Late Treatment Effects and Cancer Survivor Care in the Young

From Childhood to Early Adulthood

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Kelley K. Hutchins, Rudolf Steiner, Emma R. Lipshultz, Stephen E. Sallan, and Steven E. Lipshultz

1.1 Introduction

Childhood cancer survivorship has become a great success story over the past few decades. More than 80% of patients with childhood cancer are surviving longer than 5 years in some developed nations, whereas these malignancies were nearly universally fatal prior to the 1960s. Unfortunately, with this amazing success has come appreciation of the adverse late effects of cancer therapies. Survivors of childhood cancer have markedly higher rates of morbidity and mortality than those of their healthy counterparts.

One important adverse effect is cardiotoxicity. Heart failure, myocardial disease, valvular disease, hypertension, and early cardiac death are among the adverse cardiac outcomes that affect an increasing number of childhood cancer survivors. Cancer treatment, especially chemotherapy and radiation, as well as several additional risk factors, puts survivors at substantially increased risk of cardiotoxicity. Extensive screening guidelines have been developed to identify and treat these patients as early and effectively as possible. Current position papers and guidelines, however, are consensus-based, and their ability to prevent cardiotoxicity or improve long-term outcomes needs to be validated. Several treatment modalities have also been proposed to reduce therapy-induced cardiotoxicity, but many are not evidence-based. One effective cardioprotectant is dexrazoxane. Further research is needed to determine the best means of preventing, screening for, and treating cardiotoxicity among childhood cancer survivors.

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1.2 Cardiotoxicity Among Cancer Survivors

Cardiotoxicity is the third leading cause of morbidity and mortality after cancer recurrence and secondary malignancies among survivors of childhood cancer [1, 2]. Cardiotoxicity decreases quality of life and can lead to premature death [3]. Several large, multicenter studies, such as the Childhood Cancer Survivor Study and the British Childhood Cancer Survivor Study, found significantly higher mortality rates among survivors than among age-matched controls, and the differences are largely related to adverse cardiac outcomes [1].

Cardiotoxicity has a variety of forms and ranges in severity. Many survivors never become symptomatic, whereas others experience severe, debilitating disease that can lead to premature death. This great variation in the severity of toxicity may be attributed to several risk factors, as well as to possible genetic differences.

Survivors have substantially higher rates of heart failure, dysrhythmias, valvular disease, pericardial disease, and coronary artery disease than those of healthy control subjects [2, 4–6]. By 30 years after diagnosis, the number of cardiac-related deaths exceeds the number of deaths from cancer recurrence in this patient population [1]. Thus, in addition to continuing to seek curative treaments for the 20% of children who die from cancer, there has been an intense effort to focus on improving the overall quality of life of long-term survivors.

1.3 Cancer Therapy Contributing to Cardiotoxicity

Treating and curing cancer involves multimodality approaches, all of which are associated with toxicities, including cardiotoxicity.

1.3.1 Anthracycline Treatment

Anthracyclines, such as doxorubicin, daunorubicin, and epirubicin, are among the chemotherapeutic agents commonly used to improve the outcomes of both hematologic and solid tumor malignancies, and they have greatly improved outcomes in patients with cancers such as acute lymphoblastic leukemia (ALL) and sarcomas [7–11]. Anthracycline therapy is also among the most cardiotoxic of therapies and is often dose limiting when cardiotoxicity develops [7, 12]. Anthracycline-induced cardiomyopathy may be acute or subacute, occurring within 1 year of treatment, or late, occurring several years post administration [13, 14].

Many long-term follow-up studies have documented the cardiac effects of anthracyclines. For example, among 755 patients with localized osteosarcoma treated with doxorubicin (median age, 15 years; range, 3–40 years), the incidence of heart failure (New York Heart Association Functional Heart Failure Classification System's moderate to severe heart failure classes II–IV) was 1.7% (13/755) at a median follow-up of 8.5 years. Of these 13 patients, 6 died and 3 needed a heart transplant [8]. The incidence was higher in females and in those treated with a higher cumulative anthracycline dose. A retrospective longitudinal study of children less than 17 years old with Ewing sarcoma found a high incidence of cardiotoxicity as detected by echocardiography [15]. Of 71 patients, cardiac function, as assessed by left ventricular ejection fraction, declined in 17 after completing therapy. Anthracycline exposure also reduces left ventricular wall thickness and mass, which in turn decreases left ventricular fractional shortening [4].

A longitudinal study of 22 survivors with malignant bone tumors treated with anthracyclines found that adverse cardiac structural changes resulted in marked and progressive cardiac dysfunction [16]. The risk of heart failure, valvular disease, and pericardial disease in survivors was five times as high as that of healthy siblings, and cardiac dysfunction developed in up to half of survivors within 20 years after anthracycline treatment [2]. Despite the adverse cardiac effects of doxorubicin and other anthracyclines, these drugs have remained critical components of therapy for many years.

1.3.2 Radiation Therapy

Radiation therapy has also long been known to increase cardiovascular toxicity. Chest irradiation can cause pericardial disease, myocardial fibrosis, coronary artery disease, cardiomyopathy, and val-

vular disease [17–20]. In the 1970s and 1980s, of three young adults with Hodgkin lymphoma who experienced acute myocardial infarctions, two had received mediastinal irradiation [21]. Pihkala and co-workers studied 91 Finnish patients who were treated with doxorubicin, radiation therapy, or both (median cumulative dose of radiation to the thorax was 24 Gy when used in combination with doxorubicin and 40 Gy when used alone). Types of malignancies treated with anthracycline and/or radiation included Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor with pulmonary nodules, soft tissue sarcoma, spinal cord glioma, intrathoracic sarcoma, and Askin tumor. Their findings showed an additive effect on anthracycline cardiotoxicity by noting abnormal systolic and diastolic function on echocardiography and radionuclide cineangiography [22].

Cardiac disease secondary to radiation has been a significant problem for patients with Hodgkin lymphoma [23]. In the early 1990s, Hancock and co-authors studied 635 patients younger than 21 years with Hodgkin lymphoma treated between 1961 and 1991, all of whom received treatment that included radiation. At a median follow-up of 10.3 years, 12 patients had died of cardiac disease, and 106 non-fatal cardiac events had been reported [23]. Although therapy had changed greatly since the earliest patients in this analysis were diagnosed, the relative risk of death was 29.6 (95% CI 16.0–49.3). An increased risk of death from coronary artery disease was highest among patients who received between 40 and 45 Gy of radiation [23].

More recent long-term follow-up studies of survivors of Hodgkin lymphoma treated with mediastinal irradiation also reported clinically relevant cardiotoxicity [24, 25]. Adams studied 48 patients (median age 16.5 years old at a median of 14.3 years after diagnosis) who had received an average radiation dose of 40 Gy (range, 27–51.7 Gy). Resting and 24-h electrocardiograms, exercise stress tests, and echocardiography screening tests detected subclinical cardiac abnormalities in 47 [25]. Abnormalities included valvular dysfunction, arrhythmias, and decreased oxygen consumption. Another review of 1279 patients with Hodgkin lymphoma (median age, 21 years; range, 3–93 years) treated between 1969 and 1998 with a median, mid-mediastinal dose of 40 Gy (range, 15–53 Gy) found that 187 patients had had a cardiac event that led to 129 surgical interventions after a median follow-up of 14.7 years (Galper et al. 2011). Although these patients were treated between 20 and 50 years ago and radiation exposure and dosing have changed, these results are important for current survivors who may have received these higher doses or extended-field radiation, as well as for current and future patients who will continue to receive radiation as part of their treatment, with or without other potentially cardiotoxic therapy.

1.3.3 Other Cardiotoxic Chemotherapeutic Drugs

Many other chemotherapeutic drugs are cardiotoxic. Alkylating agents, such as cyclophosphamide and ifosfamide, have been associated with heart failure [26]. Fluorouracil can cause cardiac ischemia, often early in therapy [27]. Newer targeted therapies, such as monoclonal antibodies, tyrosine kinase inhibitors, and vascular endothelial inhibitors, have been studied in adults. The cardiotoxicity of trastuzumab, a monoclonal antibody against human epidermal receptor-2 used to treat breast cancer, can cause left ventricular dysfunction and heart failure [7, 20]. Vascular endothelial growth factor inhibitors, such as the monoclonal antibody, bevacizumab, have been associated with myocardial infarction [27]. Bortezomib, a proteasome inhibitor, causes left ventricular dysfunction in up to 5% of patients [26]. Recent reports of fulminant myocarditis with these new medications show that clinicians need to be vigilant for cardiovascular toxicities when using these newer therapeutic agents [28].

1.4 Risk Factors for Cardiac Damage

For decades, investigators have tried to determine which patients are at highest risk for heart failure and other forms of cardiotoxicity [29–31]. Several factors have been identified, such as sex and age, choice of therapy, and lifestyle behaviors.

1.4.1 Therapy-Related Risk Factors

A critical risk factor for anthracycline cardiotoxicity is the total cumulative anthracycline dose. A cumulative lifetime dose of doxorubicin greater than 300 mg/m^2 is a significant risk factor for late-occurring anthracycline-induced cardiotoxicity. Lower cumulative doses, however, have also been associated with adverse effects, suggesting that any dose may be potentially harmful [32, 33]. Higher bolus doses of anthracycline impart more risk than lower doses [31].

The radiation field and type of radiation involved also affect the severity of toxicity [27]. In addition to thoracic irradiation, cranial spinal irradiation also potentiates the development of cardiotoxicity when used in combination with anthracyclines, possibly because of its effects on the hypothalamic-pituitary pathway [5, 34 35]).

1.4.2 Non-Modifiable Risk Factors

Many non-modifiable risk factors put certain survivors at increased risk of anthracycline-related cardiotoxicity, especially female sex, younger age at diagnosis, black race, trisomy 21, treatment with additional chemotherapeutic agents, and a longer time since completing anthracycline therapy ([29, 31, 36, 37]; Table 1.1). Females are at higher risk than males for both acute and chronic cardiotoxicity [29, 31]. The pathophysiology of this difference is not completely understood, but it

Table 1.1 Risk factors for anthracycline-related cardiotoxicity

Risk factors	Comment	References
Cumulative anthracycline dose	Cumulative doses >300 mg/m^2 are associated with significantly elevated long-term risk	Lipshultz et al. [37] Lipshultz et al. [6] Krischer et al. [29] Lipshultz et al. [31] van der Pal et al. [38]
Time after therapy	The incidence of clinically important cardiotoxicity increases progressively over decades	Lipshultz et al. [37] Lipshultz et al. [39] Lipshultz et al. [6] Lipshultz et al. [31]
Rate of anthracycline administration	Continuous infusion not cardioprotective in children	Lipshultz et al. [40] Lipshultz et al. [39]
Individual anthracycline dose	Higher individual doses are associated with increased late cardiotoxicity, even when cumulative doses are limited; no dose is risk-free	Lipshultz et al. [6] Lipshultz et al. [40] Lipshultz et al. [31]
Type of anthracycline	Liposomal encapsulated preparations may reduce cardiotoxicity. Date on anthracycline analogues and differences in cardiotoxicity are conflicting	Wouters et al. [41] van Dalen et al. [42] Barry et al. (2007)
Radiation therapy	Cumulative cardiac radiation dose >30 Gy before or concomitant with anthracycline treatment; as little as 5 Gy increased the risk	Lipshultz et al. [39] Adams and Lipshultz [19] van der Pal et al. [38] Giantris et al. [13])
Concomitant therapy	Trastuzumab, cyclophosphamide, bleomycin, vincristine, amsacrine, and mitoxantrone, among others, may increase susceptibility or toxicity	Barry et al. (2007) Giantris et al. [13]
Preexisting cardiac risk factors	Hypertension; ischemic, myocardial, and valvular heart disease; prior cardiotoxic treatment	Barry et al. (2007)
Personal health habits	Smoking; consumption of alcohol, energy drinks, stimulants, prescription, and illicit drugs	Lipshultz et al. [39]

Table 1.1 (continued)

Risk factors	Comment	References
Comorbidities	Diabetes, obesity, renal dysfunction, pulmonary disease, endocrinopathies, electrolyte and metabolic abnormalities, sepsis, infection, pregnancy, viruses, elite athletic participation, low vitamin D concentrations	Lipshultz et al. [39] Lipshultz et al. [34] Landy et al. [35] Miller et al. [43] Barry et al. (2007)
Age	Young (<1 year) and advanced age at treatment are associated with elevated risk	Lipshultz et al. [37] Lipshultz et al. [31] Lipshultz et al. [39] van der Pal et al. [38]
Sex	Females are at greater risk than males	Lipshultz et al. [40] Lipshultz et al. [31])
Complementary therapies	More information needs to be collected to assess risk	Lipshultz et al. [39]
Additional factors	Trisomy 21; African American ancestry	Krischer et al. [29]

With permission from Lipshultz SE, Alvarez JA, Scully RE (2008). Anthracycline associated cardiotoxicity in survivors of childhood cancer. *Heart* 94: 525–533

may involve multiple factors, such as increased body fat composition with decreased anthracycline clearance and different expression of the multidrug resistance gene [29, 31]. Survivors diagnosed at a younger age are at higher risk for late cardiotoxicity than those diagnosed at older ages [31, 37]. Cardiac function was assessed in 115 patients with ALL treated with doxorubicin. Mean age at diagnosis was 6.2 years. At a median follow-up of 6.4 years (range, 1–15 years) after treatment, left ventricular afterload was higher in patients less than 4 years old at diagnosis than in older patients [37].

Genetic mutations also affect cardiotoxicity among survivors. Specific genotype variants are associated with both increased and decreased risks of cardiotoxicity. Children with ALL treated with doxorubicin who have an A-1629 T genotype variant of the ABCC5 gene (an ATP-binding cassette transporter gene) have significantly lower left ventricular ejection and shortening fractions [44]. Others, with the G-894T genotype variant of the NOS3 gene (an endothelial nitric oxide synthase gene), tend to have higher left ventricular ejection fractions [44]. Doxorubicin-associated myocardial injury is also more common in patients with high-risk ALL carrying the C282Y hemochromatosis gene mutation [45]. The variants of this gene, including homozygosity for the C282Y mutation, are present in almost all patients with hereditary hemochromatosis and can lead to iron overload. One effect of doxorubicin is that it forms complexes with iron, leading to free radical injury and ultimately to cardiac damage.

1.4.3 Modifiable Risk Factors

Several behaviors and health conditions place the general population at an increased risk of heart disease, such as atherosclerosis, hypertension, and heart failure. Activities such as the excessive consumption of tobacco, illicit drugs, alcohol, and salt, as well as physical inactivity, predispose individuals to heart disease. The association between cardiovascular disease and obesity and diabetes mellitus is well established. These risk factors may be present among survivors of childhood cancer and must be considered in their care [46]. Not only may survivors be at increased risk of cardiotoxicity from cancer therapy, these potentially modifiable risk factors can further increase their risk of cardiovascular disease.

1.5 Identifying Cardiotoxicity Early

Identifying survivors at risk of cardiotoxicity is of utmost importance. Early, close surveillance for those who need it most may avoid unnecessary follow-up or assessments of survivors at lower risk [7].

Measuring biomarker concentrations during therapy may help identify patients at increased risk of cardiotoxicity [7, 40]. Cardiac troponin T (cTnT), a biomarker of myocardial injury, and N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker of myocardial stress that is elevated in the presence of cardiomyopathy or heart failure, were associated with echocardiographic findings 4 years after therapy among patients with high-risk ALL treated with doxorubicin [40]. Abnormally elevated cTnT concentrations during the first 90 days of treatment with doxorubicin were associated with reduced left ventricular mass and end-diastolic posterior wall thickness [40]. Elevated NT-proBNP concentrations were associated with an abnormal left ventricular thickness-to-dimension ratio, suggesting pathologic ventricular remodeling [40]. Although cardiac biomarkers have been validated as surrogate endpoints for late cardiac abnormalities, such biomarkers should not be used to determine sensitivity or specificity or to establish cutoffs to guide clinical decisions. Rather, these results should inform prospective randomized clinical trials assessing the trade-off between conventional cancer management and cardiac biomarker-guided therapy to see which results in the highest quality of life over time, balancing both oncological efficacy and cardiac toxicity/late effects [40].

New ways to detect early, subclinical cardiac damage induced by anthracyclines are being developed. In a mouse model of cardiotoxicity, in which mice were treated with either doxorubicin alone or in combination with dexrazoxane [47], pathologic cardiac changes were associated with 451 mitochondrial-related genes, differentially expressed with the maximum doxorubicin dose without dexrazoxane. Of these, the effects of 127 were markedly attenuated by pre-treatment with dexrazoxane. Of these 127 genes, 37 were associated with cardiac energy metabolism, apoptosis, and steroid biosynthesis [47]. Although how these 127 genes cause cardiac toxicity is unclear, transcriptional changes of particular genes may be useful as early biomarkers of subclinical, anthracycline-related cardiotoxicity.

Several guidelines have been proposed to help care for long-term survivors of childhood cancers. Groups such as the Children's Oncology Group created such guidelines based on consensus, expert opinion, and a comprehensive literature review [48]. These guidelines remain to be validated, however, and need to be reassessed and modified to maximize efficacy and cost-effectiveness [49]. In addition, evidence-based guidelines are needed as survivors age and increase in number.

1.6 Preventing Cardiotoxicity

Preventive medications, such as dexrazoxane and liposomal formulations of doxorubicin, can reduce anthracycline-induced cardiotoxicity, as can addressing the lifestyle risk factors for anthracycline-induced cardiotoxicity [40]. The potential for developing new and improved mechanisms to treat individual patients based on their specific genetic traits and risk factors should be considered when possible.

1.6.1 Protecting Against Anthracycline-Induced Cardiotoxicity

Cardioprotectant medications have been a primary focus for preventing anthracycline-induced cardiotoxicity. Dexrazoxane, first studied in beagles in the early 1980s [50], prevents cardiotoxicity among women with advanced breast cancer and has been approved by the US Food and Drug Administration for this indication [51–54]. Dexrazoxane is believed to act in part by chelating iron and ultimately interfering with iron-mediated free radicals (Fig. 1.1) [5, 55–57]. Lyu and co-authors showed that dexrazoxane shifts

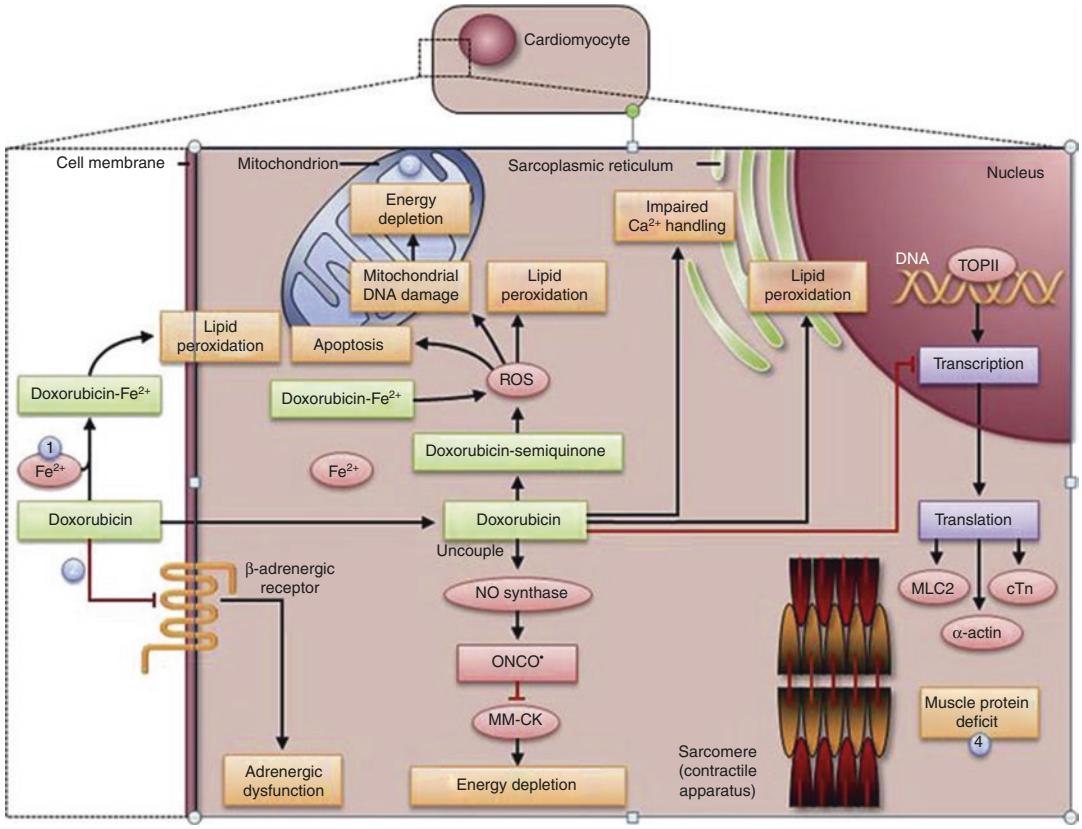

Fig. 1.1 Potential opportunities for cardioprotection. Doxorubicin chemotherapy has a range of effects on cardiomyocytes. It induces lipid peroxidation at the cell and mitochondrial membranes by way of complexing with Fe^{2+} and induces apoptosis, mitochondrial *DNA* damage, and energy depletion through its production of ROS. Furthermore, it impairs Ca^{2+} processing in the sarcoplasmic reticulum and inhibits the transcription of important muscle elements, weakening the heart muscle. It also downregulates adrenergic receptors and interrupts cell signaling. (1) Administration of dexrazoxane can prevent Fe^{2+} complex formation. (2) Intravenous immunoglobulin therapy can reduce the number of inflammatory cytokines. (3) L-carnitine can bolster mitochondrial function. (4) Anti-heart-failure therapies, such as angiotensin-converting-enzyme inhibitors and beta-blockers, can prevent further damage. Abbreviations: *cTn* Cardiac troponin, *MLC2* Myosin light chain 2, *MM-CK* Myofibrillar isoform of the CK enzyme, *ROS* Reactive oxygen species, *TOPII* Topoisomerase 2. (From: Lipshultz S.E, Cochran TR, Franco VI, Miller TL. 2013a. Treatment related cardiotoxicity in survivors of childhood cancer. *Nat Rev Clin Oncol,* 10, 697–710)

Top2's configuration to a close-clamp form by tight binding to Top2's ATP-binding sites, preventing anthracyclines from binding to the Top2 complex [58, 59].

Since these initial studies in adults, several studies have been conducted in children and adolescents with cancer treated with anthracyclines. In an open-label, randomized trial of children and adolescents with sarcomas treated with doxorubicin-containing chemotherapy, with or without dexrazoxane, those receiving dexrazoxane had less subclinical cardiotoxicity and smaller decreases in left ventricular ejection fraction and received higher cumulative doses of doxorubicin with no difference in event-free or overall survival rates [11]. The Dana-Farber Cancer Institute's Childhood ALL Consortium Protocol 95-01 determined that dexrazoxane was associated with decreased myocardial injury among children with ALL treated with doxorubicin and that event-free survival was unchanged after a median follow-up of 8.7 years [40, 60, 61].

Also, in comparing 5-year event-free survival in patients on Pediatric Oncology Group Protocol POG 9404, there was no difference between patients randomly assigned to treatment with or without dexrazoxane [40, 60]. Additionally, the Children's Oncology Group trials for localized and metastatic osteosarcoma who received both doxorubicin and dexrazoxane showed no clinical evidence of cardiotoxicity [62, 63].

Does dexrazoxane reduce the efficacy of anthracycline therapy? To date, no studies suggest that dexrazoxane decreases survival. In addition to the ALL studies above, children and adolescents with non-metastatic osteosarcoma who were treated with both dexrazoxane and doxorubicin showed that dexrazoxane did not compromise response to induction chemotherapy [64].

Is dexrazoxane associated with an increased incidence of secondary malignant neoplasms (SMNs)? Tebbi and co-authors reported that dexrazoxane increased the risk of SMNs among children with Hodgkin lymphoma treated with doxorubicin, bleomycin, vincristine, and etoposide, with or without prednisone and cyclophosphamide and radiation [65]. These findings ultimately led the European Medicines Agency contraindicating the use of dexrazoxane among children with cancer treated with anthracyclines [66]. Tebbi's conclusion has been disputed, however, particularly because the study was not intended to determine whether SMNs were associated with dexrazoxane [67]. Since then, multiple studies have found that dexrazoxane is not associated with an increased risk of SMNs and has no adverse effect on overall long-term survival [3, 68–70]. In fact, dexrazoxane may even help protect against SMNs associated with doxorubicin [71].

In a meta-analysis of randomized trials and non-randomized observational studies with a pooled sample of 4639 children with cancer treated with an anthracycline, with or without dexrazoxane, dexrazoxane was associated with a statistically significant reduction in most cardiotoxic outcomes [72]. The authors also noted that the slightly higher risk of SMNs in patients receiving dexrazoxane was more likely to be related to the concurrent therapies than to the dexrazoxane. Among the 5 randomized trials analyzed, SMNs occurred in 17 of 635 patients receiving dexrazoxane and 7 of 619 patients not receiving it. Importantly, only the two trials that treated patients with both etoposide and dexrazoxane found an increased rate of acute myelogenous leukemia (AML). When these two studies were removed from analysis, the rate of AML was equivalent among all remaining patients. One trial of treatment for ALL using cranial radiation reported an increased risk of secondary brain tumors among patients also receiving dexrazoxane. No brain tumors developed in any of the 717 patients in the other studies [72].

The preponderance of the evidence supports the conclusion that dexrazoxane prevents cardiotoxicity without adverse outcomes in a wide range of cancers. Dexrazoxane has been endorsed by the American Heart Association and the American Academy of Pediatrics for use as a cardioprotectant among children and adolescents undergoing anthracycline-containing protocols [57]. The drug has been used as the standard of good clinical care on all DFCI Childhood ALL Consortium protocols involving anthracycline therapy since 2000 and since 2015 has been mandated for inclusion on all new COG protocols involving treatment with $\geq$150 mg/m^2 doxorubicin or anthracycline administration at any dose with planned radiation treatment portals that may impact the heart [3].

Changes in the anthracycline delivery system, such as liposomal formulations, have been approved in the USA and Europe for use in adults [27]. Their effectiveness in preventing toxicity in children, however, has not been determined. Medications such as angiotensin-converting enzyme inhibitors and beta-blockers, both used to treat heart failure and hypertension, among other disorders, can improve left ventricular function in adults but have not provided long-term improvements in children. In 18 children with cancer treated with doxorubicin and enalapril, enalapril delayed but did not prevent left ventricular wall thinning [73]. Carvedilol, a non-selective beta antagonist, is currently being studied in survivors of childhood cancer treated with anthracyclines (NCT02717507).

1.6.2 Changes in Radiation Therapy

Different modalities and techniques have been developed to prevent the adverse effects of radiation, primarily those related to cardiotoxicity. For example, dosing in children is limited when possible, ideally to less than a cumulative dose of 25 Gy [25]. Delivering conformal radiation rather than extended-field or mantle irradiation also decreases toxicity by delivering radiation directly to the tumor and avoiding normal, healthy surrounding tissues [25] (Galper et al. 2011). New studies of patients with Hodgkin lymphoma may also eliminate radiation altogether, depending on stage and response of disease [74]. In the randomized phase III study to evaluate response-adapted therapy utilizing PET imaging, Radford and co-workers suggested that radiation may be able to be avoided in patients with stage IA and IIA Hodgkin lymphoma without mediastinal bulk disease who have negative PET findings after three cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine based on very good prognosis compared to patients who received the addition of radiation ([74]; NCT00943423). Longer follow-up is required to determine whether this strategy reduces long-term cardiotoxicity.

1.7 Can We Tailor Therapy?

More research continues to support the need for patient-specific adaptations to therapy based on risk stratification, which supports the need for precision medicine. Additional risk factors for cardiotoxicity should be taken into account when patients begin therapy. As noted, female sex, specific gene variants, significant familial cardiac history, and younger age at diagnosis, among other factors, increase the risk of cardiotoxicity and should be considered in treatment decisions (Table 1.1).

Imaging studies, such as echocardiography, are also often used during and after chemotherapy because a large percentage of survivors experience reduced LV function such as LV fractional shortening within just a few years after completing therapy [37]. Unfortunately, echocardiography during therapy does not detect early subtle cardiac damage or dysfunction that is associated with late cardiotoxicity in long-term survivors [3, 5]. Additionally, the frequency of screening and the best treatment options if an abnormality occurs are still debated [55].

1.7.1 Other Preventive Options

Changing the administration and dosing of chemotherapy to reduce cardiotoxicity has also been investigated. For example, continuous intravenous infusions of doxorubicin reduced peak plasma levels and ultimately resulted in reduced cardiotoxicity among adults [30]. Unfortunately, this finding was not replicated in children treated with anthracyclines in terms of reducing late cardiotoxicity in long-term survivors [75].

1.7.2 A Heart-Healthy Lifestyle

Living a heart-healthy lifestyle is important for everyone, but it is probably even more important for survivors of childhood cancer. Survivors should be encouraged to maintain a well-balanced diet and to exercise medically tailored to safe capabilities [76]. These patients should also be monitored, given the potential of diminished cardiac reserve caused by disease-related therapies [46]. Minimizing traditional cardiovascular risk factors, such as smoking, obesity, illicit drug use, heavy drinking, and inactivity, is also of utmost importance for survivors.

1.8 Treatment Options for Cardiotoxicity

Unfortunately, there is no established, evidence-based treatment for anthracycline-related cardiotoxicity. No specific therapy has been established as the standard of care for cardiac disease secondary to chemotherapy or radiation. Beta-blockers and ACE inhibitors, for example, are standard-of-care medications for treating and

managing heart failure, but their effects on progression-free or overall survival, or even quality of life among survivors, have not been established [57], and the beneficial effect of the ACE-inhibitor enalapril in this population with either asymptomatic left ventricular dysfunction or heart failure was transient, delaying but not preventing progression [73].

1.9 Economic Impact

In an era when people are living longer than ever, the financial aspects of medical care need to be considered. Cost-effective strategies for preventing and treating disease should be developed and implemented when possible. A cost-effectiveness analysis in France among patients with aggressive non-Hodgkin lymphoma estimated the potential economic costs of treatment with dexrazoxane or liposome-encapsulated doxorubicin [77]. The analysis, which included direct medical costs of providing cardioprotection and treating heart failure, suggested that cardioprotective therapies were both clinically and financially effective. Because the number of patients at any given institution is too small for meaningful and broadly applicable results, the establishment of pediatric cardio-oncology as a subspecialty will encourage collaborative clinical research and foster patient transition to adult care to study long-term outcomes and provide critical expertise.

1.10 Conclusion

The progress in curing childhood cancer is one of the greatest advances in pediatric medicine during the past several decades. With continued success in finding cures and improving survival, we must also make improvements in preventing and treating the long-term adverse effects of cancer therapy. In addition, improving quality of life must also be a priority as more and more patients survive their disease. Survivors should be cared for by a multidisciplinary team that considers all aspects of their care. Given the large population of survivors, preventing the late effects of treatment should be at a forefront of research with a primary emphasis on cardiotoxicity.

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2 Kidney Disease in Childhood Cancer Survivors

Roderick Skinner and Lars Hjorth

2.1 Introduction

Chronic kidney disease (CKD) is common in childhood cancer survivors (CCS). Although it may represent a legacy of the initial malignancy, more commonly it is a consequence of the treatment received, especially systemic chemotherapy or radiotherapy or surgery, involving the kidney. Additional treatment-related causes include immunotherapy or supportive treatment (e.g. aminoglycoside antibiotics). The prevalence of CKD in CCS varies greatly according to the treatment received by the study population and the renal outcome measures employed.

A cohort of 1442 CCS was studied with each survivor being evaluated once at a median age of 19 years and median follow-up of 12.1 years from initial diagnosis. Blood pressure, serum magnesium, serum phosphate and urine albumin concentrations were measured and glomerular filtration rate (GFR) calculated using the Schwartz (in children) or CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) (in adults) formula [1]. Overall, 28.1% of survivors had at least one abnormality, including hypertension in 14.8%, albuminuria in 14.5%, reduced GFR (<90 mL/min/1.73 m^2) in 4.5%, hypomagnesaemia in 8.8% and hypophosphataemia in 3.0%. Risk factor analysis found associations between low GFR and nephrectomy with or without nephrotoxic chemotherapy (cisplatin, carboplatin, ifosfamide) and/or radiotherapy, higher cumulative ifosfamide doses and high-dose cyclophosphamide (≥1 g/m^2/course). In addition, hypomagnesaemia was associated with cisplatin dose and/or nephrectomy, albuminuria with ifosfamide dose and hypertension with abdominal radiotherapy [1].

In another large cohort study, GFR was calculated with the CKD-EPI formula in 1122 5-year CCS seen in a single long-term follow-up (LTFU) clinic, with longitudinal data (median of 6 GFR measurements) available in 920 survivors. The median follow-up from diagnosis was 21 years, and all survivors were at least 18 years old at study [2]. Glomerular dysfunction was defined as GFR <90 mL/min/1.73 m^2 and potentially nephrotoxic treatment as ifosfamide, cisplatin, carboplatin, high-dose methotrexate, high-dose cyclophosphamide, radiotherapy to the kidneys or nephrectomy. In survivors previously given potentially nephrotoxic treatment,

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compared to survivors who had not, GFR was lower (mean 95.2 [95% CI, 92.2–97.9] versus 100.2 [98.1–102.3] mL/min/1.73 m^2; $p < 0.001$) and the likelihood of glomerular dysfunction higher (mean 26.4 [20.6–33.0] versus 6.6% [4.4–9.6]; $p < 0.001$), up to 35 years post-treatment. GFR continued to fall with time. The highest risks were observed with larger cumulative doses of ifosfamide and of cisplatin (especially >500 mg/m^2) and with nephrectomy (especially in survivors who were older at the time of nephrectomy) [2].

The prevalence of nephrotoxicity is higher in studies that focus on CCS who have received potentially nephrotoxic chemotherapy, with 20–50% suffering CKD after ifosfamide [3, 4] and 40% after cisplatin [3]. Likewise, historical data has shown that 46% of adults with peptic ulcers treated with radiotherapy that included the left kidney developed evidence of chronic nephrotoxicity within 19 years, including 10% with severe hypertension or glomerular impairment [5]. Glomerular hyperfiltration is well documented as a long-term consequence of nephrectomy [6]. However, a recent study found a mildly reduced GFR (CKD stage 1, 60–89 mL/min/1.73 m^2) in 23% and chronic albuminuria in 9% of 35 adult-aged, long-term (≥5 years) survivors of childhood non-syndromic unilateral renal tumours (83% Wilms' tumour) treated by unilateral nephrectomy, some of whom received additional chemotherapy (31 survivors) and radiotherapy (8) [7]. Malignant disease itself may occasionally cause CKD by direct tumour infiltration or the long-term consequences of urinary tract obstruction or tumour lysis syndrome.

Data from the Childhood Cancer Survivor Study of over 10,000 CCS, treated in the 1970s and 1980s, found that 0.5% had developed renal failure or were requiring dialysis by a mean age of 27 years (mean 18 years from initial cancer diagnosis), representing a ninefold increased risk compared to their siblings [8]. Although current treatment protocols seek to reduce chronic renal toxicity, the greater use of potentially nephrotoxic chemotherapy since the 1970s and the ever-increasing intensity of treatment regimens for many poor prognosis malignancies make it likely that chronic nephrotoxicity will remain prevalent in contemporary CCS cohorts.

The consequences of nephrotoxicity are not restricted to the immediate sequelae of renal impairment. Significant glomerular impairment may limit further chemotherapy options available to the patient, during both first-line and subsequent relapse treatment, and may ultimately have an adverse effect on the patient's outcome by preventing use of optimum chemotherapy agents and schedules. Furthermore, potentially nephrotoxic treatments are also highly effective at treating cancer so it is important to enable their continued use to maximise the chances of cure for as many children as possible. It remains important to learn how to use existing potentially toxic treatments more safely until we find better alternatives [9].

2.2 Chemotherapy

Several cytotoxic drugs may cause chronic nephrotoxicity, frequently with an acute or subacute presentation followed by incomplete recovery and sometimes with a later onset or deterioration even after the causative treatment has been discontinued. The chemotherapy agents most frequently associated with severe chronic nephrotoxicity are ifosfamide and cisplatin. Less frequently, carboplatin, methotrexate (especially in high doses) and the nitrosoureas (especially semustine) can cause chronic nephrotoxicity which may occasionally be severe. Although several other cytotoxic agents, including actinomycin D, anthracycline agents, melphalan and vincristine, have been associated with chronic renal damage, they are rarely recognised as the principle cause of chronic nephrotoxicity in CCS. Whilst cyclophosphamide has been implicated as a contributing factor in CKD, its relevance in the absence of other nephrotoxic treatments is uncertain.

2.3 Ifosfamide

Ifosfamide causes both acute and chronic glomerular and tubular damage. Acute glomerular damage manifesting as severe acute kidney injury (AKI) is uncommon in children but is recognised in adults [10]. AKI may resolve, or incomplete recovery may cause CKD, which may also occur even in the absence of previous overt acute toxicity [11, 12]. Stage 2 and 3 CKD (GFR 30–89 mL/min/1.73 m^2) have been reported in 20–50% of children and adolescents and may only become apparent months after completion of ifosfamide treatment [13, 14]. Acute proximal tubular toxicity occurs in up to 25% of children given ifosfamide, most commonly causing phosphaturia and hypophosphataemia [14], leading to hypophosphataemic rickets (HR) in children [15] or osteomalacia in adults [16] if severe and prolonged. Additional characteristic features of proximal tubular impairment are often present including renal glycosuria (in the absence of hyperglycaemia), aminoaciduria and proximal renal tubular acidosis (RTA). In severe cases generalised proximal tubular reabsorptive impairment presents as the Fanconi syndrome [14, 15]. Much less commonly, distal tubular nephrotoxicity causes nephrogenic diabetes insipidus, presenting with severe polyuria, and distal RTA has also been described [15]. Tubular toxicity may persist for years, necessitating continued oral electrolyte and mineral supplementation, but long-term studies have suggested that it improves over a period of several years [4], although similar recovery is not usually seen in glomerular function. Significant chronic ifosfamide nephrotoxicity is also common in adults, with 53% of 5-year survivors suffering from CKD stage 3 or greater (GFR <60 mL/min/1.73 m^2) in a large cohort study of 154 survivors [17]. Chronic nephrotoxicity may also cause hypertension, albeit uncommonly, and untreated HR may impair growth [15, 18].

Studies of the very long-term outcomes of ifosfamide nephrotoxicity have shown improvements in tubular toxicity but persistence of CKD. A cross-sectional study of 183 children and adolescents previously treated with a median dose of 54 g/m^2 at a median age of 9.3 years, and studied once at a median follow-up of 10 (5–20.7) years, found a reduced GFR (<90 mL/min/1.73 m^2) in 21%. Although tubular phosphate reabsorptive capacity was reduced in 24%, only 1% were hypophosphataemic. Proteinuria was observed in 12% [3]. A longitudinal study of 25 patients given a median of 106 g/m^2 ifosfamide showed considerable inter-individual variability, but more patients had a low GFR (<87 mL/min/1.73 m^2) at 1 (72%) and 10 (50%) years than at the end of treatment (26%). In contrast, clinically significant tubular toxicity present at the end of treatment had resolved in all patients 10 years later [4].

Several patient- and treatment-related risk factors have been described for the development of ifosfamide nephrotoxicity. Treatment-related risk factors are well established, especially high cumulative ifosfamide dose [12, 14, 19], previous or concurrent treatment with cisplatin and prior nephrectomy [20]. In terms of patient-related risk factors, the frequently cited importance of young age at treatment [12] as an independent predictor of toxicity, especially tubular impairment, remains uncertain due to conflicting evidence. Clinical experience, several case reports and some studies suggest an increased risk in young children [12, 18, 19, 21], whilst other studies have not found such an effect [14, 20], and uncertainty remains about the role of confounding factors such as cumulative dose and additional cisplatin treatment. Furthermore, very-long-term studies have shown no increase in toxicity in patients treated at a younger age [3, 4]. Pre-existing renal impairment is widely recognised as a risk factor by clinicians, consistent with the known adverse impact of prior nephrectomy [20]. There is no conclusive evidence that the ifosfamide infusion duration (bolus, short or prolonged infusion), nor the drug's pharmacokinetic profile, influence long-term nephrotoxicity [22].

The very-long-term follow-up studies described above did not find a clear relationship

between ifosfamide dose and severity of glomerular toxicity. However, the Oberlin study found that reduced GFR was related to older age at treatment and longer duration of follow-up. Likewise, the severity of phosphaturia was related to higher cumulative ifosfamide dose (p = 0.02) and longer duration of follow-up (p = 0.0005); of these factors, ifosfamide dose had the larger effect on phosphaturia [3].

Ifosfamide nephrotoxicity is believed to be due to a toxic metabolite produced in significant amounts in the kidney by the breakdown of ifosfamide but not that of its structural isomer cyclophosphamide, resulting in cellular oxidative stress leading to mitochondrial damage and energy depletion [23]. Although not proven conclusively, chloroacetaldehyde has been implicated as a potential candidate, and the considerable inter-patient variability in its production may account for the wide range in severity of nephrotoxicity in ifosfamide-treated patients [24].

2.4 Platinum Agents (Cisplatin and Carboplatin)

Cisplatin may also cause both acute and chronic glomerular and tubular toxicity. There are numerous descriptions of cisplatin-induced AKI and subsequent CKD [25–27], with CKD manifest by reduced GFRs (stage 2 or greater, i.e. GFR <90 mL/min/1.73 m^2) reported in 60% in children [25, 26]. However, the pattern of cisplatin-induced tubular damage is very different to that caused by ifosfamide and is manifest by magnesuria and hence chronic hypomagnesaemia which is reported in 10–30% of children [25–27]. Hypocalcaemia occurs less frequently and appears to be secondary to hypomagnesaemia [28]. Distal nephron damage is described, resulting in the association of hypocalciuria and hypokalaemic metabolic alkalosis, as well as polyuria, but is seldom clinically significant [29]. Mild but untreated cisplatin nephrotoxicity has been associated with growth impairment in children; the authors speculated that it might be due to increased phosphate and magnesium urinary losses [30]. CKD is also common in adults with a cohort study reporting stage 3 disease in 33% of 397 5-year survivors treated with cisplatin [31]. Hypertension is well described but may be in part due to vascular toxicity in addition to nephrotoxicity [32].

Carboplatin nephrotoxicity is similar in nature to that seen with cisplatin, but markedly less common causing glomerular impairment in 0–25% of CCS and hypomagnesaemia in 0–10%, and is usually much less severe [33, 34].

A longitudinal study evaluating 27 patients given a median cisplatin dose of 500 mg/m^2 revealed marked inter-individual variability over the 10 years of follow-up. However, there was no significant overall change in the frequency of reduced GFR (<90 mL/min/1.73 m^2) and hypomagnesaemia over follow-up [35].

Several patient- and treatment-related risk factors for the development of cisplatin nephrotoxicity in children have been investigated. The importance of total dose is uncertain due to conflicting evidence. However, marked glomerular (GFR) and tubular toxicity (hypomagnesaemia) was reported after a high dose rate of cisplatin (i.e. ≥40 mg/m^2/day) in adults [36, 37], and higher dose rates (>40 mg/m^2/day) have been associated with greater glomerular and tubular toxicity than a lower dose rate (40 mg/m^2/day) in children [26]. Although initial studies found no relationship between age and cisplatin nephrotoxicity in children [25, 26], a very-long-term study found that glomerular, and to a lesser extent tubular, toxicity was more common in children treated at an older age [35]. Extensive clinical experience and some published evidence suggest that treatment with other potential nephrotoxins, including ifosfamide, methotrexate and aminoglycosides, may exacerbate nephrotoxicity [20]. There is no convincing evidence that the risk of nephrotoxicity in clinical practice can be reduced by pharmacokinetically guided dose modification.

In contrast to cisplatin, the frequency and severity of carboplatin-induced chronic hypomagnaesemia in children is related to cumulative dose as well as older age at treatment, whilst long-term glomerular impairment is also more

common in older children [33, 35]. Since the main route of carboplatin clearance is via glomerular filtration, it is unsurprising that other potentially nephrotoxic chemotherapy (e.g. cisplatin, ifosfamide, melphalan) [38–41] and pre-existing renal dysfunction [42] have been shown to increase carboplatin-induced renal damage.

The mechanism of platinum nephrotoxicity is unclear although the differential nephrotoxicity of cisplatin and carboplatin suggests that the greater frequency and severity of toxicity after cisplatin may result from the formation of increased amounts of a putative nephrotoxic metabolite due to the increased lability of the chloride ligand of cisplatin compared to the cyclobutane dicarboxylate group of carboplatin. Several mechanisms of platinum nephrotoxicity have been proposed, invoking direct cellular toxic and vasoconstrictive and pro-inflammatory effects [43]. Of the numerous protective agents suggested, amifostine has generated most interest. It is an organic thiophosphate prodrug hydrolysed in vivo to an active cytoprotectant compound, WR-1065, which protects healthy cells preferentially to malignant cells. Amifostine reduced nephrotoxicity in a randomised clinical trial in women receiving cisplatin for ovarian cancer [44]. Although American Society of Clinical Oncology (ASCO) guidelines recommend consideration of its use in patients receiving cisplatin [45], neither amifostine nor any other nephroprotective agent has shown convincing benefit in children, and none is used routinely in clinical practice.

2.5 Other Chemotherapy Drugs

High-dose intravenous methotrexate regimens (>1 g/m^2) may rarely cause serious or even fatal systemic or renal toxicity [46] and more frequently cause subclinical acute nephrotoxicity in children, with considerable reductions in GFR [47] and rises in urine excretion of renal tubular biomarkers [48]. The risk of methotrexate acute nephrotoxicity is reduced greatly by prophylactic intravenous fluid and alkalinisation regimens to prevent tubular precipitation [46]. However there is little information about the frequency of chronic methotrexate nephrotoxicity.

Melphalan has been linked with nephrotoxicity, usually when given in high doses prior to BMT, but understanding of its role in causing renal damage in this setting is unclear due to the concurrent use of other potentially nephrotoxic agents. AKI has been reported after the combination of high-dose carboplatin and melphalan in four children, with incomplete renal recovery in one of two survivors [40].

The nitrosourea compounds carmustine (BCNU), lomustine (CCNU) and semustine (methyl-CCNU) may all cause irreversible chronic glomerular impairment, which often develops only after completion of treatment. In six children receiving >1500 mg/m^2 of semustine, end-stage renal disease (ESRD, GFR <15 mL/min/1.73 m^2) developed in four and CKD in one, and the authors recommended a dose limit of 1200 mg/m^2 [49]. Nephrotoxicity due to the other nitrosoureas is rare. Of 89 patients given carmustine, four adults suffered from an insidious onset of mild glomerular impairment [50], whilst slowly progressive ESRD may follow lomustine treatment [51].

2.6 New Agents

It is now acknowledged that several of the new generation of targeted anticancer drugs can cause nephrotoxicity, although most published information is from adult studies [52] and there is insufficient data to clarify long-term outcomes, particularly in children. AKI with histological features of acute tubulointerstitial nephritis has been described in up to 2% of adults treated with immune checkpoint inhibitors, although corticosteroids led to partial improvement in most patients [53, 54]. Nevertheless, active surveillance has been recommended in view of the potentially severe and lasting consequences [55]. Minimal change/focal segmental glomerulosclerosis and thrombotic microangiopathy have been reported in patients treated with vascular endothelial growth factor (VEGF) inhibitors although they appear to be reversible with drug discontinu-

ation [56]. Growing recognition of the frequency and potentially severe implications of a range of nephrotoxic outcomes after treatment with new as well as existing anticancer agents has generated a new field of onconephrology [55–57].

2.7 Radiotherapy

Although well described in 10–50% of children receiving radiotherapy to a field including both kidneys [58], the true extent of chronic radiation-induced nephrotoxicity in children is unclear and may be under-recognised due to its late onset and the presence of other potential causes of renal damage in most patients [5]. Acute and subacute nephrotoxicity is often asymptomatic but may be revealed by a raised serum creatinine. Chronic renal damage may present with haematuria, proteinuria, hypertension, oedema and anaemia, often progressing to CKD [5].

2.8 Surgery and Hyperfiltration

Residual renal tissue in children with single kidneys or those who undergo unilateral nephrectomy demonstrates compensatory structural and functional changes, characterised by renal hypertrophy [59] and higher GFRs when corrected for renal surface area [60]. It is expected that such hyperfiltration of the remaining kidney may cause long-term damage demonstrated by proteinuria and microalbuminuria (found in up to 35% of Wilms' tumour survivors) [59, 61], hypertension (described in 7% in a series of 1171 patients studied up to 5 years after treatment completion) [62] and rarely focal glomerulosclerosis resulting in CKD [63]. A large cohort study confirmed the importance of nephrectomy as one of the principle causes of CKD (stage 2 or greater) in CCS [2].

Hyperfiltration may be seen at diagnosis, during and after completion of therapy [64–66]. Whether this is an indicator of early and/or late nephrotoxicity is unclear. It has been suggested to be the result of tumour breakdown and debris at diagnosis, but this is unlikely to explain its occurrence later during or after treatment. Hyperfiltration was found to be particularly prevalent in patients with CNS tumours where tumour volumes are usually smaller and therefore tumour cell breakdown also is expected to be lower. The authors speculated that a hypermetabolic state may play an important role in the pathophysiology of hyperfiltration [65].

Functionally significant tubular dysfunction was not observed in one detailed study of 40 Wilms' tumour survivors, 47.5% of whom had radiotherapy exposing the remaining renal tissue [59]. Albuminuria, hypertension and more rarely glomerular impairment appear to be the main features of renal toxicity in Wilms' tumour survivors [59].

2.9 Impact of Very-Long-Term Nephrotoxicity

There is still little published information about the prevalence and nature of very-long-term nephrotoxicity in the overall CCS population. This is particularly important given the expected decline in renal function that occurs as part of the natural ageing process in apparently healthy older individuals and the recent observation that many CCS display evidence of an accelerated ageing phenotype manifest by frailty [67]. It is concerning that chronic nephrotoxicity in a proportion of CCS may interact adversely with diminishing physiological reserve as survivors age, potentially leading to an increased risk of clinically significant renal impairment in middle-aged and older survivors.

2.10 Management of Nephrotoxicity

Although nephrotoxicity should ideally be minimised prior to the onset of chronic damage by stopping or modifying further treatment with the causative agent, this is frequently impractical due to the delayed onset of clinically significant renal damage in many cases, particularly of ifosfamide nephrotoxicity [13]. In addition, finding the opti-

mal balance between the risk (for renal function) of continuing potentially damaging treatment and the potential risk (for the likelihood of cure of malignancy) of stopping it is frequently difficult especially given the paucity of evidence to guide clinicians. Therefore, management of chronic nephrotoxicity is frequently supportive, aiming to ameliorate manifestations of established toxicity.

For those individuals with established severe treatment-related glomerular impairment, standard renal monitoring and management should be instituted. In ESRD, standard renal replacement treatment strategies (dialysis or transplantation) are usually appropriate in CCS, but the feasibility of some may be limited by previous treatments and interventions. Blood pressure and urine protein should be monitored regularly since the pace of progressive glomerular impairment may be delayed by optimal control of hypertension and introduction of an angiotensin-converting enzyme inhibitor or angiotensin II blocker in survivors with significant proteinuria [68]. Patients with severe tubular toxicity may require prolonged supplementation with high electrolyte or mineral doses to improve plasma concentrations and prevent subsequent complications such as HR and symptomatic hypomagnesaemia.

2.11 Strategies to Prevent Nephrotoxicity

Since accurate prediction of renal toxicity is not yet feasible despite considerable study of potential risk factors, there is an important need for further research into other potential factors including treatment-related pharmacokinetic variables and genetic polymorphisms.

Nevertheless nephrotoxicity may be prevented or reduced by general or specific strategies. General approaches to the use of potentially nephrotoxic agents may include dose limitation where the increased toxicity of higher doses is clear (e.g. for ifosfamide and radiotherapy) [5, 14] or subtotal rather than total nephrectomy (nephron-sparing surgery) [69]. For drug-induced nephrotoxicity, hyperhydration is used with most cisplatin, ifosfamide and methotrexate regimens to reduce renal accumulation of toxic metabolites, although the benefit of mannitol diuresis in some cisplatin administration schedules is uncertain [70].

Ideally, nephrotoxicity will be reduced or hopefully eliminated in the future by the development of less toxic agents, but this relies on greater understanding of the causative toxic mechanisms.

2.12 Surveillance Guidelines

Surveillance for late adverse effects is an important part of the LTFU care of CCS, and several national paediatric oncology societies have published LTFU surveillance clinical practice guidelines. The International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) is developing renal toxicity surveillance guidelines. Until these are available, it would appear reasonable to follow the existing national guidelines by identifying high-risk CCS as those who have received ifosfamide, platinum drugs, renal radiotherapy including total body irradiation (TBI) or nephrectomy, and probably survivors of haematopoietic stem cell transplant conditioned with chemotherapy. Currently available national guidelines all recommend surveillance for both glomerular and tubular impairment, including measurement of serum creatinine, electrolytes, magnesium (if the patient received a platinum drug), phosphate and bicarbonate (for recipients of ifosfamide), as well as more general measures including urinalysis (for proteinuria) and blood pressure measurement. However, the efficacy of surveillance following these recommendations remains unproven, and indeed these tests have been shown to yield few positive results in at-risk previously undiagnosed survivors [71]. A more targeted approach, whereby higher-risk CCS (e.g. those treated with higher-dose ifosfamide or with total body irradiation) are prioritised for surveillance, has been proposed as a more efficient use of screening resources [72]. Although the forthcoming IGHG renal surveillance guidelines

will hopefully clarify some of these uncertainties, these findings illustrate the difficulties of designing effective surveillance strategies that will detect potentially treatable renal late toxicities to allow improved renal health outcomes in a significant number of survivors.

2.13 The Future

It is to be hoped that improved prediction (and hence prevention), aided by earlier detection and management of emerging toxicity, will reduce the frequency of nephrotoxicity in CCS. Furthermore, improved understanding of the pathogenesis of nephrotoxicity, and possibly of genetic polymorphisms that may predispose certain survivors to earlier and more severe toxicity [73], may also lower the burden of renal toxicity. However, it is important to recognise that continued vigilance is required since the nephrotoxicity of ifosfamide was not predicted by preclinical studies and that apparently normal renal function on completion of treatment does not necessarily exclude the later development of significant nephrotoxicity. Indeed CKD may not become evident until months or years later, as shown by the often delayed onset of nitrosourea nephrotoxicity [50], highlighting the importance of LTFU studies. Therefore, particularly given the proliferation of novel targeted drugs, some of which are already showing evidence of nephrotoxic potential, it will be necessary to maintain awareness of the risk of renal damage in CCS.

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Ototoxicity After Childhood Cancer

3

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3.1 Introduction

Many drugs that are used in the treatment of cancer can, as a side effect, damage the ear. These include anticancer drugs and also aminoglycoside antibiotics, glycopeptide antibiotics, macrolides, nonsteroidal anti-inflammatory drugs, loop diuretics, quinine, ototopical medication, and cranial irradiation (Fig. 3.1). The short- and long-term effects of these ototoxic drugs on patients' hearing can be severe, as impaired speech perception can have significant effects on language development, psychosocial development, educational attainment, and employment prospects and therefore on the individual's quality of life [1–3]. Drug-induced tinnitus can also greatly impair quality of life [4]. Balance impairment resulting from vestibular injury is described less often in the literature but may be underreported [5, 6]. Balancing the benefits of the planned drug treatment against these potential effects should be a key consideration for oncology professionals.

3.2 Ototoxic Hearing Loss

The prevalence of ototoxicity varies considerably in the literature, from 4 to 90% of those who have been treated with potentially ototoxic agents (see below for details) [7, 8]. Factors affecting this broad range include the drug administered, the patient's age (children and elderly patients are more at risk), cumulative dose, and method of administration (with a rapid infusion presenting a higher risk [7]). Aminoglycosides and platinum-based chemotherapy agents are of greatest concern as they may lead to permanent ototoxicity. Other risk factors for ototoxicity are renal dysfunction, blood–brain barrier disruption, concomitant ototoxic agents, pre-existing hearing loss, cranial irradiation, and exposure to noise. There is, however, substantial inter-individual variability in susceptibility to ototoxicity. The signifi-

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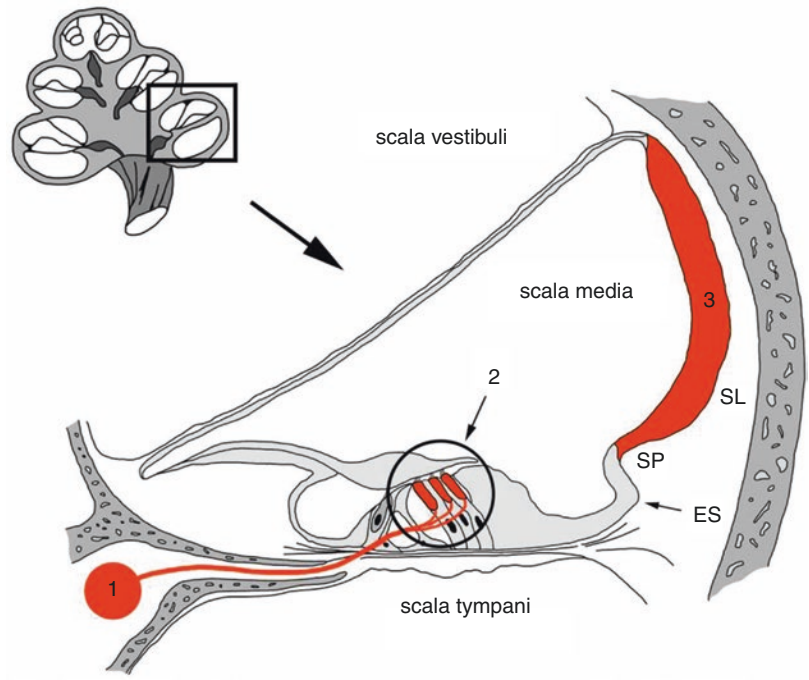

Fig. 3.1 The inner ear and ototoxic noxae. Chemotherapy with cisplatin may result in ototoxity, mainly affecting the scala media of the cochlea. Targets in detail are the spiral ganglion cells (1), the outer hair cells (2) of the basal turn, and the stria vascularis (3). *SL* Spiral ligament, *SP* Spiral prominence, *ES* External sulcus

Cytostatics	Loop diuretics	Aminoglycoside antibiotics	Cranial irradiation
Cisplatin	Etacrynic acid	Kanamycin	
Carboplatin	Furosemide	Gentamicin	
Oxaliplatin	Bumetanide	Amikacin	
		Tobramycin	
		Netilmicin	

cant role played by genetic factors is discussed later in this article and is being investigated in a current European Study (PanCare LIFE, lead investigators: Van den Heuvel-Eibrink, Zolk, Langer and am Zehnhoff-Dinnesen) [9–12].

The typical manifestation of ototoxic hearing loss is a bilaterally symmetrical high-frequency sensorineural hearing loss, progressing over time from higher to lower frequencies (Fig. 3.2). The ability to recognize sibilant and fricative speech sounds is initially affected, as these sounds are located higher in the frequency range of the auditory spectrum than others, such as vowel sounds [13].

3.3 Platinum Compounds

The most commonly used platin compounds are cisplatin, carboplatin, and oxaliplatin. Cisplatin is a highly effective chemotherapeutic agent in pediatric oncology, but its use is limited by side effects such as ototoxicity and nephrotoxicity [7]. Cisplatin (cis-diamminedichloroplatinum II) is a plane complex with two cis-bound chloride atoms and two ammonia ligands. The cytotoxic effect occurs because of building up DNA cross-links and the induction of apoptosis by DNA replication and the functioning of repair mechanisms being hindered [14]. The ototoxic effects of cisplatin are mainly attributed to the increased production of reactive oxygen species (ROS) in the cochlea via various mechanisms. This leads to the depletion of the antioxidant glutathione and its regenerating enzymes, an increased rate of lipid peroxidation, oxidative modification of proteins, nucleic acid damage, and S-nitrosylation of cochlear proteins and to the induction of apoptosis of the outer hair cells and supporting cells (Fig. 3.3a, b). Studies of human temporal bones and animals revealed damage in different regions of the cochlea after chemotherapy with cisplatin. Possible targets in the cochlea

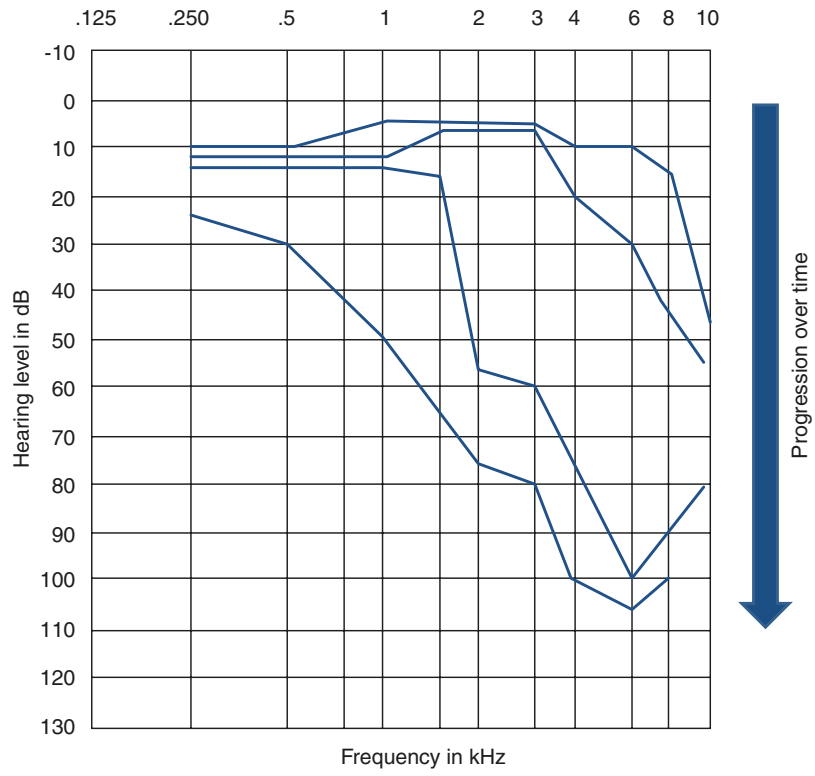

Fig. 3.2 Typical progression over time of a cisplatin-induced ototoxic hearing loss.

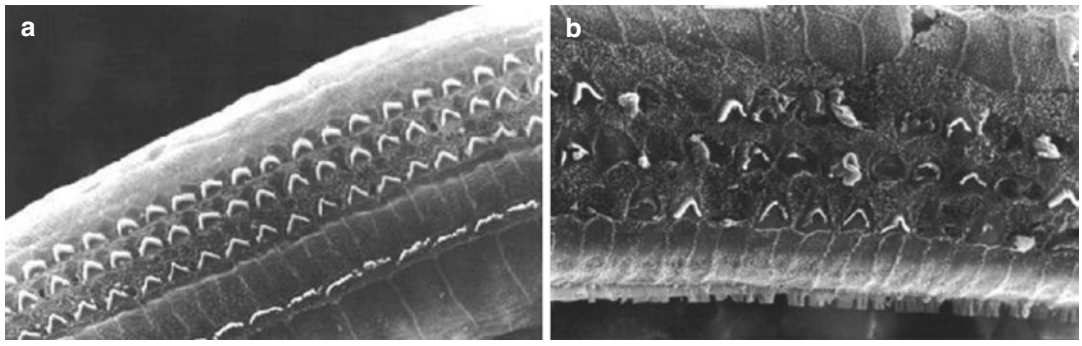

Fig. 3.3 (**a**) Three rows of outer hair cells before and (**b**) after ototoxic damage by cisplatin in an animal experiment [15]

are the spiral ganglion cells, the outer hair cells, and the stria vascularis. The accumulation and retainment of the platinum agents in the cochlea for months to years might explain the possible long-term progression of hearing loss in these cases [16, 17].

The basal turn of the cochlea is affected first, and hearing loss therefore begins in the high frequencies before progressing to the lower frequencies [18] (Fig. 3.2).

The reported prevalence of cisplatin-related ototoxic hearing loss in children covers a wide range, from 1.7% to 90.5% [8, 19–27]. This is, in part, due to differences in study design (study populations, timing of the measurements, definitions of hearing loss used to indicate ototoxicity, and low sample sizes) but also to a number of key confounding factors which differ for individual patients across all of the studies. These factors include the administration schedule, the use of

other potentially ototoxic agents, the order in which agents are administered, patient age, renal function, hypoalbuminemia, the presence of a pre-existing hearing impairment, and the cumulative dose [7, 21, 28–31].

There is considerable inter-individual variability in the relationship between the tolerated ototoxic platin dose and hearing loss: some patients can tolerate cumulative doses of 360–480 mg/m^2 of cisplatin without hearing loss, whereas others develop severe hearing loss after just 120 mg/m^2 [32]. Various approaches to the assessment of genetic predisposition have attempted to illuminate this variability and are displayed in detail in the chapter "Genetic Predisposition to Late Effects: Pharmacogenomics of Cisplatin-Induced Ototoxicity."

A progression of hearing loss after the therapy was seen in up to 37% of affected children up to 136 months after the end of therapy [19, 33–35]. Forty-nine percent of patients have been reported to require hearing aids during post-therapeutic follow-up, but cochlea implants were very rarely necessary [33, 36]. Tinnitus can be an early sign of ototoxicity and has been reported in 25–60% of small cohorts of adults or older children after cisplatin therapy [4, 8, 37, 38].

Carboplatin (cis-diammine-1,1-cyclobutane dicarboxylatoplatinum II) is applied in children with retinoblastoma and malignant brain tumors and as part of high-dose chemotherapy prior to stem cell transplantation. Permanent, progressive hearing loss, tinnitus, and vertigo can result from apoptosis of the outer and inner hair cells (progressing from the base to the apex) and impairment of the peripheral vestibular system [39]. Carboplatin is reported as being less ototoxic than cisplatin but can be ototoxic in myeloablative doses or in conjunction with other risk factors (e.g., osmotic opening of the blood–brain barrier in malignant brain tumors/metastases), in which cases incidence rates of up to 50% are reached and the onset can occur as late as >3 years after the last dose, or in cases of accidental overdose [22, 29, 40–43]. Ototoxicity from oxaliplatin, which was introduced much later into the clinic compared to cisplatin and carboplatin, is so far rarely reported [44]. Even when clinical risk factors are taken into account, considerable variability in the level of risk of cisplatin-induced ototoxicity faced by individual patients still remains [40, 45].

The ototoxic side effects of platin-based chemotherapy are being explored for more than 20 years. Beck et al. described already in 1995 the elevated risk for hearing loss in platinum-treated patients and recommended an audiological follow-up [46]. Actually, the PanCareLIFE Study tries to evaluate the potential clinical and genetic risk factors for ototoxicity in a wide multinational European cohort pro- and retrospectively.

Here, we will give an overview of cancer entities at risk and related treatment protocols with a selection of published studies (Table 3.1).

3.4 Ototoxic Tinnitus

Tinnitus is the perception of a phantom sound in the ear or head, usually expressed as a constant ringing, buzzing, hissing, or whistling tone [56]. In the majority of patients, this sound is chronic (present for at least 3 months) and subjective (i.e., it cannot be perceived by an examiner) [57, 58]. Tinnitus is frequently accompanied by hearing loss [59]. Tinnitus can have a significant impact on the patient's quality of life, with impact varying in severity, ranging from mild to highly distress [60]. In children, tinnitus can negatively affect concentration and speech discrimination [61], leading to problems with school performance and social life [62]. Accompanying symptoms seen in adults include depression and anxiety [63], occasionally even leading to self-harm and suicide [64].

A recent systematic review by Meijer et al. [73] reported the prevalence of tinnitus in childhood cancer survivors as 3–60% (Table 3.2) [4, 35, 65–72]. The variation in frequency rates seemed to depend on the sample size, childhood cancer subtype, type of treatment, and time to follow-up. In studies with a low risk of bias, a prevalence rate of 3–17% was observed [35, 65–70]. In addition, in comparison with their siblings, survivors had a relative risk of up to 3.7 for developing tinnitus more than 5 years after diagnosis. The risk factors reported were treatment

Table 3.1 Overview of studies involving cisplatin/carboplatin in children/adolescents

Study	Cancer type	Study protocol	Ototoxic drug	Cumulative dose	Radiotherapy	Prevalence of ototoxicity
Children						
[47]	Neuroblastoma	COG (Children's oncology group) A3973 trial	Cisplatin Cisplatin + carboplatin	According to protocol cisplatin 400 mg/m^2, carboplatin 1700 mg/m^2	Yes	Brock criteria: Overall ≥grade 1:87% ≥grade 2 66% Grade 1 21% Grade 2 36% Grade 3 or 4 30% Hearing aids: 59.8%
[25]	Neuroblastoma	NB90 and NB97	Cisplatin, many pts. + carboplatin	Cisplatin range 1–800 mg/m^2, carboplatin according to protocol 1500 mg/m^2	?	WHO criteria >grade 2 hearing aid treated symptomatic hearing loss/ tinnitus: 12.5%
[19]	Neuroblastoma, Hepatoblastoma, Germcell tumor, osteosarcoma	Different SFOP protocols	Cisplatin/ Carboplatin/ Both	Cisplatin median 400 mg/m^2, range 80–800 mg/m^2 Carboplatin median 1600 mg/m^2, range 400–8000 mg/m^2	No	Brock criteria: ≥Brock grade 2: 32.5%
[41]	Retinoblastoma	Not mentioned	Carboplatin	Median 2880 mg/m^2, range 560–6160 mg/m^2	No	Brock criteria: ≥Brock grade 1: 3.4% Grade 1 1.7% Grade 2 0.6% Grade 4 1.1%
[48]	Retinoblastoma	CHP-582	Carboplatin	According to protocol 111.6 mg/kg	Yes	Participants with hearing loss (no exact def.): 0%;
[49]	Retinoblastoma	CHP-582	Carboplatin	Not mentioned	Partly	Definition not mentioned; 0/163
[50]	Medulloblastoma	HIT-SIOP PNET 4	Cisplatin	560 mg/m^2	Yes	Use of hearing aids (questionnaire): 16%
[51]	Hepatoblastoma	SIOPEL 3	Cisplatin	According to protocol 480 mg/m^2	No	Brock criteria: 31.5% hearing loss; grade 1 11.9% Grade 2 12.5% Grade 3 4.2% Grade 4 3%

(continued)

Table 3.1 (continued)

Study	Cancer type	Study protocol	Ototoxic drug	Cumulative dose	Radiotherapy	Prevalence of ototoxicity
[52]	Different types of tumors arising in the pons *n* = 113	POG-9239	Cisplatin	According to protocol 300 mg/m^2	Partly	Subjective and objective hearing loss according to the POG toxicity criteria: ≥ grade 1: Subjective HL 2.7% Grade 2 1.8% Grade 3 0.9% Objective HL: Overall 15% Grade 1 9.7% Grade 2 4.4% Grade 3 0.9%
[53]	Extracranial high-risk malignant germ cell tumors *N* = 295	POG-9049 and Children's Cancer Group 8882	Cisplatin	800–1200 mg/m^2 in the high-dose Group and 400–600 mg/m^2 in the standard-dose group	No	Subjective and objective hearing loss according to NCI criteria Subjective HL: 1.7%; Objective HL 7.1%
Adolescents						
[54]	Osteosarcoma	Various	Cisplatin	210–480 mg/m^2	?	Functional scale Overall hearing loss 41.6%; functional grade 1(>20 dB hearing loss >4000 Hz) 30.5%; grade 2 (>20 dB hearing loss at 4000 Hz and above) 11.1%, No patient grade 3 (>20 dB hearing loss at 2000 Hz and above)
[26]	Osteosarcoma	COSS	Cisplatin	Median cumulative dose: 360 mg/m^2	No	51% hearing loss (>20 dB) of >20 dB in the frequency range of 4–8 kHz. One patient a hearing loss was found at 2 kHz
[55]	Osteosarcoma and soft-tissue sarcoma	COSS-96 and CWS-96/2002P	Cisplatin/ Carboplatin/ Both	Cisplatin 360 mg/m^2 (IQR, 360–480)/ carboplatin median 1500 mg/m^2 (IQR, 1500–1500 mg/m^2)/cisplatin (median dose, 240 mg/m^2; IQR, 240–360 mg/m^2) + carboplatin (median dose, 1200 mg/m^2; IQR, 600–3000 mg/m^2)	Some patients	Modified Münster score: Overall hearing impairment in 47.3% of patients

Table 3.2 Studies on tinnitus frequency and risk in childhood cancer survivors

Authors	*N*	CC type	CC treatment			Age at diagnosis (%)	Median time to FU (range)	Tinnitus at FU (%)	Tinnitus risk ≥5 years after diagnosis[a]
			CT type (%)	RT type (%)	Combined modality(%)				
[65]	14,358	LL, ST, BT	CIS (5.1%) CARB (0.5%)	CRT (57%)	NA	<10 y: 62% ≥10 y: 38%	NA	5.6%	RR 1.7 (95% CI 1.4–2.1)
[66]	4151	HT	MTX, other (94%)	CRT (64.5%)	RC (61%)	<10 y: 82% ≥10 y: 12%	14.1 y (5.0–29.7)	3.3%	RR 1.6 (95% CI 1.2–2.1)
[35]	2061	LL, ST, BT	CIS, CARB, other (84%)	CRT (54%)	NA	Median: 5.0 y (0.0–15.0)	15.0 y (5.0–38.0)	6%	NA
[67]	1876	BT	CIS, CARB, VCR, NAA (49%)	CRT alone (1%)	SR (37%) SRC (25%)	<10 y: 74% ≥10 y: 36%	23.0 y (5.1–38.9)	NA	NA
[68]	1607	BT	Any (30%)	CRT (72%)	SR (42%) SRC (28%)	<10 y: 64% ≥10 y: 36%	NA	11%	RR 3.7 (95% CI 2.7–5.1)
[69]	606	ST	NA	NA	SRC (77%) RC (1%) SC (20%)	<10 y: 71% ≥10 y: 29%	15.7 y (5.2–28.8)	6%	RR 1.3 (95% CI 0.7–2.3)
[70]	380	BT	CIS, CCNU, CPM (59%)	CSRT (94%) CRT (3%)	NA	<10 y: 73% ≥10 y: 27%	NA	17.4%	HR 4.8 (95% CI 3.5–6.8)
[71]	185	LL, ST, BT	Any (98%)	Any location (61%)	RC (40%)	Mean: 8.3 y ± 4.8	Mean: 15.3 y ± 5.8	26%	OR 2.3 (95% CI 1.1–4.6)
[72]	44	LL	MTX, other (100%)	CRT (41%)	NA	Median: 5.5 y (3.0–16.0)	7.5 y (2.0–18.0)	13.6%	NA
[4]	15	ST, BT	CIS, CARB (100%)	CRT (20%)	NA	Median: 4.3 y (0.4–18.0)	9.1 y (0.8–16.5)	60%	NA

Abbreviations: BT Brain tumors, *CC* Childhood cancer, *CCNU* Lomustin, *CCS* Childhood cancer survivors, *CI* Confidence interval, *CIS* Cisplatin, *CPM* Cyclophosphamide, *CARB* Carboplatin, *CSRT* Craniospinal radiotherapy, *CRT* Cranial radiotherapy, *CT* Chemotherapy, *HR* Hazard ratio, *HT* Hematological tumors, *LL* Leukemia/lymphoma, *MTX* Methotrexate, *NA* Not available, *NAA* Nonplatinum alkylating agent, *OR* Odds ratio, *RC* Radiotherapy + chemotherapy, *RR* Relative risk, *SC* Surgery + chemotherapy, *SRC* Surgery + cranial radiation + chemotherapy, *ST* Solid tumors, *UNK* Unknown, *VCR* Vincristine, Y Years

[a]Relative to siblings

with platinum agents, cranial radiation more than 30 Gy, and a history of central nervous system (CNS) tumors [65, 66, 68, 69]. Other risk factors for tinnitus development reported in the literature include hearing loss, noise exposure, and female gender [74–76].

Further research has been carried out over the past decade to gain knowledge about the underlying mechanisms of tinnitus pathology. Tinnitus seems to be generated by multiple neural sources, such as various brain structures and neurotransmitters. Damage to the outer and

inner hair cells of the cochlea (which is typical of sensorineural hearing loss) decreases the neural output to the central auditory pathway. Neurons located in the central auditory pathway respond to this reduced output by upregulating spontaneous neural activity, which is likely to be caused by alteration in the normal balance between excitatory and inhibitory nerve transmission, eventually leading to increased firing rates. Such neural changes can occur at different levels of the central auditory pathway (Fig. 3.4). The dorsal cochlear nucleus, which receives input from the descending branch of the auditory nerve, plays an important role. Other levels at which neural changes can occur include the inferior colliculus, which sends activity to higher levels of the central auditory pathway; the medial geniculate body located in the thalamus, which projects to the amygdala, which itself plays a role in auditory fear conditioning; and the auditory cortex [78, 79]. Cisplatin is reported to induce increased spontaneous activity mostly within the dorsal cochlear nucleus [80, 81].

Increased activity of neurons can cause reorganization of the tonotopic maps within the auditory cortex in some cases. Neurons in the tonotopically organized cortical region affected by hearing loss shift their preferred tuning to

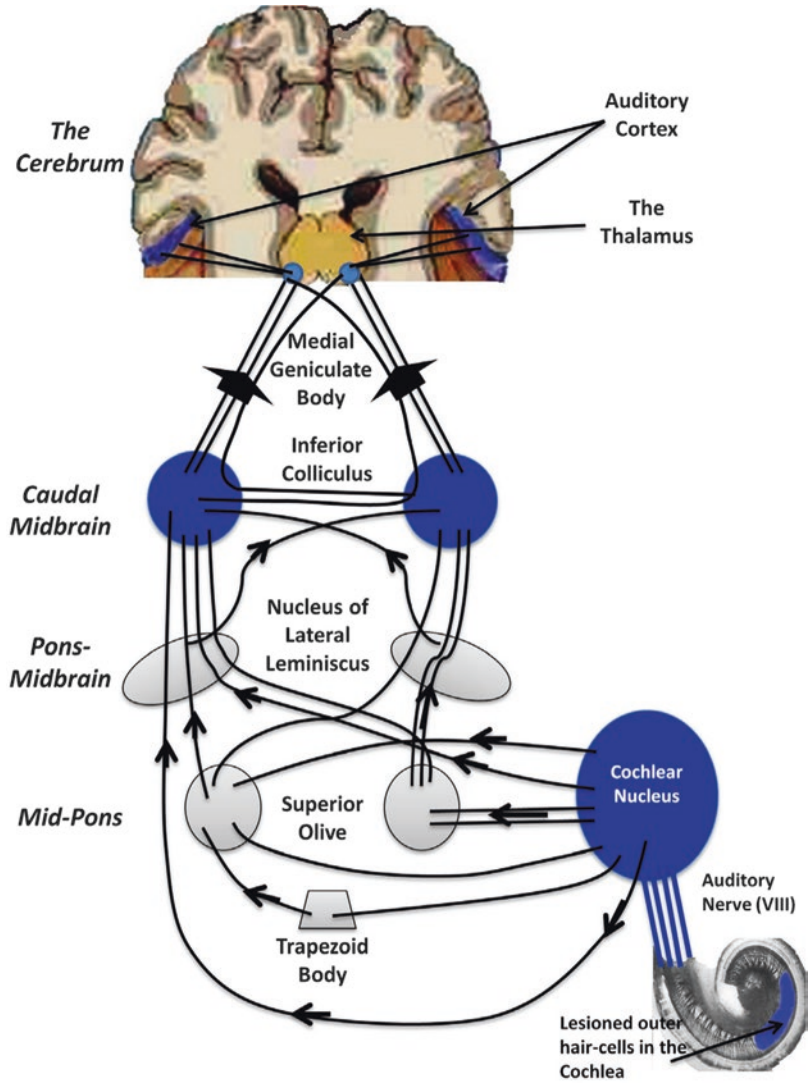

Fig 3.4 The central auditory pathway involved in tinnitus perception [77]

frequencies close to the edge of normal-hearing frequencies, leading to over-representation of these edge frequencies. Activation of the auditory cortex may explain how loud the tinnitus is perceived, in that the mismatch between expected auditory input and real auditory input can lead to reactivation of areas responsible for attention, memory, and executive functions in the brain. Reactivation of these resting areas seems to be associated with attention to or conscious perception of the sound, its salience, and the resulting distress felt by the patient [78, 79].

3.5 Cranial Irradiation

Cranial irradiation alone can impact upon hearing ability by damaging different areas of the auditory system. Conductive hearing losses can result from the increased risk of external ear infections, accumulation of cerumen, and serous middle ear effusion [82]. Permanent sensorineural hearing loss can be the result of the effect of radiation on the cochlear structures, the auditory nerve, or the brainstem. Such sensorineural hearing loss can occur shortly after therapy but more commonly with a latency of 1.5–3 years ([83], Mujica-Mota, [84, 85]). The ototoxic effect of radiation seems to be dose-related, with sensorineural hearing loss occurring at doses ≥30–35 Gy and young patients <3 years of age and patients with a shunt, with infratentorial tumor location, or receiving concomitant ototoxic medication being at higher risk [83, 84, 86, 87]. Therefore, in case of combined therapy with cisplatin, radiation can exacerbate the amount of hearing loss associated with platinum chemotherapy [87–92]. Kortmann et al. saw a higher incidence of ototoxicity in medulloblastoma patients treated with radiation followed by cisplatin chemotherapy (34%), compared to 10% who received neoadjuvant chemotherapy before radiation [93].

Radiation-induced tinnitus has been under-evaluated and under-reported in the literature so far. Three studies of childhood cancer survivors have identified cranial radiation as a risk factor for long-term tinnitus development. However, results regarding the radiation dose and irradiated region (temporal lobe, frontal lobe, and/or posterior fossa) associated with tinnitus in this population varied. Two studies reported a cranial radiation dosage of ≥50 Gy as a risk factor for tinnitus development [67, 70], whereas one study reported a risk of tinnitus development from a radiation dose of ≥30 Gy [65]. The temporal lobe and posterior fossa were identified as high-risk areas in two studies [65, 67] and the temporal and frontal lobe in one study [70]. Lee et al. [94] attempted to determine a safe intensity-modulated radiation therapy (IMRT) dose for the cochlea, in order to avoid tinnitus in their sample of 211 patients treated for head and neck cancer (HNC). They suggested that an IMRT dose of <32 Gy was needed to maintain a low incidence of mild to moderate tinnitus in HNC patients.

3.6 Aminoglycosides

Aminoglycosides (amikacin, apramycin, gentamicin, kanamycin, netilmicin, neomycin, paromomycin, spectinomycin, streptomycin, and tobramycin) may be sometimes used in parallel with a chemotherapy when severe infections occur. They are antibiotics whose bactericidal effect is achieved by binding to the 30S-part of ribosomes, thus leading to errors in protein production. They have a broad action spectrum and are particularly effective against gram-negative aerobic bacteria but have severe ototoxic and nephrotoxic side effects. Their use is therefore mostly restricted to severe infections. However, as bacteria are becoming increasingly resistant, aminoglycosides have once again begun to be used more widely [95, 96].

Ototoxic and vestibulotoxic adverse effects can occur together or separately, and the mechanisms of both are similar to those of platinum compounds: aminoglycosides are transported via cell transporter molecules into the outer hair cell of the cochlea and into the vestibular hair cells where they accumulate. Complexes formed with iron salts catalyze the production of reactive oxygen species (ROS), which thus leads to cell death (apoptosis) and permanent hearing loss which begins in the higher frequencies and is sometimes accompanied by tinnitus [97].

The incidence of aminoglycoside-related hearing loss varies from 2 to 25% [6]. As with platin-induced ototoxicity, susceptibility to aminoglycoside ototoxicity seems to have a component of genetic predisposition: several mitochondrial gene mutations causing impaired mitochondrial protein synthesis have been linked to enhanced susceptibility for ototoxic side effects [97]. Hearing loss usually occurs significantly later than application, and this is explained by the slow clearance of aminoglycoside from the inner ear.

Kanamycin, gentamicin, and amikacin seem to be approximately equal in the risk of cochleotoxicity that they present, followed by the lower-risk tobramycin and netilmicin [30, 98, 99]. Streptomycin is vestibulotoxic, and gentamicin, amikacin, tobramycin, and netilmicin are both cochleo- and vestibulotoxic aminoglycosides [6]. As aminoglycosides are mainly excreted by the kidney, serum levels depend greatly on kidney function as well as the dose administered.

Strict dosage limits for each medicament and regular serum level controls are the most important ways to limit ototoxicity. Further research is being conducted by various study groups into potential protection from aminoglycoside ototoxicity by apoptosis inhibitors, antioxidative agents, and other strategies, as well as the role played by genetic susceptibility [97].

3.7 Other Agents

Other agents used in parallel with cisplatin chemotherapy can also have an ototoxic effect.

Loop diuretics, usually furosemide, are sometimes used to enhance kidney function. In addition, loop diuretics can induce tinnitus and mid- to high-frequency hearing losses that are usually reversible, but their ototoxic effect can be substantially accelerated when combined with aminoglycoside antibiotics [100, 101].The ototoxic effect is mostly transient and is thought to result from fluid and electrolyte shifts in the inner ear, which may result in edema of cochlear tissue and an associated decrease in endocochlear potential [102]. The risk of ototoxicity increases with higher serum levels, rapid intravenous administration, and concurrent administration of other ototoxic medication [7].

Macrolide antibiotics, such as erythromycin and azithromycin, can induce bilateral, symmetrical, and relatively flat sensorineural hearing loss that is usually reversible after the end of treatment [103]. Tinnitus can precede or coincide with this type of hearing loss. A higher risk of audiological complications has been observed with higher drug doses and serum levels [104]. In patients treated with macrolides, bilateral edema of the stria vascularis in all cochlear turns has been observed, together with a decrease in the endocochlear potential [103, 105].

Vincristine and *vinblastine* are chemotherapeutics that have strong neurotoxic side effects. Ototoxic side effects on the cochlea as well as possible neurotoxic effects on the central auditory system have been described in animal studies and case reports after high-dose treatment, but could not be significantly shown in larger cohorts [106–108].

The possible ototoxic effect of *methotrexate* was evaluated in rats, but no effect was found on Distortion-Product Otoacoustic Emission (DPOAE) or auditory brainstem response (ABR) tests following intratympanic administration [109].

A synergism between ototoxic agents and noise was also described [110–116], making noise protection a very important topic of counseling.

3.8 Audiological Practice

Recommendations for audiological monitoring include a baseline hearing test, regular testing during therapy, and follow-up after the end of therapy for at least 3 years, though preferably 5 years, in order to monitor for possible progression of hearing loss [19, 33, 34, 41, 117, 118]. Regular audiological monitoring is necessary for several reasons: firstly, to monitor the effects of drug treatment; secondly, to take preventative steps where the onset of hearing loss is detected; and thirdly, to make patients, family members, and carers aware of possible

hearing deterioration in order to help ensure that any necessary rehabilitation can begin as soon as possible.

The schedule by which auditory monitoring takes place is not yet uniform across audiological services, and recommendations vary in the literature [7, 8]. The best time points for audiological monitoring during therapy depend upon the nature of the drug administration: in cases where there are long gaps between cycles, monitoring could in principle occur between each cycles; where drugs have quicker administration cycles, monitoring between every 2 cycles could be appropriate. Alternatively, monitoring could occur on a chronological basis, where a strict time schedule is followed regardless of drug administration cycles.

The guidelines of the American Speech-Language-Hearing Association (ASHA) (1994) [119] propose that audiological monitoring should take place within 24 h *before* a cisplatin block. Audiological monitoring is not performed directly *after* the administration of cisplatin because patients are often in poor physical condition and may be unable to fully participate in the tests, with the risk of unreliable results being obtained. Temporary hearing loss following cisplatin administration has also been reported [21, 54].

Various schedules for audiological monitoring during the post-treatment period have been proposed, and audiological testing at 3, 6, and 12 months is common, though longer follow-up duration is recommended depending upon the type of drug administered among other factors [117, 118]. The German Society of Pediatric Oncology and Haematology cite Weissenstein et al. [118] in proposing hearing tests every 6 months during the first 2 years after chemotherapy and annual controls for at least the following 3 years [118]. In cases of progression or late onset of hearing loss, the audiological control period should be extended. Where children are treated with cisplatin and cranial irradiation, closer monitoring and a longer follow-up period are recommended because of the increased risk of late-onset hearing loss [83, 91].

Therapy regimens vary broadly and change quickly, so it is only possible to give baseline recommendations. A management plan for follow-up should be tailored to the specific patient [118].

The key diagnostic indicator of ototoxicity is a measurable worsening of hearing threshold (the lowest sound pressure levels at which the individual hears pure tones of different frequencies). Subjective and objective hearing tests can be combined in order to determine this.

Subjective hearing tests range from behavioral tests designed for young children, classic pure-tone audiometry for older children and adults, to speech recognition tests designed for different ages. The typical frequency range tested is 250 Hz to 8 kHz, and international threshold norms for older children and adults are well established (https://www.iso.org/standard/42916.html). Including the inter-octave frequencies 3 and 6 kHz is recommended whenever possible, since platinum-induced hearing loss is typically steeply sloping.

The results of subjective audiological tests vary depending on the capabilities, concentration, and cooperation of the patient, an aspect which is especially important when testing younger children or patients with disabilities. Especially in such cases, an approach to testing which employs a team, generally of two testers, is recommended. The role of the second tester is to manage the patient's attention, which can involve changing play activities quickly when needed, providing positive reinforcement, and encouraging continued participation, among other things. Because of the risk of not obtaining complete audiological data in a single test session, the frequencies that provide the most useful information about hearing with reference to questions of dose modification should be measured at the beginning. Threshold results at 2 and 4 kHz are often crucial for decisions around dose modification and so should be prioritized. It can be useful to establish thresholds at a single test frequency in each ear before moving onto another frequency, rather than measuring all frequencies in one ear, then the next ear, in order to ensure that a unilateral hearing loss is detected early.

Sound field testing is necessary when a child does not tolerate wearing insert earphones or headphones. Sound field testing is performed

using amplitude-modulated pure tones ("warble tones") in order to avoid the risk of uncontrolled stimulation levels at the patient's ears resulting from standing waves. Sound field test results are not ear-specific and may miss unilateral or asymmetrical hearing loss. One advantage of sound field testing is that the tester and the families/caregivers are able to directly observe what the child is and is not able to hear [117].

If it is not possible to obtain actual threshold data on subjective testing, it can be appropriate to take a screening approach. This simply means that stimuli are not presented any lower than an agreed level (typically within the range 15–25 dB HL, which represents the upper boundary of the normal range of hearing). Thresholds worse than this level are still precisely measured, but the exact threshold within the normal range is not.

As ototoxicity-related hearing loss affects thresholds at high frequencies before those at low frequencies, audiological testing within the "extended high-frequency range" (EHF) (i.e., frequencies >8 kHz) can be beneficial for the early detection of ototoxicity [21, 120]. Raised thresholds in this frequency range can serve as a first warning sign in clinical practice, enabling preventative steps to be taken before hearing loss progresses further and the effects become potentially life-changing. It has been reported that children younger than 4–5 years of age show higher false-positive rates on testing in the EHF range and that inter-subject variability is higher on EHF testing than testing in the standard frequencies [121–123].

Wherever possible, speech audiometry, including tests featuring the speech signal in background noise, should also be conducted to better estimate the impact of the hearing loss [124]. The aim of these tests is to assess the best possible speech perception in a standardized manner, though still not representing the patient's real life performance in complex environments that involve multiple sound sources from different directions, reverberations, and other complicating factors that influence speech understanding. There are a great number of speech tests available for children, each using different speech stimuli (such as phonemes, words (familiar or nonsense, monosyllables, spondees), or sentences of various formats, live voice or pre-recorded stimuli, presented at various levels), with different types of responses and approaches to scoring possible (e.g., open or closed set, verbalized responses (scored for whole or partial word correct) or picture−/toy-based responses), with each country and language having its own variants. Examples of speech tests for younger children include tests of the child's perception of the Ling sounds or the phonemes /k/ and /t/, or the University of Western Ontario Plurals Test [117]. High-frequency word lists such as the Gardner High-Frequency Word List could also be useful. Other possible additional tests are the Bamford-Kowal-Bench Speech-in-Noise (BKB-SIN) Test and Quick Speech-in-Noise (QuickSIN) Test [117]. A detailed description and discussion of the benefits of different speech tests is beyond the scope of this article.

Objective audiological tests, such as otoacoustic emissions (OAE) and auditory brainstem responses (ABR), do not require the active cooperation of the patient during testing and are therefore extremely useful in difficult-to-test populations, such as young children. They do, however, have their downsides, being in most cases tests of specific parts of the auditory system, rather than the functioning of the auditory system in its entirety (as is the case with subjective audiometry). Tympanometry and otoscopy are also objective tests and should be always performed in order to rule out outer or middle ear problems but are not discussed in detail here.

Transient-evoked otoacoustic emission (TEOAE) testing, which uses the relatively broadband click stimulus delivered at a fixed level, provides a yes/no answer to the question of whether or not hearing sensitivity is essentially normal. Distortion-product OAE (DPOAE) tests, however, are frequency-specific and can therefore be a useful tool for the early detection of changes in auditory function, with reduction in DPOAE response amplitude reported to be the first clinical symptom of cochlear damage [21, 125, 126]. Studies of DPOAEs in children receiving platinum chemotherapy have shown high correlations between DPOAE responses and hearing thresh-

olds, but with greater deviations found in the high frequencies [120, 127, 128]. Comparisons of estimated pure-tone thresholds based on extrapolated DPOAE input/output functions have been found to have discrepancies of up to 40 dB and even higher in the high frequencies, suggesting that the usefulness of this test technique may be limited in this high-frequency range [129, 130]. In conclusion, DPOAEs alone cannot be used as the basis of clinical treatment decisions [117]. Two studies have reported that ototoxicity was first detected on EHF audiometry before DPOAE testing and only later on conventional audiometry [21, 131].

In ABR testing, clicks (representing a frequency range of approximately 2–4 KHz), tone-bursts (up to 4 KHz), or chirps (up to 4 or 6 KHz on clinical tests) may be used as stimuli but give no information about hearing loss in the higher frequencies [132]. 6 and 8 kHz measurements are not yet routinely used [133]. Objective measurements of high-frequency click-evoked OAE, ABR, auditory steady-state responses (ASSR), and cochlear microphonics are being developed [134–139].

The frequency of other clinical signs of ototoxicity induced by platinum drugs and aminoglycosides, such as the onset of tinnitus, vertigo, or disequilibrium, is often underestimated [4–6, 65]. Tinnitus is diagnosed on the basis of patient report. Because tinnitus can have many underlying causes, a detailed diagnostic assessment is required. This should consist of case history, otoscopy, audiological measurement of hearing loss, and identification of the tinnitus severity. The case history should include questions on the history and characteristics of the tinnitus (e.g., initial onset, pattern, affected site, and loudness) and questions regarding factors that exacerbate or reduce the tinnitus, relevant comorbidities, and the influence of tinnitus on the patient's daily life. Otoscopy is necessary in order to exclude any underlying pathologies of the outer ear, middle ear, or tympanic membrane that could be associated with tinnitus. Audiological assessment, including pure-tone audiometry, speech recognition thresholds, tympanometry, and/or otoacoustic emissions, is important in order to identify any type of hearing loss in patients with tinnitus [140, 141]. Many validated questionnaires which aim to provide insight into the severity of tinnitus are available. Such questionnaires can help to provide clinicians with information about the disabling and handicapping effects of tinnitus on the patient at emotional, psychological, and social levels. Examples of well-known tinnitus questionnaires include the Tinnitus Severity Scale (TSS), Tinnitus Handicap Questionnaire (THQ), Tinnitus Handicap Inventory (THI), and the Tinnitus Severity Index (TSI). The items in these questionnaires are scored by the patient and then summed or averaged to determine the level of tinnitus severity (e.g., low, moderate, or severe) [141–145].

The diagnosis of tinnitus in young children is challenging, since they themselves are usually unable to report symptoms and they are more capable of ignoring the tinnitus due to being distracted by external influences [62, 146]. Kentish et al. [147] developed a practical guideline for the diagnosis of tinnitus in children up to 16 years of age. They recommended that children should be routinely asked during audiological checkups whether they experience noises in the ear or head. A questionnaire for parents is useful in order to identify any changes in the child's behavior that could be indicators of the presence of tinnitus (e.g., sleeping problems, difficulties listening or understanding speech in the classroom, avoiding quiet or noisy environments, or signs of anxiety and/or depression). However, clinicians should not rely solely on information from the parents; even young children should be actively involved in the tinnitus assessment. It is therefore crucial that clinicians adapt their communication to the child's age, cognitive understanding, and linguistic level. The use of toys or drawing material can be helpful to gain insight into the presence of tinnitus and any accompanying symptoms.

The caloric test is the gold standard for vestibular diagnosis in adults, and rotatory-chair tests and videonystagmography are also well-established and commonly used. Pediatric application of these tests is, however, more challenging, and there is not yet a standard protocol for screening. The most commonly occurring

vestibular symptoms, such as oscillopsia, dizziness, disequilibrium, and postural instability, are often compensated for by other senses or attributed to underlying diseases [6], which means that their detection in the pediatric population is even less likely.

A number of different audiological classification systems which aim to describe the severity of hearing loss are commonly used in cancer care in order to compare and stratify patients as well as guide their treatment ([40, 148–150], [119]: www.asha.org/policy; WHO Grades of Hearing Impairment: http://www.who.int/pbd/deafness/hearing_impairment_grades/en; **NCI** Common Terminology Criteria for Adverse Events (CTCAE) v.3.0, 2006: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf). In a consensus review after the 42nd Congress of the International Society of Pediatric Oncology (SIOP) in Boston in 2010, Brock et al. recommended the use of a scale reflecting absolute values of hearing thresholds, rather than the degree of change in hearing thresholds from previous tests (as used in, e.g., the CTCAE scheme). This enables hearing loss to be classifiable where no baseline audiological measurement has taken place and the impact on speech intelligibility to be more directly estimated [40]. While most classification systems were developed primarily as outcome measures [28], the Muenster Classification [150] was designed to detect early stages of ototoxicity during treatment by including the presence of tinnitus and thresholds in the 11–20 dB HL range as an initial abnormal grade on the scale. The presence of a Muenster Grade 1 hearing loss after two cycles of cisplatin was found to have a high predictive value for the eventual need for hearing aids (sensitivity 67%, specificity 87%, associated likelihood ratio 5.00) [151]. The SIOP and Muenster classifications are currently being used and evaluated in a study of over 10,000 patients as part of the PanCareLIFE project (http://www.pancarelife.eu/) (Table 3.3). The International Late Effects of Childhood Cancer Guideline Harmonization Group is currently reviewing the use of audiological classifications in the development of international guidelines [10–12].

Table 3.3 The Muenster and SIOP Boston classification systems for ototoxicity grading

Grade	Muenster criteria	SIOP Boston criteria
0	≤10 dB HL at all frequencies	≤20 dB HL at all frequencies
1	>10 and ≤20 dB HL in at least one frequency, or tinnitus	>20 dB HL above 4 kHz
2	>20 dB HL at 4 kHz and above 2a: >20–≤40 dB 2b: >40–≤60 dB 2c: >60 dB	>20 dB HL at 4 kHz and above
3	>20 dB HL at <4 kHz 3a: >20–≤40 dB 3b: >40–≤60 dB 3c: >60 dB	>20 dB HL at 2 kHz and above
4	≥80 dB at <4 kHz	>40 dB HL at 2 kHz and above

The CTCAE criteria (NCI Common Terminology Criteria for Adverse Events (CTCAE) v.5.0, 2017: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf) are commonly used for the classification of tinnitus and vertigo. CTCAE grade 1 indicates the presence of mild symptoms; grade 2 indicates moderate symptoms which limit instrumental activities of daily living (ADL), such as shopping or using the telephone; and grade 3 indicates severe symptoms which limit self-care ADL, such as taking medication.

3.9 Treatment

Where hearing loss and impaired speech perception is detected, hearing aids with high-frequency amplification specifically fitted to the individual should be prescribed by a pedaudiologist [124, 152]. Cochlear implantation, with or without concurrent electroacoustic stimulation, is indicated in the rare cases of ototoxicity leading to severe-profound sensorineural hearing loss, and where conventional acoustic hearing aids do not provide sufficient benefit. Hearing ability is not restored to normal when using hearing aids or cochlear implants [153], so the use of additional

assistive devices can be beneficial. Signal transmission systems, often called FM (frequency modulation) systems, can be used to transmit sound from an important sound source, such as a teacher, directly to the patient's hearing aids, and can greatly improve speech perception in the presence of background noise or across distance. Other modifications at school, such as preferential classroom seating, better sound absorption to reduce reverberation, and the influence of background noise in classrooms and simply giving appropriate information to teachers should also be implemented where possible. Secondarily occurring speech development difficulties, learning difficulties, and literacy/numeracy difficulties must be taken into account and treated [1, 2].

There is, up to now, no cure for tinnitus, mainly due to its multidimensional clinical characteristics. Many clinical management strategies have so far failed to succeed, leaving a large number of patients untreated [79]. However, in some patients, the help of multiple professionals (e.g., audiologists, neurologists, otolaryngologists, and psychologists) can provide some relief [141]. Treatments focus on psychological aspects and/or auditory stimulation. Psychotherapeutic approaches include counseling, tinnitus retraining therapy (TRT), and cognitive behavioral therapy (CBT). Counseling is vital in order to inform patients and help them cope with their tinnitus and accompanying symptoms. TRT combines counseling and sound therapy to retrain the brain to habituate to the tinnitus percept, so that the patient perceives the tinnitus as a neutral stimulus. CBT consists of psycho-education, relaxation therapy, mindfulness, imagery training, and exposure therapy, aiming to help the patient cope with the condition by reducing emotional and behavioral responses [59, 141, 154]. In recent years, the Internet and smartphone-based devices for tinnitus self-help have been used more frequently, including auditory treatments, Internet-based CBT, serious games, and questionnaires [155]. Auditory stimulation includes the use of hearing aids or cochlear implants in tinnitus patients who also suffer from clinically diagnosed hearing loss. The basic function of hearing aids is to amplify environmental sounds, thereby reducing the comparative loudness of the tinnitus. Because hearing aids only provide amplification up to ca. 6 kHz, this approach is especially beneficial in patients with lower-pitched tinnitus [59, 141, 156]. Cochlear implants increase the activity of the auditory nerve by electrical stimulation, thereby potentially reversing plastic changes in the brain [59, 141, 154].

3.10 Prevention

Protective approaches aim to prevent the onset or progress of ototoxicity by reducing the dose of cisplatin (in cases of early onset ototoxicity) or replacing cisplatin with a less ototoxic analogue. Some treatment protocols specify such changes, and the precise guidelines vary by disease and treatment regimen [25, 34, 117, 151].

Treatment with antioxidants or anti-inflammatory drugs may be feasible according to the hypothesis that platinum ototoxicity is generated through the creation of reactive oxygen species (ROS). Amifostine was one of the first such compounds tested in clinical trials. It is a prodrug for a pharmacologically active free thiol metabolite, WR-1065, which binds to and thereby detoxifies reactive metabolites of cisplatin and may also deactivate ROS. It is thought to be concentrated in normal tissues, due to pH differences, the higher level of the activating enzyme, and other mechanisms. Nausea and/or vomiting, transient hypotension, and hypocalcemia are typical adverse reactions of amifostine, which is administered as a 15-min IV infusion immediately before chemotherapy. Although some studies have shown positive results for otoprotection [157], clinical trials and meta-analyses have not provided clear evidence for its efficacy to reduce platinum-induced ototoxicity [158–162]. The current American Society of Clinical Oncology (ASCO) guideline does not recommend the routine use of amifostine for the prevention of platinum-associated ototoxicity [163]. Forty-eight studies applying amifostine as cytoprotectant in polychemotherapy in adult and pediatric cancer populations are currently listed in clinicaltrials.gov, a registry of ongoing medical studies involving humans.

Another potential otoprotective compound is sodium thiosulfate (STS), a reactive thiol agent that is believed to provide otoprotection by directly binding to and inactivating platinum cytotoxic agents and may also act as a free radical scavenger. STS has been tested for its otoprotectve ability in adult and pediatric patients in several clinical studies, among them two recently randomized controlled trials (Table 3.4). Irrespective of the STS treatment schedule, subjects showed significantly lower rates of ototoxicity than patients without STS treatment [31, 164–170]. These studies suggest that STS treatment did not protect the tumor from platinum cytotoxicity in local disease, but one study [165] showed a decrease in 3-year event-free survival and overall survival in metastasized disease. Their results raise the possibility that STS may offer otoprotection to patients treated with platinum compounds, especially children (who are at higher risk than adults).

D-methionine, another antioxidant working against cisplatin- or aminoglycoside-induced side effects, was investigated largely in vitro and showed promising results [171–175]. One small-scale clinical trial in humans has shown complete otoprotection [176], *but, as far as we know, no other clinical studies have been published or are recruiting for this purpose*. Larger-scale clinical trials are needed.

The risk of possible interaction between chemoprotection and the efficacy of chemotherapy is still of concern to oncologists because the data from clinical trials is still limited [28]. Most potential otoprotective drugs are administered systemically, a method which includes the danger of such negative interaction on the efficacy of the therapy. This risk could perhaps be reduced by the local application of the otoprotectant directly to the ear. The feasibility of transtympanic application was tested by Riga et al. in a phase I/II study in 20 cisplatin-treated adult cancer patients, where injections of 10% N-acetylcysteine in Ringer's solution significantly reduced hearing loss [177]. According to this result, the transtympanic administration seems to be practicable in adolescents. Whether it is reasonable in older children remains to be shown; general anesthesia would be necessary in small children. Still further studies are needed.

Although numerous potential protective agents have been tested pre-clinically, only a few have reached the stage of clinical testing, and none of them are yet routinely used. To date, no drug has been approved by the FDA (US Food and Drug Administration) or EMA (European Medicines

Table 3.4 Recent studies on STS for prevention of hearing loss in childhood cancer patients

	SIOPEL 6 (2018), Brock et al. [164]	COG (2017), Freyer et al. [165]
Trial/duration	Phase III/7 years	Phase III/4 years
N	109 (57 STS/52 controls)	125 (61 STS/64 controls)
Diagnosis	Hepatoblastoma	All except leukemia/lymphoma
TCD cisplatin	6 courses of 80 mg/m^2	STS: 393 mg/m^2 (91–605) Controls: 387 mg/m^2 (198–625)
STS administration	20 g/m^2 IV 6 h after end cisplatin	16 g/m^2 IV 6 h after end cisplatin
Audiological assessment	Pure-tone audiometry, before and throughout treatment	Pure-tone audiometry, before, throughout, and 1 year after treatment
Ototoxicity grading	Brock	ASHA
Frequency	STS: 33% (95% CI 21–47) Controls: 63% (95% CI 48–77)	STS: 29% (95% CI 17–43) Controls: 57% (95% CI 42–70)
Risk (STS vs. controls)	RR 0.52 (95% CI 0.33–0.81)	OR 0.31 (95% CI 0.13–0.73)
3-year OS rate	STS: 98% (95% CI 88–100) Controls: 92% (95% CI 81–97)	STS: 70% (95% CI 56–80) Controls: 87% (95% CI 76–93)
3-year EFS rate	STS: 82% (95% CI 69–90) Controls: 79% (95% CI 65–88)	STS: 54% (95% CI 40–66) Controls: 64% (95% CI 50–74)

STS Sodium thiosulfate, *TCD* Total cumulative dose, *OS* Overall survival, *EFS* Event-free survival, *IV* Intravenous

Agency) for the prevention of platinum-induced hearing loss, although STS and N-acetylcysteine are designated for an FDA orphan status for this application and STS was recently approved for fast track designation by the FDA which shall facilitate development and expedite review of the drug for this indication. More clinical studies have begun within the past few years, so the transition of otoprotective agents from bench to bedside may increase.

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4 Complications in Tumour Orthopaedics

Jendrik Hardes and Arne Streitbürger

4.1 Introduction

Before the introduction of (neo)adjuvant chemotherapy protocols during the 1970s, ablative surgical procedures were usually required in patients with osteosarcomas. It was only after that time that extremity-preserving surgical techniques came into use to a significant extent in tumour orthopaedics. Nowadays, it is fortunately possible to preserve the extremity in the majority of patients by a combined chemo (e.g. EURAMOS-1 protocol)- and surgical approach mainly treated in specialized sarcoma centres, and amputation is only necessary with very extensive tumours [1].

Following wide tumour resection according to Enneking [2], the resulting bone defect usually has to be reconstructed. A large number of surgical procedures are available to the tumour orthopaedist when choosing how to carry out the reconstruction. In the majority of cases today, reconstruction of metadiaphyseal defects is carried out using tumour endoprostheses, which are also available for children in the form of growing prostheses [3]. Rotationplasty, although being done increasingly rarely, is certainly also still valuable, particularly in very young patients [1].

Table 4.1 Common reconstruction techniques in sarcoma surgery

Tumor endoprostheses
Biological reconstructions
• (Vascularized) autologous fibula
• Allograft
• Combination auto−/allograft
• Bone transport

When the defect location is diaphyseal, biological reconstruction procedures are often used in children, such as fibula reconstructions with vascular pedicles, in combination with an allograft if appropriate [4]. Generally, it should be noted that the choice of the appropriate reconstruction procedure depends on many different factors and also varies from surgeon to surgeon and hospital to hospital (Table 4.1).

The reader is also referred to the Chaps. 29 and 30 of this book.

4.2 Tumour Endoprostheses

In contrast to traditional endoprostheses, tumour prostheses are capable of compensating for bone defects in all long bones. Only one adjacent joint is usually reconstructed, although a total bone replacement—e.g. a total humerus replacement—may also be used. When megaprostheses were first introduced around 40 years ago, individually customized prostheses were initially used, but

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today's tumour orthopaedist now has modular tumour prosthesis systems available from various manufacturers for immediate implantation. In recent decades, megaprosthesis implantation has become an established procedure for reconstructing large metadiaphyseal bone defects following tumour resection [3].

The 5-year survival rate for megaprostheses has also markedly improved over the last 30 years—even though the patients are mostly young and active [5]. Despite this, it is still the case that complications are frequent even today. In a multicentre study including 2174 patients with megaprostheses, Henderson et al. [6] reported failure of the reconstructions in 24.5% of cases for all locations. The mean overall time to failure was 47 months.

When megaprostheses are used, however, the positive aspect that should be emphasized is that long-term preservation of the extremity is possible in most patients, despite any revision operations that may become necessary [7]. In a study including 1261 patients with megaprostheses, Jeys et al. [8] noted secondary amputation rates of only 8.9% at a mean of 20 years postoperatively, with statistically significantly lower amputation rates in megaprostheses implanted after 1980. The amputation rates were 15% with proximal tibia replacements and 5% with proximal femur replacements. The main reasons for amputation were local recurrences (63%) and periprosthetic infection (34%).

4.3 Periprosthetic Infection

Alongside local recurrences, periprosthetic infection is the most serious complication. In the great majority of cases, infection becomes manifest within the first 2 postoperative years with exogenous infections, although late hematogenic infections are also possible [9, 10].

Immediately within the first postoperative weeks, painful reddening and hyperthermia in the surgical area may suggest acute infection (e.g. with *Staphylococcus aureus*). C-reactive protein (CRP) is usually markedly raised. However, even when there are only slight signs of local inflammation, increasing movement restriction may develop months after the operation due to tissue induration. Fistula development is also possible. These cases often involve infection with low-virulence bacteria such as *S. epidermidis.* CRP is usually only slightly raised [9]. Late hematogenic infections (e.g. following bacterial tonsillitis or soft-tissue infection in whitlow) may develop even years after implantation of the prosthesis—usually with acute signs of inflammation [9].

The incidence of infection varies, particularly relative to the location of the prosthesis implant [10]. While periprosthetic infections are a rarity in connection with proximal humerus replacements, they occur in up to 19% of cases with proximal femur replacements, up to 11% of cases with distal femur replacements and up to 23% of cases with proximal tibia replacements [7, 10]. However, the infections here are certainly only partly due to the implant (particularly with the large foreign-body surface it presents). Other risk factors for infection involve patient-related factors (cancer, chemotherapy-induced immunosuppression and poor soft-tissue situations resulting from radiotherapy), the often long operating times and—particularly with proximal tibia replacements—difficulties in achieving muscle coverage over the prosthesis [10, 11].

In cases of infection of a tumour prosthesis, an attempt is usually made to eliminate the infection using one-stage or two-stage exchanges (with explantation of the prosthesis, temporary implantation of an antibiotic-loaded cement spacer and reimplantation of the prosthesis). However, reinfections are possible, and ultimate amputation is not always avoidable—often due to poor soft-tissue conditions, including those following (neo) adjuvant radiotherapy [8, 9]. Hardes et al. [9] showed, for example, that patients with periprosthetic infection have a 55.5% risk of secondary amputation if they have undergone radiotherapy and only 25% if they have not.

4.4 Mechanical Complications

Directly implant-related mechanical complications include in particular aseptic shaft loosening, failure of the joint mechanism with tumour pros-

theses in the vicinity of the knee joint and fracturing of the implant. Independently of the implant, periprosthetic fracture—particularly with prostheses in the region of the knee joint—also represents a problem. With proximal humerus and femur replacements, (sub)luxations may occur [6, 7]. In comparison with infection, however, these complications require fewer revision procedures. Jeys et al. [10] reported that a mean of 3.5 additional operations is needed after the primary implantation in patients with periprosthetic infection, in comparison with a mean of only 1.7 revision procedures in patients without infection. Amputation due to mechanical complications is also a rarity, with percentages of 0.4–2.2% [7, 8].

4.5 Implant Fracture

Although fractures in the body of the prosthesis nowadays no longer play any role in clinical practice [7, 12], shaft fractures were in the past a frequent complication (Fig. 4.1). In our own group of patients, the fracture rate in the lower extremity was 2.7% [7], while other authors reported fracture rates of 3.3–15% [5, 13, 14]. When the shaft fractures, the patient feels acute instability and is no longer able to place weight fully on the leg. There is usually no pain before the event, so that typical warning signals are absent. This complication can be successfully treated by exchanging the shaft—although usually with some loss of local bone.

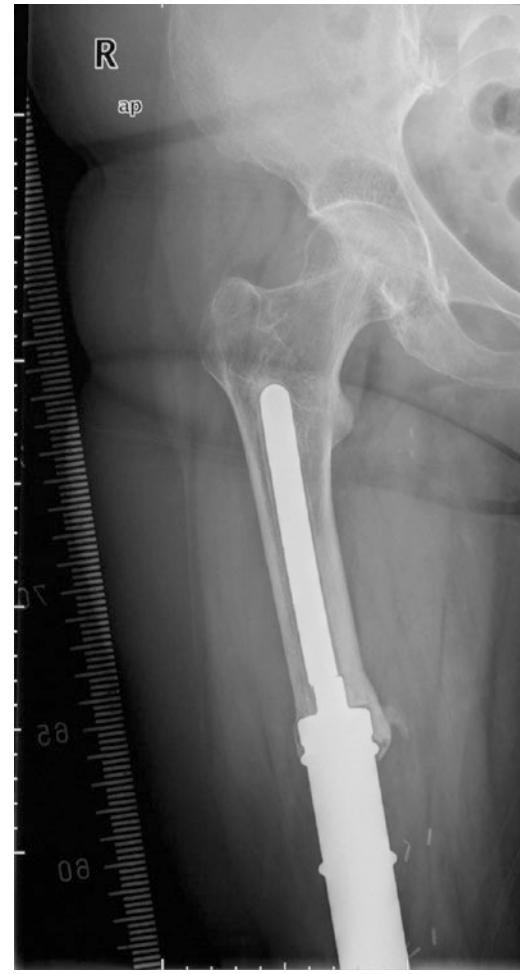

Fig. 4.1 Anteroposterior radiograph in a 60-year-old patient with a femoral shaft fracture after a distal femur replacement

4.6 Aseptic Shaft Loosening

Aseptic loosening of the shaft occurs more often in comparison with shaft fractures (7–11%) [5–7, 14]. This complication is a rarity in treatments in the region of the upper extremity, due to the lesser biomechanical demands involved [15], but it occurs more often with prostheses in the region of the knee joint [7]. Aseptic shaft loosening is usually noticed as a result of weight-bearing-dependent pain, which the patient describes as being directly over the affected bone. It is only in a few patients in the final stage that rotational instability of the shaft can be provoked during the clinical examination. Conclusive confirmation of the suspected diagnosis is usually possible with biplanar radiography. In cases of uncertainty, this can be supplemented with three-phase skeletal scintigraphy. In the presence of shaft loosening, renewed anchorage of the prosthesis can usually be achieved using a shaft exchange [7]. Septic loosening of the shaft always has to be distinguished from aseptic loosening. Septic loosening is often associated with discrete signs of systemic infection on laboratory tests, as well as local signs of infection (on histology). Septic

shaft loosening is often only diagnosed after a shaft exchange, using positive microbiological samples obtained intraoperatively.

4.7 Wear on the Joint Mechanism in Distal Femur and Proximal Tibia Replacements

Failure of the joint mechanism used to occur quite frequently in tumour prostheses involving a hinge joint. Capanna et al. [16] reported wearing of the polyethylene in the hinge joint of the first-generation Kotz prosthesis in 42% of cases after a mean of 64 months postoperatively. The wear rate was markedly reduced by using joints that allowed end rotation, but wear is still reported in the literature in up to 10% of cases [5, 7]. In our own opinion, wear on the joint mechanism is often only a matter of time in active patients with long-term survival, and it should only be regarded as a complication in cases of early failure. We tell patients that when there is greater clinically reproducible joint instability that disturbs everyday activities, the joint mechanism should be exchanged. Otherwise there is a risk of aseptic shaft loosening caused by particles of polyethylene or metal abrasion particles [5]. However, the risk of periprosthetic infection should not be underestimated when the joint mechanism is exchanged. Jeys et al. [10] calculated that exchanges of the joint mechanism represented a significant ($P = 0.05$) risk for infection, with a frequency of 17.8%. The time point at which the exchange can be carried out while the instability is still tolerable should therefore always be carefully considered in consultation with the patient.

4.8 Dislocation of a Proximal or Total Femoral Replacement

Dislocation of a proximal or total femur replacement is the most frequent complication with this type of reconstruction [17]. The highest dislocation rates, at 25–33%, are reported in patients with a fixed-implant unipolar acetabular cup [7, 18]. By contrast, the dislocation rate when a bipolar implant is used is substantially lower, at 1–5% [17, 19]. We therefore recommend a bipolar acetabular cup in hip joints without any considerable arthrosis and a tripolar one when arthrosis is present. Bipolar cup systems have longer durability. van Egmond et al. [20] reported implant survival rates of 96% after 15 years and 60% after 20 years. The main reason for fixed-implant cups being exchanged was painful wear on the acetabular cartilage [21].

Implantation of proximal femur replacements in children under the age of 10 is a special case. Due to growth disturbances in the acetabulum—of unknown pathogenesis—hip dysplasia and subsequent dislocation of the prosthesis can occur (Fig. 4.2). When there is evidence of incipient dislocation on radiography, a procedure to improve the acetabulum must therefore be carried out in order to prevent complete dislocation.

High-grade dislocations of humeral replacements are a rarity [7, 15]. Cranial subluxations may occur immediately after extra-articular resection of the proximal humerus despite the use of an attachment tube, but we only carry out revision operations if the patient has symptoms or there is imminent skin perforation.

