved site or involved node) and lower prescribed doses (<30 Gy) have reduced normal tissue volume exposure from the historical approaches associated with SMN and CV risk. In a retrospective comparison of radiation plans from HL survivors, lower breast, heart, lung and thyroid doses were observed for patients on COG trials between 2002–2012 compared with CCSS participants treated between 1970–1986 (Zhou *et al*, 2016). The possibility of further reducing normal tissue exposure with PET-based response adaptation in combination with conformal fields, deep inspiration breath hold and proton therapy is being evaluated in paediatric trials (NCT02166463; NCT03907488; NCT02684708)(Hoppe *et al*, 2017).

Harmonization of risk and response across trials

In order to continue tailoring primary therapy there are several priorities. Frontline trials need to harmonize risk classification and response criteria, so that trial data are more easily comparable across groups. Toward this end, the Staging Evaluation and Response Criteria Harmonization (SEARCH) initiative was created in 2011. This international collaboration among members of COG, European Network for Paediatric HL (EuroNet-PHL), St. Jude-Stanford-Dana-Farber consortium and Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA) is working toward standardized staging and response criteria for paediatric trials and reporting of outcomes (Flerlage *et al*, 2017).

While adult HL trials have used the international prognostic score (IPS) (Hasenclever & Diehl, 1998), there have been no clinical risk predictors beyond Ann Arbor staging and the presence of bulk at presentation in *de novo* paediatric HL. The Childhood Hodgkin International Prognostic Score (CHIPS) was based on the experience in the COG AHOD0031 trial of patients with intermediate-risk HL (Schwartz *et al*, 2017). The score range is 0–4, with one point assigned for each of the following presenting features: Stage 4 disease, large mediastinal mass, albumin (<35 g/l) and fever. The CHIPS was highly predictive of EFS, identifying a subset of patients with a 4-year EFS of <80% and identifying higher risk patients who were not identified by early PET or CT response. CHIPS is being validated in an ongoing COG trial (NCTN 02166463). Its components will be further evaluated alongside the adult IPS composite score in the intergroup Phase III trial among those ≥12 years of age with advanced stage HL (NCT03907488).

Need for integral biomarkers in children and adolescents

Tumour markers to identify refractory patients as early as possible will facilitate optimization of the choice of treatment agents and intensity. Tumour biopsy samples have been used to characterize the microenvironment. The promising 23-gene expression profile of the tumour microenvironment in

adult HL with advanced stage disease (Scott *et al*, 2013) has not yet been validated in younger patients (Mottok *et al*, 2015). Flow-sorting tissue for Hodgkin Reed-Sternberg (HRS) and intratumour T cells and optimizing low input exome sequencing has provided preliminary information on genomic alterations in HL, including paediatric cases (Reichel *et al*, 2015). HRS cells evade antitumour immunity by multiple means, including gains of 9p24.1 and perturbed antigen presentation (Ansell *et al*, 2015). A higher degree of 9p24.1 molecular alteration and a higher degree of PD-L1 (also termed CD274) expression by immunohistochemistry was associated with improved response and superior DFS (Roemer *et al*, 2018). Given that major histocompatibility complex class II expression on the HRS cell was also predictive, it remains to be seen if these factors will hold true in disease response to checkpoint inhibitors and other modulators of the tumour microenvironment in younger children.

Peripheral blood biomarkers include several malignant cell, tumour microenvironment, and immune response-related markers, such as neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, serum thymus and activation regulated chemokine (TARC), galectin 1, micro-RNAs, serum CD163 and serum CD30 (Aoki & Steidl, 2018). Decreases in TARC correlated with tumour reduction following brentuximab vedotin (Bv) and gemcitabine in adolescent patients with relapsed/refractory HL (Cole *et al*, 2018). However, TARC has yet to be validated as an independent risk predictor in de novo paediatric HL. Circulating tumour DNA (ctDNA) reflects DNA fragments released from apoptotic and necrotic cancer cells and can be measured in peripheral blood by next-generation sequencing (Spina *et al*, 2018). Epstein–Barr virus (EBV) DNA in cell-free blood has been shown to be a marker of inadequate tumour response in EBV-associated paediatric HL (Welch *et al*, 2017). In the future, a more complete understanding of the molecular and immune pathogenesis of paediatric HL will guide the development of new and better treatments.

Novel agents in de novo paediatric HL

The potential to incorporate tumour biology to guide novel therapies in paediatric and adolescent HL came with the advent of the anti-CD30 antibody drug conjugate, Bv, and with checkpoint (programmed death pathway) inhibitors.

ECHELON-1, a randomized Phase III trial of Bv (Adcetris) plus AVD (Bv-AVD) compared to non-PET-adapted ABVD in patients aged ≥18 years with previously untreated advanced stage HL, noted a 2-year modified PFS (mPFS) of 82·1% in the Bv-AVD group vs. 77·2% in the ABVD group ($P = 0{\cdot}04$) (Connors *et al*, 2018). The efficacy was attained with the elimination of bleomycin therapy, and with recognition of the role of GCSF to support patients through myelosuppression.

The overall response rate in early phase trials of Bv as a single agent in paediatric HL was 47% (95% CI 21–73), notably lower than the response in adult early phase trials (Locatelli *et al*, 2018). All patients had a treatment-emergent adverse event and 44% had at least one ≥grade 3 adverse event; 33% patients had transient, peripheral neuropathy. This paediatric experience with Bv contrasts with the phase II trial of Bv in combination with gemcitabine, where 67% (95% CI 51–80) of 42 evaluable patients had a complete response within the first four cycles of treatment (Cole *et al*, 2018). Four (31%) of 13 patients with a partial response or stable disease had all target lesions with Deauville scores of 3 or less after Cycle 4. These experiences raise caution with regard to the direct application of agent efficacy from adult to paediatric trials, and comparison with newly-defined response endpoints, such as mPFS.

Early phase trial efficacy with Bv set the stage for bringing anti-CD30 targeted therapy into *de novo* paediatric HL. The COG randomized clinical trial (NCTN 02166463) compares Bv with the AVEPC (adriamycin, vincristine, etoposide, prednisone, cyclophosphamide) backbone to conventional ABVEPC (adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide). The experimental arm evaluates Bv in a dose dense regimen with cumulative anthracycline dose limited to 250 mg/m^2 and no bleomycin. Response-adapted involved site radiation (ISRT) (Zhou *et al*, 2016), based on interim PET-CT, is the goal of further reducing normal tissue volume exposure. The St. Jude-Stanford-Dana-Farber consortium Phase 2 trial of Bv, etoposide, prednisone, doxorubicin/cyclophosphamide, Bv, prednisone and dacarbazine (AEPA/CAPDac) in high-risk patients similarly built on the EuroNet-PHL OEPA/COPDac backbone, substituting Bv (Adcetris) for vincristine (NCT01920932), and will extend this experience to patients with high risk disease in NCT03755804. An industry-sponsored trial (NCT02979522) of Bv-AVD in advanced stage *de novo* paediatric HL is ongoing. All these trials will provide insight into the short- and long-term toxicity and pharmacokinetics (Flerlage *et al*, 2016) of Bv in paediatrics and the ability to further tailor RT.

The incorporation of PD-1 (also termed PDCD1) blockade into initial therapy in adult HL aims to overcome the negative prognostic impact of PD-1 pathway alteration (Ramchandren *et al*, 2019). The preliminary findings evaluating the addition of nivolumab to doxorubicin, vinblastine, dacarbazine (AVD) as initial therapy in patients with newly diagnosed advanced stage (stage IIB, III, IV) HL (CheckMate 205, cohort D) indicate ORR was 84% and the CR rate was 67% in the intent to treat analysis (Ramchandren *et al*, 2019). Nivolumab and pembrolizumab both target epitopes on the PD-1 molecule with high affinity and specificity. Whereas nivolumab and post-transplant consolidation with Bv is approved for relapsed or progressive in adults, the US Food and Drug Administration granted accelerated approval for pembrolizumab for both adult and paediatric relapsed/refractory patients who have refractory classical HL (Geoerger *et al*, 2018). Early experience with checkpoint inhibitors in paediatric patients suggest that toxicity is not increased over

Table II. Comparison of cumulative dose* exposure of selected adult or paediatric chemotherapy regimens (mg/m^2 or units/m^2) for Hodgkin lymphoma.

