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Relevance of Historical Therapeutic Approaches to the Contemporary Treatment of Pediatric Solid Tumors

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Abstract

Children with solid tumors, most of which are malignant, have an excellent prognosis when treated on contemporary regimens. These regimens, which incorporate chemotherapeutic agents and treatment modalities used for many decades, have evolved to improve relapse-free survival and reduce long-term toxicity. This review discusses the evolution of the treatment regimens employed for management of the most common solid tumors, emphasizing the similarities between contemporary and historical regimens. These similarities allow the use of historical patient cohorts to identify the late effects of successful therapy and to evaluate remedial interventions for these adverse effects.

Keywords

Childhood cancer therapy; late effects; long-term follow-up

Introduction

The prognosis of children and adolescents with solid tumors, most of which are malignant, has improved dramatically over the past five decades. For the most common of these

Conflict of Interest Statement

Drs. Green, Kun, Matthay, Meadows, Meyer, Meyers, Spunt, Robison, and Hudson affirm that they have no affiliations that they consider to be relevant and important with any organization that to any author's knowledge has a direct interest, particularly a financial interest, in the subject matter discussed. Such affiliations include, but are not limited to, employment by an industrial concern, ownership of stock, membership on a standing advisory council or committee, a seat on the board of directors, or being publicly associated with a company or its products.

tumors, five-year survival now exceeds 70%.[1] Although select patient groups require less morbid surgical procedures and abbreviated courses of chemotherapy, the majority need intensive systemic and multimodal local interventions that may cause unavoidable long-term toxicity.

Monitoring of the long-term health of survivors of pediatric solid tumors identifies cancer-related morbidities for which early detection, prevention, and remediation are needed. In a companion paper[2] in *Pediatric Blood and Cancer*, we recently described the evolution of major therapeutic trends for pediatric hematological malignancies. The current review provides a complementary overview of solid tumors that: 1) summarizes major trends in the evolution of pediatric solid tumor therapy since 1960; 2) identifies treatment-specific exposures in cohorts treated before 2000 that may affect patients treated on clinical trials during the past decade; and, 3) identifies the extent to which studies of cohorts of long-term survivors can predict the risk of late effects in patients receiving contemporary treatment.

Central Nervous System Tumors

Tumors of the central nervous system (CNS) are the most frequent group of non-hematopoietic tumors of children and adolescents. Therapeutic approaches for these tumors, and the evolution of these approaches, has differed according to tumor type, location and biology. Advances in neuroimaging, neuropathology, and neurobiology have better defined CNS tumors, and progress in neurosurgery, radiation therapy (RT) techniques, and incorporation of chemotherapy has improved disease control and functional outcomes.

Low grade gliomas (LGG) are the most common pediatric CNS tumors, and pilocytic astrocytoma is the dominant histology. Complete surgical resection is usually curative of cerebellar, cerebral, and thalamic lesions (Supplementary Table I). A prospective, multi-institutional, non-randomized study of LGG found eight-year survival to be 96%; progression-free survival (PFS) was 93% after gross total resection (GTR) but only 55% after incomplete resection. Overall survival was affected by site, as patients with optic chiasmatic/hypothalamic tumors fared less well.[3]

Optic chiasmatic/hypothalamic LGG are responsive to chemotherapy and RT but are problematic due to their central location, associated ophthalmic and endocrine impairment, younger age of onset, and association with neurofibromatosis type 1. By the 1970s, long-term disease control, often with preservation of vision, was achieved by RT[4]; subsequently, 10-year PFS rates approximated 75% in a non-randomized, single institution study after the introduction of three-dimensional RT techniques. [5] RT-related toxicities (especially neurovascular compromise and neurocognitive deficits in younger children) prompted the evaluation of primary chemotherapy in the 1990s.[6,7] Five-year PFS as high as 75% was achieved by treatment with vincristine (VCR) and carboplatin (CBDCA) (±-temozolomide), which are now the standard initial therapy for progressive or symptomatic centrally located LGG in younger children (Supplementary Table I).[8] Durable disease control may ultimately require post-progression RT.[5,9]