4.9 Periprosthetic Fractures

Periprosthetic fractures are rare. In our department, we have retrospectively identified 31 (5.2%) out of approximately 600 megaprosthesis implantations. The fracture usually occurs in the lower extremity. Adequate trauma was only present in 29% of the patients. Radiotherapy in the surgical region had been carried out significantly more often in patients in whom there was no adequate trauma. At the time of fracture, the patients were a mean of 38 years old, so that this complication appears to be a rarity in children. Accordingly, we do not restrict children with

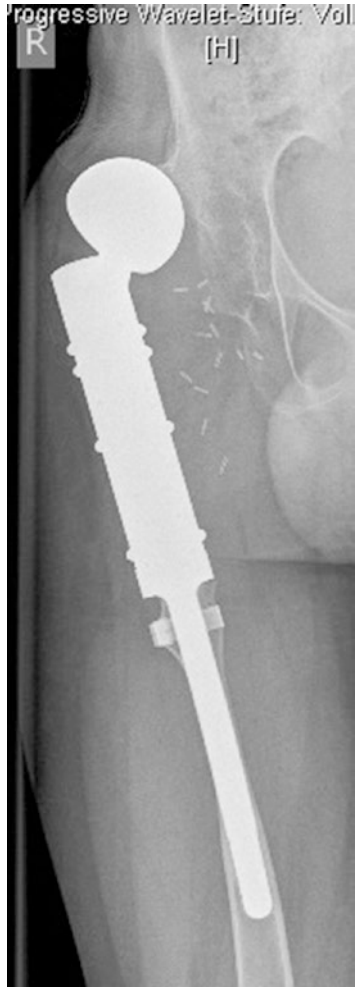

Fig. 4.2 Anteroposterior radiograph in a patient currently 14 years old, in whom a proximal femur replacement with a bipolar acetabular cup was implanted when the patient was aged 9. Probably due to secondary hip dysplasia, chronically progressive dislocation developed over the course of the years

tumour prostheses to specific exercise recommendations, but encourage them to take part in exercise activities as far as the operated extremity permits.

Attempts can be made to carry out osteosynthesis in a few cases when periprosthetic fracture occurs. With fractures in the vicinity of the prosthesis shaft, however, a shaft exchange with bone resection is usually necessary (Fig. 4.3a, b).

4.10 Biological Reconstructions

In the biological procedures, the relevant defect is reconstructed after tumour resection using autologous or allogenic bone. In biological reconstructions, the bone defect is substituted with biological material over the medium term or long term, and ideally the function of the bone that has been removed will be replaced with dynamic equivalent bone [4]. However, stability has to be achieved using additional osteosynthesis material (usually plates or intramedullary nails) until biological reconstruction that is fully weight-bearing is achieved.

A common biological reconstruction procedure involves using autologous fibula to supply diaphyseal defects; with defects >10 cm, fibula with a vascular pedicle is usually used [22]. The diaphysis of the patient's own calf together with the afferent vessel is removed, introduced into the defect and anchored. The afferent vessel for the fibula is then attached locally using microsurgical techniques. This makes local integration possible, with adaptation of the bone quality to the new weight-bearing situation (e.g. with increased size during weight-bearing).

Bone transport to bridge a bone defect is also aimed at generating autologous bone. Following an osteotomy, the callus that forms can be lengthened using an external fixator or increasingly using extensible intramedullary nails (callus distraction) [23].

Another way of reconstructing the defect is to use allografts. Diaphyseal and osteoarticular allografts are used as needed. A prerequisite for this is that a sufficiently large bone bank should be available to allow selection of the appropriate allograft. A considerable disadvantage in using allografts is that they involve nonvital bone. Osseous remodelling does not take place. Complications such as fractures or infection of the allograft are therefore frequent, and this procedure is therefore now only rarely used [24].

All biological reconstructions using autografts require a sufficient potential for bony regeneration. If the regeneration potential is lacking, failure

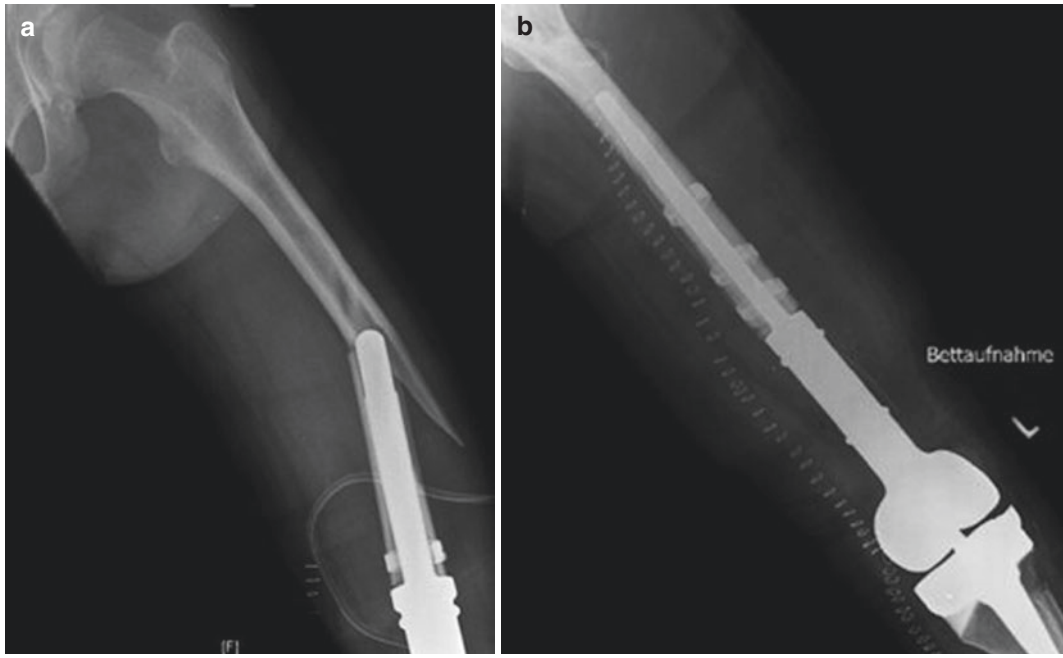

Fig. 4.3 (**a**, **b**) A periprosthetic fracture with a distal femur replacement in place. As the femoral shaft has not loosened, the local bone had to be resected, followed by reimplantation of a new shaft

of the additionally introduced metal support will occur sooner or later, as it is not designed for permanent weight-bearing. Generally speaking, the potential for regeneration will certainly be compromised as a result of chemotherapy and/or local radiotherapy.

Failure of the biological regeneration potential usually becomes evident through a fracture in the autograft/allograft and/or the development of pseudarthrosis between the introduced allograft/autograft and the local bone [4, 22] (Fig. 4.4a, b). These complications are rarer in the area of the upper extremity, as mechanical loads are only slight there. In the region of the lower extremity, by contrast, these complications are frequent and often require multiple revision operations [22]. The patients have to relieve the treated extremity for very long periods and need to wear an orthesis to reduce shearing forces. In cases of long-term failure of the autograft, it may become necessary to remove it and administer endoprosthetic treatment.

When autologous fibula is being used, another potential complication that needs to be taken into account is potential sequelae in the donor fibula, known as 'donor-site morbidity'. Severe complications here involve paralysis of the peroneal nerve and compartment syndrome. In addition, the development of claw toe may be noted, as a donor-site sequela that can certainly be regarded as acceptable.

On the basis of the potential complications listed above, the recommended follow-up for patients who have undergone biological reconstruction procedures must include regular conventional radiographic examinations until complete regeneration of the autograft has taken place, so that any revision operations that may become necessary (e.g. freshening of the pseudarthrosis) can be indicated at an early stage and decisions can be taken regarding weight-bearing on the extremity or the use of ortheses. The 3-month interval used for oncological follow-up during the first 2 postoperative years is usually sufficient here. When there is a full weight-bearing situation biologically, further radiographic follow-up is based on oncological needs, not due to the reconstruction technique.

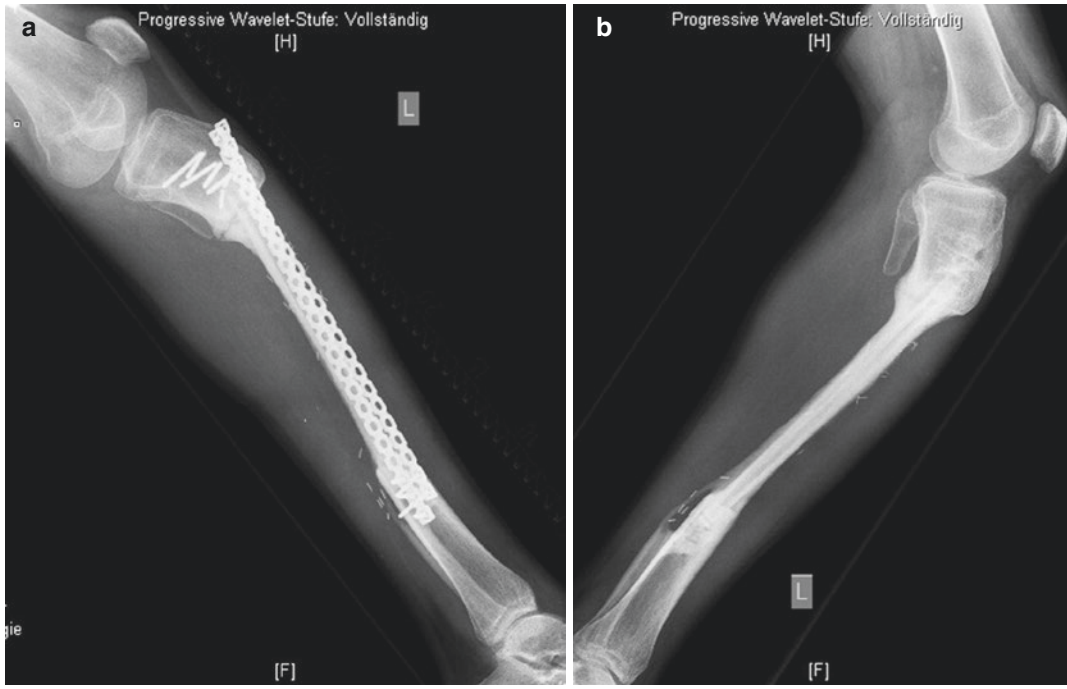

Fig. 4.4 (**a**, **b**) Lateral radiograph of the lower leg in a 16-year-old boy. Following treatment with autologous fibula with a vascular pedicle from the contralateral side, pseudarthrosis with a subsequent plate fracture developed. Following several revision operations, there is a fully weight-bearing situation here, with residual axial deformity

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5 Causes and Course of Severe Late Effects in Young Cancer Patients: Gastrointestinal Tract

Alexander Stein

5.1 Introduction

Multimodality treatment of children with cancer has dramatically improved cure rates during the last decades [1]. Among other toxicities, treatment associated gastrointestinal (GI) side effects may have significant impact on treatment tolerability, quality of life, and beyond; the rather acute effects may result in relevant long-term sequel. Whereas acute or subacute GI side effects are well-known for each treatment modality, e.g. nausea and vomitus, diarrhoea, constipation, appetite loss or infections for chemotherapy, adhesions and obstruction to intra-abdominal surgery or enteritis and deregulated motility after abdominal irradiation, data on the incidence and even more important the pathophysiology of late side effects on the GI tract are rare.

5.2 Late Side Effects of the Gastrointestinal Tract

The main data set on long-term GI side effects is derived from the Childhood Cancer Survivor Study (CCSS), a study of 14,358 survivors of childhood cancer who were diagnosed between 1970 and 1986 [2]. In this CCSS analysis, data were compared with those from siblings ($N = 3899$).

Of note, in this analysis the cumulative incidence of GI complications is continuously increasing by about 8–10% every 5 years to more than 40% 20 years after cancer diagnosis and is still rising even 30 years after diagnosis. In addition, compared to siblings the probability of experiencing a relevant late GI toxicity was greater for most categories evaluated (16 out of 17).

GI complications in this analysis were grouped according to *upper GI complications* including ulcer, oesophageal disease, frequent indigestion or heartburn, nausea/vomiting or other upper GI trouble; *liver conditions* including gallstone or other gall bladder issues, liver cirrhosis, jaundice, liver biopsy or other liver trouble; and *lower GI complications* including intestinal polyps or diverticular disease, colitis, frequent constipation, chronic diarrhoea, fistula or stricture, colostomy or ileostomy, or other lower intestinal trouble and analysed separately. Among these three groups, upper GI complications were most commonly observed (cumulative incidence of 25.8% at 20 years after diagnosis), followed by lower GI complications (15.5%) and liver conditions (9.4%). The highest relative risks (adjusted for age, sex and race) relative to the siblings were for liver biopsy (24.1), liver cirrhosis (8.9) and colostomy or ileostomy (5.6).

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Another analysis of the CCSS (n = 12,316 survivors) focused on intestinal obstruction [3]. This analysis was grouped for abdominopelvic tumours (n = 2002), mainly Wilms tumours (60%) or neuroblastoma (23%), non-abdominopelvic tumours (n = 10,314) and siblings. Cumulative incidence for intestinal obstruction was 5.8% in abdominopelvic tumours, 1.0% for non-abdominopelvic tumours and 0.3% for siblings 35 years after childhood cancer diagnosis, which is in line with prior smaller data sets [4]. Even after 30 years, no plateau was reached; in contrast a steady increase in the cumulative incidence was noted.

Already during treatment metabolic disorders may occur, e.g. obesity, which is linked to long-term GI complications, like hepatic dysfunction or gastrooesophageal reflux disease [5, 6]. Besides the chronic liver damage, obesity as part of the metabolic syndrome complex is associated with increased cardiovascular morbidity and mortality as well as chronic oesophageal diseases including cancer [7, 8].

5.3 Causes of Late GI Effects

5.3.1 Chemotherapy

Acute GI toxicity of chemotherapy is well described and known for the majority of agents used in paediatric cancer. New agents are only rarely used initially in children with curative disease; thus unknown or unexpected acute side effects are rare events. Late GI toxicity may result from repeated acute toxicity, finally causing injury and scarring of tissue or chronic GI infections due to immunosuppression. In addition, myelosuppression or myeloablation results in the need for blood products, thus increasing the risk of viral hepatitis, particularly in regard of transfusions >35 years ago [9, 10]. In the CCSS analysis by Goldsby et al., chemotherapy in general was not associated with long-term GI complications in multivariate analysis, whereas higher alkylating agent score (AAS = 3) or cumulative dose anthracyclines (>200 mg/m^2 doxorubicin) were significantly related to GI complications, mainly long-term liver toxicities [2]. There were no significant relations of intestinal obstruction to application of chemotherapy [3].

The pathogenesis of metabolic disorders is multifactorial, although chemotherapy and the reduced physical fitness and ability to be physically active due to the disease itself and the treatment in general likely are the main causes [6]. Recently, reduced microbial diversity was noted in survivors of paediatric leukaemia, which may account for chronic inflammation-related disorders like obesity or impaired glucose tolerance [11]. Although not fully understood, these changes occur early during treatment, likely induced by chemotherapy, but may remain for years. Therefore, early interventions focusing on a healthy lifestyle including physical activity and adequate nutrition and potentially specific treatment to restore the intestinal microbiome may be beneficial [12].

5.3.2 Radiotherapy

Relevant late effects of abdominal or retroperitoneal radiotherapy are intestinal fibrosis, vascular damage and organ dysfunction, particularly the liver or kidneys [13]. Although dose dependency of late effects is a well-known issue, the optimal radiotherapy dose balancing efficacy and long-term side effects need to be established.

The rate of intestinal fibrosis shows a dramatic increase within the total radiation dose above 40 Gy from 5% to nearly half of patients with a dose of 60 Gy [14]. In the CCSS cohort, a significant correlation between radiotherapy and occurrence of late intestinal obstruction was observed likely related to fibrosis [3]. Patients with abdominal tumours receiving radiotherapy had a cumulative incidence of intestinal obstruction of 7.5% after 30 years, compared to 3.1% without radiotherapy or 0.6–1.1% for non-abdominal tumours. Of note, in patients with total radiation doses above 40 Gy, the risk to develop an intestinal obstruction was more than eightfold compared to those without radiotherapy. In addition, higher radiation doses were significantly associated with mortality in patients developing

obstruction, with a nearly threefold increased mortality for doses >50 Gy. Mediastinal radiotherapy may cause late effects in the proximal intestinal tract, like oesophagogastral dysmotility and stricture, due to mucosal damage and chronic ulceration [15].

The induction of long-term liver toxicity is dose- and volume-dependent but usually only occurs at doses >20 Gy to larger parts of the liver or higher doses to small parts of the liver [13, 16]. The strong association of total body irradiation with liver toxicity noted in the CCSS cohort may be influenced by the setting of allogenic bone marrow transplantation, including veno-occlusive disease and graft vs. host disease.

Furthermore, radiation can cause vascular damage including clinically relevant decrease growth of vessels or stenosis and thus compromising abdominal blood supply causing intestinal damage and organ dysfunction [17].

5.3.3 Surgery

Side effects of abdominal surgery are mainly occurring in the short- or midterm period following the procedure, e.g. anastomotic leakage or adhesions. Although reports on long-term toxicities are rare and mainly anecdotic, adhesive small bowel obstruction may occur years or even decades after abdominal surgery [13]. In multivariate analysis of the CCSS cohort, abdominal surgery was only associated with liver injury but not with intestinal complication [2]. Similarly intestinal obstruction in patients with abdominal tumours was not associated with abdominal surgery, although on the other hand, once an obstruction occurred, prior surgery was associated with mortality [3].

5.4 Conclusion

Despite being a relevant issue affecting a large number of long-term survivors, data on the causes and course of severe gastrointestinal toxicity are rare. Available data show a continuous increase in the cumulative incidence of GI side effects even 30 years after initial cancer diagnosis, thus urging for a lifelong specialized follow-up of this patient population. Clearly abdominal or pelvic radiotherapy and to a lesser extent chemotherapy and surgery are the causative treatment modality. Therefore, recent approaches are focusing on improved multimodal treatment tolerability, e.g. by new radiation techniques to reduce long-term toxicity like proton beam therapy or early interventions to avoid chronic metabolic disorders [12, 18].

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6 Pulmonary Toxicity: Causes and Course of Severe Late Effects in the Lungs of Young Cancer Patients

Jennifer E. Agrusa and Andrew C. Dietz

6.1 Background

The lungs are a uniquely susceptible organ without the ability to repair in the same way as other parts of the human body. Toxicities from cancer and cancer therapy can be profound. Late pulmonary-related death has now been reported in multiple cohorts in the United States and Europe with a standardized mortality ratio ranging from 5.9 to 8.3, a cumulative incidence exceeding 0.5% by 25 years after diagnosis, and pulmonary causes comprising upward of 16% of all non-cancer causes of death [1–3]. Less is known about pulmonary complications than areas such as cardiac toxicity; however, with more recent growing interest in the field, much progress has been made in our understanding of this area. This chapter reviews self-reported pulmonary outcomes and directly measured pulmonary outcomes and discusses risk factors for these outcomes.

6.2 Review of Self-Reported Pulmonary Outcomes

One of the earliest and most comprehensive studies on self-reported pulmonary outcomes looked at the Childhood Cancer Survivor Study (CCSS) in North America. Among 12,390 5-year survivors of childhood cancer, there were significantly increased risks of lung fibrosis, recurrent pneumonia, chronic cough, pleurisy, use of supplemental oxygen, abnormal chest wall, exercise-induced shortness of breath, bronchitis, recurrent sinus infection, and tonsillitis compared to a cohort of siblings [4]. An updated report on 14,316 5-year survivors of childhood cancer from the CCSS with additional longitudinal follow-up showed a cumulative incidence of any pulmonary condition of 29.6% (95% CI 29.1–30.0%) by the age of 45 years. While less likely to be smokers compared to siblings, survivors were still at significantly increased risk for chronic cough, oxygen need, lung fibrosis, and recurrent pneumonia. Additionally, the impact of chronic cough on daily activities was higher for survivors than it was for siblings [1].

Self-reported and physical exam-based pulmonary outcomes have also been reported in Europe, first in the Netherlands. Among 1362 survivors at a median follow-up of 17 years, overall adverse events were in seen in 74.5%, with pulmonary adverse events accounting for 5% of all events [5]. More recently in 1894 5-year

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childhood cancer survivors in Switzerland, there were higher rates of pneumonias and chest wall abnormalities than siblings, with a cumulative incidence of any pulmonary disease after 35 years of follow-up of 21%. Additionally, in those exposed to thoracic surgery, there was an elevated risk of lung fibrosis [6].

6.3 Review of Measured Pulmonary Outcomes

6.3.1 Pulmonary Function Tests (PFTs)

Pulmonary function testing has been incorporated into the Children's Oncology Long-Term Follow-Up (COG LTFU) Guidelines as a way to monitor subclinical pulmonary disease among childhood cancer survivors. Pulmonary function tests (PFTs) are performed to identify obstructive or restrictive lung disease, diffusion defects, or hyperinflation using a variety of tests, including the measurement of flow and volume (spirometry) and diffusing capacity of the lungs for carbon monoxide (DLCO). Results are expressed as a percent of predicted value, based on the individual's age, height, gender, and race [7]. Currently, the COG LTFU Guidelines recommend that survivors with specific exposures, including bleomycin, busulfan, nitrosoureas (carmustine, lomustine), chest radiotherapy, allogeneic hematopoietic stem cell transplant (HSCT) with chronic graft versus host disease (GVHD), and pulmonary surgery, routinely obtain PFTs upon entrance into long-term follow-up care and repeat them as clinically indicated. Though the prevalence of clinical symptoms is low among survivors and >80% of survivors are asymptomatic regardless of PFT findings [8], abnormal PFT results may indicate disease well in advance of diagnosis and impact survivors' long-term quality of life [6, 9].

Monitoring survivors for late effects using PFTs has demonstrated a high prevalence of pulmonary dysfunction. Impaired lung function has been described in 33–65% of all survivors undergoing evaluation with PFTs [7, 10] and in 44–84% of survivors with at least one pulmonary toxic exposure [11–13]. Despite an attempt to minimize therapy-related toxicity over the years, recent studies continue to demonstrate a high prevalence of pulmonary dysfunction, as 41–65% of survivors treated for cancer between 1997 and 2012 have abnormal pulmonary function based on PFTs [8, 14, 15]. Pulmonary function abnormalities increase with longer follow-up and age, and the cumulative prevalence at 50 years old is as high as 81.3% [10]. When measured by the Common Terminology Criteria for adverse events (CTCAE), the majority of dysfunction is minimal (grade 1), though at least one study found that up to 44% of survivors have grade 2 or higher dysfunction [13], and another showed that 21% of survivors have grade 3–4 pulmonary dysfunction [10]. It has been additionally noted that those with pulmonary dysfunction have significantly poorer health-related quality of life [11].

6.3.2 Types of Defects

Restrictive lung defects in childhood cancer survivors occur as a result of intrinsic lung diseases or chest wall pathologies following certain therapy exposures. They are caused by functional volume reduction, defined by a decreased total lung capacity (TLC) and/or residual volume (RV), which can be ascertained by measuring lung volumes on PFTs with whole-body plethysmography or gas dilution. Among those with pulmonary toxic exposures, 13% of survivors have restrictive lung disease [8], and the odds for restrictive defects are increased 6.5-fold compared with healthy controls [11]. Specifically, studies have demonstrated the prevalence of restrictive defects to be 7–11% in survivors treated with bleomycin [14, 15] and 11–15% in survivors treated with pulmonary radiation [16, 17]. Survivors with this defect may have reduced exercise capacity [9]; however, no difference in self-reported pulmonary symptoms or health-related quality of life has been described [11].

Survivors with pulmonary toxic exposures may also develop obstructive lung defects, including asthma, obliterative bronchiolitis, and chronic

GVHD [18]. Obstructive defects affect flow; thus, forced expiratory volume in 1 s (FEV_1), FEV_1/functional vital capacity (FVC), expiratory flow rate between 25% and 75% of the exhaled vital capacity (FEF25–75%), and peak expiratory flow rate (PEFR) are decreased on PFTs. The prevalence of these defects among childhood cancer survivors with exposure to bleomycin or pulmonary radiation therapy is 22–26% [8, 14, 16, 17], though one study found that as many as 70% of survivors exposed to bleomycin have evidence of obstruction on PFTs [15]. With respect to additional contributory factors, similar to a non-cancer population survivors who smoke have a greater risk of obstructive lung disease compared with those who have never smoked [19].

Abnormalities of lung diffusion also occur as a consequence of pulmonary toxic therapy. Diffusion capacity of the lungs for carbon monoxide (DLCO) is a measurement that is often included with PFTs to evaluate gas exchange between the alveolus and red blood cell in pulmonary capillaries. This value is frequently corrected for alveolar volume and hemoglobin. DLCO is reduced in interstitial lung disease or pulmonary fibrosis that may occur after cancer therapy or with pulmonary edema or pulmonary vascular diseases. The prevalence of diffusion defects varies in the literature, possibly because studies differ in their definition of abnormal DLCO. Nonetheless, diffusion defects exist in 3–19% of survivors treated with bleomycin and/or pulmonary radiation [14–17], and the odds for diffusion defects are increased 5.2-fold compared with healthy controls [11]. Survivors with diffusion defects are more likely to report symptoms and have poorer health-related quality of life [11]. Similar to those with obstructive lung disease, survivors who smoke have a greater risk of diffusion defects compared with those who have never smoked [19].

Hyperinflation is an additional measurement included on PFTs that is not often evaluated in childhood cancer survivors; however, hyperinflation is often the most common abnormality in studies assessing this parameter. It is defined as residual volume (RV) >120% of predicted and a RV/TLC ratio >28% predicted. The prevalence of hyperinflation was found to be 20–41% among survivors with pulmonary toxic exposures [8, 14, 16, 17]. Though the implications of this abnormality is yet to be studied in childhood cancer survivors, it has been shown that hyperinflation contributes to dyspnea, exercise intolerance, and reduced physical activity in other populations [11].

6.4 Risk Factors for Pulmonary Outcomes

6.4.1 Chemotherapy

Bleomycin is an antineoplastic antibiotic used to treat lymphoma and germ cell tumors that has been associated with acute and chronic pulmonary toxicity. It is thought that the mechanism of lung injury is the result of reactive oxygen metabolite formation and subsequent inflammatory response. The lungs have relatively low levels of the bleomycin-detoxifying enzyme, bleomycin hydrolase [9]; thus, bleomycin accumulates and can cause fibrosis by damaging the lung vasculature, which leads to an influx of inflammatory cells and fibroblasts [20, 21]. Bleomycin-mediated pulmonary injury is associated with a variety of pulmonary diseases, including bronchiolitis obliterans organizing pneumonia (BOOP), eosinophilic hypersensitivity pneumonitis, and interstitial pneumonitis that can progress to pulmonary fibrosis [9, 15, 22].

Treatment with bleomycin has been associated with more PFT abnormalities than other chemotherapeutic agents [23], though few of these patients have symptoms or adverse pulmonary clinical outcomes, including asthma, chronic cough, emphysema, oxygen need, lung fibrosis, or recurrent pneumonia [1, 14, 15]. Studies from the 1970s to 1980s demonstrate that the most common PFT abnormalities include decreased DLCO, TLC, and FVC among patients treated with bleomycin [24, 25]. While toxicity has been seen in doses as low as 20 units per meter squared (U/m^2), studies have shown that cumulative dose greater than 450 U/m^2 to be more predictive of bleomycin-related pulmo-

nary toxicity [13]. Many treatment regimens now use lower doses of approximately 60 U/m^2, and though dose is not significantly associated with abnormal PFTs (median cumulative dose 65 U/m^2, range 10–120 U/m^2), >50% of survivors who were treated with bleomycin still demonstrate at least one PFT abnormality [14].

Cyclophosphamide is another chemotherapeutic agent that is associated with late pulmonary complications. It is an alkylating agent used to treat hematologic malignancies or solid tumors, used in HSCT preparative regimens or used as immunosuppressant therapy for non-malignant disorders. Cyclophosphamide may cause diffuse alveolar damage and, less frequently, nonspecific interstitial pneumonia and BOOP [26]. Dyspnea, cough, and fever have also been associated with its use [27], and while some studies show no association with PFT abnormalities [13, 14], others have found a significant association with abnormal gas exchange and reduced lung volume [9]. No correlation between cumulative dose and PFT abnormalities has been observed [9, 22, 23].

Several additional chemotherapeutic agents have been associated with late pulmonary toxicity. Anthracyclines, such as doxorubicin, are antibiotics that have been shown to increase the risk of emphysema, supplemental oxygen use, chronic cough, and shortness of breath [1, 9, 23]. In older studies, doxorubicin has also been a risk factor for reduced DLCO and lung volume on PFTs, though no correlation between cumulative dose and PFTs was observed [9, 23]. In more recent studies, use of this agent was not found to be significantly associated with PFT abnormalities in survivors who had received bleomycin [14]. Methotrexate, a commonly used antimetabolite, has occasionally been associated with PFT abnormalities when used in treatment of hematologic malignancies [23]. Busulfan, another alkylating agent often used as part of conditioning regimens for HSCT, is also a known pulmonary toxic agent. As damage occurs insidiously, the average time to develop adverse effects is 3.5 years [28], and radiation therapy may magnify the effects. Though it is unclear if the effects of busulfan are dose-dependent, there have been no reports of adverse effects with doses <500 mg as long as no concomitant agents are used [9]. Finally, nitrosoureas, including carmustine and lomustine, that have been used to treat gliomas, other CNS tumors, and as part of conditioning regimens for autologous HSCT, are also pulmonary toxic agents. The effect is dose-dependent and is as high as 50% if doses >1500 mg/m^2 are used [29]. Damage due to this agent also occurs insidiously and results in emphysema or fibrosis as a long-term effect [1, 9]. Interestingly though, a large cohort study among survivors enrolled in the Childhood Cancer Survivor Study (CCSS) showed no significant association between the development of clinical pulmonary outcomes and agents such as methotrexate, busulfan, and carmustine [1].

6.4.2 Radiation Therapy

Radiation therapy is often a necessary component of cancer treatment that can cause injury to the lungs via a direct cytotoxic effect on normal lung tissue and by triggering an inflammatory cascade that can eventually leads to fibrosis. The first phase of damage, radiation pneumonitis, may occur 3–12 weeks after exposure, while the final phase, radiation fibrosis, may be evident as early as 6 months after radiation exposure and can progress over time. Pulmonary radiation exposure can result in both subclinical pulmonary impairment and adverse clinical outcomes, as the cumulative incidence of pulmonary fibrosis is 3.5% at 20 years after diagnosis [4]. Pulmonary radiation therapy increases the risk of pulmonary function impairment [9], and abnormalities on PFTs are apparent in two-thirds of survivors [16]. While restrictive impairment has been associated with doses of pulmonary radiation >20 Gy among survivors [11], another recent study of survivors treated with bleomycin did not find a significant association between radiation dose and PFT abnormalities. However, the median dose was only 21 Gy, and the two patients who received higher doses did develop restrictive lung disease, though the relationship was not significant [14].

These aforementioned studies did not specify the fields of radiation exposure, however, and this is important to consider now that radiation oncologists are using more targeted techniques to minimize adverse effects when appropriate. While doses >20 Gy have been shown to predict the risk of lung function abnormalities among survivors who receive mediastinal radiation therapy [30], among survivors of Hodgkin lymphoma treated with involved field radiation therapy, older age at diagnosis is the only factor significantly associated with worse subclinical pulmonary outcomes in multivariate analysis [31]. Pulmonary function changes are also common in survivors treated with whole lung irradiation, as 85.7% have evidence for obstructive, restrictive, hyperinflation, or diffusion defects [16]. Additionally, >50% have more than one abnormality, and FVC, FEV1, and TLC significantly decline over time [32]. Similarly, survivors receiving craniospinal irradiation are also at risk for reduced lung volume and DLCO [9].

Pulmonary radiation therapy also increases the risk of adverse late clinical pulmonary outcomes among childhood cancer survivors. Among CCSS survivors, pulmonary radiation therapy is significantly associated with pulmonary fibrosis, supplemental oxygen use, recurrent pneumonia, and chronic cough [1, 33], and the cumulative incidence of pulmonary fibrosis, chronic cough, and shortness of breath with exertion increases up to 25 years from diagnosis [33]. Additionally, mortality is associated with higher pulmonary radiation doses. There appears to be a dose effect, as pulmonary radiation doses ≥15 Gy are associated with chronic cough, and doses ≥10 Gy are associated with supplemental oxygen need and pulmonary fibrosis [1]. A study of more recent survivors found that mean lung dose (MLD) is the only dosimetric parameter that predicts adverse pulmonary outcomes, including pneumonitis, chest wall deformity, chronic cough, dyspnea, interstitial lung disease, supplemental oxygen need, and pneumonia [17]. Among 12 survivors receiving whole or partial lung irradiation, nearly half (5/12) report clinical symptoms, including asthma or shortness of breath with exertion [16]. In contrast to this, survivors receiving craniospinal irradiation for treatment of CNS malignancies are 10.4 times more likely than those not exposed to have chest wall deformities but have no increased risk of a pulmonary condition [34]. Likewise, there is a low prevalence of clinical symptoms among survivors treated with involved field radiation therapy [31].

6.4.3 Thoracic Surgery

Surgery involving the lung parenchyma is occasionally necessary as a treatment for pulmonary metastases. While children are better than adults at compensating through hypertrophy and hyperinflation [35], thoracic surgery is a risk factor for long-term pulmonary complications among childhood cancer survivors. One-third to two-thirds of survivors of osteosarcoma after metastasectomy had abnormal PFTs [36], with the variance depending upon the type of pulmonary evaluation and number of thoracotomies. Specifically, thoracic surgery prior to radiation therapy increases the odds of obstructive disease and hyperinflation [16]. Among CCSS survivors, chest wall or lung surgery is significantly associated with chronic cough, supplemental oxygen need, and pulmonary fibrosis [1].

6.4.4 Combination Therapy

Malignancies are often treated with combination therapy, including chemotherapy, radiation therapy, and surgery to improve survival outcomes. With combinatorial therapy toxicities of each individual therapy may be exacerbated. For instance, the use of bleomycin with cyclophosphamide, methotrexate, doxorubicin, or vincristine increases the incidence of bleomycin-induced pulmonary fibrosis, and using nitrosoureas with cyclophosphamide causes toxicity at lower doses [9]. In addition, several chemotherapeutic agents, known as radiomimetics, magnify the effect of radiation therapy on the lungs. These include dactinomycin, bleomycin, cyclophosphamide,

doxorubicin, and busulfan [9]. Various studies have shown that the highest risk of pulmonary complications or pulmonary function impairment occurs when radiation therapy is used with bleomycin compared with bleomycin alone [13, 23, 37]. The use of surgery in addition to these exposures further increases the risk [13].

6.5 Comments on Hematopoietic Stem Cell Transplantation (HSCT)

As already discussed, HSCT is a known risk factor for pulmonary complications in survivors of childhood cancer. However, HSCT is a complicated process involving many factors that may be contributing, including the use of high-dose chemotherapy or radiation for conditioning, profound immune suppression with resultant pulmonary infections, a noninfectious entity known as idiopathic pneumonia syndrome (IPS), diffuse alveolar hemorrhage (DAH), pulmonary veno-occlusive disease (VOD), alloreactive inflammation in the form of lung GVHD, and bronchiolitis obliterans syndrome (BOS) [22]. Noninfectious etiologies generally outweigh the infectious complications when it comes to long-term complications in the lungs [38]. Many of these complications, including IPS and BOS, can carry a very high risk of both short-term and long-term mortality [39, 40], but if initial pulmonary insults show good recovery, then survival can be significantly improved [41]. The review of pulmonary complications after HSCT is complex, the topic of which could constitute its own book.

6.6 Conclusions

There are a wide variety of cancer therapy-associated outcomes affecting the lungs causing both measured and clinically symptomatic issues that can profoundly impact the lives of survivors. Careful attention to the lungs in follow-up is a necessary part of comprehensive survivorship care. Ongoing studies will hopefully continue to refine the risk based surveillance currently in practice based on the materials reviewed in this chapter.

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Growth Hormone Deficiency in Young Cancer Survivors

7

Stéphanie Espiard, Marianne Jarfelt, and Gudmundur Johannsson

7.1 Introduction

The progress in the treatment for childhood cancers led to an impressive improvement of survival rates. Subsequently, late effects of the cancer diseases and their treatments among adult survivors have been described during the last decades. Among them, endocrine complications are the most frequent ones. In the Childhood Cancer Survivor Study (CCSS), 44% of the childhood cancer survivors (CCS) self-reported at least one endocrinopathy [1], and in the St. Jude Lifetime Cohort Study (SJLIFE), 63% of survivors had endocrine disorders according to medical reports [2]. In addition, endocrine diseases are the second most common cause of excess hospitalizations in adult CCS after the neurological sequelae [3].

Hypopituitarism is the most frequent endocrine complication [2, 4, 5] and the most common endocrine cause of hospitalization among survivors of leukemia and CNS tumors [6]. Growth hormone (GH) deficiency (GHD), especially after cranial irradiation, is the most common and the earliest endocrine defect [7]. In the CCSS, GHD was self-reported by 2.9% of all patients. In the subgroup of patients with CNS tumors, GHD was reported by 10% [8], while after screening of patients' medical reports, GHD was reported for 21% [9], suggesting that many patients are not evaluated and therefore not aware of their GHD.

GH is a multifunctional hormone [10]. Its main function, growth, was first identified in 1921 by Evans which isolated the hormone in 1944 [11, 12]. GH plays an increasing role on growth from 2 to 3 years of age until puberty. At the end of puberty, a rapid decline of the GH secretion is observed, and this decline continues progressively over life. In healthy adults, GH secretion is correlated to body and visceral fat and physical fitness [13]. Beyond these physiological actions, GH secretion anomalies in patient and animal models have highlighted numerous additional

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functions, including a role in liver metabolism, cardiovascular system, adipocyte tissue, skeletal muscle trophicity, and a functional interaction with other endocrine function as gonads, thyroid, and adrenals [10]. GHD in adult leads also to mild perturbation of multiple organs function but overall to an alteration of the health status [13].

7.2 Etiology of Growth Hormone Deficiency in Childhood Cancer Survivors

7.2.1 External Radiotherapy

7.2.1.1 Prevalence and Risk Factor of Growth Hormone Deficiency after Radiotherapy

GHD after external radiotherapy was described in 1975 in patients who received irradiation for head and neck neoplasia [14] or brain tumors [15]. Radiation is used for different types of cancer, and the hypothalamic-pituitary (HP) area is often included within the irradiation field during the radiotherapy of children with brain tumors. In hematologic malignant diseases, cranial irradiation for acute leukemia or total body irradiation (TBI) before bone marrow transplantation exposes an high risk of GHD, especially when associated with intensive chemotherapy [16]. The risk to develop GHD after radiation, its severity and its timing of onset depend mainly on the biological effective dose delivered to the HP (Table 7.1) [7]. The biological effective dose depends on the total exposure dose but also the cumulative radiation dose. Moreover, higher fractional doses, i.e., larger dose over a shorter time, may be more likely to cause GHD than lower fractional doses for the same total exposure dose [7, 17]. However, a single dose (>2 Gy) can still induce neuronal damage [18].

The prevalence of radiation-induced GHD varies considerably from 0 to 90% between the different published studies, notably because of different GH cutoff limits, assessment methods, and different radiation regimens. When pooling three studies including patients who received doses from 13 to 55 Gy, the prevalence was 35.6% using a cutoff of GH at 5 μg/L after a stimulation test [19].

Table 7.1 Risk of GHD and other endocrine disorders according to the biological dose exposure

Radiation dose	Malignancy	Frequency GHD	Other hormonal abnormalities
TBI (7–12 Gy)	Hematological malignancies	Isolated GHD	
18–24 Gy	Hematological malignancies	Isolated GHD rare in adult	Precocious puberty in girls only
30–50 Gy	Nonpituitary brain tumors	GHD (50–100%)	Precocious puberty TSH deficiency ACTH deficiency Hyperprolactinemia
50–70 Gy	Nasopharyngeal carcinoma and skull base tumors Optic glioma	GHD (in almost all patients 5 years after therapy)	Gonadotropin deficiency TSH deficiency ACTH deficiency Hyperprolactinemia
30–50 Gy	Pituitary tumors Retinoblastoma	GHD (in almost all patients 5 years after therapy)	Gonadotropin deficiency TSH deficiency ACTH deficiency Hyperprolactinemia

Adapted from Darzy and Shalet, 2006 [18]
GHD Growth hormone deficiency, TBI Total body irradiation, Gy Gray, ACTH Adrenocorticotropic hormone, TSH Thyreo-stimulating hormone

GHD usually occurs within the 5 first years after the irradiation [17, 19–21]. In the CCSS, the cumulative incidence of GHD stagnated at 15 years after cancer diagnosis. This late delay reflects an under-ascertainment of GHD in adult CCS without a prior diagnosis of GHD during childhood due to a lack of systematic clinical follow-up [1]. The speed of onset and the GH trough level decline is dependent on the radiation dose [17, 21]. GHD after irradiation for cranial tumor can also be predicted to occur at 12 months for a mean dose to the hypothalamus >60 Gy, at 36 months for 25–30 Gy, and at 60 months for 15–20 Gy [17].

Age at the time of the irradiation has been described as a risk factor of GHD [7]. In a meta-analysis, the global prevalence of GHD after irradiation during adulthood (dose between 40 and 97Gy) for brain tumors was estimated to be 33% [22] that is considerably lower than observed in children. This may reflect a higher sensitivity of children HP but may be also due to the more conservative thresholds of diagnostic tests used in adults. Some studies also suggested other risk factors such as male sex, brain tumor location, and hydrocephalus [7, 19].

At a dose ≤24 Gy, GHD is usually isolated [7, 19] while other pituitary axis are affected by higher doses (>30 Gy) [2, 7, 20] (Table 7.1). In the latter case, GHD is usually the first deficiency to appear, followed by TSH, gonadotropins and ACTH deficiency [7]. Usually, once established, radiation-induced GHD is permanent and irreversible [7].

7.2.2 GHD in Other Condition of CCS

7.2.2.1 Surgery

Surgery of any tumor located in the HP area may lead to GHD. Craniopharyngiomas are rare but represent the most frequent tumors developed directly from the HP area in children. In fact, about 75% of patients had already a GHD at the diagnosis. This is explained by a disorganization of the area or by the destruction of the pituitary normal cells [23]. Presence of GHD before treatment in patients affected by brain tumors located outside the HP area may be underestimated, especially in patient who required cerebrospinal fluid shunt [17]. The absent of assessment of the GH status before anticancer treatment may also be a limitation of many studies.

Occurrence of GHD after surgery for a brain tumor not located in the HP area may be frequent in adulthood, which is described in about 30% of patients [24], however has been observed also in children [5]. The occurrence of this type of GHD is not correlated to the surgical approach. This may suggests that the deficiency is caused by a hypoperfusion of the pituitary gland during the surgical procedure rather than a direct damage of the axis. The lateral wing of the anterior lobe, which contains the somatotroph cells, is one of the most vulnerable vascular region of the hypophyseal portal system [24]. In the CCSS brain tumor group, 2.5% of patients who underwent only surgery presented with GHD [9].

7.2.2.2 Chemotherapy

In the CCSS brain tumor group, the prevalence of GHD in patients who received chemotherapy in addition to surgery and radiotherapy was higher than in patients who had only surgery and radiotherapy [9]. In addition, GHD several months to several years after single chemotherapy in patients treated during childhood for solid or hematologic cancers has been reported [25–27]. The prevalence of GHD after solely chemotherapy was estimated around 45% in two small series of solid tumors and acute leukemia survivors [26, 27], while in another small series including 35 acute lymphoblastic leukemia survivors, none of the patients treated solely with chemotherapy developed GHD [28]. In a cohort of 235, ALL survivors treated only by chemotherapy, growth failure, and subsequently GHD were observed in only two subjects [29]. In the

SJLIFE, 4.5% of ALL survivors who received only chemotherapy required GH replacement [16]. The wide diversity in multimodal chemotherapy regimens makes it difficult to isolate agents or combination of agents associated with the risk to develop GHD. However, an intrathecal high dose of methotrexate and systemic alkylating agents as cyclophosphamide and ifosfamide was often part of the chemotherapy in children who developed GHD [26, 27, 29].

7.2.2.3 Immunotherapy

Immunotherapy is a new treatment modality of cancers during the last few years. Especially, the amplification of natural immune response by checkpoint inhibitors mediates unprecedented benefit in some adult cancers. Few clinical trials have focus on checkpoint inhibitors in recurrent or refractory pediatric cancers, and best responses were observed for Hodgkin's lymphoma and tumors related to mismatch repair deficiency [30–32]. Synthetic immunotherapies designed to initiate new responses are more promising and several clinical trials are running [31]. Pituitary dysfunction, especially hypophysitis, is a frequent side effect of immunotherapy in adults. Somatotroph function appeared to be relatively spared but in fact is not often assessed in adults [33]. In one clinical trial assessing 33 patients with a recurrent or progressive solid tumor after ipilimumab treatment, a cytotoxic T lymphocyte antigen 4 inhibitor, one of these patients developed a severe hypophysitis complicated by a panhypopituitarism [34]. Long-term follow-up of CCS after immunotherapy will also reveal if GHD is a more often observed complication of these therapeutic approaches.

7.3 Recognition of GHD in Adult Survivors

7.3.1 Signs and Symptoms

Compared to childhood cancer survivors where GHD should be suspected when growth is impaired, most of the symptoms and signs of GHD in adults as asthenia, muscular weakness, and weight gain are nonspecific and also more difficult to recognize, especially in CCS who already have a significant alteration of their health condition [8, 35]. In the SJLIFE, more than half of patients with GHD were not diagnosed before the systematic standardized evaluation [2]. Signs, symptoms, and complications (summarized in Table 7.2) are the same in adults whatever the cause is of GHD. A deleterious metabolic profile with increased waist circumference, increased fat mass, decreased lean mass, dyslipidemia (higher total cholesterol, high low-density lipoprotein cholesterol, and triglycer-

Table 7.2 Signs and symptoms of GHD and benefits of GH therapy

	Signs and symptoms	Benefit on GH treatment
Body composition	Weight gain ↓ Lean body mass ↑ Fat body mass ↑ Waist circumference	Not demonstrated Improvement Improvement Improvement
Metabolic profile	Atherogenic lipid profile (↑ LDLc, ↑ triglycerides) Hyperinsulinism	Improvement Improvement No change, increased
Muscular	↓ Skeletal muscle strength	Improvement
Cardiovascular	↑ Cardiovascular mortality ↓ Cardiac capacity? ↓ Exercise performance	Not demonstrated ? Improvement
General symptoms and well-being	Impaired cognitive function ↓ Quality of life Fatigue Psychosocial problems Depression, anxiety, impaired sleep	Partial improvement Improvement Improvement ? ?
Bone	↓ Bone mineralization density ↑ Risk of fracture	Improvement Not demonstrated
Overall mortality	May be increased	Not demonstrated

ides), and hyperinsulinemia [36–40] have also been observed in adult CCS with GHD. This profile seems to worsen with time [41, 42]. Decreased muscle mass and exercise tolerance has been shown in adult CCS with untreated GHD [4]. Bone mineralization density (BMD) decreased with time and could lead to a premature risk of osteoporosis [38, 39, 43]. Quality of life (QOL) in adult CCS is also more severely impaired by GHD [38, 39]. Finally, GHD in CCS is associated with an increased risk of cardiovascular diseases [44]. Data on cardiac function and the association with GHD and premature mortality in GHD adult patients, whether they are CCS or not, are more controversial [39, 41].

7.3.2 Biological Assessment

7.3.2.1 Methods to Assess GHD

Because of its pulsatile pattern of secretion, GH measurement is not used to diagnose GHD in adults. Plasma insulin-like growth factor-I (IGF-I) is often reduced in GHD but can be normal, especially in older patients and in patients who have received radiotherapy. In addition, other conditions can lower the IGF-I level such as fasting, oral estrogens, liver disease, poorly controlled diabetes mellitus, and other catabolic conditions [45]. A GH provocative test is therefore needed to diagnose GHD in adults. Only adults with hypopituitarism with three or more anterior pituitary hormone deficiencies and a low serum IGF-I concentration have a very high likelihood of having GHD, and a stimulation test in these patients is not needed to confirm the diagnosis of GHD [46].

The insulin-induced hypoglycemia, arginine, and glucagon tests act mainly on the hypothalamus, while the GHRH test acts mainly on the pituitary glands. Also, the combined GHRH and arginine test could be falsely negative in CCS patients, especially during the first 10 years after cranial irradiation, if the hypothalamus is the primary site of damage [47]. The ITT may be initially more reliable and remains the best validated [48]. However, this test is contraindicated in older patients and in patients with coronary heart disease or history of seizures which is a frequent comorbidity in adult CCS. Moreover, the performance of this test needs a close supervision by an experienced team, and it is demanding for patients. The combined test arginine-GHRH is therefore an alternative [48]. The supposed inhibition of somatostatin by arginine allows a better reproducibility of the GHRH stimulation test. The tolerance of this test is better, and it has no contraindication. A glucagon stimulation test can be another alternative, but other provocative tests are not recommended [13, 45, 46]. Recently, a new oral GH secretagogue, macimorelin, has been developed as a diagnostic test for GHD that may simplify and improve the diagnostic procedure of GHD in adults [49]. Testing for GHD should be performed after other hormonal deficiencies are adequately replaced.

7.3.2.2 Definition of GHD in Adulthood

A GH peak below 5 ng/mL for the ITT is usually used as threshold for the diagnosis of adult GHD [46]. For the GHRH-arginine test, since obesity blunts GH responses, several thresholds have been proposed according to the BMI (BMI > 30, 4 ng/mL; 25–30, 8 ng/mL; <25, 11 ng/mL) [46]. In guidelines, adult severe GHD is defined by a GH peak lower than 3 ng/mL (≈9 mU/L) during an ITT or lower than 4 ng/mL during the GHRH-arginine [46, 50, 51]. During the transition period, i.e., in young adults who achieved final height, the cutoff for severe GHD should be somewhat higher, 5–6 ng/mL [50, 52].

7.3.2.3 Indication of Screening

Adult patients with history of surgery or irradiation of the HP axis should be considered for evaluation for acquired GHD [46, 50]. Since chemotherapy and any brain tumor surgery may lead to GHD, this recommendation might be extended to every CCS. In the guidelines, reassessment of GH status at transition into adulthood is not recommended in patients with irreversible structural

damage including organic GHD due to a mass lesion, after pituitary surgery or high-dose irradiation of the HP area [46]. Indeed, reversion to a normal GH status is very rare. In addition, deficiencies in three or more pituitary axis associated with a low serum IGF-1 level (≤2 S.D. after stopping the therapy for 2–3 months) strongly suggest the presence of GHD, and provocative testing is optional [46]. However, a provocative test may still be necessary in some countries for the reimbursement of the GH therapy (see Sect. 7.4.3).

7.4 Treatment of GHD in Adulthood

7.4.1 Benefit of GH Replacement in Adult CCS

Recombinant human GH is approved to treat GHD in adults. Clinical trials, post-marketing registries, and prospective studies have demonstrated its short- and long-term efficiency [53–56]. The benefits (summarized in Table 7.2) of the therapy have also been demonstrated in the group of adult CCS. In this specific subgroup of adult patients, several studies showed that GH replacement therapy improves BMD and body composition and reduced prevalence of metabolic syndrome by decreasing plasma glucose, leptin, waist circumference, and fat mass and improving the lipids profile [25, 39, 41, 57, 58]. Cardiac systolic function and muscle strength may also be improved by this therapy [57]. Most of these effects are observed after 2 years therapy. QOL is also improved [25, 39, 59], and this improvement is observed in some studies already after 3 months of therapy [39]. Performance for sustained attention and visual-spatial memory was improved after 2 years of therapy in another study [60]. However, in all adult GHD, it has not been determined yet if long-term treatment has beneficial effects on cardiovascular mortality and fractures [46, 61].

7.4.2 Risk of GH Replacement in Adult CCS

Despite the clear benefits on GH replacement therapy, GHD in adult CCS remains underdiagnosed and undertreated. For instance, in the SJLIFE study, 99.7% of patients with GHD were not treated [4]. Indeed, in the group of CCS, the question of the risk of underlying tumor progression or secondary and de novo neoplasia remains a fear shared by both physicians and patients. The role of GH in tumorigenesis which has been suggested by several observations included the association between acromegaly and cancers, experimental in vitro, and animal data and epidemiological studies [13, 62]. In a population-based study, the cumulative risk for a second cancer before the age of 50 was estimated between 8.6 and 13.3% [63]. Cohort studies have showed that CCS have a 15 times higher risk to develop a second malignant neoplasm than a control population [8]. One major issue is the question of the association between GH therapy and malignancy. This issue is difficult to assess due to the lack of appropriate control groups and the heterogeneity of the studies regarding the etiology of GHD, the risk factors of neoplasia, the GH dose exposure, and the follow-up duration. The majority of the studies [64, 65] and subsequent meta-analysis [58, 66, 67] have failed to demonstrate that GH therapy increased the risk to develop a second malignancy or recurrences. In the subset of patients who underwent cranial irradiation for CNS tumors, the risk of second CNS tumors is markedly increased [68]; this increased risk has been linked to the cranial irradiation and not the GH treatment itself [54, 69].

Safety data related to GH therapy and mortality are conflicting [70–72]. In particular, data from the French cohort of the Safety and Appropriateness of Growth hormone treatments in Europe had suggested an increase in cardiovascular mortality in young adults after childhood GH treatment [73]. However, data from the other cohort of this multinational study, large-scale pharmaceutical company registries, and meta-analysis do not show an increased risk of mortality or stroke after GH therapy [66, 67, 74]. The mortality is mostly increased in patients with organic background, and the risks of mortality have been mainly related to the primary cause of GHD rather than the treatment [75]. Finally, the risk of type 2 diabetes after initiating GH treatment in adult patients may be increased in those harboring classical risk factors of diabetes mellitus [66, 67, 70].

7.4.3 Indication and Modality of Treatment

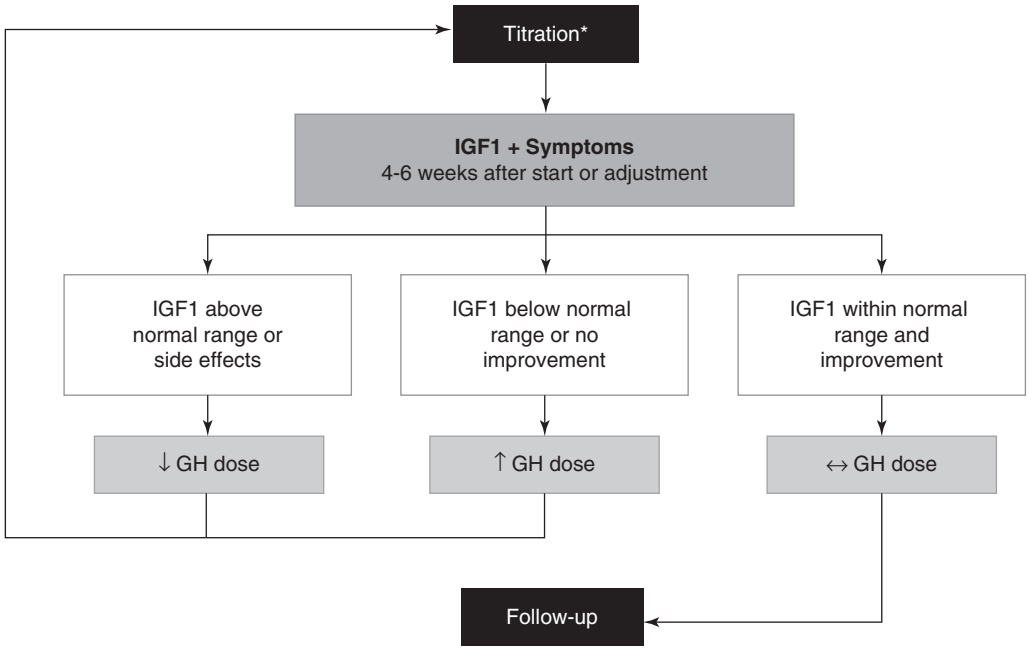
The importance of GH therapy in adults is well recognized in the recent guidelines of the Endocrine Society [46], which are mostly in agreement to the previous guidelines from the Growth Hormone Research Society [50] and the American Association of Clinical Endocrinologists [76].

GH therapy was initially contraindicated in patients with previous history of malignancy [76], but in more recent guidelines, leaning toward the reassuring safety data, the treatment is only contraindicated in patients with active malignancy [46]. Budgetary constraints and high therapy costs strongly restrict GH reimbursement in many countries. Reimbursement of GH therapy in adult is also usually limited to patients that meet the criteria of [46, 51]: (1) severe GHD defined by response to provocative test as mentioned above (in some countries two different provocative tests are required); (2) association with another pituitary hormone deficiency except prolactin deficiency; (3) impairment of QOL (in some countries a suggested criteria and mandatory in other countries).

For patients with childhood onset GHD, continuation of therapy is recommended until adult peak bone mass is achieved (normally around 25 years of age) [46, 51, 52]. After that, the decision to continue GH treatment should be based on the abovementioned criteria.

Information to the patients about the benefits and the risks of the therapy, especially about the current knowledge concerning the risk of secondary malignancy and recurrence in all patients, is essential. Management by a specialized team is recommended. GH therapy requires daily evening subcutaneous injection, and adherence may vary considerably. In case of adherence issues, administration on alternate days or three injections per week using the same total weekly dosage could be considered [61]. GH therapy is started at low doses and then titrated according to the response. Age, gender, and obesity may affect the response to treatment [61, 77]. Female sex and oral estrogen administration reduces GH responsiveness, and it is recognized that these women need considerably higher doses of GH than men [61, 78].

The response to treatment is difficult to assess in adults contrary to children where linear growth constitutes an objective marker [77]. Combination of clinical response and IGF-I level should be used to monitor patients with the objective to maximize the clinical benefits while minimizing side effects (Fig. 7.1). The side effects include headache, paresthesia, joint pain, swelling, and muscle pain. Monitoring glucose metabolism during GH replacement is essential, in particular in patients with risk factors for type 2 diabetes. Antidiabetic medications may need to



	Baseline	After maintenance dose achieved	During follow-up
IGF-1	×	×	2/year
Glucose, lipid profiles	×	×	1/year
Blood pressure, waist circumference and BMI	×	×	at each visit
Quality of life questionnaire	×	×	1/year
DXA	×	–	/2-3 years if low
Cortisol	×	×	If symptoms
Free T4	×	×	2/year

Fig. 7.1 Monitoring of patients under GH therapy
Flow chart summarizing the management of GH therapy in adult patients according to current guidelines from the GH Research Society [50] and the Endocrine Society [46]
DXA, dual energy X-ray absorptiometry

*Initial dose and titration are adapted to the age of the patients. Dose usually recommended are <30 years, 0.4–0.5 mg/day; 30–60 years, 0.2–0.3 mg/day; >60 years, 01–0.2 mg/day. Higher dose is usually required for female patients on estrogen therapy

be adapted in those with diabetes before initiation of treatment [61].

7.5 Conclusion

GHD is frequent in adult CCS, due to cranial irradiation and surgery of the HP area but has also been described after other type of brain surgery and chemotherapy. GHD contributes to the alteration in QOL and the health status of patients. Screening for GHD should be done in adult CCS after cranial irradiation and/or surgery in the hypothalamic area. Additional studies are necessary to answer the question if screening should be proposed in patients treated with chemotherapy, cranial surgery, and maybe after modern immunotherapy. It is important to identify patients

eligible for GH replacement therapy, since GH therapy has shown benefits on metabolic profile, BMD, exercise capacity, and QOL in adult GHD. In patients eligible for GH replacement, basic evaluation includes serum IGF-I and a GH stimulation test suitable for the patient and done in experienced centers. The treatment appears to be as safe in CCS patients as it is in adults with other causes of GHD. Meta-analysis and post-marketing surveillance registries are reassuring about the potential higher risk of second malignancies or recurrence under GH therapy. Complete information about the benefits and the potential risks of this therapy must be explained to each patient. Initiation and follow-up of GH therapy by a specialized team is advised.

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8 Endocrine Late Effects in Young Cancer Patients: Thyroid Gland

Georg Brabant and Helmuth G. Dörr

8.1 Background

With better survival rates following cancer therapy in childhood and adolescence, the number of survivors with adverse therapy-induced effects is increased in parallel. Alterations in thyroid function and proliferation are among the most frequent problems recognized under these conditions. They are primarily associated with an irradiation of the thyroid itself, but regarding functional deficiencies, central irradiation through damage to hypothalamus and pituitary plays an additional role. Concerning direct effects to the thyroid, animal studies and investigations in humans identified three major mechanisms:

- Direct damage to the thyroid epithelium.
- Irradiation dependent damage to the local capillary supply
- Induction of immunological damage to the thyroid

Large register-based follow-up studies in the USA and Great Britain allowed to characterize the nature of the thyroid damage and estimate their incidence and severity.

Hypothyroidism represents the most frequent problem of cancer survivors in childhood and adolescence [1–4]. In patients following treatment of Hodgkin lymphoma, 27.5% of the survivors demonstrated an underactive thyroid when followed up to 25 years, whereas hyperthyroidism was only observed in 3.1% [5]. Both, the incidence of hyper- and hypothyroidism clearly exceeds the expected frequency from German population-based data. In addition to these, direct detrimental effects to the thyroid most frequently induced by irradiation to the organ or surrounding structures like the upper mediastinum central hypothyroidism commonly associated with a deficiency of other pituitary functions may occur. When the hypothalamus/pituitary region is irradiated with doses of 40–70 Gy, the risk of central overt hypothyroidism is 3–13%. These data increase to 9–22% when subclinical forms of an underactive thyroid are additionally included [5]. The clinical relevance frequently escapes diagnosis because of the insidious onset and because measurement of TSH may be misleading. This is explained by a discrepancy between biological active TSH and generally less glycosylated bioinactive but immunologically detectable TSH following irradiation. The measurement of free hormones is helpful under these conditions and should be accompanied by the assessment of pituitary hormones which

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commonly react more sensitive like the somatotropic and/or gonadotropic axis.

A number of more recently introduced drugs in oncology like receptor tyrosine kinase (RTKI) inhibitors but also PD inhibitors impact on the thyroid. It is speculated that three mechanisms may induce RTKI-dependent damage to the thyroid. RTKI may lead to vasoconstriction, it may act at the cell membrane to block a major transporter of thyroid hormones in the thyroid, the "monocarboxylate transporter 8" (MCT8), and, finally, it may alter the intracellular activating deiodinases of thyroid hormones [6, 7]. Large prospective studies indicate that initially almost 50% of patients transiently develop an overactive thyroid before hypothyroidisms is observed. This pattern is mimicked by a new class of immunomodulatory drugs stimulating the immune system via an inhibition of PD. Nivolumab broadly used in melanoma therapy and increasingly tested for other epithelial tumors elicits a comparable pattern, whereas ipilimumab, again stimulates the immune response acts on the pituitary and may induce hypophysitis in up to 10% of patients.

Larger and long-term experience is only available with RTKIs. When monitored longitudinally, 30–50% develop clinically relevant hypothyroidism [6]. Drug-specific differences are discussed with a clearly higher frequency of adverse thyroid effects following sunitinib as compared to sorafenib therapy [8]. These data are relevant for the intervals in monitoring thyroid effects.

Therapy-induced alterations in thyrocyte proliferation are described. The most extended experience rests with the effects of low doses of irradiation to the thyroid. Radiation doses to thyrocytes below a lethal dose may induce long-term damage with a gradual increase in the rate of thyroid carcinomas during the decades to follow. This may even be augmented by co-treatment with chemotherapeutic agents like anthracyclines and bleomycin which may further increase the risk of secondary carcinomas but may stimulate secondary neoplasms of the thyroid without radiation as well.

The long-term follow-up of children irradiated 50 years ago because of tinea capitis illustrated the effects as the cumulative incidence of thyroid carcinomas dramatically increased [3, 4]. Comparable data have been published following exposure to the atomic bomb fallout in Japan. In comparison to data from population studies, the risk of thyroid cancer in these cohorts increased by 10- to 15-fold, and females appear to be more frequently affected than males. Papillary carcinomas dominate the histological pattern of these tumors [9].

8.1.1 Demand for Clinical Assessment and Surveillance of Cancer Survivors

Patients with risk factors for an alteration of the thyroid need lifelong follow-up. Particularly, when initial tumor treatment included irradiation of the hypothalamic or pituitary region, clearly the risk to develop central hypothyroidism is increased. Long-time assessment of thyroid function is mandatory for these patients and should include not only measurement of serum TSH concentrations but as well of peripheral thyroid hormones. TSH may be misleading as bioactivity of the hormone may be impaired, but immunoreactivity in the standard TSH tests is preserved. As frequently other pituitary hormone axes are insufficient as well, these patients should be tested for other pituitary dysfunctions.

Guidelines suggest that follow-up tests should be performed in yearly intervals during the first 10 years and should be continued at least every second year thereafter. This applies not only for centrally irradiated patients but also for patients whose thyroid was exposed to any irradiation including total body irradiation protocols. Similarly, thyroid function should be checked in yearly intervals, but when brain structures were spared from irradiation, screening with a single TSH measurement may be sufficient. In case the thyroid was irradiated, secondary thyroid

carcinomas may arise within an interval of several decades since initial exposure. Thus, biannual sonographical assessment of the thyroid and regional lymph nodes is suggested.

Patients treated with RTK inhibitors need frequent at least half yearly assessment of thyroid function.

8.2 Primary and Secondary Hypothyroidism

8.2.1 Diagnosis

Symptoms and clinical signs of hypothyroidism are uncharacteristic as symptoms like fatigue, weight gain, obstipation, dry skin, and hair loss may as well be related to other conditions particularly in cancer survivors. Most guidelines suggest to exclude thyroid dysfunction by measuring TSH and free thyroxine (fT4) early in the diagnostic workup (e.g., [10]). The TSH cutoff to suspect a developing hypothyroidism is under debate, but there is consensus that all patients with a confirmed elevation of TSH beyond 10 mU/L should be treated whereas lower levels between the upper reference range and 10 mU/L especially when combined with low fT4 concentrations may either be started on thyroxine or closely monitored for the development of underactive thyroid disease. Confirmation is usually achieved by a second assessment within 3 months and is especially important in subclinical hypothyroidism which is defined by an isolated elevation of TSH despite of fT4 levels within the reference range. Under these circumstance large studies suggest that up to 50% of patients spontaneously normalize over time [11]. Known reasons for such unstable results are recovery from severe non-thyroidal illness or interference with drugs.

Central forms of hypothyroidism are much more difficult to diagnose, as measurement of TSH fails in many instances. In case of a hypothalamic or pituitary deficiency of the thyreotropic axis TSH levels may be measurable or even elevated. This is related to a defect of normal glycosylation of the hormone which affects bio–but not immunoactivity of thyrotropin [12]. Diagnosis thus rests on free hormone levels, particularly on fT4. Assessment of clinical symptoms is usually not helpful as these are uncharacteristic. As other pituitary axes are affected as well, particularly the gonadal and somatotropic regulation, these defects may guide the clinical diagnosis. Early referral of these patients at risk to an endocrinologists is therefore advised [13].

8.2.2 Therapy

Treatment is based on a standard replacement of thyroxine, regardless of the cause of the disease, e.g., central or primary hypothyroidism. Following optimal dosing of thyroxine which targets a TSH between 1 and 2 mU/L in primary hypothyroidism, follow-up assessments are required in app. Yearly intervals. Changes in thyroxine requirements may be induced by substantial alterations in muscle mass, therapy with other interfering drugs, or changes in sex steroids as in pregnancy. In all these conditions, the thyroxine dose needs adaptation and TSH as fT4 should be retested after approximately 4–6 weeks when a new steady state is reached. Particularly in pregnancy the dosage of thyroxine is increased, most frequently by app. 25% [14].

When therapy of central hypothyroidism is monitored, TSH no longer serves as a marker. As other pituitary functions may be affected and treatment with thyroid hormones may induce an Addisonian crisis when the adrenocortical was affected, all subjects with central hypothyroidism should be tested for their adrenal function before thyroxine therapy is started. As some rest function of the thyroid can usually be expected, thyroxine dosage is slowly increased with an average maximal dose of 1.6 μg/kg bw when thyroid function completely failed [10].

8.3 Disturbance of Thyroid Proliferation

The thyroid gland is radiation-sensitive gland. Following irradiation directed to the thyroid, long-term follow-up is mandatory. This applies especially for low-dose irradiation which does not completely destroy thyroidal tissue [3, 4]. Even several decades after the initial treatment, nodular changes and the development of a secondary thyroid cancer have been observed. Diagnosis may be achieved by palpation but should be performed using thyroid ultrasound [15]. For radiation-induced thyroid malignancies, the same particularly sonomorphological criteria are implied as in the diagnosis of any thyroid neoplasm. They are almost uniformly defined by various societies. Any suspicious change in the sonomorphology should be further diagnosed by cytological assessment following fine-needle aspiration. The results allow a classification of the process with reasonable high precision (10–15% insufficient material, app. 10% with incorrect diagnosis). With the high long-term risk of children and adolescents for the development of a thyroid carcinoma when previously irradiated to the neck, a surgical correction should be discussed early in suspicious cases. Apart from measurement of thyroid function, assessment includes as well measurement of thyroid autoantibodies, whereas measurement of the thyroid tumor marker, calcitonin, is not routinely advocated because medullary thyroid carcinomas are not typically observed in cancer survivors.

Following irradiation of the thyroid all patients should be followed every 2 years by thyroid ultrasound [16]. Because of the long-term development of these secondary tumors, we suggest that the follow-up should be continued for at least 30 years.

Treatment of an irradiation-induced thyroid carcinoma is based on the same criteria as the therapy of any primary thyroid carcinoma.

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9 Disorders of Gonadal and Reproductive Function in Survivors of Childhood and Adolescent Cancer

Christian Denzer

9.1 Introduction

Endocrinological disorders are particularly common in long-term survivors of pediatric cancer because of the high vulnerability of the endocrine system to the effects of various cytostatic agents, and in particular to radiotherapy. In the baseline survey of the CCSS study, more than 20% of long-term survivors reported being affected by at least one endocrinological disease [1]. Clinical case series report prevalence rates of endocrine disorders in adolescent and young adult survivors of up to 40% [2]. The type, severity and time of manifestation of endocrine sequelae usually depend on exposure to cytostatic drugs, their cumulative dose, dosage and fractionation of radiotherapy, and the patient's age at the time of therapy.

The endocrine late effects with the highest prevalence are growth disorders and thyroid dysfunction. In addition, there are frequently disorders of the onset and progression of pubertal development as well as functional disorders of the hypothalamo-hypophyseal-adrenal and hypothalamo-hypophyseal-gonadal axes. Especially late effects impairing reproductive function and possibly also the health of the offspring are among the most important topics concerning survivors of childhood cancer. Since many of these treatment consequences manifest themselves or become symptomatic only in the course of years, long-term endocrinological aftercare is indicated for all oncological patients in childhood and adolescence.

Delayed or arrested pubertal development, overt or subclinical hypogonadism, and impaired fertility may arise from damaging impacts to hypothalamic nuclei and the pituitary (e.g., by tumor localization, tumor growth, cranial irradiation, neurosurgical procedures) or from direct gonadal toxicity of a wide range of commonly used cytotoxic agents, or exposure of ovaries and testes to ionizing (scatter) radiation (Figs. 9.1, 9.2, 9.3, and 9.4).

9.2 Precocious Puberty

Premature pubertal development can occur as a direct result of a tumor of the CNS or due to radiogenic damage to the hypothalamic GnRh pulse generator. Among the most frequent tumors of the CNS causing precocious puberty are malignant tumors such as optic glioma or astrocytoma, germ cell tumors, but also benign lesions such as hamartoma, cysts, or craniopharyngioma [3]. What these tumors have in common is that the disturbance of hypothalamic or pituitary

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function usually results from a direct mechanical effect, i.e., increased pressure caused by locoregional growth or obstruction of cerebrospinal fluid circulation. Intracranial (and extracranial) germ cell tumors can also cause precocious puberty by secretion of hCG [4].

Cranial irradiation can induce precocious puberty in the low dose range from 18 to 30 Gy as well as in the high dose range >30 Gy (Fig. 9.2). The reason for this effect is presumably a direct radiogenic damage of neurons which inhibit the hypothalamic GnRH pulse generator. Very high radiation doses (>50 Gy), on the other hand, also carry the risk of developing hypogonadotropic hypogonadism, which usually does not occur in isolation, but in the context of further failures of hypothalamic and pituitary function (Fig. 9.1). Survivors of childhood and adolescent cancer who received chemotherapy alone do not appear to be at increased risk of premature pubertal development [5].

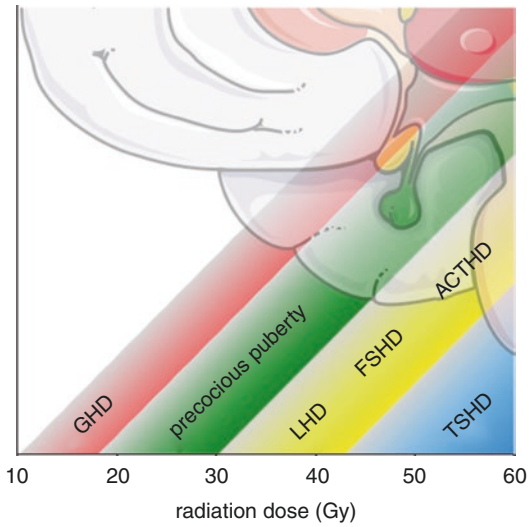

Fig. 9.1 Disorders of hypothalamic and pituitary function in childhood cancer patients exposed to increasing doses of cranial irradiation

Girls are more frequently affected by precocious puberty or an acceleration of the progression of pubertal development as a result of cranial radiation than boys. This observation applies both after exposure to low irradiation doses (>18 Gy), as used, e.g., in the context of prophylactic cranial irradiation for certain acute leukemias [6, 7], and after exposure to high irradiation doses in the therapy of many brain tumors [8]. For example, data from the Childhood Cancer Survivor Study (CCSS) show that female patients with acute lymphocytic leukemia (ALL) who received prophylactic cranial irradiation at doses both less and greater than 20 Gy had a sixfold increased risk of early menarche (<10 years) compared to healthy sibling controls [5]. Risk factors for precocious puberty and early menarche are a younger age at the time of radiation exposure and a higher Body Mass Index (BMI) [9, 10].

The not age-appropriate increase of sexual steroids in the context of premature pubertal development leads to a rapidly advancing maturation of the growth plates and thus to a restriction of growth prognosis. This finding is particularly important for patients after cranial

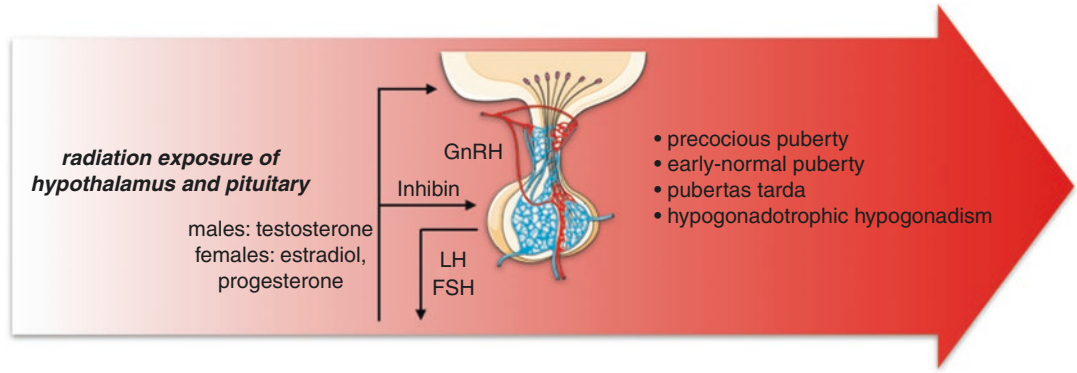

Fig. 9.2 Disorders of pubertal development, hypogonadism, and infertility in childhood cancer survivors following radiation exposure of hypothalamus and pituitary

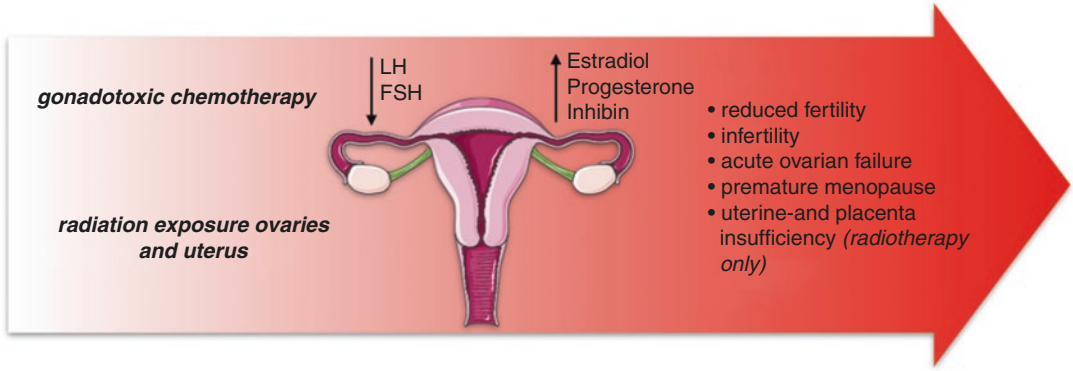

Fig. 9.3 Disorders of pubertal development, hypogonadism, infertility, and uterine function in female patients following exposure to gonadotoxic chemotherapy and direct radiation exposure of ovaries and uterus

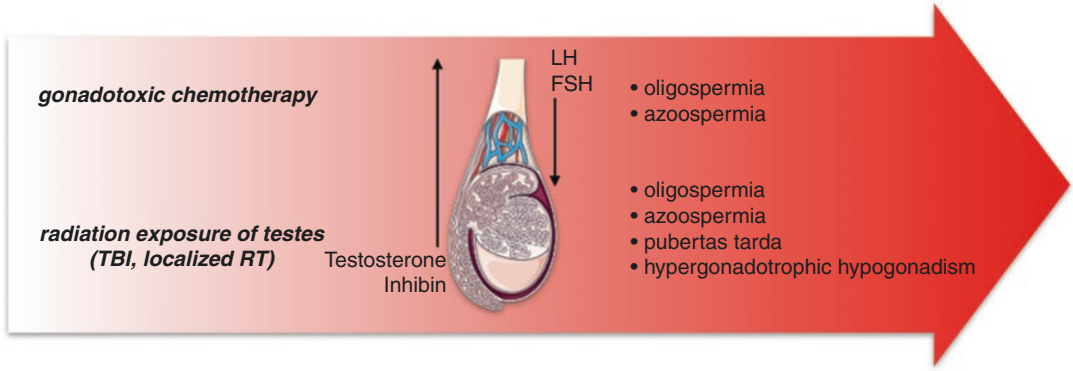

Fig. 9.4 Disorders of pubertal development, hypogonadism, and infertility in male patients following exposure to gonadotoxic chemotherapy and direct radiation exposure of testes

radiation, since they are frequently affected by growth hormone deficiency and thus there is an additive effect which clearly restricts achievable final height. For the same reason, there may be no acceleration of growth velocity as a clinical indicator of premature pubertal development in survivors of childhood cancer.

9.3 Diagnostic and Therapeutic Approach

The clinical diagnosis of premature pubertal development in girls should be based on the occurrence of thelarche before the age of 8 years. In contrast, testicular enlargement >3 mL before the age of 9 years in boys after cancer is not a reliable indicator of pubertas praecox, since damage to the germ cell epithelium caused by gonadotoxic therapy modalities (e.g., high-dose alkylants, testicular radiation) can lead to testicular volume that is inappropriately low for the stage of pubertal development already reached, while testosterone synthesis remains unaffected. Furthermore, in case of simultaneous growth hormone deficiency, the acceleration of height velocity as a sign of premature pubertal development may also be absent in survivors of childhood cancer. Additional information can be obtained by assessing skeletal maturation using an X-ray of the left hand. Based on an evaluation according to the references of Greulich and Pyle [11], most patients with precocious puberty have an acceleration of skeletal age by more than two standard deviations compared to chronological age. In addi-

tion, ultrasound of the uterus and ovaries in patients with precocious puberty shows premature uterine growth [12], which usually precedes enlargement of the ovaries. In laboratory tests, basal estradiol, or testosterone, respectively, is usually elevated above the prepubertal reference range. The GnRH or the GnRH agonist test can be used to confirm the diagnosis of a central precocious puberty. An example for a risk-adapted screening strategy for precocious puberty is provided in Table 9.1.

In the case of *pubertas praecox vera*, treatment with a GnRH agonist should be initiated, as this slows down premature skeletal maturation and improves the achievable adult height [14].

Table 9.1 Risk-adapted follow-up recommendations for gonadal late effects in childhood cancer survivors according to German evidence-based guidelines [13]

	S3-Guideline: "Endokrinologische Nachsorge nach onkologischen Erkrankungen im Kindes-und Jugendalter" (2014) [13]
Precocious puberty	
	CRT > 18 Gy: • Screen for precocious puberty every 6 months in prepubertal children until age 8 years (♀)/9 years (♂)
Hypogonadotropic hypogonadism	
	CRT > 40 Gy: • Tanner stages at least annually until end of puberty, then yearly history for symptoms of hypogonadism • LH, FSH, testosterone/estradiol at least at age 13 years (♀)/14 years (♂)
Hypergonadotropic hypogonadism	
Testicular function	*Any radiation to testes:* • Repeat semen analysis during long-term follow-up *Radiation to testes >20 Gy, exposure to gonadotoxic chemotherapy:* • Tanner stages at least annually until end of puberty, then yearly history for symptoms of hypogonadism • LH, FSH, testosterone at least at age 14 years
Ovarian function	*Any radiation to ovaries, exposure to gonadotoxic chemotherapy:* • Tanner stages at least annually until end of puberty, then yearly history for symptoms of hypogonadism • LH, FSH, estradiol at least at age 13 years

This applies in particular to patients after cancer in childhood and adolescence who are additionally treated with recombinant growth hormone due to growth hormone deficiency [15].

9.4 Hypogonadotropic Hypogonadism

Sellar and suprasellar brain tumors may not only cause precocious puberty but can also be the cause of hypogonadotropic hypogonadism. The main symptoms of hypogonadotropic hypogonadism in childhood and adolescence are absence of pubertal development, arrest of pubertal development that has already begun, or secondary amenorrhea. Typical CNS tumors that can cause hypogonadotropic hypogonadism are craniopharyngioma, intracerebral germinomas, optic gliomas, pituitary tumors, and CNS involvement in Langerhans cell histiocytosis. Among the possible therapeutic exposures, high-dose cranial irradiation (>30 Gy) is the most important risk factor for the development of hypogonadotropic hypogonadism. The risk for the development of hypogonadotropic hypogonadism increases not only with radiation dose but also with age at the time of treatment [16, 17]. Hypogonadotropic hypogonadism after high doses of cranial radiation does not usually occur in isolation but is often associated with other hypothalamic-pituitary functional failures (growth hormone deficiency, central hypothyroidism, central adrenal cortex insufficiency), which can manifest themselves progressively in the long-term, possibly decades-long course of follow-up care (Figs. 9.1 and 9.2) [18]. Whether cytostatic drugs can exert a direct effect on gonadotropin release is currently unclear.

Not only high radiation doses in childhood and adolescence lead to a clearly reduced probability of pregnancy. Even a low dose of cranial irradiation can change the pulsatility of gonadotropin secretion in the long term and lead to an overall reduced LH secretion as well as to a lower LH-"surge". These changes may cause a shortened luteal phase and subsequent reduced fertility in affected patients [19].

Follow-up recommendations for the detection of hypogonadotropic hypogonadism are detailed in Table 9.1.

9.5 Hypergonadotropic Hypogonadism

9.5.1 Impairment of Ovarian Function Following Gonadotoxic Chemotherapy

Therapy-induced damage to ovarian function may occur as acute amenorrhea during the intensive therapy phase or immediately after the end of therapy. Amenorrhea can be permanent in the sense of an acute ovarian insufficiency, but more often it is only transient, and after months (or even years), there is a spontaneous recovery of the ovarian function. Even if there are no menstrual cycle abnormalities during or immediately after the end of antineoplastic therapy, many patients show a significantly increased risk of premature menopause (before the age of 40) and limited fertility. The risk of premature ovarian insufficiency in survivors of childhood and adolescent cancer is about ten times higher than in healthy individuals [20].

If ovarian insufficiency exists before the beginning of puberty, pubertal development does not progress and primary amenorrhea results. If ovarian insufficiency develops during or after puberty, pubertal development may be arrested, or secondary amenorrhea and menopausal symptoms may occur (Fig. 9.3). Girls and young women with a premature loss of ovarian estrogen production have an increased risk of developing osteoporosis [21] as well as possibly coronary heart disease.

As ovarian reserve decreases with increasing age, similar therapeutic exposures exert more pronounced gonadotoxicity in older compared to younger patients. The risk for the development of secondary amenorrhea or acute ovarian failure following gonadotoxic treatment modalities is significantly higher in postpubertal or young adult patients compared to the risk for primary amenorrhea in prepubertal patients. Nonetheless, exposure to high-dose gonadotoxic agents (especially alkylants) also causes ovarian insufficiency in younger girls (Table 9.2) [23].

At highest risk for the development of ovarian insufficiency are pre- and postpubertal girls and young women undergoing high-dose, myeloablative conditioning regimens containing alkylating agents (e.g., busulfan, melphalan) for HSCT [24, 25]. On the other hand, ovarian function remains intact or recovers shortly after completion of intensive antineoplastic therapy in the majority of patients undergoing standard risk therapy for most childhood and young adolescent cancers [26, 27]. Nonetheless, histology of ovarian tissue from pre- and postpubertal girls who received chemotherapy, e.g., for acute lymphoblastic leukemia, demonstrates a significantly reduced number of follicles and impaired follicle growth compared to healthy controls [28, 29]. These findings explain the observation of seemingly normal ovarian function in a subgroup of patients following therapy with alkylating agents, who nevertheless carry a high risk of experienc-

Table 9.2 Risk categories of gonadal toxicity of various antineoplastic agents in female childhood cancer patients (adapted from [22])

Gonadotoxicity in female cancer patients	
Class	Agents
High risk	
Alkylating agents	Mechlorethamine
	Cyclophosphamide
	Chlorambucil
	Melphalan
	Busulphan
Non-classic alkylators	Procarbazine
	Dacarbazine
Medium risk	
Heavy metals	*Cis*-platinum
Antimetabolites	Cytosine arabinoside
Anthracyclines	Doxorubicin
Podophyllotoxins	Etopsoide (VP-16)
Alkylating agents	Carmustine, lomustine
Vinca alkaloids	Vinblastine
Low risk	
Antimetabolites	Methotrexate
	6-Mercaptopurine
Vinca alkaloids	Vincristine
Antibiotics/alk. agents	Mitomycin

ing premature menopause in the third or fourth decade of life [20, 30, 31].

Data from the *Childhood Cancer Survivor Study* demonstrates a decreasing probability for pregnancy in female patients with increasing alkylating agents dosages compared to healthy sibling controls [32]. Reassuringly, course of gestation and the risk for inborn diseases or malformations of the newborn seem to be unaffected by previous exposure to gonadotoxic agents [33].

9.5.2 Impairment of Ovarian Function Following Radiotherapy

Abdominal radiotherapy, radiation of the pelvis or the lumbar spine all are associated with a significant risk for the development of ovarian failure (Fig. 9.3) particularly when both ovaries are exposed [5, 20, 26, 34, 35]. A radiation dose of 6 Gy may lead to irreversible ovarian damage in older, adult patients. In children and adolescents, permanent ovarian insufficiency is observed following higher ovarian radiation doses between 10 und 20 Gy [35, 36]. A radiation dose to the ovaries exceeding >20 Gy was associated with the highest cumulative incidence of acute ovarian failure affecting 70% of patients according to data from the *Childhood Cancer Survivor Study*. Intrapubertal or postpubertal girls >13 years had the highest risk for ovarian insufficiency compared to younger, pre- or early pubertal girls ≤12 years [23]. Of note, radiation exposure of the ovaries and exposure to gonadotoxic cytostatic agents exert additive effects on gonadal function, which may lead to the manifestation of permanent ovarian failure also following lower radiation doses [20]. The probability for pregnancy in adulthood is also reduced following lower radiation doses to ovaries (>5 Gy) during treatment for childhood cancer [32]. Furthermore, data from numerous studies demonstrate that almost all female patients undergoing total body irradiation (TBI) during adolescence are affected by premature ovarian failure [37, 38].

9.5.3 Impairment of Testicular Function Following Antineoplastic Chemotherapy

Male survivors of childhood cancer who were treated with gonadotoxic chemotherapy are affected by some degree of fertility impairment in 40–60% of cases. In contrast to antecedent assumptions, younger age or a prepubertal stage of development at the time of therapy do not have any protective effect from infertility in later life [39, 40]. Testicular germ cell epithelium is significantly more vulnerable to the effects of gonadotoxic agents compared to Leydig cells [41]. As in female patients, the most pronounced gonadotoxic effects on male germ cells are exerted by alkylating agents, but also other substances are characterized by substantial gonadotoxic side effects (Table 9.3). Besides the class of cytotoxic agents, cumulative dosage, maximum single dose, and probably also the age of the patient at the time of therapeutic exposure are important modifiers of the extent of testicular impairment [42–44] (Fig. 9.4, Table 9.3). Leydig cell function is unaffected after exposure to gonadotoxic chemotherapy (without concurrent

Table 9.3 Risk categories of gonadal toxicity of various antineoplastic agents in male childhood cancer patients (adapted from [22])

Gonadotoxicity in male cancer patients	
Class	Agents
High risk	
Alkylating agents	Mechlorethamine
	Cyclophosphamide
	Chlorambucil
	Busulphan, melphalan
Non-classic alkylators	BCNU, CCNU
	Procarbazine
Medium risk	
Heavy metals	Cisplatin
Antimetabolites	Cytosine arabinoside, Methotrexate
Anthracyclines	Doxorubicin, daunorubicin
Low risk	
Vinca alkaloids	Vincristin, vinblastin
Glucocorticoids	Prednisone
Antimetabolites	5-Mercaptopurin

radiation exposure of the testes) in the vast majority of cases. Nonetheless, mild subclinical testosterone deficiency may become apparent following high-dose therapy regimens [45, 46].

9.5.4 Impairments of Testicular Function Following Radiotherapy

Impairments of spermatogenesis may occur following testicular radiation doses as low as 0.1 Gy. After radiation doses of 1–2 Gy, recovery of spermatogenesis is frequently observed over the course of several years of follow-up, whereas recovery is rarely seen following higher doses exceeding 2–3 Gy [43, 44]. TBI causes impaired germ cell function in almost all exposed male patients [47] with recovery rates lower than <20% even during long-term follow-up [48]. Leydig cell dysfunction occurs only following exposure to higher radiation doses (>20 Gy in prepubertal boys, >30 Gy in male adults) [49] (Fig. 9.4, Table 9.3).

9.5.5 Diagnostic and Therapeutic Approach

As in central hypogonadism, premature ovarian failure may present as delayed or arrested pubertal development, primary or secondary amenorrhea, or premature menopause. Key laboratory findings for the diagnosis of ovarian insufficiency in adolescent girls and adult women are significantly increased levels of gonadotrophins, particularly FSH with concomitantly low levels of serum estradiol (Table 9.1). In prepubertal girls, gonadotrophin levels may be in the normal range despite marked ovarian damage and will rise only to levels in the pathologic range during progression of pubertal development. Hormone substitution therapy for the advancement of pubertal development or during adult life should follow established guidelines [50].

Diagnosis of impaired Leydig cell function relies on regular clinical evaluation of the progression of pubertal development and documentation of symptoms suspicious of testosterone deficiency. Impaired germ cell function often becomes clinically apparent by subnormal testicular volume despite normally progressing pubertal development. History and clinical examination should be complemented by laboratory determination of LH, FSH, and testosterone (Table 9.1). Testosterone replacement therapy should follow existing guidelines [50]. Spermiograms should be repeatedly offered to patients following gonadotoxic (chemo-)therapy, as recovery of spermatogenesis may occur during long-term follow-up [51].

9.6 Impairment of Uterine Function Following Radiotherapy

Radiogenic impairments of the uterus comprise decreased uterine volume or uterine growth, alterations of uterine vasculature, and a reduced endometrium. The degree of impairment depends on the age of the patient at the time of radiation, as the prepubertal, developing uterus is significantly more radiosensitive than the pubertal or the mature uterus [52]. Radiation doses between 14 and 30 Gy leads to impairments of the uterine vascularization and decreasing muscular elasticity [53]. Despite the comparably low total radiation dose, TBI causes a significantly reduced uterine volume, disordered uterine blood flow and a reduced or missing endometrium [53, 54]. These structural abnormalities following radiation exposure most likely explain the observation of markedly increased pregnancy risks in affected patients. Radiation exposure of the uterus is associated with an increased risk for premature delivery and low birth weight [55, 56]. In young adult women who underwent TBI, hormone replacement therapy with sex steroids resulted in improvements of uterine function (endometrium, blood flow) [53]. In contrast, exposure to higher radiation doses or younger age at radiotherapy may result in irreversible impairments of uterine function which cannot be ameliorated by estrogen substitution [29, 53, 57].

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10 Fertility Protection in Childhood, Adolescents and Young Adulthood Cancer Patients

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10.1 General Considerations

The first option to preserve fertility in girls and young women is the choice of a chemotherapy regimen affecting ovarian function as less as possible. Under highest risk for loss of ovarian endocrine and reproductive function are girls treated for sarcoma and undergoing autologous bone marrow stem cell transplantation.

Radiotherapy also imposes a considerable risk to the ovaries. As described in the Chap. 13, Pregnancy and Birth, of this book, the sterilizing dose in women at the age of 40 years is 7 Gray. In children the sterilizing dose is higher due to a higher ovarian reserve. It is 16 Gray in 20 years old women and 18 Gray in 10 years old girls. Furthermore, radiation can also severely affect the function of the uterus. Therefore, children should not get pregnant if the uterus received a radiation dose of >25 Gray. The corresponding dose for adults is 45 Gray [1].

Substantial problems occur if the reproductive organs itself suffer from cancer. For these girls fertility-sparing surgery with preservation of the healthy contralateral ovary can be a suitable strategy.

10.2 Cryopreservation of Ovarian Tissue

For young prepubertal girls, cryopreservation of ovarian tissue is the only option for fertility preservation, as they cannot undergo ovarian stimulation and aspiration like postpubertal girls or women due to their young age. An ovary or parts of an ovary can be removed surgically, mostly during laparoscopy or in conjunction with other surgical procedures that the child has to undergo for her disease. Later, when there is a pregnancy wish, the tissue can be transplanted. Successful births have been reported in adult women after cryopreservation and transplantation of ovarian tissue [2]. In adults tissue cryopreservation and transplantations have already moved away from the experimental status and are slowly becoming an established technique in the hands of experienced centres. However, tissue cryopreserved in children and transplanted in adulthood has not yet led to a pregnancy. Therefore, this procedure still needs to be categorized as experimental if

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performed in prepubertal children. Basically, the chances of getting pregnant are greater the higher the ovarian reserve and follicle density in the cryopreserved and transplanted tissue. For a later transplantation of the ovarian tissue different possibilities exist. The transplantation can take place laparoscopically or by laparotomy in the pelvic peritoneum, in the ovary or on the ovary. It is unclear which of the methods provides the highest pregnancy rate, and it remains unclear how much cryopreserved tissue should to be transplanted. It is advisable to check the tubal patency during the operative procedure. The success of the procedure has been documented in adult women with the delivery of more than 100 babies worldwide [2, 3]. In case of blood borne diseases such as leukaemia, ovarian tissue may contain malignant cells. In these patients the tissue cannot be transplanted. One possible option is xenografting cryopreserved ovarian tissue into severe combined immunodeficient mice [4]. However, this procedure is still experimental and no births have been reported afterwards. In general, the risk of transplanting malignant cells is low [5]. Furthermore, oocytes can be cultured and matured in vitro, but this procedure is also experimental and no births have been reported so far [6].

10.3 Transposition of the Ovaries

In girls undergoing radiation of the pelvis, ovarian transposition can be considered. The ovaries on one or both sides are transposed and, for example, attached proximally to the peritoneum of the abdominal wall. Indications include any kinds of pelvic radiations. Ovarian transposition can be carried out together with staging laparoscopy or pelvic lymphadenectomy. Shielding of the ovaries is also an option but has only been described in same case reports [7].

10.4 Cryopreservation of Oocytes

In some cases ovarian stimulation and oocyte collection can be an alternative method of fertility preservation in postpubertal girls. The ovaries are stimulated with gonadotrophins, which can be started at any point in the cycle and requires a stimulation time of up to 2 weeks. Depending on age and ovarian reserve an average of 10–13 oocytes can be obtained per treatment cycle [8]. It always needs to be considered that the use of a vaginal probe when performing the ultrasound and oocyte aspiration can be traumatic in adolescents. Ovarian stimulation and cryopreservation of oocytes is not possible in prepubertal girls.

10.5 Medical Ovarian Suppression

Co-treatment with GnRH-agonists during the course of chemotherapy has been suggested as a way of protecting the ovaries of adult women in case of chemotherapy. The mode of action is still unknown. It possibly acts by inducing a hypoestrogenic state causing a reduction in the uteroovarian perfusion. As ovarian protection by GnRH-agonists still have not been proven to be effective, this procedure is just recommended as an additional therapy next to oocyte and ovarian tissue cryopreservation [9]. In the prepubertal girl, there is no rationale in using GnRH-agonists as gonadotropin concentrations are still very low.

10.6 Fertility Preservation in Boys

Cryopreservation of semen is the easiest procedure to preserve fertility in adolescent and adult males, if the testes are at least 6–8 mL, there is a reasonable probability of sperm in an ejaculate [10]. Semen cryopreservation should be offered to all boys who are mature enough to produce sperm. If the pubertal boy is unable to produce an ejaculate, methods like electrostimulation during anaesthesia can be considered [11]. Sperm cryopreservation should always be offered for boys at the time of initial malignant diagnosis as sperm cryopreservation is not possible if the boy has already started the chemotherapy. Cryopreservation of testicular tissue can be considered in prepubertal boys. However, this technique should only be performed in highly

specialized centres under study conditions and needs to be considered as experimental as no pregnancy has been achieved so far.

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11 Endocrine Late Effects in Young Cancer Patients: Adrenal Gland

Helmuth G. Dörr and Georg Brabant

11.1 Introduction

Endocrinopathies are among the most commonly observed sequelae in childhood cancer survivors [1–6] (Fig. 11.1). They result from direct damage to the hypothalamic-pituitary (HP) region (tumor or surgery) or from cranial radiation, chemotherapy, and immunotherapy. After cranial radiotherapy, a characteristic pattern of hormone deficiencies develops over several years. The somatotropic axis is the most vulnerable to radiation damage and growth hormone deficiency remains the most frequently seen endocrinopathy followed by gonadal, thyroid, and adrenal hormones [7, 8]. Among all endocrine disturbances, secondary adrenal insufficiency (SAI) is rare in childhood cancer survivors [9, 10]. An estimated prevalence of 3.2% was calculated among 1089 participants treated with HP radiotherapy [11]. CRH deficiency is more common than ACTH deficiency, since the hypothalamus is more sensitive to radiation than the pituitary [12]. The severity and rate of development of hypopituitarism is determined by the dose of radiotherapy delivered to the HP axis. SAI was observed in 8% of the patients receiving <20 Gy, and in 83% of the patients after radiotherapy with ≥40 Gy [13].

Among childhood cancer survivors who were treated with chemotherapy alone due to hematological malignancies or solid tumors, 81% developed one or more endocrine abnormalities 13 years posttreatment, but none had ACTH deficiency [14]. No adrenal insufficiency was observed in survivors in survivors of nephroblastoma and neuroblastoma [15]. However, there are increasing reports of adrenal insufficiency in patients treated with immune checkpoint inhibitors due to autoimmune side effects such as adrenalitis and hypophysitis [16].

SAI is common in childhood cancer survivors after prolonged high doses of glucocorticoid therapy. Glucocorticoid doses >7.5 mg prednisone equivalent for more than 3 weeks cause a suppression of the hypothalamic–pituitary–adrenal (HPA) axis [17]. The Cochrane review on adrenal insufficiency in childhood acute lymphoblastic leukemia after glucocorticoid therapy reported SAI in nearly all children in the first days after cessation of glucocorticoid treatment. The majority of children recovered within 7 weeks, but a small number of children had ongoing adrenal insufficiency lasting up to 34 weeks [18]. Additionally, high-dose fluconazole was suggested as a risk factor for prolonged adrenal insufficiency.

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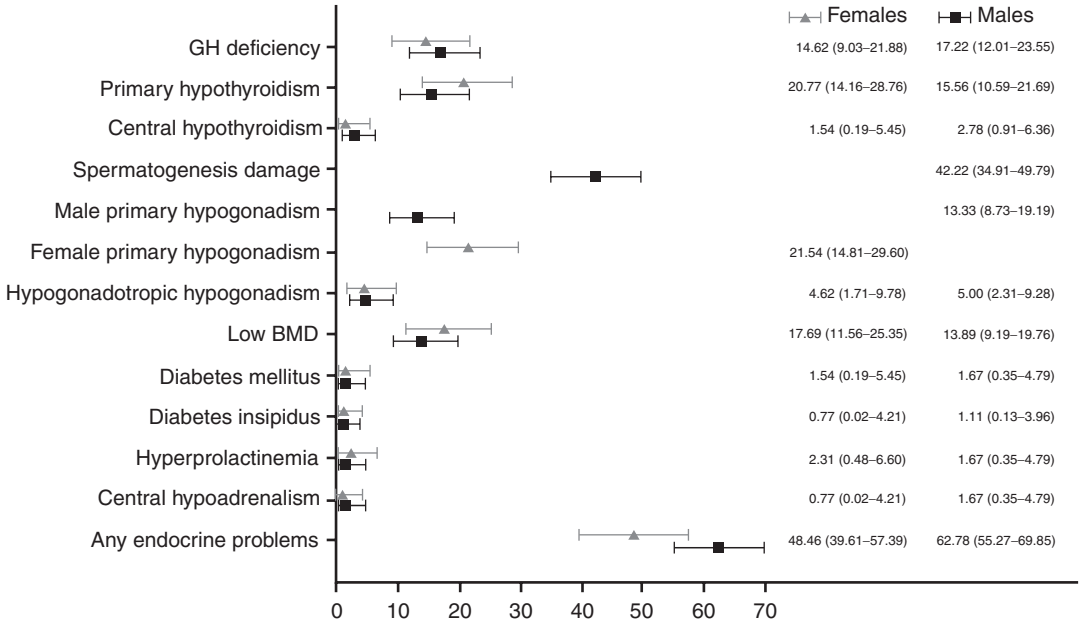

Fig. 11.1 Prevalence of endocrine disorders at last follow-up visit, by gender. Reprinted with permission from Brignardello et al. [1] (Copyright 2013, European Society of Endocrinology)

11.2 Clinical Symptoms

The symptoms of SAI are nonspecific and include the following: weight loss, nausea, fatigue, reduced school performance, increased susceptibility to infection, and/or hypoglycemia. In acute stress-situations, patients with SAI can develop a life-threatening adrenal crisis with weakness, hypotension, and shock.

11.3 Diagnosis

All childhood cancer survivors should have a regular endocrinology examination of the HPA axis. A recently published guideline related to childhood cancer survivors, suggested a lifelong annual screening for ACTH deficiency in childhood cancer survivors treated for tumors in the HP region and in those exposed to ≥30 Gy HP radiation, and a screening for ACTH deficiency in childhood cancer survivors exposed to ≥24 Gy and 30 Gy radiation who are 10 years after radiation or develop clinical symptoms suggestive of ACTH deficiency [19]. It was also advised using the same screening and dynamic testing procedures to diagnose ACTH deficiency in childhood cancer survivors as used in the noncancer population. Overall, the laboratory diagnosis of children with SAI is difficult, and there is still an ongoing controversial debate about the appropriate evaluation of the HPA axis [10, 20].

The Children's Oncology Group Long-Term Follow-Up Guidelines recommended annual screening with a morning (8 AM) cortisol level for at least 15 years after treatment [21]. In children with SAI, early morning serum cortisol and plasma ACTH levels are low. However, there are two questions: (1) Which morning cortisol levels are considered to be low? and (2) Do the morning cortisol levels indicate the adrenal capacity to respond to stress [22]? In a meta-analysis of healthy children, a morning cortisol >365 nmol/L (>13 μg/dL) was seen as normal [23]. SAI is evidenced with a morning cortisol level <100 nmol/L (<3 μg/dL) and suspected with a morning cortisol level <200 nmol/L (<7 μg/dL) [24]. A basal morning cortisol level of >300 mmol/L (>10.8 μg/dL) has been reported to exclude significant ACTH deficiency

in patients post-radiotherapy [25]. When using the cut-off level of 365 nmol/L, low basal cortisol levels were found in 71% of the patients after brain tumor therapy, whereas only 31% of these patients had blunted cortisol levels after the low-dose ACTH test [13]. Thus, it was suggested not to rely on basal cortisol levels but to perform a dynamic test of the HPA axis [13].

There are many different tests to assess the function of the HPA axis, e.g., corticotrophin-releasing hormone (CRH) test, insulin tolerance test (ITT), metyrapone test, and/or ACTH test, but the optimal evaluation for ACTH deficiency is still controversial [26–28]. The pros and cons of the common investigations used to assess HPA function in childhood cancer survivors were recently reviewed in detail by Wei and Crowne [10]. The ITT is considered to be still the gold standard for diagnosis of ACTH deficiency, but the test has some limitations and is associated with potentially dangerous side effects [29]. The ACTH stimulation test is used to evaluate the HPA axis under the assumption that long-term chronic ACTH deficiency results in atrophy of the adrenal cortex causing adrenal insufficiency. There are currently two versions of the ACTH test in use, a high-dose standard test (250 μg i.v.) and a low-dose test (1 μg i.v.). Cortisol is measured in both tests usually 1 h after ACTH administration. The peak cortisol level should be >500 nmol/L (>18 μg/dL) or >550 nmol/L (>20 μg/dL). Patients with complete ACTH deficiency in whom the adrenal glands have not been exposed to ACTH for several weeks fail to respond with an adequate increase of cortisol in both ACTH tests, whereas patients with partial ACTH deficiency may have a normal serum cortisol response in the high-dose ACTH test, but no response in the low-dose ACTH test [30, 31]. Therefore, it was suggested that the results of the low-dose ACTH test closely correlate with those of the ITT [32–34]. Based on peak serum cortisol levels <500 nmol/L defined as low, SAI was diagnosed in 35% of the patients after brain tumor therapy with the 1 μg ACTH test, and in only 11% of the patients with the high-dose ACTH test [13]. The advantage of the low-dose ACTH test was recently questioned, since it could be shown that both ACTH stimulation tests had a similar diagnostic accuracy. Both tests are adequate to rule in SAI, but not to rule out SAI [35]. Furthermore, the accuracy in 1 μg low-dose cosyntropin dilution methods is doubted since no commercial preparation is available [36]. In a systematic review and meta-analysis of both tests for assessing HPA insufficiency in children, the lack of standardization of assays and protocols with regard to timing, frequency, and dose was also addressed [20]. In conclusion, there are still many different arguments for the superiority of one test about another test for the evaluation of the HPA axis. The choice of the used test depends additionally on factors such as availability, practicability, and the experience of the doctor. One has to keep in mind that a gray zone exists for all tests and repeat testing of patients with conflicting results may be appropriate.

The diagnosis of SAI in children after prolonged high doses of glucocorticoid therapy is slightly different from children after radiation therapy of the HP axis. The major problem in glucocorticoid withdrawal is the difficulty of determining when complete recovery has occurred. However, identifying patients with potential SAI is absolutely necessary to ensure treatment is continued or discontinued appropriately. It was suggested to assess morning cortisol and ACTH monthly until they normalize, and then to perform a low-dose ACTH test until the stimulated cortisol level exceeds 500–550 nmol/L [37]. In a study from Canada, following children treated with supraphysiological doses of glucocorticoids, it was shown that 58% of the patients had a peak cortisol level >500 nmol/L after the low-dose ACTH test and that a normal baseline cortisol level did not exclude a subnormal response to ACTH (28%) and that a subnormal prior or baseline cortisol level did not exclude a normal response [38]. The authors suggested two options for physicians: (1) empirically advocate glucocorticoid stress coverage during 18 months after cessation of high-dose glucocorticoid treatment or (2) perform serial ACTH testing in all such patients until a normal peak cortisol level is attained.

11.4 Therapy

Clinicians should use the same glucocorticoid regimens as replacement therapy in childhood cancer survivors with ACTH deficiency as used in the noncancer population [19]. For children with SAI, the drug of choice is hydrocortisone. Mineralocorticoid substitution is not necessary. The daily dose of hydrocortisone for replacement therapy of 8–10 mg/m^2 is divided into two or three doses, with the largest dose being given in the morning. The dose is lower than the dose used in patients with primary AI. The dose must be titrated carefully to prevent over- or undertreatment. The clinical parameters weight, height, blood pressure, and general well-being are the most useful parameters to monitor therapy. The pharmacokinetics of hydrocortisone does not allow mimicking the overnight rise in cortisol. Therefore, a modified-released hydrocortisone was developed and approved as maintenance therapy of adults with adrenal insufficiency. The tablet provides high levels of cortisol during the morning, followed by a gradual decrease throughout the day, thereby mimicking normal secretion more closely than conventional therapy [39, 40].

During times of illness or stress (e.g., fever, gastrointestinal illness), the oral dose of hydrocortisone should be immediately tripled. The importance of early intervention when infection occurs has been shown by a 1.6-fold higher risk of death in patients with ACTH deficiency than in those without ACTH deficiency [41]. Moreover, the relative risk of death was 7.1 in participants with hypopituitarism [42]. ACTH deficiency may coexist with other pituitary hormone deficiencies, and the diagnosis may be unmasked after the supplementation of these hormones. For example, growth hormone (GH) therapy normalizes 11β-hydroxysteroid dehydrogenase type 1 overactivity and causes an increase in the conversion of active cortisol to inactive cortisone [43]. Thus, it is important to check for SAI and start appropriate replacement therapy with hydrocortisone before the initiation of GH replacement to avoid adrenal crisis.

If children are unable to tolerate oral therapy under stress conditions, the parents can administer glucocorticoid suppositories or inject hydrocortisone (i.m.) to gain time and present the child to the nearest children's hospital. All children with adrenal crisis require emergency care in a hospital. The standard therapy comprises fluids and electrolytes intravenously, and, an intravenous glucocorticoid bolus (e.g., hydrocortisone 100 mg/m^2). The initial hydrocortisone bolus is followed by the same dose at a constant rate over a 24-h period. The hydrocortisone dose should be reduced to the replacement therapy dose as soon as the crisis is over or the medical status improves. If synthetic glucocorticoids (e.g., prednisone) are used instead of hydrocortisone, then the correct equivalent dose has to be calculated. The Endocrine Society recommends that clinicians instruct all patients with ACTH deficiency regarding stress dose and emergency glucocorticoid administration and instruct them to obtain an emergency card/bracelet/necklace regarding adrenal insufficiency and an emergency kit. This recommendation must include the family of the patient (parents, caregivers) and all doctors involved in long-term follow-up.

In summary, SAI is rare in childhood cancer survivors. All physicians involved in the long-term follow-up must be aware of individuals at risk of developing ACTH deficiency. Implementation of an appropriate treatment together with a detailed instruction regarding stress dose and emergency glucocorticoid administration is necessary to prevent life-threatening adrenal crises in SAI patients.

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Pregnancy and Birth After Cancer in the Youth

12

Magdalena Balcerek, Anja Borgmann-Staudt, Sebastian Findeklee, and Michael von Wolff

12.1 Getting Pregnant

A survey among former childhood cancer patients revealed that nearly all survivors wished to have an own child in adulthood, this wish being comparable to the desire in the general population [1]. Nevertheless, a reduced rate of pregnancies has been shown among childhood cancer survivors when being compared to the general population [2]. Despite the fact of increased time to pregnancy among childhood cancer survivors [3], the rates of pregnancy remain reduced in all age groups [1] due to an increased risk of fertility impairment after cancer therapy in childhood and adolescence [2]. Noteworthy in this context is the reduced reproductive window among childhood cancer survivors due to premature ovarian failure after irradiation and alkylating agents [4]. This emphasizes the importance of patient education and motivation to decide on early family planning rather than postponing the decision to a later time point. The prevalence and risk factors for fertility impairment are further described in chap. 9 of this book.

Fertility impairment may make the use of assisted reproductive technologies necessary (chap. 10 of the book). The likelihood of a live birth after assisted reproductive technology procedures among women with cancer history using autologous oocytes was reduced compared to women without cancer. Factors acting in the pre- or periconceptional periods are possibly responsible for this decline [5]. When donor oocytes were used, no difference in the outcome among women with and without cancer history was seen [5]. Postpubertal pelvic irradiation or total body irradiation was followed by an implantation rate of 31% with oocyte donation, which was comparable to the unit's general implantation rate [6]. Autologous retransplantation of cryopreserved ovarian tissue following cancer therapy has led to successful pregnancies and more than 130 live births worldwide [7]. Generally, the risk of retransplantation of malignant cells using cryopreserved ovarian tissue of cancer patients has to be considered [8–10]. A future possibility to avoid this risk may be presented by in vitro maturation of oocytes from ovarian tissue and options of artificial ovaries [11].

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If survivors of childhood cancer conceived, they used their chance to have a child more often than the German general population, shown by rate of induced abortions being significantly reduced among childhood cancer patients when compared to the rate in general population [12]. Regarding the diagnosis of the formerly diseased parent, pregnancies among female heritable retinoblastoma survivors or the partners of male survivors were more likely to be terminated because of reasons relating to the health of the fetus, whereas there was no increased rate of termination among survivors of other cancer diagnoses [13]. Both, cancer treatment for children and adolescents, as well as patient counseling have sustainably improved within the last decades. These improvements may have led to a decreased fear among survivors that their children could suffer from late effects from their cancer or its treatment or that offspring may get cancer as well because of inherited genetic traits [1].

Besides, the risk of fertility impairment or fear of impairment in own offspring's health, a fear of relapse following pregnancy can additionally prevent survivors from getting pregnant [14]. For early breast cancer patients, however, data showed a statistically higher overall survival among patients who became pregnant at least 10 months after diagnosis [15]. A further study showed similar results, suggesting a "healthy mother effect" [16], which may be due to possible immunization against breast cancer cells during pregnancy [17]. A registry-based cohort study that investigated pregnancy in women surviving leukemia, lymphoma, malignant melanoma, cervical, breast, thyroid, or ovarian cancer showed a significantly lower risk for cause-specific death in women with a post-cancer pregnancy than in the reference group [18].

12.2 Pregnancy Following Chemotherapy and Radiotherapy

In women, who get pregnant after oncologic therapy, late effects of cytostatic agents like cardiac or renal impairment may lead to severe pregnancy complications, and preterm delivery has to be considered. Irradiation in children seems to have a more negative effect on the uterus than radiotherapy in adults. A radiotherapy of the adult uterus within total body irradiation therapy (12 Gray) is associated with an increased risk for miscarriage, preterm delivery, and low birth weight. In general, irradiation of the uterus with >25 Gray in childhood or with >45 Gray in adulthood goes along with the recommendation of avoiding a future pregnancy as a severe radiotherapy-induced fibrosis has to be expected.

Generally, pregnancy and labor are related to various changes in the female body. In childhood cancer survivors who may experience organic late effects due to their previous cancer treatment, special attention during pregnancy and labor is necessary.

The cardiac output during pregnancy is higher in second compared to first and lower in third compared to second trimester [19]. After delivery cardiac output is lower than at any time point during pregnancy. These physiologic changes during pregnancy with a higher cardiac output may lead to severe problems for asymptomatic patients treated with cardiotoxic agents like anthracyclines. Women who have received anthracycline-containing chemotherapy should be recommended to undergo preconceptional transthoracal echocardiography. Close cardiological surveillance during pregnancy should be provided to women with an ejection fraction < 40% [20]. An established heart disease may cause decompensation or worse pregnancy outcome [21]. Childhood cancer survivors who received 500 mg/m^2 or less of doxorubicin were found to generally have no changes in fractional shortening (FS) before and at least 6 months after pregnancy [22]. While FS sustained in patients with a FS >30% before pregnancy, FS was decreased by 19% during pregnancy in patients with an intial FS <30%. Despite the fact that this finding was not significant, it is clinically relevant as it represents the deterioration from a mild to moderate left ventricular dysfunction after pregnancy. In one case deterioration occurred within 2 h after birth. Therefore those with baseline left ventricular dysfunction are to be considered at increased risk and need increased surveillance during pregnancy and spe-

cial care within the first 24 h after delivery [22]. Childhood cancer survivors with a left ventricular ejection fraction of less than 40% should be counseled about the potential risk of cardiac failure that may occur in pregnancy. Care should take place at specialized centers. Women with a left ventricular ejection fraction <20% should be warned off a pregnancy since they are under severe risk of not being able to sustain cardiac output [20].

Generally, female childhood cancer survivors showed no increase in the risk of gestational diabetes, preeclampsia, and anemia in comparison with women without history of cancer [23]. Former patients with a bone tumor, however, seem to have an increased risk for gestational diabetes. An increased risk for anemia during pregnancy occurred in former brain tumor patients or childhood cancer patients who were treated with chemotherapy initially [23]. Childhood cancer survivors were found to have normal diastolic blood pressure during pregnancy [24].

Chemotherapy in general has no distinct effect on entered pregnancy. Au contraire, use of chemotherapeutic agents can be considered during pregnancy after careful balancing of pros and cons [25]. Radiotherapy, though, may affect gonadal function in female and male childhood cancer patients, dependent on age and dose (Table 12.1.)

Table 12.1 Effects of different irradiation doses due to age in female and male childhood cancer survivors [26]. (Gy= Gray; POF = premature ovarian failure

Irradiation dose to the gonads	Effect
</=1.5 Gy	Girls: no relevant effect
2.5–5 Gy	Girls/women: risk for POF ca. 60%
7 Gy	Women: 100% POF with 40 years
14 Gy	Women: 100% POF with 30 years
16 Gy	Women: 100% POF with 20 years
18 Gy	Girls: 100% POF with 10 years
20 Gy	Girls: 100% POF in every age
2 Gy	Girls/women: reduction of the follicular pool of about ca. 50%
>/=2 Gy	Boys/men: long persisting azoospermia possible
>/=4 Gy	Boys/men: permanent azoospermia possible
>/=1.2 Gy fractioned	Men: permanent azoospermia possible

Higher abdominal or pelvic radiation doses, total body irradiation and direct irradiation of the uterus significantly increase the risk of adverse pregnancy outcomes, with irradiation in (pre) pubertal children being more harmful to the uterus than in postpubertal children [27]. The uterine size in adulthood correlated with age at irradiation, showing the younger age at radiation being associated with a smaller uterus [28]. The uterine growth starts before onset of clinical signs of puberty, reaches its greatest increase of volume between Tanner Stages III and IV and is not completed before 7 years after menarche [29, 30]. Additionally, the uterine artery flow velocity increases during puberty [31]. Both leads to a higher vulnerability to irradiation of the uterus before and during puberty. Regarding the radiation dose administered to the uterus, a uterine irradiation dose of 4 Gray or less does not seem to impair uterine function. The post-irradiated uterus after whole abdominal or pelvic, e.g., as part of treatment in children suffering Wilms tumor, rhabdomyosarcoma or Ewing sarcoma, or total body irradiation (usually 12 Gray) as part of treatment before stem cell transplantation showed a reduced mean uterine length and no detectable uterine blood flow in ultrasound examinations [27, 28]. Following total body irradiation in childhood acute lymphoblastic leukemia patients, the average uterine volume may decrease to 40% of normal adult sizes [32]. MRI imaging supported these findings of reduced uterine volume 3 months after therapy [33]. Myometrial changes such as atrophy, including fibrosis in submucosal and edema in serosal parts, loss of uterine zonal anatomy and local ischemia may appeare as early as 1 month after treatment. A trophic endometrium with thicker and smaller blood vessels may occur 6 months after therapy [33]. These changes result in decreased elasticity of the uterine musculature [27, 28]. A study among patients receiving stem cell transplantation in childhood showed that total body irradiation and busulfan had the worst effect on uterine size [34]. High-dose radiation of 20–25 Gray or more in children commonly lead to irreversible uterine damage effecting vascular and muscular function [27, 35]. It still remains unclear whether radiotherapy and uterine irradiation predispose

for placentation disorders and uterus rupture during pregnancy. Literature just reveals case reports. However, there are several hints for a thinner and structurally altered myometrium in women who have been exposed to radiotherapy [36].