	Adult HL therapy			Paediatric HL regimens		
	ABVD	Escalated BEACOPP	Bv-AVD†	ABVE-PC‡	Bv-AVEPC	OEPA/ COPDac
Cycles (*n*)	6	6	6	5	5	2/4
Doxorubicin (D)	300	210	300	250	250	160
Bleomycin (B)	120	60	–	75	–	
Vincristine (V; O)	–	12	–	15	7·5	21
Etoposide (E)	–	3600	–	1875	1875	1250
Cyclophosphamide (C)	–	7200	–	6000	6000	4000
Prednisone (P)	–	3360	–	1400	1400	3922
Procarbazine (P)	–	4200	–	–	–	
Vinblastine (V)	72	–	72	–	–	
Dacarbazine (D; Dac)	4500		4500			3000
Brentuximab vedotin (Bv)			14·4		9·0	

*Doses listed reflect the cumulative chemotherapy dose (per m^2) to an individual survivor if the entire number of intended cycles are delivered.
†ECHELON-1 trial (Connors *et al*, 2018).
‡On Children's Oncology Group (COG) trials AHOD0831 (Kelly *et al*, 2019), AHOD0031 (Friedman *et al*, 2014) the cumulative dose of cyclophosphamide was 3200 mg/m^2; this contrasts to AHOD1331 (NCT02166463) where the dose is 6000 mg/m^2.

that noted in adults, however, longer term follow-up is needed to ensure that younger patients are not at elevated risk for acute or late onset immune related adverse events (Ihara, 2019).

Biologically-based targeted approaches in paediatric HL are a key primary prevention strategy to reduce exposure to RT and to cumulative doses of anthracycline and alkylating agents (Table I).

Expansion of trials of novel agents to younger adolescents

Based on recent guidance from the American Society of Clinical Oncology (ASCO) and the Friends of Cancer Alliance to include children ≥age 12 years in late phase trials (Kim *et al*, 2017), the COG examined outcomes on legacy trials to inform the optimal lower threshold age for enrolment on trials of novel agents in HL. Adolescent age emerged as an independent risk for DFS (≥12 years Hazard ratio 1·52 [95% CI 1·06–2·19; reference <12 years] and age ≥15 years was identified as an independent risk for OS (≥15 years Hazard ratio 2·58 [95% CI 1·24–5·38]) (Kahn *et al*, 2018). These data suggest that a "one fit" approach for all paediatric HL may not be warranted.

Future trials incorporating novel agents in paediatric HL need to consider how to achieve gains in younger adolescents (12–15 years of age) and adolescents/young adults (15–39 years of age), a population known to lag in benefit behind their older and younger counterparts (Kahn & Kelly, 2018). Toward this goal, the National Cancer Institute's National Clinical Trials Network (NCTN) will facilitate intergroup trials in North America. A recently activated Phase III trial in (NCT03907488) advanced stage HL exemplifies adult and paediatric collaboration. Patients ≥12 years of age will be randomized to Bv or nivolumab alongside AVD. Similar efforts are ongoing for early unfavourable and relapsed disease. An international collaboration is examining the safety and efficacy of pembrolizumab in combination with chemotherapy in children and young adults with newly diagnosed HL who are slow early responders (SERs) to frontline chemotherapy (NCT03407144) (Mauz-Korholz *et al*, 2018).

While novel therapies including the antibody-drug conjugates and various immunotherapy approaches offer a promise of improved lymphoma-free survival and OS, these agents are expensive and are associated with a different slate of symptom burden, such as peripheral neuropathy (Bv), rash, colitis, pneumonitis and endocrinopathies (checkpoint inhibitors) (Brahmer *et al*, 2018; Vardhana *et al*, 2019). Potential immune-mediated adverse events of drugs that target the tumour microenvironment need to be carefully tracked in younger patients. Importantly, adverse symptoms, poor HRQoL and financial hardship can limit full delivery of novel agents, which, in turn, may alter disease outcomes.

Novel salvage regimens

Novel approaches after initial therapy or following autologous HSCT are needed for the 15–30% of children with recurrent or refractory HL. Small numbers of patients have limited the opportunity to evaluate novel agents in paediatric specific trials. In a COG retrieval trial, the combination of Bv with gemcitabine was highly active. The high complete response rate facilitated reduction of alkylating agent dose in a young group who often need subsequent HSCT (Cole *et al*, 2018).

An analysis of children and AYA <30 years of age who underwent autologous HSCT for relapsed/ refractory HL

reported PFS and OS of 56% and 73%, respectively (Satwani *et al*, 2015). Risk factors for reduced survival post-HSCT included first remission <12 months, poor performance status, chemo-resistance, extra-nodal disease at relapse and receipt of first line therapy regimens other than ABVD/ABVD-like. Patients with late relapse of low-stage disease are predicted to have excellent outcomes with conventional chemotherapy or chemo-radiotherapy, and thus may be able to avoid the acute and long-term toxicity associated with HSCT (Harker-Murray *et al*, 2014). A strategy to stratify the intensity of salvage treatment based on time to relapse and stage of disease at relapse in paediatric HL is under evaluation (NCT02927769). The role of CD30-directed chimeric antigen receptor T cell (CAR T) therapy for chemo-refractory patients is of promise (NCT02690545) (Park *et al*, 2017).

While inclusion of children ≥12 years of age has been advocated for generalizability in late phase trials (Kim *et al*, 2017), translation of this principle to early phase trials in HL will be beneficial to having younger adolescent access to targeted lymphoma therapies more quickly. Given the excellent response rates to PD1 blockade described in relapsed and refractory HL in adults, nivolumab is currently under study for paediatric patients through the NCTN in combination with ipilumumab and Bv for relapsed/refractory lymphoma (E4412; NCT01896999) and in combination with Bv for relapsed HL (Checkmate 744: AHOD1721; NCT02927769).

Pharmacogenomics

While many late effects in HL survivors follow a dose-response pattern with conventional chemotherapy or RT, variation in risk is confounded by genetic basis for differential sensitivity to radiation carcinogenesis or chemotherapy-associated cardiotoxicity, pulmonary injury or neuropathy. Understanding those risks in survivors can be assimilated into individualizing future front-line therapy for HL. Recently a breast cancer polygenic risk score (BC-PRS), consisting of 77 single nucleotide polymorphisms previously associated with breast cancer in the general population, was noted to substantially increase the risk of breast cancer in women who received chest RT for HL (Opstal-van Winden *et al*, 2019). Similarly, several polymorphisms that predict increased risk of anthracycline cardiomyopathy have been found. These range from effects on anthracycline drug transport, to effects on regulation of reactive oxygen species (Armenian & Bhatia, 2018). The pharmacogenomics of neuropathy in HL has not been explored.

Supportive care/Cardioprotection

As anthracylines remain an intergral component of paediatric HL therapy, the primary strategy to date has been to keep the cumulative dose <300 mg/m^2. Dexrazoxane, a topoisomerase II inhibitor with cardioprotective potential, reduces reactive oxygen species formation. Its use concomitant with anthracyclines is theorized to be associated with reduction of the risk of congestive heart failure (Lipshultz *et al*, 2014; Chow *et al*, 2015). The only randomized trials of its use in paediatric HL raised a concern of it potentiating the risk of therapy-related secondary leukaemia, myelosuppression and typhlitis in regimens that also included etoposide (Tebbi *et al*, 2007; Schwartz *et al*, 2009). A subsequent analyses across three trials where patients were randomized to dexrazoxane indicated no difference in mortality or in SMN rates by dexrazoxane arm; the rate of typhlitis and overall myelosuppression was not studied (Chow *et al*, 2015). An ongoing study examining the long-term efficacy of dexrazoxane on cardiac outcomes across a range of anthracycline exposures (NCT0179012) will be informative for its future adoption.

Fertility preservation prior to start of therapy

Fertility preservation is a recognized priority for adolescents, but the uniformity of access to preservation options and discussions varies by paediatric centre and gender (Levine *et al*, 2010; Moravek *et al*, 2019). While doses of alkylating agent therapy have been reduced, there is no paediatric HL-specific knowledge on the uptake of sperm banking, testicular preservation or of counselling and discussion around oocyte cryopreservation or fertility restoration approaches after HL. Tracking of fertility preservation and long-term reproductive outcomes within contemporary clinical trials with novel therapies are needed.

Fatigue, HRQoL – risk or harbinger of poor outcomes

Despite its debilitating impact on health, there is a paucity of data on cancer-related fatigue, or longitudinal HRQoL among adult or paediatric HL patients during or following treatment (Linendoll *et al*, 2016). A longitudinal prospective evaluation of HRQoL in adults with HL enrolled on therapeutic trials noted severe levels of fatigue was common prior to the start of chemotherapy, and differed significantly by disease stage, whereas persistent fatigue in survivors did not correlate with level of therapy intensity (Kreissl *et al*, 2016). While severe fatigue at baseline was associated with a risk of poorer PFS, this effect was abrogated in the patients randomized to escalated therapy for any given group (Behringer *et al*, 2016).

An ongoing COG randomized Phase III trial in newly diagnosed high risk HL (NCT02166463) is measuring HRQoL from baseline to 3 years off-therapy as a secondary outcome while evaluating the efficacy of the novel therapy, Bv. Importantly, HRQoL is being evaluated simultaneously with patient and clinician reports of targeted toxicities, including neuropathy (Henderson *et al*, 2016; Parsons *et al*, 2018a).

