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REVIEW ARTICLE

New Agents, Emerging Late Effects, and the Development of Precision Survivorship

Eric J. Chow, Zoltan Antal, Louis S. Constine, Rebecca Gardner, W. Hamish Wallace, Brent R. Weil, Jennifer M. Yeh, and Elizabeth Fox

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Eric J. Chow, MD, MPH, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, M4-C308, PO Box 19024, Seattle, WA 98109; e-mail: ericchow@u.washington.edu.

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ABSTRACT

Incremental improvements in the treatment of children and adolescents with cancer have led to 5-year survival rates reaching nearly 85%. In the past decade, impressive progress has been made in understanding the biology of many pediatric cancers. With that understanding, multiple new agents have become available that offer the promise of more-effective and less-toxic treatment. These include agents that target various cell surface antigens and engage the adaptive immune system, as well as those that interfere with key signaling pathways involved in tumor development and growth. For local control, surgery and radiation techniques also have evolved, becoming less invasive or featuring new techniques and particles that more precisely target the tumor and limit the dose to normal tissue. Nevertheless, targeted agents, like conventional chemotherapy, radiotherapy, and surgery, may have off-target effects and deserve long-term follow-up of their safety and efficacy. These include injury to the endocrine, cardiovascular, and immunologic systems. New radiation and surgical techniques that theoretically reduce morbidity and improve long-term quality of life must also be validated with actual patient outcomes. Finally, with advances in genomics, information on host susceptibility to late effects is beginning to emerge. Such knowledge, coupled with improved metrics that better describe the spectrum of potential late effects across the entire lifespan, can lead to the development of decision models that project the potential long-term health outcomes associated with various treatment and follow-up strategies. These developments will help extend the current focus on precision medicine to precision survivorship, where clinicians, patients, and families will have a better grasp of the potential risks, benefits, and tradeoffs associated with the growing number of cancer treatment options.

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INTRODUCTION

Almost 85% of children diagnosed with cancer will become long-term survivors.[1] Nevertheless, many cancers remain difficult to treat, with survival rates < 70% (Fig 1). Other cancers are highly curable but still rely on treatments that cause significant long-term toxicities. In recent years, a better understanding of the biology of many pediatric cancers has led to the development of multiple new agents that offer the promise of more-effective and less-toxic treatment (Table 1). For local control, surgery and radiotherapy also have evolved, becoming less invasive or featuring new techniques and particles that more precisely target the tumor and limit the dose to normal tissues. Nevertheless, targeted agents, like conventional chemotherapy, radiotherapy, and surgery, may have off-target effects, and it will be important to follow children long-term for incidental late effects and to develop precision survivorship. This is survivorship that incorporates host genetics and statistical approaches that improve clinicians' and patients' understanding of the potential trade-offs between different treatment regimens with similar oncologic efficacy but varying toxicity profiles.

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EVOLVING APPROACHES FOR PEDIATRIC CANCER TREATMENT

Hematologic Malignancies

Although outcomes for pediatric leukemia and lymphoma have improved substantially due in large part to combination chemotherapy, acute myeloid leukemia (AML) and relapsed disease in general remain difficult to cure. However, new targeted agents are leading to promising options for some of these patients. An initial success came in Philadelphia-positive acute lymphoblastic leukemia

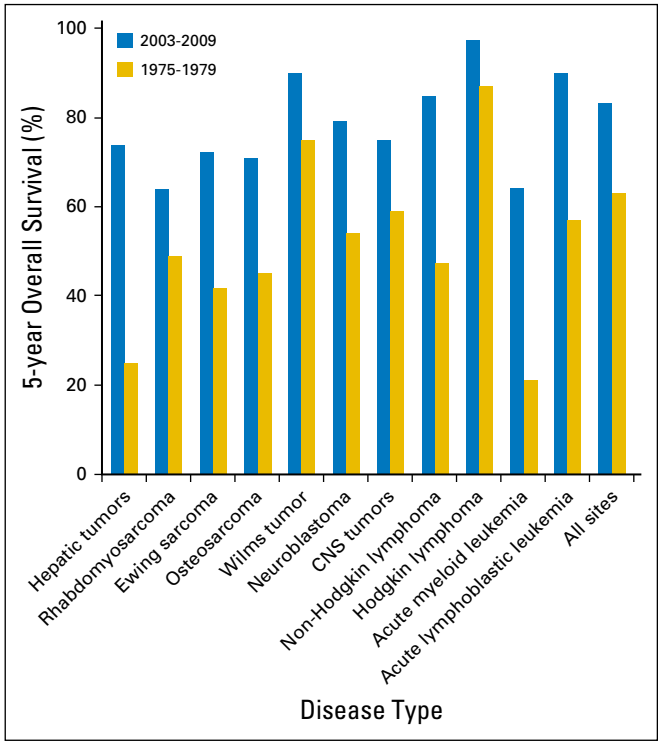

Fig 1. Five-year survival rates for two time periods for patients with pediatric cancer diagnosed from birth to 19 years old. Five-year survival is presented for all sites (International Classification of Childhood Cancers) and specific histologic subtypes contrasting outcome for children with cancer diagnosed between 1975 and 1979 with those with cancer diagnosed between 2003 and 2009. Data obtained from the National Cancer Institute SEER program from nine SEER registries on the basis of patient cases observed through 2010. Reprinted with permission.[1] 2014 American Society of Clinical Oncology. All rights reserved.