The most common malignant CNS tumor is medulloblastoma. Post-operative wide-field RT and staging (i.e., extent of resection and subarachnoid metastasis) cured more than 25% of children before 1970.[10] Improved surgery and craniospinal irradiation (CSI) (35 Gy) with a boost to the posterior fossa (54 Gy) resulted in five-year PFS rates of 60% – 70% for the more than 75% of children with average-risk disease (localized/M_0 with complete or near complete resection).[11,12] Reduction of CSI to 23.4 Gy in 13 fractions was demonstrated in a multi-institutional, randomized trial in the 1990s to be safe when cisplatin (CDDP)-based chemotherapy was added. Five-year EFS was 81%± 2.1% among average-risk cases, and did not differ significantly between those who received CDDP, VCR and CCNU and those who

received CDDP, VCR and cyclophosphamide (CTX) (Table I).[13,14] Modifications of RT technique and reduction of the volume of the boost to the tumor bed appeared to diminish the risk of neurocognitive deficits and ototoxicity in patients receiving three-dimensional conformal or intensity-modulated RT (3D-CRT, IMRT) and amifostine with CDDP further reduced ototoxicity.[15] For high-risk disease, dose-intensive chemotherapy (CDDP, CTX, VCR) with CSI to 36 – 39.6 Gy, or concurrent CBDCA with RT, achieved disease control rates of 65% – 70%.[16,17]

Management of CNS tumors in young children is particularly challenging. Clinical studies of primary chemotherapy for embryonal tumors (medulloblastoma, supratentorial primitive neuroectodermal tumors [PNET], and atypical teratoid/rhabdoid tumors [AT/RT]) in young children began in the 1980s.[18–20] Drug regimens included CDDP, etoposide (VP16), CTX, and VCR; the German HIT trials added high-dose systemic and intrathecal methotrexate. RT evolved from systematic delayed, response-adjusted CSI to planned local, 3D-CRT or IMRT, or proton beam regimens for M_0 tumors or elective, attenuated CSI for consolidation or salvage.[18,21] A recent multi-institutional, non-randomized treatment study reported five-year PFS of 58% ± 9% in medulloblastoma and 82% ±9% in resected M_0 tumors.[20]

Ependymomas present most commonly in the IVth ventricular region. Complete resection is curative for differentiated supratentorial ependymomas. [22] Long-term local disease control has been reported for 87.3% (95% confidence interval 77.5% – 97.1%) of patients who participated in a single institution, non-randomized study of high-dose 3D-CRT after maximal tumor resection. Local therapy shifted to RT even in younger children after studies indicated preservation of neurocognitive function (Supplementary Table II). [23,24] Radical resection, achievable in almost all cases, is sometimes associated with significant post-operative bulbar deficits. Adjuvant chemotherapy has yet to show a benefit in patients with resected ependymomas.

In summary, post-resection radiation remains a crucial component of therapy for most CNS tumor subtypes, although contemporary approaches optimize protection of normal tissues. Chemotherapy, introduced in the 1970s, has permitted the delay of CNS irradiation in young children and improved disease control when incorporated into combined-modality regimens for specific subtypes.

Retinoblastoma

Retinoblastoma (RB), the most frequent primary ocular tumor in children, may occur as nonheritable (usually unilateral) or heritable (usually bilateral) form.[25] Unilateral sporadic disease is curable by enucleation, and metastatic disease can usually be prevented by adjuvant chemotherapy. The heritable form, associated with a significant risk of second malignant neoplasm,[26] is identifiable by multifocal intra-ocular tumors or a positive family history. For these children, RT is recommended only when surgery, chemotherapy, and focal measures cannot preserve vision in at least one eye. However, 10%–15% of children with heritable RB have a single eye tumor and no family history of cancer [27] and are thus indistinguishable from patients with non-heritable, unilateral RB.

Until the 1990s [28] ophthalmologists were the primary caregivers for RB, as surgery was the main treatment [29] and could cure 95% or more of unilateral tumors. [30,31] Bilateral disease could be cured by enucleation and RT. The challenge of treating RB is to maximize long-term survival while preserving vision. Treatment with external-beam radiation therapy (EBRT) can usually preserve vision in at least one eye but causes severe orbital hypoplasia.[32] In the early 1990s, CBDCA and VP16 proved effective in reducing the volume of intra-ocular disease in bilateral RB.[33–35] With subsequent focal therapy (cryotherapy, thermotherapy, laser or scleral radioactive plaque), this approach allowed the

preservation of many eyes that would otherwise have required removal or EBRT (Supplementary Table III).[36]

Chemotherapy is used as an adjunct to surgery when there is high risk of metastasis, as in cases of optic nerve, massive choroidal, or scleral invasion.[37] The drugs most useful for chemoreduction include CBDCA, VCR, and VP16.[38] The addition of subconjunctival CBDCA to intravenous chemotherapy improves the rate of eye and vision salvage.[39] Newer RT modalities, such as IMRT and proton beam therapy, may enhance protection of normal tissues.[40,41] Some children with metastatic RB, involving the bone marrow and bones, may be cured by aggressive chemotherapy with the same drugs used for primary therapy and autologous hematopoietic cell transplantation (HCT).[42–44] As treatment of RB changed very little until the end of the 20th century, evaluation of the outcomes of historic therapies remains relevant.

