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Recent Advances in Childhood Cancer

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Although the incidence of childhood cancer is extremely low, it remains the second most common cause of death in children over the age of 1 year. Today, two-thirds of children with access to optimal medical treatment are cured of cancer, but the different types of cancer have highly variable cure rates. As determined by the German National Cancer Registry, children with Hodgkin's disease, retinoblastoma, and Wilms' tumour all have a 5-year survival rate of 86% or higher. Patients with acute lymphocytic leukaemia, non-Hodgkin's lymphoma, and germ cell tumours also have a favourable long-term prognosis, but children with many of the subtypes of acute myeloid leukaemia, central nervous system tumours, neuroblastoma, and hepatic tumours continue to have a poor prognosis. Depending on the type of cancer and the stage at which it is diagnosed, children may be treated with one or more modalities, including chemotherapy, radiotherapy, and surgery. Various combinations of chemotherapeutic agents have been extremely effective in inducing, consolidating, and maintaining remission. Advances in orthopaedic surgery have reduced the number of therapeutic amputations that are performed and made possible the administration of smaller doses of radiation. A growing knowledge of the immunohistological, genetic and molecular characteristics of many types of cancer have facilitated the accurate diagnosis and stratification of patients into risk groups. As a result, children can receive individualised treatment and many low-risk patients can receive less intensive therapy, thus avoiding some of the late sequelae of intensive cytotoxic therapy, such as severe organ damage, infertility, and second malignancies. © **1997 Published by Elsevier Science Ltd.**

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INTRODUCTION

THE INCIDENCE of cancer in children and adolescents is extremely low, and paediatric cancer accounts for only about 1% of all cases of cancer. One important source of information about the incidence of childhood cancer is the German National Cancer Registry, a nationwide database of childhood cancers [1]. This population and hospital-based registry, which classifies persons under the age of 15 years as children, indicates that the current incidence of paediatric cancer is approximately 14 per 100 000 children [1]. This rate is typical of incidence rates reported in other Western countries. Understandably, the incidence of childhood cancer per total population is more variable, depending on the age structure of individual national populations.

To put these statistics into perspective, two-thirds of children who have access to optimal medical facilities and resources can be cured of cancer. Despite this encouraging statistic, paediatric cancer continues to be the second most common cause of mortality following accidents in children above the age of 1 year [2–4].

THE SPECTRUM OF CHILDHOOD CANCER

The pattern of malignant diseases in children is very different from that observed in adults (Table 1) [5]. In children, carcinomas are responsible for less than 1% of all malignant diseases. Many childhood cancers have a mesodermal or mesenchymal origin. Approximately half are systemic, primarily affecting the haematopoietic system, while the others are solid tumours. Acute lymphoblastic leukaemia (ALL) is the most common malignancy, representing about 30% of all paediatric cancers and 60% of all systemic cancers. Non-Hodgkin's lymphoma (NHL) is the most common lymphoma, accounting for approximately 8% of paediatric cancers [2].

Many paediatric solid tumours, including astrocytomas, medulloblastomas, and ependymomas, arise in the central nervous system (CNS). Of peripheral solid tumours, the most common are neuroblastomas, nephroblastomas, and soft-tissue sarcomas. The most commonly occurring bone tumours are osteosarcoma and Ewing's sarcoma. Because bone tumours are most likely to occur during the second

Table 1. Incidence of childhood cancer from the German National Childhood Tumour Registry [5]

Cancer type	Relative incidence (%)*
Systemic	50
Leukaemias	36
Acute lymphoblastic leukaemia (ALL)	30
Acute myeloid leukaemia (AML)	5
Chronic myeloid leukaemia (CML), myelodysplastic syndrome (MDS), and other forms	1
Lymphomas	14
Non-Hodgkin's lymphoma (NHL)	8
(B) Burkitt's lymphoma	3
T-cell lymphoma	2
Other	3
Hodgkin's disease (HD)	5
Other forms (including Langerhans cell histiocytosis)	1
Solid	50
Central nervous system (CNS) tumours	15
Astrocytoma	5
Medulloblastoma	4
Ependymoma	2
Other forms	4
Neuroblastoma	8
Nephroblastoma (Wilms' tumour)	7
Soft tissue sarcoma	7
Rhabdomyosarcoma	5
Other forms	2
Bone tumours	6
Osteosarcoma	3
Ewing's tumours	2
Other forms	1
Germ cell tumours	3
Retinoblastoma	2
Liver tumours (hepatoblastoma, hepatocellular carcinoma)	1
Carcinomas and other malignancies	1

* Percentages are based on data from the German Childhood Cancer Registry, 1980–1994, and are rounded to whole numbers for each tumour.

decade of life, their incidence is underestimated in registries that exclude patients over the age of 15 years [2].