(Ph-positive ALL), where imatinib plus chemotherapy improved the 3-year event-free survival to 80% (*v* 35% historically).[2] Many of these patients are now able to avoid hematopoietic cell transplantation. With the discovery of a large subset of patients with high-risk ALL with gene expression profiles similar to Ph-positive ALL, current studies are now incorporating tyrosine kinase inhibitors (TKI) with up-front chemotherapy.[3] Combining TKIs with conventional chemotherapy is also occurring in AML and lymphoma treatments. On the basis of promising adult data,[4] sorafenib is being tested in children with newly diagnosed AML with *FLT3*-internal tandem duplication mutations. Crizotinib, a TKI with specificity for anaplastic large-cell kinase, has demonstrated 90% response rate with durable remissions as a single agent in children with relapsed anaplastic large-cell lymphoma.[5]

Adding antibodies to chemotherapy also is improving the treatment of leukemias and lymphomas. In mature B-cell lymphoma, rituximab plus chemotherapy conferred a 1-year event-free survival rate of 94.2% versus 81.5% with chemotherapy alone.[6] Brentuximab, an antibody drug conjugate targeting CD30, has shown high response rates in both anaplastic large-cell and Hodgkin lymphomas and has largely become standard of care for relapsed and refractory Hodgkin.[7,8] It is now being tested as part of up-front treatment. Gemtuzumab ozogamicin (CD33 with calicheamicin) has been making a resurgence in the treatment of AML,[9] and the development of inotuzumab ozogamicin (CD22 with calicheamicin) is showing promise in ALL.[10] Antibody therapy targeting immune checkpoints may also become more commonplace. Pembrolizumab targets programmed cell death protein 1 (PD-1) and has been approved by the US Food and Drug Administration for refractory or relapsed Hodgkin lymphoma, while ongoing studies are investigating both PD-1 and cytotoxic T-lymphocyte associated protein 4 (CTLA4) inhibition.

T-cell–based immunotherapy is also undergoing intensive investigation. In phase II studies, blinatumomab, a bispecific antibody targeting both CD19 and CD3 (which facilitates T-cell–directed killing of CD19-positive leukemia cells), has demonstrated a 27% complete response.[11] Alternatively, genetically engineered chimeric antigen receptor (CAR) T cells allow for the direct targeting of tumor cells, with the potential for lifelong activity through in vivo persistence of the CAR T cells. Trials in relapsed pediatric ALL have shown complete remission rates > 80%, and CAR T-cell technology is being applied to target other liquid tumors as well.[12-14]

Solid Tumors

Outcomes for pediatric solid tumors also have improved over the past decades. However, significant disparities remain, and treatment of patients with metastases or relapse remains challenging. Nevertheless, treatment of high-risk neuroblastoma exemplifies how a deeper understanding of tumor biology can improve survival. On a backbone of cytotoxic chemotherapy, radiotherapy, and surgery, dinutuximab, a monoclonal antibody targeting disialoganglioside GD2 expressed on neuroblastoma, combined with immunomodulatory (aldesleukin, sargramostim) and differentiating (isotretinoin) agents, have improved the 5-year overall survival of children with high-risk neuroblastoma from < 30% to approximately 50%.[15,16] However, acute toxicities are extensive, including capillary leak and neuropathic pain.

Clinical trials have recently demonstrated that identifying genomic alterations in pediatric solid tumors and selecting appropriately targeted therapy are feasible.[17] The National Cancer Institute and the Children's Oncology Group are conducting Pediatric MATCH (Molecular Analysis for Therapy Choice), a phase II basket trial, in which patients with relapsed solid tumors receive drugs paired to specific tumor molecular abnormalities (Fig 2).[17] Other targeted agents being tested in children include larotrectinib for infants with fibrosarcoma or mesoblastic nephroma harboring *NTRK* fusions[18]; crizotinib for neuroblastoma, anaplastic large-cell lymphoma, or inflammatory myofibroblastic tumors associated with anaplastic lymphoma kinase aberrations[5]; and the *RET* inhibitor vandetanib for medullary thyroid cancers associated with multiple endocrine neoplasia 2B and germline *RET* mutations.[19] The drug development paradigm for targeted agents encourages aggressive symptom management of on-target toxicity, because manifestation of these toxicities can sometimes correlate with increased drug efficacy.[20]

Investigation of immune checkpoint inhibitors is ongoing.[21] Thus far, serious immune-related toxicities observed in adults seem to be less common in children.[22,23] However, duration of exposure of these inhibitors in children has been limited to date. New cytotoxic agents with novel mechanisms of action, such as selinexor,[24] or new formulations of existing cytotoxic agents, such as doxorubicin,[25] irinotecan,[26] or tubulin-binding agents,[27] are in clinical trials. Antibody drug conjugates that target highly potent

Table 1. Molecularly Targeted Agents Being Used or Under Consideration for Pediatric Cancers