Neuroblastoma

Neuroblastoma, the second most common solid tumor of childhood, behaves variably depending on the clinical and molecular features of tumor and host. In the 1960s, treatment for localized neuroblastoma included surgery with or without RT (Table II). Most patients presented with inoperable or metastatic disease, which was uniformly fatal. Early chemotherapy included large doses of vitamin B_{12} or actinomycin D (AMD). CTX and VCR were also evaluated, but neither improved survival.[45] Other agents available during the 1970s, including doxorubicin (DOX), DTIC, and peptichemio,[46] improved the outcome of metastatic disease only in infants <1 year of age. Other drugs, including the epipodophyllotoxins and CDDP, were shown during this period to produce tumor responses in patients with neuroblastoma.[47,48]

During the 1980s, cooperative group studies showed that neither chemotherapy nor RT was necessary for treatment of localized neuroblastoma,[49,50] ENREF 49 The relative radiosensitivity of neuroblastoma led to reduction of RT doses those with regional disease.[51] In the late 1980s, targeted RT with ^{131}I-mIBG was used extensively in Europe and the U.S. for relapsed neuroblastoma, with significant response rates.[52] Induction regimens that incorporated CDDP and epipodophyllotoxins produced response rates as high as 70%.[53] Ifosfamide (IFOS) and CBDCA were identified as agents with activity against neuroblastoma.[54] Myeloablative therapy followed by autologous or allogeneic HCT produced tumor responses in patients with recurrent neuroblastoma.[55] Immunotherapy for neuroblastoma was developed during this decade, with the production of murine monoclonal antibodies that targeted the GD2 ganglioside expressed on more than 95% of neuroblastoma cells.[56]

The theme of the 1990s was increased dose intensity. In a randomized trial, patients with high-risk neuroblastoma showed significantly improved EFS with myeloablative chemotherapy and autologous HCT.[57] However, the relapse rate was high, and the focus shifted to elimination of minimal residual disease (MRD). Patients treated with six months of the differentiating agent isotretinoin after either myeloablative therapy or chemotherapy had significantly better outcomes than those randomly assigned to no further treatment. The best survival was seen among children who received both HCT and isotretinoin.[57] New pilot studies of the chimeric Ch14.18 anti-GD2 and GM-CSF, and then with GM-CSF and interleukin-2 (IL-2), demonstrated that the antibody could be combined safely with these additional agents.[58]

Contemporary treatment of low- and intermediate-risk NB is similar to that used during previous decades, with continued reduction of intensity according to biologic risk factors. Targeted therapy with ^{131}I-mIBG for high-risk disease has been incorporated into large

cooperative trials.[59] The significant improvement in EFS, estimated from the date of autologous HCT (post-autologous HCT EFS), provided by myeloablative therapy followed by ch14.18, cytokines, and isotretinoin for MRD, as compared to isotretinoin alone (two-year post-autologous HCT EFS, 66% vs. 46%, P=0.01), will be the benchmark against which new therapies will be evaluated during the coming decade.[60] Future challenges are focused on overcoming resistance using targeted small molecules and immunomodulation, and reduction of the late complications of therapy.

Wilms Tumor

The management of Wilms tumor (WT), the most frequent primary renal tumor of children, has progressed from a solely surgical approach with a low survival rate[61] to multi-modality treatment with excellent long-term outcomes.[62,63] Before the effectiveness of AMD[64–68] was discovered, all patients received post-operative flank or whole-abdomen RT. Subsequent demonstration of the activity of VCR[69–71] and DOX[72–77] against WT, and early awareness of the adverse effects of high-dose, hemi-abdomen RT on young children,[78,79] provided the basis for refinement of therapy (Table III).

The initial randomized trials of the National Wilms Tumor Study (NWTS) Group, conducted between 1969 and 1978, employed age-adjusted abdominal RT doses.[80,81] Contemporary patients receive the lower doses (10.8 Gy) evaluated in NWTS-3 (1979–1986).[82] The benefit of combination chemotherapy with VCR and AMD was confirmed in NWTS-1, which randomly assigned patients to VCR or AMD only or to combination treatment.[80] In NWTS-2, the relapse rate was lower among patients treated with the VCR, AMD and DOX combination than among those treated with only VCR and AMD. This three-drug regimen included a cumulative DOX dose of 300 mg/m^2.[81] Contemporary patients treated with DOX, VCR, and AMD receive a lower cumulative dose of anthracycline (150 mg/m^2), which was shown in NWTS-4 (1986–1994) to produce relapse-free survival rates equivalent to those obtained with 300 mg/m^2.[62,63]

Treatment intensification based on loss of heterozygosity at 1p and 16q is being evaluated in current studies.[83] The number of children who receive abdominal RT has decreased substantially, and some patients treated with anthracyclines since 1994 have received the lower cumulative doses prescribed in contemporary regimens. Therefore, evaluation of outcomes of patients treated during the past three decades should provide information about the late effects resulting from more widespread adoption of trial-validated regimens and will serve as the baseline for comparison of the anticipated reduction of late morbidity after reduced–intensity treatment.