AETIOLOGY OF CHILDHOOD CANCER

The aetiology of childhood cancer is seldom known [6]. Although families of an affected child often link the disease to an environmental factor, such as exposure to insecticides or ionizing radiation, such a linkage can rarely be confirmed. Due to the long latency for most radiogenic cancers, few childhood tumours result from radiation. The International Agency for Research on Cancer (IARC) is presently coordinating the European Childhood Leukaemia/Lymphoma Incidence Study (ECLIS) to study the possible impact of the Chernobyl accident on the incidence of paediatric cancer in Europe [1]. Another ongoing study seeks to determine whether the administration of vitamin K to newborns as prophylaxis against haemorrhage can lead to an increased risk of leukaemia [1].

Our expanding knowledge of the cytogenetic and molecular changes that may occur in cancer, and especially of the mutations that arise in genes normally regulating orderly cell growth and differentiation, suggests that attributing cancer to a particular environmental exposure or to any other single factor is an oversimplification. We now know that many childhood cancers are associated with characteristic cytogenetic or molecular abnormalities [7, 8]. However, we still do not understand the relative contributions of critical events in tumour initiation and progression, random changes, and environmental factors to the make-up of the eventual tumour [2].

Viruses play a role in the aetiology of some types of childhood cancer. It is known that Epstein–Barr virus (EBV) is associated with Burkitt's lymphoma and nasopharyngeal carcinoma, and that hepatocellular carcinoma usually occurs in patients who have had prenatal or early childhood exposure to the hepatitis B virus (HBV). Researchers are now trying to establish the sequence of events that takes place between initial infection and the development of a malignant tumour [9, 10].

DIAGNOSIS OF CHILDHOOD CANCER

Childhood cancer is usually diagnosed in response to symptoms. This is problematic, since prognosis is primarily related to tumour burden and clinical symptoms may not become evident until the tumour burden is considerable. The characteristic symptoms of haematopoietic malignancies are pallor, fatigue, and thrombocytopenic haemorrhage, whereas palpable swelling, pain, and loss of function are the usual symptoms of solid tumours. Some childhood cancers may be detected by the presence of biological markers, including elevated levels of alpha-fetoprotein in hepatoblastomas and germ cell tumours of yolk sac origin, human chorionic gonadotropin in certain germ cell tumours, and catecholamine metabolites in neuroblastomas [11–13]. Techniques used in the diagnosis of childhood cancer include laboratory testing of blood, serum, urine, bone marrow aspirates, and other specimens. Today, immunochemical, cytogenetic, and molecular techniques often are used in conjunction with more routine techniques. X-ray examination, sonography, computed tomography (CT), magnetic resonance imaging (MRI), and other imaging techniques are used to describe the primary tumour and to detect its regional or systemic spread [2–4]. In leukaemias, the disease burden is generally classified according to the number of circulating leukaemic cells, the presence of lymphonodal disease, and organomegaly. Treatment stratification usually relates to burden parameters and to immunochemical or cytogenetic characterisation. For soft tissue sarcomas, nephroblastomas, germ cell tumours, and some other childhood malignancies, TNM (tumour, node, metastases) staging systems have been standardised. For other solid tumours, staging systems with a scale of I–IV are used; in these systems, stage I indicates local, stage II regional resectable, stage III regional non-resectable, and stage IV disseminated disease [2–4].

A TREATMENT OF CHILDHOOD CANCER

Most childhood cancers, and especially acute leukaemias and lymphomas, respond to cytostatic therapy. In treating peripheral solid tumours, systemic chemotherapy is usually complemented by local therapy with surgery and/or radiation. Brain tumours are routinely treated with surgery and radiotherapy, but the addition of chemotherapy is now under investigation.