Target	Drug	Notable Toxicities*
ALK/ROS1	Ceritinib Crizotinib Ensartinib	Arrhythmia Hyperglycemia (ceritinib) Neuropathy/neuromuscular Pulmonary embolism (crizotinib) Respiratory Vision changes
BCR-ABL1, *KIT*, PDGFR	Dasatinib Imatinib Nilotinib Ponatinib	Cardiac dysfunction Edema, effusions Growth and stature* Pulmonary hypertension (dasatinib) Thyroid dysfunction Vascular events, including myocardial ischemia, peripheral arterial occlusion, and stroke (ponatinib)
BRAF	Dabrafenib Vemurafenib	Hyperglycemia (dabrafenib) New acute development of skin cancers QT prolongation (vemurafenib) Radiation sensitivity
CD3	Blinatumomab	B-cell aplasia (CAR T cells)* Cytokine release syndrome Neurotoxicity
CD19	Blinatumomab CAR T cells	Same as with CD3-targeted agents above
CD20	Rituximab	B-cell aplasia
CD30	Brentuximab vedotin	Neuropathy Progressive multifocal leukoencephalopathy
CD33	Gemtuzumab ozogamicin	Hepatotoxicity, sinusoidal obstruction syndrome
CDK	Palbociclib Ribociclib	QT prolongation (ribociclib)
EZH2	Tazemetostat	Limited experience to date
GD2	Dinutuximab 3F8 Hu14.18K322A	Capillary leak syndrome Neuropathic pain Reversible posterior leukoencephalopathy
HDAC	Entinostat Vorinostat	Pulmonary embolus, QT prolongation (vorinostat; limited experience for entinostat)
MEK/MAPK	Selumetinib Trametinib	Cardiac dysfunction Skin toxicity Vision changes, retinopathy
mTOR	Everolimus Sirolimus Temsirolimus ABI-009 (Nab-Rapamycin)	Dyslipidemia Hyperglycemia
PD-1, PDL-1, CTL4 (immune checkpoint)	Atezolizumab Avelumab Durvalumab Ipilimumab Nivolumab Pembrolizumab JS001 MEDI4736	Autoimmune/inflammatory, including: Endocrinopathies Myocarditis Neurotoxicity Pneumonitis
PI3K	CUDC-907 LY3023414	Hyperglycemia
TRK	Entrectinib Larotrectinib	Limited experience to date
VEGF, VEGFR, PDGFR, *RET*	Axitinib Bevacizumab Cabozantinib Lenvatinib Sorafenib Vandetanib	Cardiac dysfunction Hemorrhage, impaired wound healing Hypertension, proteinuria Intestinal perforation/fistula (bevacizumab) Thromboembolism Thyroid dysfunction (axitinib, sorafenib)

Abbreviations: CAR, chimeric antigen receptor; CDK, cyclin dependent kinase; CTL4, cytotoxic T-lymphocyte associated protein 4; HDAC, histone deacetylase; MAPK, mitogen activated protein kinase; mTOR, mechanistic target of rapamycin; PD-1, programmed cell death protein 1; PDGFR, platelet-derived growth factor receptor; PDL-1, PD-1 ligand; PI3K, phosphatidylinositol 3-kinase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
*Toxicities that may persist well after cessation of therapy or develop later.