Rhabdomyosarcoma

Rhabdomyosarcoma is the most frequent histological subtype among children and adolescents with soft tissue sarcomas. Before the discovery of effective chemotherapy, surgery and RT alone were curative in approximately one-third of children with rhabdomyosarcoma (RMS).[84] In the 1960s, VCR,[70,85] AMD,[64,65] and CTX [86] were shown to produce tumor responses in childhood RMS. Studies combining these three agents quickly followed.[87–89] Today, VA (VCR and AMD) and VAC (VCR, AMD and CTX), the standard chemotherapy regimens for childhood RMS in the U.S., cure 70% of patients (Table IV).[90] Similar outcomes have been achieved in Europe with VA or IVA (IFOS and VA).[91] Although chemotherapy dose intensification played a role, advances in pathologic classification, diagnostic imaging, surgical techniques, RT treatment planning and delivery, and supportive care contributed to this improved outcome.

Efforts to improve systemic therapy focused on dose intensification and the introduction of new agents. The relatively low-dose, protracted VAC regimen employed in the Intergroup Rhabdomyosarcoma Study (IRS) Group, IRS-I study[92] was modified to the more dose-intensive, repetitive-pulse VAC regimen introduced in IRS-II. Doses of AMD were recently reduced in an effort to reduce the risk of hepatopathy.[93–95] Many novel agents have been tested in patients with childhood RMS, including doxorubicin,[96] CDDP,[94,97] VP16,[94,97] dacarbazine,[94]IFOS,[96,98] melphalan,[98] topotecan,[99,100] and irinotecan,[101] but none has improved the outcome of low- and intermediate-risk RMS.

Local control approaches have also evolved. Definitive RT for unresected tumors uses doses ≥ 50 Gy with modern conformal techniques; patients who undergo initial wide or marginal tumor resection now receive lower doses (36 – 41.4 Gy) or may forgo RT altogether (embryonal histology group I).[102] The International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumor (MMT) studies and recent Children's Oncology Group (COG) studies for low- and intermediate-risk RMS have evaluated RT dose reduction in patients with a favorable therapy response and/or favorable second-look surgery.[91]

In the 1970s, ablative surgical approaches (e.g., anterior pelvic exenteration) were employed to achieve tumor control.[103] The recognition that RT could produce high rates of local tumor control led to the use of more conservative surgery in the 1980s and 1990s.[104] Recently, more aggressive surgery has been performed in some clinical settings to avoid the long-term adverse effects of RT.[105,106]

Therapy for children with parameningeal RMS (~10% of cases)[107] has changed significantly over the years.[108–110] Patients with parameningeal RMS treated on IRS-I were at significant risk of meningeal tumor dissemination when the tumor eroded the skull base, extended intracranially, or produced cranial nerve palsy. Although treatment of these patients was intensified on IRS-II through early CSI and intrathecal chemotherapy, these interventions were subsequently eliminated when local control was improved by higher chemotherapy dose intensity and better adherence to RT treatment guidelines. Early RT of the primary tumor is the standard approach.

Systemic therapy for childhood RMS has changed very little over the past few decades. VA, VAC, and IVA are the regimens most frequently utilized for treatment of patients with low- and intermediate-risk disease, and dosages are similar to those employed since the late 1970s. Patients with high-risk disease receive additional agents such as DOX, IFOS, VP16, and irinotecan, which have been evaluated in clinical trials over the past 40 years. Local control therapies have undergone minor changes. Although RT is reserved for a smaller subset of patients, the doses are similar in most cases, and differences in dose are too small to significantly alter late effects. Growing awareness of the substantial long-term toxicity of RT is raising the possibility of more aggressive surgical interventions to avoid RT.