Reduced uterine function after irradiation leads to higher rates of spontaneous abortions as well as preterm delivery [37, 38, 40–44], with threshold uterine doses of more than 10 Gray in girls treated before menarche increasing the risk of stillbirth and neonatal death [43]. Even though assisted reproductive technologies are available, reduced uterine volume and uterine blood flow are linked to poor outcomes during these procedures [34]. In women with premature ovarian failure following irradiation during childhood or pregnancy, uterine function perhaps can be improved by therapeutic application of sexual steroid hormones. Literature describes estradiol 100–150 microgram every 24 h transdermal and progesterone vaginal 400 mg every 24 h to be most effective compared with oral contraceptives.

Generally, the rate of spontaneous abortions among childhood cancer patients has been reported to be increased [12]. Pregnancy complications seem to further increase when conception results after use of assisted reproductive technologies[45]. A significant increase was seen in the rate of spontaneous abortions after oocyte donation and multiple agent chemotherapy in childhood [46], in midtrimester miscarriage, in preterm delivery as well as in intrauterine growth retardation [27, 42]. Also when conception occurred within the first year after end of treatment, an increased risk of stillbirth, premature birth, and a reduced birth weight has been observed [47].

Pregnancy after stem cell transplantation is possible; however, patients who underwent transplantation at older age or who were exposed to total body irradiation were more likely of being nulliparous. Women who underwent allogeneic stem cell transplantation in childhood or early adulthood showed higher rates of cesarean section (42% vs. 16% general population), preterm delivery (20% vs. 6%), and low birth weight (23% vs. 6%) [48]. After conditioning regimen in pre- and postpubertal women that included total body irradiation as part of stem cell transplantation, a significant increase in spontaneous abortions (37%), preterm delivery (63%) with low to very low birth weight was seen [49].

Independent of irradiation, in a group of patients who suffered Wilms tumor, uterine anomalies were found that may contribute to risk of stillbirth or neonatal death [50].

A review performed by the "Scottish Intercollegiate Guidelines Network" (SIGN) refers to the potential risk of reduced bone mineral density with a consecutive elevated bone fracture risk during pregnancy after irradiation of the cervical region [51].

12.3 Birth and Postpartum

In general, pregnancies and labor in cancer survivors are typically uncomplicated [52]. Nevertheless, women with cancer diagnosed in childhood, adolescence or early adulthood, are at elevated risk for induction of labor and elective rather than urgent cesarean delivery [23, 52]. This may be due to an increase in surveillance and a lower threshold for interventions in these patients [37]. Former patients with a bone tumor in childhood were more likely to undergo cesarean section, whereas those who had an abdominal or pelvic tumor had no increased rate of cesarean sections [23]. No increase in the risk of instrumental vaginal delivery, malpresentation, placental pathologies, and postpartum hemorrhage appeared in survivors of cancer in childhood or young adulthood [52]. Highest risk for adverse obstetric outcomes was found in women treated in childhood (0–14 years) [52]. Childhood cancer survivors who underwent abdominal irradiation had an increased risk of postpartum hemorrhage, without the increased risk of manual removal of placenta reaching statistical significance [24].

It is generally known, that breastfeeding is beneficial in regard to different aspects of health, such as metabolism, including diabetes and obesity, cardiovascular disease, bone mineral density as well as second malignant neoplasms. It is likely that not only healthy women and their

children, but also women with a history of cancer and their offspring profit from breastfeeding. However, lactation may be impaired in cancer patients. Women who suffered breast cancer with treatment including radiotherapy are at risk for lactation problems. Patients who formerly suffered from Hodgkin's disease with treatment including mantle radiotherapy showed only 61% of breastfeeding attempts being successful. In the subgroup of patients diagnosed at 21 years of age or younger, the rate was 66% but still lower than in the sibling control group [53]. Among childhood acute lymphatic leukemia survivors who had received cranial radiotherapy of 24–25 Gray and chemotherapy , only 17% were able to lactate successfully [54], suggesting cranial radiotherapy being a risk factor for lactation impairment.

12.4 Offspring and Offspring Health

Children born to childhood cancer survivors showed a comparable gender ratio and a normal postnatal adaption according to APGAR score [23, 24]. Children born to mothers who received abdominal, pelvic, or total body irradiation including the uterus, were more often preterm with a low birth weight, also increasing their risk for perinatal death [37, 38, 40, 41, 43, 44]. Low birth weight after adjustment for gestational age seems to be comparable to general population, though [24]. Stillbirth and neonatal death were most likely linked to uterine damage rather than mutagenesis to the germ cells [43]. Men exposed to gonadal irradiation or total body irradiation do not seem to have an increased risk of stillbirth or neonatal death for their children [43].

Children from women that were treated with doxorubicin (<500 mg/m^2) in childhood were reported of being born after induction of labor more often, showed lower birth weight, and were more likely of neonatal hospitalization in intensive care unit and longer hospital stays [21].

Fear of health impairment in their offspring may prevent survivors of childhood cancer from having own children [14]. Generally, studies have shown no increase in the risk for genetic diseases or nonhereditary cancers among offspring of childhood cancer survivors [43, 55–57]. Even though most studies report no increased risk for malformations, there have been reports of a slight increase of malformations among these children, with this increase not being clinically relevant [58]. Regarding the frequency and reasons for hospitalization, childhood cancer survivors' offspring were found to be hospitalized just as often and for the same reasons as children of parents without a history of cancer, with the exception that, due to increased surveillance in these children, former patients' offspring were more likely of being hospitalized due to hereditary cancers or to rule out a cancer disease [59].

Up-to-date, there is no information on the further development of health in children of former childhood cancer patients. A study on children born after prenatal exposure to maternal cancer with or without treatment, however, did not show impaired cognitive, cardiac or general development in early childhood [60].

12.5 Conclusion

Women with cancer history that are at elevated risk for pregnancy or birth complications should be counseled and treated in specialized centers. For German-speaking countries the FertiProtekt Network provides addresses of experts in the field [www.fertiprotekt.de].

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13 Obesity and Metabolic Syndrome After Childhood and Adolescent Cancer

Christian Denzer, Judith Gebauer, and Georg Brabant

Obesity and an increased risk of developing diabetes mellitus and cardiovascular disease are common late complications of childhood and adolescent cancer, but as such are often detected late and receive inadequate treatment [1]. Increased morbidity due to cardiovascular disease is a major burden for this growing patient population and leads to reduced quality of life and excessive mortality [2–4].

13.1 Obesity in Childhood Cancer Survivors

13.1.1 Epidemiology

Newer data from the *Childhood Cancer Survivor Study* (CCSS) demonstrate an increased relative risk of developing obesity in childhood and adolescent cancer survivors who received either cranial radiation ≥18 Gy or abdominal or total body radiation [1]. Previous analyses of the CCSS cohort showed a differentiated risk of adverse changes in body composition, including an increased risk of underweight, depending on cancer diagnosis, age at cancer diagnosis, sex, ethnicity, and therapeutic exposure [5]. Among the main categories of cancer diagnoses in the CCSS cohort, only adult survivors of acute lymphocytic leukemia showed an increased risk of BMI ≥30 kg/m^2 compared to a reference population. Furthermore, sex-specific risk factors for obesity were found in this population. Female survivors were more likely to be obese in adulthood if they were younger at the time of cancer treatment, were of black, non-Hispanic descent, and received cranial radiation. In adult male survivors, Hispanic origin and cranial irradiation were associated with obesity in adulthood [5]. Data from follow-up investigations in the CCSS cohort and from a variety of other, mostly smaller cohort studies confirmed the association of childhood acute lymphoblastic leukemia with an increased risk of obesity, but also showed significant heterogeneity in terms of possible pathogenetic factors that could contribute to increased weight gain and persistent obesity in ALL survivors [6]. This heterogeneity in study results may be explained by methodological and statistical reasons that lead to a lack of certainty and

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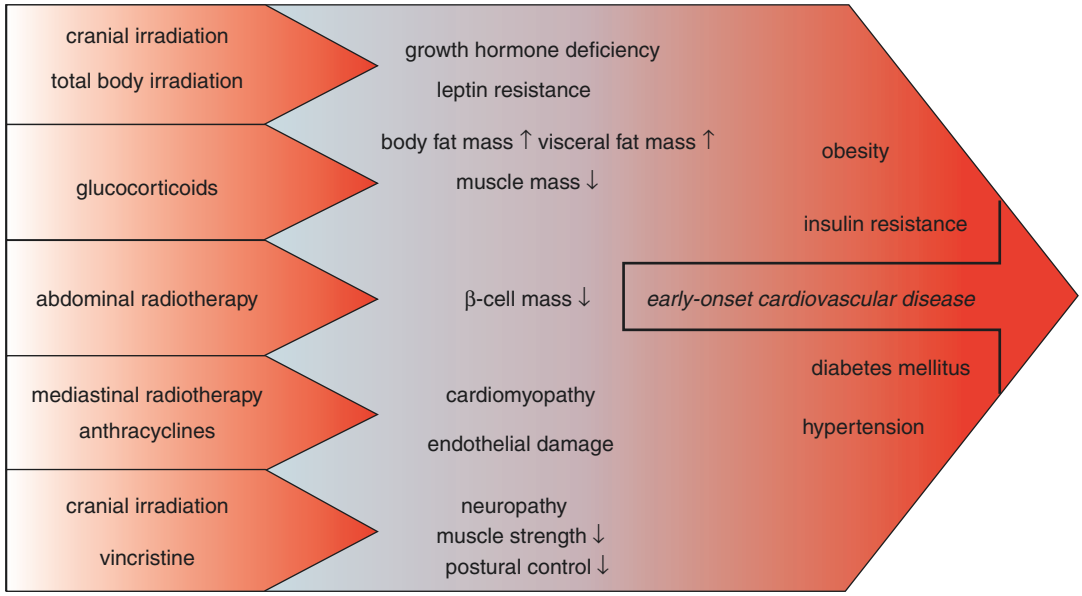

Fig. 13.1 Concepts of the pathogenesis of obesity and cardiovascular risk in survivors of childhood and adolescent cancer

consistency in the identification of underlying etiological factors of increased risk of obesity in ALL survivors.

The majority of published studies use BMI as an indicator of overweight and obesity. However, childhood and adolescent cancer survivors are often characterized by an increased body fat mass, and in particular an increased visceral fat mass, with a simultaneous reduction in lean mass [7–11]. For this reason, studies using dual-energy X-ray absorptiometry to estimate body fat mass show that BMI is the least sensitive anthropometric parameter for the correct detection of obesity in childhood cancer survivors, with up to two-thirds of the patients examined being erroneously classified as non-obese [12, 13].

13.1.2 Risk Factors

Possible pathophysiological factors that can lead to overweight and obesity in childhood cancer survivors include growth hormone deficiency and hypothalamic leptin resistance after cranial irradiation [14] and high-dose therapy with corticosteroids. Discussed consequences of these therapy modalities include permanently increased energy intake, unfavorable changes in body fat distribution, impairment of the satiety signaling pathway, permanently altered food preferences [15], reduced physical activity and physical function [16, 17], reduced adherence to dietary recommendations [18], use of antidepressants [19], and possibly interactions of therapeutic exposures with genetic variants that promote weight gain [20]. Figure 13.1 summarizes current concepts of the etiology of obesity and cardiovascular risk as long-term consequences of childhood and adolescent cancer treatment.

13.1.2.1 Cranial Irradiation (CRT)

The centers for the integration of afferent and efferent homeostatic signals that regulate body weight are located in the anterior (paraventricular nucleus), middle (arcuate nucleus, ventromedial nucleus), and posterior hypothalamus (dorsomedial nucleus, dorsal hypothalamic region). Exposure of the hypothalamus to radiation may therefore lead not only to growth hormone deficiency and subsequent unfavorable changes in body composition but also to a disturbance of satiety regulation, increased energy intake and reduced energy expenditure [14, 21, 22]. In fact, a number of studies report an association

between cranial irradiation and a significantly increased risk of developing obesity (e.g., [5, 23–26]), while in other studies this association was less clear or could not be reproduced (e.g., [27–31]). Studies that reported a positive association between CRT and obesity also identified subpopulations with a more pronounced risk of excessive weight gain. These include female patients, female patients receiving CRT at <10 years of age, patients at <4 years of age at cancer diagnosis, patients receiving higher doses of radiation (>20 Gy), and patients receiving higher doses directed to the hypothalamus (e.g., [20, 23, 25, 32]. The potentially adverse effects of CRT on body composition [7] may be further mediated by a genetic predisposition, e.g., by polymorphisms in the leptin receptor gene or also by variants in genes previously associated with body fat mass or the regulation of neuronal growth and repair [20, 33].

13.1.2.2 Glucocorticoid Therapy

Persistently increased cumulative incidence of obesity in survivors of acute lymphocytic leukemia, although cranial radiation is no longer part of current treatment protocols for most standard and medium risk leukemia [34, 35] and the characteristic pattern of weight gain in ALL patients during therapy [35, 36] and especially during induction therapy [37] revived interest in glucocorticoids as a potentially pivotal pathogenetic factor for obesity risk. High-dose glucocorticoids (prednisolone, dexamethasone) are an important component of induction chemotherapy in ALL. Therapy with glucocorticoids causes the pronounced clinical picture of an iatrogenic Cushing's syndrome in pediatric ALL patients with rapid weight gain, significantly increased energy intake [15], abdominal obesity and other typical changes in body fat distribution, impaired sense of satiety, mood, and sleep disorders and—in a subgroup of patients—steroid-induced diabetes mellitus. However, published studies on the effects of glucocorticoids on the risk of obesity in cancer survivors showed inconsistent results [6], which—as discussed above—may be due to heterogeneous clinical cohorts and the use of potentially unsuitable surrogate markers for obesity.

13.1.2.3 Physical Activity

Results of the CCSS and other cohort studies show an increased prevalence of an inactive lifestyle with significantly reduced physical activity in childhood cancer survivors [16, 38–40]. In addition, survivors are often characterized by a lower physical activity level compared to control populations [41–43]. The physical activity of cancer survivors may be directly affected by therapeutic exposures that cause reduced muscle strength (e.g., GHD after CRT [17, 44]) and left ventricular dysfunction (anthracyclines [45]) and negatively affect balance, postural control [46, 47], flexibility (asparaginase), and neuropathy scores (vincristine [48]). A reduced resting metabolic rate [49] and comparatively low rates of total energy expenditure [50, 51] may be additional factors contributing to a positive energy balance in childhood cancer survivors.

13.1.3 Survivors at Highest Obesity Risk

Patients with sellar and suprasellar tumors, and patients who suffer damage to the hypothalamus due to tumor growth or neurosurgical interventions, form a high-risk group for the development of pronounced, usually therapy-refractory obesity. Hypothalamic obesity is characterized by rapid, extreme weight gain, hyperphagia, reduced resting energy expenditure, and reduced physical activity. These main features of hypothalamic obesity have been best studied in craniopharyngioma patients [52], but have also been reported as sequelae of other tumor entities (e.g., ganglioneuroma, ependymoma) [53]. In general, brain tumor survivors exposed to high-dose irradiation of the hypothalamus region may be at increased risk of obesity [54, 55]. Other cancer survivors at risk for obesity include the large group of childhood ALL survivors and, among those female patients, younger patients and patients exposed to CRT and, in particular, higher doses of CRT (>20 Gy) [23, 25]. As described above, BMI does not adequately reflect the altered body composition in cancer survivors characterized by increased fat mass, visceral fat depot, and

decreased lean body mass. Further risk groups for the development of a phenotype of sarcopenic obesity are therefore childhood cancer survivors exposed to CRT and TBI, childhood malignant lymphoma and ALL survivors, and childhood and adolescent hematopoietic cell transplantation survivors [7–10, 12, 13, 56–58].

13.2 Metabolic Syndrome and Cardiovascular Disease

Cardiovascular disease is a major cause of increased morbidity and mortality of childhood and adolescent cancer survivors in long-term follow-up [4, 59]. Cardiovascular disease can be promoted by exposure to treatment modalities with direct myocardial or vascular toxicity (e.g., anthracyclines, platinum, bleomycin, mediastinal radiotherapy) [60, 61] or by accelerated atherosclerosis resulting from clustering of cardiovascular risk factors [62].

13.2.1 Metabolic Syndrome in Childhood Cancer Survivors

The metabolic syndrome is a constellation of traditional risk factors consisting of visceral obesity, insulin resistance and impaired glucose tolerance, dyslipidemia, and hypertension. The metabolic syndrome is associated with a significantly increased risk of developing type 2 diabetes mellitus, atherosclerosis, and cardiovascular disease [63, 64]. The highest prevalence rates of metabolic syndrome or components of the syndrome were found in cohorts of ALL survivors as well as in survivors of hematopoietic stem cell transplantation in childhood and adolescence [62, 65]. Nottage et al. reported a prevalence of metabolic syndrome of more than 30% after a median survival of 26.1 years after diagnosis of childhood ALL [62]. Taskinen et al. reported a prevalence of key features of the metabolic syndrome (insulin resistance and hypertriglyceridemia) of 39% in long-term survivors of childhood bone marrow transplantation [66]. In particular, the available data clearly show that the cumulative incidences of cardiovascular risk factors and metabolic syndrome do not reach a plateau as survivor's age and the length of the follow-up period increases [62].

13.2.2 Risk Factors for the Metabolic Syndrome in Childhood Cancer Survivors

Important factors that adversely affect cardiovascular risk include cranial irradiation, TBI, and abdominal irradiation [67]. Exposure to CRT and TBI can result in increased body fat mass, increased visceral fat mass and decreased muscle mass as described above. This phenotype of sarcopenic obesity in turn causes marked insulin resistance. Insulin resistance is the central pathogenetic motif of the metabolic syndrome [68, 69]. Data from CCSS show an increased risk of type 2 diabetes compared with sibling controls after each radiotherapy with the most significant risk increases in those who underwent abdominal radiation or TBI [70]. Higher doses of radiation to the pancreas, and in particular to the pancreatic tail, as may occur with abdominal radiotherapy, are a risk factor for the development of diabetes mellitus, independent of changes in body fat distribution, and most likely due to a directly damaging effect on beta cell capacity in affected survivors [71, 72]. Therefore, the increased risk for the development of type 2 diabetes can be understood as a combined occurrence of insulin resistance due to visceral obesity, possibly radiation-induced impairment of insulin signaling at the skeletal muscle level [73] and the progressive failure of the beta cell to compensate for the increasing insulin resistance [74, 75] (Fig. 13.1).

Patients who received total body irradiation were significantly more likely to develop dyslipidemia (hypertriglyceridemia, low HDL cholesterol) [76, 77] and arterial hypertension [76, 78] compared to non-TBI-exposed survivors and to meet the criteria for metabolic syndrome during follow-up [76].

Growth hormone deficiency after CRT and probably also after chemotherapy alone [65, 79] could be another factor contributing to an unfavorable cardiovascular risk profile in cancer survivors [65, 80, 81], a relationship first described by Talvensaari et al. [82].

13.2.3 Cardiovascular Disease in Childhood Cancer Survivors During Long-Term Follow-Up

Data from the *Danish cancer registry* show a significantly increased cumulative risk of cardiovascular disease in childhood and adolescent cancer survivors [4]. According to the population representative data from this large-scale register, cancer survivors in the 20–59 age group have an absolute excess risk of 400 additional cases of cardiovascular disease per 100,000 person-years compared to the general population. Relative morbidity risks are increased across all diagnostic categories of cardiovascular disease, from hypertension, through ischemic heart disease and cerebrovascular disease, to arterial disease. According to CCSS data, childhood cancer survivors are significantly more likely to take antihypertensive, dyslipidemic, or diabetes drugs than sibling controls [83].

While relapse, progression or secondary malignancies are the main causes of increased cumulative mortality among childhood and adolescent cancer survivors [3], CCSS data also show that survivors are seven times more likely to die from cardiac causes than the general population [2, 3]. Cardiac radiation exposure and high-dose anthracycline therapy were identified as the most important treatment-related factors associated with cardiovascular disease and cardiac death [2, 84], but exposure to directly cardiotoxic treatment modalities does not explain the observation of significantly increased prevalence rates of an adverse cardiovascular risk factor profile in childhood and adolescent cancer survivors [62].

13.2.4 Metabolic Syndrome and Cardiovascular Disease: Special Risk Groups

Patients with sellar and suprasellar tumors, and here especially patients with craniopharyngiomas, are frequently affected by pronounced cardiovascular morbidity and mortality [85, 86]. Similarly, traditional cardiovascular risk factors and the metabolic syndrome are highly prevalent in long-term survivors of childhood and adolescent hematological malignancies. Treatment-related factors that put patients at highest risk for metabolic syndrome and cardiovascular disease include exposure to hematopoietic stem cell transplantation, CRT, TBI, abdominal radiotherapy, and cardiotoxic treatments (anthracyclines, mediastinal radiation).

13.3 Long-Term Follow-Up and Therapeutic Approaches

Survivors of childhood and adolescent cancer should have an annual assessment of their weight status, including a calculation of their BMI. This is especially true for patients after cranial irradiation or TBI. Caring physicians must be aware of the limitations of BMI in accurately diagnosing increased body fat mass in cancer survivors and should therefore consider measuring waist circumference as a supplementary measure or, in selected cases, using technical methods (e.g., DXA) to determine body composition. Weight gain in patients exposed to CRT and TBI should initiate a diagnostic evaluation for growth hormone deficiency, hypogonadism, or hypothyroidism.

All currently available guidelines for the follow-up care of childhood cancer survivors include monitoring of cardiovascular risk factors, but the indications, extent and frequency of clinical investigations vary between guidelines [87–92]. The Scottish SIGN guidelines and the German S3 guidelines recommend annual moni-

toring of weight, height, and BMI in long-term cancer survivors [91]. This is also recommended by the CIBMTR/EBMT [89] and COG [88] guidelines for long-term childhood stem cell transplant survivors. Blood pressure should be measured at least once a year in long-term survivors [89, 91], and lipid status plus fasting glucose or HbA1c should be measured every 2 years in overweight or obese patients and every 5 years in normal-weight survivors according to the SIGN recommendations [91] and also every 5 years in "standard risk" stem cell transplant survivors [89]. More frequent testing of serum lipids and glucose homeostasis (fasting glucose or HbA1c) is indicated in survivors treated with TBI or abdominal irradiation (every 2 years [88] or mediastinal irradiation (every 3–5 years [92]). More frequent evaluation (every 3–6 months) of lipid status and impairment of glucose metabolism has been proposed high-risk HCT-recipients actively treated with corticosteroids, sirolimus, or calcineurin inhibitors [89].

No specific recommendations or programs have yet been developed for the treatment of the metabolic syndrome or its components in childhood cancer survivors. Lifestyle changes and drug therapy should therefore follow age-appropriate guidelines where available. Possible endocrinological late effects of cancer treatment, and in particular growth hormone deficiency, hypogonadism, and hypothyroidism, must be diagnosed in a timely manner and treated adequately, as these diseases may further contribute to an overall increased cardiovascular risk in affected survivors [80, 93].

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14 Subsequent Primary Cancer After Childhood, Teenage and Young Adult Cancer

Michael M. Hawkins, Clare Frobisher, Raoul C. Reulen, and David L. Winter

14.1 Introduction

Survivors of childhood cancer experience substantial premature mortality, for example, from the original British Childhood Cancer Survivor Study (BCCSS) cohort (n = 17,981) by 50 years from diagnosis, 30% of 5-year survivors have died when 6% would be expected to have died from mortality rates in the general population (see Fig. 14.1) [1]. Analysis of the same cohort revealed that among survivors at least 45 years from diagnosis, 51% of excess number of deaths were caused by subsequent primary cancer [1]. The original cohort included survivors of cancer diagnosed before 1992, and the cohort has now been extended to include 5-year survivors diagnosed up to 2006 (n = 34,489), and analysis of this extended cohort revealed that among survivors aged 40–49, 50–59 or 60 and older subsequent primary cancer caused 37%, 41% and 31% of the excess number of deaths [2].

We report recent evidence relating to risks, risk factors, and the international initiative to standardise clinical follow-up guidelines which have been published mostly during the past decade. Given the space limitations, we have had to focus on selected research areas where important new data has emerged or where a specific area of research has been identified which is likely to be important for the future.

14.2 Risks of Subsequent Primary Cancer After Childhood Cancer

The types of subsequent primary cancer observed in excess of expected from the general population vary strongly by both attained age and interval from diagnosis. For example within the BCCSS brain tumours (21%) and sarcomas (41%) accounted for 63% of the excess number of SPNs observed among survivors aged 5–19 years; in contrast 52% of the excess number of SPNs observed among survivors aged over 40 years were carcinomas of digestive, genitourinary, respiratory and breast sites, which account for 18%, 18%, 9% and 7% of overall 52%, respectively [3]. These findings were broadly similar to the large-scale population-based cohort from the Nordic countries which also had sufficient follow-up beyond 40 years of age to satisfactorily assess risk [4].

Recently the German Childhood Cancer Registry (Deutsches Kinderkrebsregister, DKKR)

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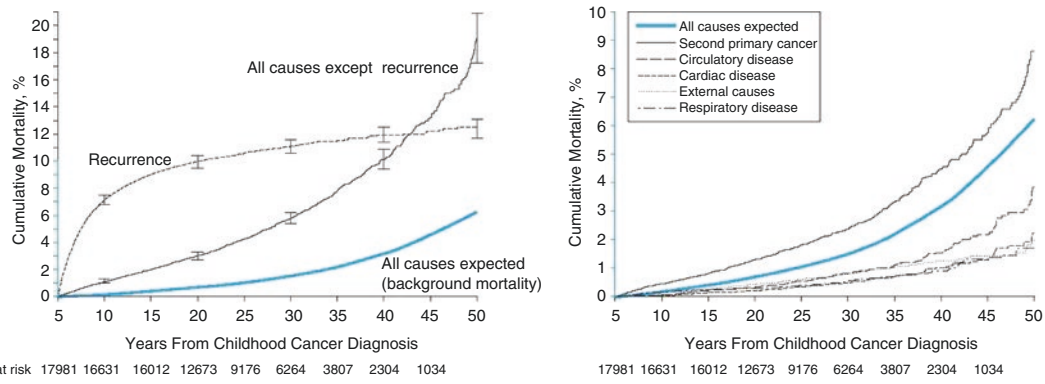

Observed cumulative mortality of all causes of death other than recrrence was 19.0% at 50 years from initial diagnosis, whereas 6.3% was expected based on rates from the general population. Cumulative mortality of death due to recurrence increased rapidly with time from diagnosis to 8.9% by 15 years but then levelled off to 12.4% by 50 years. Cumulative mortality for each cause of death takes into account other causes of death as a competing risk. For second primary cancer, cumulative mortality increased gradually with time to 2.4% by 30 years but then increased rapidly to 8.6% by 50 years. For circulatory disease, the cumulative mortality was low by 30 years (0.8%) but increased to 3.9% by 50 years. Segment of y-axis shown in blue indicates cumulative mortality range of 0% to 10%. Error bars indicate 95& confidence intervals.

Fig. 14.1 Cumulative mortality of causes of death among survivors of childhood cancer. With permissions from [1]

published on subsequent primary neoplasms after a follow-up of up to 35 years in 47,650 survivors a cumulative incidence of 8.27%. Subsequent primary neoplasms were more common in female patients and in those who had a systemic cancer as their initial malignancy. However only patients were included (1980–2014) who were no more than 14 years old at the time of diagnosis and survived at least 6 months thereafter and there are no detailed data on the therapy approaches [5].

In the British Childhood Cancer Survivor Study, the finding that subsequent primary digestive cancer accounted for 18% of the excess number of subsequent primary cancers observed overall among those aged over 40 years is of particular interest because of well-established success of bowel cancer screening in the general population. We therefore compared the risk of bowel cancer among childhood cancer survivors who received direct abdominopelvic radiotherapy with those who have at least one or at least two first-degree relatives previously diagnosed with bowel cancer (see Fig. 14.2) [3]. It is clear that those receiving abdominopelvic radiotherapy experience a risk of subsequent primary bowel cancer which exceeds that observed among the population of individuals with at least two first-degree relatives diagnosed with bowel cancer. In Britain the latter population are currently being considered for screening colonoscopy under the National Health Service bowel cancer screening programme, but currently there are no British survivorship guidelines relating to the directly irradiated abdominopelvic group of survivors of childhood cancer.

Survivors of Wilms' tumour were particularly at risk because 50% of the excess number of deaths observed beyond 30 years from diagnosis was caused by subsequent primary cancer, digestive cancer and most frequently bowel, accounted for 41% of the excess number of cancers observed beyond 30 years from diagnosis [6].

As indicated above brain tumours account for a substantial proportion of the excess number of subsequent primary neoplasms observed in the initial years following diagnosis of childhood cancer. In the BCCSS 9.1% of those irradiated for a childhood brain tumour experienced a sub-

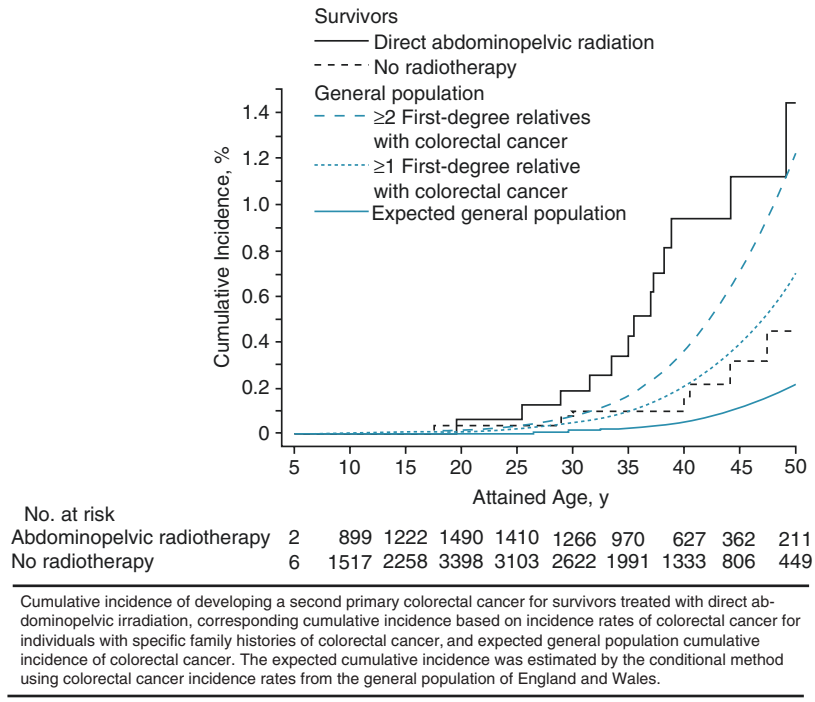

Fig. 14.2 Cumulative incidence of developing subsequent colorectal cancer for survivors treated with direct abdominopelvic irradiation. With permissions from [3]

sequent primary brain tumour by 40 years from diagnosis of original childhood brain tumour [7].

Recently a pan-European collaboration has begun to exploit the advantages which Europe has, one of which relates to the establishment of population-based cancer registration in the Nordic countries and the UK during the 1940s, 1950s and 1960s. The PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies (PanCareSurFup) subsequent primary cancer cohort comprises the largest ever assembled such cohort comprising 69,460 5-year survivors of cancer diagnosed before 20 years in 12 European countries within which there was systematic ascertainment of all subsequent primary cancers diagnosed [8, 9].

Although there was ascertainment of all subsequent primary cancers diagnosed among the PanCareSurFup survivors, there was particular focus relating to subsequent primary bone, soft tissue sarcoma, digestive and genitourinary cancers because these four cancer types account for a substantial proportion of the excess number of subsequent primary cancers in the short and long term. The original aim was to include approximately 300 subsequent primary cancers of each of these four types in a nested case-control study to investigate the extent to which cumulative dose of radiation from radiotherapy, cumulative dose of specific cytotoxics and particular genotypic factors extracted from saliva were related to risk of developing specific types of subsequent primary cancer. So far we have published the cohort studies relating to bone [10] and soft tissue sarcoma [11].

14.3 Risks of Subsequent Primary Cancer After Adolescent and Young Adult (AYA) Cancer

Previous large-scale studies of survivors of AYA cancer have tended to focus on risks of subsequent primary neoplasms after the common cancers such as lymphoma, testicular and breast cancer. Only two studies have investigated the risks of developing any subsequent primary neoplasm after each type of AYA cancer. One study was based on SEER registry data, and the main finding from this study was that AYA cancer survivors had a higher absolute risk of developing a subsequent primary neoplasm compared to childhood or adult cancer survivors [12]. However, this study did not investigate the risks of specific subsequent primary neoplasms after each AYA cancer [12]. Recently published is the largest ever study to investigate the risks of subsequent primary neoplasms after each specific AYA cancer and the first to provide excess risks of specific types of subsequent primary neoplasm after each of 16 types of AYA cancer: breast, cervix, testicular, Hodgkin lymphoma (female), Hodgkin lymphoma (male), melanoma, CNS, colorectal, non-Hodgkin lymphoma, thyroid, soft tissue sarcoma, ovary, bladder, other female genital, leukaemia and head and neck, the Teenage and Young Adult Cancer Survivor Study (TYACSS) [13]. The TYACSS is a population-based cohort of 200,945 5-year survivors of cancer diagnosed when aged 15–39 years in England and Wales from January 1971 to December 2006. During 2,631,326 person-years of follow-up, 12,321 subsequent primary neoplasms were diagnosed in 11,565 survivors [13].

We reproduce, Table 14.1, from a recent publication relating to TYACSS which illustrates two key new findings [13]. Firstly, in individuals who survived at least 30 years from diagnosis of cervical cancer, testicular cancer, Hodgkin lymphoma in women, breast cancer and Hodgkin lymphoma in men, we identified a small number of specific subsequent primary neoplasms that account for 82%, 61%, 58%, 45% and 41% of the total excess number of neoplasms, respectively, and provide an evidence base to inform priorities for clinical long-term follow-up [13]. Secondly, lung cancer accounted for a substantial proportion of the excess number of neoplasms across all AYA groups investigated and indicates a need for further work aimed at preventing and reducing the risk of this cancer among future survivors. This latter finding is in marked contrast to survivors of childhood cancer who do not experience such substantial excess risks of lung cancer, and this likely relates to the evidence that survivors of AYA smoke notably in excess of expected from the general population, whilst in contrast survivors of childhood cancer smoke much less than expected from the general population [13].

14.4 Factors Related to the Risk of Subsequent Primary Neoplasms

14.4.1 Radiation from Radiotherapy

The extent to which tissue is sensitive to the carcinogenic effects of radiation from radiotherapy varies greatly depending on the organ/tissue which is exposed. In Fig. 14.3 this variation on radiation dose–response is illustrated from published reports from the North American Childhood Cancer Survivor Study [14]. The dose–response relationships were all linear with the exception of the thyroid for which there was a reduction in risk beginning between 15 and 20 Gy exposure [14]. The organs/tissue with a linear dose–response comprised two distinct groups: sarcomas, basal cell carcinomas of skin and meningiomas were each characterised by a steep increase in the dose-response; whilst sali-

Table 14.1 AER of all and specific subsequent primary neoplasms after specific first primary neoplasm by time from diagnosis, with percentage of total AER contributed by specific subsequent primary neoplasms

	5–9 years			10–19 years			20–29 years			≥30 years			*p* value[b]
	Obs/exp	AER per 10,000 person-years (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person years (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person yean (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person years (95% C1)	% of total AER[a]	
First primary neoplasm: Female breast													
Total subsequent primary neoplasms[c]	371/190.4	11.7 (9.3 to 14.2)	100%	730/391.7	19.6 (16.5 to 22.6)	100%	581/338.5	34.5 (27.8 to 41.2)	100%	195/149.0	25.6 (10.4 to 40.8)	100%	<0.0001
Corpus uteri	46/9.9	2.3 (l.5 to 3.7)	19.7%	100/36.0	3.7 (2.6 to 4.8)	18.9%	51/36.8	2.0 (0.0 to 4.0)	5.8%	7/12.9	−3.3 (−6.2 to −0.4)	..[d]	0.97
Ovary	74/20.6	3.5 (2.4 to 4.6)	29.9%	128/43.0	4.9 (3.6 to 6.2)	25.0%	71/31.2	5.7 (3.3 to 8.0)	16.4%	18/10.1	4.4 (−0.2 to 9.0)	15.7%	0.50
Other female genital	38/30.9	0.5 (−0.3 to l.2)	4.3%	50/33.1	1.0 (0.2 to l.8)	5.1%	18/13.7	0.6 (−0.6 to 1.8)	1.7%	5/4.3	0.4 (−2.1 to 2.8)	1.4%	0.25
Colorectal	24/19.8	0.3 (−03 to 0.9)	2.6%	63/51.6	0.7 (−0.2 to 1.6)	3.6%	65/51.9	1.9 (−0.4 to 4.l)	5.5%	27/26.9	0.1 (−5.6 to 5.7)	0.3%	0.13
Lung	37/14.6	l.5 (0.7 to 2.2)	12.8%	112/48.5	3.7 (2.5 to 4.9)	18.9%	154/58.6	13.6 (10.1 to 17.0)	39.2%	54/30.5	13.1 (5.1 to 21.0)	45.2%	<0.0001
Melanoma	30/23.1	0.4 (−0.3 to 1.1)	3.4%	45/34.0	0.6 (−0.1 to l.4)	3.1%	17/18.1	−0.2 (−1.3 to 1.0)	..[d]	8/5.8	1.2 (−1.9 to 4.3)	4.1%	0.57
Other	122/71.5	3.3 (1.9 to 4.7)	28.2%	232/145.5	5.0 (3.3 to 6.7)	25.5%	205/128.2	10 9 (6.9 to 14.9)	31.4%	76/58.4	9.8 (0.3 to 19.3)	33.8%	0.0001
First primary neoplasm; cervix													
Total subsequent primary neoplasms[e]	241/179.6	5.7 (2.9 to 8.5)	100%	618/509.3	6.9 (3.8 to 10.0)	100%	609/465.2	18.3 (12.2 to 24.5)	100%	207/152.9	32.3 (15.4 to 49.1)	100%	<0.0001

(continued)

Table 14.1 (continued)

	5–9 years			10–19 years			20–29 years			≥30 years			*p* value[b]
	Obs/exp	AER per 10,000 person-years (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person years (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person yean (95% C1)	% of total AER[a]	Obs/exp	AER per 10,000 person years (95% C1)	% of total AER[a]	
Breast	89/104.4	−1.4 (−3.1 to 0.3)	..[d]	251/294.6	−2.8 (−4.7 to −0.8)	..[d]	157/227.0	−8.9 (−12.1 to −5.8)	..[d]	35/58.8	−14.2 (−21.1 to −7.3)	..[d]	[f]
Bladder	11/2.1	0.8 (0.2 to 1.4)	11.3%	40/8.4	2.0 (1.2 to 2.8)	20.6%	52/12.9	5.0 (3.2 to 6.8)	18.3	23/6.1	10.1 (4.5 to 15.7)	21.7%	<0.0001
Colorectal	23/10.4	1.2 (0.3 to 2.0)	16.9%	66/37.9	1.8 (0.8 to 2.8)	18.6%	110/46.7	8.1 (5.4 to 10.7)	29.7%	38/20.0	10.7 (3.5 to 17.9)	23.0%	<0.0001
Lung	45/7.3	3.5 (2.3 to 4.7)	49.3%	101/34.5	4.2 (3.0 to 5.5)	43.3%	137/52.0	10.8 (7.9 to 13.8)	39.6%	52/23.2	17.2 (8.8 to 25.6)	37.0%	<0.0001
Other	73/55.3	1.6 (0.1 to 3.2)	22.5%	160/133.9	1.7 (0.1 to 3.2)	17.5%	153/126.6	3.4 (0.3 to 6.5)	12.5%	59/44.8	8.5 (−0.5 to 17.4)	18.3%	0.24
First primary neoplasm; testicular													
Total subsequent primary neoplasms[g]	124/81.9	3.8 (l.8 to 5.7)	100%	378/246.2	9.0 (6.4 to 11.6)	100%	605/318.3	46.6 (38.8 to 54.4)	100%	328/161.1	127.0 (l00.0 to 154.0)	100%	<0.0001
Prostate	[h]	[h]	[h]	26/20.0	0.4 (−0 3 to 1.1)	4.4%	79/66.3	2.1 (−0.8 to 4.9)	4.5%	79/45.7	25.3 (12.1 to 38.6)	19.9%	<0.0001
Bladder	9/5.0	0.4 (−0.2 to 0.9)	10.5%	30/17.4	0.9 (0.1 to 1.6)	10.0%	84/25.0	9.6 (6.7 to 12.5)	20.6%	41/14.0	22.8 (13.0 to 32.7)	18.0%	<0.0001
Colorectal	16/9.4	0.6 (−0.1 to 1.3)	15.8%	45/33.4	0.8 (−0.1 to 1.7)	8.9%	97/44.1	8.6 (5.5 to 11.7)	18.5%	48/22.3	19.6 (9.2 to 29.9)	15.4%	<0.0001
Lung	7/7.1	−0.0 (−0.5 to 0.5)	0.0%	42/32.0	0.7 (−0.2 to 1.6)	7.8%	83/49.9	5.4 (2.5 to 8.3)	11.6%	39/26.6	9.5 (0.1 to 18.8)	7.5%[a]	<0.0001
Other	91/59.1	2.8 (1.2 to 4.5)	73.7%	235/143.4	6.3 (4.2 to 8.3)	70.0%	262/133.0	21.0 (15.8 to 26.l)	45.1%	118/52.6	49.7 (33.5 to 65.9)	39.1%	<0.0001
First primary neoplasm; female Hodgkin lymphoma													
Total subsequent primary neoplasms[i]	66/38.6	8.0 (3.4 to 12.7)	100%	316/104.2	44.7 (37.4 to 52.1)	100%	374/100.8	119.5 (102.9 to 136.l)	100%	147/44.6	168.6 (129.5 to 207.8)	100%	<0.0001

Breast	20/17.0	0.9 (−l.7 to 3.5)	11.3%	168/52.0	24.5 (19.1 to 29.9)	54.8%	181/48.8	57.8 (46.3 to 69.3)	48.4%	62/18.4	71.8 (46.4 to 97.2)	42.6%	<0.0001
Lung	7/1.0	1.8 (0.2 to 3.3)	22.5%	25/4.8	4.3 (2.2 to 6.3)	9.6%	48/8.0	17.5 (11.6 to 23.5)	14.6%	21/5.2	26.0 (11.2 to 40.8)	15.4%	<0.0001
Other	39/20.6	5.4 (1.8 to 9.0)	67.5%	123/47.4	16.0 (11.4 to 20.6)	35.8%	145/44.0	44.2 (33.9 to 54.5)	37.0%	64/21.0	70.8 (44.9 to 96.6)	42.0%	<0.0001
First primary neoplasm; male Hodgkin lymphoma													
Total subsequent primary neoplasms[j]	51/25.1	5.9 (2.7 to 9.1)	100%	192/72.9	19.5 (15.0 to 23.9)	100%	289/105.1	60.2 (49.3 to 71.1)	100%	171/68.8	121.9 (91.3 to 152.4)	100%	<0.0001
Lung	6/2.1	0.9 (−0.2 to 2.0)	15.3%	56/9.8	7.5 (5.2 to 9.9)	38.8%	82/17.5	21.1 (15.3 to 26.9)	35.0%	54/11.9	50.2 (33.0 to 67.3)	41.2%	<0.0001
Other	45/23.0	5.0 (2.0 to 8.0)	84.7%	136/63.1	11.9 (8.2 to 15.7)	61.3%	207/87.7	39.1 (29.8 to 48.3)	65.0%	117/56.9	71.7 (46.4 to 97.0)	58.8%	<0.0001
First primary neoplasm: Female thyroid													
Total subsequent primary neoplasms[k]	61/47.0	5.0 (−0.5 to 10.5)	100%	155/107.8	13.6 (6.6 to 20.6)	100%	133/95.1	23.9 (9.7 to 38.1)	100%	48/38.9	21.9 (−10.9 to 54.7)	100%	0.03
Breast	27/22.1	1.7 (−1.9 to 5.4)	34.0%	63/53.2	2.8 (−1.7 to 7.3)	20.8%	59/41.2	11.2 (1.7 to 20.7)	46.9%	21/13.7	17.6 (−4.1 to 39.3)	80.4%	0.06
Other	34/24.9	3.3 (−0.8 to 7.3)	66.0%	92/54.6	10.7 (5.3 to 16.1)	79.2%	74/53.9	12.7 (2.1 to 23.3)	53.1%	27/25.2	4.3 (−20.2 to 28.9)	19.6%	0.12

With permissions from [13]

AER Absolute excess risk, *Obs/exp* Observed number of subsequent primary neoplasms/expected number of subsequent primary neoplasms

[a]The total AER (for the purposes of calculating percentages) after each specific first primary neoplasm is the sum of the positive values for the contributing subsequent primary neoplasms

[b]Multivariable *p* value

[c]All subsequent primary neoplasms in female survivors excluding subsequent primary neoplasms of the breast

[d]Negative numbers for the AER, represented by ··

[e]All subsequent primary neoplasms in female survlvors excluding subsequent primary neoplasms of female genital sites

[f]*p* value not calculated due to negative AERs for all years

[g]All subsequent primary neoplasms In male survivors excluding subsequent primary neoplasms of other male genital sites (prostate sites allowed)

[h]Results not reliable because of small number of subsequent primary neoplasms(<5 observed subsequent primary neoplasms)

[i]All solid subsequent primary neoplasms in female survivors (excluding non-solid tumours)

[j]All solid subsequent primary neoplasms in male survivors (excluding non-solid tumours)

[k]All subsequent primary neoplasms in female survivors excluding subsequent primary neoplasms of the thyroid

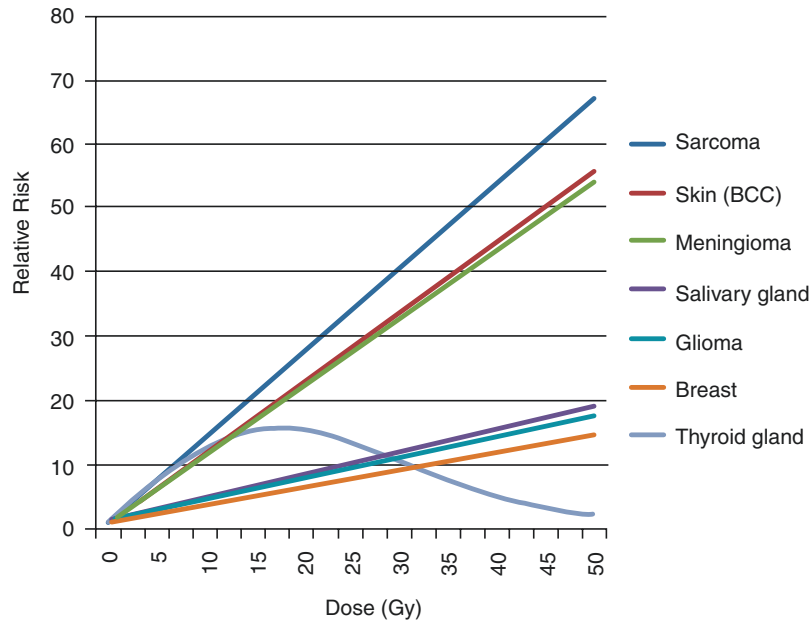

Fig. 14.3 Fitted radiation dose-response by type of second cancer, based on results from published studies. The order of second cancers from top to bottom in the graph is the same as in the key to the right of the panel. BCC-Basal cell carcinoma. With permissions from [14]

vary gland cancer, glioma and breast cancer were associated with a flatter dose–response [14].

There has been a systematic review of the risks of CNS tumours in survivors of childhood cancer [15]. As illustrated by Fig. 14.3, the dose–response for meningioma is much stronger than that for glioma. There has also been a study of the morbidity and mortality associated with meningioma after cranial radiotherapy for mostly leukaemia and brain tumours in childhood, which confirmed significant neurological morbidity [16].

There is on-going debate regarding the benefits/harms of MRI screening for the early detection of meningioma [17–19]. The International Late Effects of Childhood Cancer Guideline Harmonization Group [20] is currently assessing the available evidence and will produce recommendations in due course (see below).

As mentioned above survivors who received abdominopelvic radiotherapy have a risk of bowel cancer which exceeds that experienced by individuals with two first-degree relatives with bowel cancer. There has been a recent systematic review of the risk of gastrointestinal cancers among survivors of childhood cancer which confirmed abdominopelvic radiotherapy as a risk factor and also suggested that exposure to procarbazine and platinum anti-cancer agents may also be risk factors [21]. A very recent study compared the risk of advanced colorectal neoplasia (including advanced adenomas, advanced serrated lesions and colorectal cancer) in survivors of Hodgkin lymphoma treated with abdominopelvic radiotherapy or procarbazine with the risk in the Dutch general population [22]. The prevalence of advanced colorectal neoplasia was higher among Hodgkin lymphoma survivors than controls [25 of 101 (25%) v. 171 of 1426 (12%); $p < 0{\cdot}001$]. The authors suggested that the implementation of a colonoscopy surveillance programme should be considered [22]. The International Late Effects of Childhood Cancer Guideline Harmonization Group [20] is also currently considering evidence relating to survivors of childhood cancer treated with abdominopelvic irradiation and the potential risks/benefits of colonoscopy screening (see below).

14.4.2 Chemotherapy

It has been established for many years that alkylating agents, epipodophyllotoxins and anthracyclines increase the risk of leukaemia in survivors treated with these drugs. Alkylating agent-related leukaemia develops mostly beyond 5 years from exposure and is often characterised with chromosomal anomalies relating to chromosomes 5 and 7. Topoisomerase II inhibitors (epipodophyllotoxins and anthracyclines) related leukaemia tend to develop after a shorter period from exposure and are often characterised with 11q23 anomalies [23–25].

More recently with greater follow-up, there is increasing evidence that specific types of chemotherapy increase the risk of particular subsequent primary solid cancers. Alkylating agent exposure increases the risk of sarcoma, lung, stomach, colorectal, bladder cancer and thyroid cancers [23, 25, 26]. Anthracycline exposure has been reported to increase the risk of breast cancer and sarcoma [26–28].

14.4.3 Genetic Factors

A recent article reviewed the role of genetic variation as a modifier of the association between therapeutic exposure and the risk of subsequent primary neoplasms and reported that almost all studies have focused on candidate gene studies exploring genetic variants in DNA damage detection and repair mechanisms [29]. However most studies were limited by insufficient sample size and absence of replication in independent data. In recent years there have been a small number of genome-wide association studies (GWAS) to identify: loci associated with therapy-related myeloid leukaemia susceptibility [30]; variants associated with therapy-induced subsequent primary neoplasms after Hodgkin lymphoma [31]; and loci modifying the radiation-related risk for breast cancer after childhood cancer [32]. The role of germline genetics in identifying survivors at risk of adverse effects of cancer treatment (including subsequent primary neoplasms) was reviewed recently [33].

14.5 Clinical Follow-Up Guidelines

In recent years there has been a worldwide initiative to establish collaborations to produce (whenever possible evidence-based) internationally standardised guidelines for the long-term follow-up of survivors of childhood and young adult cancer—the "International Late Effects of Childhood Cancer Guideline Harmonization Group". [20]

There have been two guidelines published so far which relate to subsequent primary neoplasms: "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" [34]; "Balancing the benefits and harms of thyroid cancer surveillance in survivors of childhood, adolescent and young adult cancer: recommendation from International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup consortium" [35].

There are two guidelines currently being developed in relation to subsequent primary cancers: one concerns subsequent primary brain tumours, including meningiomas and the other concerns colorectal or bowel cancer, as mentioned above.

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15 Neuropsychological Short Assessment of Disease- and Treatment-Related Intelligence Deficits in Children with Brain Tumors

Holger Ottensmeier, Bernhard Zimolong, and Paul G. Schlegel

15.1 Introduction

With successes in improving survival rates and more long-term survivors of children with brain tumors in clinics, the researchers' attention has been shifting to also improve the neuropsychological outcome [1], which necessitates methods to measure and differentiate neuropsychological deficits [2–4].

The problems encountered with these methodical approaches are the choice of psychological tools and the required testing times for comprehensive evaluations. Extensive neuropsychological testing during follow-up is hampered by a number of disease-related and organizational factors. In addition, multicenter therapeutic trials require a short, precise, and theory-driven test battery based on a developmental perception theory for healthy *and* diseased children. Until recently, standard tests have been applied which do not meet the specific needs of children with brain tumors, notably with tumors of the posterior fossa: these standard tests do not take into account the tactile and motor deferrals related to cerebellar changes. Therefore, the HIT 2000 study group has designed a factor-based neuropsychological testing that has been subsequently applied within the brain tumor working group. This testing allows for the differential testing of specific well-defined subfactors according to the psychological model of Cattell-Horn-Carroll (CHC).

The theory regarded as the gold standard basis for psychological diagnostics is named "stratum theory" and was originally formulated by Cattell-Horn-Carroll (CHC) [5] and then expanded by Carroll, Flanagan, and McGrew [5–7]. The CHC or stratum theory differentiates three levels in a hierarchical model (Fig. 15.1). Stratum I includes 69 narrow abilities. Stratum II differentiates 8–16 factors such as fluid intelligence, psychomotor,

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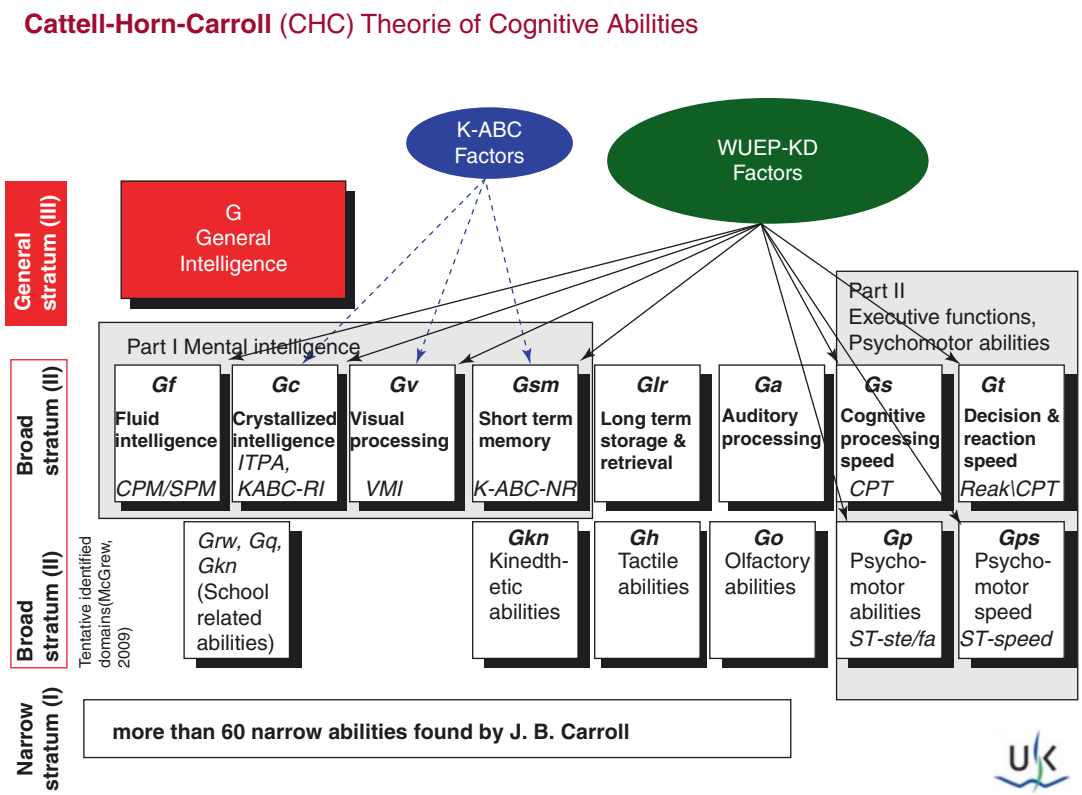

Fig. 15.1 Part 1 and 2 of Wuerzburg Short Psychological Test (WUEP-KD) and assessed CHC-based factors

and attention abilities [6–8]. Stratum III is the general factor "g" or general intelligence that relates to "fluid intelligence," "crystallized intelligence," "visual processing," "short-term memory," "cognitive processing speed/selective attention," "reaction speed," "psychomotor abilities," and "psychomotor speed" as well as to the other group factors (Fig. 15.1). Complete testing of all factors at Stratum II requires several hours. This pioneering work of the German pediatric brain tumor group has been favorably received by the European Brain Tumour Quality of Survival Group (SIOP-E) [9], which recommended the international use of the CHC-model-based neuropsychological testing tool for pediatric brain tumors.

For children with brain tumors, the CHC test profile at Stratum II may serve as a first quality step for a comprehensive assessment. The next important step was the chosen subtests within the used CHC factors to examine children with brain tumors, especially of the fossa posterior. We took the Coloured Progressive Matrices (CPM) [10] within the Gf "fluid intelligence" factor (the capacity to think logically and solve problems in novel situations), which reflects the fundamental networking of the cerebrum without any motor components [8]. CPM reflects the genetically predispositioned networking capacity of different brain areas of the individual with the purpose of internalization, conceptual manipulation, and problem-solving.

[11, 12].

To detect disturbances of appropriation in environmentally oriented features of the sensorimotor perception, the developmental test of visual-motor integration (VMI, factor: Gv) is needed [13]. Therefore, according to the theories of Luria [14] and Piaget [15], shape detection can be better used to analyze feature detection in younger children than the use of the speech features of crystallized intelligence (Gc). Thus, the method of "redrawing" the capability of a child is to extract the

information from his/her surroundings. To save this information of surroundings for the purpose of generating an "internal image" of the outer reality is assessed for the possibility to reproduct it [16]. Shape detection and reproduction are superior age appropriate tools used to analyze feature detection. In younger children, this is a better way than an analysis of the speech features of crystallized intelligence (Gc) as used in most conventional intelligence tests. The short-term memory (Gsm) was measured by the subtest short-term memory of the K-ABC (K-ABC-number recall), the ability to store and hold information in immediate awareness and use it within a few seconds, which is a task of working memory.

Previously, we reported disease- and therapy-related neuropsychological dysfunction in children with medulloblastoma using a 2½ h lasting test including K-ABC, CPM, and the VMI [1]. In this article, we report on the application of the WUEP-KD, namely, on the results obtained by WUEP-KD in comparison to those of the standard intelligence test K-ABC.

15.2 Materials and Methods

15.2.1 Experimental Design

Testing the usefulness of the shorter battery had three parts: (i) to assess if useful data for the most important questions can be obtained, (ii) to assess if those data are valid, and (iii) measuring in a shorter testing time. We report the short WUEP-KD test battery, part one, Coloured Progressive Matrices (CPM [17–19]), visual-motor integration (VMI [16]), and short-term memory (K-ABC-NR) and compare them to the published manual norms of the full mental test battery Kaufman Assessment Battery for Children (K-ABC [20, 21]).

Part two of the WUEP-KD evaluates executive functions of psychomotor abilities (ST-speed), processing speed, and attention abilities with the continuous performance test (CPT-short). Thus, the WUEP-KD saves assessment time avoiding repeated measurements of the same factor, a common phenomenon when using standard intelligence batteries. Detailed descriptions of WUEP-KD are available in [1]. So we can test the correlation between den main intelligence factors Gf, Gv, and Gsm of both tests (Fig. 15.1). The motor and selective attention-oriented tests were in both batteries the same.

15.2.2 Statistical Analysis

Individual age-related test scores were scaled as age-independent standardized scores (SS) of test norms with a mean of 100 and standard deviation of 15.For construct validity we used SPSS to compute a factor analysis with Kaiser's varimax orthogonal rotation method on 13 different test scores from 10 subtests of WUEP-KD based on a norm sample of $n = 201$ children. We calculated simple linear regression with K-ABC test scores not included in the WUEP-KD test as criterion and three subtests CPM, VMI, and K-ABC NR of WUEP-KD as predictors. Additionally, the multiple correlation coefficient R serves as a measure of convergent validity between K-ABC subtests and WUEP-KD subtests. Data entries were the scores of three tests of WUEP-KD and three K-ABC subtests on 201 children from the norm sample.

15.3 Results

15.3.1 Test Time and Retest Reliability

The mean duration for testing patients and controls with the WUEP-KD was 65 min (SD 27 min). The range of retest reliability coefficients was between 0.95 (tapping: speed) and 0.70 (attention test: CPT). Scores >0.70 are regarded as appropriate for individual testing.

15.3.2 Test Quality and Correlation with K-ABC

The total IQ of CPM, VMI, and K-ABC-Number-Recall (part 1 of WUEP-KD) correlated significantly ($r = 0.89$, $p < 0.001$; Pearson) (Table 15.1)

Table 15.1 Prediction of three subgroup scales of the K-ABC (full scale IQ; simultaneous processing (SMP) and sequential processing (SQP) without number recall (SQP-NR) with WUEP-KD scales CPM, VMI, and K-ABC-NR

Criterion variables K-ABC scales	Predictor variables WUEP-KD	WUEP-KD standard beta weights	Correlation R	Variance explained R^2 corr. R^2
K-ABC MPC	CPM	0.386		
(Full scale) IQ	VMI	0.350	0.850	0.693
Mental processing composite (MPC)	NR	0.424		
K-ABC—simultaneous processing (SMP)	CPM	0.516		
	VMI	0.701	0.793	0.604
	NR			
K-ABC—sequential processing (SQP-)	CPM			
	VMI			
(without number recall)	NR	0.714	0.714	0.509

Table 15.2 Rotated factor matrix with WUEP-KD scores; $n = 201$ healthy children, ages 7–14 years

Intelligence domains	Mental intelligence				Executive functions/psychomotor abilities		
Factors	Fluid	Crystallized	Visual process	Short term memory	Cognitive processing speed/selective attention	Reaction speed	Psycho-motor speed
	Gf	**Gc**	**Gv**	**Gsm**	**Gs**	**Gt**	**Gps/Gp**
CPM	**0.952**	072	0.114	0.059	−0.021	−0.004	−0.108
ITPA	0.070	**0.992**	0.003	0.036	−0.041	−0.075	0.006
VMI	0.124	0.005	**0.916**	0.132	−0.151	0.031	0.004
K-ABC-NR	0.056	0.036	0.127	**0.941**	0.007	−0.133	−0.113
CPT-S: Speed	0.149	0.029	−0.322	0.283	**−0.492**	0.385	0.332
False	0.011	−0.038	−0.203	0.050	**0.910**	−0.009	0.093
Simple vis.	−0.140	0.003	0.050	−0.111	−0.040	**0.880**	0.078
Reaction: aud.	0.120	−0.095	−0.022	−0.041	−0.031	**0.863**	0.104
Tapping: Speed	0.074	−0.008	−0.049	0.159	0.072	0.118	**0.850**
Steadiness	−0.223	0.012	0.038	−0.180	−0.038	0.066	**0.811**

Varimax rotation; Kaiser normalization. Seven factors were extracted
Maximum factor load in bold values

with full K-ABC (mental processing composite) score and ($r = 0.96$, $p < 0.001$) of extensive function-specific neuropsychological assessments (K-ABC with all subtests, CPM, and VMI sum score) of the same.

The construct validity of the WUEP-KD was tested using factor analysis. The results strongly support the association of the theoretically assigned subtests of the WUEP-KD to the group factors of Stratum II of CHC theory as outlined in Table 15.2. Thus, three basic neuropsychological functions of young children are evaluated by the WUEP-KD: mental intelligence, executive functions with psychomotor performance, and attention abilities. The concurrent validity of the mental abilities of part 1 of the WUEP-KD was determined with multiple linear regression computations. The results provide high to medium correlations between K-ABC scales and WUEP-KD scales indicating a high agreement between scales.

15.4 Discussion

We evaluated an abbreviated test battery for the purpose of neuropsychology evaluations of children in large multicenter clinical trials and describe the results of a population of medulloblastoma patients (see [1]). Using the novel and

shorter method, we confirmed previous results using more comprehensive tests: patients who had received craniospinal radiation and high-dose methotrexate chemotherapy to be most affected and patients, who had received intraventricular and systemic methotrexate least affected [2]. With longer clinical follow-up since treatment, the new data also describe the development of these children over the years, indicating that the deficits may increase with increasing normal development of healthy controls.

In Table 15.1 we see that the prediction between the short and the long version of the test battery confirmed the validity of the abbreviated test battery.

The concept of the abbreviated neuropsychological test battery WUEP-KD includes the CHC or stratum theory [5–7] as well as the psycho-developmental models of Luria and Piaget [22, 23]. It includes three tests to measure the main mental abilities: CPM, VMI, and K-ABC-NR. Executive functions of psychomotor abilities and selective attention abilities were derived from tests of cognitive processing, and exact computerized measurements of finger tapping speed scores were developed from empirically derived models of the structures of intelligence, which went beyond single test-associated concepts. Contrary to classical intelligence tests, the WUEP-KD has not been developed to create a single general IQ score alone; instead, it reflects a multidimensional profile of essential and independent factors as offered by the CHC theory, demonstrated by the own factor analysis (Table 15.2). This specifically demonstrates the variable processes affecting the main intelligence factors when analyzing the functional disturbances in individual children with brain tumors. While concepts may be debatable on various levels, our data show that the resulting product here was functional and can be used to answer therapeutically relevant questions, thereby validating the underlying concepts.

Visual processing is one of the factors described in CHC [6, 8], and the WUEP-KD assesses it using the VMI. Contrary to simple visual differentiation of size and color, the sophisticated understanding of object characteristics requires an active sensorimotor exploration of the child using all cognitive channels for the identification of environmental facts and objects; this capability should be measured quantitatively [24]. This developmental theory-based requirement is perfectly met by the visual processing factor (Gv) in the CHC model description of McGrews: "The ability to generate, store, retrieve and transform visual images and sensations in 'the mind's eye'" [8] measured by the VMI. Thus, individual patients' results can in turn initiate individually tailored occupational therapy acknowledging the stage of psychomotor development [25, 26]. The VMI represents non-verbal knowledge of characteristic features which reflect the learned and internalized structures of the knowledge of objects (visual-spatial and conceptual intelligence) [8, 16, 24, 27, 28]. It closely correlates with higher cognitive abilities [16, 28, 29]. VMI also reflects the level of internalization of acquired everyday intelligence integrated in the WUEP-KD to identify adequate strategies of developmental psychology for further rehabilitative intervention. The general use of VMI has been questioned in Europe because it is based on North American norms. Our own data of 201 healthy German children did not support this theoretical concern; there were only negligible differences to IQ scores of the VMI test.

The prognosis of children with medulloblastoma younger than 3 years at diagnosis was historically inferior compared to older children, which was attributed to both tumor biological differences and age-related limitations to deliver treatment [1]. Long-term neuropsychological deficits may be caused by the tumor, increased intracranial pressure, and treatment elements such as surgery, craniospinal radiotherapy (CSI), and chemotherapy (CHT) [30]. Among those, the choice of drugs, dose and route of application of chemotherapy as well as the timing and field of radiation has been subject of major clinical trials as prominent components for decreasing intellectual and psychomotor capabilities [31–34]. The main contribution of the HIT-SKK trials in the field was the reduction of radiation and the addition of intraventricular

methotrexate. This study describes follow-up neuropsychological data. We confirm the harmful effect of radiation to the brain of young children, and we confirm that intraventricular methotrexate was significantly less harmful than radiation: results of patients with intraventricular MTX only were still within normal limits. The test results from relapsing patients of group 1 indicate clearly that a treatment with intraventricular methotrexate should only be used in children with a very high chance to avoid craniospinal radiotherapy. After confirmation of the HIT-SKK'92 experience and the impact of histological subtypes in the subsequent trial HIT-SKK'2000, young children with nodular desmoplastic medulloblastoma seem to especially qualify for this treatment [35]. The mechanisms of the damage to the developing central nervous system are likely multi-factorial. Significant correlations between the loss of gray and white brain matter and the pathological results in the Raven matrix test and correlation of inadequate development of white matter and deficient neurocognitive performance [36] have been reported.

In conclusion, the WUEP-KD fulfills the criteria of short testing times and yields valid results and can thus be a highly useful tool for assessment of children with various neurological diseases, notably brain tumors. WUEP-KD is an excellent tool for longitudinal monitoring in prospective multicenter trials [37].

In the most recent publication [38] the impact on psychomotor and executive functions besides general intelligence was explored. Additional classification of children included position of brain tumors (medulloblastoma and ependymoma), and treatment (surgery and chemotherapy).

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16 Long-Term Positive and Negative Psychosocial Outcome in Young Cancer Survivors and Their Healthy Peers: Posttraumatic Stress Disorder/Somatoform Disorder

Mandy Niemitz, Dunja Tutus, and Jörg M. Fegert

16.1 Background

Every year approximately 215,000 children (aged 0–14 years) are diagnosed with an oncologic disease worldwide. The cancer mortality for both children and adolescents declined for multiple cancer types [1–3]. Advances in treatment increased the overall 5-year survival rates to approximately 80% for many oncological diseases [4–6]. Despite advances in medical therapies, cancer is, however, still the second leading cause of death (following accidents) in children and adolescents [1, 6]. Cancers as well as its treatment represent a specific form of traumatic event [7]. When a child is diagnosed with cancer, it always means a great shock for the entire family, which is affected by demands of the illness and its treatment. The cancer diagnosis ranks among the most serious triggers of a traumatic crisis. Oncologic diseases are described as a potentially traumatic experience within the diagnostic criteria for posttraumatic stress disorder (PTSD) of the DSM-IV [8]. Traumatic events and posttraumatic stress symptoms (PTSS) might further increase the risk for other disorders and vice versa [9]. Cancer-related challenges (such as premature confrontation with mortality, changes in physical appearance, increased dependence on parents, disruption in social life and school/employment because of treatment, loss of reproductive capacity, and health-related concerns about the future) may be particularly distressing for patients [10, 11]. Psycho-oncology has developed as a subdiscipline of the oncology at the mid-1970s and has consequently become more and more important because of addressing the individual's attitudes and beliefs about cancer, the psychiatric comorbidity and psychosocial problems [12]. In the meantime psychosocial care of children and adolescents is a crucial part of the multidisciplinary therapy. In recent years, the International Society of Paediatric Oncology (SIOP) published a series of guidelines on psychosocial issues in paediatric oncology [13–19]. Furthermore, in Germany the S3 guidelines for the psychosocial care in paediatric oncology and haematology were published [20].

16.2 Psychosocial Effects of Paediatric Cancer

Chronic diseases in childhood such as cancer have important consequences for the psychosocial well-being of children and their families [21–23]. Compared to same age children/adoles-

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cents without the diagnosis, cancer survivors report significantly more psychological distress [24–27]. The achievement of developmental milestones (decisions about their education or gaining independence) might be seriously impeded due to cancer [28, 29]. Especially survivors of childhood cancer are at an increased risk for different psychological long-term consequences. Chronic health conditions (e.g. cardiac, endocrine and pulmonary) resulting from childhood cancer therapies contribute to emotional distress in adult survivors [30].

Nevertheless, children/adolescents who suffered from cancer as well as their family members can react differently to similar burdens in the course of this disease. Some of them are psychologically impaired and show PTSS, depressive symptoms and/or anxiety. The others cope with the disease and emerge from it stronger than before. According to O'Leary and Ickovics [31], four developments if a person's life has been shaken by an extremely stressful event, in the aftermath of the diagnosis, are conceivable (see Fig. 16.1):

- A continuous downward course occurs, the initial disabling effect is intensified, and the person collapses and succumbs to the disease-related burdens.
- It is also possible that the person overcomes this adverse event. However, the person has experienced lasting restrictions in some areas of life and returns to a lower level of functioning than before the event occurred.
- Some patients are considered resilient; they return to their original level of functioning more or less rapidly.
- There are patients who can even pull positive consequences from this event in the long-term, they grow on it, and in the process they achieve a higher level of functioning than before [32].

16.3 Depression and Anxiety

Anxiety is a known psychological consequence in children, immediately after having received the cancer diagnosis [33]. However, compared to healthy peers, at the time of diagnosis, adolescent cancer patients are not more anxious or depressed [34, 35]. Only the minority of adolescents recently diagnosed with cancer score in the clinical range of psychological distress [36]. In contrast, the period after treatment is characterized by a higher risk of psychosocial distress than within the actual treatment period [24, 37]. A significant proportion of childhood survivors experience persistent anxiety and depression symptoms after treatment completion. The prevalence of elevated anxiety symptoms appears to decrease within the first year of treatment but increases again after therapy completion, to a level similar with that observed when receiving the diagnosis

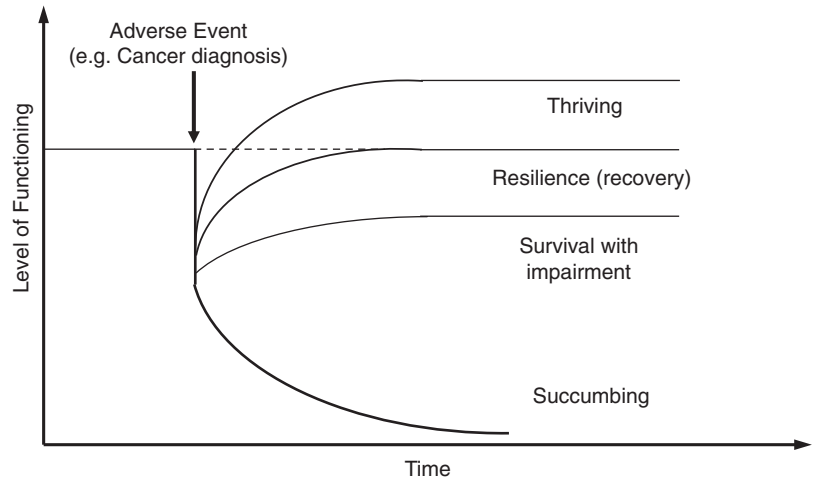

Fig. 16.1 Potential reactions to stressful life events (modified according to O'Leary and Ickovics) [31, 32]

[31]. Several studies have shown a vulnerability to develop anxiety symptoms among a subset of adolescent cancer survivors, particularly during the transition to survivorship. This might be explained by the stress related to the cancer diagnosis, treatment and transition into survivorship [32]. Higher levels of anxiety symptoms are shown for both male and female survivors (>5 years since diagnosis), when compared to the general population [25].

Compared to healthy peers, children with clinically relevant anxiety and depression symptoms at early therapy stages report an increased risk for persisted distress after treatment completion [33, 38, 39]. Invasive chemotherapy is associated with a significantly increased risk for depression [40]. Moreover, physical health, cancer-related pain, depression and primary central nervous system (CNS) tumour diagnosis are associated with a heightened risk for suicidal ideations in survivors [41]. Survivors with less than 12 years of education are at a higher risk for developing a major depression [42]. Risk factors for anxiety and depression symptoms include low socioeconomic status (SES), physical health status, female gender, unhealthy family functioning and less reliance on social support coping behaviours [33, 38, 43–45]. On the contrary, being more optimistic about the further course of the disease, less gathering information about the disease as well as patient agency are associated with lower level of anxiety [46, 47].

16.4 Posttraumatic Stress Disorder

Paediatric cancer survivors had a more than four times greater risk for developing PTSD, compared to healthy peers [41, 48], with a prevalence of 5–7% [49]. Meanwhile, adult survivors of childhood cancer report a significantly higher prevalence, up to 21% meet the diagnostic criteria for PTSD. The existential threat caused by the diagnosis is the central point of the posttraumatic stress concept. Furthermore, the treatment with possible complications and invasive interventions can be life-threatening experiences [49]. Most of the survivors do not meet the full criteria for a PTSD diagnosis. PTSS (intrusive thoughts, avoidance of reminders and dysfunctional cancer-related cognitions, hypervigilance) are frequently reported but seem to decrease with time [50–52]. The individual perception of the treatment and its effectiveness are the strongest predictors of PTSS [51]. Survivors with PTSD have significant functional impairments and high psychological comorbidity [53]. Patients at younger age, female gender, low self-esteem, immature defence style, somatization and lack of emotional coping, who recently underwent treatment, are at higher risk for developing PTSS. Lower SES, less perceived social support and difficulties in communication with health care professionals (HCPs) facilitate this relationship [48, 51, 54–56]. Furthermore, poor family functioning, including the intrafamilial problem-solving skills, affective responsiveness and involvement, increases the risk for developing cancer-related PTSS in adolescent survivors [57].

16.5 Posttraumatic Growth

Despite psychosocial restrictions, survivors can derive personal benefits from the experiences made with cancer. The concept of posttraumatic growth (PTG) refers to positive changes resulting from the struggle with a traumatic event [58, 59]. Tedeschi and Calhoun suggested that stress causes growth by challenging the individual's world view and precipitating a rethinking or reordering of priorities [60]. Cancer survivors commonly report personal growth in three specific life domains: improved coping skills, enhanced social and personal resources [51]. So far, it is not clear which aspects of cancer treatment contribute to the personal growth [59]. PTG is associated with perceived threat regarding the disease (concerns about recurrence, death and experienced stress). Furthermore, less years off-therapy, female gender, younger age at diagnosis, warmth in parenting, being member of ethnic/minority groups, perceived social support and emotional/cognitive processing of cancer facilitate PTG [7, 51, 54]. Experiencing

childhood cancer might inoculate individuals to other negative life experiences and provides them with feelings of life satisfaction and overall psychological well-being [61].

16.6 Somatoform Disorders

Cancer-related fatigue occurs typically in almost all oncological patients and might persists after treatment completion. Fatigue is associated with low health-related quality of life (HrQoL) and has an impact on the treatment course. Chronic fatigue might be present for years and impairs patient's lifestyle [49, 62]. Little is known about the etiological causes of fatigue. Several risk factors in survivors could be identified: female gender, congestive heart failure, pulmonary fibrosis, depression and being unmarried [63]. For further information see Chap. 18.

A significant proportion of adult survivors, especially with CNS tumours, report sleep disturbances (excessive daytime sleepiness, obstructive sleep apnoea, central sleep apnoea, hypersomnia, narcolepsy and insomnia) which are associated with physical and psychological health [64–66]. Insomnia symptoms might be associated with a migraine headache history [67].

Headaches (migraine, tension type and chronic headaches) are the most common neurologic condition in acute lymphoblastic leukaemia (ALL) survivors, but only a minority reports disability and reduction of HrQoL [68]. Furthermore, compared to leukaemia, younger age at diagnosis and history of non-Hodgkin lymphoma, Wilms tumour or neuroblastoma are associated with greater risk for pain conditions. A history of bone cancer or soft tissue sarcoma correlates with using analgesics and cancer-related pain attribution. Non-brain-directed scatter irradiation elevates risk for migraines and cancer-related pain attribution. Female gender, lower SES, minority status and being single are related to greater risks for pain conditions [69]. In a case of similar diagnosis, physical status, duration of diagnoses and pain causes, girls reported higher cancer-related pain intensity than boys [70].

16.7 Health-Related Quality of Life

HrQoL is a multidimensional construct including physical, psychological and social well-being and functioning [71]. Increased long-term cancer burdens required inpatient treatment, and substantially longer stays in hospitals may profoundly influence HrQoL of survivors [1, 72]. However, survivors report generally good HrQoL with exception of some bone tumours [73]. Low HrQoL is correlated with increased anxiety, depression, PTSS and vice versa [74]. Adult survivors with disease onset during adolescence experience less life satisfaction and report impaired HrQoL, compared to the general population [75]. Recent research identified the following risk factors for impaired HrQoL in cancer survivors: female gender, diagnosis (CNS tumours, ALL and lymphoma), lower SES, unmarried status and cranial radiation in combination with low education [76–79]. Older age at diagnosis, longer time since diagnosis and certain cancer or treatment types are related to lower physical well-being [73]. Survivors of CNS tumours and ALL are at risk for educational deficits, difficulties obtaining work, health and life insurance [80, 81]. Survivors have problems with development and maintenance of peer and family relationships, lower rates of marriages and parenthood and are worried about their reproductive capacity and/or possible health problems of their future children [82, 83]. The oldest adult survivors continue to be at risk for treatment-related complications that potentially decrease their life expectancy and compromise their HrQoL [84]. Patients with severe psychosocial long-term consequences show impairment in the domains body image, emotional and physical functioning and cognitions [85]. HCPs tend to underestimate or misjudge the health preferences and support needs of the patients [86].

16.8 Family

When a child is diagnosed with cancer, the entire family is affected by the demands of the illness and its treatment. The collective experience of

the life-threatening disease and the unpredictable course of the illness place a burden not only onto the child with cancer but also onto his/her parents and "healthy children" in the family, who do not suffer from cancer [21, 87].

16.8.1 Parents

Parents play a crucial role in their child's recovery from cancer-related traumatic experience and in the development and maintenance of PTSS [88]. Emotional distress, higher level of family conflict and feelings of uncertainty, anxiety, depressive symptoms and PTSD often occur shortly after the parents are confronted with child's cancer diagnosis, or among parents of children who are in treatment [89–92]. Almost 80% of the children being currently in treatment had at least one parent with moderate-to-severe PTSS [93]. Three months after the treatment, the PTSS level is stable [94], and 10–30% parents show PTSS [95, 96]. Emotional distress remains elevated 1 year after the diagnosis but appears to decrease in the following years [21]. However, psychological symptoms persist in a substantial proportion of the parents, even many years post-treatment [89]. The factors past time since receiving the diagnosis, child treatment status and relapse history significantly predict parental PTSS. There is some evidence of gender differences in levels of anxiety, depression and PTSD, although these differences are not always statistically significant and may reflect gender differences in the general population [21]. Common risk factors are pre-existing psychological problems, high trait anxiety, low SES and financial worries, child behaviour problems, high perceived caregiving and reported less social support [89]. Caregivers with their own psychological symptoms report communication problems with their child [97]; they are less likely to provide support for their children and model appropriate coping strategies. Hence, parental psychopathology can be seen as a risk factor regarding the recovery of their child from PTSD [88]. Social support has a buffering effect, especially among mothers, and might influence psychosocial well-being. Furthermore, parents benefit from open and frequent communication about their child's disease in terms of both psychological and physical well-being [21, 98]. Maternal reports of children's behavioural problems are predicted by maternal health and marital status (i.e. being single parent) [99]. Single parents caring for children with cancer experience several additional stressors. The synergy of these cumulative stresses may have long-term health and financial implications [100]. Hence, they frequently report needs for more social-emotional, practical and financial support [101]. However, this impact, in terms of caregiving demand and HrQoL, is similar to that of parents from two-parent families [102]. Nevertheless, similarly to their children, parents might also experience PTG [103].

16.8.2 "Healthy Siblings"

"Healthy siblings" face multiple challenges (witnessing the emotional and physical pain of the child with cancer, his/her physical changes, changes in family life and routines, separation from the child with cancer/parents during hospitalization, loss of parental attention and their distress) [104–108]. Family activities are reduced as a consequence of the treatment protocol. Conversations in the family are dominated by illness and treatment [109]. For all these reasons, the "healthy siblings" are often considered as "forgotten children" [110].

There is strong evidence that "healthy siblings" are prone to psychosocial problems [23]. They report significantly more emotional distress and behavioural problems (fear, grief, anger, helplessness and impaired HrQoL), but typically not at clinical levels [21, 104, 105, 110, 111]. Due to the diverse burdens on "healthy siblings", national German guidelines [20] and international recommendations [17, 112] advise to specifically address the emotional distress of the siblings. Hence, psychosocial care of children with cancer should include the "healthy siblings". Nevertheless, a subgroup of "healthy siblings" report positive psychological health, good HrQoL, satisfaction and PTG [61].

16.9 Clinical Implications

Communication of relevant information about the child's diagnosis and prognosis, at the initial stage of the disease, improves the child's emotional well-being and reduces anxiety and depression [113]. Survivors require age-appropriate and flexible care and treatment-related education that foster autonomy for long-term survivorship [114].

Screening of psychological symptoms and HrQoL in children/adolescents with cancer is highly recommended, at early stage of the disease, and years after successful treatment completion [25]. If these problems remain undetected and appropriate support is not provided, the distress may become a barrier to physical recovery, resulting in a vicious cycle of physical and mental disability [115].

Sleep hygiene is highly recommended, since neurocognitive function in long-term survivors appears particularly vulnerable to the effects of fatigue and sleep-disruption [116].

As cancer-related pain might diminish HrQol, pain management is highly recommended [117].

Early identification and treatment of cancer-related PTSD can enhance HrQoL [118]. Children/adolescents with cancer-related PTSD and their parents may benefit from trauma-focused cognitive behavioural therapy [119, 120], or other psychotherapeutic interventions including exposure technique, desensitization and stress management training [51] and internet-based CBT [121, 122].

Assessment of parental psychological symptoms [123] and HrQoL is important in order to identify those parents requiring psychological support. Certain coping strategies (e.g. active problem-solving, seeking social support, optimism) can serve as protective factors. Parents at risk might benefit from tailored interventions based on strengths and weaknesses that are targeted to their specific needs with respect to the phase of childhood cancer [89, 124].

Psychopathological screening of "healthy siblings" is recommended. Each "healthy sibling" could benefit from a treatment model within he/she could experience more attention to their own individual needs (e.g. more knowledge about cancer, dealing with their emotions) [125].

It is important to note that all family members who report PTG might experience PTSS at the same time. Thus, they also need to be regularly screened and provided with psychological support, if needed [103].

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Cancer-Related Fatigue

17

Judith Gebauer, Jens U. Rüffer, and Georg Brabant

17.1 Definition and Classification

Cancer-related fatigue (CrF) is observed as a consequence of cancer treatment. It is characterized by more than 6 months of persistent or relapsing exhaustion affecting everyday life, not relieved by sleep or rest.

According to National Comprehensive Cancer Network (NCCN) 2014 Practice Guidelines for CrF, it is a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning [1].

CrF is classified as mild, moderate or severe depending on the degree of impairment (mild, able to care for one self, but days off work to rest are needed; moderate, reduced mobility, disturbed sleep patterns and need to sleep in the afternoon; severe, significantly reduced mobility and difficulty concentrating).

17.2 Epidemiology and Natural Cause

Fatigue is a common complaint in the general population and the principal reason for consultation in up to 7% of cases in primary care [2].

It is a serious condition that can significantly impair quality of life and affect all aspects of everyday life. Even though improvement is possible, CrF can cause long-term illness and disability [3].

In the majority of studies, 30–60% of cancer patients report moderate to severe fatigue, depending on the patient population, type of treatment received and method of assessment [4]. A prospective, longitudinal study on 1494 cancer patients in Germany revealed that 32% of the patients were classified as fatigued at hospital admission for the initial cancer therapy. This rate increased to 40% at discharge from treatment and dropped to 34% another 6 months later. These fatigue prevalence rates differed according to tumour stage, site, age and sex of the patients [5].

These data correspond well to previous data in different cancer entities such as Hodgkin's disease, breast and prostate cancer [6–8].

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Although CrF typically improves in the year after treatment completion, about one-quarter to one-third of long-term cancer survivors experience persistent fatigue for up to 10 years after cancer diagnosis [4].

The natural cause of CrF is currently underresearched. A recent large study on mortality of patients with proven chronic fatigue syndrome demonstrated in a cohort of 2147 subjects that overall mortality is unchanged but evaluation of suicides within this cohort in comparison to data in the general population of UK supported a grossly elevated rate of suicide with a SMR increased to 6.85 [9].

Another population-based prospective study of 18,101 men and women aged 40–79 years in the UK (mean follow-up: 16.6 years) showed that fatigue was significantly associated with premature mortality. Participants within the highest quartile of reported fatigue levels had a 40% higher mortality risk than those in the lowest quartile, mainly concerning CVD-related but not cancer-related death. As vital exhaustion constitutes a known risk factor for ischaemic heart disease, fatigue appears to pose a significant cardiovascular risk factor with an observed unadjusted mortality risk of high-level fatigue similar to that of being a current smoker [10, 11].

In a large cohort of more than 5000 Hodgkin's lymphoma survivors, a high incidence of severe acute and persistent fatigue was demonstrated. Recovering from CrF was observed only in the first year after treatment. No higher incidence of suicides was observed up to 5 years after treatment [7].

17.2.1 Known Causes of Chronic Fatigue in Relation to Cancer

The underlying aetiology of CrF in cancer survivors is speculative to date. The fact that a high proportion of patients complain of fatigue before cancer diagnosis and initial treatment of the underlying carcinoma suggests a relation to the tumour itself [2]. Some data indicate that secretion of cytokines by the tumour may represent a potential cause [12].

Furthermore, cancer and its treatment activate the immune system, inducing a release of pro-inflammatory cytokines that contribute to peripheral inflammation. This mechanism triggers a series of events including alterations in endocrine functions, HPA axis dysfunction as well as mitochondrial impairment. This process is influenced by genetic factors, e.g. polymorphisms in cytokine-related genes that are associated with fatigue [13].

Consequently, skeletal muscle dysfunction can occur as well as fatigue, depression, sleep disturbance and cognitive impairments influencing physical function and performance. The stage of cancer, type of cancer treatment, comorbidities, concomitant medications and other factors can affect these events (Fig. 17.1) [14].

Psychological reasons may play an important role, and the cancer diagnosis may uncover any underlying psychological problem. Among psychosocial risk factors, especially childhood adversity, has been identified as a consistent predictor of CrF [13]. Familiar causes, genetically encoded as with coping, may play an additional role. These patients are at risk for psychiatric comorbidities and need close psychological supervision.

In an analysis of data from 751 adult survivors of childhood Hodgkin's lymphoma who participated in the North American Childhood Cancer Survivor Study, emotional distress, pain and physical functioning limitations all increased the risk for fatigue (OR 8.38, 3.73 and 3.28, respectively) in comparison with survivors not affected by these complications. Moreover, female survivors and survivors currently unemployed had higher risk of fatigue (OR 4.75 and 2.9, respectively) [15].

The frequently observed sleep disturbances may be related to the depressive mood of the patients but may as well represent treatment-related problems affecting day/night rhythms and melatonin secretion. A major causes with insidious onset many months or years following cancer treatment are hormonal deficiencies which are most frequently observed following irradiation to endocrine organs such as to hypothalamus/pituitary, thyroid or gonads.

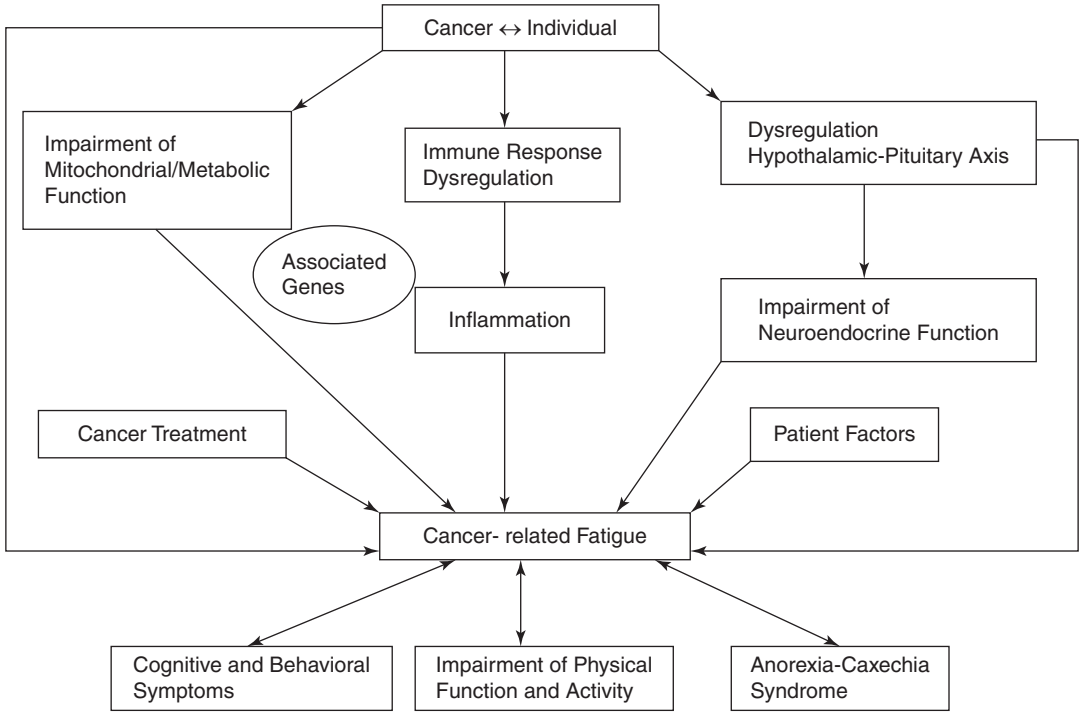

Fig. 17.1 Influencing factors of cancer-related fatigue, modified [14]

It is important to mention that great individual variability in the experience of fatigue has been reported, mainly as a consequence of different combinations of predisposing, precipitating and perpetuating factors. Predisposing factors are defined as enduring traits increasing an individual's general susceptibility to develop fatigue symptoms, precipitating factors as situational conditions that trigger the onset of these symptoms and perpetuating factors as circumstances contributing to the maintenance of fatigue symptoms over time. This has been illustrated in detail in a recent review by Julienne Bower [13].

17.3 Diagnosis

Existing national guidelines for the diagnosis of CrF vary between countries but only the guideline of the ASCO specifically mentions cancer survivors and defines treatable conditions under these circumstances [16]. The UK-based National Institute for Health and Care Excellence (NICE) defined specific criteria including a duration of at least 4 months, the lack of any other conditions explaining the major symptoms such as lack of energy, problems in sleeping, feeling anxious and depressed, muscle pain, shortness of breath, problems to concentrate and loss of interest [17].

Because of the heterogeneity of symptoms and the overlap between CrF and depression, the anamnestic exploration is of great importance and should include a standardized questionnaire for depression. All patients should be screened at least annually by a standardized questionnaire and an evaluation of their sleep pattern, social and environment related factors, their drug history, their use of any addictive drugs as well as their medical history and their physical activity.

First, a focused fatigue history including onset, pattern and duration as well as change over time and possible associated factors of the symptoms should be assessed. Furthermore, a detailed evaluation of the cancer disease regarding, e.g. risk of recurrence is needed. Moreover, treatable contributing factors should be assessed. These are cardiac, renal, pulmonary or endocrine dysfunctions as well as anaemia, arthritis or neuro-

muscular diseases which should be excluded when clinically appropriate. The drug history of the patients (as well as possible drug or alcohol abuse) should be elucidated carefully. Besides, an evaluation of nutritional issues, functional status and activity level is recommended (Table 17.1).

For an assessment of the extent of fatigue, a visual analogue scale from 0 = no fatigue to 10 = severe fatigue is used. All scores beyond four are further assessed. Potential instruments for the measurement of fatigue, which could be used to supplement this initial screening, include unidimensional (tending to measure the physical impact of fatigue, e.g. EORTC QLQ C30, FACT-F) as well as multidimensional (tending to measure cognitive or affective symptoms, e.g. BFI, FSI) scales, validated in mixed cancer populations (Table 17.2). A more detailed review is provided by the American Society of Clinical Oncology Clinical Practice Guideline [16].

Table 17.1 Potential treatable factors possibly associated with fatigue symptoms and their possible diagnostic evaluation (should be undertaken only when clinically appropriate), modified [16]

Treatable factors Possibly associated with fatigue symptoms	Possible diagnostic evaluation
Cardiac dysfunction	Echocardiogram, (stress) ECG
Endocrine dysfunction	Measuring HgbA1C, fasting blood sugar, TSH, free thyroxine, testosterone, short synacthen test
Pulmonary dysfunction	Pulmonary function test, oxygen saturation, chest x-ray
Renal dysfunction	Kidney and electrolyte chemistries
Anaemia	Complete blood cell count
Arthritis	Sedimentation rate, serologies
Sleep disturbance	Assessing sleep with standardized questionnaire, sleep laboratory
Neuromuscular complications	EMG, grip strength test, neuropathy sensory testing
Pain	Evaluation with standardized assessment tool
Emotional distress	Evaluation with standardized assessment tool

Note: This list is not meant to be exhaustive
ECG electrocardiogram, *HgbA1C* glycosylated hemoglobin, *TSH* thyroid-stimulating hormone, *EMG* electromyogram

Among the treatable conditions, endocrine disturbances are most important.

Hypopituitarism is well-known to develop as a consequence of external beam irradiation to hypothalamus and pituitary. It rarely occurs when irradiated with doses below 20Gy, but this threshold is age-dependent [18].

Among the different pituitary axes, GH is most sensitive affected with doses <40Gy and resulting in isolated GH deficiency. Consequently growth hormone deficiency (GHD) is the most common pituitary hormone deficit following cranial radiotherapy and due to its symptoms needs to be excluded in cancer survivors with CrF. In GH deficient patients, mental alertness and physical activity are impaired, and typically body fat distribution is altered with an abdominal fat accumulation. Diagnosis of GH deficiency is made by using two independent GH stimulation tests when an isolated GH deficiency is suspected and all other pituitary hormones are normally secreted. If there are clear other deficiencies than GH, a single pathological stimulation test is sufficient to diagnose GH deficiency. Upon diagnosis of GH deficiency, replacement treatment with recombinant GH may help to improve symptoms in cancer survivors classified as CrF. On the basis of increasing data concerning the safety of GH replacement (GHR) in childhood cancer survivors, there is no known increase in recurrence rates [19, 20].

Other pituitary functions are affected less likely with ACTH and TSH secretion least sensitive and the posterior pituitary function only very rarely affected.

Gonadal failure may result as primary failure following direct radiation of the ovaries or testes. The gonads are exquisitely sensitive to irradiation but may as well respond to many chemotherapeutic agents with premature failure [21]. The resulting symptoms are fatigue due to hypogonadism, lack of pubertal development, osteoporosis, infertility and sexual dysfunction. They are more easily detected in females where oligo-amenorrhea results, whereas in males the gradual decrease of testosterone levels may escape diagnosis. Hypogonadism due to primary damage to ovary or testes characteristically lead to grossly elevated gonadotropins, LH and FSH with low peripheral sex steroids (estradiol/pro-

Table 17.2 Selected instruments used to measure cancer-related fatigue, modified [16]

Scale	Description
Unidimensional (dimension: severity)	
FACT-F	13-item standalone questionnaire Studied in mixed cancer populations
EORTC QLQ C30	30-item quality-of-life questionnaire with 3-item fatigue subscale (independently validated) Independently assessed in lung cancer, bone marrow transplantation and metastatic cancer
POMS-F	65-item questionnaire with 7-item fatigue subscale Assessed in both noncancer and cancer populations
Multidimensional	
BFI	9-item numeric scale Validated for use in mixed cancer population Dimensions: severity and interference
Chalder fatigue scale (FQ)	11-item scale Validated in general practice setting Dimensions: physical and mental
FSI	13-item scale Validated in breast cancer population and mixed cancers Dimensions: severity, duration, interference
MFI-20	20-item scale Designed for use in patients with cancer, validated in Army trainees and physicians undertaking shift work as well as in patients with cancer Dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, reduced activity
MFSI-30	30-item scale Investigated in patients with breast cancer undergoing treatment and in mixed cancer population Dimensions: general fatigue, physical fatigue, emotional fatigue, mental fatigue, vigour
Revised piper fatigue scale	22-item revised version of original scale Validated in breast cancer survivors Dimensions: behavioural, severity, affective meaning, sensory, cognitive/mood
Schwartz cancer fatigue scale	28-item scale Validated in mixed cancer population undergoing treatment Dimensions: total score and physical and perceptual subscores

BFI Brief Fatigue Inventory, *EORTC QLQ C30* European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30, *FACIT* Functional Assessment of Chronic Illness Therapy, *FACT-F* Functional Assessment of Cancer Therapy-Fatigue, *FQ* Fatigue Questionnaire, *FSI* Fatigue Symptom Inventory, *MFI-20* 20-item Multidimensional Fatigue Inventory, *MFSI-30* Multidimensional Fatigue Symptom Inventory 30-item short form; *POMS-F* Profile of Mood States-Fatigue

gesterone in females where history of menstrual cycles is more important and testosterone in males). Gonadotropin deficiency may be functionally supported by an increase in prolactin which is as well observed following brain irradiation [22].

ACTH deficiency is the most important to diagnose as an adrenal crisis can be life threatening. Partial ACTH deficiency may lead to symptoms as in CrF, so all diagnostic procedures to exclude ACTH/cortisol deficiency should be widely applied if the patient underwent irradiation of >20Gy. It occurs almost never as a single deficiency but is accompanied by other pituitary deficits mainly GH and gonadotropin deficiency [18]. Furthermore, prolonged treatment with dexamethasone can suppress the hypothalamic-pituitary-adrenal axis and subsequently results in isolated ACTH insufficiency. This places patients at risk to develop hypoadrenal crisis as recovery of the HPA axis subsequent to glucocorticoid excess may take up to 2 years. A relevant ACTH deficiency is almost certainly excluded when morning cortisol levels are within the normal range (>550 nmol/L). In doubt, it can be diagnosed using insulin tolerance test, glucagon stimulation test or a short synacthen test.

Patients with symptoms of CrF who have undergone cancer treatment to the hypothalamic-pituitary axis or head and neck including the thyroid need to

be tested for thyroid dysfunction. Again irradiation is an important factor in developing primary hypothyroidism, particularly in females. In addition, new biological agents such as tyrosine receptor kinase inhibitors (TKI) are increasingly important to affect thyroid function, both via pituitary and primary thyroid mechanisms [23–26].

The diagnosis of central hypothyroidism is difficult, whereas primary failure of the thyroid can easily be detected by measurement of TSH and free thyroid hormones, namely, free thyroxine. Deficiency of TSH occurs following other hormone deficiencies, and not typically within the first 2–3 years post radiotherapy. TSH, frequently used to diagnose thyroid status, is no longer helpful as a marker of thyroid function when central hypothyroidism is suspected. Thus, diagnosis rests on low free thyroid hormones (in association with an inappropriately low/normal TSH).

Of course, total thyroidectomy for treatment of head and neck or thyroid cancer will result in postsurgical hypothyroidism and a life-long requirement for L-thyroxine replacement.

Apart from radiation damage to the hypothalamus/pituitary leading to secondary hypothyroidism, direct radiation-induced damage to the thyroid gland may result in hypothyroidism, particularly when radiation doses are >30 Gy. According to large studies, e.g. in Hodgkin patients, this will occur in app. 30% of patients [13].

Finally, isolated deficiency of anterior pituitary function particularly affecting single axes like the adrenocorticotropic or thyreotropic axis may occur in relation to lymphocytic hypophysitis induced by new immunomodulatory treatment modalities like checkpoint inhibitors [27]. These deficiencies may closely mimic CrF and need to be investigated in patients exposed to such treatment.

17.4 Treatment

Treatment for CrF aims to reduce the symptoms. If a clear underlying cause of CrF is detected such as in endocrine deficiencies, this needs to be supported as well to avoid further problems in the future. The hormone deficiency therapy will be performed as suggested by specific international guidelines.

It is important to inform patients about a possible persistence of fatigue after cancer treatment. This should include an overview of the causes and contributing factors as well as information about the difference between normal and cancer-related fatigue. Furthermore, advice on the management of fatigue-related symptoms should be offered. For instance a continuous self-monitoring of fatigue levels can be helpful for the evaluation and development of therapeutic strategies. If a specific treatment is initiated, regular reevaluations of therapy effectiveness are recommended. To date, no consistent recommendations on when to start fatigue treatment and which patient may benefit from a specific treatment are available [16].

Whether people with CrF improve over time remains unclear. There are conflicting results concerning recovery. This is mainly due to the fact that there are missing data in observational studies in respect to individually applied interventions. It is also likely that there will be periods when symptoms get better or worse. Children and young people with CrF are more likely to recover fully [7].

The general approach to CrF management, especially education and counselling, should be used for survivors of all fatigue levels. Other specific interventions are grouped into nonpharmacologic and pharmacologic interventions [28].

17.4.1 Nonpharmacologic Interventions

This group includes psychosocial interventions, exercise, yoga, physically based therapy, dietary management and sleep therapy. Psychosocial interventions and exercise have the most supportive evidence in treatment of CrF and are thus presented in more detail.

17.4.2 Exercise

Physical exercise may prevent or reduce cancer-related fatigue. Several trials demonstrated a reduction of CrF when an adequate level of phys-

ical activity after cancer treatment was initiated or maintained, respectively [29–31].

A meta-analysis on breast cancer patients undergoing different exercise programs showed significant beneficial effects of physical exercise on general fatigue but mostly on physical fatigue. The authors concluded that this might be the fatigue dimension most sensitive to physical exercise, as effects on cognitive and affective fatigue could not be demonstrated [32].

A recently published Dutch study described CrF and its relation to physical activity over time in childhood cancer patients aged 7–18 years. It provided evidence that, during a 1-year follow-up, increased physical activity was longitudinally associated with less general, sleep/rest and total CrF in this population [33]. Physical exercise aimed to improve CrF may be more successful in children than in adult patients as there is often no chronic deconditioning before the disease and children have usually more adaptability to training [34].

It is therefore recommended to encourage all patients to optimize their level of physical activity. The choice of the individual training program depends strongly on the patients' preferences as well as its physical preconditions as cancer survivors generally are at a higher risk of injury due to treatment-related late effects such as cardiomyopathy or neuropathy. As a beginning the American College of Sports Medicine recommends walking programs which seems generally safe for the majority of cancer survivors [35].

Nevertheless a consultation of a physical therapist or exercise specialist prior to the onset of a new training program is reasonable and may be supplemented by formal exercise testing.

Some patients struggle to adapt these recommendations in daily life. There are numerous causes ranging from disease-related limitations (e.g. pain, weakness) to personal issues (e.g. lack of encouragement, interest, time) and local limitations (e.g. lack of facilities) [36, 37].

To encourage exercise adherence, regular counselling as well as information on how to integrate a minimum level of regular physical activity in daily life may be beneficial for these patients [16, 38].

17.4.3 Psychosocial Interventions

There is evidence that (cognitive) behavioural therapy can reduce fatigue symptoms (e.g. dysfunctional thoughts about fatigue, poor coping strategies, sleep disturbance) in some patients. These improvements may even sustain over a long period of time [39, 40].

Furthermore, (psycho)educational therapies focussing on the comprehensive presentation of cancer-related fatigue, its symptoms and possible interventions can be beneficial for cancer survivors [41].

Therefore patients should be referred to psychosocial service providers specializing in cancer and cancer-related fatigue.

17.4.4 Other Nonpharmacologic Interventions

Complemental interventions such as yoga, physically based therapy (acupuncture and massage therapy) and mindfulness-based approaches have demonstrated effectiveness in managing fatigue [16, 42–44]. Moreover, as sleep disturbances may exacerbate CrF, some patients also benefit from sleep therapy [28].

17.4.5 Pharmacologic Interventions

Several trials demonstrated that patients benefit from psychostimulants (e.g. methylphenidate) and other wakefulness agents (e.g. modafinil) when applied during cancer treatment. However, the efficacy of modafinil on CrF showed weaker correlations compared to the results from the methylphenidate studies [28]. These agents are the most frequently prescribed drugs aiming at improving CrF in cancer survivors, although supporting evidence on their efficacy is weak and their role in the therapy of cancer-related fatigue following active treatment still needs to be evaluated [28, 45]. Antidepressants may be applied when CrF is accompanied by depression but are not recommended as a primary treatment of CrF as they did not show improvement in CrF

levels. Corticosteroids for CrF have shown effectiveness in reducing CrF but, due to their long-term toxicity, are usually only applied in a palliative care setting. Vitamins and supplements as well as complementary agents such as ginseng and guarana have been studied in the treatment of CrF but have shown no benefit or inconclusive results and are thus not generally recommended [28].

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Part II

Diagnostics in the Detection of Late Effects in Different Cancer Entities in Children, Adolescents and Young Adults

18 Late Effects After Treatment of Acute Lymphoblastic Leukemia in Childhood and Adolescence

Franziska Cuntz and Gabriele Escherich

Abbreviation

ALL	Acute lymphoblastic leukemia
B-AL	Mature B-cell acute leukemia
BFM-SG	Berlin-Frankfurt-Muenster study group
BM	Bone marrow
CAR	Chimeric antigen receptor
CI	Cumulative incidence
CNS	Central nervous system
COALL-SG	Cooperative study group for childhood ALL
EFS	Event-free survival
GVHD	Graft versus host disease
HD	High dose
HR	High risk
HSCT	Hematopoetic stem cell transplantation
MDS	Myelodysplastic syndrome
MR	Medium risk
MRD	Minimal residual disease
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PCRT	Preventive cranial irradiation
PGR	Prednisone good responders
PPR	Prednisone poor responders
PVA	Prednisone vincristine asparaginase
SG	Study group
SMN	Secondary malignant neoplasm
SR	Standard risk
TBI	Total body irradiation
TKI	Tyrosine kinase inhibitor
TRM	Treatment-related mortality

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18.1 Introduction, Epidemiology, and Clinical Features

Acute lymphoblastic leukemia (ALL) is the most common malignant disease in children and adolescents <18 years accounting for almost 25% of cases [1]. In Germany, between 550 and 600 young people are diagnosed with ALL every year. The wide majority is precursor cell leukemias, others are mature B−/T-cell leukemias. The age standardized incidence rate for ALL in children is 39 per million with an age peak of 2–4 years and a sex ratio (m/f) of 1.3 [1].

Prognostic factors that have been established and used for patient stratification into risk groups are response to treatment ("induction failure" in the 1960s established as an adverse factor, "pred-

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nisone response" after one week of treatment [2–4] since the 1980s, since the 1990s minimal residual disease (MRD)), age (>10 years) leukocyte count (>25/nL) at diagnosis (since the 1980s), presence of extramedullary disease and since the 1980s immunophenotype (Pro-B and T-ALL). Cytogenetic abnormalities such as high hyperdiploidy (51–66 chromosomes) which is detected in one third of patients with ALL and the most frequently found molecular translocation ETV6/RUNX1 (25% of patients [5, 6]) are associated with a good prognosis [7, 8], whereas t(9;22), iAMP21, MLL-translocations, and hypodiploidy are related to a higher relapse risk [7]. Increasing knowledge of the biology of ALL allows definition of new adverse prognostic markers. Among those are IKAROS (IKZF1) deletions [9] and a Ph-like subtype [10]. Some of these aberrations might be suitable as targets for individualized treatment in the future.

Refinement and, if possible, reduction of chemotherapy, advanced supportive care, and the correct allocation of patients to hematopoetic stem cell transplantation (HSCT) within multicenter studies have improved survival rates of ALL markedly. Whereas the disease was incurable in the earlier decades of the twentieth century, the probability of overall survival (pOS) now exceeds 90% [1]. Balancing undertreatment with the risk of relapse and overtreatment with the risk of acute toxicity and late effects remains a challenge. Various late effects after treatment of ALL are known, e.g., cardiac, renal, or auditive impairment, osteonecrosis, neuropsychological deficits, secondary malignant neoplasms (SMN), or dysregulation of endocrine functions. Previously reported cumulative incidences (CI) of SMN after treatment of ALL vary depending on intensity and duration of antileukemic treatment and completeness of follow-up [1], and treatment of SMN, especially in heavily pretreated patients, is difficult. The introduction of new, immune-based therapies during the recent years offers the opportunity to reduce toxicity by providing a targeted treatment. However, late effects of these new treatment options have not completely been revealed yet due to the relatively short follow-up.

18.2 Treatment of pB−/T-ALL

(Inter-)National collaborations of pediatric oncology study groups (SG) have led to a standardized yet risk-adapted treatment of patients with ALL with increasing survival rates and reduction of toxicity [11]. In Germany and other European countries, the Berlin-Frankfurt-Muenster (BFM) SG and the cooperative SG for childhood ALL (CoALL-SG) have been conducting randomized multicenter studies since 1970 and 1980, respectively.

ALL treatment consists of four main chemotherapy combination phases lasting in total 2 years. Induction treatment aims at achieving remission by using chemotherapeutics with different mechanisms of action. This is followed by the consolidation and reintensification phase to maintain remission and target more resistant subclones. After the intensive treatment phase, oral maintenance therapy is added for several months to prevent relapses or, in subgroups, HSCT (see below). For cumulative drug doses and dosage of intrathecal treatment, see Tables 18.1 and 18.2.

18.2.1 Evolution of the Different Treatment Phases for ALL

18.2.1.1 Induction and Reintensification

BFM trials were preceded by the "West-Berlin study" from 1970 to 1976, a clinical trial that combined the at the time most effective antileukemic agents (eight-drug remission induction lasting 8 weeks with prednisone, vincristine, asparaginase, daunorubicin, cyclophosphamide, cytarabine, methotrexate, and mercaptopurine called "protocol I") with central nervous system (CNS)-directed radiotherapy to control (sub)clinical CNS involvement [12]. This was followed by an antimetabolite-based maintenance phase (see below). The initial CoALL studies used a comparable, modified treatment regimen (later use of asparaginase) with the aim to reduce treatment-related morbidity and mortality (TRM) [13]. Since ALL-BFM 83, induction was preceded by a cytoreductive prednisone prephase to limit

Table 18.1 Cumulative drug doses in AIEOP-BFM ALL and CoALL protocols

Drug	Decade/protocol	Risk group	Dose	Unit
6-Mercaptopurine	BFM 80	All risk groups	1680	mg/m^2
	BFM 90/since 2000	All risk groups except HR (since 2000)	3080	
	BFM since 2000	HR	1680	
	BFM maintenance	Risk group dependent	Approx. 25,000	
	CoALL	Risk group dependent	Approx. 27,000–41,000	
6-Thioguanine	BFM 80/90/2000	All risk groups	840	mg/m^2
	ALL-BFM 2009	HR	2520	
	CoALL 80 and since 97	LR/HR	1008/2100	
	CoALL92	LR randomization, HR randomization	1400/29,650, 2100/ 26,850	
CNS irradiation	ALL-BFM 81	SR/MR	18	Gy
	ALL-BFM 81/83	HR	24 (CNS+ 30)	
	ALL-BFM 83/86	SR-1, MR1 (86)	12	
	ALL-BFM 83/86	SR-2/MR, MR2/HR (86)	18	
	CoALL since 80	LR	12–18	
	CoALL since 80	HR	16–24	
	ALL-BFM 90	MR/HR	12 (CNS+ 24)	
	CoALL since 92	HR subgroups	0–12 (CNS+ 18)	
	ALL-BFM 95/2000	MR (T-ALL)/HR	12 (CNS+ 18)	
	ALL-BFM 2009	Subgroups HR/T-ALL	12 (CNS+ 18)	
Clofarabine	CoALL 09	LR	200	mg/m^2
Cyclophosphamide	BFM 80	SR	2000–3000	mg/m^2
	ALL-BFM 83	HR	4000	
	CoALL since 80	All	1800–3600	
	BFM 90	All risk groups, except HR (since 2000)	3000	
	CoALL since 90	LR/ HR	900/3600	
	BFM since 2000	HR	3500–5000	
Cytarabine	ALL-BFM 81/83	All risk groups (81), SR/ MR (83)	1200–1800	mg/m^2
	ALL-BFM 83	HR	2400	
	CoALL 80–82	All (except LR 82)	2160–2640 (1440)	
	ALL-BFM 86	MR2	9800	
	ALL-BFM 86	HR	17,800	
	CoALL 85	LR/HR	1080/1320–25,320	
	Since ALL-BFM 86	SR/MR/MR1 (86)	1800	
	ALL-BFM 90	HR (if no SCT)	36,000	
	ALL-BFM 95	HR	24,600	
	ALL-BFM 2000	HR	25,800	

(continued)

Table 18.1 (continued)

Drug	Decade/protocol	Risk group	Dose	Unit
	ALL-BFM 2009	pB−/T-ALL HR SCT (FLA)	13,800 (23,800)	
	ALL-BFM 2009	pB−/T-ALL HR	15,000	
	CoALL since 2000	LR (randomization)	12,660 (660)	
		HR	13,320/ 25,320	
Daunorubicin	BFM 80	All risk groups	120–160 (CoALL-144)	mg/ m^2
	BFM 90/ since 2000	SR/MR	60–120	
	BFM 90	HR	180–270	
	CoALL 80	All	144–180	
	BFM since 2000	HR	150–180	
	CoALL since 2000	LR	144–216	
	CoALL since 2000	HR	144–288	
Daunoxome	ALL-BFM 2009	pB/T-ALL HR SCT/ FLA	180	mg/ m^2
Dexamethasone	BFM 80	SR	166.25–236	mg/ m^2
	BFM 80	MR/HR	236–306.25	
	CoALL 85	HR	280	
	CoALL since 89	LR/HR	140/280	
	BFM 90	SR/MR	236	
	BFM 90	HR	837–900	mg/ m^2
	ALL-BFM 2000/2009	SR/MR-PRED/pB-ALL SR/MR (2009), HR PRED 2000	236, 716	
	ALL-BFM 2000	SR/MR-DEXA/T-ALL non HR (2009), HR-DEXA	472, 1192	
	ALL-BFM 2009	pB HR SZT FLA/T-ALL HR SZT FLA, pB/T-ALL HR	526, 829	
Doxorubicin	BFM 80, CoALL 80	SR (in CoALL 82 for LR 0 mg/ m^2)	60–120	mg/ m^2
	BFM 80/90	MR/HR, SR/MR (90)	120	
	BFM 90	HR	120–360	
	ALL-BFM 2000	All risk groups (2000), pB ALL non HR/T-ALL non HR/MR	120	
	ALL-BFM 2009	pB−/T-ALL HR SZT FLA, pB/T-ALL HR	60, 160	
	CoALL since 2000	LR (HR)	0–120 (−150)	
Fludarabine	ALL-BFM 2009	pB/T-ALL HR SZT FLA	150	mg/ m^2
MHD-MTX	ALL-BFM 81/83	SR, all risk groups (83)	2000	mg/ m^2
	CoALL 80	All	0–3000	
	CoALL 82/85	LR/HR	1500/4000–9000	
	CoALL since 89	LR/HR	3000–4000	

(continued)

Table 18.1 (continued)

Drug	Decade/protocol	Risk group	Dose	Unit
HD-MTX	ALL-BFM 86/90	All risk groups, SR/MR (90)	20,000	mg/m^2
	ALL-BFM 90	HR	30,000	
	ALL-BFM 95/2000	All risk groups	20,000	
	ALL-BFM 2009	pB/T-ALL non HR	24,000	
	ALL-BFM 2009	pB/T-ALL HR SZT FLA	10,000	
Mitoxantrone	ALL-BFM 86	HR	40	mg/m^2
MTX/ARA-C/Pred i.t.	BFM 90	HR	9× (95 6×)	Age
	ALL-BFM 2000	HR	6× (CNS + 12×)	Dep.
MTX i.th.	ALL-BFM 81	Risk group dependent	10× (SR no irradiation), 6× (all others)	Age
	CoALL 80, 82	All/ 82 LR	6×/5× (− CNS–Rx), 11× (+ CNS–Rx)	Dep.
	ALL-BFM 83	Risk group dependent	8× (SR1), 10× (SR2/MR), 12× (HR)	
	CoALL 85	LR/ HR	8× (+ CNS–Rx), 14× (− CNS–Rx)/9×	
	ALL-BFM 86	All risk groups	9×	
	CoALL 89	LR/HR	18× (− CNS–Rx), 12× (+ CNS–Rx)/12×	
	ALL-BFM 90/95	SR/MR	11×, since 2000 15× (if CNS+)	
	CoALL 97	LR/HR	12×/9× (+ CNS–Rx), 18× (− CNS–Rx)	
	ALL-BFM 2000	HR	7× (CNS−), 11× (CNS+)	
	ALL-BFM 2009	pB/T-ALL non HR/SZT/FLA	11× (CNS−), 15× (CNS+)	
	ALL-BFM 2009	pB/T-ALL HR SZT	10× (CNS−), 14× (CNS+)	
	ALL-BFM 2009	pB-ALL/T-ALL HR	14× (CNS−), 20× (CNS+)	
	Since CoALL 03	LR	11× (+ CNS–Rx), 14× (− CNS–Rx)	
	CoALL 03/07	HR	8–10× (+ CNS–Rx), 14–16× (− CNS–Rx)	
Prednisone	BFM 80/90/2000	All risk groups, SR/ MR (90), SR/ MR/HR-PRED (2000)	1838	mg/m^2
	CoALL 80	LR/HR	4836–4980/5676–5820	
	Since CoALL 82	All/CoALL 82 HR/CoALL 09 intensification	1680/3360/5680	
	ALL-BFM 86	MR2	3238	
	ALL-BFM 86	HR	4638	
	ALL-BFM 90	HR	1418	
	ALL-BFM 2000/2009	SR/MR/HR-DEXA, T-ALL non HR (2009)	420	
	ALL-BFM 2009	pB-ALL non HR/T-ALL HR/pB ALL HR	1838	
Vincristine	BFM 80, CoALL 80	SR, CoALL LR	6–9, 7.2–27	mg/m^2
	BFM 80, CoALL 80	MR/HR, CoALL HR	12, 14.4–30.6	

(continued)

Table 18.1 (continued)

Drug	Decade/protocol	Risk group	Dose	Unit
	BFM since 90	SR, HR	6–12, 12–18	
Vincristine	CoALL since 92	LR/ HR (CoALL 09 intensification 13.5)	9/12	mg/ m^2
	BFM since 2000	SR/ MR, HR	9–12, 12–18	
VP-16 (Etoposide)	BFM 90	HR	1000–1350	mg/ m^2
	Since 2000	HR	500–10,000	
	Since CoALL 09	LR/ HR	165/330 (for subgroup since 2010: 1330)	

Abbreviations: *SR* standard risk, *HR* high risk, *LR* low risk, *MTX* methotrexate, *ARA-C* cytarabine, *Pred.* prednisone, *age dep.* age dependent, *i.t.* intrathecal, *CNS* central nervous system, *+CNS-Rx* with CNS irradiation, *−CNS-Rx* without CNS irradiation, *SCT* stem cell transplantation

Drug doses are displayed for treatment decades, whenever possible

BFM 80: Protocols ALL-BFM 81, 83, 86; BFM 90: Protocols ALL-BFM 90, 95; BFM 2000: Protocols ALL-BFM 2000, 2009

CoALL 80: Protocols CoALL 01–80, 02–82, 03–85, 04–89; CoALL 90: Protocols CoALL 05–92, 06–97; CoALL 2000: Protocols CoALL 07–03, 08–09

Table 18.2 Dosage of intrathecal drugs within the CoALL and AIEOP-BFM ALL protocols

Age/drug	MTX	ARA-C	PRED	Unit
<1 year	6	16	4	mg
≥1 and <2 years	8	20	6	
≥2 and <3 years	10	26	8	
≥3 years	12	30	10	

early toxicity including tumor lysis syndrome. Dexamethasone was randomized against prednisone in induction in ALL 2000 and has been used since AIEOP-BFM ALL 2009 for all T-ALL prednisone good responders.