Neurocognitive impairment in ≥2 cognitive domains was noted in 30% of HL survivors at a median age of 28 years and 24·7 months from completion of therapy. There was no association with fatigue, and executive function was most

commonly affected. (Trachtenberg *et al*, 2018). A similar finding was noted in an adult cohort of survivors of childhood HL, where magnetic resonance imaging additionally indicated multifocal leucoencephalopathy associated with impaired cardiac diastolic function and impaired pulmonary function at a mean of 27 years from therapy given in an early era (Krull *et al*, 2012). There is no data on neurocognitive function in paediatric HL survivors of contemporary therapy.

Financial hardship and societal costs of HL

Despite the high OS rates, the impact of premature loss of lives from relapsed or refractory HL and the treatment-related morbidity of initial therapy from historical regimens has indicated a high societal burden of HL. In a European analysis of the cost-per-death from malignancies, HL had the second highest lost productivity cost due to premature cancer-related mortality (Hanly *et al*, 2015). Adult survivors of paediatric cancers have high productivity loss related to work limitations, and compromised work attendance and performance, all of which can lead to financial instability. In addition, high out of pocket costs are associated with deferred care, treatment, and follow-up (Parsons *et al*, 2018b; Parsons & Kumar, 2019). Prospective studies are necessary to determine how a diagnosis of paediatric HL affects education, employment and resources that influence survivors' access to life-long health care services.

Secondary prevention of late effects to enhance survivorship

Risk-based screening for late effects

Secondary prevention (Table I) spans screening for, and intervention against, medical and psychosocial morbidities, which can appear or continue for decades after initial therapy. HL survivors were characterized as one of the childhood cancer groups with a large burden of cure (Oeffinger *et al*, 2006). International groups have created guidelines for risk- and exposure-based screening and care (Landier *et al*, 2004), with recent efforts (Kremer *et al*, 2013) to harmonize recommendations germane to HL survivors, including: breast cancer, cardiomyopathy, premature ovarian failure, male gonadotoxicity and thyroid cancer (http://www.ighg.org/guidelines/topics/) (Mulder *et al*, 2013; Armenian *et al*, 2015; Brown *et al*, 2015; Skinner *et al*, 2017; Clement *et al*, 2018). National Comprehensive Cancer Network (NCCN) HL-specific follow-up guidelines apply to those treated when aged ≥18 years (NCCN, 2019), but are less granular in terms of frequency and additional risk factors for specific end organ toxicity than are the COG guidelines (Landier *et al*, 2004).

Gaps in post-treatment care are known for HL survivors (Hahn *et al*, 2019). A Dutch initiative facilitates reimbursed targeted survivorship care for HL survivors based on national guidelines (www.beternahodgkin.nl) which include online calculators to generate risk-, gender- and age-based care. Initial data indicate 43% of patients invited did not attend the clinic; emotional burden and personal financial circumstances were some of the identified barriers to participation (Nijdam *et al*, 2019). Interventions to enhance awareness and acquisition of screening and care for late effects after paediatric HL include education and personalized counselling in survivors at risk (Oeffinger *et al*, 2011; Hudson *et al*, 2014), introduction of electronic personal health records to facilitate the transition from paediatric to adult care (Williamson *et al*, 2017), and engagement and education of primary care providers with regard to screening and follow-up needs of this young and transient population.

Interventions to mitigate late effects

Interventions toward secondary prevention of CV late effects in HL have been hampered by lack of biomarkers of late events. An ongoing medication trial will assess the impact of a two-year course of low-dose carvedilol on surrogate echocardiographic indices of heart failure risk, natriuretic peptides, troponins and galectin-3 (NCT02717507) (Armenian *et al*, 2016). While self-reported exercise habits within the CCSS indicate a strong inverse association between high levels of exercise and mortality (Jones *et al*, 2014), application of exercise interventions efficacious in the general population with CV disease and in other cancer survivor groups to HL survivors has lagged. An ongoing feasibility trial (NCT03923504) to compare the effects of a tailored multilevel physical activity intervention to a healthy living intervention on exercise capacity, CV and cognitive function, HRQoL, strength, and fatigue among lymphoma patients undergoing active treatment with anthracycline-based chemotherapy has potential to extend exercise science to HL survivors.

Future directions for primary and secondary preventions to close the survivorship gap

Decision models

Despite overall excellent outcomes, there is no consensus on treatment with regards to conventional chemotherapy, the role of radiotherapy and the incorporation of novel agents across age groups, or for individual patients. Adult HL patients indicate that primary cure is of utmost importance (Kreissl *et al*, 2019). Helping clinicians and patients assess individualized treatment options and subsequent screening remains a challenge in the absence of data on the long-term effects of current treatment strategies. A cumulative burden metric is one approach to assimilate multiple morbidities and competing risks estimated from historic observational cohorts of HL patients (Bhakta *et al*, 2016). The availability

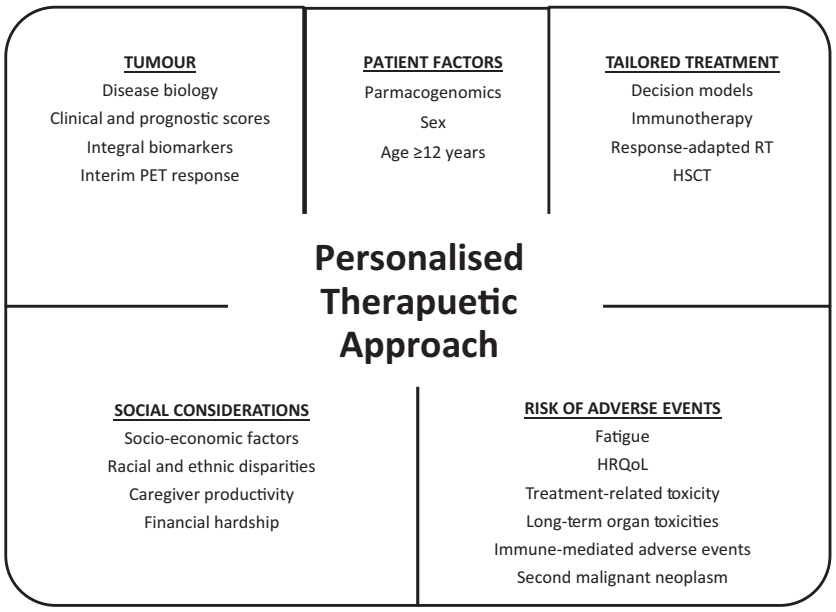

Fig 2. Closing the survivorship gap through a personalized therapeutic approach requires attention to host and tumour factors prior to, during and following curative therapy. HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; PET, positron emission tomography; RT, radiation therapy.

of biomarkers, new targeted drugs, pharmacogenomics, and the application of imaging-guided interim response will create opportunities for personalized approaches (Fig 2).

Decision models are useful when treatment options involve trade-offs, and when risks and benefits vary substantially by patient characteristics, as is the case in patients with HL (Parsons *et al*, 2019). Simulation modelling can systematically and explicitly incorporate assumptions and information from multiple data sources to explore how alternative treatments affect outcomes of interest. These range from acute to late toxicity, risk of relapse and risk of late effects. A dynamic decision model for patients with early stage HL provides a proof of principle that incorporating contemporary trial-based probabilities of transition through health states (from diagnosis through treatment and survivorship) and applying utility weights estimating HRQoL can be useful (Parsons *et al*, 2018c). Harmonization of individual level data from contemporary trials across many cooperative groups is ongoing to further refine and test this model across age and risk groups. The ultimate goal is development and implementation of a tool useful for shared decision-making between patients, caregivers and providers as diagnostic and therapeutic options evolve for HL.

Conclusions

Currently, approaches with curative intent in paediatric HL incorporate response-adapted chemotherapy alone or in combination with RT to control chemo-insensitive disease and minimise bystander organ toxicity. Among patients that relapse, several different chemo-immunotherapy regimens are being evaluated to maximize complete response prior to consolidation therapy with HSCT, as well as to identify subgroups who can benefit from salvage therapy without HSCT. Barriers to further study of primary and secondary prevention approaches and their eventual application to clinical practice include: the relatively low prevalence of HL, the overall favourable prognosis with conventional therapy, lack of strong preclinical testing models and the absence of validated biomarkers.

However, targeted novel agents are encouraging in the *de novo* and relapsed setting and have the promise of further reducing therapy burden. These, together with secondary prevention approaches, will continue to close the gap in survivorship in paediatric HL. Collaborations with both international paediatric and adult HL research groups, especially for the AYA population, will assist in moving the field forward.

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SMC, SKP and KMK performed the literature search, wrote the review and critically reviewed the manuscript.