Osteosarcoma

Successful treatment for osteosarcoma (OS), the most frequent primary malignant bone tumor of children and adolescents, requires effective systemic chemotherapy and surgical resection of all clinically detectable disease. Before the introduction of systemic chemotherapy, patients with non-metastatic OS of the extremity underwent immediate surgical resection of the primary tumor yielded five-year survival rates of 11% - 25%.[111] During the early 1970s, single agents, including high-dose methotrexate (HDMTX) with leucovorin rescue,[111] CDDP,[111] and DOX[74,111] were evaluated. Several studies found that single-agent or combination chemotherapy after primary tumor resection improved survival as compared to that of historical controls (Table V).[111] Other reports suggested that the apparent improvement in outcome was attributable to improved diagnosis and surgery rather

than adjuvant chemotherapy,[112,113] but two randomized prospective trials subsequently confirmed the benefit of adjuvant chemotherapy.[114,115] Single institution, non-randomized trials evaluating DOX and HDMTX or DOX and CDDP regimens after primary tumor resection reported three- to five-year EFS of 50% – 60% or more in patients without clinically detectable metastases.[111,116–118] During the 1980s, several studies established the activity of IFOS or IFOS and VP16 for recurrent and metastatic OS.[119,120]

Initial chemotherapy followed by definitive surgical resection rather than immediate amputation was investigated in the 1970s.[121,122] A randomized study comparing this strategy to immediate definitive surgery followed by adjuvant therapy revealed no difference in survival.[123] Initial chemotherapy permits evaluation of primary tumor necrosis at the time of definitive surgical resection and was associated with improved EFS and overall survival. Clinical trials of combinations of agents with demonstrated activity (DOX, CDDP, HDMTX, and IFOS with or without VP16) from 1990 to the present reported 60% – 70% EFS for localized OS and identified no clearly best combination.[124–127] A COG randomized trial investigating the addition of IFOS to CDDP, HDMTX, and DOX reported identical results for both treatment arms.[127,128] The same trial found that EFS and survival were improved for both localized and metastatic OS when liposomal muramyl tripeptide (L-MTP) was added to combination chemotherapy.[127–129] However, the analysis was complicated by what appeared to be an interaction between the addition of IFOS and the addition of L-MTP.[130] L-MTP was denied approval by the United States Food and Drug Administration in 2007, but was licensed by the European Medicines Agency in 2009. As a result the addition of L-MTP to treatment regimens for osteosarcoma remains investigational in the U.S.

Current treatment of OS includes initial multi-agent chemotherapy, using chemotherapy regimens developed during the 1980s, followed by definitive surgical resection of clinically detectable disease and subsequent adjuvant chemotherapy.

Ewing Sarcoma

Before the discovery of active chemotherapeutic agents, both surgery and RT were used for local control of Ewing sarcoma (ES); RT was regarded as the standard modality (Table VI). In the 1960s, after the discovery that ES responded to VCR [69,85], CTX [131], and AMD[132], these agents were combined in multi-drug regimens, [133,134] usually with RT.[135,136] Although long-term disease control was accomplished, investigators soon realized that combined-modality therapy increased the risk of second malignancies.[137]

In the 1970s, several single-institution studies reported that the addition of DOX to chemotherapy improved outcome.[138] These studies used 60 – 70 Gy to the primary tumor plus combination chemotherapy with CTX (2400 mg/m^2/cycle x 5 cycles), VCR, DOX (60 mg/m^2/cycle x 5 cycles), and AMD[139] or high-dose local radiation (65 Gy) plus multi-agent chemotherapy (VCR, CTX [300 mg/m^2/day up to 10 daily doses]) for as many as five therapy pulses.[140] The first Intergroup Ewing Sarcoma Study (IESS) (IESS-I; 1973–1978), comparing VAC, VAC with whole-lung irradiation, and VAC and DOX (VAC-Adria), showed that addition of doxorubicin improved EFS. This four-drug regimen became the standard against which the efficacy of therapy modifications was measured.[141] The IESS-I trial used RT doses ≤ 65 Gy for local control.[142] The second IESS study (1978–1982) compared two different schedules of four-drug therapy and demonstrated improved overall outcome on the high-dose, intermittent schedule.[143]

In the 1980s, IFOS was found to have significant activity against recurrent ES.[144] When given in combination with VP16, IFOS showed substantial activity against recurrent [120] and previously untreated [145] disease. Sequential POG-Children's Cancer Group (CCG) intergroup studies demonstrated improvement in five-year EFS among those who received

VAC-Adria plus IFOS and VP16 compared to those who received only VAC-Adria [146] and no statistically significant difference in five-year EFS between those who received standard (48 weeks) compared to intensified (30 weeks) treatment with VAC-Adria plus IFOS and VP16.[147] IE did not improve the outcome of patients with metastatic disease.[146] The standard and intensified arms used similar cumulative doses of doxorubicin (375 mg/m^2), VCR, and IFOS (72 g/m^2), but different doses of CTX (standard - 10.8 g/m^2 *vs.* intensified - 12 g/m^2) and VP16 (standard - 4 g/m^2 *vs.* intensified - 5 g/m^2). [147] In the trial comparing standard and intensified regimens, 12 patients developed secondary leukemia and seven developed secondary solid tumors.[147] These two studies demonstrated that a shorter, more intensified treatment regimen produced similar EFS without increasing the risk of acute toxicity or second malignant neoplasms.

