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REVIEW ARTICLE

# Infants with Cancer: A Unique Population

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Cancer occurring in infants often has a clinical and biological behavior that is different from cancers occurring in older children. The histological distribution of cancers in infants is different from that in older children. The five most common types of cancer occurring in infants in Taiwan are leukemia, neuroblastoma, germ cell tumors, central nervous system neoplasms, and retinoblastomas. Cancer in infants represents a unique situation in which to study cancer etiology. A significant number of infants with cancer have a genetic susceptibility to the disease; however, some emerging studies suggest a potential role for environmental, dietary, and drug exposures in the etiology of infant cancers. Further definitive trials will be necessary to establish clear associations, however. Because of their very young age and the immaturity of many of their physiological systems, the approach to treatment in young infants differs from that in older children. The infant's response to treatment also differs from older children, indicating the unique biological properties of cancer in infants that may explain different clinical outcomes in this unique population. Infant acute lymphoblastic leukemia has a much inferior outcome compared with the outcome in older children. In contrast, neuroblastoma in infants has a superior outcome to that seen in older children. The care of infants with cancer is extremely challenging as a result of their increased vulnerability to the acute complications associated with intensive, multimodal treatment and to the long-term sequelae of chemotherapy and radiotherapy on the rapidly growing and developing infant. The chemotherapy-related toxicity seen in very young infants of less than 3 months of age may be due to a lower total body water content, lower P450 enzyme activity, lower serum protein binding, and immature renal function. The high susceptibility of immature tissues to radiotherapy-induced damage has led to the delivery of radiotherapy being limited in this age group. Protocols specific to the characteristics of this population are currently yielding promising results.



## 1. Introduction

Cancer during the 1st year of life represents approximately 10% of all cancers in children under the age of 15 years.[1–7] The infant population has a frequency distribution of tumor types which differs from that in older children. In addition, the relative frequencies of the major subtypes of cancer in infancy vary among countries and racial groups.[1–7] Infant cancers have distinct clinical manifestations and responses to chemotherapy and radiotherapy.

This paper reviews the major types of cancer in infants, contrasting their characteristics and behaviors with cancers in older children up to 15 years of age. We also contrast the incidence of cancer in infants in Taiwan with the incidence of cancer in infants in different countries. We discuss the current knowledge of the major types of leukemia, brain tumors, and extracranial solid tumors seen in infants.

## 2. Epidemiology

Recent data from the Surveillance, Epidemiology, and End Results program of the USA indicate that the incidence of all types of cancer in infants is 234 patients per million infants.[8] The incidence in the USA for children aged 0–14 years has been increasing at a rate of 0.6% per year over the period 1993–2010.[9] Similarly, the Israel National Cancer Registry has recently reported an incidence of cancer in infants less than 1 year of age of 228.5 per million infants during the period 1998–2007,[9] compared with the estimated incidence of malignancy in all children aged 0–14 years of 153.4 per million.[10] Infants with cancer account for 10.2% of all children with cancer younger than 15 years of age. This unique pediatric

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population therefore has a higher incidence of cancer.[9] Among the infants, neonates during the first 28 days after birth are at an even higher risk of cancer.[2,9,11]

In Taiwan, the incidence of cancer in children aged 0–4 years has been increasing 1.5 times since the 1980s (Figure 1).[12] Although government-funded universal health coverage can encourage healthcare utilization, which might have contributed to rising cancer incidence and lowing cancer mortality (Figure 1),[13] the changing trends in incidence and mortality remained significant after the implementation of national health insurance in 1995.[12] These data may suggest that an increasing environmental exposure in the process of industrialization may be related to the rising incidence of cancer in infancy.