In trial ALL-BFM 76, the reintensification element "Protocol II," a chemotherapy combination similar to the induction phase (prednisone and daunorubicin in induction versus dexamethasone and doxorubicin in "reinduction," combined with vincristine, asparaginase, cyclophosphamide, cytarabine and thioguanine), improved outcomes for high-risk (HR) patients [14] so that reintensification "Protocol III" was introduced for standard-risk (SR) patients as well [15]. Concurrently, a risk adapted reinduction has been an important element in CoALL studies [13]. The importance of reinduction in SR patients was demonstrated in ALL-BFM 83 with a superior outcome of randomized low-risk patients receiving reinduction [16, 17]. In summary, the concept of "delayed intensification" can be counted among the essential breakthroughs in ALL treatment.

Improvement of event-free survival (EFS) in HR patients was achieved by intensification of HR blocks (short, intensive chemotherapy combinations of dexamethasone, vincristine, high-dose (HD) cytarabine, HD methotrexate, cyclophosphamide, asparaginase, vindesine, daunorubicin, ifosfamide, and etoposide) and reintroduction of Protocol II as late reintensification in ALL-BFM 95.

18.2.1.2 CNS Treatment and Consolidation

In the West-Berlin study, all patients were irradiated with 8.5 Gy (neuroaxis) and after 1972 in the BFM and CoALL study group with 18 Gy (cranium and the three upper cervical segments) with dose reductions in children <2 years. All patients received intrathecal methotrexate, and this remains an essential element of treatment until today.

Several therapeutic attempts are aimed at reducing irradiation toxicity. Among these were stepwise reduction of the irradiation dose, narrowing of the irradiation field (craniospinal versus cranial), and limitation of the indication for irradiation by identification of patients with high CNS relapse risk (CNS positive, high white blood

count [WBC], T-ALL). Intensification of consolidation treatment (protocol M) by introduction of HD-methotrexate (4 × 5 g/m²/24 h) in ALL-BFM 86 [18] enabled omission of preventive cranial irradiation (pCRT) in SR patients. In AIEOP-BFM ALL 2000, only patients with T-ALL and HR patients received pCRT. In AIEOP-BFM ALL 2009, pCRT was omitted in T-ALL patients with adequate prednisone response as well as pB-ALL patients of the HR group with favorable MRD response. Patients <2 years no longer received pCRT due to the high rate of radiation-associated late effects.

The CoALL SG achieved risk-adapted treatment deintensification and replacement of CNS irradiation through MHD-methotrexate (1 g/m²), HD-cytarabine, and intrathecal treatment also during maintenance therapy.

18.2.1.3 Maintenance Treatment

Maintenance treatment consists of daily 6-mercaptopurine and weekly methotrexate with the therapeutic aim of 2–3/nL WBC. Duration of maintenance, use of drug pulses, and choice of antimetabolite differed over the last decades. The randomized use of vincristine and prednisone pulses had not shown benefit for SR patients in ALL-BFM 79 and patients in CoALL 80 [13, 19]; neither did dexamethasone/vincristine pulses for MR patients in ALL-BFM 95 [20]. A by 6 months shortened maintenance treatment (18 months total treatment duration) which has been randomized against a 24 months total treatment duration in ALL-BFM 81 and 83 was associated with a higher event rate [21]. The use of 6-mercaptopurine was randomized against 6-thioguanine in CoALL 92, COG, and UKALL studies with EFS-benefit of 6-thioguanine for males <10 years old but no difference in OS [22].

18.2.2 Risk Stratification and Risk-Adapted Treatment

Results and treatment outcomes of the mentioned multicenter studies revealed risk factors that were used for patient stratification into risk groups and, subsequently, risk-adapted treatment. Both BFM and CoALL SG soon aimed at reducing acute and long-term toxicity and treatment burden for low-risk patients and intensifying, as much as necessary, treatment for HR patients.

Early in vivo treatment response (prednisone response) after 1 week of prednisone pre-phase plus one dose of intrathecal methotrexate was prospectively evaluated and identified as important prognostic factor in ALL-BFM 83. Prednisone poor responders (PPR, patients with >1000 blasts/μL blood at day 8 of therapy) accounted for approximately 10% of patients and had an inferior prognosis [3].

In ALL-BFM 95, a new stratification strategy based on age, initial WBC, cytogenetics, immunophenotype, and prednisone response was introduced [23]. SR patients tolerated a significant reduction of the anthracycline dose with excellent EFS rates.

Treatment intensity in CoALL consolidation differs between low- and high-risk (>10 years, > 25/nL WBC and Pro-B or T-ALL) patients (four versus six consolidation elements and less intensive reinduction) aiming at preventing toxicity in favorable-risk groups.

In AIEOP-BFM ALL 2000, patient stratification and treatment adaptation due to early molecular response to treatment (MRD) were prospectively applied, as well as in CoALL 07–03. Therefore, patient stratification was substantially changed and EFS rates further improved. For patients being MRD negative at the end of induction, reinduction therapy was markedly reduced since CoALL 07–03 without a decrease in EFS.

18.2.3 Implementation of Strategies to Avoid and Reduce Late Effects of Treatment

With satisfying survival rates, BFM/CoALL trials were designed to reduce or avoid not only acute but also late toxicities and adverse effects of treatment. Treatment stratification became more and more refined.

A major milestone was the stepwise reduction of the cranial irradiation dose and limitation of pCRT indication (see above). The gradual reduc-

tion in CNS irradiation led to a decreased incidence of brain tumors as SMN [24].

Another approach was the dose reduction of chemotherapeutic agents, e.g., anthracyclines, which have been associated with an increased risk of cardiomyopathy [25, 26]. Since CoALL trial 06–97 omission of anthracyclines during delayed intensification has been performed for patients, with excellent prognosis, without jeopardizing efficacy.

Reduced-intensity delayed intensification was randomized against standard-intensity delayed intensification in AIEOP-BFM ALL 2000 in SR patients, resulting in an increased relapse risk within the reduced treatment group [27].

Late effects: Numerous long-term sequelae after (frontline) treatment for ALL have been reported. Steroid treatment has been associated with development of osteonecrosis [28]. Irradiation significantly increased the risk of SMN [29, 30], especially if performed at a young age [31]. A strong association of SMN and previous treatment with alkylating agents (cyclophosphamide, ifosfamide) has been shown [32]. Additionally, drugs as etoposide or 6-mercaptopurine as well as germline predisposition syndromes may favor development of SMN. The most frequent SMN after ALL were MDS/AML (9.3%, long-term follow-up of German Childhood Cancer Registry), astrocytoma (5.2%), and other brain tumors (3.9%) with a median time from start of primary treatment to diagnosis of SMN of 6 years [33]. Anthracyclines have been linked to cardiac impairment and vinca-alkaloids to peripheral neuropathy [34], and an overall increased incidence of chronic musculoskeletal, cardiac, or neurological medical conditions [35] after treatment for ALL has been described.

18.2.4 Current Treatment Regimen for ALL in Germany

Newly diagnosed patients are included into CoALL 08–09 (2010–2019) or AIEOP-BFM ALL registry (since January 01, 2017, until opening of AIEOP-BFM ALL 2017).

In CoALL 08–09, the MRD-based cytotoxic efficacy of clofarabine versus HD cytarabine is tested in a randomized manner [36]. Clofarabine is a purine analogue used since 2000 for refractory and relapsed ALL and has been shown to be effective in combination with etoposide and cyclophosphamide [37]. The frequency of infectious complications after a randomized use of doxorubicin versus daunorubicin during reinduction is evaluated [*Haematologica*, under submission].

The most recent BFM-study, AIEOP-BFM ALL 2009 (recruitment completed), aimed at further reducing the anthracycline dose in induction in SR patients, whereas induction treatment in T-ALL patients and PPR was intensified.

18.3 Treatment of B-AL

Mature B-cell leukemia (B-AL) accounts for 1% of malignancies in children and adolescents [1]. The molecular features are that of mature B-cell non-Hodgkin lymphoma (B-NHL), so B-AL is treated accordingly (currently within clinical trial B-NHL 2013). Until the 1970s, survival rates were poor [38]. Results from study BFM-NHL 75 demonstrated the efficacy for ALL-BFM-type chemotherapy for T- but not for B-NHL. Treatment strategy was adapted to the high proliferation rate of the disease, and thus high-intensity chemotherapy courses with short time intervals in between and efficient CNS-directed treatment were applied [38]. 5y OS for B-AL in children under 15 years of age is currently reported with 88% [1]. Total treatment duration for B-AL is 4–6 months of intensive chemotherapy blocks. A cytoreductive prephase with steroids, cyclophosphamide, and triple (methotrexate/prednisolone/cytarabine) intrathecal treatment is followed by short, intensive chemotherapy combination courses (dexamethasone, methotrexate, cyclophosphamide, ifosfamide, cytarabine, etoposide, doxorubicin, vincristine, and vindesine). Almost all pediatric B-NHL express CD20. Therefore, the anti-CD20 antibody rituximab is suitable as a targeted treatment for this disease entity. Rituximab has been administered as a single agent within a phase II upfront window study from 2004 to 2008 [39]. CI of SMN after B-AL in children under 15 years of age has been reported with 8.4% within 30 years [1].

18.4 Treatment of Infant ALL

ALL in infants <1 year of age at diagnosis is rare (4% of cases), and inferior outcomes of this subgroup mainly due to relapses but also because of a higher incidence of TRM have been described [40]. In the 1980s, treatment consisted of intensive chemotherapy blocks, followed by maintenance treatment, resembling the regimen for B-ALL. In the 1990, infants with ALL were treated as HR patients. Since the establishment of the INTERFANT group in 1999, infants with ALL have been included into an international protocol [41]. The majority of infant ALL are immature pro-B-ALL with MLL-rearrangement [42]. The susceptibility of the malignant cells is different from patients >1 year; this accounts especially for cytarabine which is metabolized in a different way [43]. Therefore, the INTERFANT scheme contains a substantial higher amount of cytarabine already in induction as compared to BFM or CoALL protocols. In INTERFANT 2006, AML-like chemotherapy blocks with mitoxantrone and etoposide were randomized in MR and HR patients (results are still pending). Risk stratification is based on presence or absence of MLL rearrangement, age (more or less than 6 months), leukocyte count, and prednisone response. For HR and patients with poor treatment response, HSCT is indicated. The role of HSCT in infants remains difficult despite or because of the overall dismal prognosis with early relapses and high TRM; however patients with poor prognostic factors treated with the INTERFANT 99 protocol had a significantly better DFS with HSCT [44]. Because of the high SCT-related mortality in infants with ALL, a less toxic conditioning regimen with busulfan, thiotepa, and fludarabine is recommended.

18.5 Treatment of BCR/ABL+ ALL

The translocation t(9;22)(q34;q11), found in 3–5% of patients with ALL, equals the BCR/ABL1 rearrangement known as "Philadelphia chromosome" and has been associated with a poor prognosis in ALL patients [45]. This patient group is currently being treated with the national chemotherapy backbone for HR patients and additionally with the tyrosine kinase inhibitor (TKI) imatinib within trial EsPhALL [46]. Integration of TKI in 2003 into treatment improved prognosis for this patient group. TKI were administered subsequently for 14 days after chemotherapy blocks until 2010 and since then concurrently with chemotherapy, continuously for 2 years in total or until 1 year after HSCT. Children with BCR/ABL+ ALL were subsequently transplanted until 2015. For patients with a very good treatment response, omission of HSCT is currently evaluated.

Late effects after treatment with TKI have been described in the context of CML treatment (see Chap. 20).

18.6 Treatment of Relapsed ALL

With improved frontline treatment for children with ALL, relapse numbers have decreased from ~25% in 1983 when relapse trials were commenced [47] to currently 5–15% of cases, and treatment of relapsed or refractory ALL remains challenging with leukemic cells more resistant to chemotherapy [48]. Relapsed ALL contributes to a significant proportion of cancer-related deaths [49], and EFS rates for HR patients have been reported as low as 30%. Stratification of patients is based on time point and site of relapse (BM, extramedullary, or combined) and immunophenotype. Treatment response monitored by MRD is of high prognostic value also at relapse [50, 51] and has been used for therapeutic decision-making (allocation of SR patients to HSCT and optimization of remission on HR patients before HSCT).

Standardized treatment of relapsed ALL in Germany and other European countries has been introduced with the pilot protocol ALL-REZ BFM 1983. Relapse treatment consists of intensive short polychemotherapy blocks containing drugs also used in first-line treatment and non-cross-resistant chemotherapy to achieve a second remission. In ALL-REZ BFM 2002, induction treatment was two polchemotherapy blocks

(containing steroids, vincristine, intermediate-dose methotrexate, asparaginase, triple intrathecal treatment, and high-dose cytarabine). Intermediate-dose methotrexate (1 g/m^2/36 h) has been established as feasible application for this drug at relapse [52]. For consolidation, patients received either rotating short chemotherapy courses or a continuous element containing idarubicin. This was followed by further short chemotherapy blocks and maintenance treatment or, for HR patients and patients with poor treatment response, HSCT [53].

CNS-directed treatment with intrathecal triple therapy (methotrexate, prednisolone, cytarabine) is an essential part of ALL relapse protocols. PCRT (plus three upper cervical segments) with 18 Gy (in children <2 years 12 Gy) plus prolonged triple intrathecal chemotherapy was introduced in ALL-REZ BFM 87 after an excess of CNS relapses after isolated BM relapse treated without irradiation in the preceding trial. This significantly reduced the occurrence of CNS relapses and improved outcome [54]. Irradiation dose in patients with BM relapse was reduced to 12 Gy in ALL-REZ BFM 90. In the most recent trial IntReALL2010, pCRT is omitted in patients with isolated BM relapse and replaced by intrathecal chemotherapy during maintenance treatment. Patients with CNS relapse received craniospinal irradiation up to 24/20 (cranial/ spinal) Gy in ALL-REZ BFM 83–87, and reduced doses of 18/18 Gy in following trials, depending on age and previous irradiation dose. Since ALL-REZ BFM 95, only cranium and upper three cervical segments were irradiated although craniospinal irradiation was permitted.

Local treatment for testicular relapse included removal of a clinically involved testis and irradiation with 15/18 Gy of a contralateral clinically not involved and by biopsy negative/positive testis, respectively. This allows spontaneous puberty in a number of patients [55].

The duration of maintenance treatment with oral 6-mercaptopurine and intravenous methotrexate (after 2002 oral methotrexate) varied during the ALL-REZ studies with a total treatment duration between 1.25 and 2.5 years. In ALL-REZ 96 and 2002, MR patients (risk group S2) received additional reinduction pulses with etoposide.

Patients with relapsed ALL are currently treated within the IntReALL2010 trial. For SR patients, the most effective treatment strategies of the largest study groups are randomized, and the efficacy of an anti-CD22 antibody (eprazutumab) is tested. Maintenance treatment includes, in one of the treatment arms, vincristine and dexamethasone pulses. Overall treatment duration is ~2.5 years. The proteasome inhibitor bortezomib has demonstrated synergistic activity with steroids and chemotherapy and will be integrated into induction treatment for HR patients [56]. Before HSCT, HR patients may be subjected to an investigational window randomizing blinatumomab against a conventional chemo block.

18.7 New Agents in Treatment of ALL

While most agents used for childhood (relapsed) ALL were developed before the 1980s [57], increasing molecular and genetic knowledge allows development of new drugs with more specific antileukemic activity. Among those are TKIs, proteasome inhibitors, mTOR or FLT3 inhibitors, apoptosis regulators, (un)conjugated monoclonal antibodies, and genetically modified immune effector cells. Ideally, the integration of new agents into treatment will replace conventional chemotherapy and thereby reduce acute and long-term toxicity of chemotherapy. Humoral immunotherapy includes the use of (un)conjugated monoclonal antibodies. Blinatumomab is a bispecific T-cell engager binding to CD19/CD3 [58] which exerts its cytotoxic effect in close proximity to the CD19-expressing tumor cell. Eligible pediatric patients with relapsed/refractory ALL in Germany have been treated with blinatumomab since 2012. A phase I/II study revealed antileukemic activity across all age groups with acceptable toxicity [59]. Inotuzumab ozogamicin is a humanized anti-CD22 antibody which has shown superior results as standard treatment in adults with relapsed ALL [60]. Cellular immunotherapy

comprises genetically modified immune effector cells expressing chimeric antigen receptors (CAR) that enhance cytotoxicity against otherwise resistant tumor cells. (CAR-)T cells induced high remission rates in children and adults with relapsed ALL. Both inotuzumab ozogamicin and CAR-T cells have only been used in very few patients in Europe so far.

Few new agents are available and attractive for use in primary and relapsed/refractory T-ALL. Nelarabine is a purine analogue with specific activity on T-lymphocytes that showed efficacy as monotherapy in adults and children with relapsed T-ALL [61] and is being integrated in several studies for (relapsed) ALL in children and adults worldwide. Severe acute neurotoxic side effects have been observed in some patients.

Main challenges of these new treatment approaches were acute toxicities so far not observed in ALL treatment, e.g., severe cytokine release syndrome [62], as well as severe acute neurotoxicity different from what is known after chemotherapy [60, 63]. Late effects may result from sustainable modulation of the immune system with B-cell aplasia but will be revealed in future years when long-term follow-up is possible.

18.8 HSCT in Children with ALL

Despite successful treatment of most patients with ALL, HR patients require intensive therapy after achieving CR with chemotherapy. Allogeneic HSCT can provide antileukemic disease control exhibited by graft-versus-leukemia effect but is associated with TRM of 5–10% [64] as well as various late effects. Allogeneic HSCT has been applied since the late 1980s in a small number of patients and more uniformly in the following studies. Indications for HSCT differed over the years and have altogether decreased. Currently, less than 10% of children with frontline ALL are eligible for HSCT.

For decades, total body irradiation (TBI) has been the most frequently used myeloablative regimen in patients with ALL before HSCT. Other conditioning regimens included TBI/etoposide, TBI/cyclophosphamide, busulfan, fludarabine, treosulfan, and thiotepa. GvHD prophylaxis was performed with cyclosporine, MTX, and antithymocyte globulin. During the last decade, better matching of the donors by HLA typing led to less severe graft-versus-host disease (GvHD), and intensified supportive care (e.g., antifungal and anti-infectious treatment) helped in improving the outcomes after HSCT. Since 2003 transplant procedures are recommended within the European ALL-SCT trial.

Among late effects after TBI are growth impairment (especially if TBI was performed in patients <10 years), SMN, development of cataract, and infertility [65, 66]. Busulfan has been linked with gonadal insufficiency and pulmonary complications. The reduced immune surveillance after HSCT can lead to uncontrolled (EBV-associated) proliferation of B-cells and development of SMN. Chronic GVHD can affect multiple organs and thereby decrease quality of life and life expectancy significantly.

18.9 Recommendations for Follow-Up of Patients Treated for ALL

As ALL therapy is adapted to risk groups, intensity and duration may differ significantly. Follow-up of patients after treatment for ALL should therefore be performed in a risk-adapted way, depending on the received treatment. Important considerations are time point and treatment intensity of the used regimen, use of prophylactic or therapeutic irradiation, HSCT with or without TBI, and individual risk factors such as pre-existing conditions. Follow-up includes (of course not all of the following each time) assessment of physical status, growth and weight, vital parameters, puberty stages, blood sampling (blood count, clinical chemistry, endocrinological tests), urine sampling, ECG/echocardiogram, EEG, neuropsychological testing, and auditive and ophthalmological assessment. In year one after end of treatment, monthly visits are recommended, during year two three-monthly, during year three twice/year, and after year four once/year.

18.10 Summary of Late Effects

All patients should be informed according to theier risk group on late effects. The survivorship care has to be adjusted to the many treatment changes during decades for example in minimizing CNS irradiation. Most important CNS toxicities are neurocognitive impairments, endocrine disorders and secondary tumours mainly after irradiation. Special attention should be given also on cardiovascular diseases, the metabilic syndrome and osteonecrosis. For further information please use: https://www.cancer.gov/types/childhood-cancers/ccss.

The reader is also referred to the Chaps. 1, 2, 7–9, 12–14, 16, 17 of this book.

For long-term follow-up an interdisciplinary care team is of utmost importance especially in the adult age of survivors.

18.11 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

18.12 Recomendation for a Long-Term Follow-Up Schedule

Long-term follow-up is performed according to the recommendations of the International Guideline Harmonisation Group (www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the LESS group (www.nachsorge-ist-vorsorge.de) in Germany.

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19 Late Effects after Treatment of Acute Myeloid Leukemia in Childhood and Adolescence

Ursula Creutzig and Wolfgang Hiddemann

19.1 Introduction

Acute myelogenous leukemia (AML) in children and adolescents is significantly less frequent than acute lymphoblastic leukemia (ALL), with a percentage of 15–20% of all leukemias [1]. Even if chemotherapy resistance is higher in AML than in ALL, treatment results in children with AML have significantly improved in the last 30 years. The 5-year survival probability is currently over 70% in children with AML in Germany [2]. Therapy is extremely intensive with high doses of chemotherapy especially with anthracyclines and purine analogs (such as cytarabine) and with hematopoietic stem cell transplantation (HSCT) in selected patients. A cranial irradiation was part of the therapy schedule in the AML-BFM protocols until a few years ago. However, intensive treatment is the only way to achieve high survival rates.

Recent reports on late effects indicate that 50% of survivors of childhood AML, who received chemotherapy only, suffered from chronic health conditions after 20 years of follow-up [3]. Late effects are related to the individual therapy modality (chemotherapy, radiation, HSCT) and may affect all organs. In patients with AML, the main complications include cardiopulmonary toxicities, endocrine dysfunction, renal and gastrointestinal impairment, and subsequent malignancies. According to the analysis of the children's oncology group (CCG), severe or life-threatening chronic health conditions are significant more frequently in the allogeneic HSCT group compared with survivors of childhood AML receiving only post remission chemotherapy (33% vs. 16%, $p = 0.02$) [4]. However, here we will focus on possible late effects, which can be traced back to the given chemo- or radiation treatment. Details on late effects after HSCT and recommendations for follow-up are reported elsewhere [5, 6].

19.2 AML Therapy

AML therapy in children and adults starts with intensive remission induction treatment, which contains anthracyclines (daunorubicin, doxorubicin, idarubicin or liposomal daunorubicin) and cytarabine, and in some protocols, a third drug like etoposide is also supplemented [7]. This kind of cytotoxic therapy is required to achieve remission. It always results in transient but severe myelosuppression with a risk of bleeding and infection. After induction therapy, further intensive post-remission courses are required to eliminate residual leukemia cells. In general, 4–5 intensive

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courses, called consolidation and/or intensification, are administered together with intrathecal therapy for CNS treatment. CNS irradiation was standard in the AML-BFM studies until 2010. The need for a subsequent, less intensive, maintenance therapy is controversial. An allogeneic HSCT may be necessary as a form of intensification for maintaining remission in high-risk patients [7].

19.3 Late Treatment Effects

Possible serious late effects include cardiomyopathy after treatment with anthracyclines, neurotoxicity after administration of vincristine and/or high-dose cytarabine, and hepatotoxicity after mitoxantrone and/or cytarabine. Cranial irradiation may particularly affect the endocrine system. One of the most severe sequelae of cancer is secondary malignancy. In more than 1800 patients of the AML-BFM studies (1993–2010), the cumulative incidence of secondary malignancies is approximately 2% after 10 years (unpublished results).

19.3.1 Cardiotoxicity

Anthracyclines are, besides cytarabine, the most effective antineoplastic drugs in AML. For both drugs, dose intensity and cumulative doses are especially important for achieving high survival rates. However, the use of anthracyclines is limited by toxic cardiomyopathy resulting in irreversible myocyte damage with both acute and subacute manifestations [8].

Anthracycline-associated cardiomyopathy can be divided into early and late cardiotoxicity. Early cardiotoxicities can happen immediately after the anthracycline administration and are both dose- and schedule dependent. These injuries may cause transient tachycardia, dysrhythmias, and non-specific electrocardiography changes. There are conflicting reports whether these abnormalities are predictive of the subsequent development of chronic toxicity [8–10].

Late cardiotoxicity may occur after more than 1 year after the end of treatment [9] and correlates with the administered cumulative dose of anthracyclines [8, 9]. The clinical manifestation is primarily congestive heart failure which may occur with other manifestations, e.g., arrhythmia and pericardial effusion.

Due to the dose-related cardiotoxicity which occurs already at cumulative doses of 300 mg/m^2 (given as daunorubicin dosage), the cumulative dose of anthracyclines was generally risk-adapted in the AML-BFM therapy protocols to 300–450 mg/m^2, and anthracyclines were given as 1- to 4-h infusions of anthracyclines with the assumed lowest cardiotoxic potential or given twice daily. [11]. Recently, liposomal anthracyclines were introduced in the AML-BFM studies. Outcome results with liposomal daunorubicin were comparable with those of idarubicin; however, the cardiac toxicity profile of liposomal daunorubicin was favorable even with an increased cumulative dose [2]. However, only early cardiotoxicity, which was low after induction in both arms, was evaluated. Results for long-term anthracycline cardiotoxicity were still lacking. Results from the prior AML-BFM trials (mainly with idarubicin treatment) showed a relatively low rate of early clinical and subclinical cardiotoxicity, and the 11-year cumulate incidence of late clinical cardiotoxicity was 2.5% [11]. Current data on acute and long-term cardiotoxicity—although preliminary—clearly reveal that an induction dose of 3 × 80 mg/m^2/day L-DNR does not increase cardiotoxicity. Cardioprotection with dexrazoxane might be another option to reduce anthracycline cardiotoxicity [12].

Our studies and others show that cardiomyopathy can occur many years after completion of therapy and that the onset may be spontaneous or coincide with exertion or pregnancy. Risk factors known to be associated with anthracycline-related cardiotoxicity include mediastinal radiation, uncontrolled hypertension, exposure to other chemotherapeutic agents like cyclophosphamide, younger age, and female gender. In general, cumulative dosages above 300 mg/m^2 in patients younger than 18 years of age at the time of treatment and ≥550 mg/m^2 in older patients are associated with significant later cardiac toxicity [13, 14].

The reader is also referred to Chap. 1 of this book.

19.3.2 Hepatotoxicity

Hepatotoxicity may be caused by high-dose cytarabine or infection (chronic viral hepatitis). It was also described after the application of 6-thioguanine, which is used during maintenance in the AML-BFM studies. However, in contrast to studies in ALL, liver toxicity with the clinical symptoms of hepatic veno-occlusive disease [15] has not been reported in these studies, which may be due to a lower dosage of the drug.

The reader is also referred to Chap. 5 of this book.

19.3.3 Neurotoxicity

Neurotoxicity, e.g., peripheral neuropathy after administration of vincristine, was rarely seen in the past. Vincristine is no longer included in the AML-BFM protocols for more than 12 years.

High-dose cytarabine may rarely cause leukoencephalopathy. Rubin et al. reported an association between the occurrence of neurotoxicity and elevated serum creatinin, increasing age, and alkaline phosphatase [16].

19.3.4 Endocrine Function

The endocrine system is particularly susceptible to the long-term effects of radiotherapy, which affect the normal function of the hypothalamic-pituitary axis, the thyroid, and the gonads [13]. Endocrinological late effects were most frequently seen after HSCT (32% of patients grade 3/4) and were, however, also found after cranial irradiation and chemotherapy (14.5% of patients) [17].

Deficiency of hypothalamo-pituitary hormones may occur after low-dose cranial irradiation (18–24 Gy). However, the cumulative incidence of further functional deficits in this group is much lower than after a higher-dose cranial irradiation [18].

Cranial irradiation can affect the normal function of the hypothalamic-pituitary axis, the thyroid, and the gonads. It may induce hypopituitarism, e.g., deficiency of one or more anterior pituitary hormones like gonadotropins [luteinizing hormones (LH), follicle-stimulating hormone (FSH)], adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), and growth hormone (GH)]. Premature or early pubertal development after low-dose cranial irradiation is usually observed only in a minority of the girls, but not in boys [18].

Growth hormone (GH): Children and adolescents who received low-dose cranial or craniospinal radiotherapy (18–24 Gy) are significantly more likely to show growth disturbances than non-irradiated patients [18]. This has been found in ALL patients with abnormalities of GH secretion even 25 years after prophylactic CNS irradiation [19]. The effects on growth are likely to be age-related, with a poorer outcome (final high score) at a lower age at diagnosis and therapy [20]. However, even when the majority of patients will have a normal final growth, GH-deficient adults complain of fatigue and have abnormal body composition (fat mass is increased and lean mass decreased), and they are osteopenic and show an increased cardiovascular risk profile [13]. GH is important for skeletal health especially in the years after achieving final height.

It has been shown that in adolescents treated for GH deficiency during childhood and receiving further GH substitution, the rate of bone marrow mass accrual was doubled compared to patients who got no further GH therapy [21].

The reader is also referred to the Chaps. 7, 8, 11–13 of this book.

19.3.5 Endocrine Function and Fertility

According to the report from Leung et al., hypogonadism and infertility were rarely seen after chemotherapy with or without cranial irradiation in contrast to patients with stem-cell transplantation. Only one male (without stem-cell transplantation) failed to have a child due to testicular irradiation after bilateral testicular relapse [20].

The reader is also referred to the Chaps. 9, 10 of this book.

19.3.6 Neuropsychological Sequelae

Neuropsychological sequelae have been compared in CNS-irradiated (12–18 Gy) vs. non-irradiated children with AML. There was no significant intellectual impairment in children with cranial irradiation when compared to non-irradiated patients. However, more irradiated patients reported learning problems and subjective concentration deficits. This was a trend ($P = 0.18$) in girls and in younger patients (<5 years) [22]. These late effects are less impressive compared to ALL patients who suffered from more intellectual and educational sequelae of cranial irradiation [23]. However, in ALL, several factors may explain the differences: (1) the median age is lower for children with ALL (4–5 years) as in AML (8–9 years), a time when brain development or modulation is largely completed, and (2) in the earlier ALL therapy protocols, usually 24 Gy was used, whereas in AML only a radiation dose of 12–18 Gy was applied depending on age.

The reader is also referred to the Chaps. 15–17 of this book.

19.4 Quality of Health

The quality of health in survivors of childhood AML treated with chemotherapy only was reported to be good and comparable with their siblings. Many survivors were smoking which may increase the risk of late effects [24].

The reader is also referred to the Chap. 43 of this book.

19.5 Recommendations for Aftercare

In late follow-up diagnostics, specific examinations are necessary for the detection of organ-related late sequelae: cardiological (anthracycline cardiomyopathy), endocrinological (by alkylated drugs and radiotherapy), hepatic (caused by cytarabine or infectious), and central nervous system examinations (after cranial irradiation).

19.6 Recommendations for Long-Term Follow-Up

Recommendations for screening were published from the Children's Oncology Group (COG) as long-term follow-up guidelines (http://www.survivorshipguidelines.org/).

Patients exposed to anthracyclines should undergo monitoring for late-onset cardiomyopathy using serial noninvasive testing (echocardiogram) and physical examination. The frequency of echocardiographic screening can range from 1 to 2 to every 5 years (http://www.ighg.org/), depending on cumulative anthracycline dose and age at exposure. Pregnant women with prior exposure to anthracyclines should be monitored closely, since changes in blood volume during the third trimester could add significant stress to an already compromised myocardium. Lifestyles that promote good heart health should be recommended to all survivors, including a regular exercise program, dietary recommendations, and screening for (and aggressive management of) dyslipidemia, hypertension, and diabetes [6]. Further specific recommendations for monitoring, based on age and therapeutic exposure, are delineated within the Children's Oncology Group's (COG) long-term follow-up guidelines (http://www.survivorshipguidelines.org/).

Screening recommendations for radiation-related second cancers include careful physical examination of the skin and underlying tissues in the radiation field [6].

19.7 Therapy Recommendations

General therapy recommendations are not useful, since chronic health conditions differ depending on differences in therapy intensity or individual condition, including age at treatment, which will influence these advices.

Special recommendation in case of growth deficiency: Survivors with premature puberty and concomitant growth hormone deficiency achieve a better final size by the combined use of growth hormone and gonadotropin-releasing hormone

agonists (GnRH) with the aim of a temporary suppression of puberty progress [25]. There is evidence that growth hormone therapy in the adult age positively affects the quality of life and improves metabolic parameters such as body fat mass, plasma lipid status, and bone density to a limited extent [18].

Finally, it has to be mentioned that most AML patients have none or rarely chronic health conditions if no stem-cell transplantation was performed. Long-term survivors should avoid tobacco, alcohol, and marijuana exposure, because this exposure is associated with a substantial health risk, and cancer survivorship may compound this risk [26].

19.8 Recomendation for a Long-Term Follow-Up Schedule

Long-term follow-up is performed due to the recommendations of the International Guideline Harmonization Group (www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and due to the LESS study (www.nachsorge-ist-vorsorge.de) in Germany.

19.9 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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20 Side Effects and Sequelae of Treatment for Chronic Myeloid Leukemia in Childhood and Adolescence

Meinolf Suttorp and Markus Metzler

20.1 The Majority of Patients with Chronic Myeloid Leukemia (CML) Probably Needs Lifelong Treatment

20.1.1 CML as a Model Disease for Oncology

In the past until to the end of the last millennium, CML—representing a hematopoietic stem cell disorder—was curable by allogeneic SCT only [1]. Introduction of the TKI imatinib as a new treatment option in 1997 dramatically improved the median survival probability from previously 50–60% to >90% [2]. Tyrosine kinase inhibitors (TKIs) administered orally block the activity of the BCR-ABL1 oncogen, thus eliminating all clinical signs of the leukemia within weeks. This is followed by a cytogenetic remission (no Ph + detectable) within 6–12 months. The achievement of a molecular minimal residual disease (MRD) threshold level below the ratio 0.1% BCR-ABL1/housekeeping gene at a defined time point ("milestone of response") is associated with a good prognosis [2, 3]. Failure of first-line treatment with imatinib due to development of resistance or drug intolerance may occur with an overall probability of 30% in all patients; however, second- or third-generation TKIs have been successfully applied in these situations [4]. Today, three out of five TKIs (imatinib, nilotinib, dasatinib) are approved for front line use in children [5–7]. As of March 2019, a phase 1/2 trial on bosutinib is ongoing, but ponatinib so far is used off-label only in minors.

CML in childhood and adolescents is rare; approximately 20 new cases younger than 18 years are diagnosed in Germany annually [8]. The etiology of CML in childhood remains obscure; contrasting acute leukemia a missing concordance in twins points to a "first hit" *post-partum* [9]. Single rare cases of CML diagnosed as secondary neoplasm following antiproliferative treatment of a primary cancer have also been described in children [10–12]. Late effect surveillance programs in these rare cases should follow guidelines established for the primary cancer (see other chapters within this book) and should be adapted to the ongoing CML treatment [13].

After having achieved a prolonged period of deep molecular remission, stopping TKI treatment can be offered to 20–30% of all patients with CML. Without further treatment, maintenance of CMR is achieved in 40–50% of adult cohorts [14, 15], while the success rate seems to

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be considerably lower in children [16]. However, for the majority of cases to achieve this goal—as shown by mathematical models describing the eradication of the malignant clone by TKIs—treatment might be necessary for more than 2–3 decades [17].

CML has become a model disease in oncology. The highly probable scenario of necessity for a lifelong treatment in most patients to control the malignant cell clone instead of eradicating it sharply separates CML from other malignant diseases dealt with in the context of this book. Monitoring of "late" effects of an ongoing antineoplastic TKI treatment is a novelty in pediatric oncology. Compared to other pediatric malignancies with an accumulated experience of late effects after treatment covering now >5 decades, the rare number of pediatric CML cases and the relatively short TKI era since the year 2000 contribute to the difficulties in describing the "untargeted consequences of targeted treatment." Systematic investigations on TKI late effects in adults are missing, and the cumulative toxicity of ongoing exposure in a growing organism is presently hard to be judged on [18, 19].

20.1.2 Late Effects in Patients with CML Treated with Stem Cell Transplantation (SCT)

Present and future management of late effects has to take into account older patients who in the 1980 may have been treated for prolonged time intervals with busulfan and/or hydroxyurea and/or interferon before undergoing SCT (Fig. 20.1). From 1990 onward, with increasing numbers of suitable marrow donors, the majority of patients underwent transplantation within a year from diagnosis [20, 21]. Late effects of SCT in CML do not differ from those observed after SCT because of other indications and depend on the selected conditioning regimen and if complicated by graft-versus-host disease (GvHD) on its severity and duration. These SCT-specific late effects are dealt with in another chapter of this book. It remains unclear so far as to which extent a prolonged treatment with CML-specific drugs (busulfan, hydroxyurea, interferon) preceding SCT may cause specific late effects. As far as busulfan is concerned, data are published sparsely [22]. Hydroxyurea is also used for long-term treatment of children with sickle cell disease.

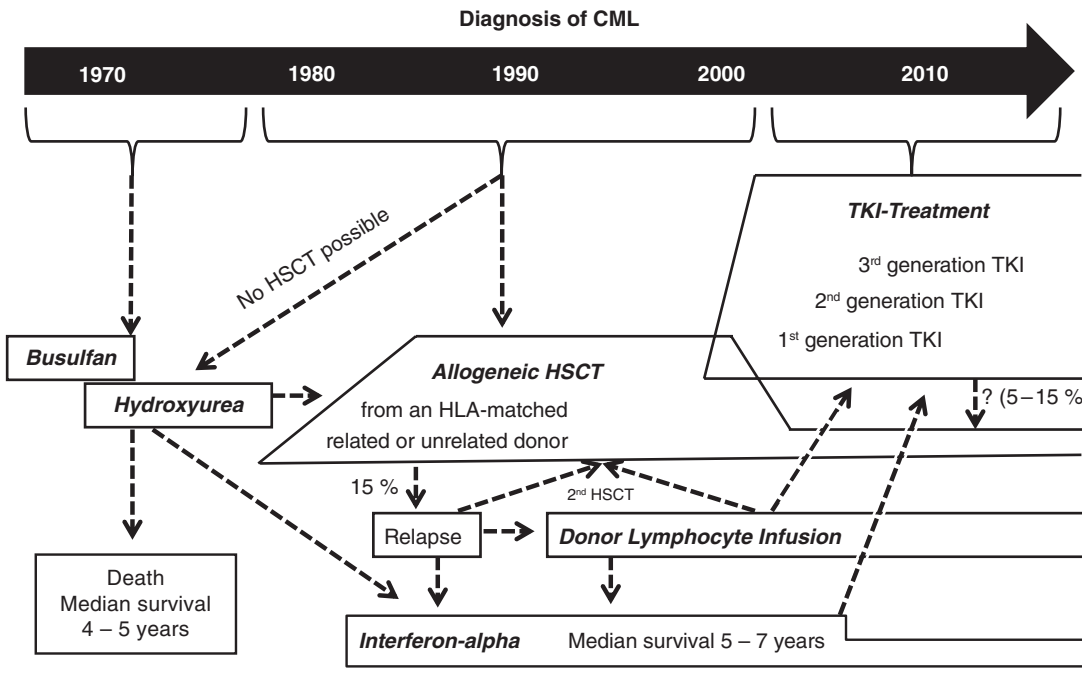

Fig. 20.1 Change of up-front treatment in CML during the last five decades

Besides well-known acute toxicities, the small number of children in long-term studies limits conclusions about late toxicities [23]. As late sequelae of interferon alpha, an increased incidence of autoimmune diseases has been described [24, 25]. However, follow-up of children treated at young age with interferon because of hemangioma showed no late toxicity [26]. Overall, late effects of SCT associated with a myeloablative conditioning can be expected to be severe thus overlaying the effects of prior treatment with CML-specific drugs administered for some months.

20.1.3 Relapse After Stem Cell Transplantation (SCT)

As a particular feature of CML, it must be kept in mind that relapse may occur still many years after SCT [27]. Follow-up examinations therefore should include analysis of the disease-specific BCR-ABL1 transcript by RT-PCR [28]. The threshold for detection using this technique is in the range of 0.001% tumor cells within healthy cells, thus being 100-fold more sensitive than analysis of chimerism by VNTR polymorphisms which is performed in most patients after SCT on a routine basis [29]. Ideally, therapeutic interventions should start when molecular relapse is diagnosed [30]. Options include donor lymphocyte infusions (DLI), which, however, also harbor the risk of inducing severe GvHD [31]. Treatment with TKI is a less risky alternative, but drug resistance has to be ruled out. In cases with no response to either DLI or TKI, a second SCT should be considered (Fig. 20.1).

20.2 Specific and Potential Side Effects of Tyrosine Kinase Inhibitors (TKIs)

20.2.1 Disturbances of Bone Metabolism

20.2.1.1 Longitudinal Growth Impairment

Soon after imatinib was administered to children, it was learned that TKIs dysregulate bone remodeling. This is caused by off-target inhibition TKIs exert on tyrosine kinases besides ABL1 like the macrophage colony-stimulating factor receptor (c-FMS) and platelet-derived growth factors alpha and beta which are key regulators of osteoclast and osteoblast activity [32–37]. A number of studies have reported impaired longitudinal growth in children with CML treated with TKIs [38–45]. Own findings in the largest pediatric cohort so far analyzed (Table 20.1) showed that children in whom TKI treatment was started at prepubertal age were affected more severely decreasing in their median height z-score by −0.75 during the first year, while at older age, the pubertal growth spurt probably partially may have compensated growth impairment [46]. Taken together, all studies suggest that children treated with TKI for several years at prepubertal age will show up as adults with a reduced body height compared to their prospective genetic final height.

20.2.1.2 Alterations in Calcium Homoeostasis and in Bone Mineral Content

Impaired bone remodeling by TKIs is associated with a disturbed calcium and phosphate metabolism. Adult patients exhibited hyperparathyroidism and a significant decrease in blood calcium levels, possibly related to net sequestration of bone minerals due to a decrease in bone resorption and increase in bone deposition. Thus, bone mineralization in adult patients is enhanced and the trabecular bone volume increased [37]. However, findings in two of four pediatric patients with CML who were on imatinib therapy detected a reduction in bone mineral density thus contrasting the adult data [39]. This could suggest that the bone metabolism in not outgrown patients is more prone to increased bone resorption. Like adults, children also exhibit moderate secondary hyperparathyroidism as a resulting consequence of imatinib treatment [37, 47, 48]. The association of impaired bone remodeling with the clinical observation that skeletal pain may be severe under TKI treatment but usually disappears by the end of the first year after diagnosis is still obscure [46].

20.2.1.3 Alterations in Bone Strength

CML at diagnosis as well as in relapse can manifest as a solid bone infiltrating tumor

Table 20.1 Changes in Z-scores of body height in pediatric patients on imatinib treatment. Results from trial CML-PAED II [46]

		Body height (z-score)		
Patients		at diagnosis	after 1 year	after 2 years
Total cohort	N	108	77	32
	mean ± SD	+0.43 ± 1.40	+0.15 ± 1.38	-0.15 ± 1.59
	median	+0.38	+0.07	-0.31
	95%CI	+0.16 – 0.70	-0.16 – 0.47	-0.72 – 0.42
Pre-pubertal	N	28	24	12
	mean ± SD	+0.76 ± 1.82	+0.12 ± 1.90	+0.26 ± 2.16
	median	+0.66	-0.29	-0.39
	95%CI	+0.05 – 1.46	-0.68 – 0.92	-1.11 – 1.64
Pubertal	N	44	31	15
	mean ± SD	+0.25 ± 1.28	+0.13 ± 1.17	-0.67 ± 1.09
	median	+0.25	+0.14	-0.44
	95%CI	-0.14 – 0.64	-0.29 – 0.56	-1.27 – -0.06
Post-pubertal	N	36	22	5
	mean ± SD	+0.38 ± 1.14	+0.22 ± 1.02	+0.43 ± 0.72
	median	+0.30	+0.06	+0.17
	95%CI	-0.01 – 0.76	-0.23 – 0.67	-0.46 – 1.32

("chloroma") resulting in a pathological fracture. These cases have to be classified as CML in blast crisis by definition of an extramedullary manifestation of the disease [49–51]. CML per se seems to be associated with an increased fracture risk in adults. A Danish population-based cohort study investigated the risk of proximal femoral osteoporotic fractures among patients with CML in chronic phase compared to a matched cohort from the general population [52]. In these adult CML patients, the adjusted hazard ratio for femoral fracture was increased by 2.67-fold. When comparing patients under TKI treatment from the years 2000–2010 to those treated in the decade before without TKIs, no statistically significant differences were found. The authors conclude that CML patients are at higher risk of osteoporotic fractures than the general population and that TKI treatment does not mitigate this risk. However, in single cases, uncommon fractures or disturbed bone healing under imatinib treatment has been described in adults and in children [53–55].

In a juvenile rat model animals were long-term exposed to different TKIs, starting shortly after weaning until young adulthood. Data generated exhibited dose-dependently reductions in femoral, tibial, and vertebral bone length in conjunction with reduced trabecular bone mass density and femoral breaking strength. The latter changes were seen only by the end of the experiment in adult animals after long-term, high-dose exposure since early age [56, 57]. These findings raise concerns that the inhibition of bone turnover will ultimately increase bone fragility due to

decreased mechanical strength. Thus, possible osseous changes mandate close monitoring in pediatric patients under long-term TKI exposure. If patients experience unprovoked bone fractures or if decreased bone mineral density is noted on plain radiograph, bone mineral density should be quantitatively evaluated by DXA radiography in patients 12 years of age or older [18].

20.2.2 Vitamin D Deficiency

In conjunction with hyperparathyroidism, patients on imatinib also exhibit pathologically low vitamin D_3 levels [47, 48]. Vitamin D is an important controller of bone mineralization [58]. In cell culture assays using keratinocytes, it was demonstrated that imatinib interferes with the pathway of vitamin D_3 synthesis by inhibiting CYP27B1, which is responsible for the renal 1-alpha-hydroxylation of 25-hydroxyvitamin D3 to the active 1,25-dihydroxyvitamin D3 [59]. Based on the current knowledge, it might be prudent to monitor calcium, phosphorous, parathyroid hormone, and vitamin D levels in patients under TKI treatment.

20.2.3 Hypothalamic-Hypophyseal Axis and Growth Hormone Deficiency

Like in adults, in pediatric patients on TKIs, there is now an increasing evidence of growth hormone (GH) deficiency/insensitivity and low blood levels of the products of downstream GH signaling cascades, e.g., insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3) [43, 60, 61]. Thus, as additional causes of poor longitudinal growth, TKIs may act in part by disruption of the GH-releasing hormone (GHRH) signaling cascade, GH signaling cascade, and IGF-1 signal transduction [43, 60]. In a small cohort of 21 pediatric CML patients on imatinib, IGF-1 and IGFBP-3 blood levels were significantly lower than those in age-matched controls, and these findings could also be modeled in the juvenile rat model described above [61]. GH stimulation testing was found to be abnormal in patients on TKI therapy pointing to pituitary or hypothalamic disturbance. Whether injection of GH or recombinant IGF-1 will improve final adult height in pediatric patients with CML concomitant TKI treatment is a matter of an ongoing debate. As a word of caution, however, although there is no conclusive evidence that pediatric GH therapy increases the risk of de novo cancers in adults, the use of GH therapy during active cancer treatment would raise a concern [62, 63]. Suggestions based on expert opinion demand to wait at least 1 year from malignoma treatment completion to ensure there is no early recurrence [62, 64].

20.2.4 Homoeostasis of Blood Glucose Level

TKIs may also interfere with glucose homoeostasis causing both hyperglycemia and hypoglycemia [65]. Several case reports followed by clinical studies showed that treatment with imatinib improves glucose control in type 2 diabetes mellitus. Up to half of the adult diabetic patients were able to discontinue their antidiabetic medications [66]. The underlying mechanism is not known in detail and debated controversely [67, 68]. However, in contrast to imatinib and dasatinib, nilotinib has been shown to lead to hyperglycemia. A mechanism of impaired secretion of endogenous insulin has been suggested, but remains poorly understood in details [69]. In the ENESTnd trial in patients evaluated with pre-existing type 2 diabetes mellitus prospectively, all grade hyperglycemia was found in 38% of those on nilotinib 600 mg, in 42% of those on 800 mg, and in 22% of those in the imatinib arm. However, no patients discontinued therapy due to hyperglycemia or had any serious diabetic adverse events [70].

20.2.5 Thyroid Function

Whether thyroid dysfunction is a side effect of TKIs is still not clear. When assessed by retrospective evaluation, either hypothyroidism or hyperthyroidism in 25 and 29% of the cases, respectively, seems to be common in adult patients with CML ($n = 73$) being treated with the first- and second-generation TKIs imatinib, nilo-

Table 20.2 Incidence of cardiovascular adverse events (AE) under TKI as reported in adults

Study	TKI	% cardio-vascular AE	Ref
ENEST	Imatinib	2.5	[57]
	Nilotinib	12.9	
DAISSION	Imatinib	2.7	[13]
	Dasatinib	7.7	
PACE	Ponatinib	7.1	[11]

tinib, and dasatinib. However, only three patients ultimately needed therapy [71, 72]. A retrospective chart review in a small cohort of seven pediatric patients reported all had normal thyroid function [44]. A pattern of either hypo- or hyperthyroidism makes it difficult to speculate on the multiple biochemical pathways being altered by TKIs and has been claimed to be causative. As a pragmatic approach, it might be prudent to monitor *thyroid function* on a regular basis. Overt hypothyroidism should be treated with levothyroxine, but subclinical hypothyroidism should be treated only if a patient develops symptoms [73].

The reader is also referred to Chap. 8 of this book.

20.2.6 Cardiovascular Side Effects

Cardiovascular toxicity (CVT) in adults is a well-known side effect of several TKIs and highly probably represents a "class effect" as the regular ABL1-kinase is inhibited by TKIs. ABL1 is essential for survival of contractile cardiomyocytes and exhibits cell protective effects [74]. In the ENEST study, 10% of patients treated daily with nilotinib 600 mg and 16% on nilotinib 800 mg, respectively, exhibited CVT compared to 2.5% of the patients receiving imatinib 400 mg [5]. CVT observed comprised coronary heart disease, ischemic stroke, and peripheral artery occlusive disease (PAOD) and occurred mostly during the first 3 years of TKI treatment (Table 20.2). Eighty-five percent of those adult patients exhibited at least one cardiovascular risk factor (e.g., hyperglycemia, hypercholesterolemia) and were not medicated optimally [75]. Pulmonary arterial hypertension and pleural effusion have been reported under dasatinib treatment affecting up to 30% of adults older than 65 years [76–78]. CVT events were similar in the BELA study (bosutinib versus imatinib) [79]. Ponatinib caused cardiovascular adverse events in 7.1%, ischemic stroke in 3.6%, and PAOD in 4.9% of adults with CML [80]. The impact of CVT in a juvenile organism is still unclear. However, as a precautionary measure, regular clinical examination during follow-up should include electrocardiogram; cardiac ultrasound; treatment of risk factors, e.g., overweight; and thromboembolic preventive measures (no smoking, optimal selection of contraception).

The reader is also referred to Chap. 1 of this book.

20.2.7 Additional Organ-Related Toxicity and Metabolic Alterations

When selecting a TKI for an individual patient, the substance-specific toxicity profile in the context of the class-specific profile (transient myelosuppression, fatigue, erythema, exanthema, laboratory abnormalities) must be taken into account [81, 82]. Besides biological features of CML, patient-specific factors (lifestyle, adherence to treatment, personal preferences) also have to be counterbalanced against data and recommendations derived from adult guidelines (Table 20.3). Side effects from TKI treatment are rarely severe, and cross intolerance between different TKI is observed only rarely [13, 83, 84]. Supportive measures aiming at compensation of side effects (e.g., gastrointestinal toxicity, skin rash, bone pain, pleural effusion) are essential to maintain adherence to TKI treatment [85]. Any change in laboratory findings or reported health

Table 20.3 Clinically observed toxicity profile of TKIs licensed for use in adult patients

	Imatinib	NiIotinib	Dasatinib	Bosutinib	Ponatinib
Hematological toxicity (grade 3 and grade 4)					
Neutropenia	++	++	++++	++	++
Thrombocytopenia	++	++	++++	+++	++++
Anemia	+	+	+	+	+
Non-hematological toxicity (grades 1–4)					
Edema	++++	+	++	++	–
Nausea	++++	++	++	++++	++
Vomiting	++	+	+	++++	–
Diarrhea	+++	+	+++	++++	+
Fatigue	++	++	+++	++	++
Rash	++	++++	++	+++	++++
Headache	++	++	++	++	++
Pleural effusion	–	(+)	++	+	–
Vascular/cardiac	–	+	–	–	++
Changes in laboratory parameters					
Liver enzymes	+	+	–	+++	+
Lipase	+	++	–	+	++
Hyperglycemia	–	+	–	–	–
Hyperlipidemia	–	+	–	–	–

Legend: Listed side effect was not investigated (–) in adult study populations. Listed side effect was observed in 0–10% (+), 10–20% (++), 20–30% (+++), or >30% (++++) of the adult study populations [76, 81, 90]
Data are derived from first-line and second-line treatments

Table 20.4 Etiology of factors influencing the response to *TKI* treatment

Etiology is tumor cell	
Dependent	Independent
Quiescence of CML stem cell ↓	Gender (male ↓ vs. female ↑)
Activation of alternative cell survival signaling pathways ↓	Previous interferon exposure ↑
Influx and efflux transporters affecting the intracellular TKI concentration (↑ or ↓)	Duration of the TKI exposure (long exposure ↑)
Selection of resistant subclones by TKI treatment ↓	Reduced intestinal drug absorption ↓
Genomic instability leading to mutations other than BCR-ABL1; clonal evolution ↓	Increased hepatic drug metabolism by enzyme induction ↓
Epigenetic reprogramming of leukemic stem cells ↑	Immune response by NK-T-cells ↑
	Drug-drug interactions (↑ or ↓)
	Noncompliance ↓

Arrows denote a favorable (↑) or negative (↓) impact (Modified from [108])

problems should take TKIs into consideration as a causative agent.

TKI treatment is typically associated with hepatic toxicity (elevated serum transaminases and bilirubin) [86]. However, grade 3 or 4 liver toxicity was observed in clinical studies on imatinib or dasatinib in less than 1% of adult patients, while nilotinib caused elevated ALT or bilirubin in 4% [87, 88]. Liver toxicity in bosutinib seems to be more frequent. Side effects with nilotinib commonly observed in adults comprise hyperglycemia, altered lipid metabolism, and increased risk of PAOD. To what extent these complications as listed in Table 20.4 also play a role when treating pediatric CML and are the reason for switching of TKI treatment still has to be investigated in a systematic fashion [84, 89].

As a more or less specific side effect of dasatinib, pulmonary hypertension and pleural effusions have been described in adults [85]; however, this side effect was not observed in minors [6]. Gastrointestinal toxicity (nausea, diarrhea) is a major side effect of bosutinib—usually observed transiently—which requires intensive supportive

measures in most adults. No clinical data on ponatinib so far are available for minors. Besides cutaneous side effects, CVT with venous and arterial thromboses are of special concern in adults harboring risk factors [80, 90].

20.2.8 Induction of Malignoma

The development of secondary malignancy is among the question raised of late effects. Secondary cancers occur in a small percentage of patients receiving TKI therapy for CML. One previous report suggested an unexpected increased incidence of cancers among patients treated with imatinib after failure to IFN [91]. Reviewing the records of 1445 TKI-treated patients experiencing malignancies demonstrated that secondary cancers occur in a small percentage of patients. However, when analyzed in the context of the underlying lifetime risk of developing cancer by the general population and in patients who survive cancer, no evidence at the moment suggests that exposure to TKIs is carcinogenic [92].

20.2.9 Gonadal Function and Pregnancy

Preclinical research in animals suggests that treatment with TKI can affect both the male and female reproductive function [93–95]. In adolescents with CML, the long-term effects of first- or second-generation TKI therapy on puberty or fertility have been investigated in small cohorts only suggesting that fertility may be impacted by TKI therapy [39]. In the largest study to date, normal testosterone and inhibin B serum levels in 13 boys (median age 13 years, range 8–19 years) receiving imatinib for a median of 18 months (range 3–58 months) were reported [95]. Data from a single study on 48 Chinese adult men treated for CML with imatinib exhibited reduced sperm counts, sperm survival rates, and sperm activity [96]. Ultrasound demonstrated that the shape and size of the testis and epididymis were normal; however, in 19 of these patients, hydrocele testes were detected. Sex hormone levels in the sera of these patients were normal. Thus, in teenagers on long-term TKI exposure, it seems reasonable to follow pubertal development every 4–6 months. If puberty is delayed or evidence of sex steroid deficiency is noted, further workup is warranted, including testis ultrasound examination and measurement of gonadotropins and sex steroids.

As of today, more than 150 men have fathered healthy children while receiving imatinib treatment. Hence, men wanting to have children can safely remain on imatinib [97, 98]. The data on second-generation TKIs dasatinib and nilotinib on this issue are sparse but in small series seem not to differ completely, while no reports concerning men taking bosutinib or ponatinib are published [97]. Evidently further studies are needed to clarify the long-term impact of TKIs on fertility endpoints for both prepubertal and postpubertal patients [99, 100].

Concerning pregnancy, all five TKIs are associated with a significant embryo-fetal toxicity in animal studies. Due to the occurrence of congenital malformations in association with imatinib in human pregnancy (ranging from minor to more severe and including skeletal, renal, respiratory, and gastrointestinal malformations), females of childbearing age who are receiving TKI therapy should be counseled on the potential teratogenicity risk to the fetus, particularly when exposure occurs in early pregnancy [101, 102]. Proper contraception should start early in teenagers at childbearing age. When a female patient becomes pregnant while receiving TKI treatment, the difficulty lies in balancing the risk of possible teratogenicity to the fetus against the risk to the patient of treatment change with potentially loosing optimal disease response [97, 103, 104].

If a woman with CML on TKI treatment plans to become pregnant, the leukemia should ideally be under control with stable low-level molecular disease. From a psychological viewpoint, teenage girls should be informed early that in adult medicine clear recommendations and treatment plans are established to manage pregnancy in CML [97, 102, 105].

20.3 Problems in Everyday Life While on TKI

20.3.1 Ongoing Monitoring of Residual Disease Is Mandatory

Operational cure means disappearance of all signs of CML and return to a "normal" healthy state. Yet, it remains obscure whether complete eradication of all leukemic cells has been achieved. Considering a patient is cured when every leukemia cell has been eradicated is probably an oversimplification. Thus, the role of adherence to treatment cannot be over-emphasized as noncompliance arises as a significant obstacle to the success of treatment [13, 106, 107]. Evaluating for adherence at each clinic visit, monitoring BCR-ABL1 test results over time to help identify nonadherence, and educating patients on staying with the prescribed treatment regimen can help to optimize treatment outcomes. Once a complete cytogenetic remission is diagnosed, molecular response should be checked every 3 months by real-time quantitative PCR technology. Secondary resistance to TKI treatment can be observed at any time, and mechanisms behind—among many others (Table 20.4)—may involve point mutations within the ABL1 kinase domain [108]. Thus, mutation analysis should be done if treatment fails, response is suboptimal, or transcript ratio increases [109]. Transplantation remains the only potentially curative option for patients in blast phase, patients with refractory mutations like T315I, and after failure or intolerance of second-generation TKI [3, 13, 19, 21, 110]. Thus, CML management of constantly increasing numbers of patients on chronic TKI treatment needs standards as set in guidelines [109], and young CML patients evidently should be monitored closely. Side effects occurring in the long-term should be treated and recorded in a standardized fashion.

20.3.2 Vaccination in TKI-Treated Individuals

Patients on TKI therapy may receive inactivated vaccines safely, although lack of knowledge about immune dysfunction with TKI is hindering routine vaccination. Giving live vaccines during TKI treatment is not recommended in general, although one study suggests that varicella vaccine can be given to some immunocompromised children [111]. In adults, a study showed that under TKI treatment, IgM humoral response to pneumococcal vaccine was impaired compared to healthy controls [112, 113]. However, one report indicated a higher seroconversion rate to H1N1 influenza vaccine in adult CML patients compared to patients with B-cell malignancies or HSCT recipients. Protective antibody titers were observed in 85% and 95% of the CML patients after the first and second doses, respectively, compared to controls (100% after the first dose) [112]. Although data are lacking, a safe alternative might be, when a deep molecular response is achieved after a few years of TKI treatment, to interrupt the TKI treatment for several weeks to provide a window for administering live vaccines [3, 18].

20.3.3 Lifelong TKI Medication and Aspects of Pharmacokinetics and Drug-Drug Interactions (DDIs)

DDIs are always a significant safety concern when continuous medication is required. Many patients may be treated with polypharmacy because of TKI side effects or other underlying diseases. Most TKIs are substrates and *inhibitors* of cytochrome P450s (CYPs), raising the potential for harmful TKI-drug interactions [114]. Overall, after oral intake, TKIs reach their maximum plasma levels relatively fast, have a so-far ill-defined absolute bioavailability, and are highly protein bound and extensively distributed [115]. The drugs are primarily metabolized by CYP3A4 with other CYP enzymes playing a secondary role. Fecal excretion dominates over a minor fraction eliminated with the urine. The efflux ATP-binding cassette transporters B1 and G2 function in cellular excretion [116]. Because of the inherent risk of either reduced activity or enhanced toxicity of the concomitant medication and/or TKI, drugs known to interact with the same CYP isoenzymes (2D6 and 3A4) as imatinib and having a narrow therapeutic

window (e.g., cyclosporine, sirolimus, tacrolimus) should be used with caution [109, 114]. In addition to drugs, grapefruit juice has been shown to increase blood serum levels of nilotinib, but not of imatinib [117, 118]. Also the medicinal herb St John's wort (*Hypericum perforatum*) should be used only with great caution [119]. Nilotinib was shown to be a potent inhibitor of CYP1A2, 2C9, and 3A4, while dasatinib is only a weak inhibitor of these CYP enzymes [120].

20.4 On the Way to Cure CML?

20.4.1 Stopping TKI Treatment

Deep molecular responses are achieved by the majority of patients under imatinib treatment. If the response is as profound as defined in the first stopping trial in adults (PCR negative for a period exceeding 2 years), cessation of TKI treatment can be successfully performed with maintained RT-PCR negativity in 40% of adult patients for a mean period exceeding 4 years. Molecular relapse in the remaining 60% of patients occurred rapidly within the first 6 months after stopping in all, but 2%, however, responded in all cases to resuming TKI treatment [14, 121]. No patients progressed to the advanced phase of CML. Contrasting these data from adults, only 28% of children fulfilling the criteria for cessation could stop imatinib successfully [16]. As this data stem from a small cohort of 14 patients only, it might be too early to conclude that the success rate of stopping attempts in minors seems to be inferior compared to adults. Given the earlier and deeper response achieved by second-generation TKIs, it seems plausible that nilotinib and dasatinib will induce a situation when the TKI may be stopped earlier. However, it should be kept in mind that this cure should be termed "operational cure" as a DNA-based PCR might reveal BCR-ABL1-positive cells that were not detected by RNA-based real-time quantitative PCR [122, 123]. Ongoing monitoring by RT-PCR for BCR-ABL1 therefore is mandatory after stopping TKI in close intervals. To make things more complicated, an ultrasensitive PCR technique can even discover a low level of BCR-ABL1 transcript in the blood of normal individuals [124, 125].

Stopping TKI in pediatric patients has so far been reported in less than ten patients [16, 126, 127]. Following recommendations as established for adults, children should have achieved a very low level of MRD (<MR4.5) and maintained this level for a 2-year period before the TKI is withheld. Evidently a 3-log reduction is not safe enough to stop treatment because in adults the STIM study used a 4.7-log reduction and the Australian Twister study used a 4.5-log reduction for their definition of complete molecular remission [14, 15]. As scoring systems applied in adults (Sokal-, Euro-, EUTOS-score) are of non-proven value in children, no prognostic parameters so far can help with decision-making in minors [128]. It must be emphasized that with the currently very limited experience accumulated, TKIs should be discontinued only in the setting of a clinical trial.

20.4.2 Antitumor Cell Vaccines

It has been learned from donor lymphocyte infusions in the context of SCT that CML cells are eradicable by immune attacks. Ongoing immunotherapy approaches are directed at (1) the immune control in stable molecular remission and (2) targeting at the leukemic stem cell [108, 129]. The BCR-ABL1 kinase represents a tumor-specific protein because of its unique amino acid sequence across the junction region. Peptides derived from this junction region have been administered in vaccination studies. Another approach is based on the use of GM-CSF transduced KJ562 cells as allogeneic vaccine. Antigens that are overexpressed in leukemic cells and either not expressed or at low level expressed in normal cells have been investigated with the most promising candidates PRTN3, WT1, and HMMR having entered already clinical trials. As a more general promising approach against leukemias and solid cancers, the generation of potent cytotoxic T-cells in vitro is considered [130–132]. It is anticipated that effective vaccination strategy would enable a greater proportion of patients to safely discontinue TKI treatment, but presently these studies are recruiting adult patients only. When having reached the age of 18 years, it might be prudent to enroll adolescents and young adults early in such vaccination trials if appropriate.

20.4.3 Cure of CML by Targeting Leukemic Stem Cell

Overcoming mechanisms of resistance for treatment of insufficient response and failure are the goals of treatment using new substances with or without in combination with TKIs. A comprehensive overview of all approaches presently tested preclinically or in phase I trials is beyond the scope of this article. Figure 20.2 gives an impression of the multiple possible cellular pathways representing possible future targets as a challenge to overcome CML stem cell resistance to all currently available TKIs [108, 133]. The strategies that specifically target CML stem cells which are currently being explored look promising; however, it seems not unlikely that side effects and late effects may also be associated with these approaches. Ongoing monitoring and a well-organized transition of pediatric patients into internal medicine are mandatory (Table 20.5).

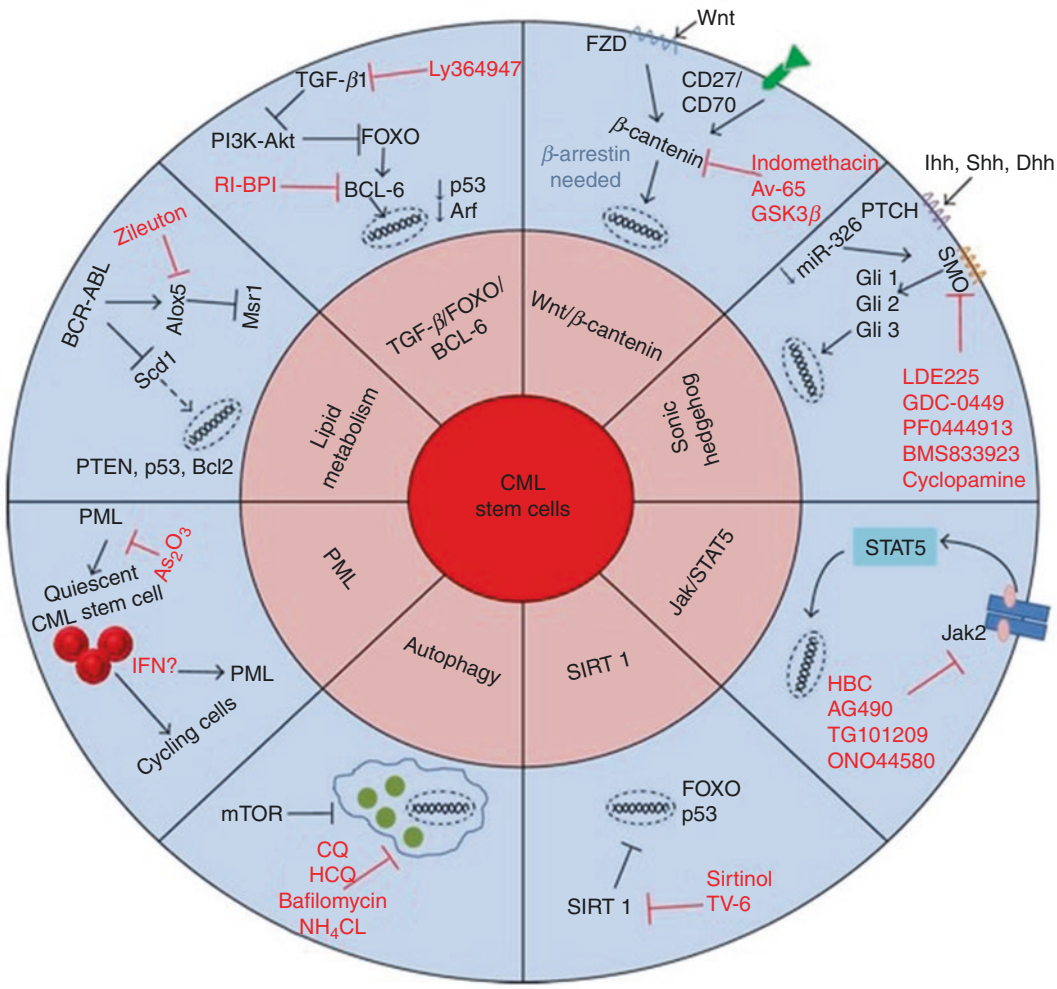

Fig. 20.2 Alternative signaling pathways for overcoming resistance of CML stem cells against tyrosine kinase inhibitors. Abbreviations: Sonic hedgehog (Shh), Indian hedgehog (Ihh), Desert hedgehog (Dhh), Smoothened (Smo), STAT5 (signal transducer and activator of transcription), Retroinverso BCL6 peptide inhibitor (RI-BPI), Chloroquine (CQ), Hydroxychloroquine (HCQ), Sirtuin 1 (SIRT1), Tenovin-6 (TV-6), Arachidonate 5-lipoxygenase (Alox5), Stearoyl-CoA desaturase 1 (Scd1), Promyelocytic leukemia protein (PML), Arsenic trioxide (As_2O_3), and Interferon alpha (IFN). (Published by: Hamad A, et al. [133])

Table 20.5 Lifelong monitoring of CML and management of possible TKI side effects

Issue	Assessment	Time point	Consequences and tests
Monitoring of minimal residual disease (MRD)	Quantitative analysis of ratio BCR-ABL1/control gene from peripheral blood	Every 3 months	None, if ratio <0.1 (MR3.0) is maintained
			If ratio increases from a very low level by half a log and if this is confirmed within 4 weeks, suspect imminent relapse or resistance to TKI, and seek advice of a CML specialist to switch to a different TKI
			If ratio <0.01 (MR4.0) is maintained continuously or even undetectable for a minimum of longer than 2 years, seek advice of a CML specialist for inclusion into a stopping trial
Monitoring to exclude or detect organ-specific side effects	Full blood count and differential count	Every 3 months	Extend diagnostics if not within the normal range, seek advice of an hematologist
	Cardiac toxicity and pleural effusions	Every 6 months	Monitoring by ECG, ECHO
	Thyroid gland	Every 6 months	TSH, T3, T4
	Skin	When side effect is complained	*Edema:* Limit sodium diet (2 g/d); add diuretics if severe *Morbilliform eruption*: topical steroids or short course of oral steroids; treatment interruption if grade III/IV *Pigmentary changes:* typically reversible with dose reduction/ termination
	Bone quality	Every 12–24 months	DEXA scan; refer to endocrinologist if irregular findings are observed
	Glucose metabolism	Every 3 months	HbA1c blood level; refer to endocrinologists if irregular glucose metabolism is suspected. Keep in mind that treatment with imatinib may result in an improved fasting blood glucose level thus allowing a consequent reduction of oral antidiabetic drugs or insulin dosage
Teratogeni-city of TKIs	Only applies to sexu-ally active and premenopausal females	Depending on contraceptive measures	Safety and practicability of optional contraceptive measures must be discussed and adopted to the individual case
Planned pregnancy	Options depend on prior duration and success of CML treatment	Individual approach	Ideally postponed until low-level MRD is achieved. TKI treatment must be stopped prior to conception and may be replaced by treatment with IFN. Seek advice of a CML expert

20.5 Recommendation for a Long-Term Follow-Up Schedule

Long-term follow-up is performed according to the recommendations of the International Guideline Harmonisation Group (www.ighg.org) and of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/). For Psychosocial Follow-Upthe reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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21 Late Effects After Treatment of Non-Hodgkin Lymphoma in Childhood and Adolescents

Thorsten Langer and Christian Mueller

21.1 Introduction

Childhood and adolescent non-Hodgkin lymphomas (NHL) are a heterogeneous group of various lymphoid neoplasms. These include all malignant lymphomas that are not classified as Hodgkin's lymphoma. NHL were a near-fatal disease until the early 1970s. Over 80% of affected children died within the first 2 years after diagnosis. This situation has changed completely as today, in modern industrial nations, more than 80% of children with NHL are cured by combination cytostatic therapy.

Lymphoblastic lymphomas are treated according to therapeutic strategies as used in acute lymphoblastic leukemia. Burkitt lymphomas and non-lymphoblastic NHL are treated with short intensive high-dose chemotherapy courses based on corticosteroids, cyclophosphamide, and methotrexate (MTX). Both therapy regimes are also effective in treatment of large-cell anaplastic lymphomas.

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Childhood NHL diseases tend to an early systemic generalization. Thus effective combination chemotherapy is the backbone of a successful treatment strategy. The risk for relapse increases with grade of spread and tumor mass which are important criteria for setting intensity and duration of therapy. Because of the high tendency for systemic spread, the treatment of the extra compartments central nervous system (CNS) and testicles has a similar importance as in the treatment of acute leukemia. A key step in the development of today's treatment concepts was the recognition that different NHL subtypes require a very different chemotherapy strategy. The distinction between lymphoblastic and non-lymphoblastic lymphomas is the most important therapeutic strategy subdivision [1]. For lymphoblastic lymphomas, therapeutic strategies of ALL based on the principle of continuous exposure to cytostatic drugs over long periods of time are an adequate treatment [2–5]. In the therapy of Burkitt-type lymphomas and other highly malignant non-lymphoblastic NHL, a strategy of short intensive chemotherapy courses with high-dose intensity based on corticosteroids, cyclophosphamide, and MTX proved more effective [2–7]. This therapy is in principle also effective in the treatment of large-cell anaplastic lymphomas [8, 9]. Internationally, a division of childhood NHL into three major therapeutic groups has prevailed:

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1. Lymphoblastic lymphomas
2. Peripheral B-cell lymphomas (B-NHL) including Burkitt lymphoma and B-ALL
3. Large-cell anaplastic lymphomas (independent of immunophenotype)

With such a stratified therapy, patients of all entities have approximately comparable chances of survival. For some numerically small subentities as peripheral T-cell lymphomas and NK-cell lymphomas, the most appropriate form of therapy is still unclear. It is noteworthy that the successes of the 1980s and 1990s were achieved with medicines already available in the 1970s. The event-free survival after 5 years increases from 61% in first NHL-BFM study to 84% in study NHL-BFM 95.

21.2 Treatment of NHL in the Past and at Present

21.2.1 First NHL-BFM Study 1975/81

In 1975 Hansjoerg Riehm initiated at Children's Hospital of Free University in West Berlin the first cooperative multicenter therapeutic study of the BFM group on childhood and adolescent NHL. From 1975 to 1981, 116 patients up to the age of 16 were included from 17 institutions in Western Germany, West Berlin, and Vienna (Austria). Due to the common lymphoid origin of NHL, the treatment strategy was based in general on childhood acute lymphoblastic leukemia (ALL) treatment protocol of the BFM group which has been effective in the treatment of children with ALL. Thus therapy in study NHL-BFM 1975/81 contained of an initial single dose of cyclophosphamide and a multidrug induction therapy for 8 weeks (protocol I) with prednisone, vincristine, daunorubicin, L-Asparaginase, cyclophosphamide, Ara-C, MTX (intrathecal), 6-mercaptopurine, and a cranial radiotherapy with 18 Gy for patients with standard risk for relapse or 24 Gy for patients with high risk for relapse; for CNS-positive patients, the dosage for cranial radiotherapy was 30 and 24 Gy for neuroaxis [2]. Additionally, patients of high-risk group received the reintensification strategy (protocol II) for 6 weeks with dexamethasone, vincristine, doxorubicin, L-Asparaginase, cyclophosphamide, Ara-C, intrathecal MTX, and 6-thioguanine. Study BFM 1975/81 was the first one which reached well results of continuous complete remission (CCR) in 61% for all patients (74% for patients with lymphoblastic NHL), but the results for B-NHL were much worse with CCR of 32%. The treatment strategy for lymphoblastic NHL is based on the elements "induction" and "reintensification" for stages III and IV which is similar to therapy of acute lymphoblastic leukemia with some modifications to minimize late effects by decreasing the dosage of radiotherapy. The therapy used in the BFM 1975/81 study was ineffective in treating patients with B-NHL. Thus a new therapy was developed for that group.

21.2.2 Study NHL-BFM 81/83: Short Pulse-Type Chemotherapy for B-NHL

Based on the results of study NHL-BFM 1975/81, the BFM group developed a new treatment regimen for patients with B-NHL in the subsequent study NHL-BFM 81/83. The therapy consisted of two alternating 5-day courses based upon dexamethasone, intermediate-dose MTX (500 mg/m^2), cyclophosphamide, and intrathecal MTX supplemented by VM26 and cytarabine in course 1 and by doxorubicine in course 2 [3]. The principles of the treatment strategy by Günter Henze, Berlin, for B-NHL were:

1. Combination of drugs with different mechanisms of action and few overlapping toxicities
2. High-dose intensity over time by keeping intervals between therapy courses as short as possible
3. Efficient CNS-directed therapy to block the strong tendency for invasion of the CNS

Dexamethasone was included because of its activity in the cerebrospinal fluid. Cyclophosphamide

had been proven to be effective as a single agent in children with Burkitt lymphoma in Africa [10]. And higher doses up to 30 mg/kg MTX in single use combined with leucovorin had been demonstrated efficacious in children with Burkitt lymphoma [11]. Pharmacologic studies showed that therapeutic levels of MTX could be achieved in the cerebrospinal fluid by systemic administration of higher doses [12] and epipodophyllotoxins had proven to be active in resistant NHL in adults [13]. The proliferation activity of Burkitt lymphoma with a cell doubling of 25 h is extremely high [14], so a principle on this course based therapy was to maintain cytotoxically active drug concentrations by means of fractionated administration or continuous infusion over a period that is long enough to impact as many lymphoma cells as possible during the vulnerable active cell cycle [6]. So in consequence the regimen of two alternating 5-day courses increased the continuous complete remission for patients with disseminated B-NHL to 67% compared to 34% in study NHL-BFM 1975/81.

21.2.3 Stratification of Treatment

The results of study NHL-BFM 1975/81 showed that stage of disease had a prognostic impact in B-NHL, so in subsequent studies, the role of stage for stratification differed between the treatment groups. In the treatment group lymphoblastic lymphoma, formerly called nonB, treatment intensity was stratified according to stage I + II versus stage III and IV since the study NHL-BFM 81/83. Patients with stages III or IV received delayed reintensification with protocol III or protocol II from starting with study NHL-BFM 86.

In therapy group B-NHL, treatment intensity was also stratified by stage. In the NHL-BFM 81/83 study, patients with stage II were subdivided into (1) the tumor was completely resected (stage II-R) or (2) not (stage II-NR). Patients with stage I and II-R received only four of the newly designed B-courses resulting in a rate for CCR of 100% [3]. In the subsequent studies for these patients, the number of therapy courses was reduced to three in study NHL-BFM 86 and only two courses in studies NHL-BFM 90 and NHL-BFM 95 without an increase of relapses [4, 15, 16]. Patients with stages II-NR, III, and IV received eight courses of the newly designed B-type therapy in study NHL-BFM 81/83 resulting in rate for continuous complete remission of 67% as described above. All in all, three parameters seemed to have significant influence on treatment outcome. That results to the subdivision into three arms of therapy intensity: bone marrow involvement, CNS involvement, and serum concentration of lactic dehydrogenase (LDH) as a parameter of tumor mass. In study NHL-BFM 86, a benefit was found for patients with NHL of stage IV and B-cell acute lymphoblastic leukemia by introducing treatment of high-dose MTX (HD-MTX; 5 g/m^2) [17]. Results of a retrospective analysis of study NHL-BFM 86 showed that patients with stage III and pretherapeutic serum LDH concentrations ≥500 U/L had a significantly worse event-free survival (43%) compared to stage III patients with LDH <500 U/L (85%). Thus in study NHL-BFM 90, LDH was used as an additional parameter for stratification of therapy intensity [15]. Since study NHL-BFM 95, stratification into four treatment arms based on stage, resection status, LDH, and CNS involvement was done. That treatment strategy provided for patients with resected disease (10% of patients) or unresected and low LDH (45% of patients) an event-free survival of >95% with only two and four therapy courses, while patients with intermediate LDH of very LDH 1000 U/L or/and CNS involvement achieved an event-free survival of >80% with five and six therapy courses [18].

21.2.4 Local Therapy

The role of local therapy changed over the period of the studies from an obligatory part of treatment to an optional role for specific patients. The initial surgery has mainly scientific reasons for asservation of appropriate tumor issue for comprehensive diagnostics. Complete resection is only beneficial for patients with localized B-NHL so they have a

favorable outcome with only 5-day chemotherapy courses. Meanwhile the outcome for patients with localized tumors is favorable with chemotherapy alone, so surgery is not required [18]. Debulking surgery for patients with large tumors has no benefit but potentially decreases the prognosis due to delay of starting treatment with chemotherapy [8].

Second-look surgery after two or three therapy courses was mandatory in studies BFM-NHL 81/83 and BFM-NHL 83/86 for patients with B-NHL and was confined to B-NHL patients with residual tumor on imaging since study BFM-NHL 86. Since study NHL-BFM 95 indication of second look surgery was reduced to B-NHL patients with residual tumors after five courses of chemotherapy [18].

In the first study BFM-NHL 1975/81, local radiotherapy was mandatory for all patients [2] and was confined to patients with incomplete response in the subsequent studies and completely canceled in study NHL-BFM 90 without increase of local relapses [4].

21.2.5 CNS Therapy and Prevention

In study NHL-BFM 1975/81, all patients received cranial radiotherapy for prevention of CNS relapses. In case of detection lymphoma cells in CNS at diagnosis, additional spinal irradiation was performed [2]. In studies NHL-BFM 83/86 and NHL-BFM 90, there was performed an intraventricular administration of MTX for CNS-positive patients by an ommaya reservoir but there was no survival benefit achieved. During the subsequent studies, irradiation of the CNS was stepwise eliminated and substituted by systemic HD-MTX combined with intrathecally administered chemotherapy without increase of CNS relapses [19]. Since study NHL-BFM 95, only CNS-positive patients up from 1 year of age with lymphoblastic lymphoma receive cranial irradiation in age-adapted dosage [20].

21.2.6 Methotrexate as a Key Drug

MTX administered by continuous infusion over 24 h combined with tetrahydrofolic acid was part of the newly designed treatment courses (by Günter Henze) which resulted in a dramatically improved outcome of patients with advanced-stage B-NHL in study NHL-BFM 81/83 [3].

In the subsequent studies, it became clear that MTX is a key drug in the treatment of B-NHL. The event-free survival increased from 50 to 75%, while the dose increased tenfold from 0.5 g/m^2 in studies NHL-BFM 81/83 and NHL-BFM 83/86 to 5 g/m^2 in study NHL-BFM 86 [17]. In contrast HD-MTX contributes to the toxicity of treatment, especially orointestinal mucositis, which increases the risk of sepsis and toxic death. Prolonging the duration of exposure to MTX increases its activity in vitro but also its clinical toxicity [21, 22]. Study NHL-BFM 95 showed that shortening the infusion time pf HD-MTX from 24 to 4 h reduced the incidence of severe mucositis [18], but in patients of higher-risk groups R3 and R4, the failure rate increased when the infusion time of MTX was reduced. By contrast, shortening the infusion time of MTX to 4 h had no adverse impact on outcome in intermediate- and low-risk groups R1 and R2. In the subsequent study B-NHL-BFM 04, the MTX regimen for patients with B-NHL was 1 g/m^2 by infusion over 4 h in risk groups R1 and R2 and 5 g/m^2 by infusion over 24 h in risk groups R3 and R4.

21.3 Late Effects After NHL Treatment

One of the treatment's consequences for childhood cancer survivors compared to the healthy control group is an increased risk for late mortality beyond 5 years after cancer diagnosis even though it was decreased over the last years due to the therapy modifications [23]. In this section the issues of late effects focused on childhood NHL survivors are described.

21.3.1 Toxicity of Substances in NHL Treatment

Substances used in treatment of NHL can cause several late effects years or even decades after finishing therapy which are:

1. Prednisone and dexamethasone: reduced bone density, osteonecrosis, and cataract,
2. Vincristine: polyneuropathy and paresthesia,
3. Daunorubicin and doxorubicin: acute myelogenous leukemia (second neoplasm) and cardiotoxicity,
4. Cyclophosphamide and ifosfamide: infertility, acute myelogenous leukemia (second neoplasm), and myelodysplastic syndrome,
5. Cytarabine: neurocognitive deficits, and reduced intelligence quotient (IQ),
6. Methotrexate: reduced bone density, neurocognitive deficits, and reduced intelligence quotient (IQ),
7. 6-mercaptopurine and 6-thioguanine: hepatic impairment and veno-occlusive disease as the result of acute toxicity

21.3.2 Summary of Late Effects

Among all childhood cancer survivors, non cancer-related mortality is the leading cause of death by approximately 30 years from cancer diagnosis. Thus survivors of childhood NHL have increased mortality rates compared to the general population. As investigated by the Childhood Cancer Survivor Study, NHL survivors are at risk for all-cause mortality [standardized mortality ratio (SMR) 4.2] and increased risk for death from subsequent malignant neoplasms (SMR 26.7), cardiac disease (SMR 6.9), and pneumonia with or without the history of splenectomy (SMR 15.4) [24].

Additionally, it is well-known that cranial radiotherapy can cause neurocognitive deficits and motor function deficits as late effects [11]. Current data about acute leukemia patients show also an increased risk of developing this issue of late effects also for those patients who received chemotherapy only [25]. Adult survivors of childhood NHL may have also impaired neurocognitive function, which is associated with lower social attainment and poor quality of life [26]. There are also signs of accelerated aging shown 25 years after NHL therapy [19]. NHL survivors have an increased risk for depression from the group of psychological diseases as well [27].

An analysis by Ehrhardt et al. which focused on childhood NHL survivors of the St. Jude Lifetime Cohort Study (SJLIFE) showed as most prevalent severe life-threatening conditions (grades 3–4) obesity (35%), hypertension (9%), impairment of executive function (13%), attention (9%), memory (4%), impaired strength (48%), flexibility (39%), muscular endurance (36%), and mobilty (36%); the most prevalent chronic conditions in the same investigation were overweight/obesity (65%), elevated fasting glucose (37%), high total cholesterol (35%), and hypertension (25%) [28].

According to an investigation by Bhakta et al. from the St Jude Lifetime Cohort Study, childhood NHL survivors experience on average 15.1 grade 1–5 and 3.9 grade 3–5 chronic health conditions per individual by 50 years of age [29]. According to that study, the diagnosis groups of late effects are auditory, infections, reproductive, neurology, muscoloskeletal, endocrine, pulmonary, gastrointestinal, ocular, hematology, renal, cardiovascular, and neoplasms.

For several years rituximab, a chimeric anti-CD20 monoclonal antibody, has led to improved response rates in the treatment of childhood B-NHL, but from the current point of view, there is no knowledge about late effects which should be investigated in future trials [30].

The reader is also referred to the Chaps. 1–17, 37–44 of this book.

Long-term follow-up of childhood NHL survivors is performed according to the recommendations of the International Guideline Harmonization Group (www.ighg.org), to the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and to the LESS study (www.nachsorge-ist-vorsorge.de) in Germany.

21.3.3 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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22 Late Effects After Treatment of Hodgkin Lymphoma in Childhood and Adolescence

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22.1 Treatment for Hodgkin Lymphoma in Childhood and Adolescence

Pediatric Hodgkin lymphoma (HL) has now been treated successfully in cooperative group trials [1–5] since the late 1970s. In adult patients with early-stage disease, high-dose extended field radiation was shown to be effective. Chemotherapy combinations of mechlorethamine, vincristine, procarbazine and prednisone as well as doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) or combined-modality treatment were only given for advanced disease [6]. For children, these treatments were modified by reducing radiotherapy and field size and applying chemotherapy across all disease stages. When concerns about late effects of treatment in aging survivors of pediatric cancer emerged [7–10], general treatment approaches started to change. The use of alkylators was reduced, and the number and composition of chemotherapy cycles were adapted to individual risk factors [2–4, 11, 12]. Radiotherapy (RT) was limited to involved fields and doses adapted to disease risk [1–4]. Furthermore, the concept of tailoring therapy in dose-dense regimens by using early response assessment was refined [12]. Procarbazine was gradually eliminated to reduce the risk of male infertility; etoposide and doxorubicine were substituted to reduce the cumulative alkylating dose [12–15]. Varied treatment approaches for pediatric HL have evolved by collaboration among cooperative groups. Most European and North American study groups have pursued combined-modality treatment approaches [4, 14, 16–25]. Central and South American groups however used to favor chemotherapy-only regimes [26, 27].

22.1.1 Evolution of Treatment by Consecutive Trials

The most recent European trial builds on the experience from eight successive DAL/GPOH study generations starting the first trial in 1978. Treatment of pediatric Hodgkin's lymphoma has stepwise been optimized since and established the current standard in the participating countries. From the second study generation (DAL-HD-82) onward, the backbone of the treatment strategy has been constituted, and changes have evolved gradually.

Patients have been stratified into three treatment groups (TG-1, TG-2, and TG-3) according to Ann Arbor stage (TG-1 stage IA/B and IIA; TG-2 stage IEA/B, IIEA, IIB, and IIA; TG-3 stage IIEB, IIIEA/B, IIIB, and IVA/B). All patients started treatment with two intensive

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induction chemotherapy cycles. Initially, the OPPA cycle comprised the standard treatment for induction, and later the OEPA cycle was used.

Patients in TG-2 and TG-3 received two and four chemotherapy cycles for consolidation, respectively. The COPP cycle comprised the standard consolidation treatment, and the COPDAC cycle was used later.

Following chemotherapy, all patients used to receive involved field radiotherapy (RT). Then involved-node RT was administered in selected cases only and based on response assessment. For details and treatment evolution over 30 years from DAL-HD 78 up to GPOH- HD 2002, see Table 22.1.

22.1.2 Elimination of Procarbazine and Introduction of Dose-Dense Chemotherapy Regimen to Preserve Male Fertility

After it became apparent that procarbazine induces male infertility [28], several attempts were made to eliminate procarbazine from the OPPA (vincristine, procarbazine, prednisone, doxorubicin) and COPP (cyclophosphamide, vincristine, procarbazine, prednisone) cycle in order to reduce male infertility and preserve high cure rates.

In the DAL-HD 85 study, procarbazine was omitted in OPA (vincristine, prednisone, doxorubicin) and replaced by methotrexate in COMP (cyclophosphamide, vincristine, methotrexate, prednisone). By eliminating procarbazine, male fertility indeed was preserved [28, 29], but treatment efficacy was compromised with 4-year EFS rate dropping to 54–86% [30]. In the following study generation DAL-HD 87, procarbazine was reintroduced into the COPP cycle but still omitted in the OPA cycle. 7-year EFS and overall survival (OS) rates for all patients improved (85% and 97%, respectively) [31] but still were lower than in the previous DAL-HD 82 study generation. Induction treatment was therefore re-intensified in the following DAL-HD 90 study: female patients received again OPPA cycles; in male patients, procarbazine was replaced by 500 mg/m^2 etoposide given over 4 days (OEPA) [4]. With this strategy, EFS rate and OS improved again to results comparable to the previous DAL-HD 82 study although therapy intensity was clearly reduced. By introducing etoposide, the rate of male infertility was significantly reduced [32] in TG-1 (2× OEPA), while about half of the male patients in TG-2 and TG-3 still showed abnormal FSH values after 2× or 4× COPP cycles. There was however a tendency for worse EFS in male patients compared to female patients. Based on the assumption that OEPA was less effective than OPPA, OEPA was intensified extending etoposide administration from 4 to 5 days (OE*PA with 20% more etoposide). Furthermore procarbazine was replaced by dacarbazine in the COPP cycle resulting in COPDAC (cyclophosphamide, vincristine, dacarbazine, prednisone) as procarbazine could not be dropped without being replaced by an appropriate substitute. Dacarbazine is less likely to cause infertility in males and a premature menopause in females. In the following HD 2002 pilot study, all male patients received a completely procarbazine-free regimen with intensified OE*PA and COPDAC cycles. Outcomes of male patients treated with the OEPA-COPDAC regimen were comparable to those of female patients receiving the OPPA-COPP standard treatment [14]. In contrast to these gender-stratified trials, the effect of OE*PA-COPDAC versus OE*PA-COPP was the subject of the following EuroNET-PHL-C1 trial. All patients now received OE*PA, but patients in intermediate- (TG-2) and high-risk (TG-3) groups were randomized to receive either COPP or COPDAC.

22.1.3 Response Adaptation to Reduce or Eliminate RT

In HL trials in adults, RT remains an essential component of treatment, especially for patients with early-stage disease who are treated with ABVD chemotherapy. The combined-modality approaches provide high response rates with EFS rates of 90%, but the risk of radiation-induced late effects such as

Table 22.1 Evolution of pediatric Hodgkin lymphoma treatment over 30 years from DAL-HD 78 up to GPOH-HD 2002

Trial	Patients (n)	Splenectomy for staging	Chemotherapy	Indication for RT	Radiotherapy: Standard dose (Gy) and field			EFS	OS
					TG 1	TG 2	TG 3		
DAL-HD 78 1978–1981	170	91%	TG 1 (I, IIA): 2× OPPA[a] TG 2 (> IIA): 2× OPPA[a], 4× COPP[a] VBL during RT	All patients	36–40 EF/36–40 IF and 18–20 to adjacent fields			87% [30]	92%
DAL-HD 82 1982–1984	203	40%	TG 1 (I, IIA): 2× OPPA[a] TG 2 (IIB, IIIA): 2× OPPA[a], 2× COPP[a] TG 3 (IIIB, IV): 2× OPPA[a], 4× COPP[a]	All patients	35 IF	30 IF 5–0[a]	25 IF 5–10[a]	94% [30]	95% [30]
DAL-HD 85 1985–1986	98	32%	TG 1 (I, IIA): 2× OPA TG 2 (IIB, IIIA): 2× OPA, 2× COMP TG 3 (IIIB, IV): 2× OPA, 4× COMP	All patients	35 IF	30 IF 5–10[a]	25 IF 5–10[a]	72% [30]	99% [30]
DAL-HD 87 1987–1990	196	30%	TG 1 (I, IIA): 2× OPA TG 2 (IIB, IIIA): 2× OPA, 2× COPP[b] TG 3 (IIIB, IV): 2× OPPA[b], 4× COPP[b]	All patients	30 IF	25 IF 5–10[a]	20 IF 5–10[a]	85% [31]	97% [31]
DAL-HD 90 1990–1995	574	–	TG 1 (I, IIA): girls: 2× OPPA[b], boys: 2× OEPA TG 2 (IE, IIB, IIEA, IIIA): girls: 2× OPPA[b], 2× COPP[c], boys: 2× OEPA, 2× COPP[c] TG 3 (IIEB, IIIB, IIIEA, IV): girls: 2× OPPA[b], 4× COPP[c], boys: 2× OEPA, 4× COPP[c]	All patients	25 IF 5–10[a]	25 IF 5–10[a]	20 IF 10–15[a]	91% [4]	98% [4]
GPOH-HD 95 1995–2001	925	–	TG 1(I, IIA): girls: 2× OPPA[b], boys: 2× OEPA TG 2(IE, IIB, IIEA, IIIA): girls: 2× OPPA[b], 2× COPP[c], boys: 2× OEPA, 2× COPP[c] TG 3 (IIEB, IIIB, IIIEA, IV): girls: 2× OPPA[b], 4× COPP[c], boys: 2× OEPA, 4× COPP[c]	All patients except for CR at end of chemotherapy	20 mIF 10–15[a]	20 mIF 10–15[a]	20 mIF 10–15[a]	88% [21]	97% [21]
GPOH-HD 2002 2002–2005	573	–	TG 1(I, IIA): girls: 2× OPPA[b], boys: 2× OE*PA TG 2(IE, IIB, IIEA, IIIA): girls: 2× OPPA[b], 2× COPP[c], boys: 2× OE*PA, 2× COPDAC TG 3 (IIEB, IIIB, IIIEA, IV): girls: 2× OPPA[b], 4× COPP[c], boys: 2× OE*PA, 4× COPDAC	All patients except for CR in TG-1	20 mIF 10–15[a]	20 mIF 10–15[a]	20 mIF 10–15[a]	98% [14]	97% [14]

Abbreviations: *CR* complete remission (≥95% reduction of initial nodal volume and ≤2 mL residual volume in any initially involved site), *EF* extended field, *EFS* event-free survival, *IF* involved field, *mIF* modified involved field, *OS* overall survival, *PET* positron emission tomography, *RT* radiotherapy, *TG 1* treatment group 1, *TG 2* treatment group 2, *TG 3* treatment group 3

[a]Boost: if <75% volume reduction or <50 mL (DAL-HD 95) or >100 mL (GPOH-HD 2002, EuroNet-PHL-C1) residual mass in any initially involved nodal site

(continued)

Table 22.1 (continued)

[b]Modified involved field: lateral margins of radiation field depend on the residual tumor extension at end of chemotherapy

Cumulative doses per cycle:

OPPA[a]: prednisone (900 mg/m^2), procarbazine (1500 mg/m^2) max. daily dose 150 mg; vincristine (4.5 mg/m^2) max. single dose 2 mg, adriamycin (80 mg/m^2)

OPA: prednisone (900 mg/m^2), vincristine (4.5 mg/m^2) max. single dose 2 mg, adriamycin (80 mg/m^2)

OPPA[b]: prednisone (900 mg/m^2), procarbazine (1500 mg/m^2), vincristine (4.5 mg/m^2) max. single dose 2 mg, adriamycin (80 mg/m^2)

OEPA: prednisone (900 mg/m^2), etoposide (500 mg/m^2), vincristine (4.5 mg/m^2) max. single dose 2 mg, adriamycin (80 mg/m^2)

OE*PA: prednisone (900 mg/m^2), etoposide (625 mg/m^2), vincristine (4.5 mg/m^2) max. single dose 2 mg, adriamycin (80 mg/m^2)

COPP[a]: prednisone (560 mg/m^2) only in 2. and 4. cycle, procarbazine (1400 mg/m^2) max. daily dose 150 mg, vincristine (3 mg/m^2) max. single dose 2 mg cyclophosphamide (1000 mg/m^2)

COMP: prednisone (560 mg/m^2) only in 2. and 4. cycle, methotrexate (80 mg/m^2), vincristine (3 mg/m^2) max. single dose 2 mg, cyclophosphamide (1000 mg/m^2)

COPP[b]: prednisone (560 mg/m^2), procarbazine 1500mg/m^2), vincristine 3 mg/m^2) max. single dose 2 mg, cyclophosphamide (1000 mg/m^2)

COPP[c]: prednisone (600 mg/m^2), procarbazine (1500 mg/m^2), vincristine (3 mg/m^2) max. single dose 2 mg, cyclophosphamide (1000 mg/m^2)

COPDAC: prednisone (600 mg/m^2), dacarbazine (750 mg/m^2), vincristine (3 mg/m^2) max. single dose 2 mg, cyclophosphamide (1000 mg/m^2)

VBL: Vinblastine 2 mg/m^2 every 2 weeks during RT (only if duration of RT is <8 weeks, starting at week 9 of RT)

secondary malignancies, cardiovascular disease, and thyroid dysfunction in survivors after pediatric HL increases throughout their lifetime [9, 10, 33–35]. Pediatric HL study groups therefore balance the risk-benefit ration differently.

The DAL/GPOH-HD/EuroNet-PHL study group successfully reduced RT over eight consecutive trials. For the development of RT regimen by systematic radiotherapy reduction and elimination strategies in the DAL/GPOH-HD/EuroNet-PHL trials, see Table 22.1.

In the GPOH-HD 95 trial, RT was omitted for the first time in patients achieving anatomic CR after OEPA-COPP chemotherapy. In contrast to patients with low-risk disease, patients with intermediate- and advanced-stage disease and CR showed a significantly lower 10-year progression-free survival (PFS) than patients who did not achieved CR and therefore received IFRT [21]. In conclusion, assessment by anatomic response at completion of chemotherapy was not adequate to identify patients in whom RT can be spared without increasing the risk of relapse. In the following EuroNet-PHL-C1 study, RT was omitted in patients whose PET scans were negative after two initial intensified OE*PA cycles. Preliminary data suggest that this strategy is feasible to identify patients to have good long-term survival without RT.

The reader is also referred to the Chaps. 39, 40 of this book.

22.1.4 Standardizing the Definitions for FDG-PET Imaging for Initial Staging and Response Assessment

Functional FDG-PET imaging was increasingly used in Hodgkin's lymphoma already in the 1990s, and it is now routinely used in most centers. FDG-PET can image the entire body detecting peripheral metastatic lesions and more lesions than detected by CT/MRI. It can also better distinguish between vital and fibrotic/necrotic residual masses. This may have impact on disease stage and thus treatment intensity for some patients. FDG-PET images are currently interpreted visually, which is subject to high intraobserver variability [36] and should therefore be centrally reviewed within a clinical trial for quality assurance. FDG-PET-guided response adaption is increasingly used, but evaluation may differ by study groups. For the current EuroNet-PHL C2 trial, the definition for PET response was changed to a higher threshold for PET positivity with the aim to omit RT in more than 50% of all patients. Figure 22.1 shows FDG PET scan at initial staging and response assessment.

22.1.5 New Agents

New drugs have been studied in patients with relapsed of refractory HL and showed so far promising results for brentuximab vedotin and nivolumab [37]. Bretuximab vedotin has already been introduced into first-line-treatment in adults and children with advanced disease [38, 39] with the aim to further reduce the number of patients who require RT. Long-term effect caused by new agents are not yet clear and need to be carefully monitored.

22.2 Late Effects of Treatment of Hodgkin Lymphoma in Childhood and Adolescence

Long-term survivors of pediatric Hodgkin lymphoma are at risk for a wide range of late effects [40], with second malignant neoplasm and cardiovascular diseases being the leading causes of death in these patients [41]. The excess risks remain significantly elevated decades after treatment and are clearly associated with extent of treatment exposures. With adoption of new agents and contemporary treatment techniques in the evolution of HL-treatment, late effect risks need to be further monitored and follow-up recommendations continuously updated.

22.2.1 Second Malignancy

Pediatric HL survivors have an excess risk of a solid second malignancy that is clearly associated with RT and persists after treatment. Cumulative incidence increased up to 23.5% at 30 years

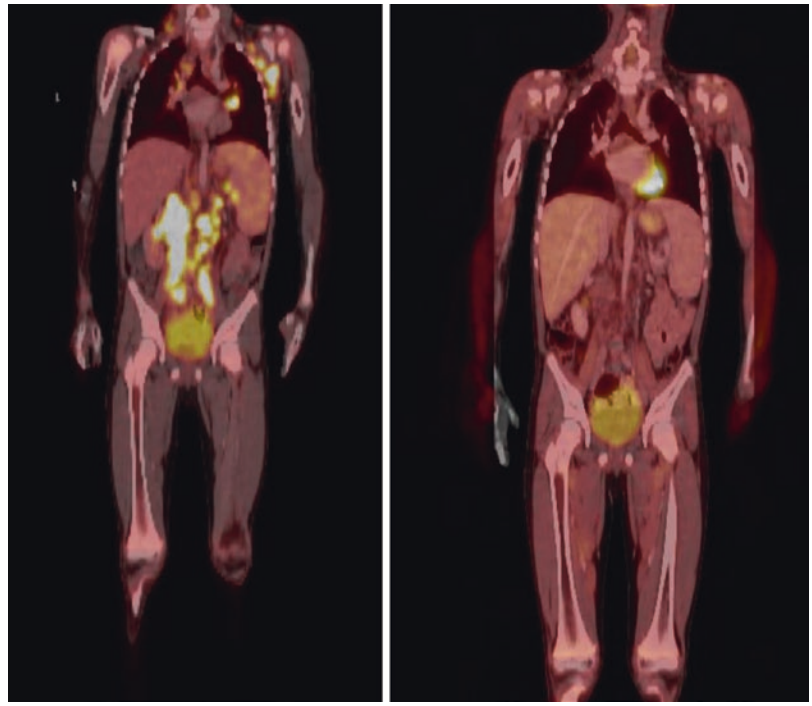

Fig. 22.1 Non-fused (^{18}F)fluoro-deoxy-glucose (FDG) positron emission tomography (PET) images of coronal slices at initial diagnosis (left) and at response assessment (right) after two cycles of OE*PA in a 10-year-old patient with classical Hodgkin lymphoma

[33, 42, 43]. Breast cancer is the most common solid second malignancy followed by thyroid cancer. Other second malignancies include tumors of the bone/connective tissue and esophagus; colorectal, lung, and gastric cancers; and melanoma at a younger age than expected in the general population, necessitating ongoing surveillance of this high-risk population Modern diagnostics, i.e., liquid biopsy, are currently under evaluation and may facilitate screening procedures in the future.

The reader is also referred to Chap. 14 of this book.

22.2.2 Cardiovascular Disease

HL survivors have a significant risk for cardiovascular disease (CVD) [34, 35]; both radiotherapy involving the heart and chemotherapy containing anthracyclines can increase the risk. Radiation-induced CVD includes coronary artery disease, valvular heart disease, myocardial dysfunction, electrical conduction abnormalities, and pericardial disease. Anthracyclines may, depending on the cumulative dose, lead to both acute cardiomyopathy and chronic cardiac conditions, especially congestive heart failure (CHF) [34, 35, 44–46]. Subclinical disease may be frequent, and sudden cardiac death due to silent coronary artery disease has been described [47]. HL survivors aged 50 will experience more than two times the number of chronic cardiovascular health conditions and nearly 5 times the number of more severe cardiovascular conditions compared to the general population. On average, HL survivors at risk have one severe, life-threatening, or fatal cardiovascular condition [48]. HL survivors were 4.4 times and 6.7 times more at risk of ischemic heart disease and cardiomyopathy/heart failure death, respectively, than expected [49]. HL survivors with radiation to the cervical or mantle region may also seem at risk to develop cerebrovascular disease such as premature carotid stenosis, transient ischemic attack, and stroke [50–52].

The reader is also referred to Chap. 1 of this book.

22.2.3 Pulmonary Dysfunction

Radiation to the lung appears to have the most significant impact upon the lung; survivors can

develop chronic pulmonary conditions such as chronic cough, oxygen need, lung fibrosis, and recurrent pneumonia. Compared to their siblings, patients after lung irradiation with 15 to ≤25 Gy have a 6.2–11.0 increased risk to develop lung fibrosis and a 2.9–3.1 increased risk for recurrent pneumonia [53].

The reader is also referred to Chap. 6 of this book.

22.2.4 Endocrinopathies

22.2.4.1 Fertility Impairment

RT and chemotherapy can both have an effect on the fertility of men and women, depending upon RT dose and cumulative dose of chemotherapy. In men, radiation doses of ≤1.2 Gy are associated with a reduced chance of recovery of spermatogenesis. In women treated at age 15–40 years, ovarian doses of 2.5–5 Gy will lead to permanent ovarian failure in 30–40% [54]. The risk for infertility after chemotherapy depends on the cumulative dose of alkylating agents. In men, procarbazine causes a high and dose-related incidence of testicular dysfunction in prepubertal as well as in pubertal boys affecting Leydig cell function and spermatogenesis, mostly resulting in azoospermia [28]. Woman appear to be less affected [55] but are at risk for premature ovarian insufficiency [56, 57].

The reader is also referred to the Chaps. 9, 10, 12 of this book.

22.2.4.2 Thyroid Dysfunction

Long-term risk in pediatric HL survivors to develop hypothyroidism can be 40% or higher after RT to the neck region [40, 58]. The risk of hypothyroidism after RT is dose related. Adult HL patients showed a risk of 70.8% to develop hypothyroidism, if the thyroid gland volume receiving 30 Gy was greater than 62.5% [54].

The reader is also referred to Chap. 8 of this book.

22.2.5 Other Late Effects

Fatigue is common after HL and local atrophy of muscle and connective tissue may occur. An increased risk of diabetes has been described [54]. Patients after splenectomy for staging are at risk for severe infections [59].

22.3 Recommendation for Follow-Up Exams After Treatment of Hodgkin Lymphoma in Childhood and Adolescence

Lifelong regular follow-up exams according to the risk given by the individual treatment are recommended as given in Table 22.2. Recent evidence-based follow-up recommendations by organ at risk can be reviewed at www.ighg.org, at

Table 22.2 Recommendation for risk-adapted follow-up care in long-term survivors after Hodgkin lymphoma in childhood and adolescence

Organ	Risk factor	Start of surveillance	Surveillance modality	Frequency	References
Heart, cardiovascular system	RT to mediastinum and anthracyclines	No later than 2 years after end of treatment	Cardiac exam, blood pressure, ECG, echocardiography, lipid profile	Every 2 years, prior to pregnancy or in the first trimester	[60–62]
	No RT, anthracycline <250 mg/m^2	No later than 2 years after end of treatment	Echocardiography	Every 5 years	
Cerebrovascular system/ subclavian arteries	RT to neck, supraclavicular, chest, mediastinal or mantle region, in particular ≤40 Gy		Neurological exam, examination of diminished pulses or carotid bruits, blood pressure	Annually	[61]

(continued)

Organ	Risk factor	Start of surveillance	Surveillance modality	Frequency	References
Thyroid	RT to neck or supraclavicular region	After end of treatment	Thyroid exam, TSH, fT4	Every 1–2 years	[61, 62][b]
Lung	RT to axilla, chest, mediastinal or mantle region	After end of treatment	Lung function testing Pulmonary exam	5 and 10 year after end of treatment, consider every 2–5 years thereafter	[61, 62][b]
Fertility					
Male	Cyclophosphamide, procarbazine, busulfan, HSCT[a], RT exposing testes	At survivors' request	Semen analysis		[63]
Female	Alkylating agents, cyclophosphamide, procarbazine, RT exposing ovaries	In case of menstrual cycle dysfunction	FSH, estradiol		[56]
Second malignancies					
Thyroid	RT to neck and supraclavicular and mantle region	5 years after radiation	Neck palpation/ ultrasound	Every 1–2 years	[64]
Breast	RT to mediastinum/ chest/axilla	8 years after radiation or at age 25	Clinical exam, MRI/ultrasound/ according to local screening program for familial breast cancer	Annually	[10, 65]
GI tract	RT to abdomen or or abdominopelvic region	5 years after radiation or at age 30	According to local screening program for familial colon cancer (i.e., colonoscopy every 5 years)		[61, 66]
Skin	Any RT	After end of treatment	Dermatological exam of irradiated field(s)	Annually	[61, 62]

Abbreviations: *RT* radiotherapy, *ECG* electrocardiogram, *TSH* thyroid-stimulating hormone, *fT4* free thyroxine, *FSH* follicle-stimulating hormone, *CT* computed tomography, *MRI* magnetic resonance imaging
[a]with conditioning regimen cyclophosphamide or fludarabine and melphalan
[b]IGHG-guideline not yet published

the homepage of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and at the LESS group homepage (www.nachsorge-ist-vorsorge.de) in Germany.

22.4 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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23 Late Effects in Langerhans Cell Histiocytosis of Young Cancer Patients

Milen Minkov and Stephan Ladisch

23.1 Introduction

Langerhans cell histiocytosis (LCH), which replaces the former terms eosinophilic granuloma, Hand-Schüller-Christian disease, Letterer-Siwe disease, and histiocytosis X, is a rare disease characterized by proliferation of abnormal histiocytes. With an incidence of 1–10 per million children under the age of 15 years, LCH is the commonest entity among the histiocytoses. It has a wide spectrum of clinical manifestations, variable natural course, and outcome. While the clinical aspects are well characterized, its pathobiology was largely unknown until recently. Recent knowledge allows characterizing LCH as a myeloid neoplasia with inflammatory properties [1–3]. Local and systemic inflammatory effects lead to granuloma formation and tissue damage in various organs.

The clinical spectrum of LCH ranges from a single bone lesion to the affection of multiple organs. It has been empirically established that patients presenting with involvement of one organ system (single-system LCH (SS-LCH)) have excellent survival chances. Patients with involvement of two or more organs (multisystem LCH (MS-LCH)), particularly those with dysfunction of the liver and of hematopoiesis, may have a progressive disease associated with considerable mortality [4]. Different prognostic factors and stratification systems [5, 6] elaborated over the last century served as a substitute for lacking biological markers to enable risk-adapted treatment. Current frontline treatment regimens have reduced mortality rate in risk organ-positive MS-LCH to 10–20% [7, 8]. However, a significant proportion of the long-term survivors suffers from permanent consequences (PC) affecting their quality of life. PC are defined as any form of permanent physical or neuropsychological handicap, attributable to the disease itself and developing at any time during the disease course. We will use the term "late effects" for treatment-related sequelae only.

23.2 Common Treatments Used in LCH

23.2.1 Historical Overview

Over the last century, surgery, topic ointments, radiation, and systemic therapy were used as single options or in combination for treating LCH depending on disease extent and location. Surgery

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has limited use in the LCH treatment. Its role is restricted to diagnostic biopsy and curettage/resection of single bone lesions, circumscribed skin lesions, or affected single lymph nodes.

Radiation had been used in the past in LCH primarily for treating bone lesions, soft tissue, and pituitary masses. Due to concerns about radiation-induced secondary malignancies and questionable benefit, its use is nowadays restricted to very rare cases of surgically inaccessible bone lesions or incipient spinal cord compression [4, 9, 10].

Systemic treatment has changed considerably over time, reflecting the changes in the understanding on the LCH biology [4, 11]. Only drugs with substantial evidence of activity in LCH, and those being currently in use, will be reviewed here.

The combination of prednisolone (PDN) and vinblastine (VBL), given in a number of variations over the years, is an effective and nontoxic treatment [7, 8, 12–16]. It is the current frontline therapy for all patients with MS-LCH.

Etoposide (VP16) emerged as a promising drug in the late 1970s. This prompted further evaluation in prospective trials [17, 18]. As a single drug, it did not show an advantage over VBL [19], and its addition to the combination PDN/VBL failed to improve survival [7]. Equivocal efficacy and potential leukemogenicity have limited its use in LCH.

Other drugs broadly used for treatment of LCH over the decades are methotrexate (MTX) and 6-mercaptopurine (6MP) [13, 20–22]. They are usually part of the continuation treatment.

Several case reports and small series suggested that 2-CdA could be effective in LCH. The results of the LCH-S-98 trial proved that it is a valuable second-line option in low-risk patients, but as a single drug, it fails to change the fate of patients with severe disease [23]. In view of the dismal prognosis of patients with very severe LCH and the promising results achieved with the combination of 2-CdA and Ara-C in a small series, this approach may be justified despite the high myelotoxicity of the regimen [24–27]. Nevertheless, restricted indications, use only within controlled prospective trials, and the availability of maximal supportive care are mandatory [26].

23.2.2 Current Guidelines for Patients Treated Outside of Clinical Trials

There is a general agreement on the indication of systemic therapy for patients with MS-LCH [4, 28–31]. An initial "intensive" phase for 6–12 weeks followed by a less intensive "continuation" phase for total treatment duration of at least 12 months is recommended based on the cumulative experience from the clinical trials of the Histiocyte Society [7, 8, 19].

The standard therapy for patients with MS-LCH is an initial 6-week course of PDN (40 mg/m^2/day orally for 4 weeks and tapering over 2 weeks) and VBL (6 mg/m^2 weekly IV bolus). Response to initial therapy is an important prognostic predictor. Hence, its assessment at the end of the initial 6-week course is essential. Further therapy depends on response to initial therapy. Responders with significant residual disease obviously benefit from a second 6-week course [8]. MS-LCH patients who do not improve after one or two initial courses of standard therapy (particularly those with hematopoietic or hepatic dysfunction) need alternative regimens [4]. Continuation therapy is recommended for all patients who after 6–12 weeks of initial therapy have attained complete disease resolution or considerable response. This consists of PDN/VBL pulses every 3 weeks ± daily oral 6MP to a total treatment duration of 12 months.

23.3 Risk Factors for Permanent Consequences

23.3.1 Age

It seems that younger age is associated with higher risk for PC, but its independent prognostic role is questionable, as it is also associated with higher disease extent and severity.

23.3.2 Disease Location

PC in LCH are per definition related to preceding direct involvement of the respective organ or tissue by active disease. Therefore, PC depend on location and extent of the underlying disease.

23.3.3 Disease Extent

Multisystem disease is associated with higher risk for PC compared to SS-LCH [14, 32–36]. The same is true for multifocal skeletal disease when compared to single-site SS-LCH [36, 37].

23.3.4 Length of Disease Activity and Disease Reactivations

Substantial evidence supports the conclusion that longer periods of disease activity are associated with higher incidence of permanent consequences [36, 38]. Reactivations per se increase the risk for PC [39–41], but they actually prolong the length of disease activity.

23.3.5 First-Line Treatment

There is no proof that aggressive chemotherapy prevents long-term effects [38, 42]. However, the results of the DAL Study Group and the low-risk arm of the LCH III trial suggest that timely initiation of systemic treatment of sufficient duration can at least reduce the risk of reactivation, which in turn could result in less PC [8, 14].

23.4 Incidence and Spectrum of Permanent Consequences

PC are associated with tissue destruction and scarring. Thus, they depend on the location of active disease. Up to 50% of the patients who survive pediatric-onset LCH have PC. The incidence figures for the various individual PC, as reported in the literature and cited in this review, vary greatly. This is probably due to methodological differences among the different studies (i.e., sample size, selection bias, cohort type, definitions, statistical methods, and observation time). As expected, there were also differences in the cohort composition among series from single tertiary centers, national studies, and international surveys [32, 35, 43]. All of those variables taken together underscore the need to interpret data with caution until rigorous prospective analyses are available. On the other hand, the impact of PC, once occurring, is mostly irreversible. While most of them are nonlife-threatening, fatal outcome due to PC has been reported in patients with end-stage pulmonary disease, sclerosing cholangitis, or debilitating neurodegeneration.