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References

Aleman, B.M., van den Belt-Dusebout, A.W., Klokman, W.J., Van't Veer, M.B., Bartelink, H. & van Leeuwen, F.E. (2003) Long-term cause-specific mortality of patients treated for Hodgkin's disease. *Journal of Clinical Oncology*, **21**, 3431–3439.

Ansell, S.M., Lesokhin, A.M., Borrello, I., Halwani, A., Scott, E.C., Gutierrez, M., Schuster, S.J., Millenson, M.M., Cattry, D., Freeman, G.J., Rodig, S.J., Chapuy, B., Ligon, A.H., Zhu, L., Grosso, J.F., Kim, S.Y., Timmerman, J.M., Shipp, M.A. & Armand, P. (2015) PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *New England Journal of Medicine*, **372**, 311–319.

Aoki, T. & Steidl, C. (2018) Novel biomarker approaches in classic Hodgkin lymphoma. *Cancer Journal*, **24**, 206–214.

Appel, B.E., Chen, L., Buxton, A.B., Hutchison, R.E., Hodgson, D.C., Ehrlich, P.F., Constine, L.S. & Schwartz, C.L. (2016) Minimal treatment of low-risk, pediatric lymphocyte-predominant hodgkin lymphoma: a report from the Children's Oncology Group. *Journal of Clinical Oncology*, **34**, 2372–2379.

Armenian, S.H. & Bhatia, S. (2018) Predicting and preventing anthracycline-related cardiotoxicity. *American Society of Clinical Oncology Educational Book*, **38**, 3–12.

Armenian, S.H., Hudson, M.M., Mulder, R.L., Chen, M.H., Constine, L.S., Dwyer, M., Nathan, P.C., Tissing, W.J., Shankar, S., Sieswerda, E., Skinner, R., Steinberger, J., van Dalen, E.C., van der Pal, H., Wallace, W.H., Levitt, G. & Kremer, L.C.; International Late Effects of Childhood Cancer Guideline Harmonization Group. (2015) Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *The Lancet Oncology*, **16**, e123–e136.

Armenian, S.H., Hudson, M.M., Chen, M.H., Colan, S.D., Lindenfeld, L., Mills, G., Siyahian, A., Gelehrter, S., Dang, H., Hein, W., Green, D.M., Robison, L.L., Wong, F.L., Douglas, P.S. & Bhatia, S. (2016) Rationale and design of the Children's Oncology Group (COG) study ALTE1621: a randomized, placebo-controlled trial to determine if low-dose carvedilol can prevent anthracycline-related left ventricular remodeling in childhood cancer survivors at high risk for developing heart failure. *BMC Cardiovascular Disorders*, **16**, 187.

Armstrong, G.T., Sklar, C.A., Hudson, M.M. & Robison, L.L. (2007) Long-term health status among survivors of childhood cancer: does sex matter? *Journal of Clinical Oncology*, **25**, 4477–4489.

Armstrong, G.T., Yasui, Y. & Robison, L.L. (2016) Reduction in late mortality after childhood cancer. *New England Journal of Medicine*, **375**, 290–292.

Bazzeh, F., Rihani, R., Howard, S. & Sultan, I. (2010) Comparing adult and pediatric Hodgkin lymphoma in the Surveillance, Epidemiology and End Results Program, 1988–2005: an analysis of 21 734 cases. *Leukaemia & Lymphoma*, **51**, 2198–2207.

Behringer, K., Goergen, H., Muller, H., Thielen, I., Brillant, C., Kreissl, S., Halbsguth, T.V., Meissner, J., Greil, R., Moosmann, P., Shonukan, O., Rueffer, J.U., Flechtner, H.H., Fuchs, M., Diehl, V., Engert, A. & Borchmann, P. (2016) Cancer-related fatigue in patients with and survivors of Hodgkin lymphoma: the impact on treatment outcome and social reintegration. *Journal of Clinical Oncology*, **34**, 4329–4337.

Bhakta, N., Liu, Q., Yeo, F., Baassiri, M., Ehrhardt, M.J., Srivastava, D.K., Metzger, M.L., Krasin, M.J., Ness, K.K., Hudson, M.M., Yasui, Y. & Robison, L.L. (2016) Cumulative burden of cardiovascular morbidity in paediatric, adolescent, and young adult survivors of Hodgkin's lymphoma: an analysis from the St Jude Lifetime Cohort Study. *The lancet Oncology*, **17**, 1325–1334.

Bhatia, S., Yasui, Y., Robison, L.L., Birch, J.M., Bogue, M.K., Diller, L., DeLaat, C., Fossati-Bellani, F., Morgan, E., Oberlin, O., Reaman, G., Ruymann, F.B., Tersak, J. & Meadows, A.T. (2003) High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *Journal of Clinical Oncology*, **21**, 4386–4394.

Borchmann, P., Haverkamp, H., Diehl, V., Cerny, T., Markova, J., Ho, A.D., Eich, H.T., Mueller-Hermelink, H.K., Kanz, L., Greil, R., Rank, A., Paulus, U., Smardova, L., Huber, C., Dorken, B., Nerl, C., Krause, S.W., Mueller, R.P., Fuchs, M. & Engert, A. (2011) Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage Hodgkin's lymphoma: final analysis of the HD12 trial of the German Hodgkin Study Group. *Journal of Clinical Oncology*, **29**, 4234–4242.

Borchmann, P., Goergen, H., Kobe, C., Lohri, A., Greil, R., Eichenauer, D.A., Zijlstra, J.M., Markova, J., Meissner, J., Feuring-Buske, M., Huttmann, A., Dierlamm, J., Soekler, M., Beck, H.J., Willenbacher, W., Ludwig, W.D., Pabst, T., Topp, M.S., Hitz, F., Bentz, M., Keller, U.B., Kuhnhardt, D., Ostermann, H., Schmitz, N., Hertenstein, B., Aulitzky, W., Maschmeyer, G., Vieler, T., Eich, H., Baues, C., Stein, H., Fuchs, M., Kuhnert, G., Diehl, V., Dietlein, M. & Engert, A. (2018) PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet*, **390**, 2790–2802.

Brahmer, J.R., Lacchetti, C., Schneider, B.J., Atkins, M.B., Brassil, K.J., Caterino, J.M., Chau, I., Ernstoff, M.S., Gardner, J.M., Ginex, P., Hallmeyer, S., Holter Chakrabarty, J., Leighl, N.B., Mammen, J.S., McDermott, D.F., Naing, A., Nastoupil, L.J., Phillips, T., Porter, L.D., Puzanov, I., Reichner, C.A., Santomasso, B.D., Seigel, C., Spira, A., Suarez-Almazor, M.E., Wang, Y., Weber, J.S., Wolchok, J.D. & Thompson, J.A.; National Comprehensive Cancer Network. (2018) Management of Immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology*, **36**, 1714–1768.

Brown, M.C., Levitt, G.A., Frey, E., Bardi, E., Haupt, R., Hjorth, L., Kremer, L., Kuehni, C.E., Lettner, C., Mulder, R.L., Michel, G., Skinner, R. & PanCareSurFup, C. (2015) The views of European clinicians on guidelines for long-term follow-up of childhood cancer survivors. *Pediatric Blood & Cancer*, **62**, 322–328.

Casasnovas, R.-O., Bouabdallah, R., Brice, P., Lazarovici, J., Ghesquieres, H., Stamatoullas, A., Dupuis, J., Gac, A.-C., Gastinne, T., Joly, B., Bouabdallah, K., Nicolas-Virelizier, E., Feugier, P., Morschhauser, F., Delarue, R., Farhat, H., Quittet, P., Berriolo-Riedinger, A., Tempescul, A., Edeline, V., Maisonneuve, H., Fornecker, L.-M., Lamy, T., Delmer, A., Dartigues, P., Martin, L., André, M., Mounier, N., Traverse-Glehen, A. & Meignan, M. (2019) PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. *The Lancet Oncology*, **20**, 202–215.

Castellino, S.M., Geiger, A.M., Mertens, A.C., Leisenring, W.M., Tooze, J.A., Goodman, P., Stovall, M., Robison, L.L. & Hudson, M.M. (2011) Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *Blood*, **117**, 1806–1816.

Chow, E.J., Asselin, B.L., Schwartz, C.L., Doody, D.R., Leisenring, W.M., Aggarwal, S., Baker, K.S., Bhatia, S., Constine, L.S., Freyer, D.R., Lipshultz, S.E. & Armenian, S.H. (2015) Late

mortality after dexrazoxane treatment: a report from the Children's Oncology Group. *Journal of Clinical Oncology*, **33**, 2639–2645.