There is a difference in the distribution of cancer types in infancy compared with that in children younger than 15 years of age. Table 1 gives the percentage distribution of major types of malignancies in infants and children less than 15 years of age in the USA.[14] The relative frequencies of the major types of cancer occurring in infancy vary among countries and racial groups.[2–7] Although the ranking varies, the four most prevalent cancer types are similar in most countries: neuroblastoma (NB), leukemias, brain tumors, and retinoblastoma (RB). In contrast with the USA,[8] infant cancer in Taiwan surveyed in 1995–2004 showed a higher incidence of leukemias, germ cell tumors (GCTs), and hepatic tumors; the incidence of brain tumors, NB, and renal tumors was slightly lower (Figure 2).[15]

With advances in treatment and technology, the mortality of infants with cancer has decreased dramatically over the past 30 years (Figure 1).[12] Unfortunately, the current mortality in Taiwan is higher than Japan by 3-fold (Figure 3). In a study of 26 high-income Organization for Economic Cooperation and Development countries, Taiwan ranks 23rd for infant mortality due to cancer (Figure 3).[16] The cause of this difference warrants further study. In addition, greater efforts should be directed to curing our infants with cancer.

## 3. Etiology

Cancer in neonates and young infants has the potential to provide important information about early developmental oncobiology and suggests a close relationship between oncogenesis and teratogenesis. Genetic susceptibility (acquired or constitutional), parental, intrauterine, and immediate postnatal environmental exposures, and transplacental metastasis should be considered as causes of cancer in infants. Children with congenital abnormalities have a two- to fourfold risk of developing cancer compared with children without congenital anormalities.[17]

Congenital abnormalities may be associated with genetic susceptibility to developing cancer in infancy. Hereditary RBs and familial Wilms tumors (WTs) occur at an earlier age than sporadic RBs and WTs. Spector and coworkers described very low birth weight and parental tobacco before and during pregnancy to be associated with an increased risk of hepatoblastoma (HB).[18,19]

**Table 1** Percentage distribution of the major types of cancer in children <15 years of age and in infants in the USA. Modified from Dreyer et al[14]

| Histology | Children <15 years of age (%) | Infants <1 year of age (%) |
|---|---|---|
| Leukemia | 31 | 14 |
| Central nervous system | 18 | 15 |
| Neuroblastoma | 8 | 27 |
| Lymphoma | 14 | 1 |
| Renal | 6 | 11 |
| Sarcoma | 11 | 5 |
| Hepatic | 1.3 | 3 |
| Teratoma | 0.4 | 6 |
| Retinoblastoma | 4 | 13 |
| Other | 6.3 | 5 |

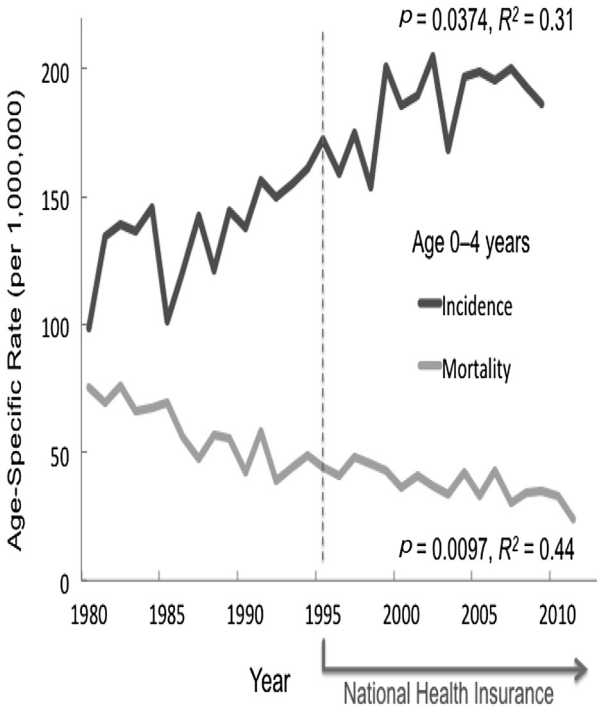


**Figure 1** Long-term trends of cancer incidence (black line) and mortality (grey line) rates in infants and toddlers aged 0–4 years in Taiwan. The significance of recent trends after the implementation of national health insurance in March 1995 was evaluated by linear regression ($p < 0.05$). Data are from the Taiwan Cancer Registry.[12]