23.4.1 Permanent Consequences Related to Skeletal Lesions

Depending on location, skeletal lesions can cause a variety of long-lasting or permanent anatomical defects of the skeleton or of the adjacent tissues and organs, with or without functional deficits. Inconsistent categorization of skeletal deformities and use of collective terms, such as “orthopedic problems” or “orthopedic disabilities” [32, 33, 35, 37, 43, 44], preclude meaningful analysis of the literature with respect to their spectrum and severity. The distinction is critical; certain bone lesions, such as vertebral lesions, urgently require rapid intervention to prevent PC, whereas assessment and treatment in a more measured manner can be sufficient for LCH lesions of flat bones. Another problem in categorization arises from the fact that most non-osseous PC resulting from skeletal lesions are usually described as individual PC associated with other tissues and organs rather than as bone-related (e.g., tooth loss, proptosis, loss of vision, hearing loss, cosmetic PC, etc.). Because few data are available, it is largely unknown how often PC related to osseous lesions are severe enough to affect quality of life.

23.4.1.1 Skeletal Deformities

Skeletal deformities encompass bony defects, deformities, or asymmetries due to extensive disfiguring bone destruction or pathologic

fractures. Osseous lesions of the skull base often extend to adjacent structures and depending on location can result in permanent defects, such as facial asymmetry, proptosis, deafness, dental abnormalities, and basilar invagination [45, 46].

Proptosis (exophthalmus) is one of the characteristic manifestations of LCH. Its reported prevalence is between 8 and 25% [35, 43, 47]. It can improve with healing of the orbital lesions but is rarely completely reversible, mostly due to residual soft tissue scars. It usually does not affect vision and has importance as a cosmetic defect contributing to facial asymmetry.

Permanent loss of teeth, jaw deformity, and abnormal dentition can be due either to LCH (mandibular, maxillary, or palatal lesions) or to treatment (tooth extraction, curettage, radiotherapy). Loss of teeth was documented in 0.6% of the French national registry [32], but no specification about its cause (PC vs. late effect) was provided.

Compression of vertebral bodies is one of the most commonly reported osseous PC in LCH. Nevertheless, it accounted for only 2.5% of the total LCH population [32]. Partial reconstitution of vertebral height at long term is possible but unpredictable upon diagnosis [48–50]. Vertebral compressions may result in spinal column deformities (e.g., scoliosis, non-physiologic lordosis or kyphosis), which are rarely severe enough to need medical treatment. Neurological deficits due to compression and permanent damage of the spinal cord are extremely rare [32, 49, 51].

Deformation or shortening of the long bones with resulting asymmetry are extremely rare in LCH, as the bone lesions are located in the (meta) diaphysis and usually do not affect the growth plate.

23.4.1.2 Loss of Vision

Single-case reports describe partial or complete loss of vision caused by LCH [52–56], but most large LCH cohorts containing information on PC do not describe this complication at all, and its prevalence in the French national registry was only 0.6% [32]. Loss of vision in LCH can evolve from compression of the optic nerve or chiasm [53, 55], from globe displacement [56], or rarely from an intraocular lesion [52].

23.4.1.3 Hearing Loss

The prevalence of hearing loss among LCH patients ranges between 3 and 16% [12, 14, 32, 35, 57]. A multi-institutional survey by the Histiocyte Society reported hearing loss in 13% of the patients [35], and residual hearing loss was found in half of the patients with documented ear involvement in a single institution cross-sectional study [43, 58]. Hearing loss in LCH is most often conductive, resulting from mastoid lesions, but cases of sensorineural deafness due to inner ear damage are also possible [46]. Since unrecognized hearing loss could lead to learning problems, aftercare audiometry seems reasonable in children with skull base involvement (particularly those with involvement of the mastoid and labyrinth) [43, 46].

23.4.2 Endocrinopathies

Endocrinopathies are the most common PC in patients with MS-LCH. They are reported in 15–25% of the total cohorts of pediatric-onset LCH [12, 14, 33, 38, 59]. The vast majority are due to functional loss of the pypothalamic-pituitary axis resulting from local granulomas. Pituitary-related hormone deficits (DI, growth hormone deficiency, and less frequently deficiency of other anterior pituitary hormones) were the most prevalent endocrinopathies in all cohorts. Clinical signs (polydipsia/polyuria, growth failure, pubertal delay, adrenal insufficiency) or abnormal auxology, suggesting DI or anterior pituitary dysfunction, is an indication for MRI of the hypothalamus-pituitary region (HPR) and for assessment by a pediatric endocrinologist (including appropriate stimulation tests). Hypothyroidism in LCH is most commonly due to anterior pituitary dysfunction, but rare cases of direct affection of the thyroid gland are reported [60].

23.4.3 Central Diabetes Insipidus (CDI)

Central diabetes insipidus (CDI) is the most frequent LCH-associated endocrinopathy. It is due to loss of function of the posterior pituitary and may become manifest either before, concurrently, or after LCH diagnosis. Compared to other CNS-related PC, it occurs early in the disease process [34, 61]. The proportion of patients with CDI varied in different cohorts from 11% [62] up to 35% [12, 35, 38, 59, 63]. In some cases, DI is an inaugural manifestation of LCH [34, 61], posing considerable diagnostic challenge [61, 64, 65]. Well-documented risk factors for CDI are MS-LCH, involvement of craniofacial bones, prolonged disease activity, or reactivations [34]. Diagnostic criteria and appropriate diagnostic tests for CDI are comprehensively described elsewhere [66, 67] and are applicable irrespective of the underlying process. The characteristic finding by MRI is the lack of a hyperintensity signal of the posterior part of the sella ("posterior bright spot"), which indicates functional loss. In LCH-associated CDI, a thickened pituitary stalk is present in 50–70% of the cases [67–69]. Changes in size and enhancing pattern of the anterior pituitary may also be present. However, these findings are not specific enough to reliably exclude inflammatory or malignant diseases. CDI is usually irreversible [70, 71] and requires lifelong administration of synthetic desmopressin. It is also associated with an increased risk of anterior pituitary dysfunction and of parenchymal brain damage in LCH patients [34, 38, 68]. Therefore, most experts advocate systemic therapy for patients with new-onset CDI with the intention to reduce the risk of subsequent involvement of the anterior pituitary and brain parenchyma. While evidence confirming this rationale is still lacking, in view of the increased risk for devastating motor and cognitive neurologic PC, nontoxic, low-intensity systemic treatment may be justified in LCH patients with CDI [70].

23.4.4 Anterior Pituitary Dysfunction

Growth hormone deficiency is the second most common endocrinopathy, observed in 8–10% [35, 59, 72] of all patients with pediatric-onset LCH and in 15% [35, 59] of those suffering MS-LCH. It is particularly frequent in patients with DI, affecting up to 50% of them [38, 68]. If the hormone loss is severe and occurs at an early age, it may result in growth failure. This PC manifests with a deceleration of growth velocity or overt short stature (height below the third percentile for age) that is manifest within 2–5 years after diagnosis. Close clinical monitoring and the use of growth charts are required to facilitate early detection. Assessment by a pediatric endocrinologist is mandatory in cases with suspected anterior pituitary dysfunction (e.g., growth failure, delayed puberty, adrenal failure). Hormonal loss in LCH is usually irreversible and mandates replacement therapy. While growth hormone replacement was previously withheld because of concerns about aggravating the underlying disease, available data suggest that growth hormone replacement in LCH patients is both effective and safe [33, 59, 72, 73]. Recombinant human growth hormone in a dose of 16–20 IU/m^2/week as a daily subcutaneous injection seems appropriate [59, 72]. Since the growth hormone has multiple metabolic effects (e.g., acquisition of peak bone mass, muscle strength, etc.), replacement at "metabolic" dose (e.g., 0.3–1.5 IU/day) should be considered even after final growth completion into the adulthood [74].

23.4.5 CNS Involvement of Non-granulomatous Type

Parenchymal brain damage, known as non-granulomatous or "neurodegenerative" CNS-LCH [75–77], is one of the most severe PC of LCH. Its prevalence in the overall LCH population is relatively low (less than 1%), but it is more frequent among patients with DI or anterior pitu-

itary dysfunction [38, 76]. It typically presents with insidious (ponto)cerebellar symptoms, and some patients may attract attention for cognitive deficits and behavioral problems [76]. MRI signal alterations are consistent with degeneration (neuronal loss and demyelination) of the affected brain tissue. The lesions typically localize in the brain parenchyma of the cerebellum, pons, and basal ganglia. Biopsies of such lesions are usually nondiagnostic for LCH and reveal neuronal loss, demyelination, and gliosis [78]. There is no good agreement between MRI findings ("radiological CNS-LCH") and the severity of clinical manifestation ("clinical CNS-LCH"). Some patients with radiological findings do not develop clinical CNS-LCH even after many years of observation.

The course of clinical CNS-LCH can vary from spontaneous stabilization to rapid deterioration with loss of motor function and mental debilitation [76, 79, 80]. Apart from serial MRI examinations, standardized neurological and neuropsychological testing at regular intervals is essential for clinical decision-making [76]. Standard neurological examination should include scoring using the International Cooperative Ataxia Rating Scale [81, 82] and the Expanded Disability Status Scale [83, 84] to assure longitudinal comparability. Psychological assessment with age-appropriate standardized tests should cover full-scale, verbal, and performance IQ, attention span, verbal and visual-spatial working memory, and speed of processing. Intravenous immunoglobulin and intermediate-dose cytarabine both seem to alleviate the course of CNS-LCH. However, there is still little evidence of the effectiveness of any treatment of this PC [9, 85–87].

23.4.6 Pulmonary Permanent Consequences

20–50% of the pediatric patients with MS-LCH have pulmonary involvement [12, 14, 88–91], either already at the time of initial diagnosis of LCH or developing later [12, 90, 91]. In contrast, isolated pulmonary LCH, a disease form common in adolescents and adults [92, 93], accounts for less than 1% of all pediatric LCH cases [88]. The most frequent clinical symptoms comprise cough, chest pain, tachypnea, and dyspnea. Interestingly, clinical manifestations, pulmonary function, and radiographic chest findings do not always concur. Therefore, the resolution of clinical symptoms is not necessarily associated with radiographic clearing or with a reversion of functional deficits by spirometry [89]. Some patients, however, present with typical findings on chest CT but without any respiratory symptoms. Others have a problematic course with recurrent pneumothoraces or develop severe respiratory impairment requiring oxygen therapy due to progressive loss of lung tissue [33]. In those rare cases, tissue remodeling and scarring could culminate in chronic respiratory failure with the radiological picture of honeycombing. Permanent lung damage is fortunately uncommon in children, possibly because of the higher regenerative potential in young children [32, 33, 35].

23.4.7 Hepatic Permanent Consequences

The liver is one of the less frequently affected organs in LCH. Hepatic dysfunction (hypoproteinemia, hypoalbuminemia, and elevated transaminases) is typically a reversible manifestation of severe active LCH in infants. In those who survive, complete anatomical and functional regeneration of the liver is the usual outcome. On the contrary, cholestatic liver disease (jaundice, elevated direct bilirubin, alkaline phosphatase, and GGT) can be either an initial manifestation of LCH or develop later during its course. It is usually irreversible. The biopsy often reveals different degrees of chronic inflammation and fibrosis of the bile ducts (sclerosing cholangitis), which is generally progressive despite remission of LCH in the other organs. There is a single cohort reporting 18% prevalence of sclerosing cholangitis in MS-LCH [94], but in other studies and the experience of the authors, it is far less common [7, 8, 14, 19, 32, 35, 36, 43, 95]. This clinical pattern is rarely reversible by the treatment of the underly-

ing disease. The course is usually progressive, resulting in liver cirrhosis and organ failure. There is no established therapy, and the only available option for cases with end-stage organ damage is liver transplantation [94, 96, 97].

Describing the prevalence and the spectrum of PC in LCH is not enough to give a realistic picture of their impact on the well-being of the long-term survivors. There is an obvious need for categorization and objective measure of the severity and clinical relevance of the PC. A grading system of the PC will provide a basis for more precise clinical decision-making concerning prevention and treatment. A morbidity score proposed by Nanduri et al. [43] is an essential step in this direction that now warrants prospective validation before broad application in routine practice [43].

23.5 Late Effects

Surgical procedures could be responsible, for at least part of the permanent skeletal defects and deformities reported in LCH patients. Still, available papers do not discriminate between disease and therapy-related complications.

The topical nitrogen mustard had been previously used for treating cutaneous LCH. Concerns about the long-term toxicity of this alkylating agent have not been substantiated by the long-term follow-up observation of the patients [98]. Nevertheless, this drug is no longer in use because of the required complex handling procedures and because of its lack of availability.

Secondary tumors have been reported in association with radiation used to treat LCH (e.g., brain tumors, osteosarcoma, and thyroid carcinoma) [99]. Anterior pituitary dysfunction in LCH could potentially be due to radiation formerly delivered to the hypothalamic-pituitary region. Limited available data suggest, however, that at the dose previously used to treat intracranial LCH masses (up to 10–12 Gy but usually 6–7 Gy), radiation is unlikely to cause significant hormone loss [38, 59]. Moreover, radiation currently has little role in the treatment of pediatric LCH.

The backbone of the systemic therapy regimens used during the last two to three decades consists mainly of steroids and antimetabolites. Those drugs have acute adverse effects but nearly negligible long-term risks (at least at the cumulative dose used in the frontline treatment of LCH). The risk for permanent late effects could be higher in patients treated repeatedly for reactivations, but systematic studies with this respect are lacking. In the 1990s, there was an animated discussion about the possible leukemogenicity of VP16 in LCH patients [100–102]. Leukemia has been observed in few patients, but these had been treated mostly for reactivations and outside of protocols. Therefore, they have received high cumulative doses (>4 g/m^2) of the drug [103, 104], in contrast to the much lower doses received by the patients on the DAL, LCH-I, and LCH-II trials.

23.6 Recommendations for the Aftercare of Pediatric-Onset LCH Patients

As evident from the previous sections, some PC may be present at the time of diagnosis of LCH. Others may develop or become manifest months, years, and even decades later. This renders monitoring for PC and late effects in routine practice challenging. Regular follow-up at least until completion of growth and pubertal development is recommended. Current recommendations for the aftercare of patients with pediatric-onset LCH [10] are summarized in Table 23.1.

Due to the lack of large-scale systematic studies with sufficiently long follow-up, existing recommendations for the aftercare of LCH patients are mostly based on expert opinion or agreement of consensus panels [10, 105]. Follow-up is recommended for at least 5 years, but preferably until completion of growth and puberty (age of 18), to detect and intervene in late manifesting PC. Beyond 5 years of follow-up, yearly examinations are recommended for patients with clinically relevant PC and those being at risk for late manifestations (e.g., growth failure, pubertal delay, neurodegeneration).

Table 23.1 Recommended aftercare for pediatric-onset LCH according to the LCH group

Indication	Risk for defined PC or late effect	Investigation/test	Intervals after end of therapy or disease resolution[a]
All patients		Ask for polyuria/ polydipsia	At each visit
		Clinical examination, height, weight, pubertal status	1st year: each 3 months; then each 6 months until 5 years Thereafter: yearly
Treatment with leukemogenic drugs	Leukemia	Complete blood counts	Yearly
Evidence of liver disease (particularly cholestasis) at the end of treatment	Sclerosing cholangitis	GPT, GGT, Bili, ALP Liver sonography	1st year: each 3 months; than each 6 months until 5 years Thereafter: yearly
Persisting radiological or clinical pulmonary abnormalities at the end of treatment	Honeycombing, chronic respiratory insufficiency	Pulmonary function tests	1st year: each 3 months; then each 6 months until 5 years Thereafter: yearly
		Radiography (or low-dose CT)	1st year: each 6 months 2–5 years: yearly Thereafter: upon clinical judgment
Previous involvement of the facial bones, jaw, oral mucosa	Abnormal dentition	Dental assessment	As clinically indicated, at least once at 5 years
Previous temporal bone involvement	Hearing loss	Audiology	At school entry and as clinically indicated
History of polyuria/polydipsia	Central diabetes insipidus	Urine osmolality in an early morning sample, water deprivation test, MRI	At manifestation
Central diabetes insipidus	Anterior pituitary dysfunction Neurodegeneration	Brain MRI[b]	1st year: each 6 months 2–5 years: yearly Thereafter: each 2 years
Radiological neurodegeneration	Clinical neurodegeneration	Brain MRI[b]	1st year: each 6 months 2–5 years: yearly Thereafter: each 2 years
		Neurological exam	1st year: each 6 months 2–5 years: yearly Thereafter: yearly
		Psychological tests	At end of treatment, 2 yearly for 5 years Thereafter: upon clinical judgment

[a]Aftercare recommended for at least 5 years after completion of treatment, preferably until the age of 18 (completion of growth and puberty). Beyond 5 years, examinations are recommended yearly or upon clinical judgment for patients with already known PC and those being at risk for late manifestations

[b]For brain MRI guidelines, see Table 23.2

Table 23.2 Quality requirements to cerebral MRI in patients with LCH (modified from [10])

The brain MRI of patients with Langerhans cell histiocytosis has to ensure assessment of the entire brain and detailed evaluation of the hypothalamic-pituitary region. The aim of the MRI is to seek systematically for both granulomatous and non-granulomatous changes.
The investigation must include:
✓ Thin axial T1-weighted sequences (3 mm, 50% gap only for the HPR; 5 mm, 50% gap for the whole brain)
✓ Thin coronal and sagittal T1-weighted sequences (≤3 mm slice thickness for HPR)
✓ Axial T2-weighted and FLAIR sequences (≤5 mm slice thickness) over the entire brain
✓ Contrast-enhanced coronal and sagittal T1-weighted sequence brain and HPR with parameters as indicated above and one 5 mm/50% gap sequence with fat suppression throughout the whole brain
Additional sequences may be performed as indicated. It is not recommended to use magnetization transfer contrast (MCT), but if so, the same technique has to be used every time (this information has to be specified in the report).

HPR hypothalamic-pituitary region

Structured transition to specialized cancer aftercare services for adults is necessary for patients with known functional deficits and those at risk for very late PC (e.g., neurodegeneration). Based on the accumulated experience with the imaging characteristics of cerebral LCH, requirements for MRI allowing reliable assessment have been elaborated (Table 23.2).

Hopefully, with a careful and systematic approach to long-term aftercare of patients with LCH, the frequency and severity of the sometimes devastating PC will be improved and eventually eliminated.

Long-term follow-up is performed according to the recommendations of the International Guideline Harmonisation Group (http://www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the LESS group (www.nachsorge-ist-vorsorge.de) in Germany.

23.7 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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24 Diagnostics and Diagnosis of Late Effects in Childhood Brain Tumour Survivors

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24.1 Scope of the Problem: A Growing Group of Very Vulnerable Young People

Primary central nervous system (CNS)[1] tumours account for about 24% of childhood cancers, thereby presenting the most frequent solid tumours and second most frequent malignancies in childhood and adolescence [1, 2]. More than 400 children and adolescents are diagnosed with a CNS tumour in Germany each year. About 95% of them are treated according to prospective, multi-centre therapy optimisation studies or non-interventional registries, respectively, conducted by the German Paediatric Brain Tumour Consortium (HIT-Network) and the European branch of the International Society of Paediatric Oncology (SIOP-E). They collaboratively coordinate trials and reference centres for different childhood brain tumour entities, thereby promoting continuous optimisation of treatment concepts with quality-controlled standards for diagnosis, treatment and supportive care.

As a consequence, the overall survival rates for paediatric patients with CNS tumours continuously improved over the past three decades from below 50% to over 70%, depending on tumour type, site, response to treatment and late effects (LE) [3]. An estimated 8000 childhood brain tumour survivors (CBTS) are currently living in Germany, and numbers are rising [4]. This story of success, however, makes both survivors and their stakeholders, in particular their families, community, local educational and health-care

[1] *The following abbreviations will be used more than once in this chapter: CBTS* childhood brain tumour survivor, *CNS* central nervous system, *HIT* Hirntumor (*German* for "brain tumour"), *LE* late effect(s), *MRI* magnetic resonance imaging, *QoS* quality of survival.

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systems and medical caregiver team, face a double-edged sword: increasing quantity of survival *vs* multifactorial LE and therefore compromised quality of survival (QoS). In fact, up to 80% of CBTS experience significant, lifelong both tumour- and treatment-associated sequelae, as reviewed by Tallen et al. [3] and also outlined in Part I of this book. Each new generation of survivors will face new challenges as treatments evolve with progressing medical technology. The resulting complexity and multitude of health-care issues experienced by many CBTS need coordinated interdisciplinary care that many health-care providers may not be experienced with yet. Thus, many health-care centres have begun to develop multidisciplinary LE clinics that specialise in childhood cancer survivors. The goal is to maintain the survivor's health by monitoring for tumour- and treatment-related LE, including mental and social functioning and well-being, and to provide health education based on the individual therapy received.

The following paragraphs serve to increase the awareness of paediatricians and general practitioners to the importance of providing a risk-based, long-term follow-up care for CBTS in the community setting. Ultimately, ongoing communication between the paediatric cancer centre, primary care physicians and LE clinics is the cornerstone for ensuring high-quality care for this particularly vulnerable cancer survivor population.

24.2 The Need for Lifelong Care

Providing a successful transition from paediatric to adult-oriented health care is a challenge when caring for CBTS, as they age out of the paediatric health-care system. Hence, survivors should be well versed regarding their own health maintenance needs, potential LE, necessary surveillance related to their treatment and health-related behaviours that can reduce their risk of potential LE. Adolescent and young adult survivors also need to know the importance of maintaining continuous health insurance coverage to ensure access to LE screening. This can be difficult, since many of them may still be in the process of defining their career goals and are, therefore, not yet receiving employer-based health insurance coverage.

Besides neurological, sensorimotor, endocrine, cardiac, musculoskeletal, reproductive and cognitive sequelae, to name a few, CBTS frequently experience psychological consequences from diagnosis of their tumour, the time of treatment and managing survivorship, which may result in compromised activity and participation, thus social and academic difficulties into adulthood [3]. Finding and maintaining meaningful employment may be challenging due to issues such as cognitive delays, fatigue and social difficulties. These issues evolve mainly when the survivor was young at tumour diagnosis. Therefore, multidisciplinary surveillance should include not only the long-term follow-up but also the acute period, i.e. the time immediately after diagnosis and before and during treatment, so that interventions to later improve school and job performance may be implemented early. Coordination of services between the school system, medical team and social services is also strongly required to maximise the survivor's potential for success in adulthood. Since the nature of most LE is rather chronic than terminal, multidisciplinary surveillance along with health education should be provided lifelong in order to guarantee optimal QoS for all patients treated for a CNS tumour in their childhood or adolescence.

24.3 Screening for Late Effects

Due to the heterogeneity of paediatric CNS tumours, thus diversity of corresponding treatment strategies, not all of the survivors may develop the same LE or may develop them to different degrees, respectively. Hence, different national guidelines and recommendations have been established for diagnosis, monitoring and management of both acute adverse events and LE based on the different tumour types and treatments, respectively [3, 5]. The current concepts, limitations and future requirements of efficient screening for LE, of which particularly survivors

of a childhood CNS tumour are at high risk for, will be discussed in the following paragraphs.

24.3.1 Surveillance Neuroimaging

During the last decades, continuous optimisation of neuro-radiological techniques has helped remarkably to better understand many of the neuroanatomical and neuro-biochemical processes that underlie the LE induced by childhood CNS tumours and associated treatments [6]. Neuroimaging for analysis, surveillance and differentiation of these are not only required for diagnosis of specific LE but also crucial in order to identify new risk factors, thereby improving both current treatment strategies and interventional concepts for management. The interpretation of neuroimaging results needs special expertise considering the multifactorial pathogenesis of LE.

For most entities of paediatric CNS tumours, the characteristic MRI features are well reported and beyond the scope of this chapter. Many features, however, have been identified as specific for medulloblastoma, dysembryoplastic neuroepithelial tumour, pilocytic astrocytoma and pleomorphic xanthoastrocytoma, partially by diffusion and fluid-attenuated inversion recovery (FLAIR) techniques [7, 8]. Besides, conventional MRI is the gold standard neuroimaging method for planning therapy and evaluating prognosis for children and adolescents with certain brainstem gliomas [9]. For those with certain tectal or infiltrative brainstem tumours, or with neurofibromatosis type 1 and optic pathway glioma, respectively, certain MRI characteristics even contribute to tumour diagnosis, thereby bypassing neurosurgical intervention for histological confirmation. Also, tumour relapse and secondary CNS tumours can be recognised by conventional MRI—often even before clinical signs occur [summarised in 10]. Whether such surveillance neuroimaging impacts prognosis has been controversial for a while, in particular regarding patients with medulloblastoma. But considering that the treatment options for the salvage of recurrent disease are continuously being improved, the benefits of identifying radiological clues of a relapse prior to symptoms occurring are by now increasingly acknowledged [11, 12]. In addition, there is growing evidence that the rate of secondary tumours related to a cancer predisposition syndrome such as Li-Fraumeni or Gorlin syndrome, to name a few, that harbour germline mutations of growth-regulating genes (e.g. *TP53*, *Ptch*, *Sufu*) is higher than previously thought and may account to up to 10% of children with CNS tumours [13]. Therefore, even in children with an initially unobtrusive family history, genetic counselling should be considered in addition to regular clinical assessments and neuroimaging surveillance.

MRI, especially with the integration of diffusion- and perfusion-weighted imaging, is also optimal for diagnosing stroke—a common LE after cranial radiotherapy, in particular, when the Circle of Willis was included in the radiation field. In fact, diffusion-weighted imaging is a highly sensitive technique in the diagnosis of cytotoxic oedema. It provides the unique option of detecting an acute ischaemic stroke in patients with apparently normal computed tomography and MRI conventional sequences [14]. Moreover, perfusion-weighted imaging can offer a prognostic value: in acute stroke, it allows to determinate the volume of tissue at risk and the vascular distribution of ischaemia; the level of perfusion to the ischaemic tissues may also help to determine the relative benefits and risks of a given therapy [15]. However, when it comes to distinguishing between tumour and other contrast-enhancing tissue, such as neurotoxic damage caused by primary, progressive or recurrent disease, intrathecal chemotherapy or craniospinal irradiation, conventional MRI is rather insufficient [16]. Instead, various MRI-based, functional imaging techniques have proven efficient in differentiating these changes, particularly those resulting from radiation injury. These include delayed-contrast MRI for calculating high-resolution treatment response assessment maps [14], proton magnetic resonance spectroscopic imaging and diffusion tensor imaging, which are helpful not only for tumour staging and treatment planning [17] but also both for distinguishing viable tumour from

radiation necrosis and for surveilling and characterising changes in white matter integrity and CNS metabolism [16]. Late-delayed effects were detected by diffusion tensor imaging also in frontal lobes of CBTS after radiotherapy of medulloblastoma [18]. The affected structures are key players in working memory and may therefore contribute to socio-emotional and other executive functions via maintaining neural overlaps in neural networks [19, 20].

In fact, various LE in CBTS may be correlated with neuro-radiological findings. Considering that certain neuroimaging studies highlight the negative effects of cranial radiotherapy and/or chemotherapy with methotrexate on white matter function [21, 22], the decline of cognitive function experienced by most CBTS after cranial radiotherapy may be caused by compromised white matter integrity [23–27]. However, most reports on radiotherapy-related LE are based on dated treatment protocols, while the focus of current irradiation strategies mainly involves fine-tuning of target volume as well as dose reductions, beam orientation and optimisation of fractionation regimens. Hence, positive changes of both clinical and neuro-radiological LE patterns are expected to be observed soon. Therefore, multi-centre prospective studies are now needed to assess the correlation of specific LE with neuroimaging findings after different treatments (such as whole brain radiotherapy or craniospinal radiotherapy plus boost to tumour site or local field radiotherapy, respectively, with or without concomitant chemotherapy). Additionally, the dose-effect dependency with respect to dose distribution within the CNS needs to be evaluated accordingly. In conclusion, the routine use of functional neuroimaging parameters may contribute to developing new treatment strategies that are associated with reduced toxicity. Since most of the numerous functional MRI techniques, which appear to be useful for the evaluation of LE, have only been validated in adult CNS tumour patients or survivors, they need confirmation in large, representative paediatric cohorts. Last but not least, neuroimaging in the young may sometimes be challenging: random movement (e.g. as a consequence of young age, sedation issues) may lead to artefacts, thus potential mis- or impossible interpretation of findings. Hence, improved equipment, including stronger magnets that result in both higher speed and resolution, as well as increased sensitivity to gadolinium enhancement will further improve the options of neuro-radiological surveillance of LE. The currently preferred neuro-radiological techniques, characteristics and limitations in diagnostics and diagnosis of various tumour- and treatment-related LE in CBTS are summarised in Table 24.1.

24.3.2 Neurocognitive Testing

Regardless of their age, CBTS may face a myriad of cognitive challenges during education and career development as well as later at work. Particularly when experiencing treatment-induced grey and/or white matter disease and/or severe ototoxicity [28], they are at risk for neurocognitive decline. The impairments may range between compromised fluid and crystallised intelligence, memory, mental processing speed, visual processing and selective attention. Restrictions in psychomotor abilities (e.g. fine motor skills) as well as a general reduction of motion sequences have also been observed [29, 30].

An integral part of the academic evaluation process for CBTS is neurocognitive testing in order to initiate appropriate education services and vocational counselling. The goal is to provide optimal functioning at school for school age survivors or, for adults, the tools and knowledge to find appropriate and meaningful employment, respectively. Ideally, neurocognitive diagnostics and corresponding interventions begin in school and continue through adulthood in order to identify the survivor's strengths and weaknesses, thereby maximising academic performance.

Neurocognitive testing should be performed regularly after certain treatments. According to the Children's Oncology Group's Late Effects Screening Guidelines, it should also be performed when the survivor is more likely to experience academic difficulties or school transition periods, for example, elementary school to mid-

Table 24.1 Reported neuroimaging surveillance techniques and characteristic findings of common tumour- and treatment-related late effects* in childhood brain tumour survivors and additional information of relevance for planning individual long-term care

Late effect*		Recommended neuroimaging techniques	Characteristic finding(s) (*corresponding imaging technique*)	Additional information	Refs.
Cerebrovascular disease	Stroke	*Conventional MRI*** (with integrated DWI and PWI) *TOF/PC-MRA* *MRS* *MRV*, all including T1- and T2- (with and without fat suppression) and PD-weighted sequences *IADSA*	• Infarction, haemorrhage (*conventional MRI*, *MRV*) • Thrombus (*MRA*, *MRV*) • Ischaemia, oedema (*MRS and DWI with MRA*) • Vascular distribution of ischaemia (*PWI*) • Vascular lesions, e.g. circumferential clefts, intimal flaps, intraluminal and intramural thrombi (*MRA*)	Increased risk in survivors with NF1, metabolic disorders, sedentary lifestyle, after RT of hpa	[56]
	Moyamoya syndrome (MMS)	*IADSA* (for diagnosis and surveillance) *Conventional MRI***, *MRA* (for surveillance)	• Bilateral ICA stenosis, collateral network (rete mirabile) with typical pattern ("puff of smoke") (*IADSA*) • Changes in flow patterns (*IADSA*, *MRA*) • Signal voids due to the development of collaterals ("ivy sign") (*MRI*, *post-contrast T1-weighted sequences*) • Slow flow in leptomeningeal vessels • Parenchymal infarction (*MRI*, *FLAIR*) • Vascular wall thickening, ring enhancement, internal carotid narrowing (*MRI*)	Increased risk in survivors with young age at CBT diagnosis, NF1, metabolic disorders, after tumour and RT of optic chiasm *DD*: irradiation arteritis	[10, 56, 57]
	Siderosis	*Conventional MRI***	• Hypointense rim surrounding brainstem, cerebellar fissures and/or cranial nerves	Source of underlying chronic SAH needs to be identified for effective treatment	[58, 59]
	SMART syndrome	*Conventional MRI***	• Temporal and occipital gadolinium enhancement • Gyral swelling	Increased risk in male survivors of PF tumours who received CRT and have no family history of migraine; onset can be decades after end of treatment	[60, 61]
	Vascular malformations (telangiectasia, cavernoma, aneurysm)	*Conventional MRI*** *MRA* *MRV* *IADSA*	• *Telangiectasia*, *aneurysm:* (localised) vasodilatation, vessel tortuosities, vessel ballooning, SAH • *Cavernoma*: vein-like caverns with low blood flow	Increased risk (for aneurysms) in patients after CRT of CWI; can be asymptomatic	[62–64]

(continued)

Table 24.1 (continued)

Late effect*		Recommended neuroimaging techniques	Characteristic finding(s) (*corresponding imaging technique*)	Additional information	Refs.
Grey and white matter disease	Radionecrosis	*Conventional MRI*** *FDG-PET* *MRS*	• Space-occupying necrotic lesion with mass effect • "Soap-bubble" or "Swiss cheese"-like interior of necrotic lesion • Chronic, persistent curvilinear contrast enhancement • Haemosiderin deposits (T2-weighted sequences)	Increased risk in survivors after high total CRT doses (e.g. due to progressive/recurrent disease); biopsy required for final diagnosis *DD:* (pseudo)progression, recurrent disease—typically occurs later than pseudoprogression (i.e. 3 months to 3 years after CRT)	[65–70]
	Leukoencephalopathy	*Conventional MRI***	• *Grade 1*: mild increase in SA space, mild ventriculomegaly, small (+/− multiple) focal T2 hyperintensities (involving <33% of susceptible areas) • *Grade 2*: moderate increase in SA space, moderate ventriculomegaly, focal T2 hyperintensities (33–66% of susceptible areas) • *Grade 3*: severe increase in SA space, severe ventriculomegaly, T2 hyperintensities involving nearly all white matter (at level of centrum semiovale/diffuse low attenuation) • Lacunes, focal white matter lesions (up to 15 mm in diameter)	Increased risk in survivors after CRT and concomitant chemotherapy with MTX	[71]
	Posterior fossa syndrome (PFS)/ cerebello-cerebral diaschisis	*Conventional MRI*** *SPECT* *DTI* *Tractography*	• Ischaemia, oedema, structural damage of midline structures (*MRI*) • Local hypoperfusion (*SPECT*) • White matter lesions (*DTI*) • Disrupted cerebello-cerebral white matter tracts (*tractography*)	Mainly clinical diagnosis; increased risk in survivors after PF surgery (especially large MB with brainstem involvement, gross radiological tumour removal, vermal incision)	[3, 20, 72–75]
CNS infections	Meningitis, meningoencephalitis, brain abscess, shunt infection	*Conventional MRT*** *DWI-MRA* *CT* (in emergency situations and/or to assess bony structures and/or to identify calcifications)	• *Common causes and consequences of CNS infections:* brain oedema, hydrocephalus, haemorrhage, infarction, parameningeal foci of infection (sinusitis, mastoiditis), intracranial air due to dural fistula, meningeal/ventricular ependymal involvement, sinus vein thrombosis, calcifications, subdural empyema • *Brain abscess:* ring-shaped, focal contrast enhancement	Increased risk for survivors with shunt/intraventricular catheters, prolonged treatment-induced immunosuppression; frequently subtle or absent clinical symptoms and limited specificity of neuroimaging regarding DD of CNS infection require combined, careful interpretation of clinical course, laboratory parameters and imaging results	[10]

Posterior reversible encephalopathy syndrome (PRES)	*Conventional MRI*** (with integrated DWI, FLAIR)	• Abnormalities occipitoparietal region (bilateral; *T2-weighed sequences*) • Vasogenic oedema (*DWI*, *FLAIR*)	Increased risk in survivors with renal dysfunction, hypomagnesaemia, immune suppression and after treatment with certain chemotherapeutic agents (e.g. VCR, HD-MTX, cytarabine, CDDP)	[10]
Pseudoprogression	*Conventional MRI** *combined with MRS and FDG-PET*	• Temporarily increasing contrast enhancement at tumour site (*T1 sequences*) • No long-term increase as in progressive disease • No mass effect as in radionecrosis or (advanced) progressive disease	*DD:* radionecrosis, progressive or recurrent disease—pseudoprogression is usually clinically asymptomatic and appears earlier than radionecrosis (i.e. within the first 3 months after CRT)	[10, 70]
Progressive disease, relapse	*Conventional MRI** *combined with MRS and FDG-PET*	• Persistent/increasing (with time) contrast enhancement any anatomical site of the CNS (including the initial tumour localisation and leptomeninges) • Mass effects/space-occupying lesions	*DD:* radionecrosis, pseudoprogression, SMN	[10, 76–78]
Secondary malignant neoplasms (SMN)	*Conventional MRI**	• Persistent/increasing (with time) contrast enhancement any anatomical site of the body (in particular CNS or other organs that have been involved in CRT field) • Mass effects/space-occupying lesions	Can occur both early and decades after the end of treatment; increased risk in survivors with hereditary cancer predisposition (e.g. Li-Fraumeni syndrome, mismatch repair deficiency, Gorlin syndrome, familial adenomatous polyposis, or Fanconi anaemia *DD:* progressive or recurrent disease	[10]

Symbols and abbreviations: * tumour- and/or treatment (chemotherapy/radiotherapy)-related ([3], Part I, Chap. 5 in this edition); ** contrast enhancement series as well as T1- and T2-weighted studies; *CBT* childhood brain tumour; *CDDP* cisplatin; *CNS* central nervous system; *CRT* cranial RT; *CT* computed tomography; *CWI* Circle of Willis; *DD* differential diagnosis; *DTI* diffusion tensor imaging; *DWI* diffusion-weighted imaging; *FDG-PET* fluorodeoxyglucose-positron emission tomography; *FLAIR* fluid-attenuated inversion recovery; *HD* high-dose; *hpa* hypothalamic-pituitary axis; *IADSA* intra-arterial digital subtraction angiography; *ICA* internal carotid artery; *MB* medulloblastoma; *MRA* MR angiography; *MR(I)* magnetic resonance (imaging); *MRS* MR spectroscopy; *MRV* MR venography; *MTX* methotrexate; *NF1* neurofibromatosis type 1; *PC* phase-contrast; *PD* proton density; *PF* posterior fossa; *PWI* perfusion-weighted imaging; *RT* radiotherapy; *SA(H)* subarachnoid (haemorrhage); *SMART* stroke-like migraine attacks after RT; *SMN* secondary malignant neoplasm; *SPECT* single photon emission tomography; *TOF* time-of-flight; *VCR* vincristine

dle school. Further testing is recommended at any time, when the survivor is experiencing any new academic difficulties [31, 32].

Diagnosing distinct neurocognitive impairments is challenging, as the performance levels of the young survivors are often compromised due to their medical condition and the effects of therapy. While a recently validated neuropsychological test battery enables health-care providers to assess the specific needs of CBTS in their daily lives and to optimise parent counselling [33], other current measurement tools [34, 35] may still need broadening regarding their feasibility, particularly for CBTS with visual loss or different ethnic and language backgrounds, respectively. In general, complete test batteries, which are usually based on theoretical models and associated with long and intense examination times, are not recommended for testing CBTS. They frequently cause additional stress for the tested individual, thereby possibly leading to biased results [33].

Hence, neurocognitive testing tools for CBTS should be carried out based on predefined cognitive domains. A specifically designed array consisting of a limited number of targeted tests can provide data that help in assessing the cognitive domains of concern individually and in a relatively short period of time, thus without causing additional stress or producing redundant results, respectively. To ensure valid comparability, however, interpretation of the results needs to be based on an established theoretical framework. The Cattell-Horn-Carroll model of intelligence [36], to name one, offers a hierarchical stratum approach. It integrates various existing models of intelligence, factors of which are predefined. The model framework is designed to individually combine different tests for different cognitive functions of interest, for example, by applying a cross-battery approach [37]. Table 24.2 gives an overview of cognitive domains and corresponding tests/subtests currently used within international studies [33, 38]. Combined tests have proven applicable and effective in international paediatric CNS tumour studies. The generated, compact information can be used as a basis for therapeutic interventions (e.g. occupational therapy, physiotherapy) or academic decisions and support, such as change of school after end of treatment.

Ideally, neurocognitive functions in CBTS are monitored regularly, as some impairments may progress over time or only occur at a later

Table 24.2 Cognitive domains of interest and corresponding test measures used within currently active international paediatric CNS tumour studies

Cognitive domain*	Specific tests (*cognitive function to be assessed*)
Perceptual/fluid reasoning	Raven's progressive matrices, Wechsler matrix reasoning (*matrices*) Wechsler block design (*visual motor reasoning*)
Visual processing	VMI, WRAVMA, subtest drawing test; NEPSY, subtest design copy (*visual motor integration*)
Short-term memory	K-ABC-II, subtest number recall; Wechsler, subtest digit span forward (*number recall*)
Working memory	Wechsler—subtest digit span backwards (*number recall backwards*)
Psychomotor abilities (*Gp*, *Gps*)	Purdue pegboard, WRAVMA—subtest pegboard (*Pegboard*), finger tapping (*speed*, *steadiness*)
Comprehension-knowledge (crystallised intelligence, *Gi*)	Wechsler, subtest vocabulary; K-ABC-II, subtest riddle (*verbal semantic memory*)
Processing speed (*Gs*)	Wechsler—subtests coding, symbol search (processing speed)
Attention (reaction and decision speed (*Gt*))	Conners' continuous performance test (sustained attention); TEA-CH, subtest sky search; TAP, subtest divided attention (selective and dual attention)
Long-term memory (*Glr*)	WMS—subtests stories, word lists, dot locations, faces (visual and verbal episodic memory)

Symbols and abbreviations: * intelligence factors according to the CHC framework, *CHC* Cattell-Horn-Carroll model of intelligence, *CNS* central nervous system, *K-ABC-II* Kaufman Assessment Battery for Children—2nd edition, *NEPSY* A Developmental NEuroPSYchological Assessment, *TAP* Test for attention, *TEA-CH* Test for Everyday Attention for Children, *VMI* Beery Test for Visual Motor Integration, *WMS* Wechsler Memory Scale, *WRAVMA* Wide Range of Assessment of Visual Motor Ability

stage after the end of cancer therapy, while initial assessment at primary diagnosis often only reveals comparably mild deficits [39]. As suggested earlier, future studies should correlate neuropsychological data with neuroimaging results to map clinical symptoms to damaged CNS regions [40]. If performed consistently, this long-term follow-up may also help to better understand the processes associated with potential recovery of functions.

The reader is also referred to Chap. 15 of this book.

24.3.3 Endocrinological Follow-Up

Tumours close to hypothalamic-pituitary axis, such as optic pathway gliomas and craniopharyngiomas, as well as their local treatments, neurosurgery and CRT, are well-known to frequently cause endocrinopathies [3, 41, 42]. However, endocrine disorders are also seen in association with CBT outside this anatomical site, particularly within the first 5 years after diagnosis [41, 43]. Therefore, consistent, lifelong endocrinological follow-up, early diagnosis and appropriate management of endocrinopathies are crucial for *every* CBTS. This follow-up should include standardised schedules for physical exams and puberty surveillance, monitoring serum hormone levels, growth and bone density, to name a few endocrinological functions, that may have been damaged. The major goal is to improve final height outcome, lean body mass and bone density [5, 44], thereby reducing late morbidity, particularly growth failure, obesity and cardiovascular events, and early detection of late-onset secondary endocrinological malignancies such as thyroid cancer.

The reader is also referred to the Chaps. 7–12 of this book.

24.3.4 Monitoring Neurologic and Neurosensory Sequelae

CBTS are at high risk for both early and late neurologic or neurosensory sequelae [3]. Hence, prospective, sometimes lifelong, surveillance is required [45]. While most neurosensory and neurologic monitoring is usually based on well-defined schedules, as represented by the example in Table 24.1, and well-established methods, including gross motor subscale, and motor-area composite testing [46], electrophysiological monitoring and surveillance of ocular and ophthalmological functions, appropriate assessment of treatment-induced hearing loss requires combined audiological, oncological and otolaryngological expertise and can be challenging. The variability of patient cohorts, different chemotherapy dosages and routes of administration, varying CRT techniques and therapy regimens, concomitant treatments with other ototoxic agents and genetic predisposition make it hard to define standardised, clinically useful ototoxicity grading criteria [3]. In fact, many reports, including those addressing the communicative, educational and psychosocial significance of high-frequency hearing loss [28], may require prospective validation, since they are based on different treatment protocols and ototoxicity grading systems.

According to the current recommendations, all patients receiving ototoxic treatments should get audiograms prior to treatment, to each successive dose, when presenting with symptomatic ototoxicity and, depending on tumour type and treatment, during follow-up [45]. Although frequency measurements range from 250 to 8000 Hz, they vary in clinical practice, especially when assessing children, which can be challenging. For example, if a child refuses to put on earphones, the audiogram may be compromised, such as to sound field testing only, which—at many centres—is usually only calibrated up to 4000 Hz but not high-frequency thresholds. Also, survivors with cognitive impairments like attention deficits may act uncooperatively during testing, thereby possibly missing measurements at certain frequencies. Many clinical trials assess treatment-induced hearing loss according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [47]. This numeric grading system includes grades from 1 to 4 to assess chemotherapy-induced ototoxicity and

combines subjectively assessed hearing loss with objective threshold shifts measured at two contiguous frequencies. However, the sensitivity of CTCAE grading is currently being discussed regarding potential underreporting of ototoxicity in both the paediatric and adult population [48, 49]. Therefore, many groups [48, 50, 51] prefer grading according to Brock [52] due to its clinical reliability. Recently, Chang's criteria have proven solid and clinically significant, especially with regard to the impact of ototoxicity on speech development and the potential need for hearing aids [53].

24.3.5 Oral and Dental Health Monitoring

Paediatric CNS tumour patients younger than 5 years of age when receiving high cumulative doses of alkylating agents and/or cranial radiotherapy including the facial skull, particularly after doses over 20 Gy, are at high risk for developmental dental abnormalities [54]. Hence, parents, patients, survivors and dental care providers need to be aware that close monitoring and dental surveillance and follow-up of CBTS are crucial to prevent compromised oral health and the resulting increased risk of developing other, e.g. cardiac, complications. While missing teeth, cavities and use of dental appliances are readily apparent to the individual, diagnosing abnormalities such as enamel hypoplasia, microdontia and root stunting requires professional expertise. Therefore, dental care utilisation, including check-ups and hygiene visits, should be strongly encouraged by the primary care physician, also to survivors, who presumably have better access to dental care and possibly greater health awareness, in order to promote early diagnosis and, hence, knowledge of specific dental conditions. Female gender, lower education level and lower household income level are associated with an increased risk of compromised oral health in childhood cancer survivors [54]. This may reflect decreased access to dental care (particularly limited access to dentists trained in caring for these complex patients) and, potentially, decreased use of preventive care.

24.3.6 Late Morbidity and Mortality

According to the North American Childhood Cancer Survivor Study (CCSS), 1.3% of CBTS develop a secondary malignant neoplasm including different CNS and other tumour types that significantly contribute to late mortality [3, 55]. Hence, regular long-term follow-up visits for physical check-ups as well as neuro- and other imaging and genetic counselling [13] should be scheduled based on the survivor's individual risk of developing a secondary cancer. This screening should be lifelong, since these malignancies can develop even decades after the end of primary cancer therapy.

In addition to screening for neuropsychological, endocrinological and cardiovascular LE, relapse and secondary malignancies on the basis of tumour type and site and previous therapeutic exposures, health counselling and promotion of healthy lifestyles are important aspects of long-term follow-up care in CBTS as well. Therefore, it is essential for the primary care physician to provide anticipatory guidance regarding health promotion and disease prevention aimed at minimising the risk of future morbidity and mortality. For example, survivors who are at risk of obesity, cardiovascular disease and osteoporosis should attain close endocrinological follow-up and be counselled regarding the importance of eating a well-balanced diet and participating in regular exercise.

The reader is also referred to Chap. 14 of this book.

24.4 Conclusion

Given the high incidence and broad spectrum of multifactorial LE experienced by CBTS, structured, multidisciplinary long-term follow-up care for this growing group of adolescents and young adults is essential, so their care is appropriately tailored to their specific tumour- and treatment-related risk factors as well as age-specific needs. This is an exciting time for providing care to a very unique group of childhood cancer survivors. Discussions regarding the best models for providing optimal QoS are emerging concomitantly with

the increasing activities of various international research and clinical initiatives, such as *CCSS*, *PanCareSurFup*, *PanCareLIFE*, *VIVE*, the *Late Effects Study Group/Late Effects Surveillance System (LESS)*, the *German Childhood Cancer Registry (GCCR)*, the *Cardiac and Vascular Late Sequelae in Long-Term Survivors of Childhood Cancer (CVSS)-Study Group* and, specifically for CBTS treated within the HIT-Network, *HITLife*.

24.5 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

24.6 Recomendation for a Long-Term Follow-Up Schedule

Long-term follow-up is performed according to the recommendations of the International Guideline Harmonisation Group (www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the LESS group (www.nachsorge-ist-vorsorge.de) in Germany.

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25 Late Effects in Children and Adolescents with Neuroblastoma

Frank Berthold

25.1 Introduction

Worldwide the proportion of long-term survivors from neuroblastoma has increased over the recent decades. In Germany, the 10-year overall survival rates have improved from 46% (1980–1989) to 63% (1990–1999) to 75% (2000–2013) [1]. According to the German Childhood Cancer Registry, approximately 2400 patients have survived their disease 10 years or more (diagnosis 1980–2009, $n = 3619$).

The proportion of patients with residency in Germany who participated in neuroblastoma trials has exceeded 98% from 1995 onward. Although the data on survival in Germany are nearly complete, the same cannot be said for records on late effects of the disease and therapy. This is not unique to Germany; indeed, a significant proportion of childhood cancer survivors appear to refuse the recommended risk-based care. Of 576 neuroblastoma participants of the Childhood Cancer Survivor Study diagnosed between 1970 and 1986 in the USA and followed up by questionnaires in 2002–2003 (response rate 77%), 15.5% reported no medical care, 9.9% general care, 62.1% survivor-focused care, and only 16.8% risk-based survivor-focused care [2]. Similarly, a single institution in New York reviewed the medical records of 286 disease-free childhood cancer patients diagnosed between 2010 and 2012 who had completed their cancer therapy at least 3 years before and found that 74.2% adhered to the recommended follow-up screening [3]. It has been reported that childhood cancer survivors carry an eightfold higher relative risk for at least one chronic medical condition 20 years after diagnosis compared to their siblings [4]. Another study on the Childhood Cancer Survivor Study cohort showed a cumulative incidence of more than 60% for chronic health conditions among neuroblastoma patients having survived 28 years after diagnosis. In more than one third, the severity was severe, disabling, or life-threatening (grades 3–5) [5]. However, general recommendations for long-term medical surveillance of neuroblastoma patients [6] should be balanced against the patients' right to nescience and to stop regular follow-up examinations.

For neuroblastoma survivors, specific conditions must be observed. Peculiarities of neuroblastoma are the young age at presentation and the wide range of biological features. The mean age at diagnosis was 16 months (range 0–306 months) in our series of 4284 patients

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from 1979 to 2015 [1]. Neuroblastoma has remarkably divergent disease patterns. Spontaneous regressions, chemotherapy-induced or spontaneous maturation, and highly aggressive, largely treatment-resistant progressions are well-known occurrences. Clinical and molecular characteristics help to assign the patients to low-, intermediate-, and high-risk categories. Low risk can be attributed to stages 1, 2, and 3 (<2 years) and stage 4S without *MYCN* amplification and without chromosome 1 p aberration (criteria from the NB2004 trial). If no threatening symptoms are present, surgical intervention alone is the recommended therapy. Low risk accounts for approximately half of the neuroblastoma patients. Intermediate risk is considered for patients with stage 2 or with stage 3 <2 years and detected chromosome 1p aberration but absent *MYCN* amplification and all stage 4 patients below 18 months. This group accounts for approximately 10% of all patients. The treatment is similar to high risk but without myeloablative therapy. High risk is defined worldwide by stage 4 >18 months or by *MYCN* amplification in stages 1, 2, 3, and 4S and stage 4 <18 months. 37–40% of all patients are considered as high risk. The treatment is extensive and includes intensive induction chemotherapy, high-dose chemotherapy with stem cell rescue, surgical therapy, radiotherapy, and some type of maintenance therapy (e.g., isotretinoin, immune therapy). The current survival probabilities for all patients are 79% at 5 years, 77% at 10 years, and 76% at 15 years [1]. However, major differences exist between the stages and risk groups. In a study published in 2018, low- and intermediate-risk patients (stages 1, 2, 3, 4S, 4 <18 months) had 92 ± 1% overall survival at 15 years, while this was much worse for high-risk patients at 44 ± 4% (stage 4 patients >18 months and normal *MYCN* 32 ± 3%, stage 4 patients >18 months and amplified *MYCN* 26 ± 3%, stages 1–3, 4S, stage 4 <18 months and amplified *MYCN* 44 ± 4%) [6]. The different prognosis (low vs. high risk) and the different treatment approaches (minimum treatment vs. extensive treatment) require tailored programs for the patients.

25.2 Late Mortality After Neuroblastoma

The late mortality of childhood *cancer* patients who have survived 5 years post-diagnosis has decreased over the recent decades. The Childhood Cancer Survivor Study reported a 15–year cumulative mortality of 10.7% in the 1970s, 7.9% in the 1980s, and 5.8% in the 1990s $p < 0.001$) [7]. The reductions were attributable to fewer deaths from recurrence or progression (7.1% in the 1970s, 4.9% in the 1980s, 3.4% in the 1990s, $p < 0.001$) and to fewer deaths from other health-related external causes including the late effects of cancer therapy (3.1% in the 1970, 4.9% in the 1980s, 3.4% in the 1990s). However, this general improvement did not apply to neuroblastoma ($n = 2632$; 15–year cumulative mortality all causes, 1970s 4.1%, 1980s 4.8%, 1990 6.5%, $p = 0.04$; recurrence/progression, 1970 3.0%, 1980s 3.3%, 1990 5.2%, $p = 0.05$; other health-related causes, 1970 0.9%, 1980 1.1%, 1990 1.1%, $p = 0.77$) [7]. This is likely a result of the increasing proportion of long-term survivors of high-risk neuroblastoma and the increasing toxicity of the treatment for intermediate and high-risk neuroblastoma. Thus, the study indicates an undiminished -if not increased- risk of 5-year neuroblastoma survivors for a late death from the tumor and/or other health-related causes.

In Germany, the late mortalities of patients surviving 5 years after diagnosis were not different between the treatment decades 1980s, 1990s, and 2000s. The all-cause 15-year cumulative mortality was 5.9% (Fig. 25.1). The risk of dying from tumor recurrence was much higher (15-year mortality 3.3%) compared to death from second malignancies (0.3%) or from deadly late toxicities (0.2%).

25.3 Health Outcome and General Quality of Life

A multitude of studies indicate a generally poor health outcome for high-risk neuroblastoma survivors.

Particularly interesting is that more recently treated survivors of neuroblastoma even had an

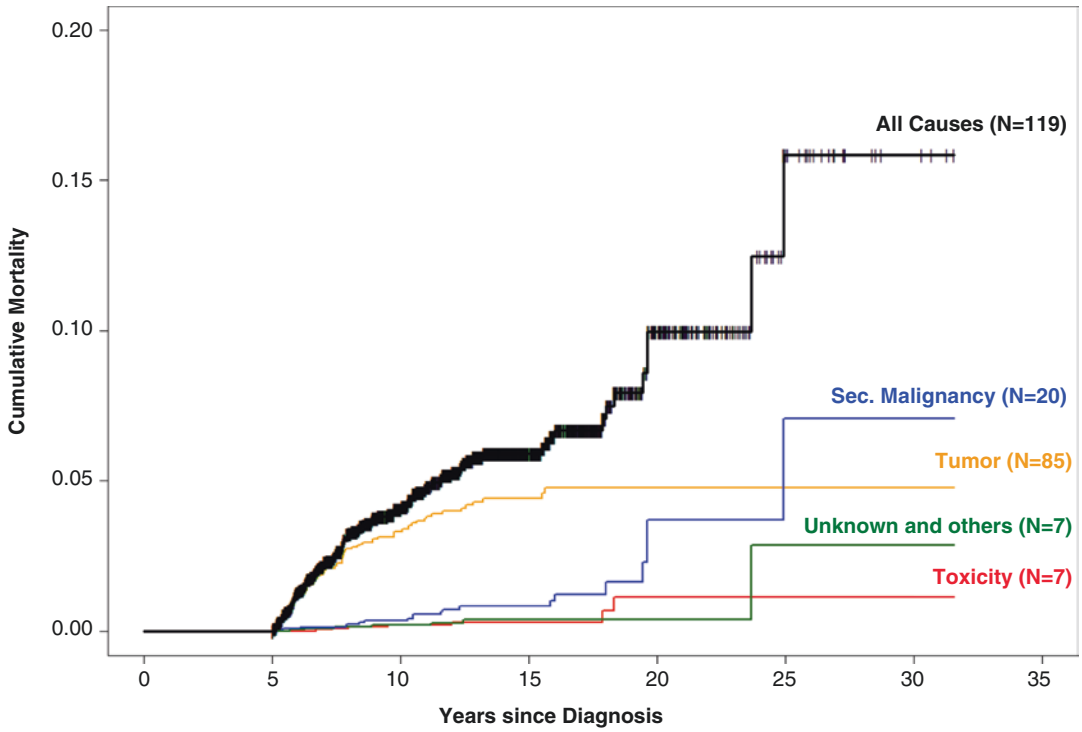

Fig. 25.1 All-cause and cause-specific cumulative mortality among 5-year survivors (n = 2444) of neuroblastoma diagnosed 1980-2010. The cumulative 15-year mortality from any cause was 5.9% [95%-CI 4.8–7.0%] from tumor (± toxicity during recurrence treatment) 3.3% [95%-CI 2.9–3.8%], from second malignancy 0.3% [95%-CI 0.18–0.67%], from other and unknown health-related causes 0.2% [95%-CI 0.09–0.43%], and from toxicity 0.2% [95%-CI 0.11–0.40%]

increased risk of long-term adverse events compared to patients treated in earlier decades. The 15-year cumulative incidence of at least one grades 3–5 condition increased from 18.0% (95% CI 14.5–21.6%, 1970–1979) to 25.0% (21.8–28.2%, 1990–1999, P = 0.0045) [8]. This is likely caused by the previously mentioned higher therapeutic intensity in the later period and the higher survival rates of high-risk patients.

Another study compared chronic health conditions among 136 ≥10-year neuroblastoma survivors with 272 community controls [9]. By the age of 35 years, survivors had experienced 8.5 grades 1–5 conditions on average (95% CI 7.6–9.3), while the controls had 3.3 on average (2.9–3.7). The higher prevalence was particularly evident for pulmonary, auditory, gastrointestinal, neurological, or renal impairment but was also reported for poor physical status, symptoms of anxiety, independent life, marriage, and unemployment. Remarkable in this context is that only 22% of the survivors initially had stage 4 neuroblastoma.

The findings are supported by a quality-of-life investigation among 919 neuroblastoma survivors compared to their siblings [10]. Depending on the age at interview of the survivors, 26–33% of the patients reported a poor condition in at least one of the outcome measures (poor general health, adverse mental health, functional impairments, activity limitations, pain, anxiety) compared to 15–20% of the siblings. This proportion was higher among the female survivors compared to male. In contrast to other malignant diagnoses, a general increase of survivor-reported quality-of-life limitations was not observed for neuroblastoma survivors as they age (Suppl. Fig. 5 in [10]).

Nathan and coworkers interviewed 432 neuroblastoma patients treated in the period 1970–1986

and having survived 16–35 years. The lack of evidence for significant deficits in physical well-being or functioning compared to population norm may be explained by the low proportion of high-risk patients in this study. But even in this cohort with limited therapeutic interventions, the emotional health of the survivors was significantly compromised in view of vitality, social function, emotional role, and mental health (subscales) [11].

A Canadian population-based survey of 99 survivors of high-risk neuroblastoma treated between 1991 and 2010 with stem cell transplants reported a distinctly impaired quality of life [12]. The health-related utility score HUI2 was 0.89 ± 0.11(0 being dead, 1.0 being perfect health) with morbidity in sensation (53%), pain (30%), cognition (28%), and emotion (24%). The HUI3 score was 0.84 ± 0.18, reflecting impairments in hearing (38%), pain (30%), cognition (27%), and speech (23%). These outcomes were not different compared to neuroblastoma survivors without stem cell transplant, but were significantly inferior compared to non-transplanted survivors of leukemia and Wilms tumor and children from the general population. However, they were superior in comparison to survivors of brain tumors.

Two single-institution studies of high-risk patients who underwent high-dose chemotherapy with autologous stem cell reinfusion investigated the organ-related health outcomes. Elzembely et al. reported that 87% of the 61 survivors developed grades 1–5 late sequelae that increased over time. The most common abnormalities were hearing loss (82%), dental defects (28%), endocrine (18%), and orthopedic (15%) late effects [13]. Among patients who underwent triple consecutive high-dose chemotherapy courses, Armstrong et al. found late sequelae in 74% (19 patients) after a median of 13.9 years (range 5.8–18.8). The most prominent were hearing loss and endocrine-related late effects (growth failure, hypothyroidism, hypogonadism) [14].

These studies highlight the necessity of discriminating between high-, intermediate-, and low-risk neuroblastoma. The highly different treatment approaches ranging from minimum intervention (surgery plus observation) to maximum intervention are likely to be overlooked in surveys including the total cohort of patients and are therefore potentially misleading. For scientific reasons, the comparisons between the groups are highly interesting; but from a practical clinical point of view, the high-risk patients are more likely to benefit substantially from long-term surveillance.

The reader is also referred to Chap. 16 of this book.

25.4 Hearing Impairment

Hearing impairment is the most frequently reported long-term harm for neuroblastoma patients.

Cisplatin and carboplatin are key drugs for the treatment of high-risk neuroblastoma and are known to be associated with significant hearing impairment. A recent report [15] demonstrated a hearing impairment in 69% (CTCAEv3 grades 1–4) and severe hearing loss (CTCAEv3 grades 3 and 4) in 47% of patients after administration of <400 mg/m^2 cisplatin. The addition of carboplatin (1700 mg/m^2) resulted in hearing impairments of 86% and 71%, respectively. Twenty-nine percent had a hearing aid after cisplatin and 58% after cis-plus carboplatin. This vulnerability increased with hospitalization for infection (82% of patients), which was a surrogate marker for the application of further ototoxic drugs like aminoglycoside antibiotics and Henle loop diuretics. The Brock scale was shown to underestimate severe hearing loss.

An earlier single-institution study [16] reported a prevalence of severe ototoxicity (Brock scale grades 3 and 4) in 16/65 (25%) of patients after 400 mg/m^2 cisplatin and in 29/58 (50%) of patients after myeloablative therapy with 1700 mg/m^2 carboplatin. In our experience [17], 27% of patients (109/405) with stage 4 neuroblastoma (no recurrence 1 year after diagnosis and exposure to up to 800 mg/m^2 cisplatin) showed grades 3 and 4 hearing impairments (WHO scale). In contrast, this was the case for only 0.4% (2/453) of patients with lower stage and without exposure to chemotherapy. This is in agreement with the results of the SFOP NBL90 study in infants exposed to 40 mg/kg (=1200 mg/

m^2) carboplatin combined with etoposide in a neoadjuvant setting for unresectable primary tumors [18]. 29/30 had no ototoxicity (grade 0, Brock scale) 4.5–9.5 years after diagnosis. In the German trials NB97 and NB2004, 8.2% of high-risk patients (stage 4 ≥18 months, $n = 710$) and 1.9% of low- and intermediate-risk patients (stages 1–3 and stage 4S, *MYCN* normal; $n = 1538$) reported deafness or significant hearing impairment ≥1 year after diagnosis.

According to Gurney et al. [19], severe hearing impairment had a negative impact on academic learning and was associated with psychosocial difficulties. A survey on 137 children aged 8–17 years detected an approximately twofold higher risk for problems with reading skills, math skills, attention, and/or special educational needs in survivors compared to those without hearing loss. Likewise a study of survivors with non-CNS tumors ($n = 226$) and severe hearing loss also demonstrated an increased risk of not living independently (OR 2.19), of not graduating from high school/being unemployed (OR1.85), and of never having married (OR 1.61) compared to those without hearing loss [20].

Thus, hearing impairment is relevant only for intermediate- and high-risk neuroblastoma patients.

The reader is also referred to Chap. 3 of this book.

25.5 Thyroid Disorders

Diagnostic mIBG scintigraphy (^{123}Iodine) for all stages and mIBG therapy (^{131}Iodine) for high-risk disease have been standard for several decades. Free circulating radioactive Iodine (from dissociation and liver metabolism) is known to harm the thyroid gland. Clement et al. [21] reported thyroid disorders in 13 of 16 (81%) long-term survivors after mIBG therapy treated between 1989 and 1999. Eight patients needed thyroxine therapy, and nine had thyroid nodules, of which two were diagnosed as papillary thyroid carcinoma. No correlation was seen between thyroidal ^{131}Iodine uptake at therapy and later thyroid disorders. Another study [22] on 160 patients following mIBG therapy during 1996–2008 found a lower incidence: 36 experienced new hypothyroidism or worsening of any grade including 9 with grade 2 requiring thyroxine supplementation.

Due to the currently unknown effect of diagnostic mIBG scintigraphy and the frequently observed incomplete thyroid blocking, all neuroblastoma risk groups should be monitored for TSH elevations during the long-term follow-up program.

The reader is also referred to Chap. 8 of this book.

25.6 Cardiotoxicity

Increased blood pressure active catecholamine metabolites (e.g., dopamine) and the constriction of the renal artery by the tumor may induce acute cardiomyopathy. Catecholamine-caused sequelae have been reported for single cases only and were reversible in most instances [23].

The regular use of anthracyclines for the treatment of high-risk neuroblastoma [1] is of greater concern. However, the extension of the infusion times and limiting the cumulative dose to less than 400 mg/m^2 of adriamycine equivalent have decreased the risk for late cardiac sequelae. Reporting on 954 neuroblastoma patients, the Childhood Cancer Survivor Study (period 1970–1986) found a 4.1-fold increased risk for congestive heart failure, an 11.1-fold increased risk for myocardial infarction, a 5.1-fold increased risk for pericardial disease, and a 7.7-fold increased risk for valvular abnormalities compared to the sibling group [24]. The recently observed general decline of major cardiac events attributed to reductions of cardiotoxic exposures (drugs, radiation) unfortunately did not include neuroblastoma [25]. Indeed, the hazard rate for heart failure increased from 3.22 (95% CI 0.89–12.53) in the 1980s to 5.72 (95% CI 1.58–20.67) in the 1990s compared to the 1970s (N=1825 neuroblastoma patients in total).

In our series (NB1997 and NB2004) of 2248 patients surviving ≥1 year after diagnosis, cardiotoxicity was observed in 1.0% of patients with stage 4 ≥18 months and in 0.1% of patients with

stage 1, 2, 3, or 4S (*MYCN* normal) without chemotherapy or with less intensive chemotherapy (low and intermediate risk).

It appears that cardiotoxicity as a late effect—mainly from chemotherapy in neuroblastoma treatment—must be considered as relevant.

The reader is also referred to Chap. 1 of this book.

25.7 Second Malignancies

The cumulative incidence of second neoplasm for patients in Germany with neuroblastoma was 2.8% within 30 years after diagnosis (1980–2015) which is less than the average for all malignancies (6.6%) [1]. Neuroblastoma as a second tumor was even more rare (0.9% within 30 years) [1]. Applebaum et al. [26] reported a cumulative incidence at 30 years for high-risk patients of 10.5% compared to 3.6% for non-high-risk patients ($P = 0.001$). No statistically significant differences were observed between the treatment eras 1973–1989, 1990–1996, and 1997–2006 (2801 patients). Of the 34 second malignancies found, 14 were carcinomas, and 10 were hematologic malignancies with six cases of acute myeloid leukemia. Federico et al. [27] analyzed the records of 646 patients and calculated a 4.6% cumulative risk for a second malignancy at 30 years. The median latency for the development of acute myeloid leukemia or myelodysplastic syndromes ($n = 4$) was 3.6 years, for sarcomas 9 years ($n = 7$), and for carcinomas 24.2 years ($n = 5$). The cumulative 10-year incidence for 644 patients treated with different doses of mIBG was 14.3% [28]. A dose-dependent increase was not found. 13/19 were hematologic malignancies and 6/19 solid tumors, including osteosarcoma, papillary thyroid carcinoma, mesothelioma, and inflammatory myofibroblastic tumor. In one study [29], fewer cycles of chemotherapy were associated with a lower incidence. A nested case-control study [30] delineated alkylating agents, which are extensively used in high-risk neuroblastoma, as the drugs with the strongest association for a second malignancy after other pediatric primary malignancies, This needs to be specifically reviewed for high-risk neuroblastoma.

Although second malignancies after high-risk neuroblastoma are rarer compared to other pediatric tumors, early detection of leukemias and myelodysplastic syndromes during the first 10–20 years after diagnosis may be relevant for the patients. The long latency period of carcinomas poses a difficult observative challenge for the surveillance programs.

The reader is also referred to Chap. 14 of this book.

25.8 Altered Musculoskeletal Health

Short stature, osteopenia, capital femoral epiphysiolysis, dental problems, the development of osteochondromas, and other late sequelae have been reported for the high-risk group [31, 32]. Short stature below the third percentile was observed in 14/21 (67%) high-risk transplanted long-term survivors [31]. The reduced height has been associated with growth hormone deficiency [31, 32], retinoid therapy [33, 34], and total body irradiation [34]. Growth hormone replacement therapy did not result in normal growth as in patients with isolated growth hormone deficiency, indicating direct impairments of the skeleton [32]. Growth plate abnormalities, premature physeal closure, and advanced bone age were detected in cohorts who received retinoids or antiangiogenic therapy [32, 33, 35].

In patients with neuroblastoma and intraspinal extension surviving ≥5 years, the proportion of scoliosis was 68% (12/19) [36]. Scoliosis may result from the tumor itself (neurologic impairment due to intraspinal tumor extension or musculoskeletal impairment due to tumor infiltration of muscles and vertebrae) and/or from treatment (local radiotherapy or neurosurgical resection).

While scoliosis is usually detected at the end of treatment in low-risk patients, long-term follow-up for chronic musculoskeletal deformities may be advised for high-risk patients.

25.9 Conclusion

A lifelong follow-up program to monitor late sequelae may be interesting for investigators but unrealistic to implement, expensive for society, and not always useful for the patients, in particular for those with good risk and limited treatment. The programs need to respect the specific risks for tumor recurrences after more than, for example, 10 years and the advantage of early diagnosis of late effects. This may be true for hypothyroidism and hearing impairment, but not necessarily for second malignancies and some skeletal abnormalities. The specific usefulness is likely to change with increasing diagnostic and therapeutic options. At the very least, low-risk and high-risk neuroblastoma patients require substantially different follow-up schedules.

Long-term follow-up is performed due to the recommendations of the International Guideline Harmonisation Group (www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the LESS Study (www.nachsorge-ist-vorsorge.de) in Germany.

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients. Even if the main focus is on acute care.

(https://www.awmf.org/leitlinien/detail/ll/025-002.html).

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26 Late Effects in Children and Adolescents with Nephroblastoma

Norbert Graf

26.1 Introduction

Nephroblastoma or Wilms' tumor (WT) is the most frequent renal cancer in childhood with an age-standardized incidence of 8.8 new cases per one million children below 15 years of age accounting for 6% of all childhood cancers with 7% occurring as bilateral disease [1]. More than 50 different genetic disorders are known that are associated with WT, and 1–2% are familiar [2]. The 5-year survival probability is currently over 90% [3, 4]. Treatment of children with WT is mainly depending on histology and stage ranging from solely tumor nephrectomy up to intensive four-drug treatment with local and pulmonary radiotherapy. In relapsed patients, high-dose chemotherapy with stem cell transplantation is indicated in high-risk relapses [5].

Late effects are related to the individual treatment given and depend on the usage of different drugs, irradiation, and surgical procedures. Main complications include renal dysfunction, cardiomyopathy, and growth abnormalities, but can involve all organs. This chapter focuses on possible late effects originating from surgery, chemotherapy, and irradiation. Congenital syndromes may enhance these late effects, like renal dysfunction in children with Denys-Drash syndrome. Recommendations for follow-up of children with WT are given in this chapter.

26.2 Nephroblastoma Treatment

Treatment of children with WT is based on surgery and chemotherapy. In around 20% of children, local and/or pulmonary radiotherapy needs to be added to gain high cure rates. In SIOP, treatment starts with preoperative chemotherapy, whereas in COG, children with WT are primarily operated. In both study groups, treatment is stratified according to age, histology, stage, and tumor volume. Response to chemotherapy is used in both study groups for patients with metastatic disease. Only in SIOP, preoperative chemotherapy allows to define the blastemal type of WT as a high-risk tumor needing more intensive treatment. On the other hand, molecular markers as LOH of 1p and 16q are risk factors for stratification of treatment intensity in COG. The intensity of treatment ranges from surgery alone up to surgery and four drugs with radiotherapy and even high-dose chemotherapy (HD-CT) with autologous stem cell transplantation in high-risk relapsed patients. Most important drugs are vincristine and actinomycin D. In case of metastatic disease and high-risk histology, anthracyclines are added. In high-risk histology as well as in CCSK and RTK, ifosfamide, cyclophosphamide,

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carboplatin, etoposide, and irinotecan are further important drugs today. In case of HD-CT, conditioning regimens include melphalan as the main drug. Radiotherapy is given in less than 20% of children with WT depending on stage and histology. It is also recommended for all patients with RTK and for patients with CCSK with the exception of local stage I. In RCC, surgery is most important. If possible nephron-sparing surgeries are done today not only in bilateral cases to avoid tumor nephrectomies. One of the most important tasks in treatment of children with WT is to avoid acute and late toxicities by reduction of treatment intensity without jeopardizing the high cure rates [6].

26.3 Late Treatment Effects

Possible serious late effects in WT [7, 8, 9] include renal dysfunction after tumor nephrectomy, ifosfamide, carboplatin and local irradiation [10–13], cardiomyopathy after treatment with anthracyclines and lung irradiation [14–17], neurotoxicity after administration of vincristine [18], hepatotoxicity after actinomycin D [19, 20], pulmonary toxicity after lung irradiation [21, 22], growth abnormalities after local irradiation [23–27], and fertility problems [28, 29]. The cumulative incidence of secondary malignancies is 1–4% after 30 years and continuously rising over time [30–33].

26.3.1 Renal Toxicity

Most patients with WT lose at least one kidney by tumor nephrectomy. Even in those patients with nephron-sparing surgery, the amount of functional normal kidney is decreased. In bilateral cases and in patients receiving radiotherapy to the contralateral kidney, the risk of developing end-stage renal disease (ESRD) is of particular concern [10]. A retrospective study of 5910 patients with WT without WT1 mutation or genitourinary anomalies and enrolled in NWTSG trials did show a cumulative incidence of ESRD of 0.6% after unilateral disease and 12% after bilateral disease 20 years after diagnosis. The incidence for renal failure was much higher for patients with Denys-Drash syndrome (62%), Wilms' tumor-aniridia syndrome (38%), and genitourinary anomalies (11%) [34]. Despite the fact that ESRD is low for patients with unilateral WT, a significant number of them develop subclinical glomerular and tubular damage over time [35], and chronic renal insufficiency is reported in up to 73% of survivors [36].

In a recent retrospective single-center study [13], a remarkable number of 37 WT survivors presented with previously unidentified subclinical signs of renal function impairment, including age-adjusted cystatin-based glomerular filtration rate (GFR) estimation below age norm in 55.9%, albuminuria in 13.5%, arterial hypertension in 40.5%, and both chronic kidney disease ≥ stage II and arterial hypertension in 24.3%. Compensatory contralateral renal hypertrophy was found by ultrasound in 83.3% of these patients and in 68% in another study [12]. Both studies showed that GFR decreases continuously over time, especially after 10 years.

Summarizing different studies of Wilms' tumor survivors, microalbuminuria or proteinuria as well as GFR decrease is found in a high percentage of patients if abdominal radiotherapy is given. Data from a paper of Daniel Green are given in Table 26.1 [11].

In patients with high-risk WT and in patients with WT relapses, nephrotoxic drugs like ifosfamide and carboplatin are used to gain higher cure rates. Even if mean GFR remains stable after three ICE cycles according to results of a prospective study in 12 newly diagnosed WT

Table 26.1 Nephrotoxicity in long-term survivors of WT [11]

	Abdominal radiotherapy	
	Yes	No
GFR <80 mL/min/1.73m^2		
Range [%]	0–36.3	0–18.1
Overall prevalence [%]	14.8	7.8
Microalbuminuria or proteinuria		
Range [%]	0–41.7	0–30.8
Overall prevalence [%]	13.8	11.1

patients [36], urinary ß2-microglobulin excretion increases during therapy. According to this study, no patient developed clinically significant renal tubular dysfunction at the end of treatment with ICE, if adjustment of carboplatin dosage on the basis of GFR and careful monitoring of renal function are performed. But they conclude that the combined treatment with nephrectomy, nephrotoxic drugs, and local radiotherapy significantly reduces GFR with the largest influence of nephrectomy [36].

Children with bilateral nephroblastoma undergoing nephron-sparing surgery (NSS) after preoperative chemotherapy show an excellent outcome and maintain renal function over time [37]. This is a clear indication for NSS whenever it is feasible for bilateral disease. In addition, this needs to be investigated also for unilateral nephroblastoma.

In summary patients with WT should be followed closely throughout life for signs of nephropathy or renal failure. Prophylactic measurements during treatment should be considered as the risk of renal dysfunction can be reduced by more nephron-sparing surgeries, less nephrotoxic chemotherapy, and optimized radiation therapy [8, 38].

The reader is also referred to Chap. 2 of this book.

26.3.2 Cardiotoxicity

Late anthracycline-induced cardiotoxicity can present as either cardiomyopathy or potentially life-threatening arrhythmias. The extent of damage can progress with cardiac dysfunction becoming rapidly lethal [39].

Anthracyclines are still important drugs in the treatment of nephroblastoma, CCSK, and RTK. In 2003 Iarussi et al. showed that there is a large percentage of WT patients treated with anthracyclines presented with a high prevalence of elevated left ventricular (LV) afterload, an increase in LV volumes at end systole, a decrease in LV mass, a decrease of LV pump function, and a normal stress velocity index that is a load-independent measure of contractility in long-term follow-up. In contrast, the Wilms' tumor survivors treated without anthracyclines had no myocardial abnormalities [15]. In this analysis, the most important predictor of worsening cardiac performance was total anthracycline dose. Patients receiving less than 240 mg/m^2 showed no deterioration of left ventricular end systolic stress at 10 years from the end of treatment [17].

The 20-year risk of congestive heart failure after primary doxorubicin treatment on NWTS-3 and NWTS-4 is calculated as 1.2% [40]. In a multicenter retrospective analysis of data from Germany, 4 out of 157 (2.5%) children had a left ventricular fractional shortening below 29% at the last follow-up of 2.9 [0–10.2] years past therapy [16]. Despite the fact that the incidence of abnormal findings is quite low, one needs to restrict the usage of anthracyclines as much as possible. There are reports of severe cardiomyopathies in children with WT in whom heart transplantation was needed [41]. To minimize the risk of anthracycline-induced cardiomyopathy, the usage of doxorubicin in nephroblastoma is restricted to only metastatic and high-risk diseases today. In SIOP 2001, it could be proven that doxorubicin can be omitted safely from chemotherapy for local stages II and III in intermediate-risk WT. There was no difference in overall survival and only a trend in event-free survival in favor of doxorubicin. According to these data, 22 children would need to receive doxorubicin to avoid a single relapse that can be salvaged in a second attempt [6]. In NWTSG, no statistically significant effects of doxorubicin were found for patients with stage II tumors as well, whereas for patients with stage III tumors, the 8-year recurrence-free survival and overall survival (OS) were 84% and 89% receiving anthracyclines and only 74% and 83%, respectively, for those treated without doxorubicin in NWTS-3 [40].

Our studies and others show that cardiomyopathy can occur many years after completion of therapy and that the onset may be spontaneous or coincide with exertion or pregnancy. An important risk factor known to be associated with anthracycline-related cardiotoxicity is lung radiation in patients with metastatic WT [42]. In 2015, a clinically useful model using demographic and cancer treatment data was developed to predict

the individual risk of heart failure among 5-year survivors of childhood cancer. The model was validated with data from the National Wilms Tumor Study Group. According to this model, cumulative incidences of heart failure at the age of 40 years were found to be between 0.5 and 11.7% using risk scores based on age, gender, and anthracycline and irradiation dosage [41].

As cardiomyopathy is a severe late effect of anthracycline treatment, prevention is of utmost importance. Both cumulative dose and the mode of administration have to be considered as risk factors for developing cardiac injury [43]. In a Cochrane analysis, an anthracycline infusion duration of 6 h or longer reduces the risk of clinical heart failure, and it seems to reduce the risk of subclinical cardiac damage. Since there is only a small amount of data for children and data obtained in adults cannot be extrapolated to children, different anthracycline infusion durations should be evaluated further in children [44]. In nephroblastoma patients who still need anthracyclines, the cumulative dose is nowadays reduced to a maximum of 250 mg/m^2 in clinical trials as recommended by Sorensen et al. [17].

There are no effective treatments known for anthracycline-induced cardiomyopathy. Although there is some evidence that enalapril temporarily improves cardiac function, it is unclear whether it improves clinical outcome in children. In addition, enalapril is associated with dizziness, hypotension, and fatigue. Clinicians need to weigh the possible benefits with the known side effects of enalapril in childhood cancer survivors with asymptomatic anthracycline-induced cardiotoxicity [45]. There are no studies analyzing cardioprotection with dexrazoxane in patients with nephroblastoma as it was shown in other cancer types, especially in adults. Interestingly in high-risk ALL, it could be shown that this drug did not increase the rate of second malignancies [46].

The reader is also referred to Chap. 1 of this book.

26.3.3 Growth Abnormalities

Radiotherapy in children is associated with side effects on growth and development of normal tissues. It is well-known that an incomplete growth arrest of endochondral ossification is observed at doses of 10–20 Gy and permanent arrest at 20–30 Gy [47]. The degree of damage depends in addition to the fractionation, the radiation field and the age of the child [8, 25, 27, 48]. In former times, only part of the vertebral column was included in flank irradiation resulting in flank atrophy on the treated side with asymmetry of vertebral bodies, vertebral end-plate irregularities, scoliosis, kyphosis, and hypoplasia of the ilium [49]. In an analysis by Sasso of 34 WT patients, who received flank irradiation, 53% developed growth abnormalities between 60 and 180 months after the end of treatment. They found scoliosis in 41%, muscular hypoplasia and length inequality in 12%, kyphosis in 15%, and iliac wing hypoplasia in 9% of these patients. In most cases, the scoliosis was mild and rarely showed a curvature angle greater than 20 degrees [25]. Similar results are reported by Paulino et al., with 16.7% muscular hypoplasia, 11.9% limb length inequality, and 7.1% kyphosis or iliac wing hypoplasia. The incidence of scoliosis in their study was 4.8% at 5, 51.8% at 10, and 56.7% at 15 years after RT with doses between 1201 and 2399 cGy. In case of lower RT doses, only 1 out of 12 patients developed scoliosis [24]. It could be shown that severe late radiation sequelae of the spine can be reduced by involving the whole vertebra into the radiation field, by using high-energy radiation techniques and by excluding children under the age of 1 year from radiotherapy [8, 27].

In addition, girls can develop breast hypoplasia as a direct consequence of thoracic irradiation even after low radiation doses (<5 Gy) at the developing breast and is also reported after successful treatment for WT [23, 50]. The occurrence and the degree of breast hypoplasia were studied by Fürst et al. in 129 women irradiated with ionizing radiation before 4 years of age for hemangioma located in the breast region. The mean absorbed dose to the breast was 2.3 Gy. Breast hypoplasia on the treated side was reported by 57% of the patients and on the contralateral side by 8% [51]. In 3 out of 4 girls with WT and thoracic irradiation for lung metastases breast hypoplasia is reported to occurr [23].

The reader is also referred to the Chaps. 39, 40 of this book.

26.3.4 Hepatotoxicity

Acute hepatic veno-occlusive disease (VOD) is a well-known complication of actinomycin or the combination of chemo- and radiotherapy in WT. Out of 511 children with WT treated according to SIOP 9 protocol, 64 patients suffered at least one episode of hepatotoxicity from whom 41 presented with VOD (8%). Children below 1 year of age and those receiving local irradiation showed an increased risk [52]. Liver toxicity in irradiated patients occurred at a median of 6.5 weeks after start of postoperative treatment. The rate of toxicity was higher in patients receiving more than 20 Gy to the major part of the liver [53]. Ludwig et al. could show that dose intensity of actinomycin is important in the development of hepatotoxicity. Therefore, too frequent cycles should be avoided, and a dosage of less than 10 μg/kg/week may lower hepatotoxicity. In smaller children (below 12 kg body weight), actinomycin should be reduced to at least 66% of the regular dosage. The same reduction is necessary under radiotherapy to the abdomen, or the drug should be postponed until a few weeks after irradiation [20].

In a single-center retrospective study, liver biopsies were performed after preoperative chemotherapy in 91 localized or metastatic WT patients treated according to SIOP 9, 93–01, or 2001, and long-term hepatic toxicity was assessed 5 years after the end of therapy. 41 of these patients (45.1%) showed histological evidence of VOD. The incidence of histologically proven VOD was significantly correlated with a single administration of 45 μg/kg actinomycin (SIOP 2001 protocol) as compared to repeated dosing of 15 μg/kg [19]. In contrast, the National Wilms Tumor Study group found no increase of hepatotoxicity using single doses of actinomycin for low- or high-risk WT or CCSK with an equivalent 2-year relapse-free survival compared to those treated with standard 5-day regimens. Based on demonstrated efficacy, greater administered dose intensity, less severe hematologic toxicity, and the requirement for fewer physician and hospital encounters, single doses of actinomycin became the new standard of application [54].

Altogether 52% of patients treated with actinomycin suffer from mild to severe abnormal liver enzymes 5 years after the end of treatment [19]. This risk of developing long-lasting hepatotoxicity demands close follow-up of hepatic function and imaging via ultrasound for many years.

26.3.5 Pulmonary Toxicity

Pulmonary irradiation is known to have acute and long-term side effects on lung tissue resulting in interstitial pneumonitis or lung fibrosis. As a consequence, it is restricted today to patients with Wilms' tumor, who show high-risk histology or do not achieve a complete remission of lung metastasis after chemotherapy and/or surgery. The authors of a report from the American Childhood Cancer Survivor Study found statistically significant associations for chest radiation and lung fibrosis, supplemental oxygen use, recurrent pneumonia, chronic cough, and pleurisy [55]. The National Wilms Tumor Study group did analyze diffuse interstitial pneumonitis in their NWTS-3 trial [56]. They reported this toxicity in 13.0% of patients. But not in all of them the etiology was radiation pneumonitis, which is why intensive evaluation in these patients is always required to determine the specific cause of the pneumonitis, especially to exclude infectious agents, like pneumocystis carinii. For that reason, prophylactic administration of trimethoprim/sulfamethoxazole in patients with pulmonary irradiation is recommended [56]. In another study, three out of seven patients with pulmonary irradiation developed radiation-pneumonitis [25]. In a follow-up study of eight patients with metastatic Wilms' tumors receiving whole lung irradiation (1200–1837 cGy), these patients were reassessed clinically, radiologically, and with lung function tests 6–26 years after radiotherapy [21]. Despite the fact that chest radiograph showed clear lung fields in all cases, only three of these eight patients were clinically asymptomatic, and all eight patients had a small chest, and the breast of four of five females were underdeveloped. In addition, lung volumes, total lung capacity, and

vital capacity were decreased. Nevertheless, interstitial lung fibrosis is found as a rare event in patients with WT after radiotherapy to the lung with doses used today [21].

The administration of actinomycin and/or anthracyclines may enhance latent radiation damage causing radiation pneumonitis. Therefore the dosing of these drugs should be reduced during pulmonary irradiation [56].

An overview of the literature on pulmonary late effects after thoracic radiotherapy is provided by Bölling et al. and not only for nephroblastoma. They conclude that whole lung irradiation is regularly followed by some kind of pulmonary function impairment and that chemotherapy and thoracic surgery also contributes to such sequelae [50]. As the number of patients with follow-up data on lung toxicity in WT is small, we need more data from large and long-term studies, to outweigh the benefits of pulmonary irradiation [22].

The reader is also referred to Chap. 6 of this book.

26.3.6 Neurotoxicity

During the administration of vincristine, peripheral neuropathy may occur and may manifest as polyneuropathy or severe obstipation. In adults with nephroblastoma, the main acute toxicity is neuropathy due to vincristine. In a series of 30 patients, 13 (43%) suffered from severe (grade 3 to 4) neurotoxicity [57]. Vocal paralysis is rarely seen in children with nephroblastoma. From the literature, this toxicity is potentially reversible with subsequent withdrawal of vincristine [58].

Patients with hereditary neuropathy are at risk of suffering severe sequelae following vincristine therapy. As the association of vincristine neuropathy and Charcot-Marie-Tooth (CMT) syndrome is known in patients with severe neurotoxicity occurring during treatment with vincristine, one should exclude asymptomatic CMT [18] in such patients without known hereditary neuropathy.

In a recent study from St. Jude, neurocognitive impairment in long-term survivors of nephroblastoma was found [59]. Mainly verbal domains having an impact on social attainment and health-related quality of life were affected. Patients with chronic neurological conditions seem to be more vulnerable than others. Such findings underline to assess neurocognitive and social outcomes also in survivors of nephroblastoma over time.

26.3.7 Fertility

Long-term fertility and successful pregnancy outcomes are significant issues for childhood cancer survivors, as reproductive organs are sensitive to cancer treatment, especially to radiotherapy. Most WT patients are bearing no or minimal risk. But female survivors of WT, who received abdominal irradiation including ovaries and/or the uterus within the radiation field, are at significant risk of poor fertility outcomes [8, 28, 60–64]. The reason of a relative high incidence of infertility, spontaneous miscarriages, and restricted fetal growth is mainly caused by late effects of radiation to the uterus and the ovaries resulting in small uterine volume and/or premature ovarian insufficiency [8, 65]. In a study of long-term survivors of WT treated between 1940 and 1972, only 1 of 25 females with whole abdominal radiation showed normal ovarian function. Twenty women of this cohort experienced primary ovarian insufficiency, and four developed premature menopause before the age of 36 years [64]. A Childhood Cancer Survivor Study including 2201 children of 1264 survivors of childhood cancer and 1175 children of 601 female siblings investigated possible long-term reproductive health effects in this female cohort [29]. Results did show that the children of survivors were more often preterm than those of the siblings. This was aggravated by the usage of radiotherapy, especially radiotherapy to the uterus. More than 500 cGy did increase the risk of preterm, low birth weight, and SGA (small for gestational age) significantly with odds ratios between 3.5 and 6.8. Such increased risks were also seen for lower doses of radiotherapy to the uterus concluding that girls surviving cancer carry the risk of early births among their offspring after pelvic irradiation [29]. The British Childhood Cancer

Survivor Study confirmed these data reporting of 32% low birth weight, 35% preterm delivery, and 22% miscarriages in children of 511 female survivors of WT with abdominal radiotherapy [33].

Knowing about these late effects, it is important to take measures of prophylactic fertility preservation. Unfortunately oocyte storage is not possible in pre-pubertal girls. The only option is ovarian cortex cryopreservation and subsequent re-implantation. Such a successful procedure is reported in an adult woman with WT who underwent high-dose chemotherapy with hematopoietic stem cell transplantation for recurrence facing premature ovarian insufficiency afterward. 10 years later, she gave birth to a healthy boy at 36 weeks' gestation after cryopreserved ovarian cortex was transplanted to the left ovary by laparoscopy [65]. Even if this procedure is still experimental in young girls, one should consider cryopreservation of ovarian tissue at least in girls undergoing pelvic irradiation. In the above reported woman, re-implantation of ovarian cortex resulted in restoration of ovarian function and natural conception with successful pregnancy.

The reader is also referred to the Chaps. 9, 10, 12 of this book.

26.3.8 Second Malignancies

Second malignant neoplasms (SMN) are well-recognized late sequelae of therapy in survivors of childhood cancer. The risk in WT is relatively small compared to other pediatric cancers [31]. According to the SEER database, out of 2851 patients with WT 34 developed a second malignancy. The cumulative incidence was calculated to be 0.6% at 10 years, 1.6% at 20 years, and 3.8% at 30 years. The median time between WT and a subsequent tumor was 12.5 years. According to these data, radiotherapy did not significantly increase the risk of a SMN. 64.5% of patients with a second cancer survived after 5 years [31].

Patients with WT treated according to NWTS protocols between 1969 and 1991 developed 43 SMNs out of a cohort of 5278 patients. The cumulative incidence was calculated with 1.6% after 15 years of diagnosis, and 73% of secondary solid tumors were diagnosed in the radiation field for WT treatment. The NWTSG showed that higher radiation doses increased the risk of SMNs and that this effect is potentiated by doxorubicin. They observed 8 SMNs among 234 patients treated with doxorubicin and more than 35 Gy of abdominal radiation in contrast to 0.22 expected SMNs. In addition, the risk for SMNs did rise by a factor of 4 to 5 after treatment for relapse [30]. Within the SIOP trials 1, 2, 5, and 6, eight SMNs occurred in 1988 patients with WT giving a cumulative incidence of 0.65% at 15 years after diagnosis [66]. In a cohort of 1872 WT patients in Germany treated according to SIOP 9, SIOP 93–01, and SIOP 2001 between 1989 and 2008, 19 (1.0%) survivors developed SMN with a mean time interval of 4.2 ± 3.7 years after WT diagnosis. Most frequently, a leukemia was diagnosed (three times ALL or AML and one patient with MDS) followed by four solid tumors (two times rhabdomyosarcomas, one patient with thyroid carcinoma, and one with PNET) and two brain tumors (sub-ependymal giant cell astrocytoma and plexus papilloma) [32]. In the British Cancer Survivor Study from 2016 with a long follow-up of up to 50 years of children with WT, the cumulative risk of developing a SPN was 3.7% after 30 years which increased to 16.4% after 50 years. They found that SMNs of the digestive sites were the most common ones, followed by the breast, bowel, and bone. All of the breast cancer patients were irradiated at the abdomen and/or the chest during WT treatment [33]. In their analysis, 40% of the SMNs developed late after 30 years underlining the need for a lifelong follow-up of WT patients.

Summarizing these reports, various types of SMNs have been described, such as leukemia, sarcomas (bone and soft tissue), breast cancer, lymphoma, gastrointestinal tumors, melanoma, and brain tumors. It can be concluded that radiation is the most important treatment-related risk factor for the development of SMNs with chemotherapy potentiating the carcinogenic effect of radiotherapy. Therefore, we need to strengthen our efforts to reduce radiotherapy and intensive chemotherapy in WT as much as possible.

Continuing close surveillance of survivors of WT is essential for early diagnosis of SMNs guaranteeing a higher chance of cure of the second malignancy [8, 30].

The reader is also referred to Chap. 14 of this book.

26.4 Quality of Health

It is well-known that survivors of any kind of childhood cancer are at risk for adverse health and social outcomes. This is also true for WT patients. According to a Childhood Cancer Survivor Study [9], WT survivors show a high frequency of chronic health conditions (65.4%), including severe health conditions (24.2%) after 25 years. They report often functional impairment and activity limitations, but their socioeconomic status and mental health status are not different from a sibling comparison group. The mortality rate in 5-year WT survivors after 25 years was 6.1% and higher than in comparison to the US population [9]. Radiation exposure seems to be the most relevant factor for the high frequency of severe health conditions as it increases the likelihood of congestive heart failure especially with the addition of doxorubicin (no doxorubicin, hazard ratio (HR) of 6.6; doxorubicin 250 mg/m^2, HR of 13.0; doxorubicin >250 mg/m^2, HR of 18.3), of second malignancies, and of death according to the above study. The overall frequency is similar to that reported in other studies like the one of Geenen et al. in [67] and that of Cotton et al. in [68]. Late relapses as a cause of late death is a rare event in patients with WT [69, 70].

There are only sparse data about environmental risks of adverse outcomes among survivors of WT after 30 years from diagnosis. Such data on cause-specific mortality and the extent of smoking and drinking, educational achievement, health status, and health service use in 1441 5-year survivors of WT are available from an investigation of the British Childhood Cancer Survivor Study in comparison to the general population [33]. They found a cumulative risk of death from all causes, excluding recurrence, of 5.4% at 30 years and 22.7% at 50 years after WT diagnosis. Most of the deaths beyond 30 years were caused by second malignancies, followed by cardiac diseases. Radiotherapy exposure was a risk factor for both outcomes. Even radiotherapy was reduced during the last years, the majority of current survivors, who are at least 30 years from diagnosis, received radiotherapy [33]. Further results of their investigation are that survivors of WT were less likely to smoke or to drink alcohol. They achieved the same level of education but were less often married, and they needed more frequently health care as an out- or inpatient compared with the general population [33]. Interestingly the physical activity of 67 Dutch WT survivors was the same as a healthy control group and better than long-term male survivors of neuroblastoma [71].

In an analysis of 654 WT survivors in a Childhood Cancer Survivor Study using a well-known and widely used and validated health-related quality of life (HRQL) questionnaire (SF-36) [72], these patients showed a clear pattern of poor emotional health. The scoring was significantly below the population mean score in performance on the vitality, social function, role-emotional, and mental health sub-scales [73]. Such a low score has been shown to have high sensitivity and specificity for developing depression. This result is important to primary care physicians who have regular contact with these patients, as they need to be aware that there is a need to screen for depression or anxiety during routine care visits [72]. Independent risk factors for these lower scores included female gender, Native American race, unemployment, and household income below $20,000 [73]. In another questionnaire analyzing Nordic patients for assessing subjective well-being, psychological distress, school contentment, self-esteem, and personality traits, the adolescent survivors of WT, AML, and infratentorial astrocytoma reported better subjective well-being and self-esteem compared to a Norwegian health survey (n = 7910) serving as a control. They had fewer social problems in school, and their school contentment tended to be higher than controls. In contrast, they showed higher levels of psychological distress. Neither the diagnosis of WT, AML,

or astrocytoma nor the time since diagnosis did affect these results [74].

The reader is also referred to Chap. 43 of this book.

26.5 Recommendations for Aftercare

Long-term survivors of WT remain at risk for serious chronic health conditions, adverse health outcomes, and excess mortality. There are opportunities for improvement in the medical surveillance and cancer screening for long-term survivors of WT [9] if one takes into account that the severest late effects are attributed to tumor nephrectomy, nephrotoxic drugs, anthracyclines, and radiotherapy. These late effects may be aggravated by underlying clinical syndromes in WT patients. In addition, future treatment protocols for WT should further try to avoid nephrotoxic drugs, radiotherapy, and anthracyclines as much as possible. Nephron-sparing surgeries should be considered whenever safely possible. There is a need on weighing the benefits of treatment and the risk of developing late side effects [48].

26.6 Recomendation for a Long-Term Follow-Up Schedule

Long-term follow-up guidelines have been published from the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/). In case of WT, echocardiographic screening needs to be done in all patients who received anthracyclines. Time intervals are depending on cumulative anthracycline dose, the addition of lung irradiation, age of exposure, and results of the echocardiography. In pregnant women who were treated with anthracyclines, echocardiography is of utmost importance, as a subclinical cardiomyopathy may rapidly decompensate. Follow-up of patients by a pediatrician and later adult nephrologist is recommended to check for signs of nephropathy and renal failure. Screening for secondary malignancies should take into consideration the radiation field. Surveillance programs for breast cancer and gastrointestinal tumors should be explained to patients with WT after radiotherapy to the abdomen or the lung. In women who received abdominal or pelvic irradiation, fertility problems need to be taken seriously as well as a close screening during pregnancy due to the higher risk of preterm deliveries. In patients with RTKs, rhabdoid predisposition syndrome must be excluded in affected families, and consultation by a geneticist is recommended. This is also true for WTs with underlying syndromes. Around 1% of WTs are familiar. Other advices to patients are similar as those for other childhood cancers in follow-up, including healthy lifestyle, engagement in sports, and dietary recommendations.

Long-term follow-up is performed according to the recommendations of the International Guideline Harmonisation Group (www.ighg.org) and the LESS group (www.nachsorge-ist-vors-orge.de) in Germany.

26.7 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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27 Late Effects After Treatment of Hepatoblastoma and Hepatocellular Carcinoma in Childhood and Adolescents

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27.1 Hepatoblastoma (HB)

Although complete resection is the cornerstone of the treatment concept, nearly all patients with hepatoblastoma receive pre- and postoperative chemotherapy. With this concept, a 5-year OS of 80% has been achieved [1]. If complete resection is not possible (PRETEXT IV, centrally situated liver tumour with vessel involvement), a liver transplantation has to be performed [2].

Until 2017 for about 20 years, children with HB were classified into two to three subgroups [3]: (1) standard-risk HB (SR-HB), PRETEXT (PRETreatment EXTent of disease) [4, 5] I, II or III (5-year OS: >90%) [6]; (2) high-risk HB (HR-HB), PRETEXT IV, tumour multifocal in the liver (F+), vessel involvement (V+, P+) or invasion of extrahepatic structures (E+) (5-year OS: 70–80%) [7]; and (3) very-high-risk HB (VHR-HB), PRETETXT I–IV with distant metastases (M+) and/or AFP <100 ng/mL (5-year OS: 50–65%) [8, 9]. With the initiation of the international PHITT (Paediatric Hepatic International Tumour Trial) study in 2017, the classification has changed as a consequence of the analyses of the CHIC (Childhood Hepatic Tumour International Consortium) database with 1605 patients [10, 11]. At the moment, there are four different risk-stratified treatment groups based on PRETEXT, metastases, AFP of ≤100 ng/mL, age and PRETEXT annotation factors [11].

However, the number of chemotherapeutic agents effective in the treatment of HB is still rather limited and has not changed over the years. The most important cytostatic drug is cisplatin given either alone in SR-HB patients [6] or in combination with carboplatin, doxorubicin, vincristine, 5-fluorouracil and/or irinotecan in the risk patients. With cisplatin-containing chemotherapy, a significant tumour reduction and improvement of resectability [6, 12] with a response rate up to 93% could be achieved [13]. Carboplatin/etoposide [14, 15] and the combination irinotecan/vincristine [17, 18] are currently used for intensification in metastatic disease with inadequate response to the induction therapy. Cisplatin/ifosfamide/etoposide (ICE) [16] is especially used as second-line treatment option.

27.1.1 Standard-Risk HB

For SR-HB, the SIOPEL group could show that the 3-year EFS and OS with six cycles of cisplatin monotherapy (cumulative dose: 480 mg/m^2) with

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83% and 95%, respectively, were not inferior to the standard care with six cycles of PLADO (cumulative doses: cisplatin 480 mg/m^2, doxorubicin 300 mg/m^2) [6, 19]. The idea was to spare anthracyclines with the possible severe long-term toxicity on the heart already present with a rather low cumulative dose [20]. With a short follow-up of 46 months, 32% of the patients tested had a hearing loss of ≥ grade I and 4% a glomerular filtration rate of <60 mL/min/1.73 m^2, not different between both groups.

In the GPOH studies, 3 (−4) cycles IPA were given (total doses: ifosfamide 9(−12) g/m^2, cisplatin 300(−400) mg/m^2, doxorubicin 180(−240) mg/m^2) [1, 12, 14]. Subclinical renal tubulopathy due to ifosfamide was detected in 17% of 41 investigated children [21]. In the HB99 trial, in 12% of the patients, a hearing loss was reported after a median follow-up of 41 months. Since 2009 ifosfamide was omitted to reduce nephrotoxicity. PLADO has been since then applied in reduced cumulative doses compared to the SIOPEL studies, since it is known that cisplatin doses of >400 mg/m^2 have a high incidence of ototoxicity [22].

The COG group has used cisplatin, fluorouracil and vincristine (C5V) as backbone [23, 24]. In the AHEP0731 study starting in 2009, LR-HB patients with stage I non-well-differentiated foetal histology and stage I and II non-small cell undifferentiated histology (SCU) were treated with two cycles of C5V after resection (cumulative doses: cisplatin 200 mg/m^2, fluorouracil 1.2 g/m^2, vincristine 9 mg/m^2) [25].

For the currently active PHITT study, the concept with cisplatin monotherapy is pursued with the idea to further reduce the number of cisplatin cycles in order to reduce long-term nephro- and ototoxicity.

27.1.2 High-Risk HB and Very-High-Risk HB

For HR-HB the standard treatment in Europe was alternating cisplatin and carboplatin/doxorubicin every 14 days (SIOPEL-3HR; cumulative doses: cisplatin 400 mg/m^2, carboplatin 2.5 g/m^2, doxorubicin 300 mg/m^2) with a 3-year EFS and OS for PRETEXT IV tumours of 68% and 69%, respectively [7].

In the VHR-HB group, dose-intense chemotherapy with preoperatively alternating cisplatin with carboplatin/doxorubicin every 7 days (A1-A3) and postoperatively with three cycles of carboplatin/doxorubicin (SIOPEL-4) has further improved the 3-year EFS and OS to 76 and 83% [8] (cumulative doses: cisplatin 570 mg/m^2, carboplatin 1.5 g/m^2, doxorubicin 330 mg/m^2). The most common side effect reported was ototoxicity in about 50% of the patients after a median follow-up of 52 months.

The former concept of the GPOH studies was two cycles of conventional carboplatin/etoposide and two cycles of high-dose carboplatin/etoposide with autologous stem cell support (cumulative doses: carboplatin 5.6 g/m^2, etoposide 4.8 g/m^2) [14, 15]. In 18% a hearing loss was reported. With a 3-year EFS of 51% and OS of 65%, no special benefit for high-dose chemotherapy could be established [26, 27]. From 2009 until 2017 the patients within the GPOH group are treated according to SIOPEL-3HR.

In the COG group, the former concept of intermediate-risk patients (stage I and II SCU histology and all stage III patients) was based on six cycles of cisplatin, 5-fluorouracil, vincristine and doxorubicin (C5VD, cumulative doses: cisplatin 600 mg/m^2, fluorouracil 3.6 g/m^2, vincristine 27 mg/m^2, doxorubicin 360 mg/m^2) [20] and for intensification in patients with stage IV disease or any stage with AFP <100 ng/mL irinotecan/vincristine, lately combined with temozolomide followed by C5VD [18]. A former COG study in children with unresectable or metastatic HB (P9645, 1999–2002) showed that the 1-year EFS of patients receiving intensified cisplatin/carboplatin every 2 weeks was inferior to C5V (37% vs. 57%) [28].

The currently active PHITT study randomises between cisplatin monotherapy (600 mg/m^2), SIOPEL-3HR (cumulative doses: cisplatin 400 mg/m^2, carboplatin 2.5 g/m^2, doxorubicin 300 mg/m^2) and C5VD (cumulative doses: cisplatin 600 mg/m^2, fluorouracil 3.6 g/m^2, vincristine 27 mg/m^2, doxorubicin 360 mg/m^2). In very-high-risk patients, SIOPEL-4 is the backbone with intensification with irinotecan/vincristine or carboplatin/etoposide for poor responders.

The reader is also referred to the Chaps. 1, 3, 9, 10 of this book.

27.2 Hepatocellular Carcinoma (HCC)

Treating HCC remains difficult since cure can only be achieved with complete surgical resection. However, in children and adolescents, less than 20% are considered eligible for initial complete resection. Several trials with different combinations of chemotherapeutic agents have been done to bring patients to resection. Historically, patients with HCC were treated with the same protocols than with HB, so primarily cisplatin, doxorubicin, carboplatin, 5-fluorouracil and vincristine were used. However, until now there are no persuasive data demonstrating a benefit for any combination to be better regarding survival.

In the SIOPEL-1 study, the 5-year EFS was 17% with only those patients surviving who had complete resection of their tumour (36%) [29]. However, it was learned from this study with PLADO (cisplatin 80 mg/m^2 and doxorubicin 60 mg/m^2 per cycle) as preoperative chemotherapy that paediatric HCCs are chemotherapy-responsive in nearly 50% [4, 29]. Katzenstein et al. [30] reported an 88% 5-year EFS in patients with completely resected HCC receiving either C5V (cisplatin, 5-fluorouracil, and vincristine) or PLADO. The German HB99 study used two cycles of carboplatin/etoposide postoperatively translating in 5-year EFS and OS probabilities of 72% and 89%, respectively [31]. However, the prognosis remained poor with 5-year EFS and OS rates between 10 and 34% in those patients who had inoperable or metastatic disease. Currently, the paediatric HCC community accepted PLADO as standard chemotherapy now combined with sorafenib [32]. The long-term toxicities of cisplatin and doxorubicin are well known but not for sorafenib when given in childhood.

In the currently active PHITT study, children with primary resection receive four cycles of PLADO (cumulative doses: cisplatin 320 mg/m^2, doxorubicin 240 mg/m^2). In those patients with metastatic and/or nonresectable tumours, three cycles of PLADO (cumulative doses: cisplatin 240 mg/m^2, doxorubicin 180 mg/m^2) are randomised with four cycles of GEMOX (cumulative doses: gemcitabine 4 g/m^2, oxaliplatin 400 mg/m^2). With GEMOX 44% of the patients' grade 3–4 toxicities were reported especially neutropenia, thrombocytopenia, diarrhoea and long-term neurotoxicity [33, 34].

27.3 Follow-Up Investigations for Hepatoblastoma and Hepatocellular Carcinoma

Since the chemotherapeutic trials in paediatric patients with hepatoblastoma or hepatocellular carcinoma are mainly based on cisplatin, doxorubicin and carboplatin, the long-term investigations must focus on ototoxicity [22], nephrotoxicity (with an impaired glomerular filtration rate and renal magnesium loss) [35] and cardiotoxicity [20]. Patients who do not receive chemotherapy can be followed up only for disease progression (physical examination, AFP in serum, tumour assessment and assessment of lung metastases) for a minimum of 5 years after diagnosis.

Time from diagnosis	1st to 3rd year	4th to 5th year	>5th year
Physical examination	3 months	6 months	Annually
AFP in serum	3 months	6 months	
Tumour assessment: Abdominal ultrasound	3 months	6 months	
Assessment of lung mets: chest-X ray p.a.	3 months	6 months	
Serum magnesium, if cisplatin or carboplatin was given	Annually	Annually	Annually
Creatinine clearance, if <80 mL/min/1.73m^2	Annually	Annually	Annually
Audiology assessment, if cisplatin or carboplatin was given	Annually	Annually	Annually
Echocardiogram (if anthracyclines were given)	Annually, if cumulative dose ≥250 mg/m^2 Otherwise every 2 years	Annually, if cumulative dose ≥250 mg/m^2 Otherwise every 2 years	Annually, if cumulative dose ≥250 mg/m^2 Otherwise every 2 years

27.4 Recomendation for a Long-Term Follow-Up Schedule

Long-term follow-up is performed according to the recommendations of the International Guideline Harmonisation Group (www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the LESS group (www.nachsorge-ist-vorsorge.de) in Germany.

27.5 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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28 Long-Term Sequelae After Retinoblastoma in Childhood and Adolescents

Petra Ketteler and Eva Biewald

28.1 Epidemiology and Genetic Background

Retinoblastoma is a pediatric eye tumor. The incidence of retinoblastoma is 1 in 20,000 live births, and most retinoblastomas are diagnosed in children under 5 years of age. Retinoblastoma is a lethal disease without therapy, but overall survival is higher than 95% with current treatment protocols in Germany [1]. The most common long-term sequelae are compromised vision and, for patients with heritable retinoblastoma, an increased risk for other extraocular malignancies in patients.

Retinoblastoma is the paradigm of heritable cancer predisposition. The etiological link between heritable and non-heritable retinoblastoma was determined by Knudson who proposed a model called the two-hit hypothesis. The mutational hits target the *RB1* gene. The spectrum of oncogenic *RB1* gene mutations is heterogeneous. In *non-heritable retinoblastoma*, mutations of both *RB1* alleles occur in the child's somatic cells. These children usually develop unilateral retinoblastoma. In *heritable retinoblastoma*, the first mutation is inherited from one parental germ cell (heterozygous carrier) or a result of a mutation that occurred during early embryonal development (mutational mosaicism). Tumor foci are caused by the second mutation occurring in the child's somatic cells. Approximately 10% of patients with heritable retinoblastoma have *familial retinoblastoma* as defined by relatives who have been afflicted with retinoblastomas or retinomas. Retinoblastoma without a family history of retinoblastoma is referred to as *sporadic retinoblastoma*.

28.2 Staging of Retinoblastoma

Staging of intraocular disease is applied separately for each eye, and different staging systems are used. Common classifications are the International Classification of Retinoblastoma (ICRB) or the Reese-Ellsworth Classification. Two further classification systems are used to determine the overall extent of extraocular disease: the International Retinoblastoma Staging System (IRSS) and the TNM classification as summarized in the eighth edition of the cancer staging manual by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC).

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28.3 Treatment of Retinoblastoma

The primary aim of retinoblastoma therapy is to save the patient's life. Secondary goals are the conservation of the globe, the preservation of vision, and the reduction of long-term sequelae. A variety of eye-preserving therapies have been developed to preserve at least one eye and vision in children with bilateral disease. Eye-preserving treatment is also offered to children with unilateral retinoblastoma and good visual potential in the affected eye. The choice of treatment modality depends on size and localization of the tumor. For this reason, treatment regimens are tailored for the individual patient.

28.3.1 Enucleation

Enucleation is still the standard therapy for advanced intraocular disease, especially if the tumors are unilateral or the affected eye has lost its function. It is of major importance to resect the tumor with the complete globe and a long section of the optic nerve to prevent diffuse scattering of tumor cells to the orbit. While the patient is still under anesthesia, an implant is fitted into the orbit to stimulate orbital growth for functional and cosmetic reasons. If the tumor has not extended beyond the natural borders of the eye, retinoblastoma is cured after enucleation alone. In Germany, only 10–20% of children need further adjuvant therapy after enucleation.

28.3.2 Focal Therapies: Laser Photocoagulation and Cryotherapy

Focal therapies are used for small- and medium-sized tumors as the primary treatment modality or in combination with chemoreductive therapy. Focal therapies include a variety of different modalities that are selected on an individual basis.

Cryotherapy. The cryocoagulation is a very effective method for local tumor control in newly occurring peripheral retinoblastoma. Potential side effects include conjunctival and retinal scars, bleeding, scleromalacia, and loss of vision.

Laser photocoagulation. Laser photocoagulation is used to treat small retinoblastomas without contact to visually sensitive structures. Potential side effects are scars of the retina, obstruction of retinal vessels, bleeding, visual field defects, reduction of visual acuity, tumor cell displacement in overthreshold treatment, traction to the retina, and fibrosis.

Thermochemotherapy. Thermochemotherapy is delivered directly on the entire tumor surface. This technique heats ocular structures to a temperature of approximately 60 °C and should be performed within 2 h after the end of carboplatin infusion to achieve the best possible penetration of the chemotherapeutic agent into the targeted tumor. Thermochemotherapy does not cause coagulation of retinal vessels and is, for this reason, the preferred modality to preserve vision, especially if the tumor is located near to sensitive structures (fovea or optic nerve). Figure 28.1 shows the typical result of successful thermochemotherapy treatment. Side effects are visual field defects, macular pucker, traction to the retina, or obstruction of retinal vessels [2].

28.3.3 Brachytherapy

Retinoblastomas are very radiation-sensitive, and episcleral brachytherapy has been used for decades as a highly effective treatment option. Especially the combination of systemic chemotherapy for tumor size reduction (chemoreduction) with subsequent consolidation with brachytherapy is very successful [3]. Brachytherapy is the preferred treatment option for medium-sized solitary tumors. Tumors located in the equatorial region or anterior retina have the best visual prognosis and less functional side effects. For episcleral brachytherapy, applicators loaded with radioactive isotopes are sutured onto the sclera for several hours or days until the previously calculated necessary radiotherapeutic dose at the apex of the tumor is reached. The risk of recurrence is extremely low, and the potential side effects are tolerable given the low penetration depth and

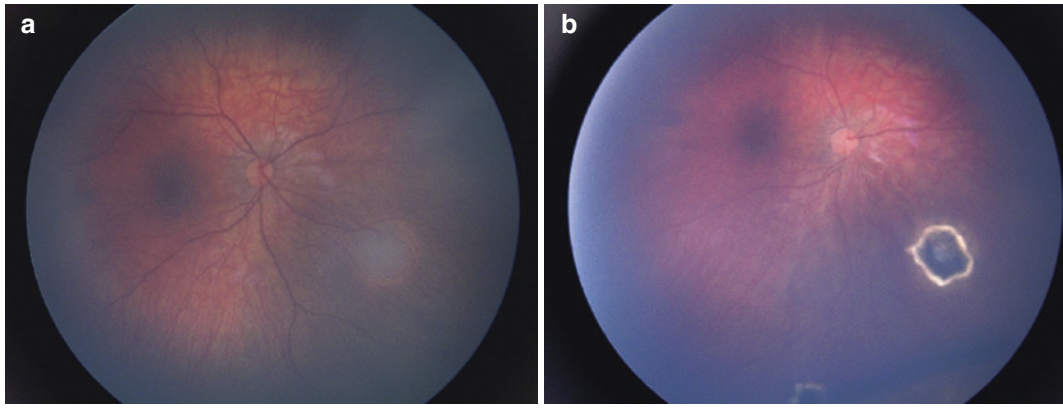

Fig. 28.1 RetCam fundus image showing the response of a retinoblastoma to thermochemotherapy. (**a**) Before and (**b**) after thermochemotherapy

low scattering of the rays. Long-term sequelae from brachytherapy include radiation optic neuropathy and radiation maculopathy/retinopathy, especially when treating tumors at the posterior pole of the eye, and possibly an increased risk for cataracts. According to current knowledge, the risk to develop second primary malignancy for patients with heritable retinoblastoma is not relevantly increased with this very localized form of radiation.

28.3.4 Systemic Chemotherapy – Chemoreduction

Systemic chemotherapy has been used for more than 40 years to treat extraocular retinoblastoma. Since 1996, systemic chemotherapy in combination with focal consolidation treatment is also used as eye-preserving therapy (chemoreduction). The chemotherapy protocol used widely in Germany and Austria until 2016 included cyclophosphamide, vincristine, carboplatin, and etoposide (CyVEC). However, chemotherapy with alkylating agents in addition to radiotherapy was shown to increase the incidence of second primary malignancies in survivors of heritable retinoblastoma [4]. To spare the potential mutagenic effect of alkylating agents, the chemotherapy regimen for preservation of the eye was changed in 2016 to the use of the international VEC protocol (Table 28.1).