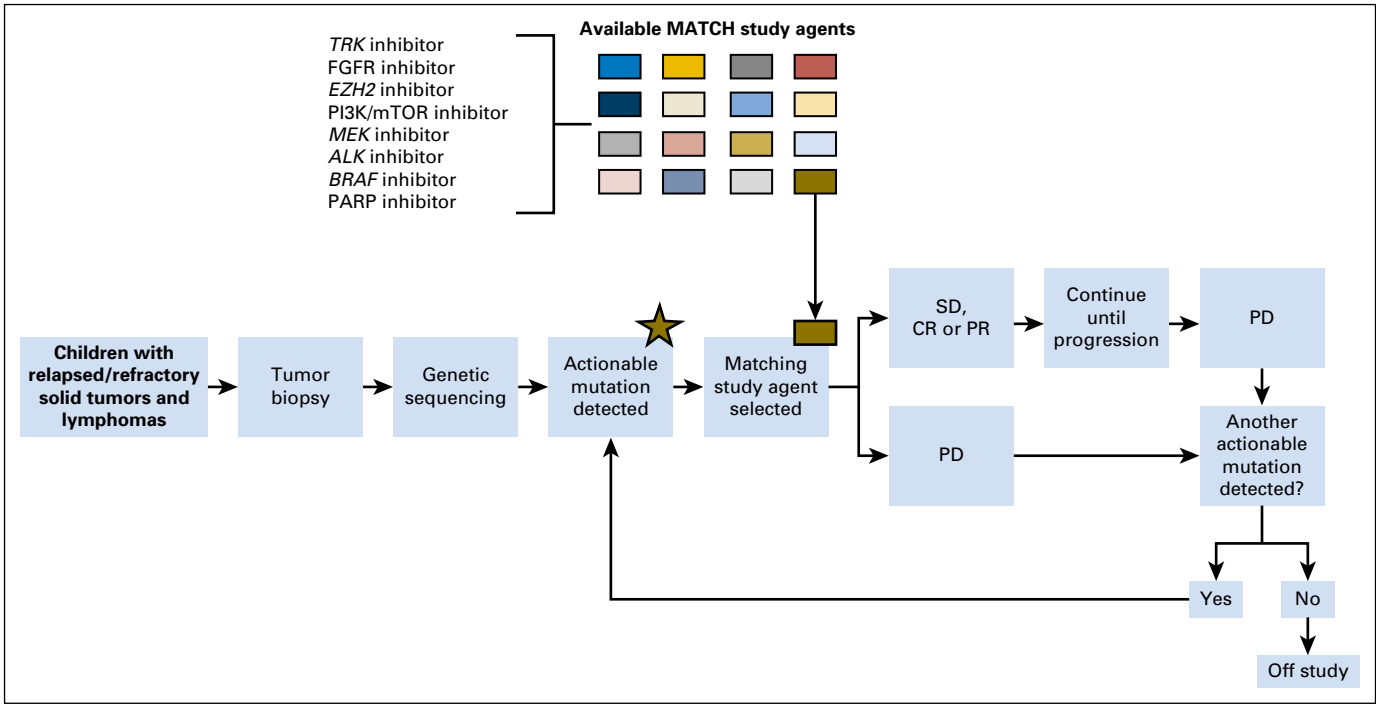

Fig 2. National Cancer Institute–Pediatric MATCH (Molecular Analysis for Therapeutic Choice) trial schema. CR, complete response; FGFR, fibroblast growth factor receptor; mTOR, mechanistic target of rapamycin; PARP, polyadenosine diphosphate-ribose polymerase; PD, progressive disease; PI3K, phosphatidylinositol 3-kinase; PR, partial response; SD, stable disease. Reprinted with permission.[17]

cytotoxic drugs to cell surface receptors such as lorvotuzumab mertansine (linking an antimitotic agent, DM1, to an anti-CD56 antibody) also are in development.[28] As new agents emerge for pediatric solid tumors, it will be essential to systematically follow patients long term to determine if there are significant expected and unexpected late effects. An example of this is the Children's Oncology Group study ALTE15N2 (ClinicalTrials.gov identifier: NCT03057626), which seeks to determine the full spectrum of late effects in the emerging generation of high-risk survivors of neuroblastoma treated with contemporary therapy.

Radiotherapy

Although use of radiotherapy has declined, it remains an essential part of treatment of many pediatric cancers.[29,30] Children treated with radiotherapy are most commonly given external beam radiation, although brachytherapy, radioisotopes, or combinations of these continue to be appropriate in select settings. The delivery of external beam radiation has been refined with conformal techniques that use modern imaging methods (primarily computed tomography) to provide three-dimensional definitions of the target and surrounding normal tissues and information about tissue density and depth from the skin. Radiation beams are then created that conform the dose distribution to the target.

Intensity-modulated radiation therapy (IMRT) is a three-dimensional conformal radiation therapy planning and delivery tool that more precisely shapes the radiation dose distribution around the target, which can help further decrease the dose to adjacent normal structures (Fig 3). With IMRT, the physician determines radiation treatment parameters to maximize dose to the target and minimize dose to normal tissues, and the planning algorithm optimizes the adherence to these parameters by modifying the beam spatially and/or temporally. However, IMRT generally results in a greater deposition of low doses to normal tissues surrounding the target (because of the multiple beams used; Table 2).[31] This conceptually could increase the risk of second malignancies. However, clinical data supporting this concern are lacking, whereas the general concept that decreasing dose to adjacent organs is beneficial has been validated.[32,33]

Standard radiation is delivered with photons created by linear accelerators. Another approach is charged-particle irradiation (eg, protons). Charged particles stop abruptly in tissues, so there is less exit radiation dose through normal tissue. Although theoretically promising (Fig 3; Table 2),[34] the benefits of protons in reducing radiation-associated malignancies and other late effects remain under study.[31,35,36] Moreover, the energy deposition into normal tissues with the use of proton therapy is still being studied; increased energy deposition (or its biologic consequences) may be responsible for adverse effects.[37]

PENTEC (Pediatric Normal Tissue Effects in the Clinic) is a key initiative within the radiation oncology community to develop evidence-based guidelines for radiation dose-volume tolerances in multiple organ systems of children. These guidelines will consider the age-associated vulnerability of these normal tissues to the effects of radiation plus the impact of chemotherapy, surgery, and host genetics.[38] Moreover, the possibility that radiation can augment systemic immune responses is being explored.[39]

Surgery

Surgical procedures performed for the diagnosis, staging, and treatment of childhood cancer can lead to long-term functional