The approach to local control has evolved because of both the short- and long-term adverse effects of RT and improved surgical techniques. In early studies, radical RT (recommended dose ≤ 65 Gy) was the primary treatment.[141,148] However, investigators recognized the risk of permanent growth arrest and second neoplasms.[137] With the development of techniques that allow preservation of function and integrated approaches for the skeletally immature child, surgical resection has been utilized more frequently for local control without compromising outcome. Most studies have shown a survival advantage for patients whose treatment included primary tumor resection.[149–151] In recent studies, surgery has been used for local control in at least two-thirds of patients with non-metastatic ES.[147]

The most recent COG trial of therapy for non-metastatic ES (AEWS0031) demonstrated that dose-compressed therapy given every two weeks was more effective and less toxic than therapy given every three weeks (five-year EFS 73% (every two weeks) *vs.* 65% (every three weeks); $p = 0.048$).[152] Patients older than 18 years of age at diagnosis had a significantly poorer outcome than those who were younger (five-year EFS 48% (≥ 18 years of age at diagnosis) *vs.* 72% (< 18 years of age at diagnosis); $p < 0.001$).[152] This dose-compressed therapy prescribes substantial cumulative doses, including DOX (375 mg/m^2), CTX (8.4 g/m^2), IFOS (63 g/m^2), and VP16 (3.5 g/m^2). These agents have been utilized in combination chemotherapy for ES since 1988, and combination chemotherapy with VCR, DOX and CTX has been employed since 1972. Thus, the risk of late effects in contemporary patients treated for ES can be derived directly from historical cohorts.

Discussion

This review demonstrates that contemporary regimens for pediatric solid tumors prescribe many of the same agents and modalities used historically. Some historical chemotherapeutic agents and combinations have particular application to contemporary treatment protocols. The VA combination remains the primary adjuvant treatment for many children with WT and low-risk RMS. Anthracyclines remain a key component of treatment protocols for OS and ES. The use of RT for pediatric solid tumors has declined during this time because of the recognition that RT produces long-term adverse effects on normal tissues. RT is no longer given to children with stage I or II favorable-histology WT and is delayed or not used in the treatment of many children with bilateral RB. RT treatment volumes have been reduced, and surgical resection has been employed more frequently for the treatment of patients with ES. Surgery for OS has evolved from universal amputation to limb-sparing procedures for most patients. By contrast, the combination chemotherapy regimens for ES, metastatic neuroblastoma, and medulloblastoma are more intensive than those used in the past but employ most of the same agents.

The therapeutic approaches for pediatric solid tumors have evolved with the goal of improving disease-free survival while minimizing treatment-related morbidity. These

changes are largely refinements of treatment protocols whose agents and modalities have been available for more than 30 years. Investigation of long-term outcomes has been instrumental in identifying childhood cancer survivor populations at high risk of specific organ toxicity and secondary carcinogenesis. This knowledge has been essential in anticipating health risks among survivors and facilitating their access to preventive and/or remedial interventions that can optimize their quality of life after childhood cancer. Treatment will continue to evolve as new agents and technologies become available; these changes will likely be slowly integrated into the highly effective contemporary regimens that allow the vast majority of children with solid tumors to become long-term survivors. Demonstration of the long-term adverse effects of historic therapy will therefore continue to play a crucial role in defining optimal therapy for these diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table I

Evolution of Therapy for Medulloblastoma

Treatment Modality	**Decade**					**Historic Treatment Modalities Used in Contemporary Therapy**
	1960	**1970**	**1980**	**1990**	**Post-2000**	
Chemotherapy	**None**	**Combination**		**Combination**	**Risk-Adapted**	**Risk-Adapted**
Agents		• CCNU • Vincristine		• CCNU • Vincristine • Cisplatin	• Cyclophosphamide • Vincristine • Cisplatin • ± HCT • Addition of etoposide for high-risk	• Cyclophosphamide • Vincristine • Cisplatin
Dose-Intensity/Duration		• 8 cycles			• Myeloablative chemotherapy with autologous HCT after radiation therapy	
Radiation	• Craniospinal radiation therapy • Brain and spinal cord (35–40 Gy) • Posterior fossa (50–55 Gy)			• Craniospinal radiation therapy • Brain and spinal cord (24–40 Gy) • Posterior fossa (54–56 Gy)	• Craniospinal radiation therapy • Tumor bed or posterior fossa (54–56 Gy) conformal • Brain and spinal cord (24–40 Gy)	• Tumor bed • Posterior fossa • Brain and spinal cord
Surgery	Total or subtotal resection					• Total or subtotal resection