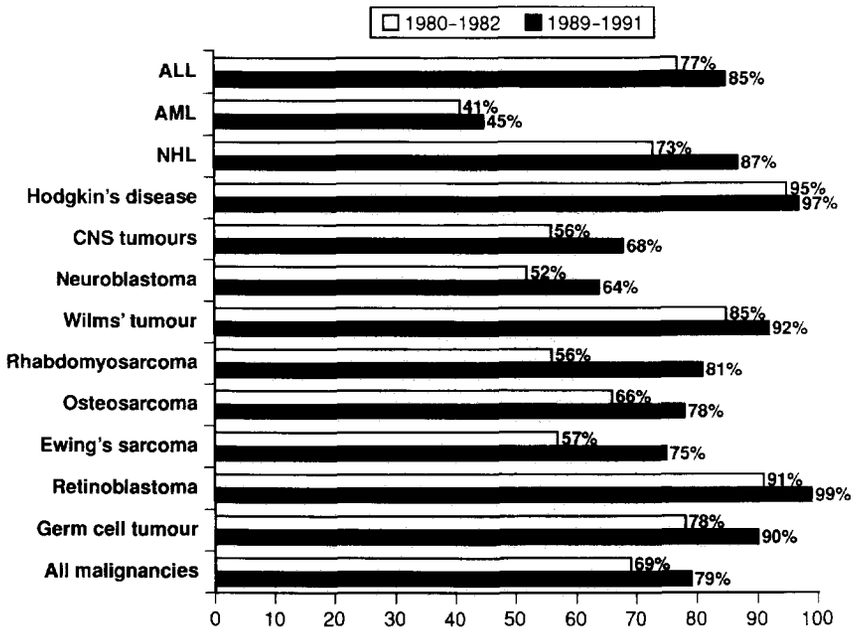

Figure 1. Paediatric cancer: 3-year survival rates according to year of diagnosis [15].

Because most childhood cancers proliferate and disseminate rapidly, 5-year survival rates were below 10% in the absence of systemic treatment. Due to the optimisation and standardisation of systemic combination chemotherapy that has occurred over the past two decades, advances have been made in the prognoses of most childhood malignancies, at least in industrialised countries [14]. Data from the German National Childhood Tumour Registry indicate that the global 5-year survival rate is approximately 70%, with a range of 20–95% depending on the type and extent of the malignancy [1]. The prognosis for patients diagnosed between 1989 and 1991, on average, has improved 10% compared with the prognosis of patients diagnosed between 1980 and 1982. This is mainly due to advances in chemotherapy as a result of multicentre, often multinational, trials (Figure 1) [15]. Since locoregional recurrences and metastatic disease tend to occur within two years of diagnosis, most patients surviving for 5 years from the time of diagnosis can be considered cured [14]. Survival data for the years 1973–1987 from the Surveillance, Epidemiology, and End Results (SEER) Registry, a U.S. database, indicate that, except for patients with ALL, more than 86% of patients who survive for 5 years after their initial diagnosis are still alive after 10 years [16]. The most common treatments and 5-year survival rates for common childhood cancers are listed in Table 2 [5].

SEER registry data indicate that females have better survival rates than males for most paediatric tumours, with the notable exception of Hodgkin's disease [16]. Analysis of population data from the U.K. has revealed a similar trend [16].

Table 2. Usual treatments and 5-year survival rates from the German National Childhood Tumour Registry for common childhood cancers [5]

	Treatment			
Diagnosis	Chemotherapy	Radiation	Surgery	5-year survival (%)
ALL	+	+*	–	75
AML	+	+*	–	42
NHL	+	+*	+†	76
HD	+	+	–	95
CNS tumour	+‡	+	+	60
Neuroblastoma	+	+	+	56
Wilms' tumour	+	+	+	85
Rhabdomyosarcoma	+	+	+	65
Osteosarcoma	+	–	+	63
Ewing's tumour	+	+	+	61
Retinoblastoma	–	+	+	96
Germ cell tumour	+	+§	+	84
All malignancies				69

*Prophylactic CNS radiotherapy when indicated; †Bulk removal when indicated, as in Burkitt's lymphoma; ‡Investigational treatment; §Depends on sub-entity; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; NHL, Non-Hodgkin's lymphoma; HD, Hodgkin's disease.