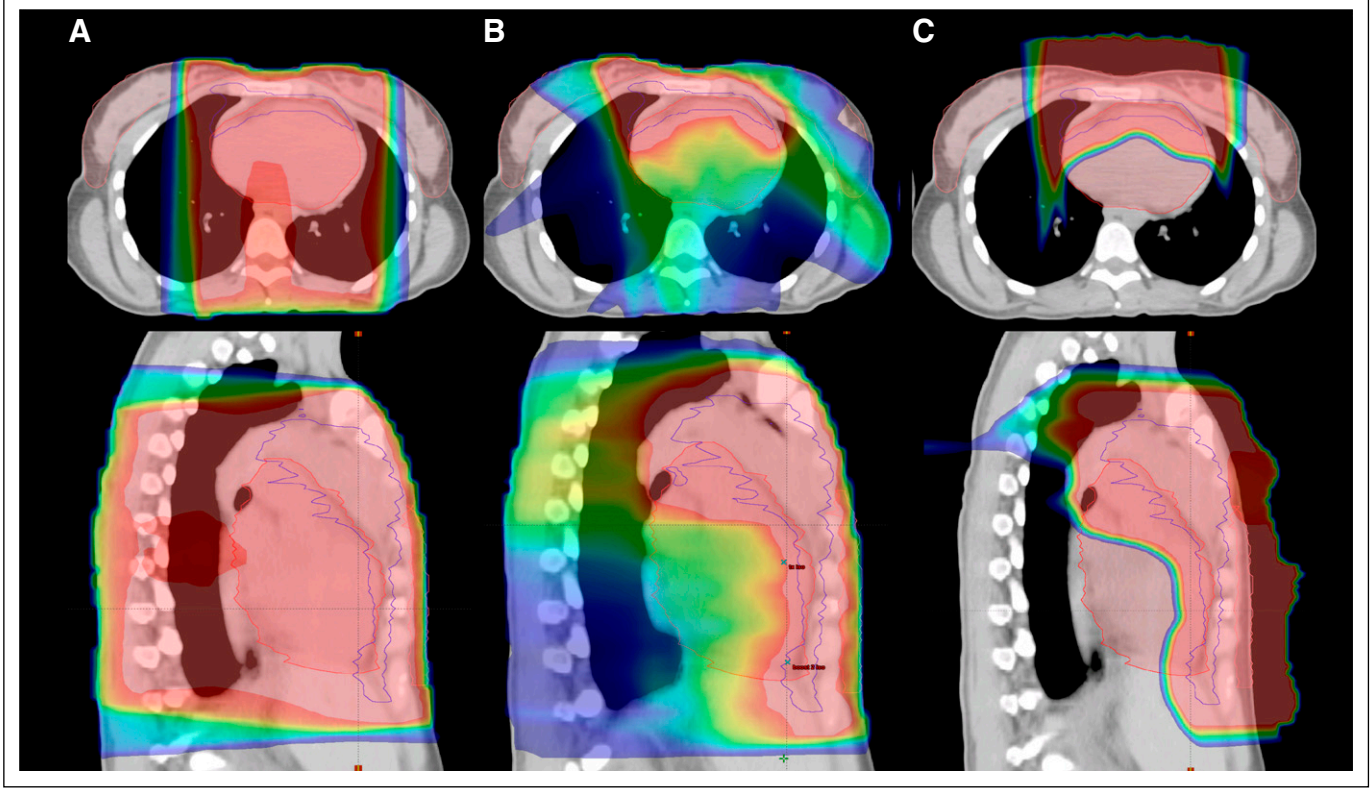

Fig 3. Radiotherapy treatment plan for representative patient with Hodgkin lymphoma across different radiation modalities. (A) Three-dimensional conformal radiotherapy, (B) intensity-modulated radiotherapy, (C) proton therapy. The colorwash dose distributions are indicated by (from lower to higher doses) blue, green, yellow, and red shading. The thin colored lines outline the heart (red), breasts (pink), and the clinical target volume (blue). Top row shows axial views and bottom row shows sagittal views. Reprinted with permission.[34]

consequences, disfiguration with psychosocial impact, and late-occurring complications. A desire to minimize this impact and preserve long-term quality of life has been implicit within many modern surgical trends. These include advancements with laparoscopy and thoracoscopy, limb salvage procedures, and image-guided biopsy techniques. Relative to open operations, laparoscopy and thoracoscopy can minimize long-term effects by improving functional outcomes (eg, improved chest wall growth/function), limiting psychosocial impact (eg, smaller scars/less disfiguration), and minimizing the frequency of late complications (eg, late intestinal obstructions known to occur in 5% of children with abdominopelvic tumors).[40,41] In addition, advancements in limb salvage techniques, now possible in > 80% of cases of osteosarcoma at specialized centers, may improve long-term function for children with extremity tumors.[42] This includes use of expandable internal prostheses and novel operations such as rotationplasty.[43] Finally, improvements in image-guided biopsy techniques and pathologic interpretation have reduced the need for large, morbid operations for diagnosis or staging, sparing children the potential long-term consequences of these procedures.[44]

However, as surgical techniques evolve to reduce long-term effects, it is critical to ensure that oncologic outcomes are not compromised. This includes studying the use of laparoscopy/thoracoscopy for Wilms tumor and osteosarcoma pulmonary

Table 2. Weighted Average Difference in Radiation Dose to Various Organs at Risk by Different Radiation Modalities Used for Lymphoma

	m-RT v 3D-RT		PT v 3D-RT		PT v m-RT	
Organ	No. Patients	Difference*	No. Patients	Difference*	No. Patients	Difference*
Heart	103	−1.4 Gy	123	−3.6 Gy	103	−2.2 Gy
Thyroid	89	+1.6 Gy	99	−1.4 Gy	103	−2.1 Gy
Breast	84	+1.1 Gy	104	−1.5 Gy	84	−2.4 Gy
Lungs	103	+0.4 Gy	123	−2.8 Gy	103	−3.3 Gy
Lung V20	56	−11%	76	−9%	56	0%