McCall et al reported that maternal use of temporary hair dyes (aromatic amine precursors of nitrosamines) before or during pregnancy may have a possible role in the occurrence of HB.[20] McLaughin et al reported an increase in the birth of children with HB after *in vitro* fertilization and the use of fertility drugs.[21] Similarly, a British study found a trivial increase in the absolute risk of HB and rhabdomyosarcoma among 106,013 children born after assisted conception.[22]

High birth weight (>4 kg) has been associated with a 26% overall increased risk of childhood leukemia.[23] Another study reported a correlation between high birth weight (>4 kg) and mixed lineage leukemia (MLL) rearrangements. High birth weight is positively correlated with insulin-like growth factor-1 levels. These increased insulin-like growth factor-1 levels may be etiologically relevant for children with one genetic mutation present before birth.[24,25] Inherited genetic alleles, such as those producing reduced function of NAD(P)H:quinone oxidoreductase are more frequently seen in infants with leukemia.[26–29] One study described a higher frequency of a deletion of glutathione-S-transferase (GSTT1 and GSTM1) gene in the parents of infants with leukemia.[30]

The NAD(P)H:quinone oxidoreductase and glutathione-*S*-transferase proteins detoxify many carcinogens; their reduced or absent function may result in the accumulation of these toxins.[26,30] In addition, alterations in folate metabolism may protect the subject from developing certain subtypes of acute lymphoblastic leukemia (ALL). For example, Wiemels et al showed that the gene frequency of the *C677T* polymorphism of methylenetetrahydrofolate reductase, leading to a low-function enzyme, is significantly lower among infant patients with ALL with an *MLL* rearrangement.[31]

Epidemiological studies have correlated many factors with an increased incidence of infant leukemia, including maternal behavior (low folate intake, antihistamine, metronidazole antibiotics, estrogen, dipyrone analgesics, herbal medicines, caffeinated beverages, alcoholic beverages, and marijuana use), paternal behavior (smoking, pesticide exposure), and medical or