Acute lymphoblastic leukaemia (ALL)

ALL, and especially T-cell ALL, occurs more commonly in males than females. Its peak incidence is at approximately 4 years of age. ALL is thought to result from malignant transformation of a single abnormal progenitor cell. Leukaemic transformation and clonal expansion occur at different stages [6]. Immunophenotyping with monoclonal antibodies has become a standard tool in the diagnosis of ALL and has shown that 80% of all cases of ALL are B-cell-precursor ALL [6]. More recently, ALL immunophenotyping has been complemented by cytogenetic and molecular characterisation [17]. Some translocations have a strong association with a particular phenotype and a propensity for relapse [6].

Our recognition of the heterogeneity of ALL and the prognostic importance of leukaemic burden at diagnosis has led to the development of treatments of different degrees of intensity [6, 18]. Virtually all modern treatment regimens have four parts: induction of remission, CNS prophylaxis, consolidation, and maintenance therapy. Vincristine, prednisone, asparaginase, and an anthracycline may be used to induce remission. Traditionally, CNS prophylaxis has consisted of cranial irradiation and intrathecal therapy. Today, some patients are receiving investigational therapy consisting of intensified intrathecal therapy, usually with methotrexate, and a dose of cranial irradiation that is reduced from the conventional 24 Gy to 18 or even 12 Gy [18]. Radiotherapy is now omitted in treating some standard-risk patients [18].

Remission is consolidated by repeating the chemotherapy regimens used during induction (reinduction) or by using new combinations of drugs [6, 18]. Maintenance therapy usually consists of daily oral 6-mercaptopurine and weekly oral methotrexate and generally lasts for 2–3 years [6]. The question of whether males require a longer course of treatment than females is under investigation. Because B-cell ALL responds poorly to standard therapy [18], it is usually treated with high doses of alkylating agents and methotrexate, followed by citrovorum factor rescue [19].

During the 1970s, survival of patients with ALL improved markedly, increasing from 10–20% at the beginning of the decade to 50–55% by the end [20]. Today, standard 5-year survival in children with ALL is approximately 70%, but survival depends on the subtype of the disease and on a number of patient traits. In patients who relapse, the prognosis is generally poor; children who relapse within a short time after initial treatment have a less favourable prognosis than those with a longer remission. Patients with a poor response to an initial course of treatment with prednisone or another steroid have a poor prognosis [18], as do children under the age of 1 year [18]. Children with early relapses or the T-cell form of the disease have a 5-year survival rate of approximately 10%, while those who relapse more than 3.5 years from the end of therapy have a 5-year survival rate of 46% [21]. Patients with extracompartmental relapses, such as involvement of the CNS, have a better prognosis than those with early bone marrow relapses [22].

Allogeneic or autologous bone marrow transplantation is the treatment of choice for patients with relapsing ALL or a poor prognosis at initial diagnosis [23]. 'Good-risk' patients have a remission rate of approximately 60% following bone marrow transplantation, while the response rate is considerably lower in patients who have already received protracted treatment for ALL [6].

Acute myeloid leukaemia (AML)

AML occurs with equal frequency in females and males and has a fairly stable incidence throughout the first two decades of life. It is one-fifth as common as ALL [6]. Of the seven morphological subtypes of AML, many are related to specific chromosomal aberrations [17]. The most effective drugs for inducing remission are anthracyclines and cytosine arabinoside, although various combination therapies are also used. CNS prophylaxis and maintenance therapy appear to improve remission rates [24, 25].

Remission occurs in 70–85% of patients receiving conventional therapy for AML, but over 50% of patients will relapse if treated with conventional chemotherapy [6]. Because of this low remission rate, which has remained relatively stable over the last decade, bone marrow transplantation figures prominently in the treatment of AML [23, 24]. It is now being used experimentally during the first remission of AML, especially in patients with a poor prognosis, and some studies have reported improved relapse rates [24]. The M3 subtype of AML also has been treated successfully with all-*trans*-retinoic acid [6]. Second remissions in patients with AML tend to be short unless they are consolidated with bone marrow transplantation.

Non-Hodgkin's lymphoma (NHL)

NHL occurs more frequently in males than females, and its incidence rises steadily with age during the first decade. In terms of histology, NHL is less diverse in children than in adults. An infradiaphragmatic presentation usually has a B-cell origin, while a supradiaphragmatic presentation may have an immature or mature T-cell origin or a B-cell precursor origin [2].