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Abbreviations: 3D-RT, three-dimensional conformal radiotherapy; m-RT, compared with conventional 3D-RT, more modern modalities, such as intensity-modulated and related techniques; PT, proton therapy; RT, radiotherapy; V20, volume receiving ≥ 20 Gy.
*Negative value favors the former *v* latter modality; positive value is the opposite. For example, −1.4 Gy for heart m-RT *v* 3D-RT means that on average, use of an m-RT plan reduced heart dose by 1.4 Gy compared with a 3D-RT plan.

metastases.[41,45] Verification that long-term functional and psychosocial outcomes truly are superior (eg, limb-sparing techniques *v* amputation) also is necessary.[43,46]

POTENTIAL NEW LATE EFFECTS

Endocrine

Select endocrine late effects are beginning to emerge among children treated with targeted agents. TKIs have been associated with growth deceleration and alterations in bone mineral and thyroid metabolism. Children treated with imatinib for chronic myeloid leukemia (CML) have demonstrated varying degrees of growth restriction. Effects on growth seem to be more significant when treatment is initiated before puberty.[47] The mechanism for the growth deceleration is unclear, but may be due to disrupted growth hormone signaling, inadequate signal transduction through the insulin-like growth factor 1 (IGF-1) receptor (a tyrosine kinase receptor), or inhibition of platelet-derived growth factor receptor signaling and disrupted chondrocyte recruitment at the growth plates.[48]

Off-target inhibition by TKIs of platelet-derived growth factor receptor and the macrophage colony-stimulating factor receptor c-fms may alter bone remodeling by affecting the differentiation and activity of osteoblasts and osteoclasts.[48] Reduced serum calcium and phosphorus levels, vitamin D deficiency, and secondary hyperparathyroidism have been noted in children with CML receiving imatinib.[49] However, these derangements do not always correlate with low bone mineral density.[50] Further studies are needed to elucidate any loss of final adult height in children treated with imatinib. However, routine measurements of IGF-1 or formal growth hormone stimulation testing are not currently recommended, particularly given concerns about growth hormone exposure during active cancer treatment.

Although case series in children treated with imatinib have reported normal thyroid function, other TKIs may affect thyroid function. In adult studies, nilotinib, dasatinib, sunitinib, and sorafenib have been associated with de novo hypothyroidism, variably preceded by hyperthyroidism.[51] Children receiving TKIs should have their thyroid function closely monitored.

At present, the effects of targeted agents on male and female reproductive function are largely unknown. In CML, pregnancy presents specific management and therapeutic challenges. There are limited data on the safety of TKIs in pregnancy and their effects on fertility. There have been some reports of congenital malformations and spontaneous abortions associated with imatinib therapy.[52] There are also concerns that inhibitors of angiogenesis (eg, bevacizumab, a vascular endothelial growth factor [VEGF] inhibitor) may affect ovarian follicle development.[53] It will be important to assess long-term gonadal function and fertility of patients receiving new targeted agents. Patients of childbearing age should be made aware of established fertility options that are available, including semen cryopreservation, ovarian or oocyte retrieval and storage, and embryo cryopreservation.[54]

Finally, late endocrine effects of immune checkpoint inhibitors in children are unknown, but these agents have been associated with hypophysitis and anterior pituitary deficiencies in adults.[55] Thyrotropin deficiency has been the most common, followed by adrenocorticotropin and gonadotropin deficiencies. Although thyrotropin deficiency may resolve, adrenocorticotropin deficiency often persists and requires long-term steroid replacement.

Cardiovascular

Although left ventricular dysfunction/cardiomyopathy and accelerated atherosclerosis are known complications of anthracyclines and chest radiation, respectively,[56] the late cardiovascular effects of novel agents described above remain largely unknown in survivors of childhood cancer. Most cardiovascular events reported in adult patients with cancer have typically occurred while receiving therapy or soon after. TKIs, particularly later-generation agents such as nilotinib, dasatinib, and ponatinib, have been associated with an increased risk of pulmonary hypertension (dasatinib) and vascular events (particularly ponatinib), including myocardial ischemia, peripheral arterial occlusive disease, and stroke.[57] Crizotinib has been associated with arrhythmia in adults.[58] VEGF inhibitors (eg, bevacizumab) and TKIs with anti-VEGF activity (eg, sunitinib, sorafenib) have been strongly associated with hypertension in adult patients and, less commonly, thromboembolic events and heart failure.[58] Hypertension with these agents has only been occasionally reported in pediatric patients, but nowhere near the rates seen in adults.[59] Mechanistic target of rapamycin inhibitors (eg, temsirolimus) can cause dyslipidemia and hyperglycemia.[60] Finally, rare autoimmune myocarditis has been reported after immune checkpoint inhibitor therapy in adults.[61]

Increased emphasis also has been placed on developing less cardiotoxic versions of conventional cytotoxic agents and effective prevention strategies. Given data that traditional cardiovascular risk factors (eg, hypertension, dyslipidemia, diabetes) synergistically potentiate the cardiotoxic effects of anthracycline and radiation therapies in children,[62] improved control of these conditions should be a focus of survivorship efforts.