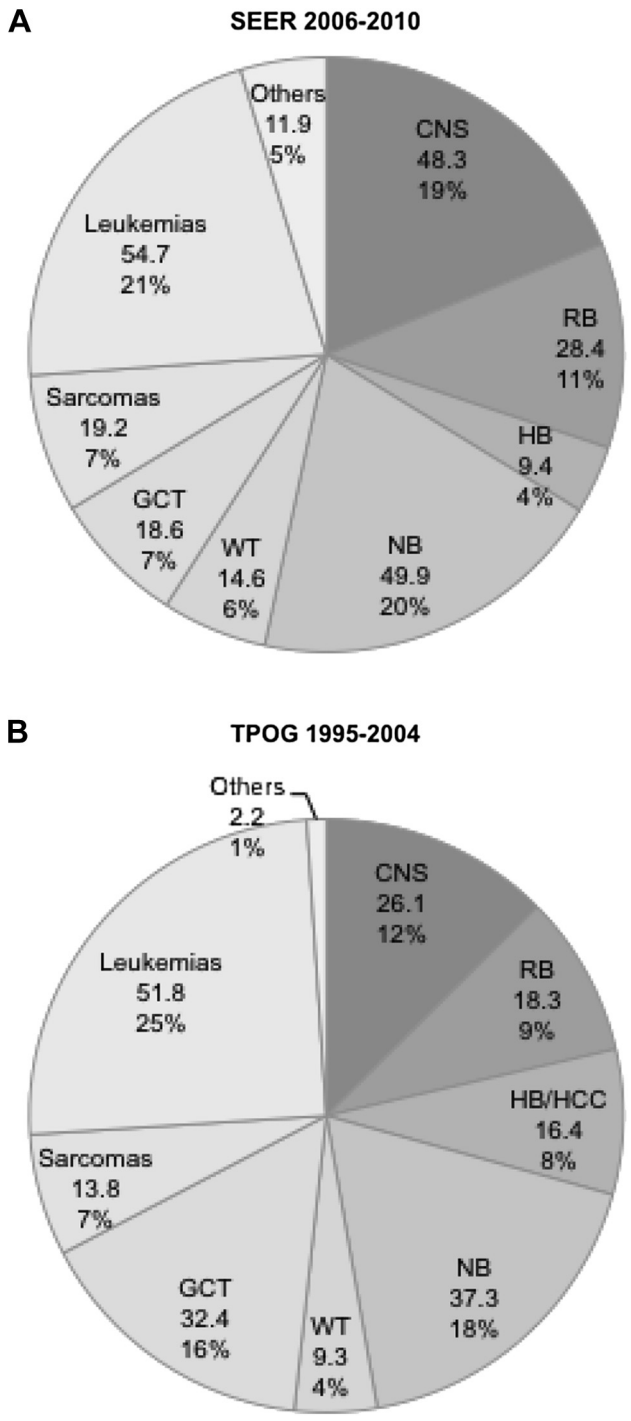


**Figure 2** Incidence and relative distribution of types of cancer in infants. Numbers represent incidence per 1,000,000 subjects less than 1 year of age. (A) Data from 18 cancer registries in the USA[8] with an overall incidence of 255.0 cases/million/year (modified from the Surveillance, Epidemiology, and End Results Program[8]). (B) Data from Taiwan with an overall incidence of 207.6 cases/million/year (modified from Yang et al[15]). CNS = central nervous system; GCT = germ cell tumor; HB = hepatoblastoma; HCC = hepatocellular carcinoma; NB = neuroblastoma; SEER = Surveillance, Epidemiology, and End Results Program; TPOG = Taiwan Pediatric Oncology Group; WT = Wilms tumor.

environmental radiation.[32–37] Given the emerging data regarding the potential role of many environmental, dietary, and drug exposures in the etiology of infant cancers, definitive trials that confirm clear associations are necessary.

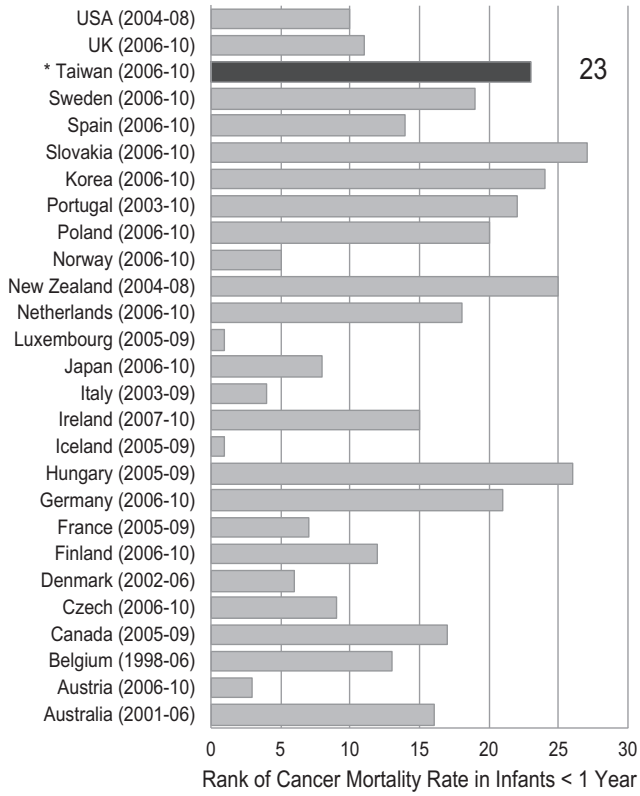


**Figure 3** Infant mortality due to cancer in Taiwan ranks 23rd among 27 high-income countries in the world. Higher numbers of rank in abscissa represent higher mortality. Data were extracted from an open-source online database established by Professor Tsung-Hsueh Lu at the Research Center for Health Data, National Cheng Kung University, Tainan, Taiwan.[16]

## 4. Common types of cancer in infancy

Table 2 summarizes the cardinal features of the major types of cancer in infancy. In general, the treatment of childhood cancer, especially cancer in infants, is mostly "risk-directed". The clinical protocol for each disease group usually stratifies the patients into two or three risk groups. The risk is determined by major clinical and biological parameters identified as independent prognostic factors in previous prospective or retrospective trials.