Chemotherapy is the main treatment for NHL. Patients with mature T-cell or B-cell precursor lymphomas generally respond to regimens used in the treatment of ALL. Patients with mature B-cell lymphomas, on the other hand, are usually treated with alkylating agents and high-dose methotrexate followed by citrovorum factor rescue. This regimen is usually complemented with steroids, vinca alkaloids, anthracyclines, and epidophyllotoxins. Radiotherapy is seldom administrated as part of the initial treatment unless residual disease remains following intensive induction therapy [26].

Until recently, the prognosis for patients with NHL was extremely poor, with overall long-term survival in several studies reported at 18% [26]. Today, however, the overall 5-year survival rate for patients receiving optimal therapy is 76%, although survival depends upon the stage of the disease at diagnosis. Patients with early-stage disease have a long-term survival rate of more than 90%, while patients with stage III and IV disease have rates between 60 and 70%. Most recurrences occur within the first 6 months after diagnosis, and late recurrences are extremely rare in B-cell NHL [27].

Hodgkin's disease (HD)

HD is extremely rare before the age of 5 years; it is more common in older children, especially those older than 15 years. The clinical presentation and histopathological features are the same as in adults. In recent years, chemotherapy has generally been used in conjunction with radiotherapy to reduce the field and dose of radiation. Standard treatment consists of radiotherapy of the involved field at a dose of 25 Gy, followed by induction chemotherapy that is tailored to the stage of the disease [28]. The 5-year survival rate in HD is

approximately 95% [1], and the major goals of current research are a reduction in the cumulative doses of alkylating agents and procarbazine to prevent infertility, second malignancies, and other late sequelae of chemotherapy [28].

Central nervous system tumours

After ALL, CNS tumours are the most common malignancy in children, accounting for 15% of all childhood cancers. CNS tumours generally arise during the first decade of life. Most of the tumours occurring in younger children are embryonal neoplasms, including astrocytomas, medulloblastomas, and ependymomas [2].

Surgical removal of the CNS tumour is followed by radiotherapy, with the dosage adjusted for the tumour type and site. Medulloblastomas are usually treated with whole-brain and neuroaxis radiation equalling 35 Gy, with a boost to the area of the primary tumour up to a total of 55 Gy. In patients with astrocytomas, radiation is usually applied only to the area of the primary tumour. Current treatment protocols include chemotherapy, at least for high-risk patients whose tumours cannot be resected completely. Medulloblastomas, the most chemosensitive of all primary CNS tumours, are particularly responsive to alkylating agents, platinum compounds, and vinca alkaloids. The role of chemotherapy in other types of CNS tumours is still being studied. The overall survival rate for patients with CNS tumours is 55% [1, 2].

Neuroblastoma

Excluding cranial tumours, neuroblastoma is the most common solid tumour in children, accounting for about 8% of all cases of paediatric cancer. Approximately 90% of patients with neuroblastoma are diagnosed within the first 5 years of life, and there is a slow decline in incidence from the first to the fifth year. Neuroblastomas, which are derived from primordial neural crest cells, eventually populate the sympathetic ganglia [2]; they can appear almost anywhere in the body. Their characteristics and behaviours depend upon the extent of their histological differentiation and their anatomic location. Some regress spontaneously, while others disseminate rapidly [17].

In recent years, we have learned that advanced cases of neuroblastoma and poor-prognosis neuroblastoma are associated with specific cytogenetic markers [29]. In some cases of neuroblastoma, there is an amplification of the proto-oncogene *MYCN*; this amplification is associated with advanced stages of the disease, rapid tumour progression, and poor prognosis [30]. It is also well recognised that the neural differentiation of neuroblastoma is accompanied by increased levels of two catecholamine metabolites, vanillylmandelic acid and homovanillic acid. These abnormal levels are detectable in serum and urine and can be used to diagnose neuroblastoma and characterise its subtype [29]. Since meta-iodobenzylguanidine (MIBG) is taken up by catecholaminergic cells, MIBG scintigraphy can be used to evaluate bone and soft-tissue involvement [31].