Abbreviations: CCNU - 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; HCT – hematopoietic cell transplant

Table II

Evolution of Therapy for Neuroblastoma

Treatment Modality	Decade					Historic Treatment Modalities Used in Contemporary Therapy
	1960	1970	1980	1990	Post-2000	
Chemotherapy		**Combination**	**Combination**	**Risk-Adapted**	**Risk-Adapted**	
Agents	• Cyclophosphamide • Vincristine	• Vincristine • Cyclophosphamide • DTIC • Doxorubicin • Peptichemio	• Cisplatin • VM26/VP16 • Doxorubicin • Cyclophosphamide	• No chemotherapy for stage 1, 2, 4s if asymptomatic • Limited chemotherapy for intermediate risk • Intensive chemotherapy for high risk		• Cisplatin • Etoposide • Cyclophosphamide • Doxorubicin
Dose-Intensity/Duration	• Standard treatment with 2 cycles beyond remission	• 12 cycles		• Intensified induction • Myeloablative therapy with autologous HCT improves EFS	• Testing of tandem autologous HCT, mIBG + ASCT	• Autologous HCT
Minimal Residual Disease Therapy		• Preclinical studies of cis-retinoic acid (cisRA)	• Development of anti-GD2 antibodies	• cisRA improves EFS • Phase I/II studies of immunotherapy	• Ch14.18+cytokines + cisRA significantly improves EFS	• cisRA • Ch 14.18 • IL-2 • GM-CSF
Radiation	• For localized and regional disease (20–40 Gy)		• Radiation for spinal cord compression and for liver enlargement 4s	• Local radiation to high risk primary site even for resected disease; • No RT to low risk disease		• Local radiation to high risk primary site even for resected disease; • No RT to low risk disease
Surgery	• Only for easily resectable localized disease	• Use of neoadjuvant therapy before surgery	• Complete resection more important for high risk disease	• INSS staging system dependent on resection	• Clinical staging with computed tomography and positron emission tomography.	

Table III

Evolution of Therapy for Wilms Tumor

Treatment Modality	Decade					Historic Treatment Modalities Used in Contemporary Therapy
	1960	1970	1980	1990	Post-2000	
Chemotherapy Agents	• Introduction of actinomycin D and vincristine	• Introduction of doxorubicin		• Introduction of cyclophosphamide to regimen for patients with unfavorable histology	• Introduction of etoposide and carboplatin to regimens for patients with loss of heterozygosity for 1p and 16q	• Vincristine • Actinomycin D • Doxorubicin
Dose-Intensity/Duration	• Single agents only	• Combination of vincristine and actinomycin D; vincristine, actinomycin D and doxorubicin evaluated; • 15 months for group II-IV • 6 months for Group I		• Single-dose administration of actinomycin D and doxorubicin • 6 months of chemotherapy adequate for all patients		• Single-dose administration of actinomycin D and doxorubicin • 6 months of chemotherapy adequate for all patients
Radiation	• High-dose abdominal radiation	• Age-adjusted abdominal radiation doses crossing midline	• Lower dose of abdominal radiation, not age-adjusted, used in patients with stage II, III and IV disease	• Lower dose of abdominal radiation, not age-adjusted, used in patients with stage III and IV disease. • Flank spill stage II criterion		• Lower dose of abdominal radiation, not age-adjusted used in patients with stage III and IV disease • Flank spill stage III criterion
Flank Dose		• 0 to ≤ 18 mo: 18–24 Gy • 19 to ≤ 30 mo: 24–30 Gy • 31 to ≤ 40 mo: 30–35 Gy • > 40 mo: 35–40 Gy	• Stage II randomized between 0 Gy and 20 Gy • Stage II and IV randomized between 10 Gy and 20 Gy	• 10.8 Gy for local stage III		• 10.8 Gy for local stage III