The goal for low-risk disease is to give the infant minimal treatment that minimizes toxicity, but does not compromise their survival rates. Some tumors, such as those showing spontaneous regression, are very low risk and should be studied because of their implications for tumor cell differentiation. The intermediate risk patients may still be cured by intensifying the chemotherapy dose.

The long-term survival rate among patients with high-risk cancer is usually less than 50%. These cancers should be treated intensively and studied for novel therapeutic targets and strategies; Phase II and III clinical trials using new drugs or drug combinations with previously proved efficacy may best benefit these patients. Research on novel biomarkers could help future patients to be assigned more accurately to the correct risk group.

### 4.1. Leukemias

Infant leukemia is ranked as the most frequent cancer in infants in Taiwan. Acute leukemia comprises 25% of cancers in infants (Figure 1). ALL and acute myeloid leukemia (AML) account for 11.0% and 14% of these cancers, respectively.[7] Infant leukemia accounts

**Table 2** Summary of common cancers in infancy

| Cancer type | Cell origin | Primary site | Metastatic sites | Common symptoms/signs |
|---|---|---|---|---|
| Acute lymphoblastic leukemia | Lymphoid precursor | Bone marrow or thymus | (Systemic) | Fever, anemia, bleeding |
| Acute myeloid leukemia | Myeloid precursor | Bone marrow | (Systemic) | Fever, anemia, bleeding |
| Brain tumor | Neuroepithelium | Brain | (Very rare) | Increased intracranial pressure, neurological signs |
| Retinoblastoma | Retinal progenitor or transition cells | Retina | Bones, brain | Leukocoria |
| Hepatoblastoma | Hepatogenesis (heterogeneous) | Liver | Lungs | Incidental |
| Neuroblastoma | Neural crest | Adrenal, sympathetic nervous system | Bone, bone marrow, liver | Incidental |
| Wilms tumor | Metanephron | Kidney(s) | Lungs, liver | Hypertension, hematuria |
| Germ cell tumor | Germ cells | Gonad, trunk | Lungs, liver | Prenatal diagnosis |
| Soft tissue sarcomas | Mesodermal cells | Various | Lungs | Incidental |

for 5–10% of all childhood leukemia. There is a clear female predominance among infants with leukemia, especially in infants with ALL.[1] Infant leukemias include subgroups of ALL and AML with distinct clinical and biological natures, including MLL gene rearrangements. MLL gene translocations or rearrangements were found in 80% of infants with ALL and 50% of infants with AML. In contrast, MLL rearrangements have only been noted in 2–8% and 10–20% of older children with ALL and AML, respectively. Central nervous system (CNS) leukemia, hepatosplenomegaly, and cutaneous manifestations occur more commonly in infants with leukemia than in older children. Fifty percent of neonates with leukemia present with leukemia cutis ("blueberry muffin baby").

### 4.2. Acute lymphoblastic leukemia

Infants represent 2–5% of pediatric cases of ALL.[38] As with ALL in older children, white ethnicity is associated with a higher incidence of ALL.[2] Infants often have high white blood cell counts at diagnosis ($>300.0 \times 10^9$/L) and more often have hepatosplenomegaly and CNS leukemia than older children. In contrast with older children, female infants may be at increased risk.