Neuroblastoma differs from most childhood cancers in that most patients present with advanced disease [31]. At diagnosis, approximately 80% of patients have regional spread to the lymph nodes or skeletal metastases. [29]. Today, surgery, chemotherapy, and radiotherapy are all used to treat neuroblastoma. The prognosis for neuroblastoma is stage dependent and has changed little in the last two decades; the overall 5-year survival rate is 55% [1]. In patients who receive chemotherapy as primary or adjuvant therapy, 5-year survival rates are approximately 90% in patients with localised disease and 60% in those with regional disease. Radiotherapy is recommended to prevent local recurrences in patients with regional disease. In patients with disseminated disease, outcome is age dependent. Most patients under the age of 3 months are cured, but older children have a 5-year survival rate of less than 20% [32]. Several new treatment regimens are now under investigation for disseminated disease. These include the use of bone marrow ablative chemotherapy followed by autologous blood progenitor rescue and the administration of 13-*cis*-retinoic acid, MIBG, or ^{131}I-labeled antiganglioside GD2 antibody 3F8 [31].

Since, as mentioned previously, neuroblastoma causes an elevation of catecholamine metabolite levels in urine, several major screening programmes have been undertaken in an attempt to identify affected children at an earlier stage [29]. Preliminary results from Japan's nationwide monitoring programme indicate that the screening of children between the ages of 3 and 6 months identifies approximately 10 times more children with neuroblastoma than are identified in response to disease symptoms, but that mortality does not change [13, 29].

The Japanese monitoring programme has been based on the assumption that the highly malignant form of neuroblastoma derives from the benign form that can be detected during the first few months of life, but it now appears that this may not be the case [13]. Other types of mass screening programmes have been conducted or are in progress in Canada, the U.K., Germany, France, Austria, Australia, the U.S.A., Italy, and Norway [29]. These programmes are testing children in various age groups to determine whether it is possible to identify neuroblastomas with the potential for dissemination at an earlier, curable stage [14, 29].

Wilms' tumour (nephroblastoma)

Seventy-five per cent of all cases of Wilms' tumour occur in children under the age of 5 years; the disease is seldom observed in adults. The histology of Wilms' tumour is diverse, including blastemal, epithelial, and stromal cells [33]. Wilms' tumour is characterised using two histological classification systems, one developed in the U.S.A by the National Wilms' Tumour Study (NWTS) and the other in Europe by the International Society of Paediatric Oncology (SIOP) [33]. The most important prognostic indicators are the presence of anaplasia and sarcomatous stroma [33]. Genetic changes have been found in Wilms' tumour tissue at 11p13, 11p15, 16q, and 1p [34]. Excellent progress has been made in the treatment of Wilms' tumour, and today the 5-year survival rate is 86% [1]. Depending on the histology and stage of the tumour at diagnosis, chemotherapy, surgery, and radiotherapy may all be used [35]. Vincristine and actinomycin D are the chemotherapeutic agents that are most commonly used, while doxorubicin may be added in more advanced disease [35]. Patients whose tumours have spread beyond the renal capsule receive regional radiotherapy [35].

With optimal management, long-term survival of more than 80% has been attained even in metastatic patients with favourable histology [34]. New research directions in the treatment of Wilms' tumour include determining the feasibility of treating low-risk stage I patients only with surgery, identifying biological prognostic factors that might allow

for less aggressive treatment for some patients with stage IV disease, and assessing whether it is possible to substitute one or more less cardiotoxic drugs for doxorubicin [34].

Soft tissue sarcoma

Soft tissue sarcomas derive from primitive mesenchymal cells with the potential to differentiate into different types of supportive tissue [17]. Soft tissue sarcomas have a less diverse histology in children than in adults. The most common sites are the head and neck (40%), the genitourinary tract (20%), and the extremities (20%); other rhabdomyosarcomas are found on the trunk or other parts of the body. Embryonal rhabdomyosarcomas, which are associated with various genetic abnormalities, usually occur during the first decade of life, whereas alveolar rhabdomyosarcomas, which are characterised by the non-random chromosomal translocations t(2;13)(q35;q14) or t(1;13)(p36;q14), generally occur during the second decade [36]. The next most common types of soft tissue sarcoma are synovial cell sarcoma and fibrosarcoma [17].

Treatment of soft tissue sarcomas includes primary surgical removal when feasible or, alternatively, removal following chemotherapy-induced tumour shrinkage. Radiation therapy is used to control the residual tumour. Alkylating agents, vinca alkaloids, and actinomycin D are the most commonly used chemotherapeutic agents, but doxorubicin may also be used, especially in alveolar rhabdomyosarcomas. The intensity and duration of chemotherapy are determined both by the stage of the tumour and its histology; embryonal rhabdomyosarcoma is more chemosensitive than alveolar rhabdomyosarcoma. Tumours of the head and neck that are located near the meninges require carefully planned radiotherapy to reduce the risk of meningeal infiltration or penetration [37].