Clement, S.C., Kremer, L.C.M., Verburg, F.A., Simmons, J.H., Goldfarb, M., Peeters, R.P., Alexander, E.K., Bardi, E., Brignardello, E., Constine, L.S., Dinauer, C.A., Drozd, V.M., Felicetti, F., Frey, E., Heinzel, A., van den Heuvel-Eibrink, M.M., Huang, S.A., Links, T.P., Lorenz, K., Mulder, R.L., Neggers, S.J., Nieveen van Dijkum, E.J.M., Oeffinger, K.C., van Rijn, R.R., Rivkees, S.A., Ronckers, C.M., Schneider, A.B., Skinner, R., Wasserman, J.D., Wynn, T., Hudson, M.M., Nathan, P.C. & van Santen, H.M. (2018) Balancing the benefits and harms of thyroid cancer surveillance in survivors of Childhood, adolescent and young adult cancer: Recommendations from the international Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Cancer Treatment Reviews*, **63**, 28–39.

Cole, P.D., McCarten, K.M., Pei, Q., Spira, M., Metzger, M.L., Drachtman, R.A., Horton, T.M., Bush, R., Blaney, S.M., Weigel, B.J. & Kelly, K.M. (2018) Brentuximab vedotin with gemcitabine for paediatric and young adult patients with relapsed or refractory Hodgkin's lymphoma (AHOD1221): a Children's Oncology Group, multicentre single-arm, phase 1–2 trial. *The lancet Oncology*, **19**, 1229–1238.

Connors, J.M., Jurczak, W., Straus, D.J., Ansell, S.M., Kim, W.S., Gallamini, A., Younes, A., Alekseev, S., Illes, A., Picardi, M., Lech-Maranda, E., Oki, Y., Feldman, T., Smolewski, P., Savage, K.J., Bartlett, N.L., Walewski, J., Chen, R., Ramchandren, R., Zinzani, P.L., Cunningham, D., Rosta, A., Josephson, N.C., Song, E., Sachs, J., Liu, R., Jolin, H.A., Huebner, D. & Radford, J.; ECHELON-1 Study Group. (2018) Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *New England Journal of Medicine*, **378**, 331–344.

Flerlage, J.E., Metzger, M.L., Wu, J. & Panetta, J.C. (2016) Pharmacokinetics, immunogenicity, and safety of weekly dosing of brentuximab vedotin in pediatric patients with Hodgkin lymphoma. *Cancer Chemotherapy and Pharmacology*, **78**, 1217–1223.

Flerlage, J.E., Kelly, K.M., Beishuizen, A., Cho, S., De Alarcon, P.A., Dieckmann, U., Drachtman, R.A., Hoppe, B.S., Howard, S.C., Kaste, S.C., Kluge, R., Kurch, L., Landman-Parker, J., Lewis, J., Link, M.P., McCarten, K., Punnett, A., Stoevesandt, D., Voss, S.D., Wallace, W.H., Mauz-Korholz, C. & Metzger, M.L. (2017) Staging evaluation and response criteria harmonization (SEARCH) for childhood, adolescent and young adult Hodgkin lymphoma (CAYAHL): methodology statement. *Pediatric Blood & Cancer*, **64**, e26421.

Friedman, D.L., Chen, L., Wolden, S., Buxton, A., McCarten, K., FitzGerald, T.J., Kessel, S., De Alarcon, P.A., Chen, A.R., Kobrinsky, N., Ehrlich, P., Hutchison, R.E., Constine, L.S. & Schwartz, C.L. (2014) Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. *Journal of Clinical Oncology*, **32**, 3651–3658.

Geenen, M.M., Cardous-Ubbink, M.C., Kremer, L.C., van den Bos, C., van der Pal, H.J., Heinen, R.C., Jaspers, M.W., Koning, C.C., Oldenburger, F., Langeveld, N.E., Hart, A.A., Bakker, P.J., Caron, H.N. & van Leeuwen, F.E. (2007) Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA*, **297**, 2705–2715.

Geoerger, B., Kang, H., Yalon-Oren, M., Marshall, L., Vezina, C., Pappo, A., Laetsch, T., Petrilli, A., Ebinger, M., Toporski, J., Glade-Bender, J., Nicholls, W., Fox, E., DuBois, S., Macy, M., Cohn, S., Pathiraja, K., Diede, S., Ebbinghaus, S. & Pinto, N. (2018) KEYNOTE-051: An update on the phase 2 results of pembrolizumab (pembro) in pediatric patients (pts) with advanced melanoma or a PD-L1–positive advanced, relapsed or refractory solid tumor or lymphoma. *Journal of Clinical Oncology*, **36**, 10525.

Gibson, T.M., Mostoufi-Moab, S., Stratton, K.L., Leisenring, W.M., Barnea, D., Chow, E.J., Donaldson, S.S., Howell, R.M., Hudson, M.M., Mahajan, A., Nathan, P.C., Ness, K.K., Sklar, C.A., Tonorezos, E.S., Weldon, C.B., Wells, E.M., Yasui, Y., Armstrong, G.T., Robison, L.L. & Oeffinger, K.C. (2018) Temporal patterns in the risk of chronic health conditions in survivors of childhood cancer diagnosed 1970–99: a report from the Childhood Cancer Survivor Study cohort. *The lancet Oncology*, **19**, 1590–1601.

Gordon, L.I., Hong, F., Fisher, R.I., Bartlett, N.L., Connors, J.M., Gascoyne, R.D., Wagner, H., Stiff, P.J., Cheson, B.D., Gospodarowicz, M., Advani, R., Kahl, B.S., Friedberg, J.W., Blum, K.A., Habermann, T.M., Tuscano, J.M., Hoppe, R.T. & Horning, S.J. (2013) Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *Journal of Clinical Oncology*, **31**, 684–691.

Green, D.M., Kawashima, T., Stovall, M., Leisenring, W., Sklar, C.A., Mertens, A.C., Donaldson, S.S., Byrne, J. & Robison, L.L. (2010) Fertility of male survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology*, **28**, 332–339.

Grubb, W.R., Neboori, H.J., Diaz, A.D., Li, H., Kwon, D. & Panoff, J. (2016) Racial and ethnic disparities in the pediatric Hodgkin lymphoma population. *Pediatric Blood & Cancer*, **63**, 428–435.

Hahn, E.E., Wu, Y.L., Munoz-Plaza, C.E., Garcia Delgadillo, J., Cooper, R.M. & Chao, C.R. (2019) Use of recommended posttreatment services for adolescent and young adult survivors of Hodgkin lymphoma. *Cancer*, **125**, 1558–1567.

Hanly, P., Soerjomataram, I. & Sharp, L. (2015) Measuring the societal burden of cancer: the cost of lost productivity due to premature cancer-related mortality in Europe. *International Journal of Cancer*, **136**, E136–145.

Harker-Murray, P.D., Drachtman, R.A., Hodgson, D.C., Chauvenet, A.R., Kelly, K.M. & Cole, P.D. (2014) Stratification of treatment intensity in relapsed pediatric Hodgkin lymphoma. *Pediatric Blood & Cancer*, **61**, 579–586.

Hasenclever, D. & Diehl, V. (1998) A prognostic score for advanced Hodgkin's disease. International prognostic factors project on advanced Hodgkin's disease. *New England Journal of Medicine*, **339**, 1506–1514.

Henderson, T.O., Castellino, S.M., Keller, F.G., Kelly, K.M., Curtis, R., Conti, R.M. & Parsons, S.K. (2016) Approach and feasibility of patient-reported outcomes (PROs) in a phase III clinical trial for advanced stage classical Hodgkin lymphoma (cHL) in children and adolescents. *Blood*, **128**, 3583.

Hoppe, B.S., Hill-Kayser, C.E., Tseng, Y.D., Flampouri, S., Elmongy, H.M., Cahlon, O., Mendenhall, N.P., Maity, A., McGee, L.A. & Plastaras, J.P. (2017) Consolidative proton therapy after chemotherapy for patients with Hodgkin lymphoma. *Annals of Oncology*, **28**, 2179–2184.

Hudson, M.M., Mertens, A.C., Yasui, Y., Hobbie, W., Chen, H., Gurney, J.G., Yeazel, M., Recklitis, C.J., Marina, N., Robison, L.R. & Oeffinger, K.C. (2003) Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA*, **290**, 1583–1592.

Hudson, M.M., Leisenring, W., Stratton, K.K., Tinner, N., Steen, B.D., Ogg, S., Barnes, L., Oeffinger, K.C., Robison, L.L. & Cox, C.L. (2014) Increasing cardiomyopathy screening in at-risk adult survivors of pediatric malignancies: a randomized controlled trial. *Journal of Clinical Oncology*, **32**, 3974–3981.

Ihara, K. (2019) Immune checkpoint inhibitor therapy for pediatric cancers: a mini review of endocrine adverse events. *Clinical Pediatric Endocrinology*, **28**, 59–68.

Johnson, P.W., Sydes, M.R., Hancock, B.W., Cullen, M., Radford, J.A. & Stenning, S.P. (2010) Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 randomized controlled trial (ISRCTN97144519). *Journal of Clinical Oncology*, **28**, 3352–3359.