Table 28.1 Cumulative doses of common chemotherapy regimens for retinoblastoma

Cumulative doses of 6 cycles of CyVEC	Cumulative doses of 6 cycles of VEC
9 mg/m^2 vincristine	9 mg/m^2 vincristine
1.2 g/m^2 etoposide	1.2 g/m^2 etoposide
1.2 g/m^2 carboplatin	3.36 g/m^2 carboplatin
4.8 g/m^2 cyclophosphamide	

28.3.5 Intra-arterial Chemotherapy

Since 2008, the intra-arterial application of a chemotherapy drug directly into the A. ophthalmica has been used increasingly. Local chemotherapy application aims to reduce systemic side effects and simultaneously increase local efficacy of the applied chemotherapy. The technique of superselective intra-arterial chemotherapy (IAC) uses a microcatheter that is advanced from the femoral artery into the ophthalmic artery, where the chemotherapeutic agent is given. The most commonly used chemotherapeutic agents are melphalan, carboplatin, and topotecan. IAC is an effective tool in the treatment of medium- and large-sized tumors (Fig. 28.2). The eye-preservation rates and the outcome in visual acuity are high, but data on adverse late effects are scarce [5]. Described late effects are persistent vitreous hemorrhages, changes in the retinal pigment epithelium, choroidal occlusive vasculopathy, or retinal arterial embolization with drastic loss of visual acuity. These changes have also been confirmed histo-

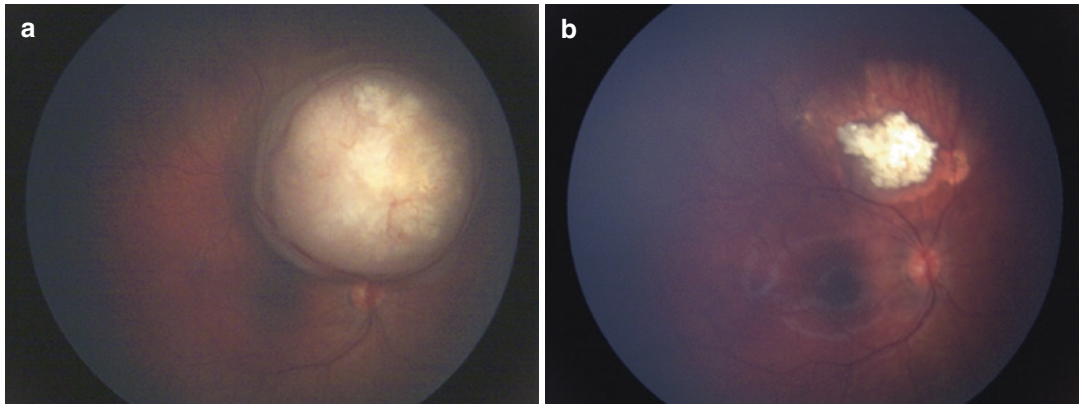

Fig. 28.2 RetCam fundus image showing the response of a retinoblastoma to intra-arterial melphalan. (**a**) Before and (**b**) 1 year after three doses of intra-arterial melphalan

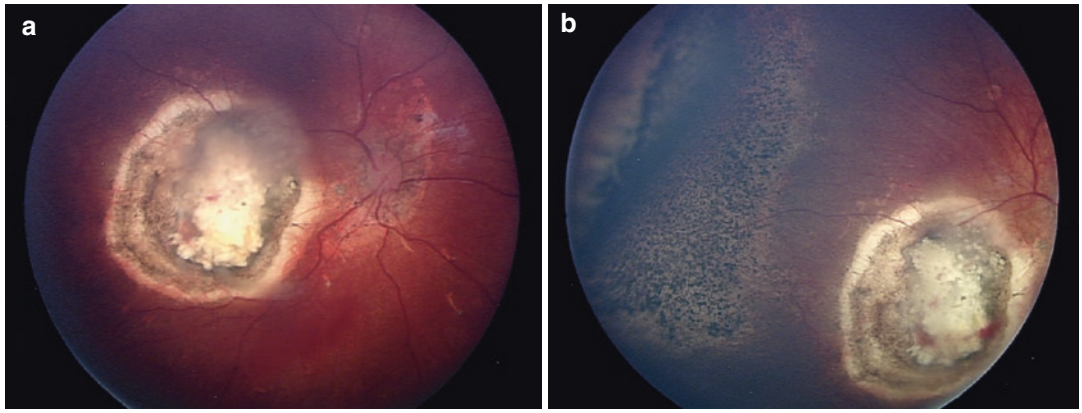

Fig. 28.3 RetCam fundus image showing a regressive retinoblastoma with vitreous seeding. (**a**) Before intravitreal chemotherapy and (**b**) "salt and pepper retinopathy" as side effect of intravitreal chemotherapy

pathologically in enucleated eyes after IAC [6]. Furthermore, repeated fluoroscopy potentially increases the risk of subsequent primary malignancies in patients with heritable retinoblastoma [7]. Potential vascular complications after arterial catheterization such as obstruction of the femoral artery or a stroke have been described in very rare cases.

28.3.6 Intravitreal Chemotherapy

Intravitreal chemotherapy (IVC) was introduced for the treatment of vitreous seeding in 2012. IVC, usually melphalan or topotecan, is injected directly into the vitreous cavity. This application route is very effective especially for the treatment of vitreous seeding, but the long-term outcome still needs to be assessed. The most common complication is a "salt and pepper" retinopathy at the injection site (Fig. 28.3) [8]. In addition, decreased amplitudes were observed on electroretinogram especially after multiple intravitreal injections. This could indicate a possible loss of visual acuity as a significant late effect [9].

28.3.7 External Beam Radiotherapy

External beam radiotherapy (EBRT) has been the primary treatment option for globe salvage for many years because retinoblastomas are

very radiation-sensitive. In the past decades, EBRT as an eye-preserving therapy has been almost completely replaced by systemic chemotherapy, because, in children with heritable retinoblastoma, the risk to develop second primary malignancies is significantly higher after EBRT. Today, eye-preserving EBRT is predominantly used as salvage therapy for therapy-refractory recurrences of retinoblastomas in the last eye. EBRT remains an important part of the multimodal treatment of extraocular retinoblastoma. EBRT can be indicated as local consolidation therapy for tumors of the orbit, for CNS tumors in patients with trilateral retinoblastoma, or for metastatic sites. Additionally, EBRT can be used in a palliative intent. The long-term consequences of EBRT to the eye, especially in early childhood, are diverse. These include sicca syndrome, radiation retinopathy/maculopathy (Fig. 28.4), optic nerve neuropathy, and cataract formation. Irradiation of the developing bone also causes growth arrest, which may lead to asymmetrical growth of the skull and facial deformities. The most serious long-term consequence, however, is the increased incidence of second primary malignancies, especially sarcomas, in children with heritable retinoblastoma after EBRT. There is evidence that proton radiotherapy has fewer late effects in children with retinoblastoma compared to photon radiotherapy [10]. For this reason, it is increasingly used worldwide as an alternative to conventional radiotherapy using photons.

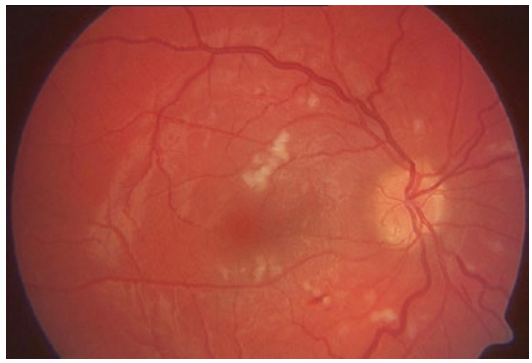

Fig. 28.4 RetCam fundus image showing radiation maculopathy/retinopathy

28.3.8 Treatment of Extraocular Retinoblastoma

Adjuvant treatment of histopathological risk factors after enucleation: In some children, histopathological examination of the enucleated eye reveals invasion of tumor cells into the choroid, sclera, anterior chamber, or optic nerve. These are considered as risk factors for extraocular metastatic spread of tumor cells after enucleation. Children diagnosed with histological high-risk factors receive for this reason adjuvant chemotherapy to reduce the risk of extraocular relapse [11]. In Germany and Austria, a risk-stratified adjuvant chemotherapy with 3–6 cycles of CyVEC or, after 2016, VEC chemotherapy is recommended.

Retinoblastoma with local metastasis: Microscopic residual disease or macroscopic local orbital disease or regional metastasis are treated with six cycles of CyVEC or VEC chemotherapy and local radiation therapy.

Retinoblastoma with distant metastases: Retinoblastomas metastasize preferentially to the orbit and then via pre-auricular lymph nodes to other lymph nodes and bones, bone marrow and CNS. Induction chemotherapy followed by high-dose chemotherapy with autologous hematopoietic stem cell rescue has been used successful for some patients with chemoresponsive disseminated disease [12]. The high-dose chemotherapy regimens varied over the last decades and so have the late effects. Most regimens included high-dose carboplatin that increase the risk for ototoxicity as a late effect [13].

Primary intracranial retinoblastoma (trilateral retinoblastoma): Trilateral retinoblastoma is a rare syndrome consisting of unilateral or bilateral heritable retinoblastoma associated with an intracranial neuroblastic tumor. The intracranial tumor is usually localized to the pineal or to the suprasellar or parasellar regions. Localized trilateral retinoblastoma is treated with six cycles of CyVEC chemotherapy and resection or radiotherapy as local consolidation. Metastatic trilateral retinoblastoma is treated according to the guidelines for metastatic retinoblastoma including autologous stem cell transplant.

28.4 Long-Term Sequelae

28.4.1 Long-Term Sequelae of the Eye

Maintaining the globe with proper vision is a crucial consideration in all treatment efforts. Healthy retinal tissue is destroyed both by retinoblastomas themselves and by the therapy. This can lead to loss of eyesight in the affected eye. While lesions in the peripheral retina rarely restrict everyday life, central tumors may significantly impair the vision. Bilateral retinoblastoma can even lead to complete blindness. Other late effects are conjunctival and retinal scarring after laser photocoagulation and cryotherapy and retinopathy after intravitreal chemotherapy or chorioretinal ischemia after intra-arterial chemotherapy. Potential side effects after radiotherapy are radiation optic neuropathy, sicca syndrome, cataract, and radiation retinopathy/maculopathy (Fig. 28.4).

28.4.2 Other Long-Term Sequelae

Ototoxicity is a potential side effect of the carboplatin-based chemotherapy for retinoblastoma and has been described in some patients with eye-reserving chemotherapy for retinoblastoma [14, 15]. Ototoxicity was a very rare side effect of eye-preserving therapy with six cycles of CyVEC, but the international VEC regimen, which was introduced in Germany in 2016, includes higher amounts of carboplatin, and ototoxicity might be observed more often in the future. Furthermore, patients receiving multiple courses of chemotherapy for relapses or high-dose carboplatin prior to autologous stem cell transplant for metastatic retinoblastoma show a higher risk to develop ototoxicity. Fertility can be affected after chemotherapy, but endocrinological impairments have not been reported after standard CyVEC or VEC regimen until today. Late sequelae in patients with intracranial retinoblastoma depend on the localization of the tumor and the extent of multimodal treatment. Common late effects after treatment for intracranial retinoblastoma are endocrinological impairments, neurodevelopmental deficits, and ototoxicity. Today, good cosmetic results are achieved after enucleation with appropriate prosthesis. However, radiotherapy of the developing bone affects its growth, and cosmetic complaints are not uncommon in patients with EBRT.

28.4.3 Risk for Second Primary Malignancies - Genetic Tumor Predisposition

All patients with heritable retinoblastoma have a tumor predisposition syndrome. Constitutional *RB1* variants predispose not only for multiple retinoblastoma in childhood but also for other extraocular tumors later in life. These tumors are often referred to as second primary malignancies. Second primary malignancies have a high mortality rate of 50% and are the main cause of death in adults with heritable retinoblastoma [1]. The most common entities are soft tissue and bone sarcomas. The spectrum of second primary malignancies is broad and includes melanoma, lung carcinomas, leukemias, and other malignancies. The incidence of second primary malignancies was approximately 1% per year in patients with heritable retinoblastoma [16]. The frequency and type of secondary malignancies depend strongly on the previous treatment for retinoblastoma. EBRT in particular increases the risk of second primary malignancies. Therefore, if possible, EBRT is avoided and substituted with chemotherapy in patients with heritable retinoblastoma today. However, also treatment with systemic chemotherapy containing alkylating agents or topoisomerase inhibitors may increase the risk of second malignancies [4, 17]. Screening for second primary malignancies is a challenge for patients, families, and attending oncologists, since second primary malignancies are described in every age group and in several locations. All patients with heritable retinoblastoma should attend throughout all their life a regular oncological follow-up clinic at a specialized center.

28.4.4 Quality of Life

The loss of vision or an eye is always perceived as very threatening by parents and family. Because of a diagnosis in early childhood, the children themselves usually adapt well to the loss of vision in one eye. However, visual impairment in both eyes has a strong influence on life planning, and early professional support is essential for these children. Furthermore, the patients and their families are often burdened by frequent anesthetic examinations in early childhood and diagnosis of multiple relapses of retinoblastoma. Perception of quality of life after treatment for retinoblastoma may change over the course of life and may be a challenge, especially in adolescence and young adulthood. Post-traumatic stress disorders, depression, and anxiety are described as long-term psychosocial consequences [18]. Age-appropriate information about retinoblastoma disease and the exchange with other survivors can be helpful in coping with the diseases.

Table 28.2 Follow-up examination 5 years after end of treatment

Non-heritable retinoblastoma
Ophthalmology: Ophthalmoscopy at least 1×/year, eye test 1×/year
Pediatric oncology: History and clinical examination every 5 years until adulthood
Otorhinolaryngology: Audiogram every 5 years until adulthood (only after chemotherapy)
Radiotherapy: Follow-up care as specified by the radiotherapist (only after radiotherapy)
Heritable retinoblastoma
Ophthalmology: Ophthalmoscopy at least 1×/year, eye test 1×/year
Pediatric oncology, clinical oncology: History and clinical examination 1×/year, immediate MRI if second malignancy is suspected
Otorhinolaryngology: Audiogram every 5 years until adulthood (only after chemotherapy)
Radiotherapy: Follow-up care as specified by the radiotherapist (only after radiotherapy)
Human genetics: Genetic counselling prior to family planning
Dermatology: Regular routine screening for skin cancer

28.5 Recommended Long-Term Follow-Up

Ophthalmological examinations are arranged individually with the patients during acute treatment. Five years after end of treatment, the patients should consult an ophthalmologist at least once a year for ophthalmoscopy and regular eye tests to monitor visual acuity. Appropriate support is necessary for visually impaired patients. All patients with non-heritable retinoblastoma need a pediatric oncological examination with a focus on late effects at least every 5 years until age of 18 years. Survivors with heritable retinoblastoma need a lifelong regular oncological follow-up at least once a year. During these oncological consultations, clinical examination and careful attention to the medical history is as important as counselling of the patient to raise awareness for symptoms of second primary malignancies. Until today, there is no evidence for a benefit of routine regular whole body screening with magnetic resonance imaging (MRI) for early detection of second primary malignancies [19]. For this reason, the current follow-up recommendation is that MRI should be performed immediately if any symptoms occur. Studies to investigate the benefit of regular cranial MRI screening in children treated with EBRT are still ongoing. Regular dermatological examination should be attended for early detection of melanoma. Furthermore, survivors of heritable retinoblastoma should receive genetic counselling prior to family planning. Survivors with heritable retinoblastoma are encouraged to participate in all recommended screening programs and to avoid irradiation whenever possible. All recommended follow-up examinations are summarized in Table 28.2.

Long-term follow-up is performed according to the recommendations of the International Guideline Harmonisation Group (http://www.ighg.org) and of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/).

28.5.1 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients. Even if the main focus is on acute care. https://www.awmf.org/leitlinien/detail/ll/025-002.html

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29 Late Effects in Children and Adolescents with Ewing Sarcoma

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29.1 Introduction

Ewing sarcoma (EwS) is a rare, often bone-associated malignancy that occurs in children and young adults; the median age at diagnosis is 15 years. At a time when radiotherapy and/or surgery were the only available treatments for EwS, an important lesson was learned: EwS is a systemic disease that consequently requires systemic treatment [1]. In the early 1960s, single-agent chemotherapy was administered. Since that time, modern multi-agent chemotherapeutic regimens have been developed. National and international groups have focused their efforts on identifying optimal treatment strategies: actinomycin D, cyclophosphamide, and vincristine were introduced in the 1970s [2]; neoadjuvant chemotherapy concepts were first introduced by Rosen et al. [3]. and subsequently developed by other groups. In the 1980s, the benefit of additional anthracyclines was shown. A beneficial synergistic effect was described when implementing a combination of ifosfamide with etoposide [4], and the introduction of high-dose ifosfamide has further significantly improved survival. Table 29.1 summarizes the agents used in Ewing sarcoma treatment and their mode of action. Furthermore, the value of platinum-based agents was investigated. The implementations of a multi-agent chemotherapy using alkylating agents, topoisomerase inhibitors, inducers of DNA strand breaks, and the introduction of intensified dosing regimens have increased the 5-year event-free survival of EwS patients from 50 to >75% [5–7].

Local control of the primary tumor, and whenever feasible of metastases, can be achieved by surgery, radiation, or a combination of both [8].

Patient survival increased under dose-intense treatment; consequently, Ewing sarcoma survivors face potential late effects. A report from the British childhood cancer survivors study documented a sixfold increase in relative risk of severe, or disabling chronic health conditions compared to the survivor's siblings and a 12.7% higher death rate among survivors than

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Table 29.1 Mode of action in agents used in Ewing Sarcoma trials

Drug	Class	Mode of action
Actinomycin D	Cyclic polypeptide antibiotic	Binding to DNA conformation within the transcriptional complex Interference with transcription elongation
Busulfan	Alkyl sulfonate, alkylating agent	DNA-DNA intrastrand crosslinking
Cyclophosphamide	Alkylating nitrogen mustard	Crosslinking between and within DNA strands
Doxorubicin	Anthracycline	Topoisomerase II inhibitor, inhibition of DNA replication (and RNA synthesis), production of free radicals, formation of DNA adducts
Etoposide		Topoisomerase II inhibitor, forms complex with DNA
Ifosfamide	Alkylating nitrogen mustard	Interferes with DNA replication and transcription of RNA
Melphalan	Alkylating nitrogen mustard	Interferes with DNA replication and transcription of RNA
Treosulfan	Alkylating agent	DNA-alkylation and DNA inter- and intrastrand crosslinking, hence interferes with DNA replication and transcription of RNA
Vincristine	Vinca alkaloid	Binds to tubulin dimers and inhibits the assembly of microtubule structures, disrupting chromosome separation during metaphase
Zoledronic acid	Pyrophosphate analogue	Slows down bone reabsorption via inhibition of farnesyl diphosphate synthase, thereby inhibiting farnesylation and geranylgeranylation of small G-proteins such as Ras, Rap1, and Rho

expected after 25 years of follow-up—second malignancies were often observed in this group of patients [9].

29.2 Ewing Sarcoma Treatment and Long-Term Organ Function

29.2.1 Doxorubicin

As in many sarcomas, anthracyclines are central to the treatment of Ewing sarcoma. The benefit from anthracycline-containing chemotherapy has been shown in a meta-analysis by Smith et al. [10]. This analysis also revealed that chemotherapy schedules containing a high intensity of anthracyclines show most promising results—in terms of survival—and that of all drugs administered in Ewing sarcoma, anthracyclines are probably the most effective [10, 11]. In an early study by Rosen et al., congestive heart failure was described in two patients who had received doses of 920 and 720 mg/m^2. In these early years of (cancer) treatment, anthracycline dosage of below 750 mg/m^2 was considered to be relatively safe [12]. A lower dose of no more than 500 mg/m^2 was recommended only for patients who received additional radiotherapy to the mediastinum [2]. Current studies recommend a dose of no more than 400 mg/m^2 [13–15]. With a marked increase in survival—mainly in patients with localized disease—this strategy seems effective.

A late effects study showed that 28% of long-term survivors (>5 years) are at risk of cardiac dysfunction [16]. All patients were treated with anthracyclines. In general, the risk of adverse effects from anthracyclines increases with dose. Dosages that present no risk of cardiotoxicity have not yet been defined [17]; it must be noted that some patients tolerate high cumulative doses without any cardiotoxicity [18]. The pathogenesis of cardiotoxicity is not well understood. Part of the anthracycline-induced effect on malignant and non-malignant cells is associated with binding to an inhibitor of topoisomerase 2b. Inhibition of topoisomerase 2b has been identified as a mediator of anthracycline-induced cardiotoxicity [19]. Notably, in a genome-wide association study including patients with Ewing sarcoma, a non-synonymous variant (rs2229774, p.Ser427Leu) in *RARG* was highly associated with cardio-

toxicity [20]. This genetic variant impairs the function of RARG and partially reverses the repression of topoisomerase 2b. Whether the variant is also associated with increased binding of anthracyclines was not investigated in the study. The authors could associate an ethnicity-related increased risk of cardiotoxicity in south Asian and Black people, as in these populations, the *RARG* rs2229774 (variant) occurs more frequently than in the Caucasian population [20].

Impaired cardiac function after treatment with anthracyclines and other drugs may remain subclinical for a long time and can exaggerate with cardiac stress (i.e., after an infection with cardiotropic virus, in pregnancy, etc.). Some long-term follow-up studies have shown that cardiac dysfunction is evident in 25–50% of survivors up to 20 years following cancer treatment [17]. Female survivors and patients treated at a very young age are associated with increased risk of cardiac dysfunction [17]. The most recent and current European Ewing sarcoma studies Euro Ewing 99 and EWING 2008 advocate a cumulative dose of 360 mg/mg^2; AEWS0031 and the Euro EWING 2012 advocate a higher dose of 375 mg/m^2.

Earlier studies have shown that infusion rate has an impact on the incidence of acute and subacute cardiotoxicity [21]. Although the cardioprotectant dexrazoxane had been associated with an increased risk of second malignancies, some protocols recommend its administration [22]. A Cochrane analysis on the publications of five randomized controlled trials showed that "dexrazoxane is associated with a statistically borderline increase in second malignancies, possibly due to an interaction with concurrent cancer therapies" [23]. The authors recommend a careful use of the drug. A randomized controlled trial in children is planned.

The reader is also referred to Chap. 1 of this book.

29.2.2 Etoposide

Etoposide is currently used in all Ewing sarcoma protocols. In the 1990s, The INT-0091 protocol could demonstrate a clear benefit from the add-on of ifosfamide and etoposide to the established combination of vincristine/doxorubicin/cyclophosphamide in patients with localized disease [24]. As a potent topoisomerase II inhibitor, etoposide may cause rearrangements involving the mixed lineage leukemia (MLL) gene on chromosome 11q23. The rearrangement is associated with secondary myelodysplastic syndrome and leukemia. The prognosis in MLL-gene rearranged (11q23 mutation) leukemia is extremely poor; thus, etoposide and other topoisomerase inhibitors may induce life-threating late effects [25, 26].

The reader is also referred to Chap. 14 of this book.

29.2.3 Alkylating Agents

The use of alkylating agents, such as the oxazaphosphorines ifosfamide and cyclophosphamide, is crucial for the successful treatment of Ewing sarcoma.

29.2.4 Cyclophosphamide

Cyclophosphamide is a pro-drug and is activated in the liver by CYP2B6. The metabolite 4-OH-cyclophosphamide-aldophosphamide can penetrate through the cell membrane and serves as a mediator for the highly active phosphoramide mustard. The antitumor efficacy unfolds after metabolic activation and is the result of direct alkylation of target cell DNA leading to inter- and intrastrand crosslinking, which ultimately induces apoptosis in non-resistant cells. It furthermore acts in an anti-angiogenic capacity by destroying circulating endothelial progenitor cells [27]. The cyclophosphamide metabolite acrolein is a causative factor in urotoxic site effects of the drug [28]. A typical cyclophosphamide-related acute toxicity is cystitis, and a severe and life-threatening late effect is bladder cancer that may occur long after treatment with cyclophosphamide [29, 30]. Whether the consequent use of sodium 2-mercaptoethane sulfonate (MESNA) may prevent this second malignancy is uncertain [31]. Cyclophosphamide is associated with the development of other, secondary sarcomas in a dose-dependent manner and

independent of additional radiotherapy with a higher risk above 9.4 g cumulative dose [32].

Cyclophosphamide is associated with increased risk of impaired spermatogenesis; higher doses posed greater risks compared to lower doses [33]. Premature ovarian insufficiency is also associated with cyclophosphamide. No clear threshold for a safe dose has been established [34].

29.2.5 Ifosfamide

Ifosfamide is a structural analogue of cyclophosphamide. It is a widely administered drug in Ewing sarcoma treatment and is usually used in combination with etoposide [7]. The toxicity profile differs from cyclophosphamide. Ifosfamide can result in renal function impairment. Ifosfamide-induced toxicity may affect both glomerular and tubular function causing decreased glomerular filtration rate, renal tubular acidosis, hypophosphatemia, hypokalemia, and hypomagnesaemia. Severe proximal tubulopathy may lead to hypophosphatemic rickets or renal tubular acidosis and may induce growth impairment [35, 36]. Young children <5 years are at higher risk of kidney damage in addition to patients with a single kidney [37]. Chronic glomerular nephrotoxicity is reported in approximately 30%, and tubulopathy is reported in approximately 25% of children and adolescents treated with ifosfamide [38].

Ifosfamide is dechloroethylated to form chloroacetaldehyde. Ifosfamide-induced encephalopathy is mediated by chloroacetaldehyde. Chloroacetaldehyde is structurally related to acetaldehyde—a neurotoxic metabolite of ethanol—and also to chloralhydrate, which is a widely used hypnotic drug. The symptoms range from mild (fatigue), moderate (hallucination), to severe (coma, status epilepticus) and can be classified according to the Meanwell criteria [39]. Fatal outcome has been reported in singular cases [40]. Risk factors for ifosfamide-induced encephalopathy are impaired kidney function, low serum albumin, low sodium, and the use of aprepitant. Aprepitant is an inhibitor of the cytochrome p450 isoenzyme CYP3A4, and the precipitation of ifosfamide-related encephalopathy is mediated by a CYP3A4 drug interaction [41]. Alkylating agents have been associated with gonadotoxicity. Although studies regarding ifosfamide have several limitations, they do reflect expert opinion. There is probably an increased risk of impaired spermatogenesis and early menopause following treatment with high ifosfamide doses >60 g/m^2 [33, 34]. In Ewing sarcoma protocols, the dose of ifosfamide is usually above 60 g/m^2 [7]. Ewing sarcoma patients should be informed about the risk of treatment-induced infertility and consult a reproduction medicine specialist prior to treatment.

Treatment with alkylating agents may induce secondary leukemia, mainly acute myeloid leukemia with a mean latency of app. 5 years. This form of leukemia is often characterized by antecedent myelodysplastic syndrome and related to cumulative dose of the alkylating agent [25, 26].

The reader is also referred to Chap. 2 of this book.

29.2.6 Busulfan/Melphalan

Busulfan can cause infertility in both male and female patients. In patients treated prior to puberty, there is a very high risk of primary impotence and ovarian failure. Furthermore, data from the Childhood Cancer Survivor Study showed that after treatment with busulfan, a significant increase in the need for supplemental oxygen and pleurisy was reported. The survivors in this study had not received radiotherapy to the lung or chest [42].

The reader is also referred to Chaps. 6, 9, 10, 12 of this book.

29.2.7 Treosulfan/Melphalan

Reports regarding late effects following treosulfan/mephalan in an autologous transplant setting (transplantation or re-transfusion of autologous hematopoietic stem cells after high-dose chemotherapy) are lacking; they will be available after the final analysis and the analysis of the long-term outcome in patients who received the drug

in the currently active EWING 2008 protocol. The long-term results that are currently published focus on patients who had received allogeneic transplantations, and the results are biased by the late effects related to the allogeneic setting. In general, treosulfan high-dose chemotherapy is associated with a mild acute toxicity and a low incidence for veno-occlusive disease [43].

29.2.8 Zoledronic Acid

Experience in long-term effects of treatment with zoledronic acid is gained from patients who received the drug for treatment of non-malignant diseases, i.e., osteoporosis, osteogenesis imperfecta, and Duchenne muscular dystrophy. No effect on the dentation was reported as well as a low incidence of atypical fractures [44]. Analyses of long-term effects after use in a malignant setting are anticipated from the French OS 2006 trial [45] and the international EWING 2008 trial [6, 7].

29.2.9 Other Drugs

The abovementioned drugs are widely used in current, first-line Ewing sarcoma treatment; however, previously, other drugs were administered. Bleomycin is associated with late pulmonary fibrosis, and, thus, lung function testing should be part of the long-term follow-up program.

Some patients were treated with high-dose chemotherapy followed by allogeneic stem cell transplantation [46].

Allogeneic stem cell transplantation is associated with an enormous burden of late complications. The mortality rate for patients who received allogeneic hematopoietic stem cell transplantation is twice as high as that of the general population among long-term survivors. A large number of survivors face challenges affecting their health and well-being. Relapses of primary disease (app. 30%) and chronic graft-versus-host disease (GVHD) are major risk factors for morbidity and mortality in this group of patients. Non-malignant late effects are manifold and diagnosed in 15–40% of patients. Common late effects include chronic GVHD; chronic immune deficiency and consecutive late opportunistic infections; ocular complications; and pulmonary dysfunction. Osteoporosis and osteonecrosis are observed in 50% of survivors. The often severe, chronic liver dysfunction may be the result of viral infections, late effects of veno-occlusive disease and other drug-related toxicity, GVHD, or iron overload. Endocrine dysfunctions are also common following allogeneic stem cell transplantation.

Relapse is associated with an unfavorable outcome. Only 20% of patients will achieve a second remission and become long-term survivors. Different chemotherapeutic regimes are used that include agents such as topotecan and cyclophosphamide, irinotecan and temozolomide, and carboplatin and etoposide. Others may be treated within phase I/II clinical trials [7]. Given the very low number of long-term survivors, knowledge regarding late effects in this sub-group is scarce.

29.2.10 Surgery

Chapter 6 gives an overview about the most common reconstruction techniques in sarcoma surgery and their possible complications. In general, these complications are also related to patients with Ewing sarcoma. In Ewing sarcoma, surgery may be followed by radiotherapy. We know that possible late effects of the reconstruction technique can be influenced by an additional local radiation therapy. In patients treated with a tumor endoprosthesis, the risk of periprosthetic infection is significantly higher in the case of an additional radiation therapy [47]. Jeys et al. [48] reported an infection rate of 9.8% in patients without radiation therapy in comparison to 20.7% in patients treated with radiation therapy (overall 1254 patients, 63 received radiotherapy). Streitbuerger et al. [49] could show that in patients with a proximal femur replacement, all patients with a periprosthetic infection and additional radiation therapy had to be amputated due to the complication of infection because of poor soft tissue conditions.

Radiation therapy has also negative effects in biological reconstructions. In patients with autologous bone reconstruction, radiation therapy is associated with significantly higher risks of pseudarthrosis and infection. Therefore, in each patient the decision for radiation therapy has to be made in an interdisciplinary team discussing its risks and oncological benefits.

The reader is also referred to Chap. 4 of this book.

29.2.11 Radiotherapy

Ewing sarcomas are radiosensitive tumors; therefore, radiation therapy (RT) is one important cornerstone of local therapy. Very often, RT will be combined with chemotherapy and surgery. This tri-modal approach can achieve a high curative potential for the majority of patients [50]. In general, the combination of surgery and RT leads to superior results regarding local control when compared to definitive RT alone [51, 52]. Radiotherapy as definitive treatment for local control is selected when the tumor is deemed inoperable or incomplete resection and/or mutilation is anticipated. However, the role of RT and its most effective implementation within combined therapy approaches still needs further investigation. Currently, radiation therapy is most often applied after neoadjuvant chemotherapy.

RT of Ewing sarcoma is disease status dependent. For the treatment of localized disease, resection with or without RT combined with systemic therapy is preferred for achieving local control. Typical concepts require total doses of 45–60 Gray (Gy) postoperatively. Definitive RT will be given up to a dose of up to 60 Gy. Metastases are treated locally if possible with doses exceeding 45 Gy.

Since RT is required in particularly complex situations, highly conformal RT-techniques such as intensity-modulated RT (IMRT) and proton therapy (PT) are used. These enable both high intensity and satisfactory protection of surrounding normal tissue. IMRT showed promising results for Ewing sarcoma of the pelvis regarding dose conformity [53]. As an alternative, PT allows the exact application of energy due to its physical characteristics (“Bragg Peak”) and can thus be used for tumors requiring high doses, as well as deep-seated tumors. Clinical experience with PT for the treatment of Ewing tumors is ever-increasing [54].

However, particularly when younger children are concerned, RT must be delivered with caution. The risk of late sequelae increases when patients are exposed to RT at a younger age, at higher doses, and to larger volumes (of tissue).

A large study on 403 children who had been treated with RT for Ewing sarcoma and had survived at least 5 years observed an increased risk of severe, disabling, or life-threatening chronic health conditions when compared to the control group of their siblings. In particular, cardiac, pulmonary, and neurological conditions were found. After 25 years, the cumulative incidence of a chronic health condition of any grade was 79.5%, and the cumulative incidence of a severe, life-threatening or disabling, or fatal chronic conditions was 46.4% [9].

Using information obtained from questionnaires from 12,390 childhood cancer survivors and 3546 randomly selected siblings, the authors evaluated the rate of first occurrence of 15 selected pulmonary conditions over three time periods: during therapy, from end of therapy to 5 years post-diagnosis, and ≥5 years post-diagnosis. Compared to siblings, survivors had a statistically significant increased relative risk (RR) of lung fibrosis, recurrent pneumonia, chronic cough, pleurisy, use of supplemental oxygen, abnormal chest wall, exercise-induced shortness of breath, bronchitis, recurrent sinus infection, and tonsillitis for all three time periods. During the period of ≥5 years post-diagnosis, statistically significant associations were present for lung fibrosis and chest radiation (RR, 4.3; $P = 0.001$); for supplemental oxygen use and chest radiation (RR, 1.8; $P < 0.001$) and busulfan (RR, 3.2; $P = 0.002$); for recurrent pneumonia and chest radiation (RR, 2.2; $P = 0.001$); for chronic cough and chest radiation (RR, 2.0; $P < 0.001$); and for pleurisy and chest radiation (RR, 1.4; $P = 0.02$) and busulfan (RR, 5.1; $P = 0.02$). Additionally, chest radiation was associated with a 3.5% cumulative incidence of lung fibrosis at 20 years after diagnosis [42].

However, prospective data from a study on RT for localized or metastatic Ewing sarcoma in 45 children and young adults showed an acceptable risk profile for long-term toxicities. Of the 40 patients who developed long-term toxicities, 7 were grade 3, and 3 were grade 4, respectively. The grade 4 toxicities were necrosis/spontaneous fracture in two patients and the development of a secondary malignancy in one patient [55]. After proton beam therapy, early results regarding late effects were promising. Reported late effects were scored predominantly mild to moderate and mainly concerned skin and bone growth. Higher-grade late effects concerned endocrine dysfunction and bone. Five-year toxicity-free survival was 90.9% [54, 56].

Any use of ionizing RT carries the risk of developing secondary malignancies. In a study on 266 patients with Ewing sarcoma surviving at least 3 years, 16 developed secondary malignancies [57]. The incidence of secondary malignancy after 5, 10, and 20 years was 3%, 4.7%–5%, and 9.2%, respectively [57, 58]. After PT in children with Ewing sarcomas, the incidence of secondary malignancies was 7% and 15% after 2 and 3 years, respectively [54].

The reader is also referred to the Chaps. 30, 40 of this book.

29.3 Follow-Up Recommendations

29.3.1 Follow-Up for Cardiotoxicity

In a consensus paper, the International Late Effects of Childhood Cancer Guideline Harmonization Group concluded that there is a level A incidence for an "Exponential increase for the risk of symptomatic cardiomyopathy with increasing lifetime cumulative dose" and that "Childhood cancer survivors treated with cumulative anthracycline doses of ≥250 mg/m^2 are at highest risk of *symptomatic* cardiomyopathy." Furthermore, the authors consented that "the risk of *symptomatic* cardiomyopathy increases with increasing radiation dose to cardiac tissues and after combined treatment with radiotherapy to cardiac tissues and anthracyclines." Surveillance in 2–5 year intervals are recommended, and the intervals are dependent on the cumulative risk. Surveillance is also recommended in pregnant women [59].

The reader is also referred to Chap. 1 of this book.

29.3.2 Follow-Up for Nephrotoxicity

Renal function tests should be performed on all Ewing sarcoma patients. Tubular function should be screened, and glomerular function should be estimated by creatinine measurements. Tubular function may be screened for by calculating fractionated phosphate reabsorption, with additional assessment of tubular amino acid handling in case of abnormalities [60].

The reader is also referred to Chap. 2 of this book.

29.3.3 Follow-Up for Pulmonary Toxicity

Ewing sarcoma patients may have received either busulfan-containing high-dose chemotherapy and a substantial group of patients underwent lung irradiation. Both busulfan high-dose treatment and lung irradiation have been associated with a higher risk of impaired lung function. Both treatments are known to cause restrictive ventilator defects characterized by decreased spirometry flow rates of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1). Radiation pneumonitis is the most common complication of thoracic radiation (see also below). Busulfan is known to cause lung fibrosis; furthermore, patients who lost considerable tissue are at risk of lung function impairment [61]. These patients should be advised to undergo regular lung function tests.

The reader is also referred to Chap. 6 of this book.

29.3.4 Follow-Up for Orthopedic "Complications in Tumour Orthopaedics"

The reader is also referred to Chap. 4 of this book.

29.3.4.1 Follow-Up for Radiotherapy-Induced Late Effects

The reader is referred to Part III, Chaps. 39, 40 of this book.

29.3.5 Follow-Up for Educational Achievements and Neuropsychologic Late Effects

The reader is referred to Part I, Chaps. 15–17 of this book. Particular emphasis must be placed on the age-specific needs and requirements of a mostly teenage and young adult population.

29.3.6 Follow-Up for Partnership Issues and Fertility

Survivors of childhood, adolescent, and young adult cancer who were treated with multimodal chemotherapy and/or radiation are at risk of having fertility problems. The International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurfUp group analyzed the risks to male and female fertility. The authors were unable to provide level A recommendations for male patients. As agents with level C evidence for impaired spermatogenesis such as cyclophosphamide, ifosfamide, busulfan, and melphalan are used in the treatment protocols for Ewing sarcoma patients, in-depth studies are needed to define the risk of infertility for male patients. Testosterone production seems unaffected by chemotherapy. Premature ovarian insufficiency was described in patients treated with alkylating agents, and the risk of POI was dose-dependent. Female survivors should receive counseling for POI and should be advised about the risk of premature menopause. Male survivors should be offered fertility counseling and—prior to treatment—sperm donation, whenever feasible [33, 34].

The reader is also referred to the Chaps. 9, 10, 12, 16, 43 of this book.

29.3.7 Follow-Up for Secondary Malignancies

Ewing sarcoma patients are at risk of secondary malignancies related to both chemotherapy and/or radiotherapy [62]. Approximately 9% of all Ewing sarcoma survivors are diagnosed with a secondary malignancy [9, 63]. The risk of secondary malignancy after chemotherapy is described above. Radiotherapy is associated with a risk of developing osteosarcoma, breast cancer, and thyroid cancer [63]. In addition to radiotherapy, patients are faced with radiation exposure as a result of standard imaging studies at diagnosis and during follow-up. The risk of secondary cancer is increased at a radiation dose of 1 Sievert by 5% in healthy subjects; the cumulative radiation exposure from imaging is far below this threshold. Whether cancer patients who received multimodal treatment have a higher risk of developing secondary malignancies due to cumulative toxicities has not yet been evaluated.

The reader is also referred to Chap. 14 of this book.

29.4 Recommendation for a Long-Term Follow-Up Schedule

Recommendations for early follow-up are summarized in Table 29.2.

Please see also the recommendations of the International Guideline Harmonization Group (www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the LESS-study (www.nachsorge-ist-vorsorge.de) in Germany.

Table 29.2 Recommendations according to the Ewingsarcoma Group.

1st year MONTH	Clinical examination	Blood FBC, Na, Cl, P, Mg, Ca, AST, ALT, γ-GT, protein, creatinine, ESR Urine Phosphate, creatinine, glucose, protein	Heart ECG/ echocardiography, blood pressure	Pulmonary function Spirometry in patients treated with thoracic surgery and irradiation to lung or chest wall, busulfan, treosulfan high-dose chemo	Hormones Sex Growth Thyroid	Primary tumor MRI CT	Lung X-Ray alternating with CT	Metastatic sites
0	X	X	X	X	X	X	X	X
2	X	X				X	X	X
4	X	X					X	
6	X	X		X		X	X	X
8	X	X					X	
10	X	X				X	X	X
12	X	X	X	X	X		X	
2nd year								
2	X					X	X	X
4	X	X					X	
6	X					X	X	X
8	X	X					X	
10	X					X	X	X
12	X	X	X	X	X		X	
3rd year								
3	X					X	X	X
6	X	X					X	
9	X					X	X	X
12	X	X	X	X	X		X	
4th year								
6	X	X				X	X	X
12	X	X	X	X	X	X	X	X
5th year								
	X	X	X	X	X	X	X	X
Later years								
	X	X	Every 3 years	X	X	See surgical guidelines	Optional	Optional

29.5 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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30 Late Effects in Children and Adolescents with Osteosarcoma

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30.1 Introduction

Osteosarcoma, the most common primary cancer of the bone, most frequently arises as a high-grade malignancy in the metaphyses of long bones in adolescents or young adults, particularly around the knee or shoulder. The evolution of osteosarcoma treatment paradigms has recently been reviewed [1]. As long as treatment was still restricted to surgery of the primary tumor, most patients succumbed to (pulmonary) metastases within a period of 1–2 years. Consequently, very few survivors will not have received systemic therapy in addition to local treatment of their primary tumor. The first reports of successful chemotherapy with high-dose methotrexate (HD-MTX) [2] and doxorubicin (Adriamycin) [3] date back to the early 1970s. Cisplatin was the third and ifosfamide the fourth drug for which relevant activity was identified [1]. Multimodal treatment of surgery plus postoperative [4–7] and soon also preoperative multidrug chemotherapy with several of these four agents [8, 9] was introduced soon thereafter. Long-term survival expectancies for localized extremity disease now reach 60–70% [1, 10–12]. The large intergroup European and American Osteosarcoma Study EURAMOS-1 relied on a MAP backbone of HD-MTX, doxorubicin (Adriamycin), and cisplatin in addition to surgery [13–15], and this is considered a current treatment standard by many. Only a small minority of survivors will also have received radiotherapy, usually to sites where surgery could not guarantee wide resection margins [16].

30.2 Osteosarcoma Treatment and Long-Term Organ Function

The Cooperative Osteosarcoma Study Group [COSS] was a cofounder of the German Late Effects Surveillance System LESS [17–19].

30.2.1 Doxorubicin

While some protocols employed lower cumulative anthracycline doses [20] or even none at all [21], most osteosarcoma survivors will have received cumulative doxorubicin doses of 360–450 mg/m^2 [1, 10]. This makes them vulnerable to suffer clinically relevant anthracycline cardiotoxicity [22, 23]. In the COSS 86 study of 171 osteosarcoma patients whose treatment included 360–450 mg/m^2 doxorubicin given as short infu-

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sions and who were investigated after a median of >8 years, five died of heart failure or had heart transplants [24].

Attempts to lower the incidence and severity of doxorubicin cardiotoxicity include administration by continuous infusion [13] or together with the cardioprotectant dexrazoxane [25]. Both strategies have shown some success in adults [26, 27]. However, results obtained in the randomized Dana-Farber Cancer Institute ALL Consortium Protocol 91-01 pediatric leukemia study question whether continuous infusions will also be able to reduce long-term cardiotoxicity in younger children [28]. The relevance of this finding for the predominantly adolescent/young adult osteosarcoma population remains to be determined. As for dexrazoxane, one trial suggested that it might increase the risk of secondary malignancies in children [29]. More recent analyses consider any excess risk of secondary malignancies associated with dexrazoxane either absent or at most borderline [30–32]. Nevertheless, dexrazoxane has so far not been granted a pediatric label. Studies comparing the two potentially cardioprotective approaches are lacking.

The reader is also referred to Chap. 1 on cardiotoxicity.

30.2.2 Cisplatin

Most osteosarcoma protocols contain cisplatin, often at cumulative doses of 480 mg/m^2 [1, 10–12]. While such treatment can be associated with permanent reduction of the glomerular filtration rate, terminal renal failure is very rare. Also, there was no platinum-induced reduction of glomerular function over time in a LESS series of 651 platinum-treated pediatric sarcoma patients [33]. In that study, hypomagnesemia occurred in 12% of patients after cisplatin therapy, but its frequency decreased with ongoing follow-up [33].

On the other hand, cisplatin-associated hearing loss is frequent [34], usually permanent, and may even result in the need for bilateral hearing aids [35]. Younger age, higher cumulative doses, and co-treatment with furosemide have all been associated with cisplatin ototoxicity [36]. In addition to limiting cumulative exposure and avoiding other potentially ototoxic agents and noise, efforts to reduce hearing loss include splitting the cisplatin dose per cycle over several days, administering it by continuous infusions over 48–72 h, or co-administering the organic thiophosphate amifostine. In two smaller non-randomized comparative studies of 39 [37] and 28 [38] osteosarcoma patients, however, amifostine did not reduce cisplatin oto- or nephrotoxicity. Cochrane Database reviews from 2016 came to the conclusion that there was no evidence from studies in children with osteosarcoma that underscored the use of amifostine or prolonged infusional cisplatin as otoprotective interventions and that it was impossible to give recommendations for clinical practice [39, 40]. In both instances, there was a clear paucity of high-level research on the matter, leading the authors to point out that "absence of evidence" should not be confused with "evidence of no effect." Accordingly, many current osteosarcoma protocols prescribe cisplatin by continuous infusions.

In males, cisplatin may also affect fertility. In a recent CCSG study of pregnancy after chemotherapy which included 10,938 survivors of childhood cancer, treatment within the highest quartile of cisplatin correlated with a reduced likelihood of pregnancy [41].

The reader is also referred to the chapters on nephrotoxicity (Chap. 2) and ototoxicity (Chap. 3).

30.2.3 High-Dose Methotrexate (HD-MTX)

HD-MTX is often well tolerated but can cause catastrophic, life-threatening acute complications. It can lead to acute renal failure, resulting in massively delayed methotrexate clearance with multiorgan toxicity and even death [42]. If survived, renal function will usually recover, and re-exposition can be attempted [43]. While some long-term effects on renal function have been suggested [44], long-term HD-MTX nephrotoxicity is not a major issue.

Acute, transient central nervous symptoms such as aphasia, hemiplegia, behavioral changes, or sei-

zures occur in some patients within days after HD-MTX. These stroke-like symptoms are usually fully reversible within hours [45]. Imaging findings on MRI may persist long after HD-MTX, but without a clear correlation to neurologic findings [46].

In pediatric leukemia, HD-MTX treatment has been associated with neurocognitive problems years after treatment [47], and some guidelines recommend neurocognitive screening for long-term survivors [48]. Such recommendations, however, have been questioned: a recent study investigating neurocognitive function of 80 former osteosarcoma patients some 25 years after treatment found neurocognitive impairment to correlate with current chronic health conditions, but not treatment with HD-MTX [49].

30.2.4 Ifosfamide

Ifosfamide can cause acute and severe central nervous toxicity, namely, encephalopathy, but this is usually rapidly reversible and not associated with long-term consequences [50]. Probably the best-known ifosfamide-specific late effect is proximal renal tubular toxicity, believed to be a consequence of ifosfamide's metabolite, chloroacetaldehyde. It can manifest as electrolyte wasting, glucosuria, and acidosis and may necessitate electrolyte substitution [51]. While sometimes temporary, severe ifosfamide tubulopathy tends to become chronic [52]. The risk is higher for younger patients and for those treated with higher cumulative ifosfamide doses, with various cutoff points reported [52–54]. Based on their experience in 148 young sarcoma patients, British investigators concluded that restricting cumulative ifosfamide dosage to <84 g/m^2 would reduce the frequency of clinically significant nephrotoxicity, while doses >119 g/m^2 would be associated with a very high risk [53]. In the German LESS study of 593 sarcoma patients, tubulopathy, defined as continuing hypophosphatemia or proteinuria, was observed in 0.4% of patients treated with a cumulative ifosfamide dose of ≤24 g/m^2, 6.5% after 24–60 g/m^2, and 8.0% after ≥60 g/m^2 [54].

High-dose alkylator treatment is a well-known risk factor for infertility, particularly in males [41]. Some recent osteosarcoma protocols, such as the experimental poor responder arm of the EURAMOS trial [15] or the most recent French studies [55], have included high cumulative ifosfamide doses >60 g/m^2. In one analysis involving 32 males treated with ifosfamide as the only gonadotoxic agent, such doses led to subfertility in two-thirds of those who underwent semen analysis [56]. Also, in an Italian analysis of 26 osteosarcoma survivors who underwent sperm analysis, 20 showed oligo- or azoospermia, with those who received high-dose ifosfamide being at higher risk [57]. Treatment with high cumulative ifosfamide doses was also identified as a risk factor for fertility in males, but not females, in the already mentioned CCSG study [41]. While mostly fertile, female cancer survivors who received high cumulative alkylator doses may suffer from decreased ovarian reserve, placing them at risk for premature ovarian failure [58]. The exact impact of ifosfamide as used against osteosarcoma remains to be determined in this context.

The reader is also referred to the chapters on nephrotoxicity (Chap. 2) and fertility (Chaps. 9, 10, 12).

30.2.5 Other Drugs

Osteosarcoma treatment has basically relied on the same four drugs detailed above since the early 1980s, but some survivors may (also) have received other agents. Both some American and some European protocols from the 1970s/1980 included the BCD combination of bleomycin, cyclophosphamide, and actinomycin D [9]. Patients treated on such protocols could be at risk for pulmonary fibrosis and therefore candidates for pulmonary function testing. Osteosarcoma survivors who received bleomycin are, however, few, and studies describing their long-term lung function are lacking.

Some patients randomized in the good responder cohort of the EURAMOS-1 trial will have received pegylated interferon α2b [14]. While its side effects are mostly acute, the drug can favor the development of autoimmune conditions, particularly immune-mediated thyroid disease. No osteosarcoma-specific analyses on these toxicities have been reported.

Based upon the results of a prospective trial [59], the macrophage activator mifamurtide (liposomal muramyl-tripeptide-phenylethanolamine, MTP) has received a European label for treatment of localized osteosarcoma (it has not been licensed by the US Federal Drug Administration). Acute side effects are mainly reversible fever, chills, headache, or fatigue [60]. So far, no data on (unexpected) late effects has emerged, even though it has been pointed out that severe hearing loss occurred in 12% of the patients treated with mifamurtide in the comparative trial, versus 7% of the others [61].

Approximately 20–25% of patients suffering osteosarcoma recurrences will become long-term survivors. These will either have received surgery as the only form of relapse treatment or any of a plethora of drugs in addition to surgery. Patients treated with second-line chemotherapy not given either methotrexate, doxorubicin, cisplatin, or ifosfamide first line will usually receive these for their recurrence. Other drugs which have been used against recurrent osteosarcoma within but mostly outside of trials include but are not limited to carboplatin, etoposide, gemcitabine, docetaxel, topotecan, cyclophosphamide, and many others [62–65].

More recently, various "targeted" treatments have been employed against refractory or recurrent osteosarcoma, most notably sorafenib with or without everolimus [66], but also uncountable others [64, 65, 67]. Some very recent patients may also have received checkpoint inhibitors [68]. Most of these will have been given to patients with very advanced disease and without any permanent benefit. Consequently, very few long-term survivors will have been exposed to such drugs.

30.2.6 Surgery of the Primary Tumor

Pediatric osteosarcomas usually arise in a long extremity bone, frequently around the knee. Axial primaries affect an older population and are associated with a much poorer prognosis, so that the number of survivors after pediatric osteosarcomas of the axial skeleton is limited.

An ever-increasing proportion of limb osteosarcomas are being treated by limb-salvage surgery, usually followed by endoprosthetic reconstruction. This presents multiple challenges for long-term follow-up, such as prosthetic wear and loosening, periprosthetic fractures, and most notably infection. A study of 230 patients who had undergone first-generation endoprosthetic replacement >25 years ago reported an average of 2.7 further operations per patient, with only 18% of patients still having the original prosthesis in place. The risk of amputation was 16% [69].

Tumors developing prior to skeletal maturity pose additional challenges, and noninvasively expandable endoprostheses have been developed to allow for extremity growth. However, these are still far from perfect: In one recent analysis of 71 patients from a major referral center, an average of 4.4 and 2.5 operations per patient were required for limb elongation and for complications, respectively. The most common complications were soft-tissue failure (46%), structural failure (28%), infection (17%), and aseptic loosening (8%) [70].

Being physically impaired after extremity surgery, bone sarcoma survivors may struggle with sexual function, depressive symptoms, and poor self-perception. Interestingly, in one study of 28 patients, survivors of limb-sparing surgeries reported more of those problems than rotationplasty or amputation survivors. In that study, male survivors of lower extremity bone tumors experienced better sexual functioning than women [71].

Taken together, the long-term consequences of bone sarcoma surgery and reconstruction will vary considerably by patient-related factors, primary tumor site, and reconstructive technique. They are covered in detail elsewhere in this book (see Chap. 4).

30.2.7 Surgery for Metastatic Disease

Osteosarcoma metastases usually affect the lungs. Bone metastases are less frequent, and metastases to other sites are unusual and rarely survived.

Survivors after treatment for primary or secondary pulmonary metastatic osteosarcoma will almost always have received thoracotomies as

part of curative treatment. Most of these will later not notice procedure-related restrictions during activities of daily living or even during physical exertion. Extended or repeated pulmonary resections can, however, result in abnormal pulmonary function tests (PFTs). A report from the St. Jude lifetime cohort study included 15 patients with a single thoracotomy and 6 with ≥2 thoracotomies who underwent PFTs a mean of 20.3 years after last thoracotomy. The authors observed that patients often had abnormal PFTs but that the reduction in lung volumes and single-breath diffusion capacity was relatively mild. A history of multiple thoracotomies correlated with greater impairment of pulmonary function [72].

The same principles as for surgery of the primary tumor apply for surgery of these bone metastases, and this includes follow-up for late effects.

30.2.8 Radiotherapy

Few patients who require radiotherapy for an inoperable osteosarcoma will go on to become long-term survivors. The administered doses will usually have been very high, sometimes in excess of 60 Gy [16]. Late effects will largely depend on the irradiated field and include fibrosis, fractures, organ damage, and an increased risk for secondary malignancies [73].

Adjuvant radiotherapy to the lungs was part of early EORTC osteosarcoma studies [74, 75]. Patients exposed to chest radiotherapy have an increased risk to develop anthracycline cardiomyopathy [23] and are also at risk for cardiovascular complications [76]. Chest irradiation, particularly during puberty, is also associated with a considerable risk for secondary breast cancer which, as expected, mainly concerns females. In one of the EORTC studies, 13 of the irradiated patients were females, of whom 2 developed bilateral breast cancer approximately 15 years later [77]. Breast cancer long after chest irradiation for osteosarcoma has also been described in at least one male [78]. It should not be forgotten that osteosarcoma patients will often require many imaging studies, particularly of the chest, and their radiation risks should also be taken into account [79].

The reader is also referred to Chaps. 39, 40 on radiotherapy.

30.3 Follow-Up Recommendations

The large European groups [80–83] cooperating on late effects research and on the development of evidence-based survivorship care are participating in the global Late Effects of Childhood Guideline Harmonization Group.

30.3.1 Follow-Up for Cardiotoxicity

According to the International Late Effects of Childhood Cancer Guideline Harmonization Group, cardiomyopathy surveillance by echocardiography for assessment of left ventricular systolic function is recommended for survivors treated with high-dose (≥250 mg/m^2) anthracyclines [23]. This would include most patients treated on modern osteosarcoma protocols. Cardiomyopathy surveillance is recommended to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis and continued every 5 years thereafter, with more frequent cardiomyopathy surveillance being deemed reasonable for high-risk survivors [23], which would again include most former osteosarcoma patients, as these will often have received 360–450 mg/m^2 doxorubicin. The few survivors who also received radiotherapy to the chest should additionally receive lifelong follow-up for cardiovascular disease, which, if at all, will usually only develop decades after treatment. A recent review concluded that the effects of exercise and other lifestyle changes in reducing cardiovascular disease in cancer survivors were unclear but that it may be beneficial to encourage survivors to engage in monitored physical activity tailored to their medical status [84].

The reader is also referred to Chap. 1 of this book.

30.3.2 Follow-Up for Nephrotoxicity

Renal function parameters should be investigated in all osteosarcoma patients who received cisplatin and/or ifosfamide. Glomerular function should be estimated by creatinine measurements. Tubular function may be screened for by calculating fractionated phosphate reabsorption, with additional assessment of tubular amino acid handling in case of abnormalities [85]. It may be prudent to check magnesium levels after cisplatin, at least until these return to normal, and to substitute where necessary.

The reader is also referred to Chap. 2 of this book.

30.3.3 Follow-Up for Hepatotoxicity

The hepatotoxicity of osteosarcoma treatment is usually transient and fully reversible. Provided that liver enzymes and bilirubin are normal post treatment and that there is no evidence of viral hepatitis, further tests investigating liver integrity or function may not be necessary.

30.3.4 Follow-Up for Pulmonary Toxicity

Montoring lung function seems appropriate for the few osteosarcoma survivors who received bleomycin or radiation therapy for the lungs. It may also be advised for patients who lost considerable pulmonary tissue during thoracotomy for lung metastases [72].

The reader is also referred to Chap. 6 of this book.

30.3.5 Follow-Up for Orthopedic Complications/Extremity Function

The reader is referred to Part 1, Chap. 6 of this book.

30.3.6 Follow-Up for Educational Achievements and Neuropsychologic Late Effects

The reader is referred to Part 1, Chaps. 16–18 of this book. A particular emphasis must be put onto the age-specific needs and requirements of a mostly teenage and young adult population.

30.3.7 Follow-Up for Partnership Issues and Fertility

Both males as well as, to a lesser proportion, females may encounter fertility problems following multimodal cancer therapy. Male survivors, particularly those who received ifosfamide and potentially also those who received high cisplatin doses, should be offered fertility counseling. Females should be advised about a potential risk of premature menopause [86]. Reassuringly, there is ample evidence that a history of chemo- or radiotherapy will lead neither to a significant excess of congenital anomalies [87] nor to a significant excess of malignancies in the offspring of former cancer patients [88].

The reader is also referred to Chaps. 9, 10, 12 on fertility.

30.3.8 Follow-Up for Secondary Malignancies

Overall, the risk of secondary malignancy after osteosarcoma does not appear to be orders of magnitudes higher than for patients treated for other sarcomas or other pediatric malignancies in general. Treatment-related and environmental factors can contribute to the development of further cancers. Given that few long-term osteosarcoma survivors will have received radiotherapy, treatment-related risk is mainly related to chemotherapy. However, cumulative radiation exposure due to multiple imaging studies such as CT, PET/CT, and bone scans at diagnosis, during therapy, and during follow-up can also increase the lifetime risk of secondary cancers [79, 89].

Some osteosarcomas develop on the basis of a genetic cancer predisposition syndrome. In a recent series from the St. Jude Washington University Pediatric Cancer Genome Project, 7 of 39 analyzed osteosarcoma patients younger than 20 years carried germline mutations in genes predisposing to pediatric cancer [90]. Osteosarcoma predisposition is most obvious in patients with germline RB1 abnormalities, where osteosarcoma usually already constitutes a second cancer after retinoblastoma [91], but also increased in Rothmund-Thomson syndrome and other inherited conditions, most notably Li-Fraumeni syndrome [92]. While long believed to be in the 3% range, recent evidence suggests that ≥10% of all pediatric and adolescent osteosarcomas may arise in patients carrying TP53 mutations or rare exonic variants [93]. These patients and their affected family members carry an increased risk to develop cancers belonging to the Li-Fraumeni spectrum. The family history should be screened for such malignancies [94] in all osteosarcoma patients, and genetic counseling should be considered at least for those patients where an association is suspected.

Breast cancer has been reported among the most frequent secondary malignancy after osteosarcoma [95], an association to which diagnostic radiation exposure, particularly by chest CT, and genetic factors may contribute. In addition to breast cancer per se, phyllodes tumors, rare breast lesions which can be benign, borderline, or malignant [96], may also affect former osteosarcoma patients. In one series, 3 of 86 osteosarcoma patients, all females, developed phyllodes tumors [97]. While the global incidence will not be this high, an association with osteosarcoma does exist, and five females who developed both tumors could be identified from the COSS database [98]. Taken together, the data on secondary breast tumors makes it reasonable to recommend that long-term follow-up of female osteosarcoma patients should include lifelong breast examinations. Patients who develop both osteosarcoma and tumors of the breast should be offered genetic counseling and TP53 testing.

In the randomized EURAMOS-1 trial, an increased incidence of acute myeloid leukemia was observed in patients whose treatment included ifosfamide and etoposide [15]. There is no evidence that efforts aimed toward an early detection of such catastrophic events will improve the overall poor outlook associated with this particular type of secondary malignancies.

The reader is also referred to Chap. 14 on subsequent primary cancer.

30.3.9 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (https://www.awmf.org/leitlinien/detail/ll/025-002.html).

30.4 Recommendation for a Long-Term Follow-Up Schedule

Long-term follow-up for late effects of osteosarcoma therapy should be performed according to the recommendations of the International Guideline Harmonization Group (www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the study (www.nachsorge-ist-vorsorge.de) in Germany.

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31 Late Effects in Children and Adolescents with Soft Tissue Sarcoma

Monika Sparber-Sauer and Thomas Klingebiel

31.1 Introduction

Soft tissue sarcomas represent a very heterogeneous group of rare but generally aggressive tumours which disproportionately affect children and young adults. They represent less than 10% of all childhood cancers but are one of the most frequently diagnosed cancers in paediatric patients. These cancers have a high rate of morbidity and mortality. The prognosis for children with localised rhabdomyosarcoma has improved dramatically since the introduction of coordinated multimodal treatment. Cure rates have improved from 25% in the early seventies, when combination chemotherapy was first implemented, to approximately 70% in more recent years. A major role in developing new strategies has been carried out by cooperative clinical trial groups in Europe and North America. They have optimised the therapy for children with RMS matching the complexity of treatment against known prognostic factors such as site, stage and pathological subtype. In fact the role of radiotherapy, surgery and chemotherapy in different risk groups has been explored in a series of multicentre clinical trials on both sides of the Atlantic. The CWS study group, including not only Germany but centres in Austria, Sweden, Poland, Finland and Switzerland, traditionally cooperated with the AIEOP Soft Tissue Sarcoma Committee (AIEOP STSC, former ICG: Italian Cooperative Group for paediatric soft tissue sarcoma) and the SIOP Malignant Mesenchymal Tumours (MMT) Committee. Having achieved an agreement in risk group definition in RMS tumours, a joint study started in 1996, randomising chemotherapy regimen in the high-risk group (VAIA vs. CEVAIE in the CWS/ICG group and IVA vs. CEVAIE in the MMT SIOP group). The EpSSG protocol for treatment of rhabdomyosarcoma in children and adolescents (EpSSG RMS 2005) has been derived from the evolving cooperation of those European groups. This cooperation will improve the quality of treatment of patients from all over Europe and will enable the study groups to improve their ability to respond to the still unanswered questions regarding therapy and prognosis of children with rhabdomyosarcoma and other soft tissue tumours. Because of the biological diversity, the long-term follow-up should be adjusted to the specific therapeutical approaches.

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31.2 Epidemiology

The incidence of soft tissue sarcomas in children in Germany is 1.0/100.000 [1]. The same incidence is seen worldwide. Soft tissue sarcoma represents the fifth most common tumour group in children and adolescents after leukaemias, CNS tumours, lymphomas and sympathetic nervous system tumours. Soft tissue sarcoma represents an extremely heterogeneous group of tumours, and the subtype with the highest incidence per year (0.5/100.000 in patients <15 years) is rhabdomyosarcoma. Boys are nearly equally affected by RMS tumours as girls (1.1:1 boys vs. girls). The peak incidence is seen early in childhood with a median age at diagnosis of about 5 years. The soft tissue sarcoma trials of the CWS, ICG and SIOP have been the only studies for the treatment of localised soft tissue sarcomas in childhood and adolescents within their participating countries. The CWS study has registered about 64 German RMS patients <21 years per year in the last 15 years, which means that about 95% of all RMS patients registered in the German Childhood Cancer Registry (Deutsches Kinderkrebsregister, DKKR) are documented in and treated according to the CWS recommendations.

31.3 General Remarks

Rhabdomyosarcoma (RMS) is thought to arise from primitive mesenchymal cells committed to develop into striated muscles. It can be found virtually anywhere in the body, including those sites where striated muscles are not normally found. The aetiology is not yet known. Genetic factors may play an important role as demonstrated by an association between RMS and familial cancer syndrome (Li-Fraumeni), congenital anomalies (involving the genitourinary and central nervous system) and other genetic conditions, including neurofibromatosis type 1 [2].

Depending on histological appearance, two main forms of RMS have been distinguished: the *embryonal* (which accounts for approximately 80% of all RMS) and the *alveolar* subtypes (15–20% of RMS). It has been shown that RMS subtypes have an impact on survival. In 1995 pathologists from the different cooperative groups agreed on a new classification, which identified prognostically significant and reproducible subtypes [3]. Three main classes have been identified:

1. *Superior prognosis*: including botryoid RMS and spindle cell or leiomyomatous RMS.
2. *Intermediate prognosis*: represented by embryonal RMS.
3. *Poor prognosis*: including alveolar RMS and its variant solid alveolar RMS.

This classification system does not include the pleomorphic category, as this is very rarely observed in children.

Molecular biology studies have identified two characteristic chromosomal alterations in RMS: reciprocal chromosomal translocations t(2;13)(q35;q14) or t(1;13)(p36;q14) in alveolar RMS [4], whilst genetic loss on chromosome 11p15.5 has been shown in embryonal RMS [5]. Different staging systems have been developed to classify RMS. The most widely used are the pre-treatment TNM staging and the postoperative IRS Grouping system. However, with the evolution of treatment and trial results, a new and more complex categorization has been used to better tailor the treatment to the risk of relapse.

Based on the results of cooperative studies, different patient- and tumour-related factors with relevance for prognosis have been defined. The most important are histology, tumour site and size as well as post-surgical stage [6–9]. More recently the patient's age at diagnosis has been recognised as a predictor of survival, showing that older children (≥10 years) have a worse outcome [6, 10]. Patients are treated according to risk stratification (Tables 31.1 and 31.2).

31.3.1 Risk Stratification for Rhabdomyosarcoma

- **Pathology**:
  - *Favourable* = All embryonal, spindle cells, botryoid RMS
  - *Unfavourable* = All alveolar RMS (including the solid alveolar variant)

Table 31.1 Risk stratification for rhabdomyosarcoma

Risk group	Sub-groups	Pathology	Post-surgical stage (IRS group)	Site	Node stage	Size and age
Low	A	Favourable	I	Any	N0	Favourable
Standard	B	Favourable	I	Any	N0	Unfavourable
	C	Favourable	II, III	Favourable	N0	Any
	D	Favourable	II, III	Unfavourable	N0	Favourable
High	E	Favourable	II, III	Unfavourable	N0	Unfavourable
	F	Favourable	II, III	Any	N1	Any
	G	Unfavourable	I, II, III	Any	N0	Any
Very high	H	Unfavourable	II, III	Any	N1	Any

Table 31.2 Risk stratification for rhabdomyosarcoma-like soft tissue sarcoma (SySa, STET, UDS)

Risk group	Pathology	Post-surgical stage (IRS group)	Initial tumour size	Node stage
Localised RMS-like	SySa, STET (EES/pPNET), UDS	I, II, III	Any	Any
Metastatic disease		IV	Any	Any

- **Post-surgical stage**:
  - *Group I* = Primary complete resection (R0)
  - *Group II* = Microscopic residuals (R1) or primary complete resection but N1
  - *Group III* = Macroscopic residuals (R2)
- **Site**:
  - *Favourable* = orbit, genito-urinary non-bladder/non-prostate (i.e. paratesticular or vagina/uterus), non-parameningeal head and neck
  - *Unfavourable* = all other sites (parameningeal, extremities, genito-urinary bladder/prostate and "other site")
- **Node stage**:
  - *N0* = no clinical or pathological node involvement
  - *N1* = clinical or pathological nodal involvement
- **Size and age**:
  - *Favourable* = tumour size (maximum dimension) ≤5 cm *and* age <10 years
  - *Unfavourable* = all others (i.e. size >5 cm and/*or* age ≥10 years).

31.3.2 Risk Stratification "RMS-Like" Tumours

31.4 Treatment Strategies

A multimodality approach involving surgery, chemotherapy and radiotherapy is necessary in the treatment of children and adolescents with RMS. The optimal timing and intensity of these three treatment modalities must be planned with regard to the prognostic factors and considering possible late effects of treatment.

Local control is necessary to cure children with RMS, and this may be achieved with surgery and/or radiotherapy. A conservative approach is recommended, and tumour resection or irradiation is usually performed taking into account the activity of chemotherapy in reducing the tumour volume.

Different drug combinations have proved to be effective against RMS. The most widely used regimen are VAC (vincristine, actinomycin-D, cyclophosphamide), VACA (vincristine and cyclophosphamide plus adriamycin alternating with actinomycin-D), IVA (ifosfamide, vincristine, actinomycin-D) and VAIA (ifosfamide and vincristine with adriamycin alternating with actinomycin-D). The multimodality approach according to different strategies and different chemotherapy regimens has been tested in several clinical trials run by the Cooperative Groups already named.

31.4.1 Treatment of Patients with Rhabdomyosarcoma

31.4.1.1 Local Treatment

Local treatment is an essential part of the multimodal therapy of soft tissue tumours. It is achieved by surgery, radiotherapy or both. The choice of local treatment in order to cure the patient with minimal long-term sequelae depends on site, size, invasiveness of the primary tumour, age of the patient and response to neoadjuvant chemotherapy.Biopsy should be the initial surgical procedure (after imaging of primary tumour and regional lymph nodes) in all patients except when primary excision with adequate margins is possible (rare except for paratesticular tumours). Radiotherapy as an integral part of local control will be needed in most cases. This should be considered from the very beginning of therapy, because timing of radiotherapy has to be coordinated with surgery.Concerning radiotherapy, it has been concluded that volume reduction after preoperative chemotherapy and primary tumour size in patients with residual tumour can be used as a basis for risk-adapted radiation. Early (10–13 weeks) hyperfractionated, accelerated radiation given simultaneously to chemotherapy improved local tumour control in patients with a good response after preoperative chemotherapy. The dose of 32 Gy when given accelerated and hyperfractionated simultaneously to chemotherapy is adequate for local tumour control in patients showing a good response to preoperative chemotherapy. Whether the same principle can be applied to other histological entities cannot be answered on the basis of the CWS studies.

31.4.1.2 Chemotherapy

Low Risk

This represents a very select group of patients, accounting for 6–8% of the whole population of localised RMS, with an excellent outcome. Most of these patients are represented by children with paratesticular RMS [11, 12].

Reducing the toxicity without jeopardizing the results is therefore the goal for this group of patients. The VA chemotherapy adopted in the previous protocols RMS-88, CWS/RMS-96 and SIOP MMT-95 showed good results with event-free and overall survival above 80% and 90%, respectively [13]. The results achieved in MMT-89 with 12 of 41 stage I patients relapsing after only 2 courses of VA suggest caution in further reducing the treatment in this subset of patients [14].

In conclusion, VA for 22 weeks (4 VA courses) represents a low-toxic, effective regimen for this group of patients.

Standard Risk

This group includes patients with a satisfactory prognosis for whom the goal is to reduce the treatment without compromising survival. These patients have been treated with IVA (nine courses over 25 weeks) both in MMT-95 and CWS/RMS-96. This represented a treatment reduction for the CWS group that used anthracyclines in the previous protocol. The total length of therapy has also been reduced from 35 (CWS-81 and ICG) to 25 weeks.

Results of the CWS-96 study show mainly local recurrences in the Standard Risk Group (15% local relapse, 3% combined and 1% metastatic relapses, 81% of the patients without failure) with a good EFS of 75% and an OS of 95% [7].

Three subgroups of Standard Risk patients have been identified with a similar outcome. However, their characteristics are quite different, and it has not been possible to design an identical treatment. Three treatment groups have been proposed, maintaining IVA as the regimen of reference.

Standard Risk, Subgroup B

These patients are similar to the ones included in the Low Risk Group, but tumour size and age are unfavourable. Most of these patients are represented by children with paratesticular RMS older than 10 years and/or with a large tumour (>5 cm).

There is increasing evidence from the European and US experience that older children (≥10 years) with low-risk characteristics fare worse than their younger counterparts [13, 14]. In the IRS studies, an increased risk of nodal relapse has been seen in Group I patients with

paratesticular tumour and age ≥10 years. This prompted the IRSG colleagues to return to a surgical staging for older patients [10]. The European experience reported a lower rate of nodal involvement. Here laparotomy with nodal exploration is avoided, but caution has been recommended in reducing the treatment in such patients. Subgroup B has been created to upgrade these patients and treat them with a limited dose of alkylating agents with the aim of reducing the risk of relapse and avoiding important toxicity.

Modern treatment concepts for **bladder/prostate rhabdomyosarcoma (BPRMS)** are designed to improve survival, to reduce therapy intensity and to increase bladder preservation **rates. Radiotherapy was used less frequently, and** the bladder preservation rate was slightly higher. Novel concepts will be required in the future to improve bladder preservation rates [15].

Vaginal/uterine rhabdomyosarcoma is one of the most favourable RMS sites. Ten-year event-free (EFS) and overall survival (OS) were 74% (95% CI, 67–79%) and 92% (95% CI, 88–96%), respectively. Local control using brachytherapy was excellent (93%). Fifty-one (51.5%) of the 99 survivors with known primary therapy and treatment for relapse were cured with chemotherapy with or without conservative surgery. About half of all patients with VU RMS can be cured without systematic RT or radical surgery. When RT is indicated, modalities that limit sequelae should be considered, such as brachytherapy [16].

Standard Risk, Subgroup C

This group is mainly represented by **orbital and head/neck non-parameningeal RMS** (favourable site). The German, Italian and North American experience is in favour of the use of systematic irradiation in these patients. However, the MMT studies have demonstrated that some children can successfully be treated with chemotherapy alone and eventually salvaged after relapse with irradiation [17]. In the more recent IRS-IV study, patients with orbital RMS in IRS Group I or II have been treated with VA and irradiation with an excellent outcome [10, 18]. The same strategy is currently used for all orbital RMS in the ongoing IRS-V study.

Therefore it seems possible in this subgroup:

- To reduce the cumulative dose of alkylating agents compared with previous European protocols using radiotherapy.
- To try to prospectively select patients with favourable features in whom irradiation can be avoided. These patients will be selected according to chemotherapy response (CR after the initial three courses of IVA) and favourable tumour size and age of the patients.

Radiotherapy (RT) as a first-line treatment of patients with head/neck non-parameningeal RMS was independently prognostic for event-free survival even if it did not impact OS. High rates of locoregional relapse were seen in head and neck rhabdomyosarcoma that should be prevented by more frequent use of RT in this primary [18].

Standard Risk, Subgroup D

An analysis of patients included in the High Risk category according to CWS/ICG RMS-96 and MMT-95 stratification showed that children with embryonal RMS, N0, favourable age and favourable tumour have a prognosis comparable to patients treated in the Standard Risk group of CWS/ICG RMS. Consequently, these patients have been included in the subgroup D in this protocol and downstaged to receive the treatment planned for the Standard Risk Group. These patients will continue to receive the IVA regimen as in the MMT-95 study, but this represents a treatment reduction in comparison with the CWS/ICG-96 protocol where the VAIA regimen was used.

High Risk

Patients with large embryonal RMS (>5 cm) localised in unfavourable sites, alveolar N0 RMS, and embryonal N1 tumours are included in this group. The different subgroups included in this category share the same unsatisfactory prognosis and therefore the need for a more effective strat-

egy. The CWS Study Group, the SIOP Malignant Mesenchymal Tumours Committee (MMT) and the AIEOP Soft Tissue Sarcoma Committee agreed in 1996 to randomize chemotherapy in the identically defined High Risk Group: The final analysis performed in 2004 did not show differences in EFS between VAIA vs. CEVAIE (3 years EFS 59% vs. 59%, 3 years OS 78% vs. 74%, CWS group, unpublished data) or IVA vs. CEVAIE (3 years EFS 65% vs. 63%, 3 years OS 81% vs. 79%, MMT study group, unpublished data). This analysis was the basis for the European consensus declaring the IVA regimen as the standard therapy, as this treatment turned out to be the less toxic one.

Alveolar Paratesticular Tumours

Despite unfavourable pathology this very small group of patients showed a good outcome in previous European studies. In the CWS/AIEOP-STSC experience, they represented 8% of all paratesticular RMS, and the 5-year survival rate was 93% after IVA ± doxorubicin chemotherapy [19, 20]. However, four relapses occurred. An evaluation of the SIOP data showed similar results. According to these data, patients with paratesticular alveolar RMS will be kept in the High Risk Group and treated with IVA × 9 (avoiding anthracyclines) [21–24].

Parameningeal Tumours

Parameningeal (PM) site is a well-known adverse prognostic factor in children with localized rhabdomyosarcoma (RMS). In a recent report, pooled data from 1105 patients treated in 10 studies conducted by European and North American cooperative groups were analysed. Ten-year EFS and OS were 62.6% and 66.1% for the whole group. Patients without initial RT showed worse survival (10-year OS 40.8% versus 68.5% for RT treated patients). A multivariate analysis focusing on 862 patients who received RT as part of their initial treatment revealed four unfavourable prognostic factors: age <3 or >10 years, signs of MI, unfavourable site and tumour size. Utilizing these prognostic factors, patients could be classified into different risk groups with 10-year OS ranging between 51.1% and 80.9%. While, in general PM localization is regarded as an adverse prognostic factor, the current analysis differentiates those with good prognosis (36% of patients with 0–1 risk factor, 10-year OS 80.9%) from high-risk PM patients (28% with 3–4 factors, 10-year OS 51.1%). Furthermore, this analysis reinforces the necessity for RT in PM RMS [25].

Very High Risk

An analysis of the High Risk Group of the CWS/RMS-96 has been made in an attempt to better define patients in the High Risk Group according to their risk of relapse. The group of patients with alveolar RMS and nodal involvement showed the poorest outcome, compared to that of IRS group IV patients. In CWS/RMS-96, the 3-year EFS were 28% and OS 29%. Results in the SIOP studies showed only partially better results with a 5-year EFS of 39%.

Until more effective treatment regimens are found, this patient group should therefore be treated with the VAIA regimen.

A randomized phase-III trial of the CWS for localized high-risk RMS and localized RMS-like soft tissue sarcoma, CWS-2007-HR, is ongoing. The primary objectives are to investigate whether the addition of oral maintenance chemotherapy with O-TIE (etoposide, idarubicin, trofosfamide) for 6 months improves the event-free survival (EFS) in patients with localised high-risk RMS and RMS-like soft tissue.

Analogous to this phase-III trial, the EpSSG recently published their data on maintenance therapy for localized high-risk RMS with cyclophosphamid/vinorelbine: In the intention-to-treat population, 5-year disease-free survival was 77.6% (95% CI 70.6–83.2) with maintenance chemotherapy versus 69.8% (62.2–76.2) without maintenance chemotherapy (hazard ratio [HR] 0.68 [95% CI 0.45–1.02]; $p = 0.061$), and 5-year overall survival was 86.5% (95% CI 80.2–90.9) with maintenance chemotherapy versus 73.7% (65.8–80.1) without (HR 0.52 [95% CI 0.32–0.86]; $p = 0.0097$). Adding maintenance chemotherapy seems to improve survival

for patients with high-risk rhabdomyosarcoma. This approach will be the new standard of care for patients with high-risk rhabdomyosarcoma in future EpSSG trials [26].

31.4.2 Treatment of Patients with Synovial Sarcoma

Chemosensitivity of synovial sarcoma (SySa), especially to ifosfamide and anthracyclines, is well known [27], but well-designed, randomised studies addressing the value of adjuvant chemotherapy in children and adolescents are lacking. Existing studies in adult patients mostly summarize a variety of different subtypes of soft tissue sarcoma without coherent and transferable results. Since 1981 the CWS Study Group and the Italian ICG study group (since 1988) have recommended systemic chemotherapy in combination with local therapy for paediatric synovial sarcoma patients. The results of these CWS/ICG studies are the only reports throughout the literature providing information about consistently documented SySa patients who were treated according to a uniform treatment Scheme [28]. The results revealed were superior to those previously published, so the therapy will be continued with two cycles of VAIA III for IRS Group I and II tumours (six courses) and three cycles VAIA III for patients with IRS Group III and all T2b tumours independent on IRS Group (nine courses) in combination with local therapy [29–33].

Patients with **localised SySa** were enrolled on the European Paediatric Soft tissue Sarcoma Study Group (EpSSG) NRSTS2005 and on the Children Oncology Group (COG) ARST0332 trials, treated with surgery alone. Patients must have undergone initial complete resection with histologically free margins, with a grade 2 tumour of any size or a grade 3 tumour ≤5 cm. The 3-year event-free survival was 90% (median follow-up 5.2 years, range 1.9–9.1). All patients with recurrence were effectively salvaged, resulting in 100% overall survival. This joint prospective analysis showed that patients with adequately resected ≤5 cm SySa, regardless of grade, can be safely treated with a surgery-only approach. Avoiding the use of adjuvant chemotherapy and radiotherapy in this low-risk patient population may decrease both short- and long-term morbidity and mortality [34].

The overall prognosis of **primary metastatic synovial sarcoma** is poor. However, individuals with oligometastatic lung metastases had very good chance for long-term survival when treated with adequate multimodal therapy [33].

31.4.3 Treatment of Patients with Other "RMS-Like" Tumours (STET (EES/pPNET), UDS)

Patients with localised soft tissue Ewing tumours (STET, consisting of extraosseus Ewing's tumour (EES) and peripheral primitive neuroectodermal tumours (pPNET)) and the undifferentiated sarcoma (UDS) showed a 5-year EFS of 57%, 53% and 55% and a 5-year OS of 81%, 69% and 72% in the CWS-96 study. The 3-year EFS rate of patients with bony counterpart of the STET treated according to the EICESS 92 study (European Cooperative Ewing's Sarcoma Study) is 66% [35, 36]. Since the primary localisation of the extraskeletal STET is quite different in comparison with classical bony tumours (i.e. parameningeal site, abdomen, genitourinary), the treatment of these patients according to the recommendation of the protocol for soft tissue sarcoma, especially concerning the local therapy, seems to be of major benefit for the patients. VAIA III cycles with increased dose intensity of ADR in combination with local control modalities are recommended following the treatment of EES, pPNET and UDS until new and better therapies are found for this tumour group [37, 38].

31.4.4 Treatment of Patients with "Non-RMS" Tumours

The so-called "non-RMS" tumours display a heterogeneous group of rare soft tissue tumours

in children and adolescents with different histiotypes and biological behaviour [39]. Some of these STS are more common in adults. In the past the different non-rhabdomyosarcoma-like soft tissue tumours (NRSTS) have been treated and studied as one group.

With the aim of improving not only the quality of treatment but also the prognosis in children with NRSTS in Europe and to gain understanding in the biology of the different histiotypes, the CWS group (in cooperation with the AIEOP STSC) introduced a risk-adapted therapy recommendation for patients with NRSTS in the CWS-96 and the CWS-2002-P studies (Table 31.3). To understand more about the different histiotypes, CWS and AIEOP STSC cooperated in performing selective retrospective analysis for any single histiotype in the past [40–44]. Tumour size and surgery (post-surgical stage = IRS grouping) are the most significant prognostic factors. Reference pathology is essential for risk stratification of NRSTS and the evaluation of prognosis. The grading of NRSTS represents one of the most debated and complex subjects concerning the information that the pathologist must give to the clinician. Different grading systems (generally three-grade systems) have been defined by paediatric and adult oncologists for predicting clinical course and prognosis of disease and to be able to define a risk-adapted treatment [45, 46]. Many NRSTS are considered moderate or poorly chemosensitive tumours [47–50]. Surgery (±radiotherapy) is therefore the mainstay of treatment and an important stratification factor. The quality of surgery is critical, and it is recommended that soft tissue sarcoma patients should be referred to specialized centres for local treatment, preferably prior to the biopsy.

The infantile fibrosarcoma is very recently discussed as a so-called NRTK fusion positive tumour, sensitive to NTRK inhibitors [51–54]. Mutilating surgery should be avoided. International consensus recommendations treating these infants are urgently needed.

Table 31.3 Risk stratification for "non-RMS-like" tumours

Risk group	Histology	Node stage	IRS group	Initial tumour size
Low	Any (except MRT and DSRCT)[a]	N0	I	≤5 cm
Standard	Any (except MRT and DSRCT)[a]	N0	I	>5 cm[b]
		N0	II	Any
		N0	III	≤5 cm[c]
High	MRT/DSRCT	N0/N1	I, II, III	Any
	Any	N0	III	>5 cm
	Any	N1	II, III	Any
Stage IV	Any	N0/N1	IV	Any

[a]**MRT** (malignant rhabdoid tumour), **DSRCT** (desmoplastic small and round cell tumour): treatment in the **High Risk Group**

[b]Exception: typical low-grade tumours (grade 1) might be treated in the **Low Risk Group**

[c]Exception: high-grade tumours (grade 2 or 3) might be treated in the **High Risk Group**

31.4.4.1 Risk Stratification "Non-RMS-Like" Tumours

- **Post-surgical stage**:
  - *Group I* = primary complete resection (R0), no microscopic tumour residuals
  - *Group II* = microscopic tumour residuals (R1) or primary complete resection but N1
  - *Group III* = macroscopic tumour residuals (R2)
- **Node stage**:
  - *N0* = no clinical or pathological node involvement
  - *N1* = clinical or pathological nodal involvement
- **Initial tumour size**:
  - *Favourable* = tumour size (maximum dimension) ≤5 cm (Ta)
  - *Unfavourable* = tumour size >5 cm (Tb)

NRSTS Low Risk Group

Low Risk patients do not require further local or systemic treatment, but careful follow-up exami-

nations at short, regular intervals are strongly recommended.

NRSTS Standard Risk Group

All patients in Standard Risk Group should be irradiated. Exception: in patients with typical low-grade tumours (grade 1), >5 cm, IRS Group I irradiation might be avoided. The role of adjuvant chemotherapy in this risk group remains unclear and has to be evaluated in a randomised way. Application of chemotherapy is therefore not routinely recommended in this guidance. Exception: patients with high-grade (grades 2–3) NRSTS and IRS Group III might be treated in the High Risk Group.

NRSTS High Risk Group

In this group, adjuvant or neoadjuvant VAIA III chemotherapy should be administered. Radiotherapy for local tumour control is clearly indicated.

NRSTS Stage IV

Patients with primary metastasized "non-RMS-like" tumours (stage IV) should be allocated to stage-IV therapy independent from other risk factors.

31.4.4.2 Treatment

Local Treatment

Local treatment decisions will follow general recommendations for localised soft tissue sarcoma.

Surgery: Surgery is the mainstay of treatment for local tumour control in NRSTS tumours. The possibility of a wide tumour resection in combination with an early reconstruction has to be considered and planned carefully. Particular care must be taken to ascertain completeness of resection (R0). A primary R1 resection in combination with subsequent radiotherapy may be the only feasible treatment concept in "non-RMS-like" tumours depending on tumour size and localisation. Tumours, which initially presented as non-resectable tumours and did not show response to chemotherapy, usually require radical resection even with functional impairment or mutilating surgery ("salvage surgery"). Careful consideration of risk and benefit of such an extensive surgical measure in interaction with the patient and its parents/guardian is strongly recommended. Experimental options such as isolated limb perfusion [55, 56], hyperthermia or hyperthermic intraperitoneal chemotherapy (HIPEC) [57, 58] can be an option in case of non-response in order to avoid "mutilating" surgery but should only be considered. Radical lymph node dissections are not routinely indicated.

Radiotherapy: Irradiation of NRSTS tumours mainly depends on post-surgical stage (IRS group), patient's age and initial tumour size. Patients in Low Risk Group (tumour size ≤5 cm and completely resected tumour, IRS group I) should not be irradiated. Patients with a maximal tumour diameter >5 cm should be irradiated regardless of their primary resection status (R0 or R1)—exception: in R0 resected low-grade tumours (grade 1), greater than 5 cm radiotherapy might be avoided. In patients with initial IRS group III, radiotherapy is indicated prior to or after delayed surgery.

Chemotherapy

Only patients in the "Non-RMS-like" High Risk Group receive chemotherapy with VAIA III. The treatment consists of alternating courses of ifosfamide, vincristine and adriamycin (I^2VAd), ifosfamide, vincristine and actinomycin-D (I^2VA) and I^2VAd again for six courses, followed by three courses of I^2VA alone (treatment scheme *VAIA III*). The interval between the courses is 3 weeks, and duration of chemotherapy is 25 weeks. Local treatment (radiotherapy + surgery) will be administered at week 13 (at least after the fourth course).

Treatment of Patients with Metastatic Disease (Stage IV)

The European Intergroup Studies (MMT-89 and MMT-91) comprising SIOP-MMT, CWS and ICG study groups investigated the effectiveness of a very intensive six-drug multiagent regimen, including most of the drugs thought

to be active against STS: ifosfamide, epirubicin, vincristine, carboplatin, dactinomycin and etoposide (CEVAIE). They were used in a concentration close to the maximum-tolerated doses when given in combination. As a result, 73% of the patients received complete remission, 46% of these with chemotherapy alone. Responses to chemotherapy (CR + PR) at week 9 and 18 were 83% and 92%, respectively [59]. The overall CR rate achieved in this trial revealed superior results compared to CR rates reported by other studies of metastatic rhabdomyosarcoma [60, 61]. Myelosuppression was the most frequent adverse effect. 5-year OS and EFS for the whole group were 24% and 20%, respectively. Thus the good response as measured by reduction of tumour mass was not translated into improved survival. The prognostic relevant factors in 201 patients with primary metastatic tumours treated according to the CWS studies from 1981 to 1996 were age (≥10 years, $p < 0.03$) and B/BM metastases ($p < 0.014$). Patients with stage IV disease, ≥10 years with B/BM metastases, had a dismal 5-year survival rate of 6 ± 4%. In contrast, the outcome of metastatic patients <10 years of age without B/BM metastases was much better with a cure rate of 41 ± 7%. Histology, single vs. multiorgan metastases and consolidation with HDC were not related to prognosis.

According to a recent data obtained from 788 patients treated in nine studies performed by the European and American cooperative groups, clinical factors, including age, histology, site of primary and site(s) and number of sites of metastatic disease were correlated with event-free survival (EFS) and overall survival (OS). Three-year EFS was significantly and adversely influenced by age, alveolar histology, location of primary tumour in unfavourable site (defined as extremity and "other" sites), presence of three or more sites of metastatic disease and the presence of bone or bone marrow involvement. EFS was strongly correlated to all factors except histology. This analysis identified subsets of patients with metastatic rhabdomyosarcoma with different outcomes to current therapy and offers a strategy to define patient candidates for experimental approaches to treatment [62].

The standard therapy recommendation for patients with metastatic STS is CEVAIE as an induction therapy and O-TI/E maintenance as consolidation for patients <10 years without B/BM metastases. The role of high-dose chemotherapy followed by autologous stem cell transplantation in patients with very-high-risk sarcoma was not effective, but oral maintenance treatment (OMT) was very promising. The proportional hazard analysis for patients with rhabdomyosarcoma (RMS) or "RMS-like" tumours demonstrated an independent benefit of OMT on outcome [63].

In conclusion, the treatment of patients with rhabdomyosarcoma is continually evolving and should be constantly adapted as new evidence emerges from clinical trials. This evolving process has led to the improved survival seen over the last decades and should continue in the future.

- Histology, staging (IRS grouping), nodal involvement, tumour site, tumour size and patients' age have been identified as major prognostic factors.
- A group of patients with localised RMS, who can be treated with less intensive treatment (VA alone ± radiotherapy), has been selected. The acute and late sequelae of alkylating agents and anthracyclines can be avoided in this group without compromising survival.
- Chemotherapy regimens based on the VAC or IVA combinations appear equally effective and may be considered the "reference regimen" for most children and adolescents with RMS. However a substantial proportion of children and adolescents are not cured with such regimens, and the search for new combinations must continue. The value of the addition of other drugs should be investigated in randomised clinical trials.
- Local treatment is a fundamental part of RMS, but the advantages and disadvantages of aggressive surgery and/or radiotherapy should be balanced against the late effects for young children and adolescents.
- Conservative surgery is recommended, and experience should be gathered to select those children and adolescents for whom surgery may be the only necessary local treatment.

- Although it is possible to cure about 30% of patients without radiotherapy, only a subgroup of them (i.e. embryonal tumour completely resected at diagnosis) can confidently be identified at diagnosis. Further efforts should be made to better define a favourable population for whom irradiation and its late effects can be avoided.

Increasing international collaboration should improve the treatment stratification and explore through well-designed, randomised studies better treatment strategies for children and adolescents with RMS and other soft tissue sarcomas.

31.5 Investigations at the End of Treatment

According to the CWS group investigations required at this point are:

- Thorough physical and neurological examination (weight, height, pubertal status).
- MRI/CT/ultrasound of primary tumour site including regional lymph nodes.
- Cerebral MRI.
- CT of the lung.
- Chest X-ray.
- Abdominal ultrasound.
- Evaluation of metastatic lesions in stage IV patients.
- Blood: full blood cell count, differential blood cell count, liver enzymes, K, Na, Ca, PO_4, Cl, Mg, glucose, AP, H_2CO_3, creatinine, immunglobulines, and viral serum analysis.
- Ifosfamide nephrotoxicity monitoring (see above).
- Urine: Na, Ca, glucose, PO_4, creatinine, pH, total protein; *24 h urine*: calculate GFR, 24 h Ca, PO_4 and glucose loss, max. PO_4 reabsorption/GFR.
- Echo, ECG, EEG, paediatric audiometry and ocular fundus examination.
- Other investigations if indicated (e.g. PET, CSF, hormonal status).
- Bone marrow aspiration and/or bone marrow biopsy plus EDTA-blood sample at week 27 in case of initial bone marrow involvement.

31.6 Disease-Related Follow-Up After Completion of Chemotherapy

Tumour status should thoroughly be monitored depending on tumour localisation and adapted to the patients' risk group. Recommended routine controls for all patients after end of treatment are shown in Table 31.4. These recommendations however only refer to patients who have been treated according to this guidance. In case of alternative therapies or inadequate local treatment, the prognosis and relapse pattern can be different. In the experiences of the CWS Study Group gained during more than 25 years, relapses are more common, and patients have a poorer prognosis if they were treated individualized and not according to a guidance or protocol.

Tumour-directed follow-up should correspond with the estimated risk of relapse. The value of more intense disease-related follow-up is unclear in paediatric soft tissue sarcoma. Most relapses are however detected due to clinical signs and symptoms, and the patients/parents should be educated to contact the paediatric oncologist immediately in case of unclear symptoms. An improved post-relapse survival of patients with imaging-detected recurrences could also not be shown [64, 65]. The risk of relapse and thus the frequency of tumour-directed follow-up in paediatric STS depend on histiotype, primary stage and—in localised rhabdomyosarcoma (see Table 31.5a–c)—tumour size.

Chest X-rays during follow-up are less sensitive to detect tumour recurrences compared with CT scans, but the incorporated radiation dose is also much lower depending on the imaging protocols that are employed. They may therefore be used if the expected relapse risk in the thorax is considered to be low. If chest X-rays are performed, they should include a postero-anterior (PA) view, and right-anterior-oblique (RAO) and left-anterior-oblique (LAO) views should be considered. According to experience, the oblique views allow a better interpretation of the phrenicocostal angles compared to lateral views. The cumulative radiation dose of PA, RAO and

LAO views are similar to a PA and lateral view [66, 67]. The risk of possible later detection of lung metastases using X-rays compared with CT scans must be taken into account and discussed with the parents/patients/guardians.

Guidelines for optimizing CT protocols for children and adolescents according to the ALARA principle (as low as reasonably achievable) can be found under www.imagegently.org.

31.7 Disease-Related Follow-Up for Soft Tissue Sarcoma Apart from Localised RMS

Some STS histiotypes show a propensity to develop metastases in sites, which are uncommon in STS otherwise. Note, e.g. the propensity of alveolar rhabdomyosarcoma to develop metastases in the breast(s) of post-pubertal girls/women or the possibility that intracranial metastases can develop in, e.g. alveolar soft part sarcoma or alveolar rhabdomyosarcoma.

Most STS histiotypes do not recur later than 5 years after first diagnosis. Because of the rarity of these tumours, the possibility of late recurrences can however not be excluded. Please consider that some STS histiotypes characteristically develop late relapses, such as alveolar soft part sarcoma, clear cell sarcoma, epithelioid sarcoma, synovial sarcoma or mesenchymal chondrosarcoma.

31.8 Disease-Related Follow-Up for Localised RMS

Localised RMS account for the largest group of patients with localised STS. Disease recurrence must be expected in every third patient with localised RMS, mainly as a locoregional relapse. More than 90% of recurrences occur within 4 years after diagnosis [68–70]. According to the CWS experience, tumour size and histologic subtype can discriminate two groups with consistent risk of relapse and distinctive post-relapse prognosis [68]:

1. *RME ≤5 cm*: this group accounts for approximately 40% of all localised RMS. The overall relapse risk is lower compared to RME >5 cm and RMA, and the proportion of systemic/metastatic recurrences is also relatively low. Recurrences involving bone/bone-marrow

Table 31.4 Routine controls after treatment for all soft tissue sarcoma apart from localised RMS according to the CWS group

Date	Investigations at primary tumour site	Staging	Additional investigations
1st year after treatment	Ultrasound (tumour site, regional lymph nodes, abdomen, pelvis) MRI/CT with contrast (every **4 months**; alternating, if applicable)	Chest-X-ray or CT thorax (intervals risk-adapted, at least every **6 months**) Ultrasound abdomen/pelvis (at least every **6 months**) Bone scan (risk-adapted, once a **year**) *For stage IV*: MRI/CT evaluation of metastases	Liver and kidney-function (glomerular und tubular) Echocardiogram/24 h ECG Hormone status (growth and puberty) Functional impairment (continence, visual and hearing faculty; musculoskeletal system) Additional investigations (according to clinical symptoms)
2nd year	See above, but **6 months'** intervals	See above Chest-X-ray every **6 months** Ultrasound abdomen/pelvis (at least every **6 months**)	
3rd–5th year	See above, but **6–12 months'** intervals	See above, **yearly**	
>5th year	Ultrasound (see above) MRI/CT with contrast (frequency at the discretion of the responsible physician)	See above (frequency at the discretion of the responsible physician)	

occur rarely. In case of relapse, these patients have a rather good salvage option as well, especially if a possibility for radiation therapy remains.

2. *RME >5 cm and RMA*: the overall relapse risk and proportion of systemic/metastatic relapses are much higher in this group, and the post-relapse prognosis is much poorer in these patients compared to RME ≤5 cm.

31.9 Late Effects Related to Follow-Up

The following regular examinations are recommended for patients to evaluate late effects. Pain in the primary site 5–10 years after therapy warrants investigation for the development of secondary bone tumours. This is applicable to all radiation treated sites. The risk of **development**

Table 31.5 Recommended routine controls after treatment for localised RMS according to the CWS group

Date	Investigations at primary tumour site	Staging	Additional investigations
(a) For localised embryonal rhabdomyosarcoma (RME) ≤5 cm			
1st year after treatment	Ultrasound (tumour site, regional lymph nodes, abdomen, pelvis) MRI/CT with contrast (every **4 months**; alternating, if applicable)	Chest-X-ray or CT thorax (intervals risk-adapted, at least every **6 months**) Ultrasound of the abdomen/pelvis (at least every **6 months**)	Liver and kidney-function (glomerular und tubular) Echocardiogram/24 h ECG Hormone status (growth and puberty) Functional impairment (continence, visual and hearing faculty; musculoskeletal system) Additional investigations (according to clinical symptoms)
2nd year	See above, but **6 months'** intervals	See above Chest-X-ray every **6 months** Ultrasound of the abdomen/pelvis (at least every **6 months**)	
3rd–5th year	See above, but **6–12 months'** intervals	See above, **yearly**	
>5th year	Ultrasound or MRI with contrast (frequency at the discretion of the responsible physician)	Frequency at the discretion of the responsible physician or only in case of clinical symptoms	
(b) For localised embryonal rhabdomyosarcoma >5 cm			
1st year after treatment	Ultrasound (tumour site, regional lymph nodes, abdomen, pelvis) MRI/CT with contrast (every **4 months**; alternating, if applicable)	Chest-X-ray or CT thorax (intervals risk-adapted, at least every **6 months**) Ultrasound of the abdomen/pelvis (at least every **6 months**)	Liver and kidney-function (glomerular und tubular) Echocardiogram/24 h ECG Hormone status (growth and puberty) Functional impairment (continence, visual and hearing faculty; musculoskeletal system) Additional investigations (according to clinical symptoms)
2nd year	See above, but **6 months'** intervals	See above Chest-X-ray or CT thorax every **6 months** Ultrasound of the abdomen/pelvis (at least every **6 months**)	
3rd–5th year	See above, but **6–12 months'** intervals	See above, **yearly**	
>5th year	Ultrasound (see above) MRI/CT with contrast (frequency at the discretion of the responsible physician)	See above (frequency at the discretion of the responsible physician)	

(continued)

Table 31.5 (continued)

Date	Investigations at primary tumour site	Staging	Additional investigations
(c) For localised alveolar rhabdomyosarcoma			
1st year after treatment	Ultrasound (tumour site, regional lymph nodes, abdomen, pelvis) MRI/CT with contrast (every **4 months**; alternating, if applicable)	Chest-X-ray or CT thorax (intervals risk-adapted, at least every **6 months**) Ultrasound abdomen/pelvis (at least every **6 months**) In postpubertal girls/women: consider imaging of the breasts (ultrasound, MRI in case of unclear findings)	Liver and kidney function (glomerular and tubular) Echocardiogram/24 h ECG Hormone status (growth and puberty) Functional impairment (continence, visual and hearing faculty; musculoskeletal system) Additional investigations (according to clinical symptoms)
2nd year	See above, but **6 months'** intervals	See above Chest-X-ray or CT thorax every **6 months** Ultrasound abdomen/pelvis (at least every **6 months**) In postpubertal girls/women: consider imaging of the breasts	
3rd–5th year	See above, but **6–12 months** intervals	See above, **yearly**	
>5th year	Ultrasound (see above) MRI/CT with contrast (frequency at the discretion of the responsible physician)	See above (frequency at the discretion of the responsible physician)	

of a second malignant neoplasm (e.g. leukaemia, lymphoma or solid tumours) should be considered.

Post therapy, all patients should be tracked for possible tumour relapse and to monitor treatment side effects (Tables 31.4 and 31.5a–c, respectively Tables 31.6 and 31.7). By improving the multimodal therapies for malignant diseases in children and adolescents carried out in multicentre trials, the overall 5-year survival rate increased up to 75%. In the evaluation of an antineoplastic therapy, not only survival should be taken into account but also the state of health after cessation of therapy. A significant group of survivors has to deal with severe impairments decreasing their quality of life [71].

Up to now, most published data on late effects resulted from retrospective investigations (limitation, selected patient groups) or investigations performed in a single centre (limitation, small sample sizes). Large prospective investigations in a well-established nationwide network of therapy trials and a follow-up system for the detection of major late sequelae are rare. In 1988, the Society of Paediatric Oncology and Haematology (GPOH) established a late effects working (Beck 1988) group consisting of oncologists as well as experts in organ toxicities, initially performing retrospective studies of major late sequelae. In 1998, the prospective and multicentre Late Effects Surveillance System (LESS) was started to investigate the late effects of patients suffering from Ewing's sarcoma, osteosarcoma or soft tissue sarcoma in Germany, Austria and Switzerland [72–77]. The main aims are the analyses of incidence, risk factors and prognosis of late effects. However these published data were restricted mainly to a follow-up of less than 5 years after finishing the oncological therapy.

Patients registered in CWS SoTiSaR will be included in these projects. A comparable group for the evaluation of radiation-associated late effects [78] was founded under the auspices of the GPOH as well as a research group investigating the quality of life [79, 80].

LESS, RiSK and QoL closely cooperate with the CWS Study Group Centre by means of regular transfers of basic patient data. LESS has also developed recommendations for the surveillance of late effects [81]. The data forms should be filled out about 4 weeks after cessation of therapy and in yearly intervals afterwards. In case of a late effect, an enhanced data form should be filled out.

During the last years, two large projects, PanCareSurFup [82] and PanCareLIFE [83], funded by the European Commission, have been performed on late effects and the development of guidelines. The later ones were structured in a harmonization group in cooperation with colleagues of the United States, Australia, New Zealand and other countries [84].

The results of these projects will be adapted and implemented in the follow-up systems of the GPOH, to improve them and to make them comparable with other countries.

The references for late effects of patients suffering from a soft tissue sarcoma and his therapy and the follow-up for those suffering from an osteosarcoma are similar, and therefore the above mentioned references on late effects are listed in the osteosarcoma chapter.

The following specific primary tumour sites may require special monitoring and late effects examinations.

Table 31.6 Recommended examinations

General examinations	
Height and weight	At 6 months' and 1 year intervals. Any child showing a growth deceleration of 20–25 percentile units on standard growth charts from the pre-treatment height should be evaluated for thyroid and pituitary function
Blood pressure	Measurements annually
Tanner staging	Annually for girls and boys until maturity. If there is delayed appearance of secondary sexual maturation, the patient warrants evaluation of gonadal hormone values, i.e. at 12–14 years of life for girls (FSH, LH and oestradiol) and boys (FSH, LH and testosterone)
Testicular size	Annual measurements in boys using volume measured by Prader orchidometer if possible. The vast majority of patients on this study will receive alkylating agents and may accrue damage to the germinal epithelium of the testis
Menstruation	Onset of menstruation in girls and regularity of periods. Because of local radiotherapy or alkylating agents therapy, ovarian failure may occur in some patients
School performance, behavioural pattern	History should include school performance and behavioural disturbances so that early intervention is possible

Table 31.7 Recommended examinations—by specific primary site

Examinations in specific primary site	
Head/neck	
Growth measurements	Annually, plotted on standard growth curves
Eyes	Annual ophthalmologic examination if eye was in radiotherapy field
Teeth	Annual dental examination if maxillary/mandibular sites were in radiotherapy field
Ears	Annual auditory examination if the ears were in the irradiated field
Bones	Bone X-rays of the primary site every 1–2 years until maturity if radiotherapy was given to the primary site. Include opposing normal side for comparison of degree of bone hypoplasia
Thyroid	Thyroid function (TSH, T3, T4) every 2 years in case of irradiation on the neck
Trunk	
Lung	Special notation on exercise intolerance or shortness of breath, if radiotherapy was given to primary tumours of the chest or to pulmonary metastases.

(continued)

Table 31.7 (continued)

Examinations in specific primary site	
Heart	Cardiac toxicity examinations, if part of heart was in radiotherapy field as well as additionally application of doxorubicin
Bone	X-rays of the bone in the primary site with the opposite normal side for evaluation of bone hypoplasia every 2 years
Abdomen/ pelvis	Monitoring of problems following abdominal/pelvic irradiation, e.g. bowel obstruction, chronic diarrhoea, inadequate absorption, rectal stenosis and sphincter problems
Kidney	Annual measurements of kidney function in patients receiving para-aortic node irradiation or other abdominal irradiation including the kidney/urogenital area
Femur/hip joints	Monitoring of limp or pain as symptoms for slipped capital femoral epiphyses, which may occur several years after therapy
Genito-urinary	
Bladder	Regularly tested kidney function in children without a bladder and with various types of urinary diversion Imaging studies every 1–2 years for hydronephrosis, evidence of pyelonephritis and renal function Kinking of ileal loops, stenosis or reflux of the ureters detected by contrast studies Bladder volume and function tests (cysto-urethrograms or other imaging studies), if radiotherapy was given to the bladder
Genital organs	Girls with uterine or vaginal tumours should be followed for sexual maturation and ovarian failure (see above). Vaginal examination under anaesthesia until 5 years' follow-up and after depending on the treatment received Boys treated for bladder, prostate or paratesticular primaries should be followed (see above). History in teenage boys should include questions of normal ejaculatory function, particularly in patients with bladder/prostate or paratesticular primaries. Semen analysis as described above
Extremities	
Growth measurements	Annual bilateral limb length measurements, if radiotherapy was given
Bones	X-rays of primary sites for bone growth abnormalities if indicated in comparison with normal site
Function	History should address limp, evidence of pain and other dysfunction of the involved extremity

For details and a late effects focussed follow-up schedule, see LESS, Late Effects Surveillance System, Nachsorgeplan Weichteilsarkome, on www.kinderkrebsinfo.de or the CWS homepage www.cws.olgahospital-stuttgart.de.

31.10 Recomendation for a Long-Term Follow-Up Schedule

Long-term follow-up is performed according to the recommendations of the International Guideline Harmonisation Group (www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the LESS group (www.nachsorge-ist-vorsorge.de) in Germany.

31.11 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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32 Potential Late Effects of Rhabdoid Tumor Therapy in Childhood and Adolescents

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32.1 Introduction

32.1.1 Clinical Facts

Rhabdoid tumors (RT) are rare and rather aggressive malignancies arising predominantly in infants and young children. Primary locations of RT are the CNS [atypical teratoid/rhabdoid tumor—AT/RT (cerebellum, IVth ventricle, hemispheres, basal ganglia, mesencephalon, pineal region, spine)], kidney [RT of the kidney—RTK], or soft tissues [extracranial malignant RT—eMRT (head and neck, paravertebral muscles, liver, bladder, mediastinum, retroperitoneum, bladder, pelvis, heart, scrotum, and subcutis)]. Over the last 25 years, RT have been described in almost any anatomical localization [1, 2].

According to the German Childhood Cancer Registry (2004–2013), AT/RT account for 0.8% of all patients below 15 years with a CNS tumor (www.kinderkrebsregister.de). The age-standardized annual incidence rate in children below 1 year is 8.1 per million and decreases to 2.2 between 1 and 4 years, 0.6 at 5–9 years, and close to 0 between 10 and 14 years. Median age at onset is 18 months. The age-standardized incidence of extracranial rhabdoid tumors (RTK and eMRT) in the first year of life is 5 per million and decreases with age to 0.6 per million at age 1–4 years, 0.1 at age 5–9 years, and 0.04 at age 10–14 years.

All series report a male predominance with 1.3–1.5:1 in AT/RT and 1.1:1 in extracranial RT [3, 4]. The absolute number of RT (AT/RT, eMRT, RTK) according to the German Childhood Cancer Registry between 2010 and 2015 is $n = 139$ (Fig. 32.1a). The age distribution of RT cases is represented in Fig. 32.1b.

Epidemiologic studies of RT have been limited by the fact that this is a rare disease; however, some publications have reported an association of RT with low birth weight, multiple births, preterm birth, late-term delivery, and also *in vitro* fertilization, although it remains to be established whether these factors truly contribute to the origin of the disease [5, 6].

32.1.2 Pathology and Genetics

RT has first been described as a distinct entity in 1978 [7]. The term rhabdoid is derived from the histological resemblance of tumor cells to rhabdomyoblasts. Immunohistochemically rhabdoid tumor cells are represented by increased expression of vimentin (a rather non-specific marker), EMA (epithelial membrane antigen), and cytokeratins and by loss of the INI1 protein, which is

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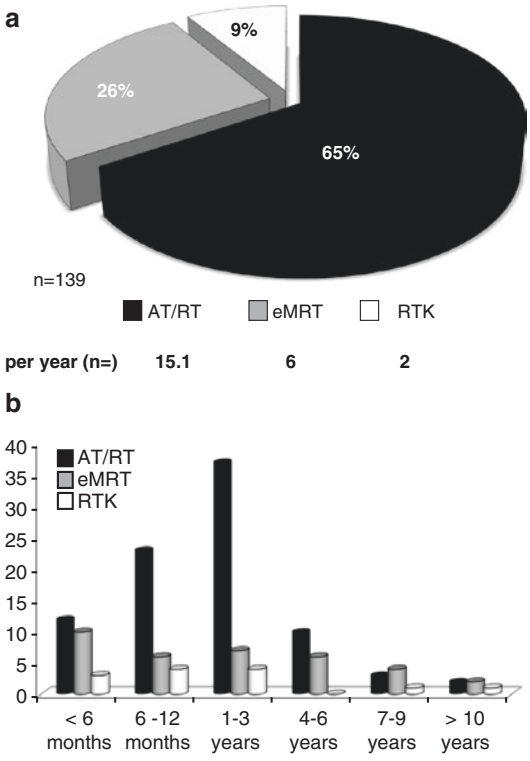

Fig. 32.1 Incidence and distribution of RT (AT/RT, eMRT, RTK) according to the German Childhood Cancer Registry. The percentage of RT subgroups, the yearly absolute number (**a**), and the age distribution (**b**) of RT patients registered in the German Childhood Cancer Registry between 2010 and 2015, https://www.kinderkrebsregister.de

a strong indicator of RT [8]. RT are characterized by a rather simple genome compared to other cancers [9, 10]. The majority of RT (70–90%) demonstrates genomic alterations only of the tumor suppressor gene *SMARCB1* or to a lesser extent (2–3%) of S*MARCA4 (BRG1)* [4, 11]. The SWI/SNF complex is a major player in the regulation of gene transcription and influences multiple signal transduction pathways involved in cancer (CDK4/6/cyclin D1/Rb, Sonic hedgehog (SHH/GLI1) pathway, Wnt/ß-catenin signaling, SWI/SNF, and polycomb complexes epigenetic regulation by EZH2, HDAC, DMNT, Aurora kinase A) [12, 13].

Among newly diagnosed patients, 25–30% have a germline alteration in *SMARCB1* (rarely *SMARCA4*) that predisposes them to cancer [14, 15]. Children with a so-called rhabdoid tumor predisposition syndrome (RTPS 1, *SMARCB1*; RTPS 2, *SMARCA4*) typically present with synchronous rhabdoid tumors (AT/RT + RTK, AT/RT + eMRT) in their first year of life and are characterized by an almost inevitably fatal course [16, 17].

32.2 Current Diagnostic and Therapeutic Approach

Demonstration of loss of the *SMARCB1* protein can tremendously help in defining this entity [18]. However rare RT with preserved *SMARCB1* are on record [11]. Moreover loss of expression of the SMARCB1 protein has also been described in other tumors such as epithelioid sarcoma, medullary renal cell carcinoma, choroid plexus, CNS primitive neuroectodermal tumors, and CRINET [5, 15, 19].

Due to the rarity of RT, a standard of therapy is difficult to define. Patients with RT have until recently been treated according to institutional preferences combining surgery, radiotherapy, and chemotherapy (COG, Dana-Farber Consortium, EU-RHAB). The EU-RHAB registry for RT regardless of anatomical origin (AT/RT, RTK, eMRT) recommends a combination including gross total resection, conventional chemotherapy (vincristine, dactinomycin, cyclophosphamide, doxorubicin, ifosfamide, carboplatin, etoposide), intrathecal methotrexate (MTX), and permissive use of high-dose chemotherapy with stem cell rescue (carboplatin, thiotepa) and radiotherapy (over 18 months of age). The feasibility of this and other intensive multimodal regimen has been documented even in the youngest patients [2].

32.3 The Multifactorial Origin of Late Effects in Rhabdoid Tumors

According to the European Rhabdoid Registry, event-free (EFS) and overall survival (OS) rates for children with AT/RT have improved to a maximum of 45 ± 0.09% and 46 ± 0.10%, respectively [20]. Particularly the use of radiotherapy

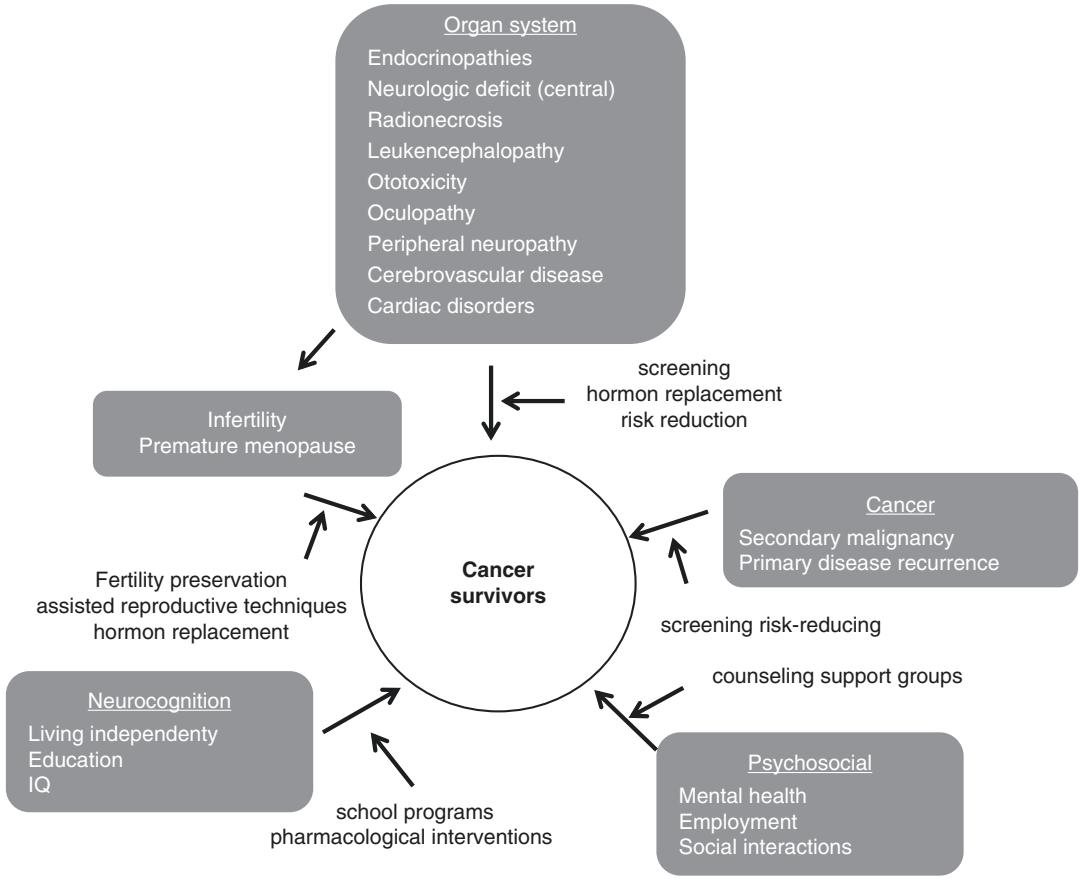

Fig. 32.2 Late effects affect several and diverse domains of life. Potential interventions to minimize the therapy-related late side effects of RT survivors

may profoundly impact on (neuro-)developmental outcome and entail significant short- and long-term side effects. Moreover as it is hoped and expected that survival rates continue to improve, the frequency and severity of late effects may increase in parallel.

Late effects of treatment include both medical (cerebro- and cardiovascular, endocrine, neurologic/sensory, secondary malignancy) and non-medical complications (neurocognitive, psychological, social) (Fig. 32.2). They may be categorized according to the modality of treatment (surgery, radiotherapy, chemotherapy) (Table 32.1) and according to the drug used (Table 32.2).

According to data from the EU-RHAB registry (2010–2015, n = 199), at least 60% of all rhabdoid tumor survivors (n = 68) suffer from late effects attributable to therapy. Most commonly neurological deficits (~25%) and endocrinopathies (~20–25%) have been detected. Neurocognitive deficiency was present in 25–30%, and psychosocial delays were present in ~20%. Secondary malignancy, such as AML, has thus far been documented in three patients.

MTX therapy-induced leukoencephalopathy has been documented in 3–5% and radionecrosis in 6% of survivors. Late effects not consistently reported to EU-RHAB are represented in Table 32.1.

Leukoencephalopathy is a rare but potentially devastating complication that develops as a consequence of chemotherapy (e.g., methotrexate, MTX) and/or radiotherapy. Elevated levels of proinflammatory cytokines and the subsequent prominent demyelination with loss

Table 32.1 Therapy-related late effects according to modality

	Late side effect	Description
Surgery	Fossa posterior syndrome	Deficits in attention, working memory, verbal fluency, executive function
Radiotherapy	Neurovascular damage	Stroke, vasculopathies, cerebral microhemorrhages, cavernosus malformations
	Cardiac dysfunction	**Congestive heart failure**, **cardiomyopathy**, myocardial infarction, **arrhythmia**, atherosclerotic heart disease, valvular disease, pericarditis, pericardial fibrosis
	Radionecrosis	Memory loss, dementia, confusion, depression, **ataxia**, **epilepsy**, hemiparesis, **delayed speech development**, focal motor signs, vomiting, headache
	Leukoencephalopathy	Especially, if MTX therapy after radiotherapy, dementia, focal motor signs, epilepsy, ataxia, death
	Neurocognitive/ behavioral impairments	**Poor concentration**, **memory loss**, **learning difficulty**, **antisocial behavior**, **delayed speech development**, **obsessive-compulsive disorder**
	Endocrinopathies	**Growth hormone** and gonadotropin deficiency, **hypothyroidism**, **ACTH dysfunction**, hypothalamic obesity
	Osteopathies	**Bone asymmetry**, **enophthalmos**, **facial and dental dysmorphism**
	Neurologic	**Epilepsy**, **ataxia**, **facial nerve paresis**, **tremor**, **hemiparesis**, **tetraparesis**
		Ototoxicity, **oculopathy**, olfactory, oral/dental
	Secondary neoplasms	Meningioma, glioma, sarcomas, thyroid carcinoma
Chemotherapy	**Leukoencephalopathy**	After **MTX** therapy, **focal motor signs**, **epilepsy**, **dementia**, **ataxia**
	Peripheral neuropathy	**Sensorimotor** (loss of deep tendon reflexes, paresthesia), proximal (oculomotor paresis, vocal cord dysfunction), **autonomy** (paralytic ileus, obstipation)
	Ototoxicity	Sensorineural hearing loss (cisplatin)
	Endocrinopathies	Premature ovarian failure, ovarian fibrosis, follicular destruction, impaired spermatogenesis (alkylating agents)
	Secondary neoplasms	**Leukemia** (etoposide, alkylating agents, cyclophosphamide)

Site effects registered in EU-RHAB between 2010 and 2015 appear in bold

of oligodendroglia, microangiopathy, and coagulative white matter necrosis with microcalcifications have been implicated in the development of leukoencephalopathy [21]. The clinical course is usually progressive, with focal motor signs, epilepsy, ataxia, mental deterioration, and death. Early initiation of steroids and ivIg may be of benefit. Unlike leukoencephalopathy, the pathology of radionecrosis is primarily vascular, affecting the endothelium of small arteries. Certain chemotherapeutics such as doxorubicin, other anthracyclines, methotrexate, and ifosfamide may directly increase the risk of radionecrosis [22]. The significant risk for leukoencephalopathy or radionecrosis in the vulnerable nervous system of the youngest, who may additionally have been treated with intraventricular MTX, raises concerns as to whether radiotherapy may be either postponed or replaced by alternative therapeutic means and/or classical chemotherapeutics may be given in combination with new targeted agents to reduce the employed doses. The same holds true for intraventricular MTX treatment.