The overall 5-year survival rate in patients with soft tissue sarcoma is 66% [1], but outcomes are both stage and site dependent. Five-year survival is greater than 90% in patients with stage I disease compared with 20% in stage IV disease. Approximately 20% of patients present with stage IV disease. The cure rate for patients with orbital rhabdomyosarcomas is approximately 90%, but children with tumours of the extremities, which tend to have an alveolar histology, have a somewhat poorer prognosis. Fifty per cent of recurrences are local. Megatherapy regimens using blood progenitor rescue for patients with disseminated or relapsing disease are now under investigation [37].

Bone tumours

The most common type of bone tumour is osteosarcoma, followed closely by Ewing's sarcoma. The incidence of both of these tumours peaks during the second decade of life [38]. Histologically, osteosarcomas have a spindle cell pattern. The anatomical sites of Ewing's sarcoma are more variable; it arises both in long and flat bones, but most tumours are pelvic, femoral, tibial, or fibular [38, 39]. Histologically, Ewing's sarcoma comprises small round cells; immunohistochemical techniques can now be used to identify subtypes with neural differentiation [38, 39]. The discovery that over 80% of patients with Ewing's sarcoma have the translocation t(11;12)(q24;q12) promises to serve as the basis for more accurate diagnosis and staging procedures in the near future, applying molecular reverse transcription-polymerase chain reaction (RT-PCR) based techniques [38–40].

Both osteosarcoma and Ewing's sarcoma are aggressive tumours, and patients who receive local therapy alone experience rapid dissemination. In randomised trials of patients with osteosarcoma, for example, patients who received adjuvant chemotherapy had a 2-year actuarial survival rate of 66%, while the rate for those without such chemotherapy was 17% [41]. Thus, treatment for both osteosarcoma and Ewing's sarcoma involves the combination of systemic chemotherapy and local control [39]. Radiotherapy is seldom used in treating osteosarcoma, but it is an important modality in treating patients with Ewing's sarcoma. In both osteosarcoma and Ewing's sarcoma, the goals of surgery are to ensure complete removal of the affected bone and surrounding tissue while preserving the limb whenever possible.

Patients with osteosarcoma are usually treated with doxorubicin and cisplatin, followed by ifosfamide and high-dose methotrexate with citrovorum rescue factor [41]. Patients with Ewing's sarcoma generally receive alkylating agents and anthracyclines, followed by vinca alkaloids and actinomycin D, although the use of etoposide is also under investigation [39]. Local treatment for Ewing's sarcoma may involve surgical removal of the affected tissue, radiation, or a combination of these modalities. Because radiotherapy alone is associated with an increased risk of local recurrence, the preferred treatment is generally a combination of surgical removal and compartmental radiation. The value of hyperfractionated radiation is under investigation [42]. Megatherapy regimens with haematopoietic progenitor rescue are under assessment in patients with disseminated or relapsing Ewing's sarcoma [43]. Less experience with such an approach is available in osteosarcoma.

Overall 5-year survival rates are approximately 64% in children with osteosarcoma [1]. Long-term survival depends to a great extent on the size of the tumour at diagnosis. Cure rates are approximately 90% for small tumours and 50% for larger tumours. Five-year survival is nearly 100% in patients with small tumours who have a positive initial response to neoadjuvant primary chemotherapy and less than 20% in those with large primaries and a poor response. As survival rates improve, many patients with osteosarcoma receive limb-salvage surgery rather than ablative surgery; however, the rate of local recurrence is 10% after limb-salvage surgery compared with only 2% after ablative surgery. Limb-salvage surgery should always be preceded by a careful analysis of the individual patient's risk factors for recurrence [44].

The overall 5-year survival rate in patients with Ewing's sarcoma is 58%, which is only slightly less than the rate of disease-free survival [1]. The overall probability of relapse is approximately 33%, and the prognosis for relapsing patients depends on the interval between diagnosis and relapse [43]. In the Cooperative Ewing Sarcoma Study (CESS)-86, patients who relapsed more than 2 years after diagnosis had a 50% probability of event-free survival after 5 years, but those with an earlier relapse had only a 2% probability [43]. The prognosis also is poor for patients with multiple sites of relapse [39]. Some investigators have found that patients with lung metastases tend to have a better prognosis than those with multifocal bone disease [39, 43]. It also has been reported that patients with tumours of the extremities have a more favourable prognosis than those with truncal Ewing's sarcoma, especially in the pelvic region [38]. Tumour mass also is an important prognostic indicator [38].