Jones, L.W., Liu, Q., Armstrong, G.T., Ness, K.K., Yasui, Y., Devine, K., Tonorezos, E., Soares-Miranda, L., Sklar, C.A., Douglas, P.S., Robison, L.L. & Oeffinger, K.C. (2014) Exercise and risk of major cardiovascular events in adult survivors of childhood hodgkin lymphoma: a report from the childhood cancer survivor study. *Journal of Clinical Oncology*, **32**, 3643–3650.

Kahn, J.M. & Kelly, K.M. (2018) Adolescent and young adult Hodgkin lymphoma: raising the bar through collaborative science and multidisciplinary care. *Pediatric Blood & Cancer*, **65**, e27033.

Kahn, J.M., Kelly, K.M., Pei, Q., Friedman, D.L., Keller, F., Bush, R., Bhatia, S., Henderson, T.O., Schwartz, C.L. & Castellino, S.M. (2017) Survival by race/ethnicity in children and adolescents with Hodgkin lymphoma treated on cooperative group trials in the U.S. and Canada: a pooled analysis of Children's Oncology Group trials. *Blood*, **130**, 607.

Kahn, J.M., Kelly, K., Pei, Q., Friedman, D., Keller, F., Bush, R., Bhatia, S., Henderson, T., Schwartz, C. & Castellino, S.M. (2018) Survival by age in children and adolescents with Hodgkin lymphoma: a pooled analysis of Children's Oncology Group (COG) trials. *Journal of Clinical Oncology*, **36**, 7543.

Keegan, T.H., DeRouen, M.C., Parsons, H.M., Clarke, C.A., Goldberg, D., Flowers, C.R. & Glaser, S.L. (2016) Impact of treatment and insurance on socioeconomic disparities in survival after adolescent and young adult Hodgkin lymphoma: a population-based study. *Cancer Epidemiology, Biomarkers & Prevention*, **25**, 264–273.

Keller, F.G., Castellino, S.M., Chen, L., Pei, Q., Voss, S.D., McCarten, K.M., Senn, S.L., Buxton, A.B., Bush, R., Constine, L.S. & Schwartz, C.L. (2018) Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: a report from the Children's Oncology Group. *Cancer*, **124**, 3210–3219.

Kelly, K.M. (2015) Hodgkin lymphoma in children and adolescents: improving the therapeutic index. *Blood*, **126**, 2452–2458.

Kelly, K.M., Sposto, R., Hutchinson, R., Massey, V., McCarten, K., Perkins, S., Lones, M., Villaluna, D. & Weiner, M. (2011) BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: a report from the Children's Oncology Group. *Blood*, **117**, 2596–2603.

Kelly, K., Cole, P., Pei, Q., Bush, R., Roberts, K., Hodgson, D., McCarten, K., Cho, S. & Schwartz, C. (2019) Response adapted therapy for the treatment of children with newly diagnosed high risk Hodgkin lymphoma (AHOD0831): a report from the Children's Oncology Group. *British Journal of Haematology*. [Epub ahead of print]. https://doi.org/10.1111/bjh.16014.

Kim, E.S., Bruinooge, S.S., Roberts, S., Ison, G., Lin, N.U., Gore, L., Uldrick, T.S., Lichtman, S.M., Roach, N., Beaver, J.A., Sridhara, R., Hesketh, P.J., Denicoff, A.M., Garrett-Mayer, E., Rubin, E., Multani, P., Prowell, T.M., Schenkel, C., Kozak, M., Allen, J., Sigal, E. & Schilsky, R.L. (2017) Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. *Journal of Clinical Oncology*, **35**, 3737–3744.

Korholz, D., Claviez, A., Hasenclever, D., Kluge, R., Hirsch, W., Kamprad, F., Dorffel, W., Wickmann, L., Papsdorf, K., Dieckmann, K., Kahn, T., Mauz-Korholz, C., Dannenberg, C., Potter, R., Brosteanu, O., Schellong, G. & Sabri, O. (2004) The concept of the GPOH-HD 2003 therapy study for pediatric Hodgkin's disease: evolution in the tradition of the DAL/GPOH studies. *Klinische Padiatrie*, **216**, 150–156.

Kreissl, S., Mueller, H., Goergen, H., Mayer, A., Brillant, C., Behringer, K., Halbsguth, T.V., Hitz, F., Soekler, M., Shonukan, O., Rueffer, J.U., Flechtner, H.H., Fuchs, M., Diehl, V., Engert, A. & Borchmann, P.; German Hodgkin Study Group. (2016) Cancer-related fatigue in patients with and survivors of Hodgkin's lymphoma: a longitudinal study of the German Hodgkin Study Group. *The lancet Oncology*, **17**, 1453–1462.

Kreissl, S., Goergen, H., Muller, H., Meissner, J., Mehnert, A., Burkle, C., Fuchs, M., Engert, A., Behringer, K. & Borchmann, P.; German Hodgkin Study Group. (2019) Survivors' perspectives on risks and benefits of Hodgkin lymphoma treatment: results of a survey by the German Hodgkin Study Group. *Leukaemia & Lymphoma*, **60**, 1389–1398.

Kremer, L.C., Mulder, R.L., Oeffinger, K.C., Bhatia, S., Landier, W., Levitt, G., Constine, L.S., Wallace, W.H., Caron, H.N., Armenian, S.H., Skinner, R. & Hudson, M.M.; International Late Effects of Childhood Cancer Guideline Harmonization Group. (2013) A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatric Blood & Cancer*, **60**, 543–549.

Krull, K.R., Sabin, N.D., Reddick, W.E., Zhu, L., Armstrong, G.T., Green, D.M., Arevalo, A.R., Krasin, M.J., Srivastava, D.K., Robison, L.L. & Hudson, M.M. (2012) Neurocognitive function and CNS integrity in adult survivors of childhood hodgkin lymphoma. *Journal of Clinical Oncology*, **30**, 3618–3624.

Landier, W., Bhatia, S., Eshelman, D.A., Forte, K.J., Sweeney, T., Hester, A.L., Darling, J., Armstrong, F.D., Blatt, J., Constine, L.S., Freeman, C.R., Friedman, D.L., Green, D.M., Marina, N., Meadows, A.T., Neglia, J.P., Oeffinger, K.C., Robison, L.L., Ruccione, K.S., Sklar, C.A. & Hudson, M.M. (2004) Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *Journal of Clinical Oncology*, **22**, 4979–4990.

Landman-Parker, J., Pacquement, H., Leblanc, T., Habrand, J.L., Terrier-Lacombe, M.J., Bertrand, Y., Perel, Y., Robert, A., Coze, C., Thuret, I., Donadieu, J., Schaison, G., Leverger, G., Lemerle, J. & Oberlin, O. (2000) Localized childhood Hodgkin's disease: response-adapted chemotherapy with etoposide, bleomycin, vinblastine, and prednisone before low-dose radiation therapy-results of the French Society of Pediatric Oncology Study MDH90. *Journal of Clinical Oncology*, **18**, 1500–1507.

van Leeuwen, F.E., Klokman, W.J., Veer, M.B., Hagenbeek, A., Krol, A.D., Vetter, U.A., Schaapveld, M., van Heerde, P., Burgers, J.M., Somers, R. & Aleman, B.M. (2000) Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. *Journal of Clinical Oncology*, **18**, 487–497.

Levine, J., Canada, A. & Stern, C.J. (2010) Fertility preservation in adolescents and young adults with cancer. *Journal of Clinical Oncology*, **28**, 4831–4841.

Linendoll, N., Saunders, T., Burns, R., Nyce, J.D., Wendell, K.B., Evens, A.M. & Parsons, S.K. (2016) Health-related quality of life in Hodgkin lymphoma: a systematic review. *Health and Quality of Life Outcomes*, **14**, 114.

Lipshultz, S.E., Diamond, M.B., Franco, V.I., Aggarwal, S., Leger, K., Santos, M.V., Sallan, S.E. & Chow, E.J. (2014) Managing chemotherapy-related cardiotoxicity in survivors of childhood cancers. *Paediatric Drugs*, **16**, 373–389.

Locatelli, F., Mauz-Koerholz, C., Neville, K., Llort, A., Beishuizen, A., Daw, S., Pillon, M., Aladjidi, N., Klingebiel, T., Landman-Parker, J., Medina-Sanson, A., August, K., Sachs, J., Hoffman, K., Kinley, J., Song, S., Song, G., Zhang, S., Suri, A. & Gore, L. (2018) Brentuximab vedotin for paediatric relapsed or refractory Hodgkin's lymphoma and anaplastic large-cell lymphoma: a multicentre, open-label, phase 1/2 study. *The Lancet Haematology*, **5**, e450–e461.

Marks, L.J., Pei, Q., Bush, R., Buxton, A., Appel, B., Kelly, K.M., Schwartz, C.L. & Friedman, D.L. (2018) Outcomes in intermediate-risk pediatric lymphocyte-predominant Hodgkin lymphoma: a report from the Children's Oncology Group. *Pediatric Blood & Cancer*, **65**, e27375.