32.4 Novel Treatment Approaches in RT and Their Potential Late Effects

32.4.1 Radiotherapy Strategies

As RT are commonly diagnosed in infants, radiotherapy is associated with a significant potential

Table 32.2 Conventional chemotherapy and high-dose chemotherapy-related side effects and toxicities according to drug

Drug	Side effects
Actinomycin D	Stomatitis, mucositis, **myelosuppression**, **immunosuppression**, **fever**, **increased liver function**, **veno-occlusive disease** (**VOD**), hypocalcemia, allergic reaction
Carboplatin	Painful gastrointestinal sensations, allergic reactions, **myelosuppression**, change of taste, optic neuritis, auditory and **peripheral neuropathy**, **decreased liver function**
Cyclophosphamide	**Myelosuppression**, hemorrhagic cystitis, water retention, **liver enzyme elevation**, **cardiotoxicity**, **VOD**, secondary malignancy, infertility
Doxorubicin	GI mucositis, **myelosuppression**, cardiotoxicity, **impaired liver function**, allergic reactions, paravasation necrosis, **acute cardiomyopathy**, extrasystole
Etoposide	**Myelosuppression**, hypotension, anaphylactic reactions, mucositis, **liver enzyme elevation**, secondary malignant disease, myalgias, central nervous system disturbances, **peripheral neuropathy**, **acute leukemia**, **arrhythmia**, heart attacks, Stevens-Johnson syndrome
Ifosfamide	**Myelosuppression**, hemorrhagic cystitis, **encephalopathy**, **increased liver function**, Fanconi syndrome, CNS toxicity, **cardiotoxicity**
Methotrexate	Neurotoxicity, allergic reactions, **myelosuppression**, GI mucositis, **liver enzyme elevation**, **leukoencephalopathy**, especially after radiotherapy
Thiotepa	**Myelosuppression**, mucositis, intestinal ulcerations, hemorrhagic cystitis, **neurologic changes**, erythroderma, chronic discoloration of the skin, allergic reactions, amenorrhea, disturbance of spermatogenesis, secondary malignancy. Death under thiotepa therapy has been reported
Vincristine	**Peripheral neuropathy**, central neurotoxicity, **constipation**, **VOD**, poly- and dysuria, inadequate ADH secretion, **myelosuppression**, neurotoxicity in combination with cyclosporin A. cross-reactivity with doxorubicin, daunorubicin, actinomycin D, metramicin, and mitomycin

Acute site effects according to the EU-RHAB registry (2010–2015) appear in bold

for severe treatment-related morbidity. A major focus of radiotherapy research has been put on the development of more focal and potentially less harmful radiotherapy. The innovative method of proton beam therapy (PBT) is unique in that protons slow down and deposit most of their energy in one point upon entering tissue, allowing for more precise radiotherapy delivery and avoiding radiation to neighboring healthy tissue. Whether the long-term benefits (e.g., avoidance of infertility, hypothyroidism, cardiac toxicity, and pulmonary fibrosis) will outweigh the risks of complications such as radionecrosis is a target of current investigations. Researchers at the University of Pennsylvania reported acceptable tolerability of PBT used in pediatric CNS malignancies ($n = 48$, thereof $n = 3$ AT/RT). The most common acute toxicities (fatigue, alopecia, and dermatitis) were manageable [23]. The Massachusetts General Hospital's experience enumerates ten consecutive patients in whom proton therapy succeeded in sparing at-risk organs such as the hypothalamus and cochlea [24]. They also report a more favorable score for health-related quality of life (HRQoL) in patients treated with PBT (75.9; $p = 0.024$), compared with photons (65.4; $p < 0.001$), compared to the score (80.9) of the normal population [25]. Researchers at MD Anderson treated 31 AT/RT patients by PBT. Median PFS and OS were 20.8 and 34.3 months, respectively. Five patients developed radiation reactions in the brainstem necessitating the use of bevacizumab or steroids [26]. A series from Indianapolis demonstrated radiographic signs of radionecrosis in 3/3 patients with AT/RT. Presumably this correlated well with the intensive, high-dose neoadjuvant chemotherapy used in all AT/RT patients in their institution [22]. Researchers at St. Jude's Hospital treated 17 very young (<3 years) children by PBT. In eight patients, radiation-induced effects were observed after completion of PBT (3.9 ± 4.3 months) [27]. A Swiss study ($n = 15$) reported 2-year OS and PFS 64.6% and 66.0% in

AT/RT treated by protons. Furthermore, toxicity was encouraging, with no greater than grade 2 acute toxicity (bone marrow toxicity, erythema) and an estimated 2-year toxicity-free survival of 90%. Using the PedsQoL tool, no decrease in quality of life was noted [28]. The current clinical trials (NCT01067196 completed 12.2015; NCT01180881 active, not recruiting; NCT01288235, recruiting) will soon report the acute and late effects associated with PBT in CNS tumor survivors.

32.4.2 Targeted Therapy

Aggressive multidrug regimens containing anthracyclines and alkylating agents as standard chemotherapy may add significant survival benefit for RT patients; however, they are also toxic agents with various late effects [29]. Moreover certain patients remain resistant to cytostatic agents [30, 31].

Current preclinical investigations have focused largely on the specific interrogation of *SMARCB1*-related biology and potential therapeutic targets, while changes in the function of the SWI/SNF complex may affect a whole array of signal transduction cascades (epigenetic targets [HDAC, EZH2, DNMT], CDK4/6/cyclin D1/Rb, Aurora kinase A, SHH/GLI1, Wnt/ß-catenin) [5, 13, 32]. In the future treatment strategies in RT patients using them concurrent with or before standard chemotherapy may help to decrease doses of chemotherapy, hence to minimize toxicity of treatment, reduce frequency and severity of late effects, and improve functional outcome for affected patients.

A phase I trial of an HDAC inhibitor [SAHA/vorinostat (NCT01076530)] has successfully been tested in patients affected by RT. Some of the novel HDAC inhibitors such as panobinostat and resminostat offer potentially favorable pharmacokinetic and pharmacodynamic properties suitable especially for small children [33, 34]. The most common side effects in adult patients were thrombocytopenia, leukopenia, neutropenia, and lymphopenia. Valproic acid is also a possible candidate for treatment of RT; however, the doses for HDAC inhibition may not be easily achieved [35].

A preliminary report of a phase I trial of the EZH2 inhibitor tazemetostat (EPZ-6438) revealed a complete response in a first rhabdoid tumor patient [36]. A clinical phase I trial employing EPZ-6438 in children with rhabdoid tumors is in recruiting (NCT02601937). Potential side effects of tazemetostat are listed in Table 32.3.

The DNMT inhibitor decitabine in combination with doxorubicin and cyclophosphamide has shown promise in phase I trials in children with neuroblastoma and other solid tumors; however, efficacy in RT has not yet been demonstrated [40].

Recently a clinical phase I/II trial, the results of which are pending, employed the CDK4/6 inhibitor ribociclib in patients with rhabdoid tumors, neuroblastomas, and CDK4-amplified malignancies. It is to be anticipated that such a compound may be used in a combinatorial trial with conventional chemotherapy (NCT01747876).

The Aurora kinase A inhibitor MLN-8237 is currently in clinical trials in phase I/II for different tumor entities in adults and children. Employing single-agent MLN-8237, also known now as alisertib, has produced noteworthy responses. Four patients affected by relapsed or progressive AT/RT received 80 mg/m^2 alisertib by mouth. All four displayed disease stabilization and/or regression of tumors, and two are alive 1 and 2 years, respectively, on therapy [41]. A trial combining alisertib with conventional therapy in newly diagnosed patients with rhabdoid tumors is currently recruiting (NCT02114229).

A phase I clinical trial employing the Hedgehog pathway inhibitor As_2O_3 in children with astrocytomas and in RT patients is in the planning phase. The most frequent side effects were nausea, vomiting, headache, and anorexia [42]. Potential molecular targets, inhibitors, their side effects, and the study completed/recruited or planned in RT are represented in Table 32.3.

Table 32.3 Molecular targets, potential inhibitors, their side effects, and trials in RT patients

Inhibitor group	Target	Mechanism	Inhibitor	Side effect	Study in RT
Histone deacetylase inhibitor	HDAC	Histone deacetylation	Vorinostat (SAHA)	Neutropenia, lymphopenia, thrombocytopenia, anemia, leukopenia	Phase I study RT, NCT01076530, completed [37–39]
			Panobinostat	Thrombocytopenia, neutropenia, fatigue, diarrhea, anorexia	Planned in RT Phase I [33]
			Resminostat	Lymphopenia, thrombocytopenia, leukopenia, neutropenia	Planned in RT Phase I [34]
			Valproic acid	Thrombocytopenia, leukopenia, lymphopenia, anemia	Planned in RT Phase I [35] Phase II (NCT00414310)
Histone methyltransferase inhibitor	EZH2	Histone methylation	Tazemetostat (EPZ6438)	Anorexia, nausea, vomiting, diarrhea, thrombocytopenia, anemia	Phase I study RT, NCT02601937, recruiting [36]
DNA methyltransferase inhibitor	DNMT	DNA methylation	Decitabine	Neutropenia, thrombocytopenia	Phase I study solid tumor, NCT00075634, completed [40]
CDK4/cyclin D1 inhibitor	CDK4/6 Cyclin D1	Cell cycle arrest G_1	Ribociclib (LEE011)	Neutropenia, anemia, thrombocytopenia	Phase I/II study RT, NCT01747876, active, not recruiting
Aurora kinase A inhibitor	Aurora kinase A	Antimitotic	Alisertib (MLN8237)	Anemia, fatigue, neutropenia, gastrointestinal disorders	Phase I/II study RT, NCT02114229, recruiting [41]
Hedgehog pathway inhibitor	GLI1	Proliferation inhibition	As_2O_3 (ATO)	Nausea, vomiting, headache, anorexia	Planned in RT Phase I/II [42]

32.5 The Need for Continued Aftercare-Future Directions

The survival time of patients with RT has been much shorter in the past; hence, late side effects of treatment were mostly unknown. As more and more patients with RT survive and enter adulthood, an insight into the frequency and severity of late effects encompassing diverse domains of life—as a consequence of multimodal treatment—both of which show a notable increase (Fig. 32.2) may be gained.

Medical teams and primary healthcare providers play an essential role in the prevention, management, and elucidation of late effects by employing novel risk-reducing treatment strategies (postponement or replacement of radiotherapy by HDCT or proton bean therapy, targeted therapy used concomitant with or before standard chemotherapy, etc.), resolving problems as they arise, and recommending regular, comprehensive follow-up screening in RT survivors. The follow-up examinations recommended in the EU-RHAB document are represented in Table 32.4.

To minimize the severity of neurocognitive delay, early interventions (special education, education intervention, cognitive training programs) are imperative. Recently pharmaceutical therapies have been proposed to improve cognition, attention, and memory of survivors by using methylphenidate, dopaminergic central nervous system stimulants, and acetylcholinesterase inhibitors [43, 44].

The early detection and management of late side effects caused by multimodal treatment

Table 32.4 Follow-up examinations in patients with RT

	1/2 years	3–5 years	6–10 years	Second decade
AT/RT				
Physical and neurologic examination	Bimonthly	Every 6 months	2× yearly/yearly	Yearly
MRI cranial	Every 3 months	2×/4× yearly	Yearly	If sym
MRI spinal	Every 6 months	If sym[a]	If sym	If sym
Lumbar tap	2× yearly if chemotherapy	If sym	If sym	If sym
Height, weight, pubertal status	Every 3–4 months	Every 6 months	Yearly	Individually
Bone age	Yearly	If sym		
T3/T4/TSH, IGF1, IGFBP3, cortisol, DHEAS[b]	Yearly	Yearly	Yearly	Every 2 years
Sonography thyroid gland	2× yearly	Yearly	Yearly	Yearly
CBC	Bimonthly	Every 6 months	Yearly	Yearly
Renal function, serum chemistry	Bimonthly	Every 6 months	Yearly	Yearly
Radiotherapist[c]	Yearly	Yearly	Yearly	Yearly
Ophthalmologist	2× yearly	Yearly	If sym	If sym
ENT consult	Yearly	If sym	If sym	If sym
Echo/ECG	2× yearly	Yearly	Yearly	Yearly
MRT/RTK				
Physical examination	Bimonthly	Every 6 months	2× yearly/yearly	Yearly
MRI local side	Every 3 months	2×/4× yearly	Yearly	If sym
Chest CT	Every 6 months	If sym	If sym	If sym
Cranial MRI	Once, at the end of treatment	If path	If path	If path
Sonography	4× yearly	4× yearly	If sym	If sym
Height, weight, pubertal status	Every 6 months	Every 6 months	Yearly	Individually
CBC	Bimonthly	Bimonthly	Yearly	Yearly
Renal function, serum chemistry	Bimonthly	Every 6 months	Yearly	Yearly
Radiotherapist[c]	Yearly	Yearly	Yearly	Yearly
ENT consult	Yearly	If sym	If sym	If sym
Echo/ECG	2× yearly	Yearly	Yearly	Yearly
Skeletal scintigraphy	Once, at the end of treatment	If path[d]	If path	If path
Lung function (if age permits)	Once, at the end of treatment	If irradiation to the lung	If irradiation to the lung	If irradiation to the lung

[a]Symptomatic
[b]With onset of puberty LH/FSH, testosterone, history of menses and contraception; 2 years after completion of therapy function testing
[c]Initiate 6 months after end of radiotherapy
[d]Pathological

may highly improve the health-related quality of life (HRQoL; an objective concept with cognitive, physical, social, work-related aspects). On the other hand, the quality of life (QoL; a subjective multidimensional indicator) of an individual can be satisfactory regardless of adverse late side effects (Fig. 32.3), which should be considered during the treatment of survivors. Overall, the various outcomes of multimodal treatment highlight the importance of personalized medicine and the need for follow-up of survivors for the rest of their lives.

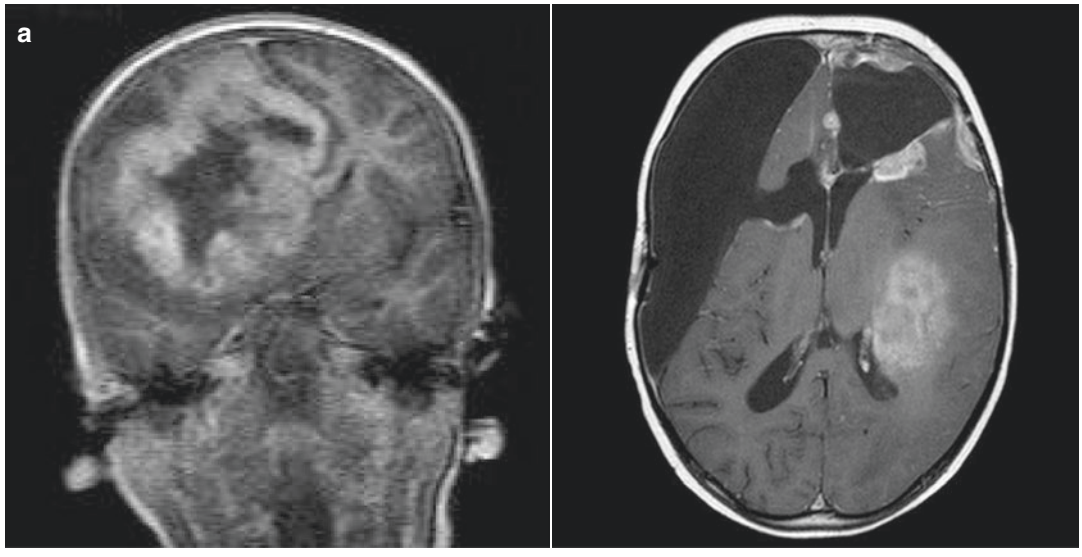

Fig. 32.3 Treatment-related late side effects in a patient with AT/RT. (**a**) Cranial MRI of a patient with right frontal AT/RT at diagnosis (age 4.9) (left panel) and following therapy (incl. intraventricular MTX, two courses of HDCT, and repeated radiotherapy including gamma knife) at age 10.8 years with tumor progression, signs of stroke, hygroma, and leukoencephalopathy (right panel). (**b**) The same patient 5 years after diagnosis on a bike tour with his father. Around the same time as MRI was taken (**a**: right panel) demonstrating the potential discrepancy of imaging results and clinical status

The EU-RHAB registry was established to generate a comprehensive European database for all RT patients with various aims: (1) to improve neuro-pathological, clinical, and molecular characterization of RT, (2) to improve our understanding of the underlying genetic of the disease, (3) to establish standardized treatment regimens, (4) to develop future treatment strategies/clinical phase I/II trials for RT patients, (5) to support pan-European cooperations, and finally (6) to promote the survivor-focused medical care by recommending comprehensive screening and through counselling on risk reduction. It will now have to be amended by developing risk-reducing therapeutic strategies for late effects in long-term survivors.

32.6 Recommendation for a Long-Term Follow-Up Schedule

Long-term follow-up is performed according to the recommendations of the International Guideline Harmonisation Group (http://www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the LESS group (www.nachsorge-istvorsorge.de) in Germany. The reader is also referred to the psychosocial follow-up guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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33 Late Effects After Treatment of Malignant Endocrine Tumors in Childhood and Adolescents

Antje Redlich, Peter Bucsky, and Peter Vorwerk

Tumors of endocrine glands and the neuroendocrine gastroenteropancreatic system are rare in childhood and adolescence, coming to less than 2% of all pediatric malignancies. The most common malignant endocrine tumors are discussed here:

- Thyroid carcinomas (differentiated and medullary)
- Adrenocortical carcinomas
- Pheochromocytomas and paragangliomas
- Gastroenteropancreatic neuroendocrine tumors

33.1 Thyroid Carcinomas

In children and adolescents, thyroid carcinomas are rare, accounting for 1–2% of childhood malignancies [1]. The tumors are classified according to the cells of origin. Differentiated thyroid carcinomas (DTC) are derived from thyroid follicular cells, whereas medullary thyroid carcinomas (MTC) arise from parafollicular c-cells.

DTC are more advanced in children, compared with adults [2]. Nevertheless, prognosis is excellent, if sufficient therapy is applied. Treatment consists of surgery (total thyroidectomy/hemithyroidectomy, neck dissection), radioiodine therapy (RIT), and TSH suppression, respectively.

Surgical outcome is significantly optimized, if surgery is performed by high-volume surgeons [3, 4]. That's why the current American Thyroid Association (ATA) guideline recommends, especially if compartment-focused lymph node dissection is indicated, the performance by a surgeon with at least 30 cervical procedures per year [5]. Sequelae of surgical procedures are permanent hypoparathyroidism and recurrent laryngeal nerve (RLN) injury.

The reported frequency of permanent hypoparathyroidism following thyroid surgery in children is up to 15% [5, 6]. Low concentration of parathyroid hormone (PTH) results in low calcium levels and increased phosphate levels in the blood. Excretion of calcium in the urine is elevated, predisposing to nephrocalcinosis. Clinical presentation of hypocalcemia comprises, inter alia, paresthesia, muscle cramps, fatigue, depression, laryngospasm, and seizures. Conventional treatment includes administration of preparations of oral calcium salts and metabolites of vitamin D. A major therapeutic challenge is the

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consistently effective management of hypocalcemia while avoiding hypercalciuria and other complications. Furthermore, hypoparathyroidism is a complex disease, which cannot be considered adequately treated just by achieving normocalcemia. Even patients with stable calcium and vitamin D levels under standard treatment report reduced quality of life, compared to healthy controls. They experience physical, mental, and emotional symptoms [7]. Recombinant PTH proteins are now available and may be associated with an improvement in quality of life, compared with conventional treatment [8].

Preserving the parathyroid gland and its blood supply is the key to minimizing the risk of hypoparathyroidism following thyroidectomy. Maintaining parathyroid vitality can be sustained best by careful dissection, identification, and preservation of the glands [9]. Parathyroid autotransplantation may be an option to restore parathyroid gland functionality in case of inadvertent removal or devascularization during surgery [10].

The reported frequency of permanent RLN injury is up to 10% in children following thyroidectomy [11]. Intermittent intraoperative nerve monitoring (I-IONM) has been proposed to decrease the rate of RLN injury and has gained rising acceptance. Nevertheless, in a review of eight meta-analyses, a nonsignificant reduction in RLN injury was reported in the majority of studies with I-IONM [12]. In the current ATA guideline, the use of a monitoring device can be considered but is not strongly recommended [5]. There are data that continuous intraoperative nerve monitoring may lead to a reduction in severity of RLN injuries, recently [13]. Besides experiences of the surgeon, the extent of surgical therapy may have impact on the occurrence of recurrent disease and the frequency of complications [14].

The aims of RIT are ablation of the remnant thyroid tissue following TT, increasing the sensitivity of serum thyroglobulin as a marker for recurrence and the treatment of metastases [15]. There are acute and long-term side effects associated with exposure to radioactive iodine (RAI). Short-term side effects include nausea, radiation thyroiditis, sialadenitis, and bone marrow suppression among others [16]. Among permanent complications, the risk of second malignancies (SM) is of concern and appears to be slightly elevated [17]. Marti et al. are describing 3850 children undergoing treatment for DTC followed in the Surveillance, Epidemiology, and End Results registry [18]. The relative risk of SM was significantly elevated among children who received RIT, whereas in children without RIT, risk of developing SM was not increased.

One of the most frequent complications of RAI is the occurrence of salivary gland damage [19]. As these glands physiologically take up iodine, this irradiation may result in transient or permanent dysfunction. The reported frequencies of salivary gland damage caused by RIT for DTC vary depending on the diagnostic strategy. Studies that investigated the incidence by means of questionnaire showed a rather low frequency of xerostomia [20]. Studies including objective measurement of salivary gland function were associated with a higher incidence [21]. Chronic sialadenitis leading to xerostomia is concerned, because of its negative impact on quality of life [22]. Inducing salivation by lemon drops or chewing gum is presumed to increase washout of RAI leading to a lower radiation exposure. However, there is no established evidence that these supportive measures decrease injury to salivary glands. Nakada et al. compared the incidence of side effects of RIT on the salivary glands in two varying regimens for sucking lemon candy [23]. They concluded that lemon candy should not be given until 24 h after RIT. A major limitation of that study is the lack of a group without lemon candy sucking. Another attempt to protect the glands during RIT was the application of amifostine with conflicting results [24, 25].

Asymptomatic transient drops in white blood cell and platelet counts may occur with usual doses of RAI, usually recovering within weeks to month. Potential effects of RIT on fertility have also been examined. In women, transient disturbances of the menstrual cycle may be observed. There is no evidence that outcomes of subsequent pregnancies are affected. Garsi et al. included 2673 pregnancies in women who were treated for thyroid carcinoma [26]. No increases were

evidenced in miscarriages and malformations in offspring conceived after RAI administration.

The current ATA guidelines for pediatric thyroid cancer differentiate between prepubertal und postpubertal boys, as in the latter, the testes may be more vulnerable to radiation [5, 27]. Postpubertal boys with advanced disease requiring high cumulative activities should be counseled, and sperm banking should be considered. In males treated with a single ablation dose, testicular function recovers within months, and the risk of infertility is minimal [28].

Lung metastases are diagnosed in approximately 20% of pediatric DTC. Despite rare, pulmonary fibrosis is of concern when treating patients with extensive pulmonary metastases. Reiners et al. are describing 234 Chernobyl-exposed Belarusian children undergoing RIT [29]. The only side effect in this high-risk cohort with radiation-induced DTC was pulmonary fibrosis in 5 of 69 (7.2%) children with disseminated pulmonary metastases. They stopped RIT after five to six courses and approximately 20 GBq cumulative activities to avoid further impact on pulmonary function. This approach is supported by Biko et al., who showed that despite incomplete remission at the end of RIT, a continuing decline of thyroglobulin and clinical stable partial remissions can be observed in children [30]. Pulmonary surveillance in cases with metastases of the lung and high cumulative RAI doses is required [29].

To minimize the risk of side effects of RIT, supportive measures can be considered [31]. Adequate hydration is essential for clearance of RAI. Regular evacuation of the bowels is necessary. Using ascorbic acid is presumed to reduce oxidative stress [32].

In the vast majority of pediatric MTC, the tumor is part of multiple endocrine neoplasia (MEN) type 2, which is caused by germline mutation of the REarranged during Transfection (RET) proto-oncogene [33]. Surgery is the most important option, as no systemic therapy can warrant cure. Vandetanib is approved for the treatment of unresectable, locally advanced or metastatic MTC in patients with symptomatic or progressive disease. It prolongs progression free survival but does not improve overall survival [34]. The benefits in delaying disease progression need to be balanced against the potential side effects, including diarrhea, hypertension, and QTc-prolongation.

In MTC and DTC after TT lifetime, levothyroxine replacement and endocrinological surveillance are necessary.

33.2 Adrenocortical Carcinomas

Adrenocortical carcinomas (ACC) are rare neoplasms in childhood with a frequently dismal prognosis. They usually are sporadic; however, they can occur in association with genetic syndromes (Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, isolated hemihyperplasia, etc.). Majority of pediatric ACC are functional, so children commonly present with virilization, Cushing's syndrome, and feminization, respectively [35]. However, some of the adrenal tumors are discovered incidentally on imaging studies performed for a reason other than suspected adrenal disease. Pheochromocytoma can be taken out of the equation by highly sensitive and specific biochemical screening with measurement of plasma und urinary metanephrines. Urinary steroid profiling might offer a diagnostic tool for discriminating ACC from adrenocortical adenoma, preoperatively [36].

Radical surgical resection, avoiding tumor rupture, remains the only treatment option, which provides the potential for cure. Preoperative biopsy and intraoperative tumor rupture are associated with a poor outcome [37]. Displacement of tumor cells leads to peritoneal carcinomatosis, near always a lethal complication. For the same reason, an open surgical approach is recommended [38]. Even after complete resection, a high risk of recurrence remains.

If there are signs of tumor spillage or residual disease following surgery, systemic therapy is recommended with mitotane and conventional chemotherapy. Mitotane, a specific adrenocorticolyticum, is the only drug approved for the treatment of ACC. The drug is badly tolerable with considerable toxicity. Activity and toxicity

correlate with blood concentration [35]. Lysosafe® is a tool making regular measurements of the drug concentration possible and optimizing benefit and safety. The most important early and late effects of the drug concern the nervous system: headache, cerebellar ataxia, confusion, depression, nausea, vomiting, fatigue, weakness, and anorexia. Chemotherapeutic regimens used for children with residual or advanced disease have derived from standard treatments in adults. A cisplatin-based combination, usually incorporating doxorubicin and etoposide, is most commonly used [35].

Long-term sequela of mitotane administration is adrenal insufficiency. Maintenance therapy requires glucocorticoid replacement. During times of stress, such as during a febrile illness, daily cortisol dose should be doubled or tripled. Mineralocorticoid supplementation is not mandatory in all patients because aldosterone production is relatively spared. Endocrinological surveillance is required for adjusting replacement therapy. Nevertheless, even after long-term mitotane therapy, recovery of the remaining adrenal gland is described [39]. Hypogonadism and gynecomastia may develop following mitotane administration needing testosterone replacement in some patients, because testicular steroidogenesis and testosterone concentration can be altered [40].

33.3 Pheochromocytomas and Paragangliomas

Pheochromocytomas (PCC) originate from chromaffin cells of the adrenal medulla. If they arise from the neural crest, they are called paragangliomas (PGL). Chromaffin cells release catecholamines, so children are commonly diagnosed with arterial hypertension, headache, and excessive sweating [41].

In children the vast majority of PCC and PGL are hereditary (von Hippel-Lindau syndrome, neurofibromatosis type 1, multiple endocrine neoplasia type 2, mutations in subunits of the succinate dehydrogenase (SDHx) complex) [42]. Risk of recurrence, malignancy, and overall survival is gene-specific. Highest risk of recurrent PCC/PGL is described for children with SDHx mutations and von Hippel-Lindau syndrome (VHL) [42]. Patients with hereditary syndromes frequently have life-threatening, syndrome-specific, extraparaganglial tumors, such as cerebral and retinal hemangioblastomas in VHL, MTC in MEN 2, and renal carcinoma in VHL.

Surgical resection of tumor lesions is the mainstay of treatment. Partial adrenalectomy is preferred in children with PCC and a high risk of recurrence to preserve adrenal function [43].

Malignant disease is established by the presence of metastases at sites where chromaffin cells are absent usually. Invasion of the tumor into surrounding tissue may indicate a malignant potential, but it does not predict that the tumor will metastasize. The percentage of malignant cases depends on tumor location and genetic background [44]. The highest prevalence of malignancy is associated with SDHB mutations. Half of metastases are present at the time of diagnosis. Others may develop even years later [45].

As in case of an ACC, according to laterality and amount of adrenal rests, adrenal insufficiency may occur.

The reader is also referred to Chap. 11 of this book.

33.4 Gastroenteropancreatic Neuroendocrine Tumors

Neuroendocrine tumors (NET) are a heterogeneous group of malignancies composed of cells with a neuroendocrine phenotype and uncommon in childhood as well. NET are classified according to anatomical site, tumor differentiation, proliferative activity or grading, tumor stage, and hormones or amines produced [46]. These tumors may be a feature of a few hereditary syndromes (multiple endocrine neoplasia type 1, von Hippel-Lindau syndrome, neurofibromatosis type 1, tuberous sclerosis etc.) [47].

In children the appendix is the most common site of appearance. Usually they are detected incidentally after appendectomy for acute appendicitis [48]. In larger tumors, infiltration of regional lymph nodes by tumor cells can be found. The meaning of these micrometastases and the need for additional surgery are unknown and a matter

of debate, respectively [49]. Right hemicolectomy (RHC) or ileocecal resection with lymph node sampling may be indicated. Only a few studies in adults have examined the changes in bowel function and their influence on quality of life following segmental resections for colorectal cancer. A questionnaire-based survey showed a satisfactory bowel function in most patients following RHC with no impairment on quality of life [50]. As majority of water is absorbed in the right colon, RHC might result in frequent fluid stools [51]. Data dealing with sequelae of RHC or ileocecal resection in children are not available.

33.5 Recommendation for a Long-Term Follow-Up Schedule

Long-term follow-up is performed according to the recommendations of the International Guideline Harmonisation Group (http://www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the LESS group (www.nachsorge-ist-vorsorge.de) in Germany. The reader is also referred to the psychosocial follow-up guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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34 Skin Cancer in Childhood and Adolescents: Treatment and Implications for the Long-Term Follow-Up

Lucie Heinzerling and Thomas Kurt Eigentler

Skin cancer in children and adolescents is rare and may be indicative of an underlying genetic disorder, some of which are associated with extracutaneous disease manifestations, including increased cancer risk or malformations in other organ systems. Dermatological findings may be the first hint to the identification of these individuals.

Furthermore, UV irradiation in early childhood especially sunburns predisposes to skin cancer in adulthood.

34.1 General Risk Factors for the Development of Skin Cancer

Oculocutaneous albinism (OCA) is a group of genetic diseases characterized by diffuse reduced pigmentation affecting melanocytes and keratinocytes of the skin, hair follicles and eyes, accompanied by reduced visual acuity with nystagmus and photophobia [1]. OCA patients are very susceptible to UV-induced skin cancer. Mutations in genes coding for tyrosinase (OCA1A and OCA1B), P protein (OCA2), tyrosinase-related protein-1 (OCA3) and MATP (OCA4) have been identified as a cause of the disease. Depending on the mutation, differences in sensitivity to skin cancer can be anticipated. In OCA1A there is no melanin synthesis at all, while in all other types, there is some pigmentation; thus the former have an extremely elevated risk. Vitiligo patients on the other hand do not carry an increased risk for skin cancer [2].

Xeroderma pigmentosum (XP) is an autosomal recessive disease that is related to a defect in DNA excision repair mechanisms resulting in a 1000-fold increased risk of developing skin cancers such as squamous cell carcinomas, basal cell carcinomas and melanomas [3].

34.2 Risk Factors for Non-melanoma Skin Cancer

Epidermolysis bullosa (EB) is a heterogenous group of inherited skin disorders characterized by mutations in genes for structural proteins of the cutaneous basal membrane. Especially patients with the severe recessive dystrophic EB subtype suffer from early and extremely aggressive squamous cell carcinomas (SCCs) which represent the first cause of death in this patient group [4].

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Cumulative UV exposure increases the risk for non-melanoma skin cancer. Thus, UV protection from early childhood on is essential. Furthermore, certain genetic factors may give rise to skin cancer. *Chronic immunosuppression*—often the result of a stem cell transplant or a solid organ transplant—and *UV exposure* are by far the most important risk factors for the development of NMSC and in particular squamous cell carcinoma. This is particularly true for immunotherapy regimens containing cyclosporin.

In addition, long-term use of the antifungal *voriconazole* and the resulting phototoxicity may promote the development of squamous cell carcinoma [5].

34.2.1 Basal Cell Carcinoma

Nevoid basal cell carcinoma syndrome, also known as *Gorlin syndrome*, is an autosomal dominant disease that leads to the development of basal cell carcinoma in childhood, adolescence and adulthood [6]. Basal cell nevus syndrome is most commonly caused by mutations in Patched1 (PTCH1), Patched2 (PTCH2) and the suppressor of fused (SUFU) genes. Each gene encodes a critical element of the patched hedgehog pathway, which is responsible for controlling cell growth, particularly in embryogenesis. Clinically, children and adolescents are struck by odontogenic tumours, especially in the lower jaw. In addition, rib and vertebral anomalies, intracranial calcification, skeletal anomalies such as bifid ribs, kyphoscoliosis, early calcification of the falx cerebri and facial anomalies may occur.

Bazex-Dupre-Christol syndrome is an X-linked dominant disease associated with a significantly increased risk for the development of basal cell carcinoma [7]. It is extremely rare. The causal genetic mutation in Bazex-Dupre-Christol syndrome is unknown, but recently a mutation in the ACTRT1 gene has been identified in such patients [8].

The *nevus sebaceus* is a congenital, yellowish, hairless plaque that typically occurs on the scalp or face. It typically presents at birth or develops in early childhood and affects girls and boys of all races equally. Postzygotic HRAS mutations (95%) and KRAS mutations (5%) are the molecular basis of the sebaceous nevus [9].

Basal cell carcinomas can develop on the bottom of such plaques, mostly in adulthood. Such plaques can rarely lead to sebum carcinoma. However, the rate of such malignant developments is low. For this reason, removal is no longer systematically recommended [10].

34.2.1.1 Therapy

Basal cell carcinoma therapy is basically surgical. The aim is complete excision with control of margins, either by means of conventional bread loaf technique or Moh's surgery. In superficial basal cell carcinomas, therapy with imiquimod is approved as a topical option, or cryotherapy or photodynamic therapy can be applied. In addition, systemic therapy with hedgehog inhibitors (vismodegib and sonidegib), which inhibit the PTCH-hedgehog pathway, is available for non-operable basal cell carcinomas. However, these might carry an increased risk for squamous cell carcinoma [11]. In the future, patients suffering from Gorlin syndrome may be able to use a topical form of such hedgehog inhibitor or anti-PD1 antibodies.

34.2.1.2 Long-Term Follow-Up

Young patients with a predisposition for the development of basal cell carcinoma should be screened at regular intervals of at least 6 months by a dermatologist. Dermoscopy can help to detect basal cell carcinomas at an early stage. The aim is to avoid mutilating operations.

34.2.2 Squamous Cell Carcinoma

34.2.2.1 Therapy

Complete surgical excision is the therapy of choice for squamous cell carcinoma of the skin. The performance of a sentinel lymph node biopsy can be considered in individual cases. However, there is no general recommendation.

Therapy in the metastatic stage is surgical whenever possible, if a complete metastasectomy can be achieved. Postoperative radiation in the

case of metastasis in the regional lymph nodes is to be discussed.

In immunocompetent patients with non-operable metastasis, the use of anti-PD1 antibodies (cemiplimab) is described as an approved therapeutic option. EGFR antagonists in combination with platinum-based cytostatics are associated with significantly lower response rates.

34.2.2.2 Long-Term Follow-Up

Children and adolescents suffering from squamous cell carcinoma of the skin must be followed up obligatorily. In addition to the frequent detection of secondary tumours, lymphogenic and haematogenic metastases may occur. This applies especially to patients with chronic immunosuppression.

34.3 Melanoma

Childhood and adolescent melanoma are rare with an incidence of five to six cases per million in children under 21 years of age [12]. It represents 1–4% of all melanoma cases and 1–3% of all paediatric malignancies [13]. Studies examining incidence rates over a long period (1973–2007 or 1973–2009) show an increase in incidence in recent decades [12, 14]. The incidence of melanoma increases with age from 1.1 cases per million in 1–4-year olds to 10.4 cases per million in 15- to 19-year olds. In the 15–29 age group, melanoma is the second most common type of cancer. Since the 1970s, an increase in the incidence of paediatric melanoma has been observed with average annual rates of 2–2.9% – comparable to adult melanoma. In addition, most paediatric melanoma patients are Caucasian as shown in the SEER analysis with 85% of melanoma cases occurring in patients under 18 years of age in Caucasians, followed by Hispanic patients (5%) and Asian-Pacific island patients (2%) [14].

Paediatric melanoma can be classified into three categories depending on age: neonatal melanoma, melanoma in prepubertal children and melanoma in adolescents and young adults.

Neonatal melanoma is extremely rare, and only a few cases have been described so far. Newborns showed melanoma based on congenital giant cell nevus or transplacental metastasis from mother to foetus in the uterus.

34.3.1 Melanoma Associated with Congenital Nevi

In cases of congenital nevi, melanomas may arise in 4.9% of cases depending on the size of the nevus (compared to a normal incidence of 1.97%) [15–17]. For very large congenital nevi (>20 cm diameter), the risk for developing melanoma is as high as 5–15% [18]. Importantly, these can arise in other sites, e.g. the brain in about one third of cases, and can be associated with malformations of the central nervous system [19]. Thus, besides dermatological consultation in children with large congenital nevi, an MRI of the head is recommended at the age of 6 months.

34.3.2 Melanoma in Neurocutaneous Melanosis

Typical for neurocutaneous melanosis are the numerous, sometimes oversized moles, which are found all over the body. The exact mechanisms of disease development are not yet fully understood, and neuroectodermal dysplasia is suspected to be the cause.

Interestingly, neonatal and prepuberant melanomas usually do not carry a BRAF V600 mutation but a NRAS mutation, which is otherwise detected in older melanoma patients with cutaneous melanoma.

Most paediatric *melanoma* cases that develop *postpubertant* are sporadic in nature and are associated with DNA damage induced by UV radiation. UV light is associated with the development of melanocytic nevi and an increased risk of melanoma. Other risk factors such as genetics or family history may interact with UV exposure to cause melanoma in younger patients. UV protection is highly recommended since evidence in Australia showed that extensive UV protection led to decreased incidence rates in the younger

cohorts [20]. Interestingly, the use of sunscreen does not provide enough protection against the development of melanocytic nevi, an indicator of melanoma risk [21].

Atypical Spitz nevi are an important differential diagnosis sometimes difficult to distinguish from melanoma [22]. They manifest as lesions with intermediate architecture and cytomorphology between Spitz nevus and melanoma. For better classification, genetic analyses including comparative genomic hybridization can be useful. The vast majority of atypical Spitz nevi have a good overall prognosis even though they show frequent involvement of the sentinel lymph node. In rare cases the diagnosis between melanoma and atypical nevus can only be made when distant metastases occur.

34.3.2.1 Therapy

Prognosis and therapy of postpubertal paediatric melanomas is not different from melanomas in adult patients [23]. Primary excision is usually performed with a small safety margin in order to perform a histological evaluation. In the histological report, it is obligatory to state the vertical tumour thickness according to Breslow (in mm), as well as whether an ulceration is present. Especially in young patients with a tumour thickness of more than 0.8 mm and/or in the presence of ulceration, a sentinel lymph node biopsy should be performed. In the case of melanomas with a tumour thickness of ≤2.0 mm, a subsequent resection with 1 cm safety margin is necessary, in the case of thicker tumours with 2 cm.

If the sentinel lymph node is affected, a radical lymphadenectomy is currently no longer recommended as it does not improve the overall prognosis [24]. Only local tumour control is affected by radical lymphadenectomy. But adjuvant treatment should be recommended dependent on BRAF mutation status. In the adjuvant situation, recent studies with PD-1 antibodies or BRAF and MEK inhibitors have shown a significant improvement in relapse-free survival or, in the latter case, an improvement in overall survival in patients with locoregional disease (stage III patients). Both therapy regimens have replaced the adjuvant therapy with interferon alpha, at least in stage III [25]. Especially in young patients, counselling with regard to reproductive issues is being implemented since data on outcome are scarce.

Therapy in the distant metastatic stage has changed fundamentally in recent years. The introduction of combined targeted therapies with BRAF and MEK inhibitors (dabrafenib and trametinib; vemurafenib and cobimetinib; encorafenib and binimetinib) in patients with proven BRAF V600 mutation and the introduction of checkpoint inhibitors directed against PD-1 (nivolumab; pembrolizumab) and CTLA-4 (ipilimumab) have increased median overall survival significantly. In studies median overall survival for BRAF/MEK-inhibitor therapy was over 2 years and 32 months for checkpoint inhibitor therapy, especially when used in combination. The 3-year overall survival rates were 40–52% for anti-PD1 monotherapy, 33% for ipilimumab and 58% for the combination of nivolumab and ipilimumab [26]. Since survival curves reach a plateau, it is expected to see long-term survivors [27]. The late effects of the targeted and immunotherapies applied for skin cancer are unknown since the first studies only date back a bit over 10 years.

34.3.2.2 Long-Term Follow-Up

Follow-up care focuses on the following aspects: The early detection of recurrences or metastases, the early detection of secondary melanomas and the psychosocial support of the patients. To detect recurrences and secondary melanomas at an early stage, risk-adapted aftercare is recommended. The aftercare of melanoma patients should be carried out over a period of 10 years. After this period, measures should be limited to regular self-examination and annual full-body examination for second melanomas. Since 80% of recurrences occur within the first 3 years after primary diagnosis, intensive aftercare is recommended for this period. Patients with thin melanoma (stage IA) are an exception, as no increased recurrence rates are observed in the first years after diagnosis. Nevertheless, these patients can

benefit from follow-up visits in the first years after surgical treatment, as secondary melanomas are more frequently diagnosed in these first years and patients have an increased need for information and counselling. The individual follow-up examinations can be carried out risk-adapted in example with an intensified follow-up schedule of 3-month intervals with different diagnostic methods. When the risk is reduced, the follow-up intervals can be extended over a 6-month interval up to 1-year interval.

Follow-up of melanoma patients should be performed at risk-adapted intervals according to the following schedule with the following examination methods.

Stage (AJCC)	Year 1–3	Year 4–5	Year 6–10
IA	Every 6 months	Annually	Annually
IB–IIB	Every 3 months	Every 6 months	Every 6–12 months
IIC–IV[a]	Every 3 months	Every 3 months	Every 6 months

[a]Stage IV: In case of completely resected metastases, only

For patients who have been treated with BRAF/MEK inhibitors or checkpoint inhibitors in the adjuvant setting, it is currently recommended to monitor for potential side effects for another 2 years after termination of treatment since side effects can arise long after cessation of therapy.

Stage	Physical examination			Lymph node sonography			Tumour marker S100			Imaging examinations[a]		
Year	1–3	4 + 5	6–10	1–3	4 + 5	6–10	1–3	4 + 5	6–10	1–3	4 + 5	6–10
IA	Every 6 months	Annually	Annually	–	–	–	–	–	–	–	–	–
IB–IIB	Every 3 months	Every 6 months	Every 6–12 months	Every 6 months[b]	–	–	Every 3 months	–	–	–	–	–
IIC–IV[c]	Every 3 months	Every 3 months	Every 6 months	Every 3 months	Every 6 months	–	Every 3 months	Every 6 months	–	Every 6 months	–	–

[a]CT-scans in adults, MRT recommended in children
[b]Only in case of a correct staging using sentinel node biopsy, otherwise follow up as like stage IIC
[c]Stage IV: In case of completely resected metastases, only

34.4 Sarcoma

34.4.1 Kaposi Sarcoma

Kaposi's sarcoma in children and adolescents is usually the result of HIV infection with AIDS [28]. The human herpesvirus 8 (HHV-8) is endemic in parts of Africa, and the infection with HHV-8 is responsible for the development of Kaposi's sarcoma since infected lymphatic endothelial cells start to proliferate. The skin lesions are usually reddish-violet in colour and can occur as single lesions, in a limited area, or widely. The lesions may occur as being flat or as nodules.

34.4.1.1 Therapy

The combination of antiretroviral therapy and chemotherapy increases the probability of remission and reduces the risk of death in HIV-infected children diagnosed with Kaposi's sarcoma.

34.4.1.2 Long-Term Follow-Up

The aim is to normalize the lymphocyte count in general and the number of CD4+ in particular. This strengthening of the T-cell-mediated immune response prevents recurrence.

34.4.2 Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) in children is extremely rare; only a few case series have been published so far [29]. DFSP belongs to the group of fibrosarcoma; it is more precisely a cutaneous soft tissue sarcoma. They begin as a small hardening of the skin with a diameter of about 1–5 cm. Clinically, it can be confused with a bruise, birthmark or pimple. Normally it is a slowly growing tumour of the trunk but can also appear on the arms, legs, head and neck. About

90% of DFSPs are classified as low-grade sarcomas, about 10% as intermediate grade sarcomas because they contain a high-grade component. DFSPs rarely metastasize (less than 5%), but they can recur locally. Most DFSPs carry the chromosomal translocation t(17;22) [30]. This translocation fuses the collagen gene (COL1A1) with the PDGF gene (platelet-derived growth factor) and leads to the inappropriate production of a growth factor instead of a structural protein, which induces the tumour to grow autogenously.

34.4.2.1 Therapy

The treatment is primarily surgical. A complete resection with control of margins must be performed. The addition of adjuvant radiotherapy improves local control in patients with narrow safety margins.

Imatinib is approved for the treatment of DFSP. It may be able to induce tumour regression in patients with recurrent DFSP, inoperable DFSP or metastatic DFSP. There has been clinical evidence that imatinib, which inhibits PDGF receptors, may inhibit tumours that are positive for t(17;22) translocation.

34.4.2.2 Long-Term Follow-Up

Follow-up care is primarily aimed at the early detection of local recurrences or lymph node metastases. Clinical examinations at half-yearly intervals for at least 5 years are recommended. Follow-up care with imaging such as lymph node sonography or sectional CT/MRT scans is only recommended in cases of known metastasis, fibrosarcomatous transformed tumours or very extensive primary tumours. For these patients, follow-up care should be based on the recommendations for follow-up care for high-grade soft tissue sarcomas.

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Late Effects in Young Breast Cancer Survivors

35

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35.1 Breast Cancer in Children, Adolescents, and Young Women: Overview

Between the ages from 18 to 39 years (which are generally considered as young adults), cancer accounts for 10–20% of incidents of death. Breast cancer is the most frequent reason for death in young women with an increasing number based on numerous registries worldwide. In contrast, the spectrum of malignancies in children and adolescents is significantly different from that in adults. In this age group, hematological malignancies and central nervous system and embryonal carcinomas predominate, while epithelial tumors, i.e., carcinomas, are exceedingly rare.

Regarding the report of the German Childhood Cancer Registry covering the period from 1980 to 2017, just 2.5% of all malignancies at the age from birth to 18 years are carcinomas [1, 2]. Among these, thyroid carcinomas represent the largest group, while in this 28-year period, only one single breast carcinoma has been registered, notably in a pre-school boy. This may reflect a selection bias, in that breast cancer patients are mostly treated in gynecology and not pediatric oncology departments so that these are not reported to childhood cancer registries. However, with the establishment of the German Rare Tumor Study Group [3], more breast tumors have been documented, but all were fibroadenomas or phyllodes tumors of the breast and not true breast carcinoma. Nevertheless, breast cancer should be in the scope of the pediatric oncologist, involved in long-term care of cancer survivors, as post-radiotherapy breast carcinoma belongs to the most frequent therapy-associated secondary cancers [4].

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35.2 Late Effects After Breast Cancer Therapy of Young Women

While the probability of cure of breast cancer is increasing and reaches up to 85% based on histology and predictive factors, we have an increasing number of long-term survivors. Thus, long-term toxicities need to come into the focus. Among those, cardiac events (after exposure to anthracycline-based chemotherapy plus/minus radiation to the thoracic wall) as well as osteoporosis (after chemotherapy and endocrine-induced postmenopause) are clinically most important. In addition to that, reduced fertility and social problems including lower income must be taken into consideration.

35.2.1 Cardiotoxicity

Cardiovascular toxicity following treatment for breast cancer may arise from different causes. First, inclusion of the heart and the large mediastinal vessels in the irradiation field increases the risk of cardiovascular disease. This problem is mostly related to "older" radiation techniques that have not allowed for tailoring radiation fields as far as modern techniques, e.g., intensity-modulated radiation or proton therapy. Second, some of the cytotoxic drugs, in particular anthracyclines, include the risk of acute and long-term cardiotoxicity. The risk is related to both, cumulative dose and time after exposure. Thus, the risk of cardiomyopathy increases with higher doses, and it may further increase over time. Compared to sibling controls, the risk of developing heart failure is sixfold increased in childhood cancer survivors [5], and symptomatic heart failure may develop as late as 30 years after treatment. Third, also non-anthracycline chemotherapy and targeted therapies, e.g., trastuzumab, may bear the risk of cardiotoxicity, in particular, when these are applied in combination with anthracyclines.

The reader is also referred to Chap. 1 of this book.

35.2.2 Osteoporosis

35.2.2.1 Background

A young patient may develop osteoporosis as a result of the performed therapies. In some premenopausal women, premature ovarian failure (POF) occurs after chemotherapy, resulting in loss of bone mass. Ovarian insufficiency develops in 63–96% of all premenopausal patients within 1 year after adjuvant chemotherapy. In particular, alkylating substances, such as cyclophosphamide and anthracyclines, destroy the proliferating cells of the ovaries (Table 35.1). The risk of ovarian failure depends on the cumulative total dose, the patient's age at therapy, and the length of therapy. If amenorrhea is diagnosed after the age of 30, it is often irreversible. Women who develop amenorrhea after chemotherapy as part of breast cancer present a 10% lower bone density in the lumbar spine compared to women of the same age [7].

But also endocrine therapy options, which are used in premenopausal patients with a hormone receptor-positive breast carcinoma, such as antiestrogens and GnRH analogue, possibly in combination with an aromatase inhibitor (AI), lead to a significantly increased risk of osteoporosis in later life. The antiestrogen tamoxifen has both—agonistic and antagonistic—estrogen effects. While premenopausal women develop a loss of bone mass, postmenopausal women have a bone-preserving effect due to the partial agonistic effect.

Previously, all premenopausal patients received endocrine therapy with a GnRH analogue for 3–5 years, but the indication was gradually differentiated due to the heterogeneous data situation. At first, the treatment was limited to patients under the age of 40 and then (on the basis of meta-analyses) to patients who had not received chemotherapy. Now, however, the large, randomized SOFT study presents a new set of data. In higher-risk collectives, i.e., after chemotherapy, breast cancer-free survival was 78.0% with tamoxifen, 82.5% with tamoxifen plus GnRH analogue (HR 0.78; 95% CI 0.60–1.02), and 85.7% with exemestane and GnRH analogue (HR 0.65; 95% CI 0.49–0.87) [8].

Table 35.1 Ovar-toxic effects of different chemotherapeutic agents (modified after [6])

Substances with a high risk of premature ovarian insufficiency:	*Substances with unclear risk*:
Cyclophosphamide	Taxanes
Chloromethines	Oxaliplatin
Melphalan	Irinotecan
Busulfan	Monoclonal antibodies (e.g., trastuzumab)
Procarbazine	Tyrosine kinase inhibitors (e.g., erlotinib)
Chlorambucil	*Substances with low or no risk*:
Ifosophamide	Methotrexate
Substances with medium risk:	5-Fluorouracil
Cisplatin	Vincristine, vinblastine
Adriamycin	Bleomycin
Epirubicin	Actinomycin
Doxorubicin	

The subgroup of patients under the age of 35 years had also a clear benefit from the addition of the GnRH analogue and the AI. However, therapy with GnRH analogues is also associated with side effects. Among others, there were more hot flushes (all grades: 93% versus 80%), sweats (62% versus 48%), and osteoporosis (20% versus 12%). GnRH analogues are generally associated with a marked decrease in spinal bone density, which can be observed already after 6 months. In studies with goserelin, bone density in the lumbar vertebra decreased by −10.5% and in the femoral neck by −6.4% after a follow-up of 2 years.

35.2.2.2 Prophylaxis and Therapy of Therapy-Induced Osteoporosis

With regard to the therapy of therapy-associated osteoporosis, prevention is of particular importance. It is recommended that all premenopausal women with therapy-induced amenorrhea should receive bone density measurements for screening purposes. There is no clear recommendation for the intervals. An interval of 1 year or individual result-dependent frequencies are possible. However, the investigation should be repeated at the latest after 2 years [9].

Since therapy-induced osteoporosis is faster and more severe than age-related bone loss, adjuvant use of bisphosphonates or denosumab may be considered for prevention following chemotherapy and/or concomitant to endocrine therapy.

The effectiveness of zoledronic acid in premenopausal women with hormone receptor-positive breast cancer and therapy with goserelin was investigated. A loss of bone mass of 14.4% was observed in the control group, while no bone loss was observed in the treatment group.

In its recommendations, ASCO stresses that all patients suffering from breast cancer can benefit from the use of bisphosphonates. However, patients should be informed of potential side effects such as osteonecrosis of the jaw, nephrotoxicity, gastrointestinal complaints, and arthralgia. Before starting a therapy, a dental examination should always be carried out.

Bisphosphonates are also established for the treatment of osteoporosis and have been shown to reduce the risk of vertebral fractures [9]. These are recommended with endocrine therapy from a *T*-score of <−2.0 or <−1.5 and the existence of two or more risk factors (e.g., BMI <20 kg/m^2, hip fracture in the family history, smoker, oral corticotherapy >6 months). Denosumab is available as an effective alternative.

35.2.3 Infertility

35.2.3.1 Background

As described under Sect. 35.2.2, new oncological treatment methods make it possible to survive even serious diseases, but often lead to impairment of ovarian function and thus to fertility disorders. For surviving young breast cancer patients

in particular, it is an important part of their quality of life to be able to fulfill their desire to have children, as family planning usually could not yet be started or completed at the time of diagnosis. Fertility maintenance, however, cannot take place only in aftercare. It is an important part of the overall treatment strategy before the start of therapies. Detailed information and advice for young patients and their relatives about risks and prophylactic and treatment options for a fertility disorder is an important basis for individual family planning. This should be tailored according to the individual risk depending on age and therapies. Methods of maintaining fertility in breast cancer patients are the administration of GnRH analogues to transform the ovaries in a prepubertal state or the cryopreservation of ova, embryos, and ovarian tissue [10]. The aim of the education should be the self-determined decision of patients with regard to family planning [11].

35.2.3.2 Possible Risk After Surviving Breast Cancer due to a Subsequent Pregnancy

Studies on this question are often small, retrospective, or without corresponding statistical power. However, most data are available for breast cancer patients. There are now a number of small cohort studies available which present a better or non-negatively influenced overall survival from pregnancy [12].

This was recently confirmed by a study of women with BRCA mutations. Women with breast cancer and BRCA mutation and subsequent pregnancy showed no worse 15-year survival than women without subsequent pregnancy [13]. However, it should be noted that mutation carriers are more likely to have hormone receptor-negative breast carcinomas. A meta-analysis from the year 2012 presented the same result, if a time interval between disease and pregnancy is kept [14]. Current recommendations are 2–3 years after primary disease. Ideally, therapy, including endocrine therapy, should be completed [15].

Since there are no prospective, randomized studies available, various possibilities of influencing the results must be taken into account, such as the so-called "healthy mother" bias: patients who are in a good health state or have a better prognosis are striving for pregnancy. Explanations and hypotheses how pregnancy can have a positive effect on cancer, e.g., the "fetal antigen hypothesis" about activation of the body's immune system, can also play a role and have not yet been clarified [16].

35.2.3.3 Follow-Up and Desire to Have Children

In premenopausal breast carcinoma patients who wish to have children, an anamnesis including information on menstruation should be made as part of follow-up care [11]. The occurrence of transient amenorrhea is also possible beyond 1 year after chemotherapy, and bleeding may occur again later [17]. This is also possible under tamoxifen, whereby amenorrhea is the side effect and menstruation is the normal state.

The anti-Müller hormone (AMH) is a measure of the ovary cell reserve, but in the assessment of fertility, it cannot always be clearly interpreted as the sole marker, especially in the middle ranges [17]. Therefore, it should be determined repeatedly over time or combined with other parameters such as LH, FSH, estradiol, and progesterone. Ultrasound examination with determination of the antral number of follicles (follicle diameter less than 10 mm at the beginning of the cycle) in the ovaries can support the assessment of the oocyte reserve [18].

The reader is also referred to the Chaps. 10, 12 of this book.

35.3 Hereditary Breast Cancer in Young Women: Implications for Therapy and Follow-Up Care

In Germany, about 71,000 women suffer from breast cancer every year. It is assumed that 25% of all breast cancers have a family background. About 5–10% of all breast carcinomas follow an autosomal dominant inheritance, mainly due to

mutations in the BRCA1 or BRCA2 gene [19]. In terms of figures, more than 7000 breast carcinomas occur in Germany every year, which could be prevented by adequate collection of family anamnesis, risk calculation, genetic testing, and introduction of primary and secondary prevention options. However, mutation testing is also useful for women who are already suffering from breast cancer, if they fulfill the inclusion criteria for testing, as the result can have direct effects on therapy and aftercare. This concerns in particular the breast carcinoma of the younger woman.

35.3.1 Identification and Genetic Testing

In clinical practice, the question often arises in which cases a genetic test is indicated. Against the background that about 85% of breast cancer cases are not caused by BRCA1/2 [20], in view of the psychological burden that may be associated with a test for patients and their relatives, and for reasons of cost-effectiveness, the German Consortium for Breast and Ovarian Cancer has defined criteria for genetic testing, which are based on the probability of a mutation detection of 10% and advocate the performance of a test (Fig. 35.1)—this applies to healthy women with a family burden as well as to already diseased women who prove the probability of a mutation due to the tumor biology and/or family history [9]. With regard to tumor biology, a BRCA1/2 analysis in patients with a triple negative breast carcinoma (i.e., estrogen/progesterone/Her2neu receptor negative) is recommended regardless of the family history, if the result has an influence on the therapy [9].

35.3.2 Options of Intensified Early Cancer Detection and Follow-Up Care

In the case of detection of a BRCA mutation as well as in the absence of exclusion of a mutation and an existing high-risk situation due to the family burden, an intensified early detection should be offered in addition to the guideline-oriented aftercare due to the increased risk of a second carcinoma as well as an ovarian carcinoma, which goes beyond the aftercare of 10 years. The following intensified aftercare and early detection program is one of the most important options following therapy.

Intensified aftercare/early detection program of the breast:

- Monthly self-scanning.
- First quarterly palpation examination up to the third year after diagnosis and from the fourth year half-yearly palpation examination by the gynecologist for lifetime.
- Half-yearly ultrasound of both sides for lifetime.
- Annual mammographies of both sides for lifetime.
- Annual magnetic resonance mammography (MRI) of both sides for lifetime.

Early detection program abdomen:

- Half-yearly palpation examination by the gynecologist from the age of 25 for life time.
- Semi-annual transvaginal ultrasound examination from the age of 25 for life time.
- Annual Pap smear for life time.

All measures are based on general experience with breast and ovarian cancer. They make it possible to detect a new carcinoma of the breast and an ovarian carcinoma earlier, but not to prevent it. This requires further secondary prevention options.

35.3.3 Options of Secondary Prevention

Already diseased mutation carriers have an increased second carcinoma risk, whereby this depends on the type of mutation (BRCA1 higher than BRCA2) and the age at first disease [21–23]. For example, a patient under 40 years of age with a BRCA1 mutation has a risk of developing contralateral breast cancer of 55.1% (45.4–64.9%) in

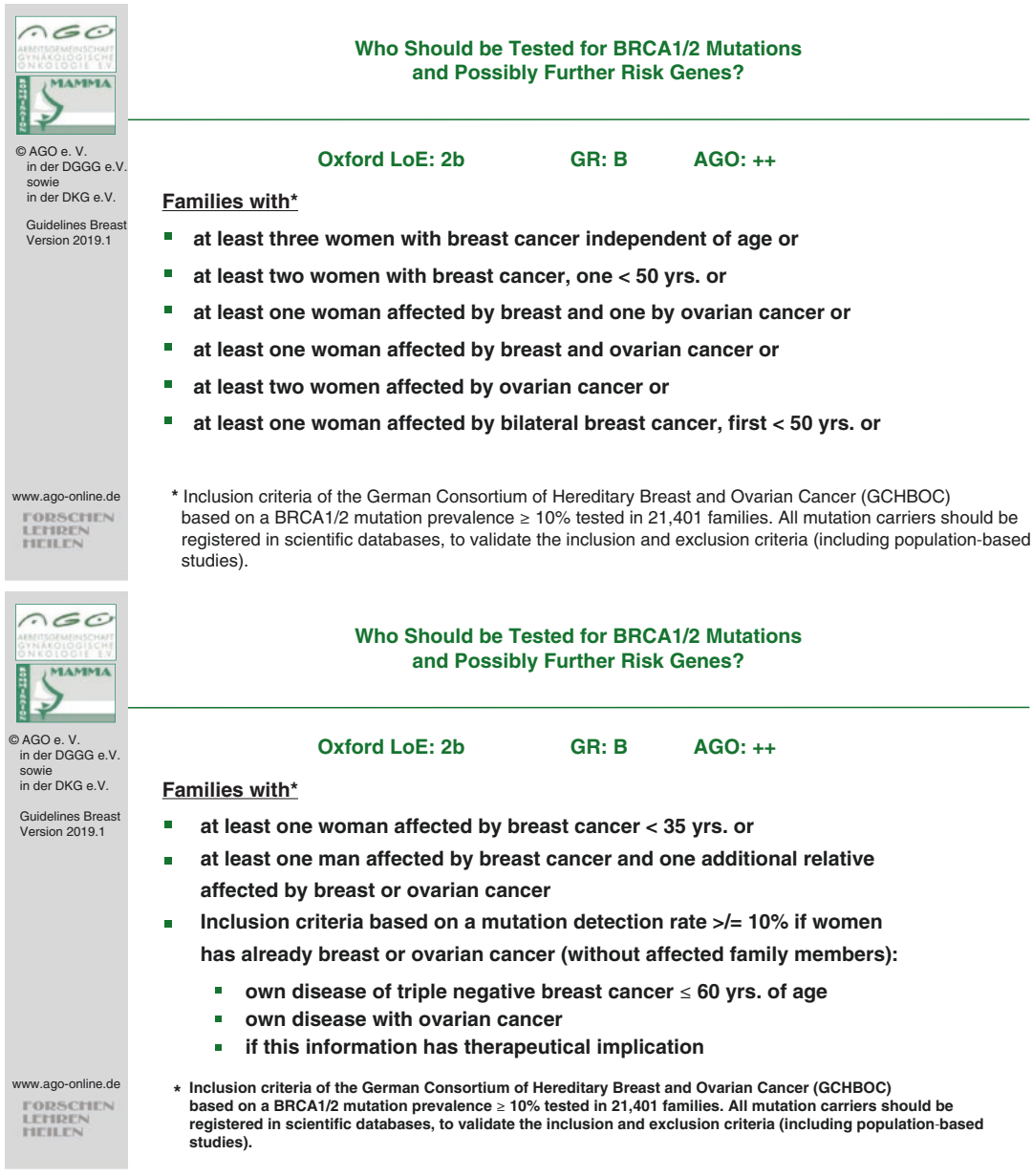

Fig. 35.1 Indications for genetic testing for a BRCA1/2 mutation [9]

the next 25 years after the first disease. Accordingly, the question of contralateral prophylactic mastectomy arose. The prognosis of the primary carcinoma should be taken into account when deciding for or against prophylactic mastectomy and discussed with the patients. Patients have to survive the first disease to benefit from further prophylactic surgery.

In the USA, approximately 50% of all mutation carriers with breast cancer receive contralateral prophylactic mastectomy. Currently, however, there is no evidence for a mortality reduction by secondary prophylactic mastectomy in already diseased mutation carriers. The data on long-term survival are mostly based on small collectives and a too short follow-up. Data from a

retrospective analysis were recently published [24]. 390 patients (86% mutation carriers; 14% without testing with a high probability of mutation) were analyzed, half of whom received initial bilateral mastectomy ($n = 44$) or contralateral mastectomy in the course of stage I or II breast cancer ($n = 137$) between 1977 and 2009. The median follow-up was 13 years. Overall, the multivariate analysis for years 0–20 after primary diagnosis presented an improvement in overall survival of 48% by contralateral mastectomy [HR 0.52, 95%CI 0.29–0.93, $p = 0.03$]. Thus, the authors conclude that bilateral mastectomy as an option should be discussed with young female mutation carriers after weighing the advantages and disadvantages.

Simultaneous reconstruction using autologous tissue or implants is possible with all forms of prophylactic mastectomy and is chosen by most patients. The immediate reconstruction reduces or even avoids the consecutive psychological deprivation and the resulting partnership problems by restoring the body image in an aesthetic way.

Another group that should be included in surveillance strategies for developing breast cancer includes childhood cancer survivors that have been irradiated with fields including breast tissue. In these patients, the risk of breast cancer increases over time, summing up to a cumulative incidence of 19% 30 years after therapy [4].

The risk of ovarian cancer after breast cancer has been investigated in several epidemiological studies [25]. A study with mutation carriers already suffering from breast cancer presented a 10-year risk of ovarian cancer of 12.7% (BRCA1) and 6.8% (BRCA2), respectively [26]. The data situation regarding the risk reduction of a contralateral or secondary carcinoma by prophylactic adnexectomy after breast cancer is heterogeneous. Domchek and colleagues reported no risk reduction of a second carcinoma in mutation carriers already suffering from breast cancer [27]. In contrast, further analyses presented a risk reduction of up to 75% and 60%, respectively, for ipsilateral secondary carcinoma and contralateral breast carcinoma in diseased mutation carriers with stage I and II breast carcinoma [28, 29]. Overall, a significant risk reduction for both ovarian and breast cancer is assumed, so that prophylactic adnexectomy should be offered to mutation carriers already suffering from breast cancer after family planning has been completed. All women must be informed in detail about the consequences of premature menopause, such as hot flushes, sweating, sleep disorders, concentration difficulties, depressive mood, osteoporosis, etc., and the consequences of the premature menopause.

35.4 Conclusion

Breast cancer in children and adolescents is exceedingly rare, but incidence increases significantly in young adults, in whom breast cancer belong the leading causes of cancer deaths. With increasing cure rates, long-term effects of breast cancer therapy come into focus. As therapy may include a broad spectrum of treatment modalities, including irradiation, chemotherapy, and hormone and targeted therapies, the spectrum of potential late sequelae is broad. Moreover, a potentially genetic predisposition should be taken into consideration, because this may indicate an additional risk of secondary cancers.

The reader is also referred to the guidelines https://www.esmo.org/guidelines/breast-cancer.

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36 Long-Term Effects of Colorectal Carcinoma in Childhood and Adolescents

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36.1 Introduction

Colorectal carcinoma accounts for over 50% of newly diagnosed malignancies over the age of 70 years while they are extremely rarely seen in children. The calculated incidence from the US SEER database is approximately 0.4–1 per million [1, 2]. Consequently, little is known about its biology and optimal management. The few existing reports describe a higher occurrence of unfavorable aggressive histotypes as well as advanced clinical stage at diagnosis leading to worse survival rates for pediatric cases compared to adult cases. We might see a biologically more aggressive sub-entity in young patients. Additionally, a particular microsatellite instability has been reported in younger patients [3]. On the other hand, a high frequency of tumor predisposition syndromes (mainly HNPCC syndrome) was reported by Weber et al., interestingly associated with less aggressive tumors and better overall survival, but frequent occurrence of second malignancies [4]. So far, the specific tumorigenesis of childhood CRC remains unclear and treatment recommendations have to follow adult guidelines. Consequently, the below described insights in late effects is basically derived from adult oncology.

36.2 Late and Long-Term Effects of Treatment

In adults, substantial improvement in the multimodal treatment of colorectal cancer resulted in significant survival. Thus, late and long-term side effects will be of increasing relevance and a challenge in colorectal cancer survivorship.

36.2.1 Oxaliplatin-Induced Peripheral Neuropathy

The best described side effect of oxaliplatin resulting in dose modification is acute neuropathy. This neuropathy is induced by cold and results in dysesthesia and paresthesia of distal upper and lower extremities but also affecting the oral cavity, neck, and pharyngolaryngeal region [5]. It was shown that acute neuropathy developed in 30–72% of patients lasting for up to 14 days, while 48–76% of patients are experiencing a chronic progressive sensory peripheral

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neuropathy which usually resolves within 18 months [5], but also may take years to resolve or even remain with substantial impairment of quality of life [6]. Unlike chronic neuropathy, the risk of cold-induced acute neuropathy resulting in dose modification and discontinuation is highest in winter [7]. Thus, external factors such as the climate may have a substantial impact on dose modification of oxaliplatin resulting in different degrees of late and long-term neuropathy.

Experimental studies have demonstrated an impairment of retrograde neuronal transport as demonstrated by molecular imaging [8]. Utilizing intramuscular injection of fluorescence dye-labeled tetanus toxin c-fragment, oxaliplatin treated animals showed a rapidly decreased transport throughout the study with comparable transport at baseline. Recently, the nerve fiber types that seem to be most vulnerable to chronic oxaliplatin-induced toxicity have been identified [9]. Colorectal cancer patients were analyzed for quantitative sensory deficits before and prior to each following cycle of oxaliplatin in addition to a comparison with age- and sex-matched volunteers. This study shows that Aβ-myelinated fibers and C-unmyelinated fibers were the most affected and thinly myelinated Aδ fibers were least sensitive. Baseline defects resulted in much more pronounced and longer-lasting deficits by oxaliplatin exposure. The mechanism, how oxaliplatin impairs sensory nerves, is not fully understood. Neurotoxicity from paclitaxel treatment was caused by interfering with intracellular calcium signaling [10]. In contrast, acute exposure to oxaliplatin had no effect on intracellular calcium signaling. In addition, cellular temperature sensors (transient receptor potential channels) were not activated [11]. Remarkably, extended exposure to oxaliplatin did sensitize cells to subsequent stimuli and enhanced intracellular calcium responses. The following year, a sodium channel isoform $Na_v1.6$ was identified to induce bursts of action potentials in the presence of oxaliplatin, when cooled to 22 °C in myelinated A fibers. This was not observed in whole-cell patch-clamp experiments from $Scn8a^{med/med}$ mice peripheral myelinated axons, lacking a functional $Na_v1.6$ sodium channel [12]. Thus, $Na_v1.6$ might play a major role in mediating acute, cold-dependent neurotoxicity of oxaliplatin and that persistent sodium currents might explain cold-aggravated symptoms. A recent publication further elaborates on the differences of oxaliplatin and paclitaxel-related neurotoxicity [13]. Acute symptoms had their maximum intensity at day 3 after exposure to either oxaliplatin or paclitaxel. Paclitaxel-induced acute neurotoxicity occurred with similar intensity in each cycle and nearly completely resolved in between cycles. In contrast, oxaliplatin-induced acute neurotoxicity did not resolve completely between cycles and strongly tends to aggravate from cycle to cycle. Both drugs caused a chronic sensory neuropathy with paclitaxel-induced toxicity resolving as soon as the drug was discontinued. After discontinuation of oxaliplatin, neurotoxicity further worsened after treatment and began to resolve 3 months later. With paclitaxel and oxaliplatin [14], acute toxicity may predict the severity of chronic neuropathy. In a systematic review, five out of six studies were able to prove an association between cumulative oxaliplatin dose administered in colorectal cancer patients and the development of more severe (≥NCI-CTC grade 2) chronic, oxaliplatin-induced peripheral neuropathy [15]. Since nearly 80% of patients reported residual neuropathy with distal loss of pinprick sensibility in 60% and loss of vibration sensibility in 83.3%, there was no recovery of sensory action potential amplitudes attributable to persistent axonal sensory neuropathy. The persistence of subjective and objective deficits in oxaliplatin treated patients contradicts previously described reversibility of oxaliplatin-induced late neuropathy [16]. These findings have been confirmed by several studies such as a prospective single institutional evaluation [17] with peripheral neuropathy persisting in 70% of patients for more than 22 months and a cross-sectional cohort study of patients with colorectal cancer surviving 2 or more years with many patients complaining about mild or moderate oxaliplatin-related neuropathy more than 2 years after such a treatment [18]. Despite remaining neuropathy most patients were still satisfied with their treatment decision not regretting oxaliplatin-based chemotherapy. A

long-term clinical and neurophysiologic follow-up on 31 consecutive patients for more than 3 years, receiving six to eight cycles of an oxaliplatin-based chemotherapy at an initial dose of 130 mg/m^2 further confirmed the persistence of chronic large sensory fiber neuropathy and the impact of cumulative oxaliplatin dosing on the development and severity of chronic neuropathy [19].

Are there markers other than cumulative oxaliplatin dosing, early onset, and persistence of acute neuropathy in a past cycle [20] available to reliably predict persistent neuropathy? The incidence of oxaliplatin-induced neuropathy was found to be higher in patients with pretreated anemia (p = 0.0001), hypoalbuminemia (p = 0.01), hypomagnesemia (p = 0.001), and the habit of alcohol consumption (p = 0.003). Duration of neuropathy conversely correlates with age, being significantly longer in younger patients (p = 0.03), with hypoalbuminemia (p = 0.04) and hypomagnesemia (p = 0.002) [21]. Recently, single-nucleotide polymorphisms (SNP) in genes involved in oxaliplatin metabolism, DNA repair mechanisms and cell cycle control, detoxification, and excretion pathways have been thoroughly investigated [22]. SNPs in the cyclin H gene and the ATP-binding cassette subfamily G, member 2 (ABCG2) can modulate the development of severe oxaliplatin-dependent neuropathy. In contrast, these and other 10 SNP could not predict the severity of peripheral sensory neuropathy as a dose limiting toxicity in a large-scale prospective study among 882 Japanese patients enrolled in the JFMC41-1001-C2 (JOIN trial) to investigate the tolerability of adjuvant modified FOLFOX6 in stage II and III CRC [23].

About one third of colorectal cancer survivors reported the use of nutritional supplements with assumed neuroprotection [24]. In addition, 10% of these patients have opioids and 15% have NSAR prescribed to facilitate oxaliplatin-related peripheral neuropathy. Remarkably, only 10% were treated with anticonvulsants such as gabapentin that has been approved for the treatment of neuropathic pain. Pregabalin being more potent than gabapentin achieved an improvement of oxaliplatin- induced neuropathy by 1–2 grades in the majority of patients [25]. Antidepressants such as duloxetine are feasible in the treatment of chronic oxaliplatin-induced peripheral neuropathy without compromising renal or liver function [26]. Mg and Ca infusions in order to prevent oxaliplatin-induced sensory neuropathy did not compromise the efficacy of oxaliplatin-based chemotherapy [27]. Nevertheless, this meta-analysis of 16 studies including 1765 patients failed to show significantly less grade 3 or higher neuropathy as a result of such infusions. Calcium canal blockers could significantly reduce acute neuropathy but failed to reduce the cumulative incidence of chronic oxaliplatin-related neuropathy [28].

36.2.2 Bowel Dysfunction

For patients with lower rectal cancer, some have the choice in between ostomy and sphincter-sparing surgery. Normal bowel function is preserved utilizing sphincter-sparing surgery thus preferred over ostomy. Nevertheless, this approach harbors the risk of incontinence and bowel dysfunction. A systematic review has recently analyzed controlled studies that compared long-term survivorship outcomes [29]. Bowel function and long-term outcome are by far better understood in ostomy. In contrast, outcomes after sphincter-sparing surgery show high variation that makes it difficult to predict bowel function to the patient. Finally, supportive interventions focusing on sphincter-sparing surgery are lacking. All survivors substantially adjusted to permanent dietary and behavioral changes independent from their ostomy status [30]. Dietary adjustments did not significantly differ by ostomy status. Not surprisingly, patients with ostomy more likely avoided carbonated drinks and vegetables. Behavioral adjustments mainly related to food intake such as smaller portions, fewer meals around social activities, even skipping dining out. Nonmeal-related adjustments included staying at home. Some patients with ostomy utilized irrigation to control bowel activity. Bowel function could also be regulated by

exercises such as running in order to increase bowel movements. Most of this data reflects the outcome of later onset survivors. Comparing 801 older with 415 younger onset survivors [31] defined as patients diagnosed with CRC in between 18 and 50 years, young adults reported significantly more abdominal and pelvic pain (12.1% vs. 7.9%, $p < 0.0001$), bloating (26.0% vs. 18.4%, $p = 0.0002$), and embarrassing bowel movements (46.5% vs. 27.8%, $p = 0.002$).

36.2.3 Late Toxicities of Radiotherapy

Neoadjuvant chemoradiotherapy substantially improved the outcome of rectal cancer patients with many of them becoming long-term survivors. Radiation-induced early toxicity includes diarrhea, cystitis, and perineal dermatitis, while late toxicity is defined by bowel and genitourinary dysfunction, fecal incontinence, perforation, bleeding, and pelvic fractures [32]. While short-course radiotherapy (SCRT) followed immediately by surgery substantially reduces acute toxicity over fractionated chemoradiotherapy with delayed surgical intervention, late toxicity remains the same. Intensifying neoadjuvant chemoradiotherapy by adding oxaliplatin or biologicals have failed to improve pCR but substantially contributed to early and late toxicity [33, 34]. Radiotherapy also has an impact on later surgical interventions within the involved field. Primary fistula repair following prostatectomy, Crohn's disease or pelvic fracture (nonradiation related) was more successful in nonradiated patients than in radiated patients (80.9% vs. 0%, $n = 59$, $p < 0.001$). Thus, most patients with previous radiation therapy require permanent colostomy and urostomy, while nonradiation-related fistulae can usually be repaired without permanent fecal and urinary diversion [35].

The role of radiation therapy for the occurrence of secondary malignancies is debated. While an increased risk for the occurrence of endometrial, lung, and bladder cancer as well as lymphomas was described, radiation for rectal cancer seems to be associated with a significantly decreased risk for prostate cancer (HR 0.43, $p < 0.001$) reducing the overall likelihood of secondary malignancies [36].

36.2.4 Incisional Hernia and Small Bowel Obstruction

Incisional hernia is a common complication following abdominal surgery with an incidence between 2% and 20% [37]. This complication often results in abdominal pain and poor body image thus substantially reducing quality of life. In a recently published study 626 patients undergoing colorectal cancer surgery in between 2005 and 2010 were investigated [38]. The cumulative 5-year incidence of incisional hernia was 7.3%. Age, BMI, waist circumference, hip circumference, open laparotomy, wound infection, visceral fat area, and subcutaneous fat area were identified to be associated with the risk of incisional hernia. Multivariate analysis revealed age (HR 1.043, $p = 0.027$), open laparotomy (HR 4.410, $p = 0.047$), and subcutaneous fat area (HR 1.013, $p = 0.005$) as independent risk factors for the development of this complication. Lower frequency of incisional hernia in children was confirmed by Mullassery et al. [39].

Early small bowel obstruction commonly complicates colectomy for colorectal cancer. Early postoperative small bowel obstruction is defined to occur within the first 30 postoperative days, presenting with nausea, vomiting, and abdominal distention, lasting for at least 2 days and representing characteristic radiologic findings. With 8%, this complication occurred independent of pelvic or colonic surgery [40]. Independent risk factors were poor systemic condition and local remnant tumor. Univariate and multivariate analysis on 1004 patients undergoing open or laparoscopic-assisted colectomy for colorectal cancer revealed open colectomy (HR 2.62, $p = 0.005$) and rectal cancer (HR 2.12, $p = 0.025$) as particular risk factors for subsequent bowel obstruction [41]. Laparoscopic-assisted colectomy can effectively reduce this complication. In contrast, late bowel obstruction is commonly associated with tumor progression

particularly after initial successful stenting [42]. In order to overcome this late complication, colectomy after successful endoscopic stenting could reveal an option.

36.3 Quality of Life

All treatment modalities might affect quality of life in colorectal cancer survivors. Ample of recent publications cover detailed analyses of health-related quality of life, their impact on mental and physical well-being as well as options to improve quality of life-adjusted outcome in long-term survivors.

36.3.1 Mental and Physical Aspects

Overall long-term mental and physical health was described to be excellent when compared with the general population [43]. The authors of this telephone survey with more than 700 enrolled patients explained this by disease-related symptoms other than colorectal cancer not detracting from good overall health. In this trial (NCT00410579) treatment-related late effects did not impair quality of life in general. A more detailed analysis revealed that a distressed type D personality, which is defined by a tendency to experience negative emotions and an inhibition of self-expression in social interaction, is prone to poor quality of life and mental health status among survivors of rectal cancer [44]. The role of type D personality in the course of health-related quality of life has been confirmed in a prospective population-based study from the PROFILES registry [45]. Colorectal cancer survivors reported a higher level of obesity and a lack of physical activity as compared with other cancer survivors [46]. On the other hand, these survivors were less likely to be current smokers. Lower levels of physical activity also correlated with low subjective health literacy among colorectal cancer survivors [47]. These survivors did not only meet the prescribed physical activity guidelines but were more likely to smoke and had significantly lower levels of mental and physical health-related quality of life scores. Not surprisingly, an association in between sedentary time and sedentary time accumulation with health-related quality of life was shown in colorectal cancer survivors as well [48]. Thus, it is likely that substituting sedentary behavior with physical activity may improve some health-related quality of life scores in cancer survivors [49]. The correlation in between physical activity and quality of life in colorectal cancer survivors has been confirmed in several studies [50–52]. Remarkably, there was a significant association also in between physical activity and depression in colorectal cancer survivors [51]. Do colorectal cancer survivors then benefit from exercise recommendations? An intention to treat analysis of a randomized controlled trial revealed that only an oncologist's exercise recommendation together with an exercise motivation package significantly improved physical activity among colorectal cancer survivors [53]. While quality of life was improved, physical activity did not have a significant impact on the level of constipation or diarrhea [54].

36.3.2 Social Aspects

A study by the Center for Disease Control and Prevention showed in 2011, that a third of families reported financial burden related to healthcare. Financial burden is particularly prevalent among cancer survivors and correlates with the patient's health-related quality of life [55]. Reported financial difficulties were similar among patients with advanced disease and those who were cancer free. For most patients, their healthcare insurance status did not change.

In older long-term colorectal cancer survivors, social participation predominantly relates to their mental health, where there was a dose-response relationship between moderate to vigorous physical activity and physical health but not mental health [56]. Survivors who participate socially benefit from mental as well as physical health when engaged in physical activity even as non-exercise or light intensity. Finally, sexual dysfunction is common in rectal cancer long-term survivors with 51% for the ostomy group and

29% for the anastomosis group being inactive before 2000. These proportions worsened for patients receiving their surgery after 2000 with 69% for the ostomy group and 58% for the anastomosis group being sexually inactive [57]. This can in part be attributed to practice changes in the frequency of radiation that increased from 37% to 65% in the ostomy group and from 28% to 41% in the anastomosis group. Sexual dysfunction was shown to be associated with several well-being outcomes such as body image, anxiety, and post-traumatic distress with permanent ostomy survivors being more likely to experience social distress. Management of physical and psychological causes of sexual dysfunction remains critical for the improvement of health-related quality of life particularly in rectal cancer long-term survivors.

36.4 Late Effects Related to Tumor Predisposition Syndromes

In a retrospective analysis by Weber et al. [4], 42% of all patients ($n = 26$) with colorectal carcinoma and genetic testing showed a positive result (eight cases of Lynch syndrome, one patient with familial adenomatous polyposis, and two patients with constitutional mismatch repair deficiency). In adults, a cancer predisposition is only described in about 1–5% of cases. These findings have not been translated into a different therapeutic approach yet due to a lack of clinical studies. However, patients with colorectal carcinoma should have a thorough genetic work-up and follow-up care should include a screening for second malignancies in case of positive results.

36.4.1 Second Malignancies After CRC and Related Cancer Predisposition Syndromes

One of the most disastrous late effects is the occurrence of a second malignancy. Several reports and reviews of late effects of chemotherapy and radiation in children and adolescents describe an increased risk of developing subsequent malignant neoplasms in survivors of childhood cancers. The occurrence of second malignancies has been primarily linked to treatment. Hence, higher rates have been reported in patients, who received multimodal treatment [58]. Preliminary data of pediatric patients with colorectal carcinoma suggest that subsequent malignant tumors are rather connected with cancer predisposition. In the abovementioned study by Weber et al., extracolic neoplasm appeared in 19% of all patients (T-cell non-Hodgkin lymphoma, glioblastoma multiforme). All of these patients were tested positive for Lynch syndrome. While in an analysis of the US American SEER database looking at 23,819 survivors with a median follow-up of 5.8 years after childhood cancer stresses the influence of radiotherapy for the occurrence of second malignancies, only few children with colorectal carcinoma receive radiotherapy. Furthermore, the importance of radiotherapy for the occurrence of second malignancies in adults is still debated and no specific studies exist for children and adolescents [36].

On the other hand subsequent malignant tumors have to be expected in case of cancer predisposition. These genetic conditions are often related with the occurrence of colonic polyps, e.g., familial adenomatous polyposis (FAP), juvenile polyposis, and Peutz-Jeghers syndrome. Recently, the role of hyperplastic polyps in right-sided microsatellite unstable colon cancers was described [59]. The mutation of the so-called Lynch syndrome (hereditary non-polyposis colon carcinoma, HNPCC) occurs in one of the genes responsible for the repair of DNA mismatch errors (MLH1, MSH2, MSH3, MSH6, and PMS2). According to studies in adults, patients with MSH2, MSH6, and MLH1 mutations have a higher risk for developing extracolonic malignancies, mainly endometrial, ovarian, pancreatic, gastric, and urinary tract cancers [60].

36.4.2 Screening

In adulthood surveillance programs are performed in case of cancer predisposition in order

to identify tumors when they are smaller, easy to resect, and less likely to metastasize. Not only clinical outcome will be improved, but less-intensive therapy and less organ toxicity are expected [61]. Data for children and adolescents is scarce, though. Only few studies have been published on the issue of surveillance programs. On the other hand, cancer predisposition seems to play a prominent role in pediatric colorectal cancer [4]. Patients with familial adenomatous polyposis (FAP) have a nearly 100% chance of developing CRC at an early age. Affected may show hundreds to thousands of precancerous colonic polyps (adenomas) and therefore frequent colonoscopy and sigmoidoscopy starting at age of 10 years should be performed. Prophylactic total colectomy should be considered at age 15 or as soon as polyps are identified. Patients with FAP are also at risk to develop extracolonic malignancies such as hepatoblastoma and thyroid malignancies. Two clinical variants of FAP, Gardner syndrome and Turcot syndrome, have the same risk of CRC, but a difference spectrum of extraintestinal tumors [62].

In patients with hereditary non-polyposis colorectal cancer (HNPCC), specific surveillance of the gastrointestinal tract, the CNS, and hematopoietic system is performed from early childhood [63]. CNS tumors occur early in life; therefore, MRI of the brain is recommended from infancy on. The use of whole body MRI is discussed as the spectrum of occurring cancers in childhood is increasing [64]. Colonoscopy should be performed annually at the age of 6 years onward and upper endoscopy at the age of 8 years. Colectomy should be considered as soon as polyps with high-grade dysplasia occur.

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Part III

Final Remarks and Outlook

37 Genetic Predisposition to Late Effects: Pharmacogenomics of Cisplatin-Induced Ototoxicity

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Polymorphisms in genes can affect the efficacy of drugs in individual patients as well as their risk for adverse drug reactions. This particularly applies for life-saving drugs with narrow therapeutic ranges, which can induce irreversible disabling side effects.

Platinum compounds are among the most potent anticancer drugs. For more than 40 years, they have been successfully used for the treatment of solid tumors in children as well as adults [1, 2]. However, platinum drugs can induce irreversible ototoxicity (hearing loss and/or tinnitus) which reduces patients' quality of life and can affect their social and economic prospects [3–6].

The ototoxicity of platinum compounds is dose-dependent, and various clinical factors, including age, pre-existing hearing impairment, radiation, or ototoxic co-medication, can increase patients' sensitivity to platinum-induced ototoxicity [7, 8].

However, even if clinical risk factors for cisplatin-induced ototoxicity are considered, there still remains a considerable variability between patients with respect to their individual risk for cisplatin-induced ototoxicity [4, 9]. Following the hypothesis that genetic variants might influence patients' susceptibility to cisplatin-induced ototoxicity, a number of studies comparing the distribution of variant genes among patients with and without ototoxicity after cisplatin treatment have been conducted (Table 37.1) [9, 10].

The first studies used gene-specific, candidate-driven approaches and selected variants (usually single nucleotide polymorphisms (SNPs) or deletions) of single genes which were considered to protect cells against damage by cisplatin or to be important for normal hearing. In contrast to these candidate gene approaches, high-throughput approaches screened simultaneously multiple variants in hundreds of genes irrespective of their possible involvement in cisplatin-induced ototoxicity. For high-throughput screens, customized SNP arrays of, e.g., metabolizing enzymes had been used as well as arrays for genome-wide association studies (GWAS). GWAS screen genetic variants distributed over the entire

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Table 37.1 Overview of studies with candidate genes that are significantly associated with hearing impairment in childhood cancer survivors [10]

Authors	*N* (cases/controls)	Ancestry	Tumor type	Treatment	Replication (*N*)	Definition endpoint	Gene	Variant	Effect allele/genotype	OR (*p*-value)
Peters et al. [11]	20/19	CAU	ST, BT	CIS	No	Muenster	GSTM3	B	A	0.11 (0.02)
Knoll et al. [12]	11	CAU	ST, BT	CIS, CRT (64%)	No	Clinically apparent HL	GJB2	rs80338939	G	NA (0.016)
Riedemann et al. [13]	25/25	CAU	ST, BT	CIS	No	Muenster	LRP2	rs2075252	A	3.45 (0.016)
Ross et al. [14]	33/20	CAU	ST, BT	CIS, CRT (17%), VM (4%), VCR (4%)	Yes (109)	CTCAE	TPMT COMT	rs12201199 rs9332377	A A	16.89 (0.0318) 5.52 (0.0261)[a]
Choeyprasert et al. [15]	54/14	AS	ST, BT	CIS, CRT (29%), AG (52%)	No	Brock	LRP2 GSTT1	rs2228171 Null	C non-null	4.33 (0.034) 10.05 (0.023)
Rednam et al. [16]	86	CAU, HISP, other	BT	CIS, CRT	No	Hearing aid use	GSTP1	rs1695	AG/GG vs AA	4.0 (0.03)
Pussegoda et al. [17]	1 06/56	CAU, other	ST, BT	CIS, CRT (19%), TM (29%), VM (22%), VCR (40%), GM (17%)	Yes (155)	CTCAE	TPMT TPMT TPMT ABCC3 COMT COMT	rs12201199 rs1142345 rs1800460 rs1051640 rs4646316 rs9332377	A G A G G A	8.9 (4.0E−5) 6.1 (0.0039) 6.6 (0.00073) 2.0 (0.0033) 1.8 (0.0068) 1.9 (0.043)[b]
Brown et al. [18]	26/45	CAU, HISP	BT	CIS, CRT, AF (39%)	No	Hearing aid use	SOD2	rs1880	C	3.0 (0.040)[c]
Vos et al. [19]	77/79	CAU	ST	CIS	No	Chang	ACYP2	rs2872328	A	12.0 (0.027)
Thiesen et al. [20]	116	CAU, AFR, AS	ST, BT	CIS, CARB, CRT (34%), VCR (54%)	No	CTCAE Chang	ACYP2	rs1872328	GG	NA (0.027)[d]

Abbreviations: *AF* amifostine, *AFR* African, *AG* aminoglycosides, *AS* Asian, *BT* brain tumors, *CAU* Caucasian, *CIS* cisplatin, *CARB* carboplatin, *CRT* cranial radiotherapy, *GM* gentamycin, *HISP* Hispanic, *HL* hearing loss, *NA* not available, *OR* odds ratio, *ST* solid tumors, *TM* tobramycin, *VCR* vincristine, *VM* vancomycin

[a]Adjusted for gender, age

[b]Adjusted for age, VCR, germ cell tumor, CRT

[c]Adjusted for age at diagnosis, gender, ethnic group, cumulative dose CIS, CRT ≥34 Gy

[d]Adjusted for age at diagnosis, gender, CRT, cumulative dose CIS, exposure to CARB and VCR

genome and can identify variants associated with cisplatin-induced ototoxicity, but do not provide information about causality [21].

Based on the assumption that mechanisms which render tumor cells resistant to cisplatin can also prevent normal tissues from cisplatin toxicity, variants of genes were examined, which encode for proteins responsible for the cisplatin resistance of tumor cells. These included glutathione-*S*-transferases (GST) which inactivate cisplatin by attaching glutathione to cisplatin; antioxidative defense mechanisms, such as superoxide dismutase 2 (SOD2); DNA repair enzymes (ERCC1, ERCC2, ERCC4, ERCC5, XPA, XPC, XPD, and XRCC1); and regulators of DNA repair (p53, eIF3a).

Protection from cisplatin-induced ototoxicity was reported for the GSTM3 SNP rs1799735 in a cohort of 39 children with cancer, for GSTM1 deletion and the GSTP1 SNP rs1695 in a cohort of 173 adults with testicular cancer and in a cohort of 86 survivors of CNS tumors, and for GSTT1 deletion among 68 children and 55 adults with solid tumors [11, 15, 16, 22, 23]. Although they observed significant associations for distinct GST variants, these studies failed in part to replicate the significant results of the other studies. In addition, Khrunin et al. found no significant associations for any of these GST variants among 104 patients with ovarian cancer [24].

Brown et al. were able to link the SNP rs4880 of the superoxide dismutase 2 (SOD2) gene with a significantly increased risk of cisplatin-induced ototoxicity in a group of 71 medulloblastoma patients [18]. Significant associations between defective DNA repair and an increased risk of cisplatin-induced ototoxicity were only observed for the XPC SNP rs228001 among 32 osteosarcoma patients and for the transcription factor eIF3a SNP rs77382849 among 282 patients with non-small cell lung cancer [25, 26].

Variants of genes involved in cisplatin transportation might also affect cisplatin toxicity. Variants of the solute carrier family 22 member 2 (SLC22A2), the solute carrier family 16 member 5 (SLC16A5), the solute carrier family 47 member 1 (SLC47A1 (MATE1)), the copper transporter 1 (CTR1), and the low-density lipoprotein receptor-related protein 2 (LRP2) have been evaluated [13, 15, 27–30]. The SNP rs10981694 of the CTR1 gene was significantly associated with an increased risk of cisplatin-induced ototoxicity among 204 patients with non-small cell lung cancer [31]. The SLC22A2 SNP rs316019 gene protected patients from cisplatin-induced ototoxicity in cohorts of 64 children and 66 adults with cancer [32]. Two studies evaluated the variant SNPs rs2075252 and rs2228171 of the LRP2 as pharmacogenomic markers for cisplatin-induced ototoxicity [13, 15]. Riedemann and colleagues analyzed 39 children with cancer and could only associate the SNP rs2075252 with an increased risk for cisplatin-induced ototoxicity, while Choeyprasert and colleagues only found a higher incidence of the SNP rs2228171 among children with ototoxicity. Using custom-designed arrays, the Canadian Pharmacogenomics Network for Drug Safety showed protection from cisplatin-induced ototoxicity for carriers of the SNP rs4788863 of the monocarboxylate transporter 5 (solute carrier family 16 member 5, SLC16A5) in a cohort of 188 patients with germ cell testicular cancer [28]. Among 206 patients with head and neck squamous cell carcinoma, the SNP rs2289669 of the SLC47A1 (MATE1) gene was also associated with protection from cisplatin ototoxicity [30].

Variants of genes involved in normal hearing and variants in the mitochondrial genome have also been evaluated. The SNPs rs77124181 and rs2291767 of the otospiralin (OTOS) gene were significantly more frequent among patients without ototoxicity after cisplatin treatment [33]. In a cohort of 39 children with cancer, Peters et al. linked the mitochondrial J haplotype with an increased risk of cisplatin-induced ototoxicity [34]. Graterol and colleagues, however, found no associations between mitochondrial haplogroups and cisplatin-induced hearing loss in a group of 72 adult cancer patients [35].

Such candidate gene approaches have been largely replaced in recent years by high-throughput screening techniques (GWAS, customized SNP genotyping assays, e.g., for key drug metabolism genes), following the clear observation that a large number of genes could be affected by the multimodal nature of most cancer therapy protocols.

Ross et al. were the first to apply a high-throughput screening approach to identify variants that were associated with cisplatin-induced ototoxicity [14]. They used a customized SNP genotyping assay that was designed to capture 1949 SNPs of 220 key drug metabolism genes and were the first to employ exploratory and confirmatory cohorts in their pharmacogenomic study. They found a significant association between the SNP rs12201199 in the thiopurine methyltransferase (TPMT) and the SNP rs9332377 in the catechol-o-methyltransferase (COMT) gene with an increased risk of cisplatin-induced ototoxicity. Detecting one or both of these SNPs identified 92.2% of patients who experienced ototoxicity from cisplatin treatment. However, as already observed regarding the replicability of the candidate gene studies, two studies confirmed the results, but three others did not [17, 23, 32, 36–38]. Xu et al. conducted a genome-wide association study (GWAS) on 238 children with medulloblastomas and identified an increased incidence of the rs1872328 in the acylphosphatase-2 (ACYP2) gene among patients who experienced cisplatin-induced ototoxicity [39]. This association was recently confirmed in a group of 229 testicular cancer patients treated with cisplatin [40]. However, in this cohort the previously reported association of the SNP 62283056 in the wolframin ER transmembrane glycoprotein (WFS1), a mendelian deafness gene, with an increased risk for cisplatin-induced ototoxicity could not be replicated. The association between the rs1872328 in ACYP2 gene and cisplatin-induced ototoxicity was also confirmed by Vos et al. [19] in a group of 156 osteosarcoma patients, by Thiesen et al. [20] in a cohort of 149 children with various tumors, and by Driessen et al. [41], who prospectively genotyped 92 patients with locally advanced head and neck cancer.

Recently various studies returned from genome-wide analysis to the candidate gene approach and evaluated panels of SNPs, which had been associated with patients' individual risk for cisplatin ototoxicity [41–44].

Apart from the ACYP2 SNP rs1872328, Driesen et al. could not associate known genetic variants of COMT, TPMT, and WFS1 with an increased risk of cisplatin ototoxicity in 92 patients with locally advanced head and neck cancer. In addition, Thiesen et al. also observed no associations for known TPMT and COMT SNPs in their cohort of 149 children.

A prospective observational study in 206 patients with head and neck squamous cell carcinoma evaluated relationships between clinical and pharmacogenetic (TPMT, COMT, ACYP2, CTR1, OCT2, MATE1, ABCC2, ABCC3, and ABCG2) covariates and ≥grade 2 ototoxicity (CTCAE v4.02) after cisplatin treatment. Patients carrying the COMT SNP rs9332377 had a higher risk for cisplatin ototoxicity, whereas the MATE1 (SLC47A1) SNP rs2289669 protected from cisplatin-induced ototoxicity [30].

Olgun et al. [44] genotyped 72 children with different tumor types for the SNPs rs11615 (ERCC1), rs1138272, rs1695 (both GSTP1), rs2075252 (LRP2), rs12201199 (TPMT), and rs9332377 (COMT). Brock and Muenster classifications were used and identified ototoxicity in 24 patients (Brock classification) and 30 patients (Muenster classification). With each grading system, the authors could associate the GSTP1 SNP rs1695 with an increased risk for cisplatin-induced ototoxicity in a univariate analysis. Multivariate analysis, however, only confirmed age and co-treatment with aminoglycosides as risk factors, but not the SNP rs1695 [44]. In another study, 106 children were evaluated retrospectively for the SNPs rs1799735 (GSTM3), rs1695 (GSTP1), rs4880 (SOD2), rs2228001 (XPC), rs1799793 (XPD), and rs4788863 (SLC16A5) and the deletion of GSTM1 and GSTT1. The children suffered from different solid tumors and received either cisplatin or carboplatin. Thirty-three children developed ototoxicity (Brock grade ≥2). In this cohort the risk for ototoxicity was significantly increased by a deletion of GSTT1, the GSTP1 SNP rs1695, and GSTM3 SNP rs1799793 [43].

Clemens et al. [42] compared the distribution of 10 candidate SNPs (ACYP2 (rs1872328), LRP2 (rs2075252), NFE2L2 (rs6721961), OTOS (rs2291767), TPMT (rs12201199), SOD2 (rs4880), SLC22A2 (rs316019), GSTP1 (rs1695), ABCC3 (rs1051640), SLC16A5 (rs4788863)) among 429 pediatric patients with and without ototoxicity after cisplatin treatment. They found

no association to cisplatin-induced ototoxicity for any of these SNPs. Like Thiesen et al. [20], they also pooled their data with previously published data and performed additional meta-analysis. Their meta-analysis associated the ACYP2 SNP rs1872328 and SLC22A2 SNP rs316019 with cisplatin-induced ototoxicity, while Thiesen et al. [20] found a significant association for the COMT SNP rs4646316 in addition to the ACYP2 SNP rs1872328 with their meta-analysis.

Tserga et al. [45] only performed meta-analysis. They pooled data from 30 studies that have been repeated twice or more and calculated meta-analytic estimates of risk. They identified an increased risk of ototoxicity for the SNP rs1872328 in the ACYP2 gene and the SNP rs4668123 in the LRP2 gene. Despite the evident heterogeneity across the evaluated studies, the authors concluded that their meta-analytic results are consistent with the view of a genetic predisposition to platinum-based chemotherapy-mediated ototoxicity.

Designing a genetic susceptibility study for tinnitus in childhood cancer survivors is challenging due to the variation in phenotype [46]. Recently, El Charif et al. [47] reported the results of their clinical and genome-wide analysis of cisplatin-induced tinnitus among testicular cancer survivors (TCS). Their study was carefully designed and based on a cohort with detailed treatment data, homogeneous cisplatin-based chemotherapy, long-term follow-up, and quantitative hearing evaluations. TCS were classified as cases if they had experienced moderate or severe tinnitus in the last 4 weeks. They evaluated comorbidities and SNP dosages in GWAS and addressed covariates like age, noise exposure, cisplatin dose, and genetic principal components. In addition, they completed their studies by pathway over-representation tests and functional studies in mouse auditory cells. In their cohort cisplatin-induced tinnitus was significantly associated with age at diagnosis and cumulative cisplatin dose. GWAS and pathway analysis identified the SNP rs7606353 near the OTOS gene as a risk factor for cisplatin-induced tinnitus, a significant enrichment of OTOS expression quantitative trait loci, and protection of mouse auditory cells from cisplatin toxicity through overexpression of OTOS. These observations revealed new insights into the pathology of cisplatin-induced tinnitus and may open up prospects for selective otoprotection strategies, because OTOS expression is important for hearing, but not for the antitumor efficacy of cisplatin.

Gilles et al. [48] performed a pilot GWAS among 167 Belgian tinnitus cases and 749 non-tinnitus controls. The phenotype of tinnitus was scored by using the question "nowadays, do you ever hear noises in your head or ears which usually last longer than 5 min." The sample size of this study was small, and none of the SNPs were genome-wide significant, but the researchers identified several metabolic pathways by gene-set enrichment analysis that were significantly enriched with SNPs with a low p-value in the GWAS. These metabolic pathways were involved in oxidative stress, endoplasmic reticulum stress, and serotonin reception-mediated signaling. This might be important with regard to tinnitus development in childhood cancer survivors, since cisplatin induces oxidative and endoplasmic reticulum stress leading to outer hair cell death in the cochlea [49, 50].

Taken altogether, the pharmacogenetic studies performed so far strongly support the hypotheses that genetic variants determine patients' individual susceptibility to cisplatin-induced ototoxicity. However, the overall reproducibility found by the replication studies performed so far was poor and many other studies still await independent replication. The reasons for replication failures are manifold. Firstly, various audiological grading systems which differed in sensitivity and specificity should not have been used [51, 52]. Using different grading results can significantly affect the classification given to patients both with and without ototoxicity. This issue is actually addressed in the International Guideline Harmonization Group ototoxicity group [53]. Secondly, the ethnic composition of different patient groups and the distribution of clinical risk factors among them must also be considered. Thirdly, the administration of cranial irradiation and the use of other ototoxic drugs, such as aminoglycosides, loop diuretics, and vincristine, require particular attention [44, 54]. Finally, the

pharmacology of cisplatin is complex, and there are numerous cross-linked pathways that play important roles in mediating cisplatin effects. Various genetic variants might therefore contribute to the risk of cisplatin-induced ototoxicity faced by individual patients.

The composition and sequence of chemotherapy varies for different tumor types. Different detoxification pathways might be used to varying extents depending upon the combination of different anticancer drugs and their sequence of administration. Thus, different genetic variants may be more or less important in different treatment protocols. In view of the fact that there are so many confounders, further pharmacogenomic studies addressing cisplatin-induced ototoxicity will need well-characterized and sufficiently large cohorts of patients who, ideally, receive the same treatment, are balanced for ethnicity and clinical risk factors, and are phenotyped according to harmonized audiological grading systems. Validation studies in comparable patient populations will be required, as well as studies in different populations. These issues are actually considered by large national and international initiatives, for example, the European network PanCareLIFE, the Children's Oncology Group in the USA, and the Canadian Pharmacogenomics Network for Drug Safety, the Childhood Cancer Survivor Study (CCSS), and the St. Jude Lifetime Cohort Study (SJLIFE) [4, 55, 56] (http://www.pancarelife.eu; http://cpnds.ubc.ca). Such a systematic and thorough approach would:

- Provide further insight into the pharmacology of cisplatin.
- Elucidate the manner in which the overall treatment of various cancers impacts upon hearing in general.
- Help to define patients' individual risks within a specific therapy protocol.

Alternative treatments or otoprotective measures could be considered for patients at high risk of cisplatin-induced ototoxicity on the basis of valid and accurate risk assessments. Additionally, the knowledge of individual risk factors could be used to make recommendations for patients' individual aftercare as well as implementation of audiological surveillance in newly developed treatment protocols. This will finally lead to a reduction in the incidence of this lifelong disabling side effect of cisplatin.

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38 Physical Activity, Exercise and Sports in Young Cancer Patients

Miriam Götte, Sabine Kesting, and Joachim Boos

38.1 From Overprotection to Exercise Promotion: Background and Rationale

The positioning of physical activity and exercise for children, adolescents and adults with cancer has changed over the recent decades. Bed rest and overprotection dominated hospital wards for a long time, but increasing evidence from exercise studies with adult cancer patients revealed the importance of physical activity to minimize or even prevent disease- or therapy-related consequences. Interventional prospective studies provide evidence for the efficacy of exercise on patient-related outcomes like fatigue [1], polyneuropathy [2], bone health [3], pain [4] and an overall improvement on quality of life [5]. There is even growing evidence for the protective effects on survival after diagnosis [6]. As a consequence, the trend in the past years has shifted from an attitude of overprotection with warnings of physical activity to a growing interest of patients, oncologists and researchers in adapted exercise programs.

Scientific evidence for such beneficial effects of physical activity and exercise during and after cancer in paediatric patients with cancer is still limited. Reasons for this are difficulties in designing randomized controlled trials due to the small number of potential study participants and their heterogeneity in terms of age, tumour type and treatment concepts. Nevertheless, the importance of physical activity in childhood for motor development, social skills [7] and general health [8, 9] is undisputed, and there is no justification for denying children with a diagnosis of cancer an appropriate level of physical activity. Taking additionally into account the high burden associated with the isolation from school activities, sports clubs and leisure time activities with friends during acute cancer treatment, it seems that exercise programs that integrate social and motor aspects are particularly recommended for this group. In addition to these social aspects of *participation and normality*, the effects of exercise on disease- and therapy-associated problems and late complications are relevant aspects of *therapy and resilience*. Physical performance

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limitations in children during and after cancer treatment have been shown during the whole cancer trajectory, from diagnosis to long-term follow-up [10–14]. Three systematic reviews summarized the current evidence about the efficacy of exercise interventions during paediatric cancer treatment and found beneficial effects on body composition, flexibility, cardiorespiratory fitness, muscle strength and health-related quality of life [15–17]. In addition, many of the late complications of childhood cancer therapy described above, such as cardiovascular, musculoskeletal and respiratory impairments, metabolic syndrome and cancer-related fatigue, have generally improved with exercise therapy. Consequently, these same effects can also be clearly assumed in children with cancer. Feasibility and safety of exercise interventions in children and adolescents during cancer treatment have been shown in several studies [18, 19].

In conclusion, children with cancer need exercise programs adapted to their possibilities, wishes and preferences. General concerns and therapy-related sports restrictions cannot be justified. Integrating physical activity programs into standard care will not only reduce unacceptable movement restrictions and improve physical and psychosocial wellbeing but will also create a sense of normality in the children's lives [20].

Key Message

Physical activity and exercise interventions in children and adolescents during cancer treatment are feasible and safe during all phases of therapy, and beneficial effects have been shown. There are no general restrictions regarding different types of sport, and the overall attitude towards exercise and sports should be positive.

38.2 Examples

During cancer treatment, children and adolescents show considerably reduced levels of physical activity [21, 22]. Many former patients have serious problems to reintegrate into physical education at school after treatment [23] and to continue pre-disease daily physical activity pattern and sports. Rehabilitation, often referred to as 'prehabilitation', begins immediately after diagnosis, and exercise promotion is indicated at all stages of cancer treatment, taking into account the acute problems, wishes and needs. The following figure illustrates the aims during paediatric cancer trajectory (Fig. 38.1).

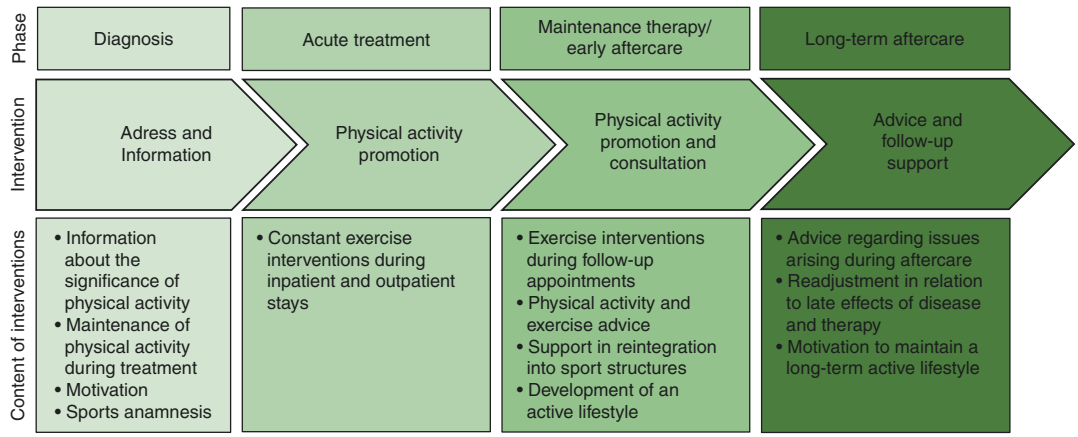

Fig. 38.1 Continuity of intervention strategies during different phases of therapy. (Modified version of Kesting et al. 2016)

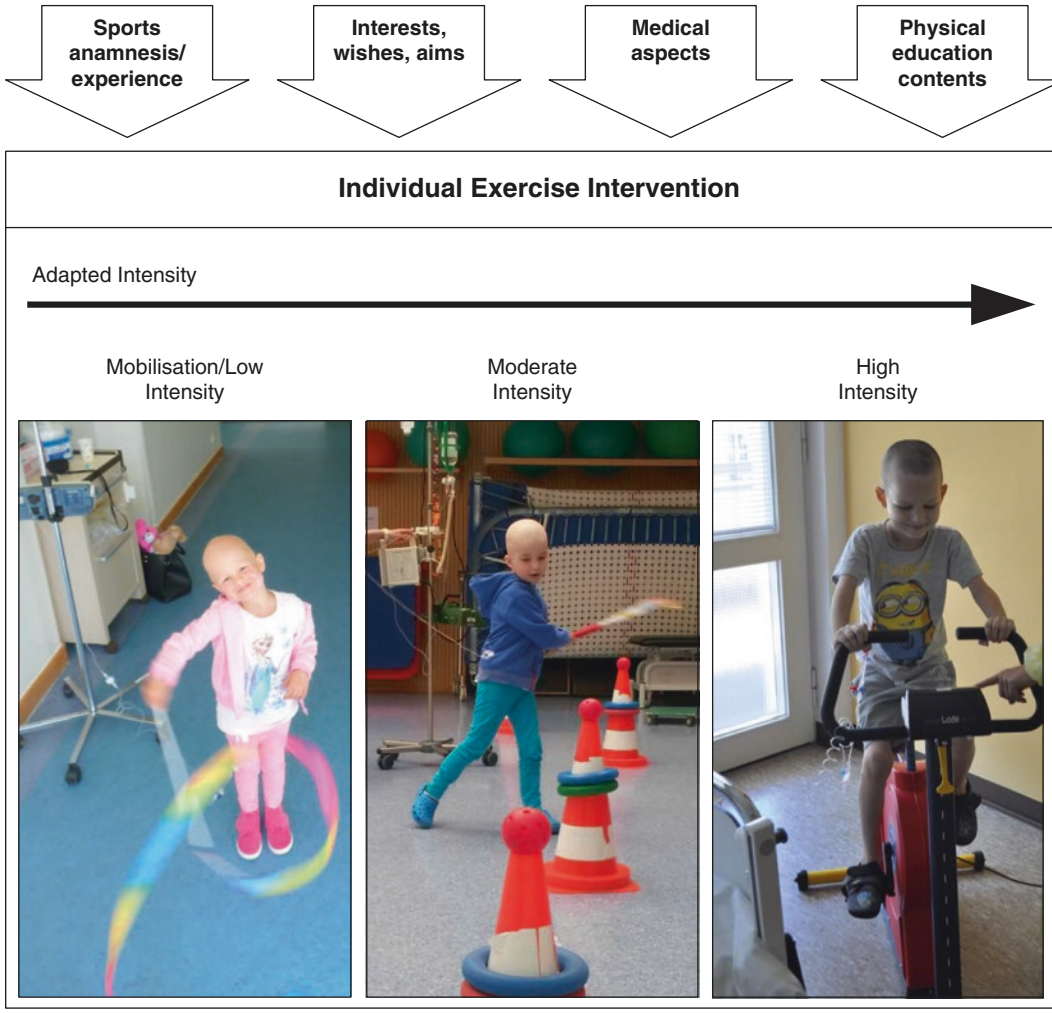

Fig. 38.2 Examples for different exercise interventions

38.2.1 During Acute Cancer Treatment

Every exercise intervention during acute cancer treatment needs to be individualized and adapted to the child's current medical, physical and psychological condition. General aspects to be considered are sports history (pre-cancer experience) and personal aims or interests. For school-aged children, the content of physical education lessons should be implemented according to age and grade. Based on these influencing factors, interventions may vary in terms of duration, intensity and content (see Fig. 38.2). Typical contents are endurance, strength and coordination interventions with small devices and motivational equipment. Depending on the hospital's facilities, other forms of exercise such as indoor bouldering and vibration training are also feasible under supervision and can increase the child's motivation and interest. Innovative programs have been developed in recent years, e.g. holistic parent interventions including exercises and educational lessons or home-based exercise interventions using individualized training plans and physical activity trackers with defined aims for steps and active minutes per day [24].

38.2.2 During Aftercare

Despite reintegration into physical education at school and sports clubs, participation in specific offers for cancer survivors has been shown highly favoured. Most traditionally, the in-patient rehabilitation in one of the five rehabilitation centres for paediatric oncology has the potential to increase fitness, reduce therapy-accompanied late effects and strengthen the psychosocial capacities of the children, adolescents and their families after cessation of treatment. Other promising approaches are personal training programs, sports groups and try-out days/weekends/weeks for specific sports. In this phase of treatment, the return to normality seems as important as regain the maybe lost connection to the peer group.

Good experiences in the ActiveOncoKids Group (see below) have been made in skiing, windsurfing, stand-up paddling, kayaking, rowing, climbing and scuba diving. Especially skiing has been extended to an adaptive sports enabling persons with long-term impairments, e.g. after sarcomas or with neurological or musculoskeletal impairments, to ski in sitting positions or with various assistive equipment for one-leg or upright skiing. Most of these sports are individual and non-competitive sports. Children, adolescents and young adults benefit a lot from experiencing their own abilities and strengths and their growing achievements without an often discouraging competition with healthy peers in most team sports. Once motivated for a specific type of sport, it is likely that the young people trust themselves to try other sports as well until maybe finding their lifetime sports (Fig. 38.3).

38.2.3 Reintegration into Physical Activity and Sports Clubs

After cessation of treatment, reintegration into existing sports structures should be supported. Participation in physical education at school, engagement in sports activities in clubs or leisure time activities can help to develop and maintain a long-term active lifestyle in order to reduce disease- and treatment-related late effects associated with physical inactivity. Physical education at school sometimes seems to be a major obstacle, both for the patients themselves due to uncertainty and lack of knowledge and for teachers who are confronted with such situations for the first time and probably once in their life. Especially, children who have undergone surgery and have resulting handicaps (e.g. after treatment of brain or bone tumours) need support and encouragement to participate and to claim their right to exercise. This support includes comprehensive involvement of parents and peers who need detailed information on the risk-benefit ratio to overcome fears.

While physical activity and sports promotion during treatment should be carefully supervised and performed under professional guidance, sports activities during childhood cancer follow-up should help survivors to exercise independently—if possible. Due to lifelong impairments, some survivors may benefit from special offers that take into account individual needs (e.g. adaptive skiing, Fig. 38.3). Sometimes such specific and individually tailored offers are necessary as first cautious steps towards a self-determined and independent sports life.

Key Message

Individual circumstances require an individual decision about the intensity and type of sports activity. Non-competitive sports often allow positive individual experiences, and expected barriers can be overcome. Integration into peer groups, on the other hand, stimulates the social component of movement.

38.3 Network ActiveOncoKids

During the last years, novel initiatives regarding physical activity and exercise in paediatric oncology developed in selected locations in Germany. Some institutions and hospitals (Status March 2020: 16, excluding rehabilitation clinics) imple-

Fig. 38.3 Feasible sports during aftercare: rowing as a team sport, windsurfing introduction after tumour surgery with endoprosthetic device and skiing with orthopaedic restrictions in a sitting position

mented exercise promotion programs and supervised training interventions during acute cancer therapy and maintenance treatment and in the phase of aftercare (see Sect. 38.2). The people behind these initiatives recognized the benefits of collaboration and exchange of experience in this very specific area of sports science and paediatric medicine.

Members of the nationwide and interdisciplinary Network ActiveOncoKids are mainly exercise physiologists, paediatricians and physiotherapists, but all professionals in the field of paediatric oncology interested in the subject of physical activity and exercise are invited to participate.