Table IV

Evolution of Therapy for Rhabdomyosarcoma

Treatment Modality	Decade					Historic Treatment Modalities Used in Contemporary Therapy
	1960	1970	1980	1990	Post-2000	
Features Used for Risk Stratification and Treatment Assignment		• Clinical group	• Clinical group	• Clinical group	• Clinical group • Stage • Histology	• Clinical group • Stage • Histology
Chemotherapy Agents	• Introduction of vincristine, actinomycin D, and cyclophosphamide	• Introduction of doxorubicin • Introduction of intrathecal chemotherapy for high-risk parameningeal tumors	• Introduction of ifosfamide and etoposide	• Elimination of intrathecal chemotherapy for high-risk parameningeal tumors	• Introduction of irinotecan	• Vincristine • Actinomycin D • Cyclophosphamide
Dose-Intensity/Duration	• Single agents and small pilots of combination therapy	• 2 years of therapy for all patients	• 1 year of therapy for lower-risk patients • 2 years of therapy for higher-risk patients • Dose intensification of all agents	• 1 year of therapy for all patients • Further dose intensification of alkylating agents	• 1 year of therapy for all patients (6 months of therapy being tested for low-risk patients) • Alkylating agent dose reductions for low- and intermediate-risk patients • Chemotherapy dose compression for high-risk patients	• 1 year of therapy

Table V

Evolution of Therapy for Osteosarcoma

Treatment Modality	Decade					Historic Treatment Modalities Used in Contemporary Therapy
	1960	1970	1980	1990	Post 2000	
Chemotherapy approach	None	• Phase II • Single agent	• Adjuvant • Neoadjuvant • Combination	• Neoadjuvant • Combination	• Neoadjuvant • Combination	• Neoadjuvant • Combination
Chemotherapy agents		• Cisplatin, • Doxorubicin • HDMTX	• Cisplatin/Doxorubicin • Cisplatin/Doxorubicin/HDMTX • Phase II Ifosfamide (+/− Etoposide)	• Cisplatin/Doxorubicin • Cisplatin/Doxorubicin/HDMTX • Cisplatin/Doxorubicin/HDMTX/Ifosfamide • Clinical trial: Chemo +/− muramyl tripeptide	• Cisplatin/Doxorubicin • Cisplatin/Doxorubicin/HDMTX • Cisplatin/Doxorubicin/HDMTX/Ifosfamide • Clinical trial: Tailoring base on necrosis following neoadjuvant chemo	• Cisplatinum • Doxorubicin • HDMTX
Dose Intensity/Duration		• Phase II	• 9–12 months	• 9–12 months	• 9–12 months	• 9–12 months
Surgery for primary tumor	• Amputation	• Amputation • Limb preservation	• Limb preservation • Amputation	• Limb preservation • (Amputation)	• Limb preservation • (Amputation)	• Limb preservation • (Amputation)
Surgery for pulmonary metastases	• Thoracotomy	• Thoracotomy	• Thoracotomy	• Thoracotomy	• Thoracotomy	• Thoracotomy

Abbreviations: HDMTX – high dose methotrexate

Table VI

Evolution of Therapy for Ewing Sarcoma

Treatment Modality	Decade					Historic Treatment Modalities Used in Contemporary Therapy
	1960	1970	1980	1990	Post-2000	
Chemotherapy approach	• Often single agents, early use of combination therapy	• Standardized use of combination therapy • Recognition of activity of doxorubicin	• Combination therapy • Introduction of ifosfamide and etoposide	• INT-0091(1988–93) established that IE improved outcome • Actinomycin D abandoned	• Standard 5-drug therapy • AEWS0031 showed dose compression improved outcome	
Chemotherapy agents	• Vincristine • Cyclophosphamide • Actinomycin • Doxorubicin	• Vincristine • Cyclophosphamide • Actinomycin D • Doxorubicin	• Vincristine • Cyclophosphamide • Actinomycin D • Doxorubicin • Ifosfamide • Etoposide	• Vincristine • Cyclophosphamide • Doxorubicin • Ifosfamide • Etoposide	• Vincristine • Cyclophosphamide • Doxorubicin • Ifosfamide • Etoposide	• Vincristine • Cyclophosphamide • Doxorubicin • Ifosfamide • Etoposide
Chemotherapy intensity/duration	Variable, 32 weeks in MD Anderson trials	IESS-I: 89 weeks IESS-II: 79 weeks	INT-0091: 49 weeks in both arms	INT-0154: Reg A: 48 weeks Reg B: 30 weeks	AEWS0031: Reg A: 42 weeks Reg B: 29 weeks	29 weeks
Radiation dose	• High dose, up to 60 Gy	• 55 Gy • Most patients on IESS-I and -II had irradiation for local control	• Both irradiation and surgery permitted • 45 Gy to initial disease + 3 cm margin boost to post induction mass to 55.8 Gy	• Both irradiation and surgery permitted • Surgery recommended for patients responding to induction chemotherapy • 45 Gy to initial disease + 2 cm margin; boost to post induction mass to 55.8 Gy	• Both irradiation and surgery permitted, but surgery preferred • PTV1 – 45 Gy • PRV2 – 55.8 Gy	• Both irradiation and surgery permitted, but surgery preferred • PTV1 – 45 Gy • PRV2 – 55.8 Gy