Mauz-Korholz, C., Hasenclever, D., Dorffel, W., Ruschke, K., Pelz, T., Voigt, A., Stiefel, M., Winkler, M., Vilser, C., Dieckmann, K., Karlen, J., Bergstrasser, E., Fossa, A., Mann, G., Hummel, M., Klapper, W., Stein, H., Vordermark, D., Kluge, R. & Korholz, D. (2010) Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. *Journal of Clinical Oncology*, **28**, 3680–3686.

Mauz-Korholz, C., Kelly, K., Keller, F., Giulino-Roth, L., Nahar, A. & Balakumaran, A. (2018) KEYNOTE- 667: Phase 2, open-label study of pembrolizumab in children and young adults with newly diagnosed classical Hodgkin lymphoma (cHL) with slow early response (SER) to frontline chemotherapy. *Journal of Clinical Oncology*, **36**, TPS7583.

Metzger, M.L., Castellino, S.M., Hudson, M.M., Rai, S.N., Kaste, S.C., Krasin, M.J., Kun, L.E., Pui, C.H. & Howard, S.C. (2008) Effect of race

on the outcome of pediatric patients with Hodgkin's lymphoma. *Journal of Clinical Oncology*, **26**, 1282–1288.

Metzger, M.L., Weinstein, H.J., Hudson, M.M., Billett, A.L., Larsen, E.C., Friedmann, A., Howard, S.C., Donaldson, S.S., Krasin, M.J., Kun, L.E., Marcus, K.J., Yock, T.I., Tarbell, N., Billups, C.A., Wu, J. & Link, M.P. (2012) Association between radiotherapy vs no radiotherapy based on early response to VAMP chemotherapy and survival among children with favorable-risk Hodgkin lymphoma. *JAMA*, **307**, 2609–2616.

Moravek, M.B., Appiah, L.C., Anazodo, A., Burns, K.C., Gomez-Lobo, V., Hoefgen, H.R., Jaworek Frias, O., Laronda, M.M., Levine, J., Meacham, L.R., Pavone, M.E., Quinn, G.P., Rowell, E.E., Strine, A.C., Woodruff, T.K. & Nahata, L. (2019) Development of a pediatric fertility preservation program: a report from the Pediatric Initiative Network of the Oncofertility Consortium. *Journal of Adolescent Health*, **64**, 563–573.

Mottok, A., Johnston, R., Chan, F., Scott, D., Friedman, D., Schwartz, C.L., Kelly, K., Horton, T. & Steidl, C. (2015) Prediction of primary treatment outcome using gene expression profiling of pre-treatment biopsies obtained from childhood and adolescent Hodgkin lymphoma patients. *Blood*, **126**, 175.

Mulder, R.L., Kremer, L.C., Hudson, M.M., Bhatia, S., Landier, W., Levitt, G., Constine, L.S., Wallace, W.H., van Leeuwen, F.E., Ronckers, C.M., Henderson, T.O., Dwyer, M., Skinner, R. & Oeffinger, K.C.; International Late Effects of Childhood Cancer Guideline Harmonization Group. (2013) Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *The Lancet Oncology*, **14**, e621–629.

NCCN. (2019) Guidelines version 2.2019 Hodgkin lymphoma (age ≥18 years). https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf.

Nijdam, A., Dekker, N., Aleman, B.M.P., Van 't Veer, M.B., Daniels, L.A., van der Maazen, R.W., Janus, C.P.M., de Weijer, R.J., Zijlstra, J.M., Stedema, F.G., Ta, B.D., Posthuma, E.F.M., Manenschijn, A., Dielwart, M.F.H., Bilgin, Y.M., van den Heuvel, M.J., Boersma, R.S., van Leeuwen, F.E. & Raemaekers, J.M.M. (2019) Setting up a national infrastructure for survivorship care after treatment for Hodgkin lymphoma. *British Journal of Haematology*, **186**, e103–e108.

Oeffinger, K.C., Mertens, A.C., Sklar, C.A., Kawashima, T., Hudson, M.M., Meadows, A.T., Friedman, D.L., Marina, N., Hobbie, W., Kadan-Lottick, N.S., Schwartz, C.L., Leisenring, W. & Robison, L.L. (2006) Chronic health conditions in adult survivors of childhood cancer. *New England Journal of Medicine*, **355**, 1572–1582.

Oeffinger, K.C., Hudson, M.M., Mertens, A.C., Smith, S.M., Mitby, P.A., Eshelman-Kent, D.A., Ford, J.S., Jones, J.K., Kamani, S. & Robison, L.L. (2011) Increasing rates of breast cancer and cardiac surveillance among high-risk survivors of childhood Hodgkin lymphoma following a mailed, one-page survivorship care plan. *Pediatric Blood & Cancer*, **56**, 818–824.

Opstal-van Winden, A., de Haan, H., Hauptmann, M., Schmidt, M., Broeks, A., Russell, N., Janus, C., Krol, A., van der Baan, F., De Bruin, M., van Eggermond, A., Dennis, J., Anton-Culver, H., Haiman, C., Sawyer, E., Cox, A., Devilee, P., Hooning, M., Peto, J., Couch, F., Pharoah, P., Orr, N., Easton, D., Aleman, B., Strong, L., Bhatia, S., Cooke, R., Robison, L., Swerdlow, A. & van Leeuwen, F. (2019) Genetic susceptibility to radiation-induced breast cancer after Hodgkin lymphoma. *Blood*, **133**, 1130–1139.

Park, S.I., Serody, J.S., Shea, T.C., Grover, N.S., Ivanova, A., Morrison, K., Eldridge, P., Mckay, K., Cheng, C.J., Covington, D., Wehner, K., Dotti, G. & Savoldo, B. (2017) A phase 1b/2 study of CD30-specific chimeric antigen receptor T-cell (CAR-T) therapy in combination with bendamustine in patients with CD30+ Hodgkin and non-Hodgkin lymphoma. *Journal of Clinical Oncology*, **35**, TPS3095.

Parsons, S.K. & Kumar, A.J. (2019) Adolescent and young adult cancer care: Financial hardship and continued uncertainty. *Pediatric Blood & Cancer*, **66**, e27587.

Parsons, S.K., Rodday, A.M., Bush, R., Pei, Q., Waheed, A., Keller, F.G., Kelly, K.M., Henderson, T.O. & Castellino, S.M. (2018a) Health-related quality of life (HRQL) trajectories during treatment for advanced stage pediatric Hodgkin lymphoma (HL). *Blood*, **132**, 3587.

Parsons, S.K., Castellino, S.M. & Yabroff, K.R. (2018b) Cost, value, and financial hardship in cancer care: implications for pediatric oncology. *American Society of Clinical Oncology Educational Book*, **38**, 850–860.

Parsons, S.K., Kelly, M.J., Cohen, J.T., Castellino, S.M., Henderson, T.O., Kelly, K.M., Keller, F.G., Henzer, T.J., Kumar, A.J., Johnson, P., Meyer, R.M., Radford, J., Raemaekers, J., Hodgson, D.C. & Evens, A.M. (2018c) Early-stage Hodgkin lymphoma in the modern era: simulation modelling to delineate long-term patient outcomes. *British Journal of Haematology*, **182**, 212–221.

Parsons, S.K., Cohen, J.B. & Evens, A.M. (2019) Optimizing decision making in Hodgkin Lymphoma. In: Hodgkin Lymphoma: A Comprehensive Overview (ed. by A. Engert & A. Younes), Vol. In Press. Springer International Publishing, Cham, CH.

Ramchandren, R., Domingo-Domenech, E., Rueda, A., Trneny, M., Feldman, T.A., Lee, H.J., Provencio, M., Sillaber, C., Cohen, J.B., Savage, K.J., Willenbacher, W., Ligon, A.H., Ouyang, J., Redd, R., Rodig, S.J., Shipp, M.A., Sacchi, M., Sumbul, A., Armand, P. & Ansell, S.M. (2019) Nivolumab for newly diagnosed advanced-stage classic Hodgkin lymphoma: safety and efficacy in the phase II CheckMate 205 study. *Journal of Clinical Oncology*, **37**, 1997–2007.

Reichel, J., Chadburn, A., Rubinstein, P.G., Giulino-Roth, L., Tam, W., Liu, Y., Gaiolla, R., Eng, K., Brody, J., Inghirami, G., Carlo-Stella, C., Santoro, A., Rahal, D., Totonchy, J., Elemento, O., Cesarman, E. & Roshal, M. (2015) Flow sorting and exome sequencing reveal the oncogenome of primary Hodgkin and Reed-Sternberg cells. *Blood*, **125**, 1061–1072.