Infant ALL usually presents with $CD10^-$ early precursor B immunophenotype ($CD34^+$, $CD19^+$) and the blast cells often express myeloid-associated antigens (CD15/CD65s) and myeloperoxidase RNA.[39–42] This indicates that these leukemias originate from very early B-cell progenitors with both lymphoid and myeloid antigens.[41] CD10-negative and age less than 3–6 months have been two of the strongest adverse prognostic factors.[39,42–47] CD10 negativity is associated with early B-cell precursors with myeloid expression and this could explain why these leukemias are resistant to standard ALL chemotherapy.[48] Infants who were 6–12 months old at diagnosis have a better event-free survival (EFS) of between 40% and 71%; infants less than 6 months of age at diagnosis have a poor EFS from 8% to 40%.[44] The response to a 7-day prednisone prophase is significantly predictive of outcome. Good responders have a 4-year EFS of 56%, compared with 30% in poor responders.[49]

It is well known that MLL rearrangements are associated with a poor prognosis in infant ALL. Using a conventional cytogenetics method, 16–40 % of MLL rearrangements are not detected. Because there are more than 55 translocation partners, fluorescence *in situ* hybridization is currently the standard method for the detection of MLL rearrangements.[50] Southern blot and MLL fusion chip have higher sensitivity than fluorescence *in situ* hybridization. Among the translocation partners, *MLL-AF4* is seen most commonly in ALL and *MLL-AF9* in AML.[50] Infant ALL patients without *MLL* rearrangements are 80–96% CD10-positive, without myeloid antigens, and having a much better 5-year EFS of 60–74%.[44,49,51] The MLL protein is critical for normal hematopoietic differentiation.

In *MLL*-rearranged ALL, overexpression of the *FLT3*, *HOXA9*, and *MEIS1* genes and partial deletion of the Ikaros (*IKZF1*) gene are frequently found. Small molecule inhibitors of *FLT3*, midostaurin (PKC412) and lestaurtinib (CEP-701), could induce apoptosis in the majority of samples from patients with ALL with *MLL* rearrangements.[52,53] In another study, lestaurtinib showed synergy with several chemotherapeutics in samples from infants with ALL.[54] *FLT3* inhibitors are probably a biological treatment in *MLL*-rearranged ALL in infants.[54]

As ALL blasts with *MLL* rearrangements are resistant to steroid and asparaginase treatment, but sensitive to cytarabine, recent protocols for infants have intensified treatment and combined both ALL and AML protocols, particularly utilizing high-dose cytarabine, leading to improved outcomes.[49–51] The role of hematopoietic stem cell transplantation in infant leukemia is controversial.[50]

### 4.3. Acute myeloid leukemia

The highest incidence of AML in children is in infancy. Infant AML accounts for 6–20% of all pediatric patients with AML.[38] Infants with AML have a slightly higher incidence than those with ALL, and more 11q23 abnormalities, which is different from the incidence seen in older children. In morphology, French–American–British types M4/M5 (myelomonocytic/monocytic) and M7 (megakaryocytic) are more common during the 1st year of life. Down syndrome, Noonan syndrome, neurofibromatosis type 1 mutations, or myelodysplastic syndrome with monosomy 7 or del(7q) are predispositions to early AML.

Ten percent of infants with AML have these predisposing conditions.[55] Infants with Down syndrome and Noonan syndrome may also develop transient abnormal myelopoiesis (TAM) from 30 weeks' gestation to 6 months of life. This is associated with specific mutations in the GATA1 gene.[55] Most patients with TAM attain spontaneous remission in 1–4 months. Unfortunately, one-third of patients with TAM develop M7 AML by the age of 3 years.