As most sports structures represent local initiatives and depend on regional charity funding, the Network ActiveOncoKids first of all intends to catalyse processes and exchange the broad spectrum of specific experiences. The main objective of the Network ActiveOncoKids is the *enhancement of exercise promotion* in paediatric patients with cancer in Germany by *enabling equal access* to physical activity programs for every child and adolescent with cancer in Germany regardless of their residence.

This aim should be achieved by (1) individual consultation and support of children during and after treatment regarding physical activity and exercise, (2) professional administration and continuous expansion of the network, (3) identifying steps to support the sustainability of the network and existing programs and to integrate exercise promotion into standard care and (4) scientific evaluation of exercise interventions in multicentre studies to develop established concepts of training control and provide specific information on exercise-related risks.

The Network ActiveOncoKids and regular network workshops are intended to serve as a platform to, e.g. expand existing care and sports opportunities, exchange experience between the different locations, provide expert-knowledge and skills on special topics, show successful examples of integration and spread new information about scientific evidence, funding opportunities, progress in implementation of programs as well as setbacks and lessons learned. Growing network structures in Germany, other German-speaking countries abroad and international contacts and collaborations contribute to the realization of the network's main objective. But much remains to be done.

The network structures and workflows in Germany are one example of how exercise promotion, guidance and scientific collaborations can be improved in a country with a large number ($n > 60$) of hospitals for paediatric oncology. Other local conditions may require different structures and approaches. However, the dissemination of expertise on physical activity in general and on specific topics such as exercising with late complications or surfing with prosthesis, in addition to the publication of scientific topics, is important to help children, adolescents and adults to adopt a long-term active lifestyle after cancer treatment.

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39 Developments and Risk-Adapted Strategies in Modern Pediatric Radiotherapy

Beate Timmermann

39.1 Introduction

Radiotherapy in childhood is a substantial part of the current multimodal therapy of cancer. Despite establishing intensive chemotherapy regimens, radiotherapy is difficult to defer or omit in many patients even when being very young. Moreover, as a local therapy, radiotherapy offers a significant chance when the limits of surgical approaches have been exhausted. Therefore, limiting the treatment burden after radiotherapy is an important aim of research and development. The common principle of modern highly conformal radiotherapy is to improve the ratio between dose to the tumor and dose to non-target tissue in order to reach maximal tumor control while reducing the risk of adverse side effects. Tissue remodeling after irradiation and functional consequences of radiation injury differ significantly between adults and children. Due to their growing, immature tissue, children are particularly vulnerable to radiation-induced sequelae. Additionally, in children induction of subsequent malignant neoplasms is another particular risk after radiotherapy [1]. Critical areas like the central nervous system as well as the head and neck region are typical sites for radiotherapy in children. Corresponding serious late adverse events may include cognitive and endocrine dysfunction impairing the quality of life of affected patients [2, 3]. Given the fact of having significantly improved survival rates of childhood cancer patients up to 80%, quality of life of adult survivors of childhood cancer becomes an essential focus of current curative approaches [4].

Over the last decades, quality and feasibility of radiotherapy benefited from major advances in imaging and irradiation techniques. As a result, dose planning and delivery was significantly better confined resulting in improved sparing of adjacent organs at risk. In parallel, indication for radiotherapy and irradiation concepts fundamentally changed over time. Moreover, modern radiotherapy concepts considering risk-adapted strategies were embedded into the treatment protocols. All these developments contributed to a lower treatment burden after radiotherapy in childhood when compared to historical experiences. Even at a very young age, better protection of healthy tissues and better prediction of potential side effects were achieved.

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39.2 Principles of Reduction or Prevention of Late Effects

39.2.1 Modern Techniques of Radiotherapy

External beam radiotherapy is the most common technique of radiotherapy. It is predominantly applied with high-energy photons. The development of advanced imaging techniques with computer tomography (CT) beside X-rays played an essential role in the evolution of modern radiotherapy technology. Collimators or apertures shaped the beam individually to the tumor volume. Additionally, using multiple beam directions, the target was covered with the required dose. Due to rapid technological advances, X-ray-based two-dimensional conventional radiotherapy techniques were substituted by three-dimensional (3D) conformal radiotherapy in the 1980s [5]. Today, CT and/or even magnetic resonance imaging (MRI) or positron emission tomography (PET)-CT taken for planning or verification of treatment positioning are the basis for three-dimensional conformal treatment planning (Fig. 39.1). This fundamental change to image-guided radiotherapy (IGRT) allows increasingly precise target definition and reduction of safety margins [6]. IGRT therefore results in generally smaller treatment volumes sparing better normal tissues from dose burden when compared to historical techniques having poor imaging information. Intensity-modulated radiotherapy (IMRT) was a further milestone of highly conformal radiotherapy techniques in the 1990s [7]. By dividing each of multiple beams into smaller portions with varying intensities, further confinement of dose distribution could be achieved. Consequently, the dose to adjacent normal tissue was even more reduced resulting in a decreased risk for side effects. Particularly in complexly shaped tumors, IMRT enhanced target volume conformity. 3D conformal radiotherapy and IMRT are the current treatment standards in most centers. However, the volume of normal tissue receiving low-dose irradiation increases with the number of beam directions as each beam goes along with an entrance and an exit dose when using photon beams.

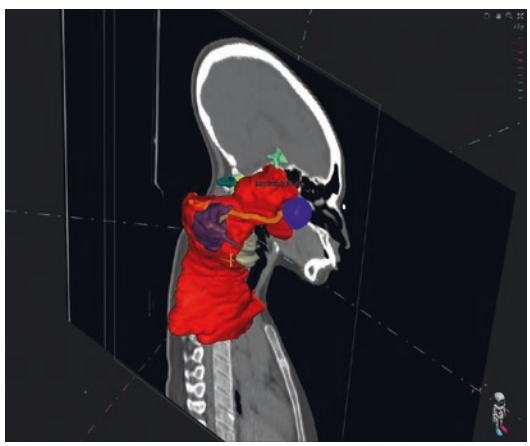

Fig. 39.1 Three-dimensional visualization of target volumes and organs at risk within a modern radiotherapy dose plan. *Legend*: Colored areas represent target volumes (lilac and red area) or organs at risk (e.g., blue area; eye). Image from the radiotherapy planning system RayStation® (Version 7, RaySearch Laboratories, Stockholm, Sweden)

During today's radiotherapy treatment sessions, innovative on-board and in-room imaging with CT, MRI, X-ray systems, laser alignment, or surface scanner can ensure accurate and reproducible positioning of the patient (Fig. 39.2). In moving tumors, also four-dimensional (4D) treatment planning using multiple breathing phases can be used to ensure robustness. Gating systems trigger beam pauses in order to align irradiation with defined phases within the breathing cycle. Additionally, adaptive radiotherapy concepts consider changes in patient's anatomy or tumors size during the treatment course. Modern planning systems are able to digest all information overlaying planning CT with all additional imaging modalities (Fig. 39.3). Any dose plan can be calculated, perturbated, and re-calculated precisely and in a robust fashion. Fast processing and calculation speed allows multiple iterations and optimizations. All these approaches help significantly to ensure highly accurate dose delivery, targeting only tumor volume while sparing sensitive structures. Sophisticated mathematical methods can even be implemented into the planning process to better predict adverse events. The normal tissue complication probability (NTCP) is a mathematical model calculating risk for

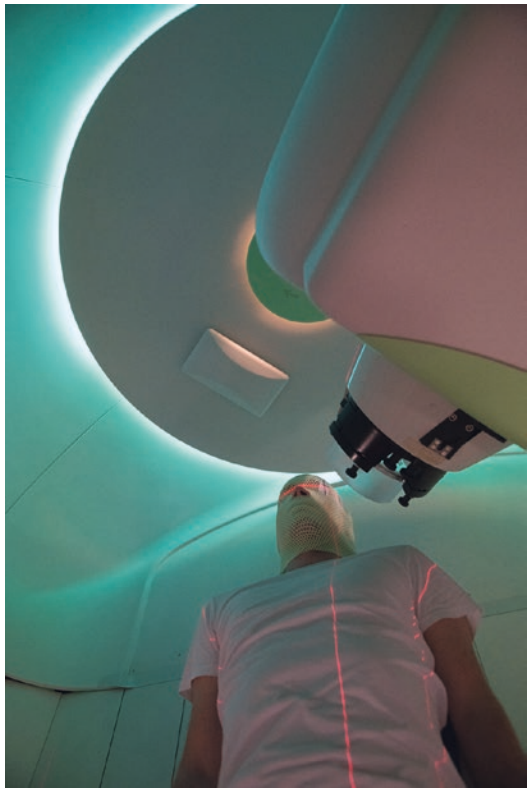

Fig. 39.2 Positioning of a patient aligned by face mask and laser system in the treatment room

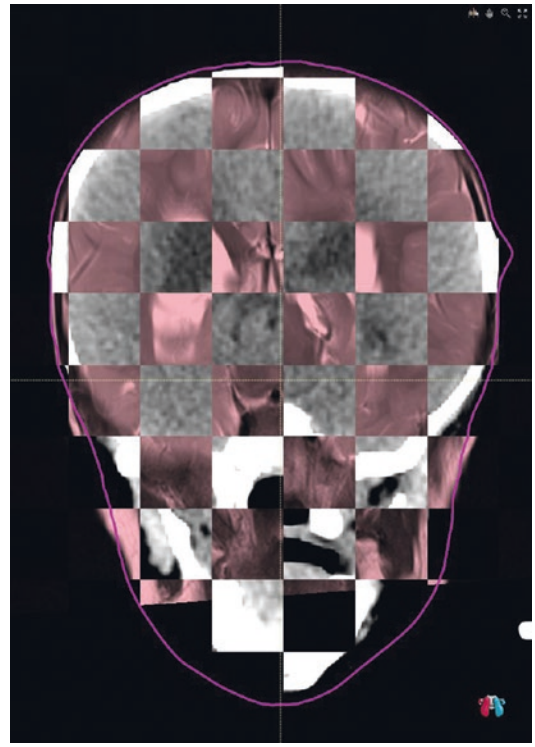

Fig. 39.3 Display of image fusion for treatment planning in a child with a brain tumor ("checker"). *Legend*: White boxes; CT scans, pink boxes; MRI, T2 scans. Image from the radiotherapy planning system RayStation® (Version 7, RaySearch Laboratories, Stockholm, Sweden)

complications depending on the dose and volume of radiation therapy. It enables the treatment team to select a personalized, optimal plan and the most appropriate radiation modality [8]. So far, NTCP models are available only for a few malignancies (e.g., head and neck cancers), but efforts are ongoing to come up with many more and also specific pediatric models.

Just like photon-based 3D radiotherapy or IMRT, proton beam therapy is another high-conformal external beam radiotherapy modality. It is understood as a promising modality when children are concerned. The particular physical characteristic of protons enables a precise and adjustable dose delivery. Thus, unintended dose deposit to healthy tissues can be reduced, limiting the risk for treatment sequelae and induction of secondary malignancies [9]. Favorable results on quality of life have been reported, so far [10]. However, as changes in tissue density within the irradiation field or motion effects can induce uncertainties, planning and delivery is particularly demanding. Therefore, reproducible positioning and imaging for planning and positioning verifications is of high importance. Also proton therapy, starting in the 1950s of the last century [11], benefited from the enormous technical developments over the last decades. Besides advanced image guidance, computing power of treatment planning systems, complex algorithms, and delivering modes progressed. To date, proton beam therapy can be delivered passively scattered, uniformly scanned, or with pencil beam scanning. At first, passive scattering was established in this field. In passive scattering, individually manufactured hardware devices (collimators and compensators) are fitted into the beam to conform the dose to the target volume. Further development lead to active scanning methods in

the 1990s [12]. Pencil beam scanning enables to deliver intensity-modulated proton beam therapy, the potentially most conformal type of proton therapy known to date [13]. Today, proton beam therapy is acknowledged as the preferred radiation modality in pediatric cancer when technically feasible and aiming for cure (Fig. 39.4). However, the capacity is still limited as only few centers can provide this demanding technique until now.

Different from external beam modalities, brachytherapy can be used to irradiate a subset of malignancies in childhood. Brachytherapy is a special form of radiotherapy providing short distance irradiation [14]. The treatment comprises the deposit of radioactive sources into or close to the tumor volume. The dose fall-off is extremely sharp. Therefore, this procedure exposes high radiation dose only to very small volumes. Consequently, required radiation dose is directly applied to the tumor while sparing surrounding healthy tissue. Whole body dose is extremely low, and the risk of late effects is decreased while focusing high doses to the tumor. Radiation sources (e.g., ^{192}Iridium or ^{125}Iodine) are positioned temporarily or permanently under image guidance or intraoperatively. Either radioactive seeds or applicators are used. Through these applicators, radioactive sources can be administered even under remote control for temporary use (afterloading procedure). Brachytherapy is applied as either low-dose, medium-dose, or high-dose treatment. In infants and young children, low-energy radionuclides and remote afterloading technology are predominantly used [15]. Tumors treated with brachytherapy have to be easily accessible presenting with rather small and well-defined volume. In pediatric cancer therapy, predominantly non-metastatic localized genitourinary tumors are treated with brachytherapy [16]. Additionally, brachytherapy can be used for focal treatment in retinoblastomas [17].

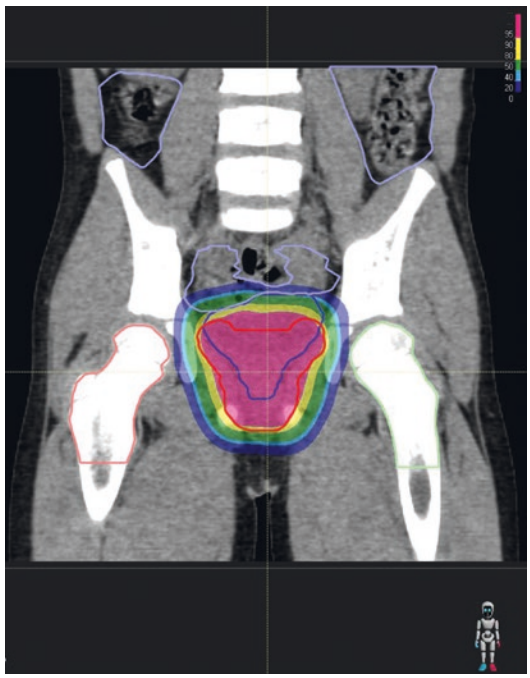

Fig. 39.4 Intensity-modulated proton dose plan for a child with a pelvic rhabdomyosarcoma with optimized hip and bowel sparing. *Legend*: Isodose bands in color wash, dark blue line; bladder, light blue line; bowel, red line; target volume. Image from the radiotherapy planning system RayStation® (Version 7, RaySearch Laboratories, Stockholm, Sweden)

39.2.2 Risk-Adapted Strategies in Radiotherapy

Late effects after radiotherapy depend on various factors such as age and developmental stage of the child at the time of radiotherapy, size of the irradiated volume, tumor location, adjacent organs at risk, and doses. Moreover, in radiotherapy planning, impact of the other components of the therapy (surgery and chemotherapy) has to be considered, maybe even interacting with radiation therapy. In addition, genetics and additional diagnoses may influence outcome.

First of all, any decision to introduce radiotherapy has to be justified by a clear need. Typically, today any application of radiotherapy is defined within interdisciplinary treatment protocols and guidelines. In Germany, the Society for Paediatric Oncology and Haematology

(GPOH) provides protocols or registries for all entities comprising treatment strategies and concepts from all disciplines [18]. Expert's networks have continuously improved strategies and techniques to prevent side effects while achieving tumor control. The indication for radiotherapy in modern concepts is highly individual and takes into account various factors. Those include histopathology, molecular and genetic characteristics, tumor stage, tumor site, extent of tumor before and after surgery, secondary diagnoses, as well as patient's age and clinical condition. In very young children and infants, radiotherapy is often avoided or deferred to prevent radiation-induced late effects of the immature tissue, whenever possible. The postponement is often compensated by intensive chemotherapy [19]. Multimodality concepts are individually tailored to allow lowest dose and smallest volume possible while still achieving tumor control. Timing of radiotherapy can be preoperatively, postoperatively, after and/or before chemotherapy, or concomitantly. Within radiotherapy planning, critical structures will be defined within the planning process and dose constraints set according to age. The preferred uses of highly conformal radiotherapy techniques as proton beam therapy particularly ensure application tailored to the tumor volume with best compliance to dose constraints of the normal tissue. Thereby, also intensification of local therapy can be provided, whenever necessary. Fractionation regimens are another instrument to individualize irradiation concepts. Herein, advantage is taken from different dose-response relationships of the tumor and the organs at risk. Conventional fractionation is predominantly used in children, delivering 1.6–2.0 Gy per day, five times per week. However, hypofractionated schedules (increased single doses per day) can be used for precise treatments of well-defined, small volumes or in palliative scenarios. In general, altered fractionation regimens as hypofractionation or hyperfractionation (more sessions with lower fraction doses) can be applied to minimize risks or allow increased total doses.

39.3 Relevance of Interdisciplinary Trials and Registries

Risk adaptation was and will only be achieved and further developed while better understanding of risk factors and contribution of all treatment parameters on tumor outcome and toxicity. Therefore, data collections in trials or registries are of enormous importance to analyze and optimize reduction of late effects and health-related quality of life after radiotherapy. As childhood cancer is a rare disease, larger cohorts can only be achieved when homogenizing parameters and using standards in an international fashion [20]. So far, analyses of late effects were mainly carried out in retrospective cohort studies, few of them being larger (e.g., Childhood Cancer Survivor Study (CCSS) and British Childhood Cancer Survivor Study (BCCSS)) [21]. However, detailed information particular on radiation of different organs and dose levels are scarce. Standardized documentation of late sequelae after radiotherapy with specific data on radiation exposure of normal tissues was increasingly implemented in prospective registries. In Germany, a multi-center registry for the detection of late sequelae after radiotherapy in childhood and adolescence (RiSK) was initiated in 2001 [22]. Later on, in order to increase the number of cases and therefore to valorize the analyses, international collaborations were introduced (e.g., IPPARCA collaboration) [23]. In the United States, the Pediatric Proton/Photon Consortium Registry (PPCR) collects data of pediatric patients treated with radiotherapy since 2012 to investigate outcome after modern radiotherapy [24, 25]. Also large European projects are currently underway, aiming at uniform prospective data registration while considering modern radiotherapy technologies (e.g., Health Effects of Ionisation Radiation Therapy in Children of the European Particle Network (EPTN) [26], Health effects of cardiac fluoroscopy and modern radiotherapy in paediatrics (HARMONIC) [27]). Besides registries, further international research

projects are ongoing. To prevent radiation-induced late effects, a deeper understanding of normal tissue tolerance is required. The international collaboration the Pediatric Normal Tissue Effects in the Clinic (PENTEC) establishes quantitative, evidence-based guidelines of dose-volume response relationships considering type and scheduling of chemotherapy as well as surgery across age ranges [28].

In addition to the standardized collection of data, the standardized treatment of patients in international projects has an increasing role, particularly in order to improve the evidence in rare pediatric malignancies. When introducing international registries, clinical trials, and other research projects, advanced radiotherapy techniques were implemented into the multimodality treatment concepts providing uniform clinical guidelines but also ensuring the basis for future analysis of outcome after radiotherapy. Today, many studies are conducted on a transnational basis organized by international societies (e.g., International Society of Paediatric Oncology (SIOP)). Within these studies, reference centers representing experts in the respective field contribute with their experiences and knowledge. In each study, reference radiation oncologists offer advising for the optimal radiation concept and outline detailed recommendations concerning radiotherapy according to the respective patient and protocol. This includes description of radiotherapy procedures (e.g., dose concept, volume definition, dose-volume constraints, and documentation) to avoid interinstitutional deviations and suboptimal therapy. Since clinical data revealed that radiotherapy protocol deviations are associated with an increased risk of treatment failure and overall mortality, radiotherapy quality assurance strategies became of significantly importance [29]. Thus, several national and international initiatives have developed radiotherapy quality assurance programs [30, 31]. To support the implementation of radiotherapy quality assurance in European clinical trials, the platform QUARTET (Quality and excellence in radiotherapy and imaging for children and adolescents with cancer across Europe in clinical trials) has been established. While quality assurance has initially only been conducted retrospectively, current trails implemented elaborate prospective programs. Herein, even the irradiation dose plan can be reviewed by an independent reference radiation oncologist before starting the treatment to allow corrections if needed. In some trials with complex radiotherapy requirements, the radiation therapy facilities therefore undergo a strict multi-stage quality process even before the first patient is enrolled and can include checklists of the facility or radiation planning of a virtual patient. All these issues aim to ensure safe and correct application of the required radiation therapy while best sparing surrounding healthy tissue. In general, standards and quality of care in pediatric radiotherapy have become a major issue. International activities are ongoing to promote best care in all facets of radiation oncology for children [32].

39.4 Conclusion and Outlook

Modern radiotherapy is one of the cornerstones of the multimodality concept. However, as it carries particular risks for the pediatric cohort, any overtreatment has to be avoided. Therefore, individual risk adaptation plays a significant role in modern radiation oncology. Doses, volumes, timing, fractionation schemes, concomitant chemotherapy, modern drugs as immune modulators or radiosensitizers, as well as irradiation techniques have to be tailored to achieve highest tumor control while having minimal side effects. New radiotherapy options were triggered by the evolution of new hard- and software. Proton beam therapy is just one good example offering a particular advantage to confine dose to the target by moderate entrance and no exit dose. Therefore, it is increasingly used in childhood cancer beside other highly conformal photon techniques. Modern radiation therapy has to be part of multidisciplinary trials and registries. Its success and feasibility will depend on many factors, and it needs to be embedded in an optimal framework of diagnostic, staging, and treatment demands. International activities comprising large late

effects registries and quality assurance programs will help to further optimize radiation therapy in the future and to ensure avoidance of unnecessary treatment sequelae.

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Late Effects After Radiotherapy

40

Diana Steinmann

Radiotherapy is an important part of modern multimodal therapy approaching to treat many pediatric malignancies. The continuously growing number of survivors has led to an increasing interest in late effects after cancer therapy. Late effects may compromise organ function and well-being.

The Surveillance, Epidemiology, and End Results (SEER) Program collected data from 1975 to 2011 to update the prevalence of survivors of childhood cancers in the United States from the Childhood Cancer Survivor Study. There were an estimated 388,501 survivors of childhood cancer in the United States as of January 1, 2011, of whom 83.5% are ≥5 years after diagnosis. The prevalence of any chronic condition among ≥5-year survivors ranged from 66% (ages 5–19) to 88% (ages 40–49). Estimates for specific morbidities ranged from 12% (pain) to 35% (neurocognitive dysfunction). Generally, morbidities increased by age [1]. Survivors with an initial diagnosis of the skeleton and CNS or patients with Morbus Hodgkin showed the highest risk.

The largest examination to analyze late effects was done in the United States: the Childhood Cancer Survivor Study (CCSS) was established to characterize retrospectively the health status of 5-year survivors of childhood cancer. Although the approach of the CCSS has led to interesting analyses of many late sequelae, this approach may not be sufficient to answer open questions regarding the dose-volume-effect relations of late effects in pediatric oncology patients treated with radiation [2].

Late effects were defined as toxicities occurring later than 90 days after the beginning of treatment or are persisting after 90 days, in contrast to acute toxicities. The classification is carried out according to the RTOG/EORTC or LENT-SOMA grading [3]. Like acute toxicities, late effects are dependent on the total irradiated dose, fractionation, localization, volume or volume parts of irradiated organs, and organ doses and can be strengthened by combination with drug therapy or surgery (see Table 40.1). Additionally, the extent of the impairment is determined of patient-dependent factors like age, growth status, gender, earlier damage to organs, and the individual disposition (morbidity, intrinsic radiation, sensitivity).

In general, chronic side effects increase the younger the patient and the less developed the organ [4].

Late effects are often irreversible and, therefore, represent a limitation in radiotherapy planning. Therefore, special requirements are placed on radiotherapy to protect normal tissue and organs of risk.

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Table 40.1 Late effects, tolerance doses of the individual organs and influencing factors [5]

Organ	Minimal dose for long-term impact of therapy (Gray)	Modification	Effect
Bone	70	Chemotherapy	Necrosis
Epiphysis	10–30	Chemotherapy/ surgery	Reduction of growth
Muscle, soft tissue	15–30	Chemotherapy/ surgery	
Brain	24–30 40–70	Chemotherapy, age, volume, fractioning, localization	Neurocognitive deficit
Eye	10–15	Steroids, fractioning	Cataract
Lung	20–25	Chx = Chemotherapy, fractioning	Pneumonitis, fibrosis
Kidney	12–15	Chx = Chemotherapy	Renal failure, hypertension
Liver	25–30	Chx = Chemotherapy, fractioning	Veno-occlusive disease
Gonads		Chx = Chemotherapy, age	Delayed puberty, infertility
Female Male	12–15 6–12		
Pituitary gland	>30	Surgery	Hormone deficiency
Thyroid gland	>30	Fractioning	Hormone deficiency

The development of irradiation machines and the irradiation techniques are described in Chap. 39.

Subsequently, the known data on late effects are summarized in relation to the individual organs.

40.1 Bones, Bone Marrow, and Soft Tissues

The impairment of growth is to be returned to a damage of chondroblasts [6, 7]. Single doses of 2–20 Gy in one fraction inhibit the proliferation of chondrocytes in the growth zones of the bone [8]. Although the relative importance of radiation effects on various compartments of the growth plate is not completely understood, the growth plate includes several rapidly proliferating stem cell populations that are exquisitely sensitive to radiation. The rapidly dividing endothelial growth buds and the cells of the proliferative zone are also both highly vulnerable to the effects of radiation [9]. Therefore, the irradiation of the epiphyseal plate with 10–20 Gy leads to an inhibition of growth and with doses of more than 20 Gy to a failure of the chondrogenesis.

During childhood, the growth plate of the metaphysis contains the connecting cartilage enabling the bone to grow; at adulthood (between the ages of 18 and 25 years), the components of the growth plate stop growing altogether and completely ossify into solid bone. An irradiation in the metaphysis leads to a reduction of absorptional processes during the calcification of the bone and cartilage [9].

The diaphysis is a middle tubular part composed of compact bone which surrounds a central marrow cavity which contains red or yellow marrow. In diaphysis, primary ossification occurs. Therefore, an irradiation of the diaphysis leads to a change of the periosteal activity and results in an abnormal contouring of the bone [10, 11].

Doses of less than 10 Gy have no or very rare an influence to the growth. The extent of the growth restriction is dependent on the percentage of the epiphyseal line on the total length growth and on the age of the patient [9].

During radiotherapy it is very important to avoid the growth zones completely or to treat homogenously. A dose gradient within the epiphysis could lead to an asymmetric growth inside the bone.

In the same way, the vertebral body should be completely avoided or completely included. An asymmetric irradiation could significantly increase the incidence of scoliosis due to the different potential of growth of the paired growth zones. An irradiation of the vertebral body could shorten the total length growth due to a decrease of the seat height [9].

Radiotherapy of bones of the pelvis, the thorax, and the facial bones could lead to deformities and cosmetic and functional deficits [9].

A decrease of the volume of soft tissues results after radiotherapy with more than 20 Gy, often with a reduction of the muscle mass and of the subcutaneous tissue. Stronger fibrosis leads to motoric deficits in the irradiated area and of joints in the near. See Fig. 40.1.

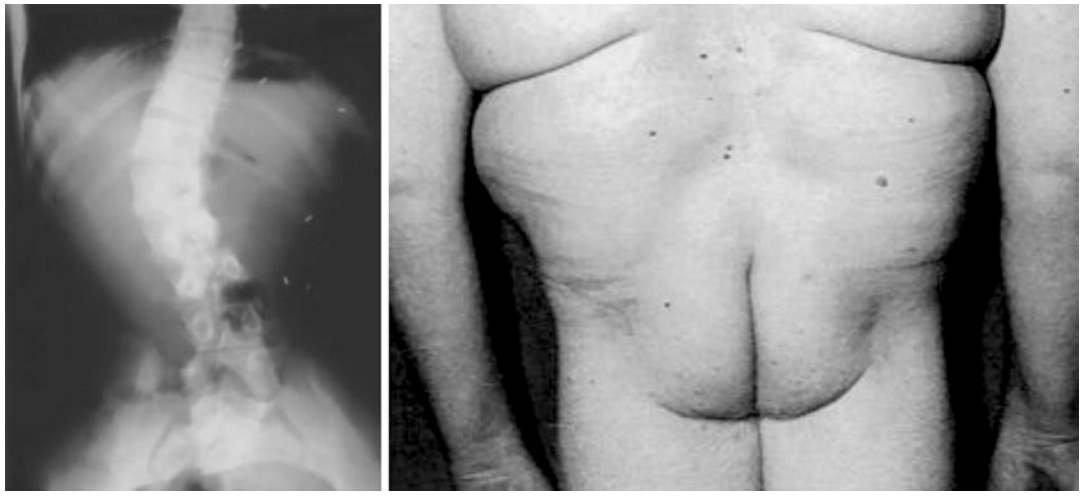

Fig. 40.1 Scoliosis in a 17-year-old patient who underwent resection of and radiation therapy for a left adrenal neuroblastoma in infancy. Radiograph depicts scoliosis, as well as the surgical clips from the previous resection

The bone marrow is radiosensitive, and already low doses could impair the hematopoiesis. Doses up to 40 Gy enable a repopulation of bone marrow cells. If a repopulation occurs, depends of the irradiated volume. If less than a quarter of bone marrow was irradiated, the non-treated part of the bone marrow compensate the hematopoiesis, and the treated part remains inactive. If more than 50% of the hematopoiesis is affected, it spreads to so far unused parts of the bone. After 2–5 years, a restitution of the hematopoiesis occurs also in prior irradiated bones [12].

40.2 Endocrine System

40.2.1 Hypothalamus and Pituitary Gland

The secretion of growth hormone depends on the dose of radiotherapy in the area of the hypothalamus and hypophysis. The threshold dose for a damage constitutes of 18 Gy. The higher the dose, the earlier an impairment of the synthesis of the growth hormone could be analyzed [13, 14]. The lack of growth hormone can substitute efficiently with synthetic analoga [13, 15]. Doses with more than 40 Gy to the hypothalamus and hypophysis lead to insufficient hormone flow of ACTH, TRH, gonadotropin, and prolactin.

A report from the St. Jude Lifetime Cohort Study refers to an anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy (1–>40 Gy). Survivors exposed to radiation developed hypothalamic-pituitary (56.4%), thyroid (13.8%), testicular (66.4%), or ovarian (11.8%) impairment [16]. Another study discussed the temporal course of fertility impairment in childhood brain tumor survivors. Participants with age ≥13 years and formerly cranial irradiation ≥30 Gray (n = 23), including 83% (n = 19) with craniospinal irradiation ≥30 Gray, had a higher median FSH concentration compared to 29 patients without chemoradiotherapy [17].

40.2.2 Hypothyroidism

Thyroid dysfunction has frequently been described in patients treated for Hodgkin disease. Bhatia et al. [18] retrospectively characterized thyroid abnormalities in 89 pediatric patients. The estimated actuarial risk of biochemical hypothyroidism developing was 60% at 11 years, with a median time to development of hypothyroidism of 6 years. Radiation to the thyroid region with doses between 30 and 45 Gy was associated with a hypothyroidism of 50% after 5 years. The relative risk increased by 1.02/Gy. Sklar et al. [19]

assessed the thyroid status in 1791 former Hodgkin disease patients in the Childhood Cancer Survivor Study. Of these patients, 79% were treated with radiation covering the thyroid region with a median dose of 35 Gy. At least one thyroid abnormality was diagnosed in 34% of the cohort. Hypothyroidism was the most common disturbance, with a relative risk of 17.1 ($p < 0.0001$) compared with sibling controls.

Bölling et al. [20] analyzed 404 patients (median age, 10.9 years) who had received radiotherapy to the thyroid gland and/or hypophysis. Follow-up information was available for 264 patients (60.9%; median follow-up, 40 months), with 60 patients (22.7%) showing pathologic values. In comparison to patients treated with prophylactic cranial irradiation (median dose, 12 Gy), patients with radiation doses of 15–25 Gy to the thyroid gland had a hazard ratio of 3.072 ($p = 0.002$) for the development of pathologic thyroid blood values. Patients with greater than 25 Gy to the thyroid gland and patients who underwent craniospinal irradiation had hazard ratios of 3.768 ($p = 0.009$) and 5.674 ($p < 0.001$), respectively. See Fig. 40.2.

For endocrine late effects, the reader is also referred to Chaps. 7–12 of this book.

40.2.3 Diabetes and Metabolic Syndrome

Survivors of ALL from the SJLIFE cohort had a higher risk of the metabolic syndrome (esp. after cranial RT), hypertension, low HDL, obesity, and insulin resistance than that of age-, sex-, and race-matched control subjects from the National Health and Nutrition Examination [21]. Metabolic syndrome was associated with older age and previous cranial radiotherapy (500 adult long-term survivors [22]). Survivors in the CCSS who received total body irradiation, abdominal irradiation, or alkylating agents at a young age were at increased risk for diabetes mellitus [23].

The reader is also referred to Chap. 13 of this book.

40.3 Testes and Ovaries

Insufficiency of hormone production or fertility after radiotherapy of the pelvis is dependent on the radiation dose and the age of the patient. The spermatogenesis is extremely radiosensitive. In adults, doses of 0.2–1.2 Gy are associated with reversible oligospermia after 9–18 months. More than 10 Gy causes much damage, and spermatogenesis is only partially restored after 10 years [24]. A report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium developed recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors and confirmed the following dose-dependent insufficiency of spermatogenesis after radiotherapy of the testis: 1–3 Gy leads to a possibly reversible azoospermia, 3–6 Gy leads to a possibly reversible (but unlikely) azoospermia, and 6 Gy or more leads to a probably permanent azoospermia [25].

Testosterone-producing Leydig cells are more resistant to radiotherapy. Doses of more than 20 Gy lead to a permanent drop in testosterone levels [24]. Before the onset of puberty, Leydig cells seem to be more radiosensitive [26].

To protect the testis and for preservation of the fertility, a testicle pouch could be used for the reduction of the scattered radiation in case of radiotherapy of the pelvis. Patients after puberty should be enlightened on cryopreservation of their sperm before the start of the radiotherapy.

Female childhood cancer survivors are at an increased risk of developing premature ovarian insufficiency because of the vulnerability of the ovaries to gonadotoxic treatment modalities such as pelvic radiotherapy and alkylating agent chemotherapy [27]. Due to the intricate relationship between the hormone-producing granulosa cells and the oocyte, ovarian insufficiency causes disruption of both endocrine and reproductive functions of the ovary. Puberty may be delayed or interrupted. Primary or secondary amenorrhea may occur depending on the pubertal stage at the

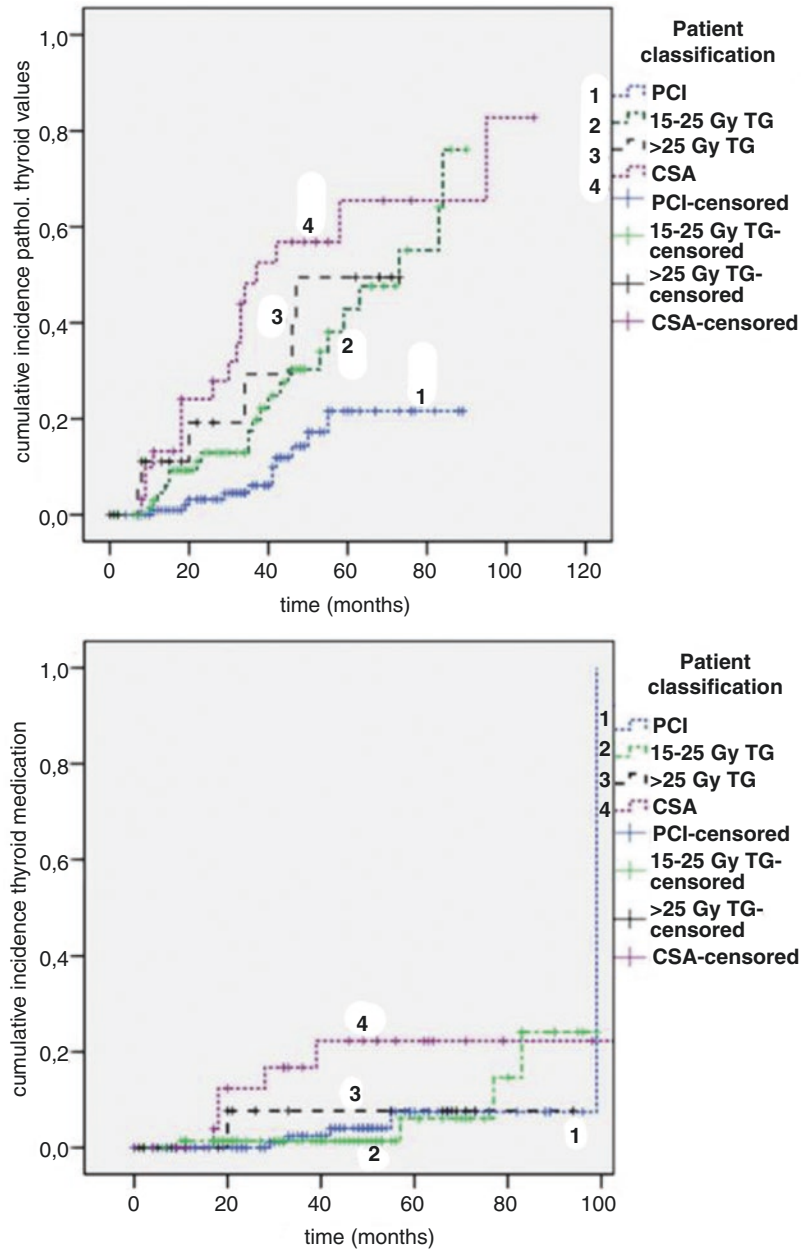

Fig. 40.2 (**a**) Cumulative incidence of pathologic thyroid blood values. The difference between the four defined subgroups is significant ($p < 0.001$). (**b**) Cumulative incidence of thyroid hormone substitution. The difference between the four defined subgroups is not significant ($p = 0.259$). *PCI* prophylactic cranial irradiation, *TG* thyroid gland, *CSA* irradiation of craniospinal axis

time of cancer treatment. POI can occur early, during, or immediately following the completion of cancer treatment or, more commonly, in the years that follow the completion of cancer treatments but prior to age 40 [27].

Ionizing radiation leads to a reduction of the number of small follicles, to impairment of follicular impairment, to a cortical fibrosis, and to atrophy of the capsule. Impairment of fertility is caused more due to radiation to follicles than to oocytes. Doses of 2 Gy destroy 50% of the oocytes, reduce the pool of primordial follicles, and lead to premature ovarian failure. Doses of more than 10 Gy result in amenorrhea and higher

rates of miscarriage, preterm labor, or lower birth weight. The uterine elasticity is reduced due to irradiation-induced fibrosis and damage to the uterine vessels [24]. See Table 40.2.

An oophoropexy can reduce the dose to the ovaries. Normally, one or both ovaries were transferred medial posterior in relation to the uterus or lateral in direction to the os ilium. A clip marking helps the radiooncologist to find the ovary during radiotherapy planning.

The reader is also referred to the Chaps. 9, 10, 12 of this book.

40.4 Central Nervous System

Radiotherapy is known to cause a broad range of adverse effects that have the potential to impact numerous functional domains and quality of life. Cognitive dysfunction and endocrinopathy are considered the most prevalent sequelae of irradiation, whereas vasculopathy with stroke and malignant transformation are more severe but less common [28]. The brain is developing during the first 3 years of a child, and maturing may end up to the sixth year. Myelinization is finished up to the puberty. Therefore, especially young children are affected.

Table 40.2 Radiotoxicity and ovarian insufficiency [24]

Risk of sterility	Ovarian radiation dosage (Gy) (patient age in years (y))
No effect	0.6
Some risk	1.5
60%	2.5–5 (15–40y)
70%	5–8 (15–40y)
100%	>8 (15–40y)
100%	2.5–5 (>40y)

Merchant et al. [28] analyzed 78 pediatric patients with a low-grade glioma (mean age, 9.7 years), who received 54 Gy of a cranial radiotherapy. Cognitive effects 5 years after CRT correlated with patient age, neurofibromatosis type 1 status, tumor location and volume, extent of resection, and radiation dose. Patients younger than 5 years experienced the greatest decline in cognition. Figure 40.3 models that correlated cognitive effect with radiation dose were generated by using dose-volume data from the supratentorial, infratentorial, and total brain volumes. The relative volumes that received doses between 0–30 and 30–60 Gy were the covariates. In most models, the parameter estimate for the percent volume that received a dose (i.e., dose-volume interval) of 30–60 Gy ($V_{30–60Gy}$) was statistically significant, whereas the significance of the dose-volume interval of 0–30 Gy ($V_{0–30Gy}$) was inconsistent. Psychological measures showed significant correlation between dose-volume parameters and math, reading, spelling, externalizing behavior, communication and visual auditory learning [28].

Palmer et al. [29] prospectively examined processing speed (PS), broad attention (BA), and working memory (WM) ability of 126 patients diagnosed with medulloblastoma, ages 3–21 years at diagnosis, over a 5-year period. The group found that

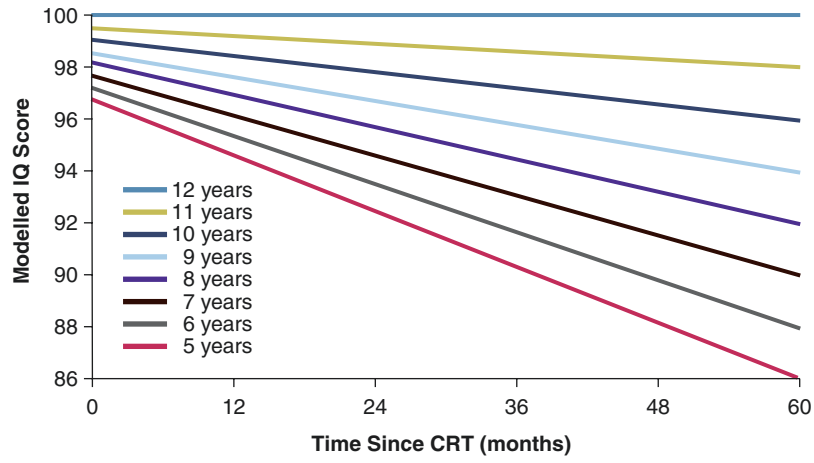

Fig. 40.3 Modelled intelligence quotient (IQ) scores after conformal RT by age for pediatric low-grade glioma [28]

Table 40.3 Significant parameter estimates to model decline in psychology test scores with radiation dose, age, and time after conformal radiation therapy for pediatric low-grade glioma [28]

Dose-Volume Interval by Psychology Test	*P* by Volume of Brain		
	Total Brain	Supratentorial	Infratentorial
IQ			
$V_{0\text{-}30Gy}$	.0193	.0091	.0032
$V_{30\text{-}60Gy}$	.0106	.0105	.0089
Math			
$V_{0\text{-}30Gy}$			
$V_{30\text{-}60Gy}$	.0705		.0165
Reading			
$V_{0\text{-}30Gy}$			
$V_{30\text{-}60Gy}$	.0013	.0025	.0106
Spelling			
$V_{0\text{-}30Gy}$			
$V_{30\text{-}60Gy}$	.0389		.0350
CBCL externalizing			
$V_{0\text{-}30Gy}$	.0043	.0053	.0061
$V_{30\text{-}60Gy}$			.0386
Vineland communication			
$V_{0\text{-}30Gy}$			
$V_{30\text{-}60Gy}$			.0481*
Visual auditory learning†			
$V_{0\text{-}30Gy}$	.0001	.0001	.0009
$V_{30\text{-}60Gy}$			

Note. Instruments for each evaluation are as follows: IQ Bayley second edition; Wechsler Preschool and Primary Scale of Intelligence revised; Wechsler Intelligence Test for Children third edition or Wechsler Adult Intelligence Scale revised, as appropriate for age; math, reading, and spelling: Wechsler Individual Achievements Test; externalizing behavior: Child Behavior Checklist; communication: Vineland Adaptive Behavior scale; and visual auditory learning: Woodcock Johnson–Revised Visual Auditory Learning subtest

Abbreviations: $V_{0–30Gy}$ percent volume between 0 and 30 Gy, $V_{30–60Gy}$ percent volume between 30 and 60 Gy, *IQ* intelligence quotient, *CBCL* child behavior checklist

*Model did not include age

†Increasing $V_{0–30Gy}$ resulted in improved scores

younger age at diagnosis, HR classification, and higher baseline scores were significantly associated with poorer outcomes in PS. Patients with an average risk received 23.4 Gy to the craniospinal axis, whereas patients of the high-risk group received 36–39.4 Gy. Patients of the high-risk group suffered from a significant decline in neurocognitive function in comparison to the average group [29].

Central nervous system (CNS) prophylaxis has been an essential component of the treatment of childhood acute lymphoblastic leukemia (ALL) for several decades. Early prophylactic treatment of CNS minimal residual disease is intended to guard against the possibility that CNS blasts not eradicated by systemic therapy will reseed the bone marrow, leading to relapse of the disease. For many years, the preferred approach to CNS prophylaxis has been cranial radiation therapy (CRT), currently given at an 18 Gy dose, combined with intrathecal methotrexate. This strategy is highly effective in preventing CNS relapse [30]. Of all the agents used in the treatment of leukemia, CRT has stimulated the most concern; the assumption is that observed cognitive deficits are primarily referable to CRT. In general, the trend is toward less severe toxic effects for protocols that involve the lower dose or to omit prophylactic irradiation. Several studies comparing groups treated with and without CRT at the 18 Gy dose document no differences in IQ or other measures [30]. Another multicenter study, however, did observe lower IQ scores in children treated with the 18 Gy dose than

in those not treated with CRT [31]. Children treated with cranial irradiation in combination with systemic methotrexate and/or intrathecal MTX were at greater risk of developing morphological brain alterations than with chemotherapy alone. These alterations were partly correlated with reduced neuropsychological performances alone [32]. The adverse impact of CRT, however, emerged only in the youngest children (less than 3 years of age at treatment), suggesting that for older children, CRT at the lower dose poses less risk.

40.5 Head and Neck, Dens

The prevalence of salivary gland dysfunction after cancer treatment varies based on measurement techniques (patient report versus stimulated or unstimulated salivary secretion rates) [33]. A review of 79 studies reported an 83.5% prevalence of self-reported xerostomia 2 years after radiation for head and neck cancer in adults [34]. However, a study of childhood rhabdomyosarcoma survivors who received head and neck radiation showed a prevalence of only 12% at a median follow-up of 7 years [35]. In a CCSS study, the prevalence of self-reported xerostomia in survivors was 2.8% compared to 0.3% in siblings, with an increased risk in survivors older than 30 years of age [36]. The discordance in xerostomia reporting between adults and children may be due to the higher doses of radiation used in adult head and neck cancers, increased comorbidities in adult patients, or underreporting of symptoms by children [37]. The largest risk factor for xerostomia is exposure to radiation. Long-term severe xerostomia can usually be avoided if one parotid gland is spared to a mean dose less than 20 Gy or both glands are spared to a mean dose less than 25 Gy [38]. Additionally, risk is reduced if submandibular glands are spared. Development of intensity-modulated radiotherapy (IMRT) has allowed dosimetric sparing of the parotid gland, with a hope of improved salivary function.

Radiation-associated acute and late side effects in view of salivary gland function and mucosal status in childhood and adolescence show a clear dose-effect relationship that is comparable to those in adults. An increase of the mean value of the maximum dose of 1 Gy to the submandibular glands resulted in an OR of 1.04 for acute toxicities of the salivary glands. Concurrent chemotherapy during radiation highly increases the risk for acute as well as late salivary gland and mucosa toxicity. Proton therapy may have the potential to reduce side effects [39].

The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers provide practitioners with exposure- and risk-based recommendations for the surveillance and management of asymptomatic survivors who are at least 2 years from completion of therapy. This review outlines the pathophysiology and risks for oral and dental late effects in pediatric cancer survivors and the rationale for oral and dental screening recommended by the Children's Oncology Group. Effinger et al. [40] discussed the impact of childhood cancer therapy on tooth development, salivary function, craniofacial development, and temporomandibular joint function placing. Esp. head and neck radiation and hematopoietic stem cell transplantation increase the risk of subsequent malignant neoplasms in the oral cavity. Craniofacial abnormalities, which may impact the oral cavity, occur in 35–90% of children who receive high-dose radiotherapy to the head and neck. Cosmetic deformities can require multiple surgical reconstructions and can deeply impact quality of life. Younger age at treatment and increased radiotherapy volume and dose (≥30 Gy) contribute to the extent and severity of bone and soft-tissue deformity. Radiation involving the oral cavity also increases the risk of dental anomalies since ameloblasts can be permanently damaged by doses as low as 10 Gy [36, 41].

Survivors require routine dental care to evaluate for potential side effects and initiate early treatment.

40.6 Lung

Pneumonitis of the lung is a subacute toxicity 1–4 months after radiotherapy. Fibrosis of the lung occurs later and could be increased in combination with a pneumotoxic chemotherapy, e.g., bleomycin.

In a recent study (295 patients, 179 late effect documentations), only a few cases of higher late toxicities of the lung were registered. Both acute and late toxicities seem to correlate with higher vol-

umes in low-dose areas. Data indicate that similar to the situation in adult patients, V_5, V_{10}, V_{15}, and V_{20} should be kept as low as possible (e.g., at least $V_5 < 50\%$, V_{10} and $V_{15} < 35\%$, and $V_{20} < 30\%$) in children and adolescents to lower the risk of toxicity. As expected, simultaneous chemotherapy and pre-existing lung impairment seem to promote toxicity of the lung. Nevertheless, the acute pulmonary toxicity rates and late side effects with a median follow-up of 3 years were quite mild [42]. Additionally, children might tolerate lung irradiation better than adults. Although the V_{dose} and normal tissue complication probability have been shown to be significant in predicting lung toxicity in different studies [43], the mean lung dose (MLD) is a predictor across different studies in children. De et al. [44] described, retrospectively, the correlation of pulmonary function abnormalities with dose volume histograms in children treated with modern lung irradiation techniques. The most common diagnosis was Hodgkin's lymphoma. The most common lung function abnormality was obstructive lung disease, which was observed in 24% of patients, followed by hyperinflation in 20%, restrictive lung disease in 15%, and diffusion defects in 14% of a total of 49 patients. Furthermore, the risk of restrictive disease and abnormalities in other lung parameters increased as the radiation dose increased from V_{10} and as hyperinflation increased from V_{20}. A retrospective study by Venkatramani et al. [45] identified 109 patients and reported a correlation between the clinical and dosimetric factors and adverse pulmonary outcomes in children after lung irradiation. The volume irradiated with at least 22 Gy was associated with the development of long-term pulmonary findings in univariate analyses. In a review [46], 17 publications examining the late effects of radiotherapy to the thorax in childhood and adolescence were summarized. Pulmonary function impairment after mediastinal irradiation occurred in one-third of all pediatric patients, even when treatment was performed with normofractionated lower doses (15–25 Gy). After whole lung irradiation, pulmonary function impairment regularly followed at differing rates, according to several reports. However, clinically symptomatic functional impairment, such as dyspnea, was less common.

The reader is also referred to Chap. 6 of this book.

40.7 Heart and Vascular System

In case of mediastinal radiotherapy, larger volumes of the heart will be affected. Specified consequences could be an acute pericarditis, coronary heart disease, and an increased incidence of cardiac infarction. An acute pericarditis was associated with a median heart dose of 46 Gy and occurred in 30% of patients [47, 48]. Improved radiation techniques with equalized opposite fields and use of a subcarinal block could reduce the incidence to 2.5% [47]. The incidence of cardiac infarction could also be reduced by improved radiation techniques and reduction of the total dose, esp. in patients with Morbus Hodgkin. Hancock et al. [49] analyzed 635 children with this disease and analyzed cardiac late effects. Twelve patients died of a heart disease after total doses of 42–45 Gy, thereof seven of a heart attack.

Van der Pal et al. [50] analyzed the risk of symptomatic cardiac events in a cohort of 1,362 childhood cancer survivors. The 30-year cumulative incidence of symptomatic cardiac events was 12.6% after exposure to anthracyclines and chest irradiation; after 30 years, one in eight will develop severe heart disease, 7.3% after anthracycline exposure alone and 4.0% after chest irradiation alone.

A report from the Childhood Cancer Survivor Study examines the incidence of and risk factors for strokes that occur in 4828 5-year survivors of childhood leukemia and brain tumors ($n = 1871$). The rate of late-occurring stroke for leukemia survivors was 57.9 per 100,000 person-years and for brain tumor survivors was 267.6 per 100,000 person-years. Mean cranial radiation therapy (CRT) dose of ≥30 Gy was associated with an increased risk in both leukemia and brain tumor survivors in a dose-dependent fashion, with the highest risk after doses of ≥50 Gy [51].

The reader is also referred to Chap. 1 of this book.

40.8 Liver

Symptoms of a chronic hepatotoxicity are a fibrosis of the central blood vessels, an atrophy of the hepatocytes, and concentric fibrosis around the portal blood vessel after liver irradiation. The tol-

erance dose of the liver is dependent on the irradiated volume, age of the patients, and simultaneously chemotherapy. Without cytostatic drugs, radiotherapy with 30 Gy to the whole liver is associated with a hepatopathy; in combination with chemotherapy, the dose is reduced to 12–15 Gy.

Rösler et. al. [52] analyzed acute and late hepatotoxicity after radiotherapy in childhood, based on prospectively collected data. Overall, analyzed toxicity was low. Only 24/109 patients with acute and 18/141 patients with late toxicity were detected; most of these toxicities were mild. However, one patient developed higher-grade toxicity. Evaluations for hepatotoxicity after radiotherapy in childhood have been reported only in few publications.

A review of the literature on abdominal irradiation in childhood and adolescence reported a dose- and volume-effect, regarding radiation-associated toxicity [53]. It was concluded that irradiation doses lower than 20 Gy to the main part of liver or higher doses applied on a smaller part, such as the left hepatic lobe, seemed to be safe.

Late effects after TBI in stage IV neuroblastoma have been reported by the "International Society of Pediatric Oncology" (SIOP) [54]. Two groups, with TBI (32 patients) or chemotherapy (30 patients), were compared. Four cases of chronic liver injury occurred in the group with chemotherapy. Due to the small corresponding group sizes in this study, no statistical analysis could be determined concerning hepatotoxicity after TBI. Another evaluation of hepatotoxicity of 15 children with TBI prior to bone marrow transplantation showed acute liver dysfunction in 73% ($n = 11$) [55]. Four patients (27%) suffered from a veno-occlusive disease. According to the "Children's Oncology Group," at risk are people with high radiation doses ($\geq$30 Gy) to the liver (parts), especially those getting the chemotherapy drugs methotrexate, mercaptopurine, and thioguanine, which are more typical for acute than for late toxicity [55].

The reader is also referred to Chap. 5 of this book.

40.9 Pancreas

The Childhood Cancer Survivor Study reported that patients who received radiation treatment for childhood cancer were 1.8 times more likely than their siblings to develop diabetes. This increased risk was 7.2 times greater after total body irradiation and 2.7 times greater after abdominal irradiation. The investigators also reported that increased diabetes incidence was unrelated to body mass index (BMI), but was higher with younger age at diagnosis of childhood cancer [23]. de Vathaire et al. [56] reported the incidence of diabetes and its risk factors in a large cohort of childhood cancer survivors treated before 1986 and followed up for an average of 30 years. Finally, 65 (out of 2520) cases of diabetes were validated. The risk of diabetes increased strongly with radiation dose to the tail of the pancreas, where the islets of Langerhans are concentrated, up to 20–29 Gy and then reached a plateau for higher radiation doses. The radiation dose to the other parts of the pancreas did not have a significant effect. Compared with patients who did not receive radiotherapy, the relative risk of diabetes was 11.5 in patients who received 10 Gy or more to the tail of the pancreas. Children younger than 2 years at the time of radiotherapy were more sensitive to radiation than were older patients.

The reader is also referred to Chap. 13 of this book.

40.10 Kidney

An application of dose more than 25 Gy has a significant increased risk for a kidney damage. Renal sensitivity could be higher in children, but doses less than 20 Gy and a fractionation with single doses of 1.5–2.0 Gy could reduce the risk of nephropathy. In a prospective study, Bölling et al. [57] did not observe any severe kidney function impairments in 126 analyzed patients with abdominal irradiation. The toxicity rates were low, and only mild to moderate function impairments were reported. However, with a median follow-up time of only 28.5 months, some further late effects may arise in the future. The kidney volumes exposed to radiation doses exceeding 20 Gy were low in the presented collective. The results of kidney function after abdominal radiotherapy may always be influenced by concurrent chemotherapy. All patients suffering from kidney function impairment also received at least one potentially nephrotoxic che-

motherapeutic agent. A statistically significant difference in the whole kidney volume exposed to 20 and 30 Gy could be seen.

Children with Wilms' tumor are at risk for impaired renal function from therapy due to the use of potentially nephrotoxic chemotherapeutic agents, surgical removal of renal tissue, and radiotherapy. In a report from the National Wilms' Tumor Study Group with a database of 5823 children, Ritchey et al. [58] described 55 patients with renal failure, of whom 15 children received radiation doses of 12–20 Gy to the remaining renal parenchyma. In another report of 100 children treated for Wilms' tumor, the incidence of impaired creatinine clearance was significantly higher for children receiving more than 12 Gy to the remaining kidney, and all cases of overt renal failure occurred in patients who had received more than 23 Gy [59]. Pötter et al. [60] observed no clinical renal dysfunction in a study on 17 children with Hodgkin's disease who had been treated with radiotherapy (para-aortic field and the splenic pedicle, 18–40 Gy), but subclinical impairment could be observed in patients who had received 20 Gy to both kidneys in combination with a dose above 30 Gy in the upper half of one kidney. The above-quoted reports dealt mainly with toxicity data from children treated for a certain tumor entity or in a special therapy setting including the typical chemotherapy regimens for these situations. That may explain why in some reports renal impairment was described already after administration of doses of 12 Gy.

The reader is also referred to Chap. 2 of this book.

40.11 Bowel

Late gastrointestinal complications of radiation therapy have been recognized but not extensively studied in children. Severe long-term toxicity seems to be rare. Manifestations of gastrointestinal toxicity include dysphagia, vomiting, abdominal pain, diarrhea, bleeding, and anorexia. Intolerance to fat, milk, gluten, and fiber-containing food may be observed in abdominally irradiated children and cause growth and weight deficits [61]. The United Kingdom Children's Cancer Study Group (UKCCSG) [62] characterized the early and late toxicity of 138 patients who had received abdominal radiotherapy within multimodal therapy of Wilms' tumor. In this group, four patients experienced late gastrointestinal effects and required laparotomy for adhesions, 7–11 years after diagnosis. Paulino et al. [63] reported 6 patients with small bowel obstruction in a cohort of 42 children with nephroblastoma. This corresponded to an actuarial incidence of bowel obstruction of 9.5%, 13.0%, and 17.0% at 5, 10, and 15 years, respectively. The most common cause of an obstruction was a bowel adhesion; the use of radiotherapy was not found to increase the incidence of small bowel obstruction. Severe gut toxicity with bowel obstructions leading to death was reported in several French Ewing's tumor patients [64]. Twenty-eight patients received radiotherapy to the digestive tract after busulfan/melphalan high-dose chemotherapy. After a median follow-up of 31 months, four lethal digestive toxicities were observed. All patients with fatal toxicities had been irradiated with doses exceeding 50 Gy in maximum to large bowel volumes. In an analysis of a similar patient collective in Germany, after a median follow-up of 21 months, no severe bowel toxicity was found [65] in 24 patients who had been irradiated with a median maximum dose to the bowel of 45 Gy (24–58 Gy) after busulfan/melphalan high-dose chemotherapy. In comparison, patients had been irradiated with lower doses and smaller volumes to those treated in France. Therefore, busulfan/melphalan high-dose therapy should be avoided if larger volumes have to be irradiated. Ritchey et al. [66] reported that after nephrectomy for Wilms' tumor, 6.9% of children (131/1910) developed small bowel obstruction. There were several factors that influenced this rate (e.g., higher local tumor stage), but the incidence of postoperative small bowel obstruction was not higher in children who received postoperative radiation therapy in comparison to those who had not. There were only three children in whom the surgeon described operative findings of radiation enteritis. In conclusion, there are no detailed data regarding the rate of late gastrointestinal complications after abdominal radiotherapy in children. Several reports describe small bowel obstruction as a sequel of surgery, but radiotherapy seems to be less important [53].

The reader is also referred to Chap. 5 of this book.

40.12 Secondary Malignancies

Subsequent malignant neoplasms (SMNs) are histologically distinct malignancies that develop among patients treated for a primary malignancy. Although a few SMNs are attributable to heritable conditions such as retinoblastoma or neurofibromatosis, the vast majority of SMNs observed in survivors of childhood cancer are largely attributed to the genotoxic insult resulting from therapeutic exposures [2].

Solid SMNs are strongly associated with irradiation and are characterized by a latency that exceeds 10 years [67]. Nonmelanoma skin cancers (NMSC), breast cancer, CNS tumors, thyroid cancer, genitourinary cancers, digestive tract tumors, bone tumors, and SMNs of respiratory sites are the most common solid SMNs observed among survivors of childhood cancer [68–71].

Bhatia et al. [2] summarizes the magnitude of the risk of subsequent neoplasms reported by survivorship cohorts. The ALiCCS cohort had a 3.3-fold increased risk of SMNs [70], the BCCSS cohort had a 4-fold increased risk [71], the CCSS cohort had a 6-fold increased risk [69], and the DCOG LATER cohort had an 11.2-fold increased risk [68]. Figure 40.4 is

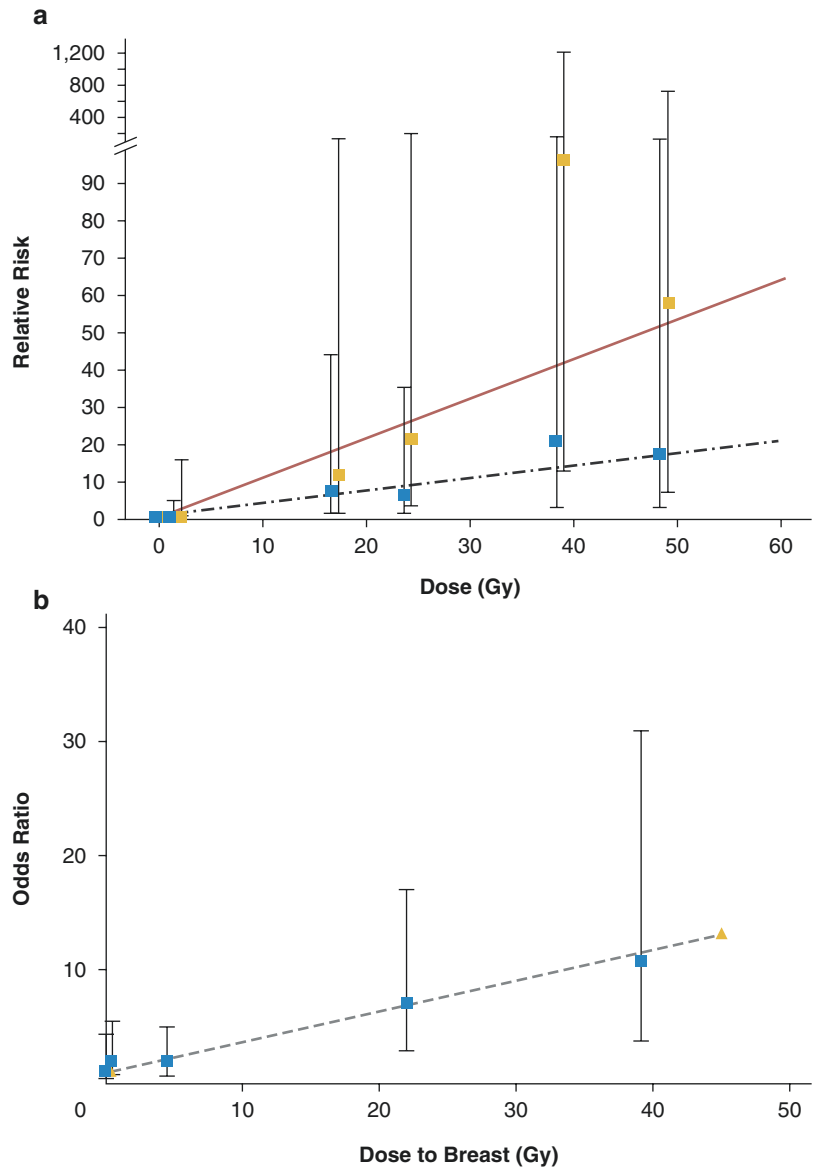

Fig. 40.4 Risk of subsequent malignant neoplasm by radiation dose for (**a**) brain tumors and (**b**) breast cancer [2]

showing the risk of subsequent malignant neoplasms by radiation dose for (a) brain tumors and (b) breast cancer.

The reader is also referred to Chap. 14 of this book.

40.13 Registry for the Evaluation of Late Side Effects After Radiotherapy for Malignant Diseases in Childhood and Adolescence (RiSK)

In Germany, several groups have been established to analyze different aspects of late effects in pediatric oncology. However, radiotherapy and especially radiation doses at the organs at risk have not been a major focus of these groups. In general, late effects after radiotherapy in childhood and adolescence have mainly been characterized retrospectively using small patient numbers. Only uncertain estimations of the radiation doses at specific organs could be performed from those studies. These circumstances have led to the establishment of RiSK by the German Group of Paediatric Radiation Oncology (APRO), a working group of the DEGRO and the GPOH.

The aim of this prospective multicenter registry study is to evaluate radiation dose-effect relationships in organs and parts of organs with consideration of combined modality treatment like surgery and/or chemotherapy.

The study has started in a pilot phase in June 2001 in few centers. During this time period, documentation forms were evaluated in view of practicability and completeness of data. Since 2004, beginning with the funding of the Deutsche Kinderkrebsstiftung, documentation has been performed all over Germany and is still ongoing. The aim of this prospective multicenter registry study is to evaluate radiation dose-effect relationships in organs and parts of organs with consideration of combined modality treatment like surgery and/or chemotherapy. During the last years, various analyses were published in the most important international journals [4].

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41 Long-Term Follow-Up of Childhood Cancer Patients from the Point of View of a Person Affected

Christian Mueller

41.1 Time of Diagnosis and Therapy

Approximately 1 month before my seventh birthday in August 1989, I was diagnosed with B-cell non-Hodgkin lymphoma. I was then enrolled in the NHL-BFM 86 study and administered with this treatment according to the strategy for B-neoplasia. The treatment consisted of two different courses, lasting 5 days each, and administered a total of three times [1]. While there was a total of 30 days of chemotherapy, the therapy as a whole lasted over 5 months. Based on the data from previous trials on the treatment of patients with b-cell non-Hodgkin lymphoma, the study center decided to include an additional treatment element from Non-B-NHL, called the reinduction therapy protocol II. I was administered with this treatment in January and February of 1990, which included 20 lumbar punctures with intrathecal methotrexate during my aftercare in order to prevent relapse in my central nervous system. For readers interested in further details regarding my course of treatment, they are invited to reference further resources [2, 3].

41.2 Time After Therapy: Reentry to School

Upon completion of my homeschool program and after summer holidays in 1990, I was able to start school again. By the fall of 1991, an important pillar in my after cancer care was taken from me. When my mother and I arrived for one of my follow-up visits, we were informed that Prof. Juergens, a doctor whom I heavily relied on during my treatment, had relocated to start a new job in pediatric oncology in Muenster. Upon hearing this, it felt as if I had fallen into an endless black hole, yet I never spoke to anyone about this increasing fear. I reminisced about how Prof. Juergens was able to painlessly place the venous access into my head when other doctors could not find a vein in my arms or feet. On top of being faced with the tragic departure of Prof. Juergens, an employee from psychosocial services, Mrs. Hoetzel, left the hospital just a few months later.

Elementary school was an excellent time in my life. Unfortunately, several problems began by the time I was in the fifth grade. About 8 years after my diagnosis, I began experiencing psychological difficulties that I could not yet conceptualize. It felt like everyone around me (professionals, friends, relatives, etc.) was trying to tell me that I should just feel happy I survived. Whenever I brought up my fear of cancer recurring, I was met with the notion that this chapter of my life was over and that there would never be

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any problems related to my cancer. I was told again and again, "Be happy you are alive." While I was completely unable to ignore these fears, I could never find anyone who understood what I was trying to express. Given my physical ailments, I became an easy victim for bullying. I recently was not surprised to learn that survivors of childhood cancer are bullied at higher rates than their healthy peers (32% vs. 25%) [4]. The worst part of my experience is that I was under the impression that every other survivor of childhood cancer was in great condition after their treatment had completed would succeed in school and eventually land the job of their dreams. Believing I was the only one going through what I went through was extremely isolating and caused me to resist seeking help.

41.3 Psychotherapy 24 Years After Cancer Diagnosis

Upon finishing school, I began studying computer science at a private college; however, I did not finish. I wanted to study medicine during my elementary school years, but this was no longer possible because I did not achieve the necessary degree after finishing school. Luckily, I learned of an opportunity to audit classes at the university, and thus I was able to take classes in medicine at the university I had been treated at over a decade and a half prior. Since this program was in line with my original career aspirations, I took this opportunity very seriously. While my exams were not officially graded per se, I was able to see my achievements and receive marks on my exams, which had a more personal character. All the reviews I received made it clear that I had actually earned this degree, and so I went through the complete medical studies curriculum as a guest auditor.

Later, I attended several medical conferences such as the German Society of Pediatric Oncology and Hematology (GPOH) as well as the German Cancer Society Cancer Congress in 2012. At the Cancer Congress, I attended a session chaired by Prof. Juergens, whom I had not seen since the summer of 1991. As soon as he entered the room, my time with him in the hospital flashed before my eyes. I approached him after the session and told him that I was one of his patients in Dusseldorf in 1989. Prof. Juergens could not believe it, and soon enough I could not hold my tears back any longer. At that moment, Prof. Juergens placed his hand on my shoulder like he did 23 years before, and it was like he had made up for all that lost time. He told me about a researcher by the name of Prof. Langer and all of his work in the field of childhood cancer late effects. In this moment, I finally became aware of the possibility of late effects after cancer treatment, and that there was a German expert in this area of research. After speaking with Prof. Langer, he asked me if I would be interested in working on his late effects surveillance system (LESS) study after I earned my degree. Around the same time, I found a psychotherapist who understood my problems and who was able to provide therapy to me for over 6 months. Prof. Langer moved the LESS group from Erlangen to Lubeck, and I began working for LESS in February 2014 for field patient information. In the summer of 2014, I completed my distance learning journalism studies. Two years later, I became a member of SIOP. Since June 2018, I have been working for the Gert und Susanna Mayer Foundation which supports research projects in childhood cancer and patients who are in need of individual support.

41.4 Need of Structured Long-Term Aftercare and Future Perspective

In 2004, I was diagnosed with diabetes mellitus, a known late effect of childhood cancer [5], which I have to treat with insulin injections. The first time I ever read about childhood cancer late effects was in 2011, where I searched for scientific articles about the BFM study group. In this search, I came across an article written by Lipschultz and colleagues about cardiotoxicity of doxorubicin, which was published in 1991 [6]. Since then, the Childhood Cancer Survivor

Study (CCSS) published many articles about late effects such as the risk of developing chronic health conditions for survivors treated in different decades between 1970 and 1999 [7]. An important theme that emerged within this research is that childhood cancer is a burden on the whole family. One study in Australia found that childhood cancer had an immense impact even on grandparents. According to the study, 47.2% of grandparents of children with cancer met criteria for depression and anxiety compared to 21.8% of grandparents of children who did not have cancer [8]. As these studies demonstrate such an immense impact on grandparents, it may be a reflection as to how much the children are also suffering.

There is no doubt that there is a serious need for special follow-up counseling sessions for adult survivors of childhood cancer as well. A risk stratification model containing three risk groups with different screening recommendations and frequencies should be established and offered to survivors of childhood cancer even when they have reached adulthood [9]. I began having this vision when I visited the Behavioural Sciences Unit at the Children's Hospital in Sydney in August 2018, chaired by Dr. Claire Wakefield. At this visit, I was given the opportunity to learn about a research group that focuses on the psychosocial late effects of childhood cancer. In my opinion, I see that there are deficits in this issue in Germany. I was so interested in the psychosocial research they were conducting in Sydney, especially given my own background of psychosocial difficulties after cancer. I was amazed to see that the offices for mental health counseling alone were larger than even some treatment rooms I saw in Germany. Nevertheless, the structure of health-care systems that serve vastly different numbers in regard to the population makes it difficult to compare long-term follow-up systems in different countries. In my own experience, what matters most to me is having an individual in charge of my follow-up care who understands me and my history. I cannot say I would attend my follow-up visits as regularly if I did not have that sort of relationship with my health-care provider. Travel distance is also an important criterion for my follow-up care as it would be unreasonable to travel hundreds of kilometers for one appointment.

How should childhood cancer survivors be cared for? The fact that childhood cancer is a rare disease from a statistical point of view cannot be an argument for not implementing meaningful offers for long-term follow-up. I would not focus on statistical rareness because a large analysis demonstrates that childhood cancer burden represents an important global issue with 11.5 million disability-adjusted life years [10] and a gap of life expectancy between 9.2, 12.3, and 16.5 years on average depending on a cancer treatment in the 1990s, 1980s, and 1970s [11].

The success of pediatric oncology in Germany is based on the therapy optimization studies from the early 1970s on [12]. Those studies are available for all entities of childhood cancer. So, it must be possible to initiate a model of care for childhood cancer long-term survivors in the form of a therapy optimization study. After the successes in the treatment, this would also lay the basis for success in long-term follow-up care. I am sure all childhood cancer survivors would be very thankful. The facts are clear as we know on the one hand from St Jude Lifetime Cohort Study that cumulative incidence of chronic health conditions in childhood cancer survivors at the age of 50 is 99.9% [13], and on the other hand, we know in detail what kind of diseases are possible late effects of childhood cancer [14]. Collaborations between international research groups are the key to success. This project does not end at national borders. As such, it is time to act now for childhood cancer survivors in the present and the current childhood cancer patients because they are the survivors of the future and are part of our community's future.

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Networks of Survivorship Care for Young Cancer Patients

42

Jörn D. Beck, Lars Hjorth, and Thorsten Langer

42.1 Introduction

Forty-two chapters have been structured according to the toxicities in cancer entities, and the late effects and follow-up proposals have been discussed by European and American authors. Cancer diseases in children, adolescents and young adults are treated within specific treatment protocols and can produce different late effects that will have to be cared for by specific follow-up recommendations. Over the last decades, the therapy which was considered the best was used to save patients' lives. The pattern of toxicities and late effects have changed over time, depending on the treatment protocols used.

Rather than delivering standard and conclusive recommendations for survivorship care in all healthcare systems, this book gives an instantaneous picture of the current and fast developing practices, as well as the work in progress. Its common, yet important aim will be to point out the development of harmonized guidelines for cancer survivors that could be implemented in different health-care systems. Since aftercare plays an increasingly important role in preventive medicine, it could also help to save money in the health-care systems.

In addition to the knowledge of late complications derived from the successful treatment of cancer in children, all aspects of long-term social, psychological, and medical problems are being currently investigated for adolescents and young adults (AYA) aged between 19 and 39 years, who are also an important group of cancer patients. With approximately 16,000 patients each year in Germany, the AYA group accounts for 3% of all cancer patients. Like children, these young adults too have 10-year survival rates of up to 80%. As outlined in the chapters of this book, there can be severe long-term medical consequences such as secondary cancers, cardiovascular long-term toxicity, hormonal disorders, and fatigue. Since these groups of long-term survivors are constantly growing, their specific survivorship care needs to be addressed.

This book is dedicated to all cancer patients and the growing number of survivors, especially children, AYA, and their families. We want to provide them with health-care system information on survivorship care. Most important is to successfully reintegrate them in their societies.

Survivorship care for patients who have undergone allogeneic bone marrow transplantation and

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those suffering from childhood cancer predisposition syndromes have not been discussed in this book since both these groups require special attention.

42.2 Remarks on the History of Childhood and Adolescent Cancer Treatment

In 1958 Pinkel worked in the group of Frei [1]. They used two antimetabolites and a corticosteroid for treating acute leukemia. In those days, it was not possible to distinguish between acute myelocytic leukemia (AML) and acute lymphoblastic leukemia (ALL) [2].

What was even more disappointing was that in 1965, Burchenal and Murphy were able to identify in the whole world only 71 acute leukemia patients who had survived for more than 5 years. Only 36 out of the 53 children and 6 out of the 18 adults were living healthy lives with no evidence of leukemia [3].

A breakthrough study was published in 1968 by Pinkel and colleagues [4] who described the "total therapy" of acute lymphocytic leukemia in children. They improved the treatment strategy and augmented the long-term remissions of childhood ALL significantly.

The German BFM Group intensified the ALL therapy and published their first improved results on high-risk patients in 1981 [5].

A paper titled "History of Paediatric Haematology Oncology" [6] published in 2002 by Pearson stated: "Advances in paediatric oncology have been particularly spectacular in the last 50 years. Using multi-modal therapy including combination chemotherapy, more than 80% of children with cancer can now be cured. During the last 50 years, Paediatric Haematology Oncology has increasingly used tools of the 'new biology': immunology, biochemistry, enzymology, genetics, molecular genetics, and others."

The results of using these tools have been published in a recent paper on ALL which states that the information gained from collaborative, international studies have helped in deciphering the heterogeneity of ALL to improve personalized treatment, which in turn, will further advance the current high cure rate and the quality of life for children and adolescents with ALL [7].

In their paper titled "Old Man River," D'Angio and Vietti [8] compared the development of pediatric oncology to a network of individual springs and small rivers flowing together and forming the main stream and stated that in a similar fashion, the flow of modern pediatric oncology could be traced back to observations made by individual investigators and then to studies conducted within single institutions, followed by multi-institutional and international cooperative study groups. They stated that while this pattern could be traced back for most of the entities included under the rubric pediatric oncology, it was more convenient and informative to do so, with respect to two specific entities: ALL and Wilms tumor. These malignancies are used as surrogates for the liquid and solid tumors [8].

Following this line, we will now examine the development of Wilms tumor therapy, research on late effects and survivorship care.

42.3 Late Effects and Survivorship Care

D'Angio and Evans in 1971 [9] stated that Wilms tumor can be cured. A single institution report published by Meadows et al. [10] in 1975 described a secondary neoplasm after a follow-up time of 2 or more years, in 3 patients out of 168. The three patients with a second primary neoplasm did not receive chemotherapy, and two of the three were treated with radiation. The authors wrote that abnormalities other than a second neoplasm were detected through specific examinations.

In the same year, D'Angio, the founder of pediatric radiation oncology, published a paper titled, "Paediatric cancer in perspective: Cure is not enough" [11].

In the year 2000, the four pediatric cancer groups of the United States voluntarily merged efforts to create the Children's Oncology Group [12]. For all cancers, oncological frontline therapies are in place, and guidelines for long-term follow-up are recommended [12]. This group is supported by the National Cancer Institute and describes itself as the world's largest cooperative children's cancer research entity. It is connected

not only with institutions in Canada but also with institutions in Australia, New Zealand, and Europe.

When more and more pediatric cancer patients were cured from their disease in later years, it seemed obvious that a part of them could take their place in society without severe late effects.

In 2006, a seminal paper was published on The Childhood Cancer Survivor Study (CCSS) [13], which analyzed late effects in more than 10,000 survivors of pediatric or adolescent cancer. Their health status was compared to that of their siblings.

In their paper, Oeffinger et al. [14] shared that in the original group almost two-thirds of survivors had at least one late effect, while around 25% experienced a severe or life-threatening late effect that impaired their quality of life not only for a short time but for the rest of their lives. In the last few years, many analysis and papers have been published by the CCSS group [15].

This was true, especially for survivors, who had received aggressive treatment to save their lives, some decades ago. The time course for late effects requires a lifelong holistic follow-up program adjusted to the cancer and the therapy protocol used.

While it is up to former cancer patients whether to make use of this offer or not, they should at least be informed of such follow-up programs, and the health-care systems of the various countries should provide these programs, for example, as advertised by a newly founded parent organization in Ireland [16].

In addition to describing milestones in the curability of pediatric cancer, Hudson [17] also highlighted late health outcomes as a driver of therapy evolution and survivorship care.

Clinical trials and long-term follow-up of childhood cancer survivors (CCS) in Japan are performed within the framework of the Japanese Children's Cancer Group (JCCG) [18]. As compared to Canadian CCS, Japanese survivors expressed less concerns regarding their cancer, but most of them preferred to visit the same doctor for long-term care as adults [19].

The development of a comprehensive Japanese guideline that addresses these issues would help to improve the clinical outcome for cancer survivors in Japan [20].

Recently, Zheng [21] described not only the incidence, mortality, and survival of childhood cancer in China but also the difficulties of their investigations in this large, floating population.

Poon [22] described the clinical ascertainment of health outcomes in Asian survivors of childhood cancer and concluded that the existing types of chronic health problems identified in this review suggest the need for active screening, better access to survivorship care, and promotion of protective health behavior in Asia.

In modern times, the survivors themselves and their families partner with the expert teams for developing survivorship care proposals [23].

A global estimate of the childhood cancer burden describes the needs for improvements [24] in frontline therapy and long-term follow-up, especially in countries with limited resources.

In Europe, the need for the development of strategies for long-term follow-up of survivors of childhood cancer was also discussed by Wallace [25] in 2001, and the British Childhood Cancer Survivor Study investigated late effects and formulated proposals for follow-up [26] (https://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/CCCSS/bccss/index.aspx).

Switzerland (https://www.childhoodcancerregistry.ch/index.php?id=3993) is using [27] a prospective cohort study, the Swiss Childhood Cancer Survivor Study (SCCSS), and its Cancer Registration Act that came into force on January 1, 2020, permits uniform and complete cancer registration.

In France, Schweisguth was invited in 1948, to join the Institut Gustave Roussy (IGR) in Villejuif, and she became the head of the pediatric oncology ward in 1952. She is considered the pioneer of pediatric oncology in Europe. Under her leadership, the International Society of Paediatric Oncology (SIOP) was established in 1969 [28].

In France, the Société Française de Lutte contre les Cancers et Leucémies de l'Enfant et de l'Adolescent, the French Society for the Fight against Cancer and Leukaemia in Children and Adolescents was established in 2002, and it is involved in long-term follow-up [29].

Bagnasco [30] analyzed late mortality and causes of death of more than 12,000 survivors of

childhood and adolescent cancer in the Off-Therapy Registry (OTR) that is integrated with L'Associazione Italiani di Ematologia e Oncologia Pediatrica (AIEOP), the Association of Paediatric Haematology and Oncology.

A survivorship passport was developed by Haupt [31] within the European Network for Cancer Research in Children and Adolescents (ENCCA) project (https://www.siope.eu/encca/), tested at the Istituto Giannina Gaslini in Genoa, Italy, and is expected to be used by survivors not only in Italy but in other countries as well. This passport can significantly improve the autonomy of former cancer patients and has already been proposed in the Austrian health-care system.

The first nationwide study performed in the largest cohort of Polish CCS concerning general health status, and frequency of organ dysfunction was published [32] in 2018. Trends in survival and late effects have also been described in Slovenia [33].

The Hungarian pediatric oncology group was founded in 1971, and since then, the whole country [34] uses the same oncological protocols.

Pediatric oncology is well structured in the Netherlands by the Dutch Childhood Cancer Oncology Group (DCOG). Survivorship care is organized by the DCOG-Long-Term Effects After Childhood Cancer (DCOG-LATER) group. The DCOG-LATER cohort includes 6165 5-year childhood cancer survivors diagnosed between 1963 and 2001 in the Netherlands [35].

Significant late effects can be studied using this cohort, and guidelines for survivors were also developed. In Europe, the DCOG-LATER team is a driving force for late effects research in the PanCare Network as well as in developing guidelines through international collaboration in the International Guideline Harmonization Group (www.ighg.org).

For childhood and adolescent cancer survivors in the Nordic countries, long-term follow-up was proposed [36], and a cohort of 47,697 CCS aged 0–19 years, with cancer as defined by the country-wide cancer registries of Denmark, Finland, Iceland, Norway, and Sweden during 1943–2005, was obtained [37].

Within the framework of the Society of Paediatric Haematology and Oncology, Gesellschaft für Pädiatrische Hämatologie und Onkologie (GPOH), the German Paediatric Cancer Registry (Deutsches Kinderkrebsregister) was founded in 1980 [38]. Today, around 95% of all new cancer patients up to the age of 18 years in Germany are reported to the registry and can be analyzed for, i.e., second malignancies [39]. Data of nearly 65,000 patients are available in the Registry in 2020.

In 1988, on behalf of the GPOH, a working group on somatic late effects was established in Germany, soon cooperating with Austrian colleagues. The follow-up recommendations of experts were implemented using basic and more specific recommendations for all cancer entities [40]. It was modified over time to the late effects surveillance system (LESS) [41], and a GPOH working group was started for long-term follow-up of survivors in Germany.

42.4 International Networks

The International BFM Study Group (I-BFM-SG) is an international network of leukemia and lymphoma groups. It consists of a number of national study groups from more than 30 countries worldwide, and its committees and working groups address specific aspects of research on pediatric leukemia and lymphoma.

The topics toxicity and late effects [42, 43] are worked on in the Early and Late Toxicity Education Committee (ELTEC).

The Erice statement was published as a consensus paper to discuss the fundamental issues of survivorship care [44]. It was revisited in 2016 to mirror the developments and changes that could be identified over the past 10 years [45]. Based on this document, the international parent organization Childhood Cancer International (CCI) produced a manifest on long-term follow-up care for children and adolescents with cancer [23].

In 2018, the World Health Organization (WHO) integrated childhood and adolescent cancer in a global health document that also pointed out the need for adequate follow-up and long-term care [46] (www.who.childhoodcancer.org).

The PanCare group [47] (www.pancare.eu) was established in 2008 as a multidisciplinary

pan-European network of professionals, survivors, and their families, with the aim of reducing the frequency, severity, and impact of late side effects of the treatment of children and adolescents with cancer. An important goal of PanCare is to work with the European community to increase awareness and research about CCS. Three European Union (EU) funded projects are the results of this international networking which focused on different aspects of childhood cancer long-term follow-up: PanCareSurFup [48], PanCareLIFE [49], and PanCareFollowUp [50].

It is the goal of the European Reference Network for Paediatric Cancer [51] to improve the outcomes of childhood cancer by reducing the current inequalities in different member states. This network also intends to establish mechanisms to facilitate the movement of information, guidelines, and knowledge via cross-border virtual tumor boards and virtual consultation systems, rather than through patients.

The International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) [52] is a worldwide endeavor initiated by several national guideline groups and the Cochrane Childhood Cancer Group, in partnership with the PanCare Guidelines Group, to collaborate in development of guidelines. Its main goal is to establish a common vision and integrated strategy for the surveillance of chronic health problems and subsequent cancers in children, adolescents, and young adult cancer survivors. Its aim is to reduce duplication of efforts, optimize the quality of care, and improve quality of life for children, adolescents, and young adult cancer survivors through international collaboration in the development of guidelines.

Guidelines developed to date include surveillance recommendations for breast cancer, cardiomyopathy, premature ovarian insufficiency, male gonadotoxicity, thyroid cancer and ototoxicity [53] (http://www.ighg.org/guidelines/topics).

A new tool for empowering citizens and cancer patients with ten key overarching rights, signposting what cancer patients should expect from their health system is described in the European Code of Cancer Practice.

The search of a genetic predisposition for developing late effects after childhood cancer therapy has just begun and more international studies on this subject are needed before results can be included in a schedule for a personalized oncological front-line therapy avoiding severe late effects without diminishing efficacy.

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43 Survivors in Their Social Environment After Cure of Cancer at Young Age

Katja Baust, Romy Streppel, and Gabriele Calaminus

Social outcomes are described by means of socioeconomic parameters, which are educational achievement, employment status, and income. Important is also the psychosocial situation: family planning, interpersonal relationships and the individual perception of the survivor's general living situation. Finally, we outline the relevance of posttraumatic mental growth as well as the survivor's perspective on their cancers experience and how this may influence society and vice versa.

The reader is also referred to Chap. 16 of this book.

43.1 Educational Achievement

Research has investigated long-term late effects of disease and treatment of cancer on occupational attainment or work ability. Given treatment-related late effects such as cognitive impairment, hearing loss due to treatment-related toxicity, functional impairment related to amputations or surgeries during education, survivors may be less likely to reach a similar educational level or educational achievement later in life than healthy individuals [1]. A meta-analysis by Frederiksen et al. [2] evaluated the evidence from more than 50 epidemiological studies, summarising heterogeneous results, which may be due to differences in definition and operationalization. In summary, it is stated that subgroups of survivors will be confronted with various socioeconomic difficulties in their life span.

In their meta-analysis, educational achievement is measured via repeating grades, special education or learning disability programs, school performance and educational level. Based on the evidence given by the reviewed studies, it was found that survivors of childhood cancer were more likely to be registered for special education programs and in general showed a poorer school performance compared to controls. Severely impaired by late effects are many survivors of a hematopoietic stem cell transplantation (HSCT) as described by Ness et al. [3]: they showed as one general finding next to others that survivors had educational difficulties such as requiring special education. Scholtes et al. [4] investigated a population of brain tumour survivors (BTS) classified by severity of the condition (defined by WHO grade) and identified the group formerly suffering malignant, aggressive high-grade tumours to be significantly less likely to graduate from high school. Other studies published results showing that fewer survivors report university education [5]. Gunn et al. [6] gathered data of BTS by means of qualitative interviews and reported learning disabilities in some participants

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of their sample ($n = 21$). In this study, half of the participants needed extra tutoring. Simultaneously, individual survivors without additional educational support had experienced difficulties because of motivational problems or difficulties in memory or motor functioning [6, p. 681].

Regarding repeating grades or the highest attained educational level, heterogeneous results were presented by Frederiksen et al. [2]: some studies describe generally a lower educational achievement for survivors of different childhood cancer entities [7], whilst other studies even depict higher educational achievement among survivors [1, 8]. In those studies, it is stated that the majority of survivors had a significantly higher educational level and occupational class than expected, even when controlling for their socioeconomic background. In this context, the concept of self-selection bias must be taken into account. There are differences concerning actual health status and level of education among the nonparticipant and participant population, i.e. [9].

Yet, authors coincide in the finding of additional determinants of educational outcome, which may explain deviant results. The most important determinants associated with a more unfavourable outcome concerning education later in life are the entities of cancer, for example, central nervous system (CNS) tumours, as described above, lymphoma, especially Hodgkin lymphoma and bone tumours. Younger age at diagnosis, neuroblastoma patients should be mentioned here, for example, and the required therapy, especially radiotherapy, contributes to an unfavourable outcome.

After more recent therapy strategies, ALL survivors, the largest group of childhood cancer patients, may suffer less severe late effects. However, in the past, a damaged morphology of the brain, detected by neuroradiology, correlated partly with reduced neuropsychological performances [10]. An accelerated aging is also suspected for some of those survivors [11].

The reader is also referred to the chapters of this book discussing the specific cancer entities.

43.2 Employment Status

Chronic health condition as a late effect of cancer disease or its treatment represents a particular risk factor of an adverse socioeconomic outcome. A meta-analysis revealed inconsistent findings regarding employment status: Frederiksen et al. [2] report survivors to have higher or similar unemployment rates compared to controls. A population-based study conducted in Sweden, which compared employment status among adult survivors of childhood cancer by the diagnostic groups leukaemia and lymphoma, CNS neoplasms and other cancers, only found an overall difference between survivors of a CNS neoplasm and controls [12]. No overall difference for non-CNS tumour survivors and controls was found. Several studies agree in this finding [5, 8].

Divergent results were presented by several studies, which found that survivors are two times more likely to be unemployed compared to their siblings and healthy controls [13, 14]. In accordance with data from North America, a large study, based on data of over 10,000 participants, conducted by the British Childhood Cancer Survivor Study (BCCSS) identified health problems or disability suffered by survivors, especially among CNS neoplasm survivors treated with RT, as the greatest risk of unemployment [15]. Such factors, in addition to lower educational achievement, might restrict the choice of occupation and will lead to lower-income jobs [4]. In line with this, a study conducted by Scholtes et al. [4] found out that former BTS were significantly more often unemployed than the norm group. Again, general factors influencing employment status and occupational level were identified: the survivors of CNS tumours investigated in this paper, especially those who had been treated with CRT, or survivors with onset of cancer at younger age were at greater risk for a higher unemployment rate compared to controls.

A lot of programs in many countries have been implemented in order to facilitate reintegration of survivors into everyday work life. One example from Germany is ‘Koordinationsstelle

psychosoziale Nachsorge' (KONA), a centre of coordination for psychosocial care for families with children during and after cancer treatment.

Prevention strategies comprise practical, emotional and informational support. One offer includes counselling and information sessions, e.g. about disability cards, disadvantage compensation or German pension insurance. Another important focus of their work is dedicated to counselling on career opportunities after childhood cancer, including support of job application and accompaniment to job interviews. An evaluative survey assessed the need for the quality of and the satisfaction with the offer of support of KONA in 866 supported families with children suffering from cancer. The survey also collected data on the psychosocial development of the survivors and revealed, among other results, that survivors attending occupation counselling services are mostly engaged in services for clarifying career orientation, career choice or career preparation, followed by support until a training place is found or the career prospects are clarified [16]. In addition, development of realistic career opportunities and support during the job application process are important elements of the counselling process. This underlines the need of survivors for support of integration into professional life.

43.3 Occupational Level and Income

For occupational achievements, again heterogeneous results are reported, whilst a French study published that survivors were more likely to be in higher occupational classes as managerial or professional jobs compared to controls in the national statistics [1]. BCCSS found out that survivors were less likely to have a higher occupational class compared to controls [15]. Yet, looking at intermediate level occupations, when survivors were compared to the group of routine or manual occupations, there was no evidence of a difference between survivors and the general population in the United Kingdom. Kirchhoff et al. [7] described a similar result; all survivors were less likely to be in professional occupations than siblings with a similar degree. This complements with findings of Scholtes et al. [4]: BTS show poorer educational attainment than controls, leading to less demanding jobs and, most probably, to a lower income. In agreement with these findings regarding income, most study results reveal that survivors had a lower income compared to controls [2]. Effinger et al. [17] investigated over 1000 astrocytoma survivors and found out that survivors report less frequent rates of household income ≥$40,000. More specific, research has shown that survivors who are employed are more often working in lower-income occupations with lesser chance of access to employee benefits, including health insurance, compared to healthy siblings [18]. Relating to this, every study included in the meta-analysis by Frederiksen et al. [2] reported the need of an increased uptake of various social security benefits by survivors of childhood cancer.

Again, differences in occupation and income were found to be associated with primary diagnosis: survivors diagnosed at a younger age, with a CNS neoplasm or treated with CRT were less likely to hold managerial occupations and more likely to have lower income compared to controls [15].

43.4 Romantic Relationships, Friendship and Parent-Child Relationship

Recent research identified certain subgroups of childhood cancer having difficulties to socially cope and find a partner [4]. In line with this, Mader et al. [5] conducted a cohort study of 160 young adult survivors and revealed that survivors of younger age at diagnosis were less likely to be married and to have a life partner compared to 999 controls. By means of qualitative interviews, Nahata et al. [19] examined the perceived impact of childhood cancer on adult survivors' romantic relationships (n = 40) and sexual/physical intimacy. Both positive and negative effects on romantic relationships were reported. Negative themes included but are not limited to physical

effects, feeling emotionally guarded and delayed dating. Positive themes were creating new perspectives, increased maturity and stronger bonds with partners. Regarding sexual/physical intimacy, 68% of participants reported a negative impact. Effective psychosexual interventions seem advisable. Also difficulties in platonic friendships were reported: Rey-Casserly and Diver [20] reviewed research in BTS, and findings revealed that BTS experience, inter alia, social adjustment problems, isolation and poor peer relations. Other studies collected data by means of interviewing parents and teachers, who reported BTS to have significant difficulties in social interaction [21]. In line with this, Ness et al. [3] report survivors after HSCT to show behaviours that indicated reduced social competence. Another study revealed results of 33% of BTS reporting 'difficulties in friendships, loss of friends, and/or difficulties in getting friends' [6, p. 680]. Yet, difficulties exposed as 'friends' reservation and incapability to deal with cancer and survivor's inability to participate in activities with friends because of physical limitations' (p. 680). Nevertheless, nearly half of the participants in the very same study report to have more than one good friend. In the study conducted by KONA named above, it is reported, that although the number of friends decreases, yet friendships become closer during and after cancer disease [16].

Cancer is thought to strengthen the relationship between survivors and their parents [22]. Survivors report that the close relationship to their parents made it more difficult to leave home and gain independence. Overprotection by parents makes this even more difficult. As described in the next section, this challenge may continue later in the lives of survivors.

43.5 Living Situation

Independence is a topic, which was identified to be very important to survivors [6]. Living independently, having a home of one's own and manage problems by oneself were mentioned to be important, yet, challenges arise in terms of emotional dependence on parents. Survivors expressed how difficult it was when they had to leave their parents [22]. Scholtes et al. [4] identified the group formerly suffering from malignant, aggressive high-grade BT to be associated with more unfavourable sociodemographic factors, such as still living with their parents or in sheltered living facilities; hence they were significantly less likely to live with a partner or in an independent living situation. Thus, independence manifests as another factor, which needs to be addressed in follow-up programs. For example, the German Childhood Cancer Foundation (Deutsche Kinderkrebsstiftung (DKKS)) offers courses and seminars for patients with various topics, directed towards self-empowerment or self-care.

43.6 Family and Life Planning

Childhood cancer survivors family planning describes a topic, which has long time been understudied whilst investigating the influence of childhood cancer on later periods of life. However, whilst heterogeneous and individual life plans as well as their acceptance increase in overall society of the western world, family planning reflects still an important societal value, for which methods diverging from the norm need further acceptance. Raising a family thereby mirrors an essential component of equal opportunities for survivors in adult life. Whilst medical conditions such as fertility, i.e. capability of reproduction, have been examined thoroughly (e.g. [23]), reproductive motivations need further investigations. For example, Korte et al. [24] report survivors to have a strong longing for biological parenthood. Those desires are, however, accompanied by a high fear of cancer recurrence, 'considerable uncertainty, distress, and unmet needs surrounding family-building decisions post-treatment' [25], (Abstract). Numerous concerns were reported. More specifically, concerns regarding in vitro fertilisation, surrogacy or adoption, with associated challenges such as uncertain likelihood of success, high costs and complicated laws regulating surrogacy and adoption were named [25]. Moreover, pregnancy concerns were mostly reported in studies exclusively focused on breast cancer patients, includ-

ing fear of cancer recurrence or tumour progression due to pregnancy [26]. In a systematic review by Schmidt et al. [27], all studies evaluated also reported on specific reproductive concerns by survivors, which were mostly related to negative consequences in terms of higher risk of cancer recurrence for the survivor or poorer health for the future child. Survivors also reported practical barriers to post-cancer parenthood, which were mostly financial or partner referred [26].

An effect of those concerns and negative emotions may be abstaining from reproduction despite strong desires, hence avoiding biological parenthood, or postponement of it. However, postponement increases the likelihood of infertility both in the general population and especially in the subgroup of survivors. To counteract this effect, counselling regarding fertility preservation is needed. One example gives the work of Borgmann-Staudt et al. [28], who made use of specifically prepared flyers and brochures to fill educational gaps and lack of knowledge of survivors. Their intervention successfully raised the level of fertility preservation knowledge in parents of older patients as well as parents with higher educational levels. Overall, the intervention improved patient and parent empowerment. The German Cancer Aid (Deutsche Krebshilfe (DKS)) followed a similar approach by publishing a series of booklets, named "Blaue Ratgeber" [29]. Also audio books and DVDs have been produced. The material is available for free and directed to patients, parents or interested people in general. They serve as an informational source about different types of cancer as well as general topics associated with it. One booklet deals with the topic 'desire to have children after cancer treatment'. In the United States, the COG provides 'The Children's Oncology Group Family Handbook 2nd Edition', available in three languages [30]. Also, more general information about childhood cancer and survivorship is given by a number of important Internet resources. These are, for example, the platform 'Together' of the St. Jude Hospital [31] or the German platform [32].

The reader is also referred to Chaps. 9, 10 and 12 of this book.

43.7 Posttraumatic Growth

The concept of secondary gain of a cancer disease also needs to be taken into account by investigating long-term effects of the disease: Gianinazzi et al. [33] surveyed a Swiss subsample of survivors in respect to the extent of posttraumatic growth (PTG). A majority of participating survivors indicate PTG in a dedicated questionnaire, most prominent in the scales 'relating to others' and 'new possibilities'. Survivors with older age at diagnosis ($p = 0.001$) and those with a longer duration of treatment ($p = 0.042$) indicated higher levels of PTG, whilst male survivors indicated lower levels. Also a qualitative study conducted by Gunn et al. [6] reports BTS describing positive mental growth stimulated by cancer and his treatment. This is expressed via 'a general expanding of worldview and a change in values, an increased approval of difference in others, and a positive attitude' [6, p. 680]. This might lead to survivors to live 'one day at a time', or permanently in the moment, which was reported by some participants.

Based on these positive experiences, some survivors are engaged in networks and communities to share their experiences with today's childhood cancer patients and society as well as to raise awareness for their concerns and care needs. One global approach is the International Childhood Cancer Day [34], '*a* global collaborative campaign to raise awareness and promote an increased appreciation and deeper understanding of the challenges faced by children and adolescents with cancer, the survivors and their families'. One more regional example constitutes "Regenbogenfahrt"—rainbow ride [35], a bike tour attended by around 100 former patients organised by German Childhood Cancer Foundation (Deutsche Kinderkrebsstiftung (DKKS)). Paediatric cancer clinics are visited on the route, and by conciliating a feeling of togetherness, the group aims to spend courage and hope to today's cancer patients. Simultaneously, former patients work pro bono, thus contribute to society and thereby increasing their own feeling of self-empowerment. As shown for chronic diseases in general, self-empowerment is assumed to have in turn a positive influence on quality of life [36].

A different approach with similar endeavours represents 'Mentorenprojekt'—mentoring project by Austrian Childhood Cancer Foundation (Österreichische Kinder-Krebs-Hilfe (ÖKKH), https://www.kinderkrebshilfe.at/das-sind-wir/survivors/mentoring-lehrgang). Besides other projects, ÖKKH offers seminars to teach survivors of cancer mentoring with children and adolescents with cancer in the hospitals. Former patients act as personal mentors to share experience, reduce fears and concerns and spend hope and courage. Also the 'little people organisation' in Romania runs a survivor project called 'Temerarii Club' (https://www.thelittlepeople.ro/en/what-we-do/).

A further example, which has proven valuable in the past, presents the survivors network of Childhood Cancer International [34]. Their mission is to connect childhood cancer survivors to each other. Sharing resources and experiences and providing information should facilitate the establishment of childhood cancer survivor groups and organisations. Those groups are found across the whole world and are organised nationwide. Aims include energizing and inspiring survivor groups worldwide or improving the care for survivors and representing and strengthening the voice of survivor groups.

The reader is also referred to Chap. 16 of this book.

43.8 Summary and Conclusion

Suffering cancer is a major critical life incident, and the way back to normal life is often long and difficult [37]. Risk factors for adverse outcomes were identified and information provided, how those might be prevented or dealt with in the long term. Empiricism agrees in the identification of particular risk factors for socioeconomic difficulties in later life: survivors of a CNS tumour, treatment with CRT and diagnosis of cancer at a young age negatively correlate with favourable outcomes in the long term. This group therefore needs intensified follow-up and care. Not at all, there are exceptions, which provide both relevant guidance for the application of the results and for future research. For example, even though younger age at diagnosis is correlated with more unfavourable sociodemographic outcomes, Gunn et al. [6] were able to point out that younger age at diagnosis, hence longer survival time, also might have positive effects: it is thought to diminish the effect of the cancer experience. Another buffer effect, which might reduce the risk factors impact, represents the factor of social resources: sustainable social relationships are an important resource for coping with critical situations [38]. Dill et al. [16] report a great majority of participant state to find support in the family, especially parents, a partner or a close friend. Insights like this should inform practical work in a larger extent—groups at high risk should be identified and, referring to the example above, protective factors such as social support should be strengthened in front of the background of secondary gain.

As late effects of cancer expose to be multifaceted, aftercare of cancer includes many fields which need to be addressed: an evaluative report of KONA [16] demonstrable reveals the need of survivors of practical support in terms of integration into professional life. Gunn et al. [6] report half of the participants in their sample to be in need of extra tutoring—survivors without additional educational support had experienced difficulties. Kuehni et al. [39] investigated 961 survivors within the frame of the Swiss Childhood Cancer Survivor Study (SCCSS), a nationwide, long-term follow-up study and found out, that 'continued educational support eventually may result in educational achievement similar to that achieved in the general population' (p. 1446). Hence, reintegration is essentially dependent on the individual support for the survivor.

Concerning interventions in the family setting, it is reported that some strategies successfully help re-entry into daily life: Studies on interventions for survivors and parents or the family as a whole reported significant positive changes in various psychosocial outcome parameters, e.g. social skills, posttraumatic stress, in children and their family members [37]. In a systematic review, a positive correlation between physical exercise and well-being in several subgroups was found. Based on empirical evidence, Peikert et al. [37] recommend to address siblings and the family as a whole in psychosocial interventions after the successful treatment of cancer. It should be also mentioned that the cornerstone

of all psychosocial aftercare is in the acute treatment phase. Even if this is not the focus of this chapter, two guidelines should be listed as examples. The 'Psychosocial Standards of Care Project for Childhood Cancer (PSCPCC), a group of paediatric oncology psychosocial professionals, collaborated with a larger interdisciplinary group of experts and stakeholders to develop evidence- and consensus-based standards for paediatric psychosocial care' [40, p. 419]. In Germany, the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) prepared guidelines for the psychosocial care of childhood and adolescent cancer patients. The main focus is on acute care [41] https://www.awmf.org/leitlinien/detail/ll/025-002.html. Psychosocial issues are also an important part of the DCOG later study [42].

Also, with regard to family planning pre- and post-therapy counselling and support should be offered: it was demonstrated that survivors of reproductive age express numerous concerns. Clinicians should address specific reproductive concerns in order to prevent avoidance and postponement of reproduction due to insecurities of survivors.

The numerous challenges named above survivors of cancer have to face in the long term of their disease stresses the need for a systematic and homologous assessment method across the different tumour entities and their treatment, in order to improve initial therapy and inform follow-up care and to meet each child's individual clinical needs. Most important, this assessment starts with diagnosis, continues in acute treatment and short-term follow-up and should be carried out as long as possible in a comparable manner during follow-up. For example, position papers by Limond et al. [43, 44] suggest a brief screening assessment of quality of survival of BTS (aged <5, aged >5) by means of assessing indirectly and directly affected core medical dimensions as well as emotion, behaviour, adaptive behaviour and cognitive functioning. Those screenings are essential to compare benefits and harms of treatment regimens and are useful to optimise health-care offers in the long term.

In response to research exposing late effects of cancer to be heterogeneous, counselling services for survivors in terms of social outcomes have been established broadly. Gunn et al. [6] report an important factor, which might be addressed by means of such programs: difficulties in friendships between patients and healthy peers were exposed as friends' reservation and incapability to deal with cancer. Raising awareness might serve as an informative source to reduce societies restraints and insecurities concerning cancer disease.

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44 Long-Term Follow-Up Guidelines and Organization of Long-Term Follow-Up Care for Childhood and Young Adult Cancer Survivors

Thorsten Langer, Jörn D. Beck, Alex Stein, Carsten Bokemeyer, and Judith Gebauer

44.1 Introduction

Despite a high long-term childhood cancer survival rate of approx. 80%, many of these patients suffer from late consequences of oncological disease and therapy, which can affect different organ systems as well as mental functions, and can range from mild restrictions to life-threatening diseases [1]. The prevalence of late effects increases with time passing since the initial oncological disease and does not reach a plateau even decades after the end of therapy [2]. Thirty years after cancer diagnosis, two-thirds of the patients are affected by chronic diseases [1]. Another US cohort of long-term childhood cancer survivors showed a cumulative incidence of chronic health problems of 99% at the age of 50 years [2]. In contrast, in the normal population, the cumulative incidence of all chronic health problems was 9%. The individual risk for the occurrence of certain long-term consequences can be determined on the basis of results of numerous studies, which were carried out in particular on American, but also on British and German long-term survivors of childhood and adolescent cancer [2].

However it should be kept in mind that the development of late sequelae depends on the cancer treatment as well as on individual risk factors. Modern therapy regimens were developed to improve therapy results while simultaneously reducing early and late toxicities.

Long-term follow-up (LTFU) guidelines are aiming at early detection and treatment of these new diseases on the basis of lifelong, risk-adapted follow-up examinations. In consideration of evolving treatment approaches and the diversity of possible long-term sequelae, multidisciplinary teams of pediatricians, internists, psychosocial staff, and specialists from other disciplines (aftercare board) are proposed to implement these recommendations in routine care offering structured LTFU for this patient cohort [3]. The high complexity of medical concerns as a result of the severe cancer illness and treatment, as well as the

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combination of medical and psychosocial needs in this survivor group, renders detection and treatment of late effects in the existing care system a major challenge [4]. However, it was shown that late consequences could be discovered earlier and hospital stays could be reduced in patients who receive regular long-term follow-up [5]. In addition, these patients have greater knowledge of their illnesses and their risks of long-term consequences, as well as greater health-related self-efficacy [6].

For many regions in Europe, there is currently no such offer of specialized LTFU care for childhood cancer survivors who are already adults. The existing programs in Germany (see also www.nachsorge-ist-vorsorge.de) are not yet sufficiently harmonized and coordinated.

44.2 International Guideline Harmonization Group

The International Late Effects of Childhood Cancer Guideline Harmonization Group, IGHG, is a worldwide group consisting of several national guideline groups and the Cochrane Childhood Cancer Group in partnership with the PanCare Guidelines Group in order to collaborate in evidence-based guideline development. The goal is to establish a common vision and integrated strategy for the surveillance of chronic health problems and subsequent cancers in childhood, adolescent, and young adult cancer survivors. This international collaboration in guideline development aims to reduce duplication of effort, optimize the quality of care, and improve quality of life for childhood, adolescent, and young adult cancer survivors.

The guidelines (evidence and recommendations) for the long-term follow-up of childhood, adolescent, and young adult cancer survivors for the specific late effects can be found at the IGHG webpage (www.ighg.org). For every topic, the underlying evidence and recommendations are presented. The recommendations are categorized using a four-color grading system: Green represents a strong recommendation. Yellow and orange represent moderate recommendations with a higher degree of uncertainty, meaning that other factors, such as the clinical scenario, family history, patient preferences, costs, and relevant risk factors, need to be considered in the decision-making process. Red is used to recommend against a particular intervention, with harms outweighing the benefits. Guidelines were developed for the topics, i.e., breast cancer, cardiomyopathy, premature ovarian insufficiency, male gonadotoxicity, thyroid cancer, and ototoxicity surveillance.

Long-term follow-up is performed following recommendations of the International Guideline Harmonization Group (www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the LESS-group (www.nachsorge-ist-vorsorge.de and www.kinderkrebsinfo.de).

44.3 How Is Long-Term Follow-Up Organized in Other Countries?

The American Childhood Cancer Survivor Study (CCSS), with 35,923 former patients, is one of the largest cohorts of long-term childhood cancer survivors [7]. Based on findings of studies concerning late effects of oncological therapy, structured follow-up recommendations were developed that are updated regularly [8]. Risk-adapted preventive examinations are carried out at defined intervals in specialized "late-effects clinics."

In the Netherlands, for more than a decade, all children and adolescents who had previously been diagnosed with cancer and who have completed regular oncological aftercare (usually 5 years after the end of therapy) have been invited to long-term follow-up (LTFU), which has so far been centralized at a few clinics and now at a single clinic in Utrecht. For this purpose, in collaboration with the "Dutch Childhood Oncology Group" (DCOG), an evidence-based follow-up plan was compiled that divides patients into three risk groups receiving long-term follow-up care at different intervals [9, 10]. With this structured approach, a high level of awareness of the possible occurrence of long-term consequences in this patient group and in addition regular coverage of costs for this

care offer by the health insurance companies have been achieved since 2016.

A similar concept, based on a risk stratification into three different groups, was also developed by the British National Cancer Survivorship Initiative (NCSI). As a result, a significant reduction in the frequency of hospital stays was achieved in certain risk populations.

Comparable multidisciplinary care services for this patient group have also emerged in other countries in Europe (including Scandinavia) and outside Europe [11]. The European late effects follow-up network "PanCare" attempts to coordinate the national structures and institutions that want to improve the long-term care of survivors of childhood cancer and adolescence, as well as the care and quality of life of these patients [12].

44.4 Pitfalls in Transition

After successful cancer treatment, childhood cancer survivors are usually under the supervision of pediatric oncologists up to the age of 18 years, even if the oncological acute LTFU has been completed after 5 years. During this time, especially with increasing time since the end of therapy, many clinics already offer a follow-up care program, which is supported by specialists for pediatric cardiology, endocrinology, pulmonology, and other disciplines [13]. At some clinics, patients care remains in the pediatric oncology clinic beyond the age of 18 years, especially if the oncological acute aftercare has not yet been completed. Sometimes they are referred to internal oncologists who continue this acute aftercare beyond the age of 18 years. Afterwards, many patients are discharged into routine medical care as cancer is considered to be cured and regular check-ups no longer appear necessary. However, with increasing knowledge of late effects occurring years to decades after the end of treatment, it is essential to care for these patients continuously in order to facilitate early detection and treatment of these sequelae. Due to the diversity of possible late effects, however, there is a corresponding person in internal medicine, as the spectrum of possible late effects affects almost all disciplines. In addition, these young adults, similarly to a genetic predisposition, carry an increased risk of complications that significantly exceeds that of the general population, but are often healthy at the time of transition. The complexity in the care of these patients can often not be depicted in the general practitioner setting, especially since the absolute number of these patients is low, so that many general practitioners care for none or only a few of these patients. As a result of these transition difficulties, care for adult long-term childhood cancer survivors is inadequate in many countries [13].

44.5 Structured National Intervention Programs Using the Example of the CARE for CAYA Program

Beside the evaluation of long-term toxicities, programs are currently established to comprehensively assess the current situation of survivors of childhood or AYA cancer and to specifically target developing problems. Along this line the CARE for CAYA program was established in 14 centers throughout Germany designed as an adaptive trial with an annual comprehensive assessment followed by needs stratified, modular interventions, currently including physical activity, nutrition, and psycho-oncology, all aimed at improving the lifestyle and/or the psychosocial situation of the patients (Fig. 44.1). Patients, aged 15–39 years old, with a prior cancer diagnosis, who have completed tumor therapy and are in follow-up care, and who are tumor free, will be included. At baseline (and subsequently on an annual basis) the current medical and psychosocial situation and lifestyle of the participants will be assessed using a survey compiled of various validated questionnaires (e.g., EORTC QLQ C30, NCCN distress thermometer, PHQ-4, BSA, nutrition protocol) and objective parameters (e.g., BMI, WHR, comorbidities like hyperlipidemia, hypertension, diabetes), followed by basic care (psychological and lifestyle consultation). Depending on their needs, CAYAs will be allocated to preventative interventions in the abovementioned modules over a 12-month period. After 1 year, the assessment will be

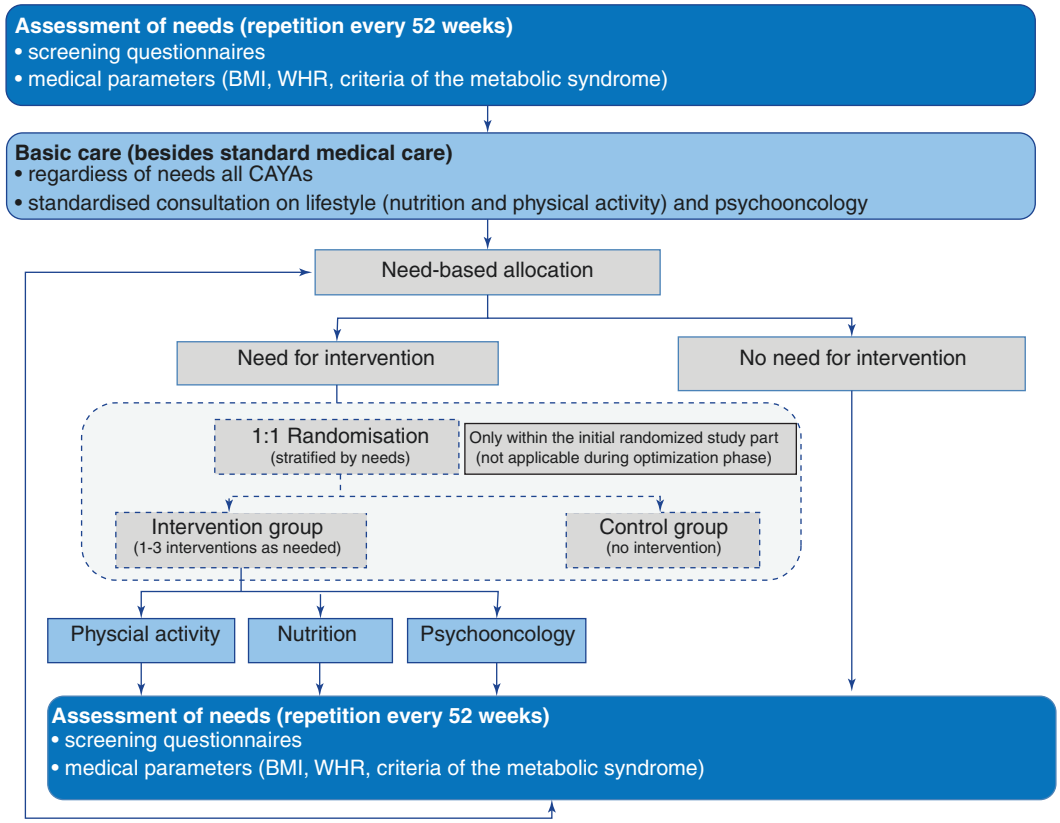

Fig. 44.1 Overview of the CARE for CAYA program including the initial trial phase

repeated, and further interventions may be applied as needed. During the initial trial phase, the efficacy of this approach will be compared to standard care (waiting list with intervention in the following year) in a randomized study. The program, funded by the Federal Joint Committee (GBA), has started beginning 2018 and already included >800 CAYA survivors.

44.6 Interdisciplinary Care Structures for Transition and Long-Term Aftercare

Different care models have been proposed to enable long-term care for children and adolescents with cancer. These efforts resulted in structures for joint long-term follow-up care between family doctors and oncological centers, family doctor-led models, and multidisciplinary LTFU teams connected to large clinics [14]. The patient's satisfaction with the care offered is largely dependent on the coordination of the necessary examinations, the communication of the doctors involved in the LTFU team, and their knowledge concerning late effects and long-term follow-up [15]. At many locations, multidisciplinary teams are preferred today, which offer all recommended examinations in one day and at the same time gain a high level of expertise in the care of these patients [3]. The core team consists of a pediatric oncologist and an internist who are supported by psychosocial staff and case manager. Physicians of other disciplines can also be invited to participate in the care of these patients. Within this LTFU team, a structured transition of patients from pediatrics to internal medicine can be organized. Additionally, knowledge about late

effects can be directly incorporated into the development of new therapy studies for childhood cancer. Additional topics such as lifestyle interventions to reduce risk and prevent possible late effects can also be addressed during the examinations at these centers [16]. Specialized LTFU centers, which have emerged at some University centers in recent years, cooperate closely with family doctors and with each other, that high-quality and complete long-term follow-up care of these patients can be achieved.

44.7 Perspective

As there is an increased risk for accelerated aging among cancer survivors [17], a standardized prospective documentation of therapy-associated long-term consequences could provide important insights into the frequency and course of these diseases. In addition, risk groups could be defined that could benefit from an intensified survivorship care program. For this purpose, genetic and clinical risk factors for late effects can be analyzed with the help of bio-samples from biobanks. Risk-adapted preventive medical examinations can reduce the morbidity of these patients in the long term and also save costs and worries by avoiding unnecessary examinations/hospital stays [18, 19]. The knowledge of late effects in certain risk populations can be incorporated directly into current cancer therapy recommendations and thus reduce the risk for new pediatric oncological patients to suffer from late effects in the future.

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