Immunologic

B-cell depletion occurs with agents that target B-cell antigens (eg, rituximab, blinatumomab). Although B-cell aplasia is usually short term, there is a potential for long-term B-cell aplasia in patients who have CAR T-cell persistence.[12-14] The health impact of prolonged B-cell aplasia is unclear but believed to be minimal so long as affected patients receive ongoing immunoglobulin replacement to minimize infectious risks. However, long-term financial costs may be important as these treatments become more widespread. To date, there have not been any reports of lymphoproliferative disorders or secondary malignancies directly related to CAR T-cell products. In addition, with gene therapy as a new field, it is possible new late effects will be uncovered. Finally, even conventional cytotoxic therapy may be associated with alterations in immunity that persist well after neutrophil recovery (eg, selective B- and T-cell subpopulations may remain depressed years after therapy).[63] Adding immune-modulating therapies may further affect normal immune reconstitution.

Development of Precision Survivorship

Five-year survival is a common oncology benchmark. However, with most children expected to survive decades after therapy,

consideration of longer-term health quality should be emphasized. Metrics such as the cumulative burden of disease may provide a more complete picture of long-term health after cancer therapy.[64] Given the interindividual variation in risks of late effects, further insights also may arise from genomics (Table 3). Large-scale genome-wide association studies have identified potential markers for multiple adverse outcomes, including cardiotoxicity,[65,66] secondary cancers,[67,68] ototoxicity,[69] and reduced ovarian reserve.[70] Using such genetic information may eventually help predict risk, individualize therapy, and reduce adverse outcomes among children with cancer. However, many genetic findings need to be replicated, and there needs to be alternative but similarly effective cancer treatments for those at increased genetic risk for toxicities associated with standard treatment.

Table 3. Published Genetic Associations for Selected Late Effects in Survivors of cancer

Late Effect	Gene, Alphabetical	First Author, Alphabetical (PMID)*
Cardiomyopathy	*ABCB1*, *ABCB4*, *ABCC1*†, *ABCC2*, *ABCC5*†	Armenian (23927520)
	CAT	Aminkeng (26237429)‡
	CBR3†	Blanco (18457324, 22124095)‡
	CELF4†§	Cascales (23576480)
	CYBA	Hertz (26799497)
	FMO2	Krajinovic (26345518)‡
	HAS3†§	Leger (26968791)
	HFE†	Lipshultz (23861158)‡
	HNMT	Rajic (19863340)‡
	NCF4†	Rossi (19448608)
	NOS3	Schneider (27993963)
	PRDM2†	Semsei (21929509)‡
	RAC2	Visscher (21900104, 23441093, 26230641)‡
	RARG†§	Vulsteke (26017071)
	SLC10A2	Wang (24470002, 26811534)‡
	SLC22A17†, *SLC22A7*†, *SLC28A3*†	Wells (28542097)
	SPG7	Wojnowski (16330681)
	UGT1A6†	
	rs28714259 (intergenic)†	
Endocrine		
Fertility	*AR*	Eberhard (15105386)
	ER	Romerius (21430602)‡
	BRSK1	van Dorp (23360674)‡
Obesity	*CDH18*	Ross (15337805)‡
	FAM155A	Wilson (25963547)‡
	GLRA3	
	LEPR	
	SOX11	
Bone density/osteonecrosis	*ACP1*	Bernbeck (14677097)‡
	BMP7†	Bond (21885611)‡
	CRHR1	Finkelstein (27957785)‡
	ESR1	French (18285546)‡
	GRIN3A†	Jones (18565889)‡
	MTHFR	Karol (26265699, 26590194)‡
	MTRR	Kawedia (21148812)‡
	PROX1†	Kechli (10064667)‡
	RAPGEF5	Park (26856247)‡
	SERPINE1	Relling (15459215)‡
	TS†	te Winkel (20015871, 20955826)‡
	VDR	
Neurosensory		
Cisplatin ototoxicity	*ABCC3*	Brown (26400460)‡
	ACYP2†	Choeyprasert (23274376)‡
	COMT†	Hagleitner (25551397)‡
	GST family (e.g., *M1*, *P1*, *TT1*)†	Oldenburg (17228018)
	NFE2L2	Lanvers-Kaminsky (25823781)‡
	OTOS	Peters (11081456)‡
	SLC22A2†	Pussegoda (23588304)‡
	SOD2	Rednam (23065688)‡
	TPMT†	Ross (19898482)‡
	WFS1†§	Spracklen (25410892, 27457817)
		Thiesen (28445188)‡
		Vos (26928270)‡
		Wheeler (28039263)
		Xu (25665007)‡
		Yang (23820299)‡

(continued on following page)

Table 3. Published Genetic Associations for Selected Late Effects in Survivors of cancer (continued)