The same standard childhood AML protocols are applied to infants and to older children with AML. The outcome for infants with AML is not different from that of older children. More recent trials have all shown improved EFS of up to 58%. Most strikingly, the Japan Infant Leukemia Study Group reported 35 infants with AML having a 3-year EFS of 72%.[56] A combination of cytarabine, doxorubicin, and etoposide has been shown to be effective in treating infants with AML.[57] The only significant prognostic factor for infant AML is a high white blood cell count ($>50 \times 10^9$/L). In contrast with infants with ALL, translocations in infants with AML are not factors for poor prognosis.[38] The t(9;11) translocation may predict a better outcome.[58]

### 4.4. Solid tumors

Solid tumors account for three-quarters of cancer in infants (Figure 2). Although infants with leukemia are treated with

chemotherapy by pediatric oncologists alone, infants with solid tumors require a multidisciplinary team experienced in delivering state-of-the-art multimodality treatments. Because of their size, organ function, and unique diseases, infants with solid tumors require specialized care. The challenges of caring for an infant with a solid tumor may include vague symptoms and signs of the disease, conscious sedation during procedures, and the vulnerability to chemotherapy and radiation exposure. The keys to the successful management of solid tumors in infants are: a comprehensive understanding of the diseases that are unique to this age group; devoted team members who are interested in performing high-quality and delicate imaging, surgery, treatment, and supportive care for young children; and an effective and communicative health care team. Importantly, incorporating laboratory-based scientists into the team facilitates both clinical care and innovative research, which will eventually help to improve the treatment outcome of these infants, who often have the most devastating tumors.

### 4.5. Brain tumors

Primary CNS tumors comprise approximately 12–19% of cancers in infants.[8,13] They are a group of heterogeneous diseases that originate from the glial, neural, embryonal, or pineal cells of neuroepithelial tissue. Because of the expandability of the developing skull, brain tumors in infancy may have variable manifestations. The most common presentations include focal neurological signs and seizures, and symptoms due to the increased intracranial pressure, such as increased head circumference and vomiting.[59] A bulging anterior fontanel may be an important first physical sign during the routine examination of an infant. In contrast with brain tumors found in older children, more than half of brain tumors in infants are supratentorial in location.[59,60]

In the USA, astrocytic tumors (astrocytoma and other gliomas combined) account for the most common category of brain tumor across all age groups from birth to 14 years of age, whereas the incidence of embryonal tumors, mainly medulloblastoma (MB), and ependymoma peak in infancy, comprising nearly 50% of the pathological subtypes in infants (Figure 4). The prognosis of these tumors in infants is very poor.[60] It has been recently confirmed that MB comprises four molecular variants with distinct genomic patterns and gene expression profiles.[61] In infants, the most favorable WNT variant is absent; the SHH variant has a relatively better prognosis than the other two subgroups of MB.[61,62]

In Taiwan, the incidence of brain tumors in infants is much lower than in Western countries (Figure 2), with a unique distribution of tumor types. In a large hospital-based case series enrolling Taiwanese patients younger than 18 years of age, intracranial germ cell tumors (CNS-GCT) are the second most common type of brain tumor, accounting for 14% of all brain tumors, a proportion that is even higher than MB.[63] Reports from Japan[64] and Korea[65] have also found a high incidence of CNS-GCT in children. Although increased alpha-fetoprotein (AFP) was identified in 40% of cases of CNS-GCT, increased beta-human chorionic gonadotropin was also noted in 22%[63]; these thus serve as important tumor markers for the diagnosis and surveillance of CNS-GCT.

Infants with CNS tumors are treated with a combination of surgical resection with or without chemotherapy or radiotherapy. Among these treatment modalities, surgical resection is the first and usually the most effective treatment for most histological types. The extent of surgical resection is an important prognostic factor for infants and children with CNS tumors. The aims of neurosurgical intervention are to obtain the maximum removal of the tumor and to minimize morbidity and mortality.