Local therapy for Ewing's sarcoma is either surgical removal of the affected area or radiation, or a combination of

both modalities. Radiotherapy carries the risk of local recurrence which is correlated to the initial tumour size. Therefore, combinations of both surgical removal and compartmental radiation have been increasingly used in recent years to assure safe local control and avoid mutilation. Five-year survival rates between 50 and 60% can be considered standard in Ewing tumours. In relapse patients, as well as patients with disseminated disease at diagnosis, megatherapy regimens with haematopoietic progenitor rescue are being explored [39, 42, 43].

Retinoblastoma

Retinoblastoma, a malignant tumour of the embryonic neural retina, affects young children and may be present at birth. It can occur sporadically and can also be inherited in association with mutations in the Rb gene on the chromosome 13q14 region. In industrialised countries, retinoblastoma is usually diagnosed while the tumour is intraocular, the most common manifestation being leukocorea. Treatment consists of surgery and radiotherapy; the extent of radiotherapy is determined by the nature of the tumour, as characterized by the Reese–Ellsworth staging system. In patients who receive an early diagnosis, 5-year survival rates are approximately 96% [1]. Patients with extensive or metastatic disease have a poor prognosis [45].

Germ cell tumours

Germ cell tumours derive from primordial germ cells and may arise within the gonads or at an extragonadal site. Most of the germ cell tumours found in paediatric patients are mature or immature teratomas, germinomas, embryonal carcinomas, or yolk sac tumours; choriocarcinomas or gonadoblastomas occur less frequently. Elevated serum alpha-fetoprotein is a marker for yolk sac tumours, whereas elevated human chorionic gonadotropin is a marker for choriocarcinomas and embryonal carcinomas [2].

The specific treatment for germ cell tumours depends on the histology of the individual tumour, but involves surgical removal, either initially or following pretreatment. Most germinomas respond to radiation therapy. Highly malignant germ cell tumours, such as yolk sac tumours, embryonal carcinomas, and disseminated germinomas, respond favourably to combination chemotherapy, usually with cisplatin, carboplatin, vinblastine, etoposide, or ifosfamide [46]. Five-year survival rates are approximately 83% [1]. In view of this high cure rate, research is focusing on the accurate identification of high-risk patients who require maximum-intensity chemotherapy.

Liver tumours

Only about 1% of paediatric cancers are malignant liver tumours. Hepatoblastomas occur more commonly than hepatocellular carcinomas, usually in children under the age of 2 years. Hepatocellular carcinomas tend to occur in older children, especially those in the second decade of life, and usually follow previous infection with HBV. Elevated alpha-fetoprotein levels are more likely to occur in patients with hepatoblastoma than in those with hepatocellular carcinoma [2].

Surgical removal is the keystone of therapy for liver tumours. Because hepatoblastomas are chemosensitive, administration of preoperative doxorubicin or cisplatin to obtain shrinkage is a frequent approach. Hepatocellular carcinomas are less sensitive to chemotherapy than hepatoblastomas. Complete excision of paediatric liver tumours is possible in approximately 50% of cases [2, 47]. Because cure is dependent on resectability, the 5-year survival rate for patients with hepatic tumours is only 47% [1].

CONCLUSION

Tremendous progress has been made in the last 20 years in the management of childhood cancer. Aggressive multidisciplinary treatment and coordination of high-quality clinical research by paediatric oncologists has resulted in the cure of two out of three children with paediatric cancer. This comprehensive approach to childhood cancer, including the inclusion of children into state-of-the-art clinical trials has led to control of these rare diseases, which would be difficult to investigate without the efforts of cooperative groups conducting similar protocols. As we approach the 21st century, several concerns in dealing with childhood cancer are paramount. The first is that all children have access to state-of-the-art, well-coordinated care [48]. It is important that we continue to standardise and optimise supportive care to treat acute conditions associated with the immunocompromised state. Vigorous efforts directed at the prevention of late-onset organ toxicity, infertility, and second malignant neoplasms should continue. All of these approaches can lead to the assurance that most patients who survive childhood cancer will go on to lead normal and productive lives.

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