Roemer, M.G.M., Redd, R.A., Cader, F.Z., Pak, C.J., Abdelrahman, S., Ouyang, J., Sasse, S., Younes, A., Fanale, M., Santoro, A., Zinzani, P.L., Timmerman, J., Collins, G.P., Ramchandren, R., Cohen, J.B., De Boer, J.P., Kuruvilla, J., Savage, K.J., Trneny, M., Ansell, S., Kato, K., Farsaci, B., Sumbul, A., Armand, P., Neuberg, D.S., Pinkus, G.S., Ligon, A.H., Rodig, S.J. & Shipp, M.A. (2018) Major Histocompatibility complex class II and programmed death ligand 1 expression predict outcome after programmed death 1 blockade in classic Hodgkin lymphoma. *Journal of Clinical Oncology*, **36**, 942–950.

Satwani, P., Ahn, K.W., Carreras, J., Abdel-Azim, H., Cairo, M.S., Cashen, A., Chen, A.I., Cohen, J.B., Costa, L.J., Dandoy, C., Fenske, T.S., Freytes, C.O., Ganguly, S., Gale, R.P., Ghosh, N., Hertzberg, M.S., Hayashi, R.J., Kamble, R.T., Kanate, A.S., Keating, A., Kharfan-Dabaja, M.A., Lazarus, H.M., Marks, D.I., Nishihori, T., Olsson, R.F., Prestidge, T.D., Rolon, J.M., Savani, B.N., Vose, J.M., Wood, W.A., Inwards, D.J., Bachanova, V., Smith, S.M., Maloney, D.G., Sureda, A. & Hamadani, M. (2015) A prognostic model predicting autologous transplantation outcomes in children, adolescents and young adults with Hodgkin lymphoma. *Bone Marrow Transplantation*, **50**, 1416–1423.

Schellong, G., Riepenhausen, M., Bruch, C., Kotthoff, S., Vogt, J., Bolling, T., Dieckmann, K., Potter, R., Heinecke, A., Bramswig, J. & Dorffel, W. (2010) Late valvular and other cardiac diseases after different doses of mediastinal radiotherapy for Hodgkin disease in children and adolescents: report from the longitudinal GPOH follow-up project of the German-Austrian DAL-HD studies. *Pediatric Blood & Cancer*, **55**, 1145–1152.

Schwartz, C.L., Constine, L.S., Villaluna, D., London, W.B., Hutchison, R.E., Sposto, R., Lipshultz, S.E., Turner, C.S., deAlarcon, P.A. & Chauvenet, A. (2009) A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. *Blood*, **114**, 2051–2059.

Schwartz, C.L., Chen, L., McCarten, K., Wolden, S., Constine, L.S., Hutchison, R.E., de Alarcon, P.A., Keller, F.G., Kelly, K.M., Trippet, T.A., Voss, S.D. & Friedman, D.L. (2017) Childhood Hodgkin international prognostic score (CHIPS) predicts event-free survival in Hodgkin lymphoma: a report from the Children's Oncology Group. *Pediatric Blood & Cancer*, **64**, e26278.

Scott, D.W., Chan, F.C., Hong, F., Rogic, S., Tan, K.L., Meissner, B., Ben-Neriah, S., Boyle, M., Kridel, R., Telenius, A., Woolcock, B.W., Farinha, P., Fisher, R.I., Rimsza, L.M., Bartlett, N.L., Cheson, B.D., Shepherd, L.E., Advani, R.H., Connors, J.M., Kahl, B.S., Gordon, L.I., Horning, S.J., Steidl, C. & Gascoyne, R.D. (2013) Gene expression-based model using formalin-fixed paraffin-embedded biopsies predicts overall survival in advanced-stage classical Hodgkin lymphoma. *Journal of Clinical Oncology*, **31**, 692–700.

SEER (2019) Cancer Stat Facts: Hodgkin Lymphoma, vol. **2019**. National Cancer Institute, Bethesda, MD. https://seer.cancer.gov/statfacts/html/hodg.html.

Skinner, R., Mulder, R.L., Kremer, L.C., Hudson, M.M., Constine, L.S., Bardi, E., Boekhout, A., Borgmann-Staudt, A., Brown, M.C., Cohn, R., Dirksen, U., Giwercman, A., Ishiguro, H., Jahnukainen, K., Kenney, L.B., Loonen, J.J., Meacham, L., Neggers, S., Nussey, S., Petersen, C., Shnorhavorian, M., van den Heuvel-Eibrink, M.M., van Santen, H.M., Wallace, W.H. & Green, D.M. (2017) Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *The lancet Oncology*, **18**, e75–e90.

Spina, V., Bruscaggin, A., Cuccaro, A., Martini, M., Di Trani, M., Forestieri, G., Manzoni, M., Condoluci, A., Arribas, A., Terzi-Di-Bergamo, L., Locatelli, S.L., Cupelli, E., Ceriani, L., Moccia, A.A., Stathis, A., Nassi, L., Deambrogi, C., Diop, F., Guidetti, F., Cocomazzi, A., Annunziata, S., Rufini, V., Giordano, A., Neri, A., Boldorini, R., Gerber, B., Bertoni, F., Ghielmini, M., Stussi, G., Santoro, A., Cavalli, F., Zucca, E., Larocca, L.M., Gaidano, G., Hohaus, S., Carlo-Stella, C. & Rossi, D. (2018) Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. *Blood*, **131**, 2413–2425.

Swerdlow, A.J., Higgins, C.D., Smith, P., Cunningham, D., Hancock, B.W., Horwich, A., Hoskin, P.J., Lister, A., Radford, J.A., Rohatiner, A.Z. & Linch, D.C. (2007) Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *Journal of the National Cancer Institute*, **99**, 206–214.

Tebbi, C.K., London, W.B., Friedman, D., Villaluna, D., De Alarcon, P.A., Constine, L.S., Mendenhall, N.P., Sposto, R., Chauvenet, A. & Schwartz, C.L. (2007) Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *Journal of Clinical Oncology*, **25**, 493–500.

Tebbi, C.K., Mendenhall, N.P., London, W.B., Williams, J.L., Hutchison, R.E., Fitzgerald, T.J., de Alarcon, P.A., Schwartz, C. & Chauvenet, A. (2012) Response-dependent and reduced treatment in lower risk Hodgkin lymphoma in children and adolescents, results of P9426: a report from the Children's Oncology Group. *Pediatric Blood & Cancer*, **59**, 1259–1265.

Trachtenberg, E., Mashiach, T., Ben Hayun, R., Tadmor, T., Fisher, T., Aharon-Peretz, J. & Dann, E.J. (2018) Cognitive impairment in Hodgkin lymphoma survivors. *British Journal of Haematology*, **182**, 670–678.

Vardhana, S., Cicero, K., Velez, M.J. & Moskowitz, C.H. (2019) Strategies for recognizing and managing immune-mediated adverse events in the treatment of Hodgkin lymphoma with checkpoint inhibitors. *The Oncologist*, **24**, 86–95.

Welch, J.J.G., Schwartz, C.L., Higman, M., Chen, L., Buxton, A., Kanakry, J.A., Kahwash, S.B., Hutchison, R.E., Friedman, D.L. & Ambinder, R.F. (2017) Epstein-Barr virus DNA in serum as an early prognostic marker in children and adolescents with Hodgkin lymphoma. *Blood Advances*, **1**, 681–684.

Williamson, R.S., Cherven, B.O., Gilleland Marchak, J., Edwards, P., Palgon, M., Escoffery, C., Meacham, L.R. & Mertens, A.C. (2017) Meaningful use of an electronic personal health record (ePHR) among pediatric cancer survivors. *Applied Clinical Informatics*, **8**, 250–264.

Wogksch, M.D., Howell, C.R., Wilson, C.L., Partin, R.E., Ehrhardt, M.J., Krull, K.R., Brinkman, T.M., Mulrooney, D.A., Hudson, M.M., Robison, L.L. & Ness, K.K. (2019) Physical fitness in survivors of childhood Hodgkin lymphoma: A report from the St. Jude Lifetime Cohort. *Pediatric Blood & Cancer*, **66**, e27506.

Wolden, S.L., Chen, L., Kelly, K.M., Herzog, P., Gilchrist, G.S., Thomson, J., Sposto, R., Kadin, M.E., Hutchinson, R.J. & Nachman, J. (2012) Long-term results of CCG 5942: a randomized comparison of chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma–a report from the Children's Oncology Group. *Journal of Clinical Oncology*, **30**, 3174–3180.

Zhou, R., Ng, A., Constine, L.S., Stovall, M., Armstrong, G.T., Neglia, J.P., Friedman, D.L., Kelly, K., FitzGerald, T.J. & Hodgson, D.C. (2016) A comparative evaluation of normal tissue doses for patients receiving radiation therapy for Hodgkin lymphoma on the childhood cancer survivor study and recent Children's Oncology Group trials. *International Journal of Radiation Oncology Biology Physics*, **95**, 707–711.