Late Effect	Gene, Alphabetical	First Author, Alphabetical (PMID)*
Cognitive function/behavior	*ABCC1*	Barahamani (18952980)‡
	APOE4	Brackett (22661588)‡
	COMT	Cole (25987702)‡
	ERCC4	Howarth (23956130)‡
	GST family (e.g., *M1*, *P1*, *TT1*)†	Kamdar (21618410)‡
	IL16	Krull (23650422)‡
	IRS1	Liu (25904748)
	MAOA	Marcoux (23612386)‡
	MS	
	MTHFR	
	NOS1, *NOS3*	
	POLE	
	SLCO2A1	
	TSER	
Second cancers	*BRCA2*	Best (21785431)‡
	ERCC1	Ma (22144180)
	FGFR2	Morton (29059430)‡
	POLD1	Relling (10406363)‡
	PRDM1†	Wang (28976792)‡
	rs4342822 (*PROX1*, nearest gene)	
	TP53	
	TPMT	
	XRCC1	

NOTE. Only studies based on human samples, as identified from PubMed as of November 1, 2017; studies based only on cell lines or drug pharmacokinetics are not listed.
Abbreviation: PMID, PubMed.gov identification number.
*Includes studies that reported null findings.
†Polymorphism in the gene has been associated with the phenotype in at least one separate sample/population.
‡Studies where the population was > 50% survivors of childhood cancer.
§Evidence for an association from in vitro (i.e., functional) experiments.

Although randomized clinical trials have been the gold standard for the investigation of new therapeutic approaches, the rarity of childhood cancer and the long latency needed to observe late effects limit the feasibility of prospective trials to evaluate a precision-medicine approach to survivorship. By synthesizing evidence from all available sources, including randomized trials, observational studies, meta-analyses, and expert opinion, decision models can provide a valuable analytic framework for simulating health outcomes associated with various treatment and follow-up strategies.[71] Decision models have been used by the US Preventive Services Task Force to inform evidence-based recommendations, including the screening of common adult cancers and chronic disease prevention approaches.[72]

Decision models may be particularly well-suited to estimate the benefits, risks and trade-offs associated with alternative treatment approaches for childhood cancer, where short-term efficacy and late toxicity risks are uncertain, but informative data from large survivor cohort studies are available to augment expert opinion. Such models are typically based on outcomes such as life-years or quality-adjusted life-years and could also incorporate genetic information that enhances prediction of individual late effects.

In conclusion, although the majority of new agents are still primarily being tested in patients with relapsed disease as part of phase I and II studies, over time some agents will demonstrate sufficient promise to become more widely used in patients with newly diagnosed disease. Drugs such as imatinib, blinatumomab, brentuximab, dinutuximab, gemtuzumab ozogamicin, rituximab, and sorafenib have already achieved this milestone in pediatric oncology. Similarly, growing numbers of children are being treated with IMRT and proton therapy and experiencing less-invasive surgeries. Although these new agents, surgical and radiation techniques, and their combinations offer the promise of improving cancer outcomes for children, they may have unanticipated late effects. Children tend to have fewer medical comorbidities but also developing bodies, which impact their vulnerability to therapy and can make extrapolations from adult data problematic. Therefore, it will be important to maintain long-term follow-up of children being treated with these new technologies, particularly because the numbers of children exposed to any single agent or modality may be more limited than those treated historically when there were fewer therapeutic options. Resources to enable long-term follow-up are critical, because most oncology clinical trials have limited follow-up and focus more on acute toxicities. Leveraging population-based cohorts and registries can also help. Given the rarity of pediatric cancers, international collaboration is essential, particularly as treatments become more refined and individualized on the basis of tumor and host biology.[73] Development of classification systems explicitly for late effects may increase the comparability of outcomes among future studies.[74] Finally, with the advances in precision medicine, the concurrent development of precision survivorship is the logical outgrowth of efforts to better understand the spectrum of late effects, genetic susceptibility, and individual family/patient preferences toward the potential risks, benefits, and tradeoffs associated with different cancer treatment choices.

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AUTHOR CONTRIBUTIONS

Conception and design: All authors
Administrative support: Eric J. Chow
Data analysis and interpretation: All authors
Manuscript writing: All authors
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Accountable for all aspects of the work: All authors

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Affiliations

Eric J. Chow and **Rebecca Gardner**, Fred Hutchinson Cancer Research Center, Seattle Children's Hospital, and University of Washington, Seattle, WA; **Zoltan Antal**, Weill Cornell Medical College, New York Presbyterian Hospital, and Memorial Sloan Kettering Cancer Center, New York; **Louis S. Constine**, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY; **W. Hamish Wallace**, Royal Hospital for Sick Children, University of Edinburgh, Edinburgh, United Kingdom; **Brent R. Weil** and **Jennifer M. Yeh**, Boston Children's Hospital, Harvard Medical School, Boston, MA; and **Elizabeth Fox**, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA.

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New Agents, Emerging Late Effects, and the Development of Precision Survivorship

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Eric J. Chow
No relationship to disclose

Zoltan Antal
Speakers' Bureau: Novo Nordisk

Louis S. Constine
Honoraria: UpToDate, Springer, Lippincott
Travel, Accommodations, Expenses: IBA

Rebecca Gardner
Honoraria: Novartis, Medscape

W. Hamish Wallace
No relationship to disclose

Brent R. Weil
No relationship to disclose

Jennifer M. Yeh
No relationship to disclose

Elizabeth Fox
Travel, Accommodations, Expenses: Helsinn Therapeutics