Some CNS tumors, however, especially those in the brain stem, are not amenable to resection. When gross total resection of the primary tumor is not achieved, chemotherapy can improve the treatment outcome for infants with MB, CNS-GCT, and some gliomas.[66–68] Although radiotherapy may provide effective and durable tumor control,[66,69] it should be used cautiously in infants due to late effects such as growth failure, neurocognitive impairment, and subsequent CNS neoplasms.[70] Several studies of infants with MB have used various combinations of chemotherapy in an attempt to postpone radiotherapy until at least 2–3 years of age. Attempts have even been made to delete it completely in some trials, with promising results.[71,72]

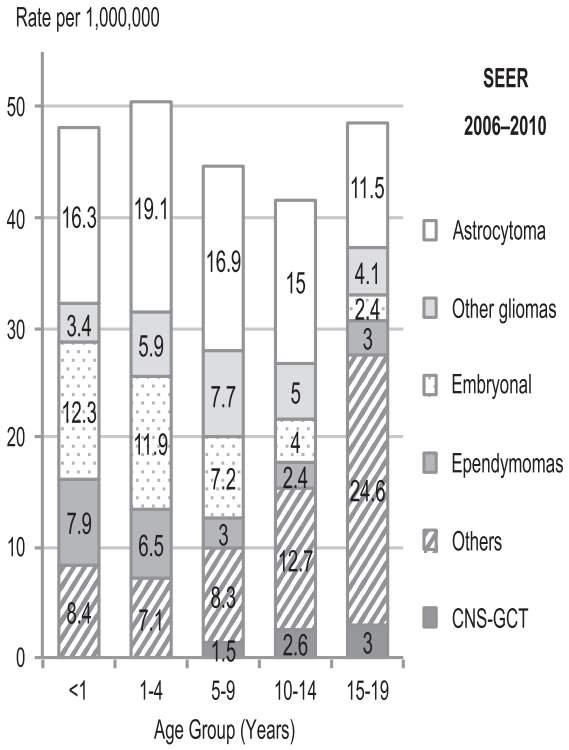


**Figure 4** Age-specific incidence of brain tumors in children and adolescents in the USA (modified from the Surveillance, Epidemiology, and End Results Program[8]). CNS–GCT = central nervous system–germ cell tumor; SEER = Surveillance, Epidemiology, and End Results Program.

High-dose chemotherapy with autologous stem cell rescue has been used to treat MB and supratentorial primitive neuroectodermal tumors in infants, with encouraging results.[73,74] Newer technology, proton therapy and intensity-modulated radiotherapy are being studied in infants in the hope of reducing the long-term sequelae of survivors who must receive radiotherapy.

### 4.6. Retinoblastoma

RB is a rare embryonal tumor arising from the progenitor or transitional cells of the retina and is caused by biallelic deletion or loss of function mutation of the *RB1* tumor suppressor gene ($RB1^{-/-}$) of the tumor cells.[75] Approximately 60% of cases of RB are sporadic and unilateral and these cases usually present later in childhood. Forty percent of cases of RB are hereditary and these patients usually present in infancy, 15% presenting unilaterally and 25% presenting bilaterally.

In hereditary RB, the congenital deletion of one allele of the germline *RB1* gene predisposes the patient to the onset of RB when the other allele is also "hit" by a genetic mutation. It has recently been shown that approximately 3% of patients with RB have the wild-type *RB1* gene in both alleles of their tumor cells. One-half of

these *RB1*$^{+/+}$ RB tumors are likely to be caused by amplification of the *MYCN* oncogene at chromosome 2p24, a potent transcription factor that is important in early neuronal development.[76]

The prognosis for the sight of children with RB depends on the extent of intraorbital disease. The prognosis for survival depends on the extraorbital disease. For more limited disease in the eye, eye-preserving local treatments may include cryotherapy and laser treatment. Radiotherapy is reserved for extensive disease. For extensive orbital disease, enucleation surgery is required. Extra-orbital and metastatic disease require postoperative chemotherapy. The most common sites of metastatic disease are direct extension into the brain and hematogenous spread to bone and bone marrow. Data suggest that *RB1*$^{+/+}$ patients with *MYCN* amplifications may have a better chance of a cure if enucleation is performed as the frontline treatment.[76]

### 4.7. Hepatoblastoma

During the past 30 years, childhood hepatocellular carcinoma related to chronic hepatitis B virus infection in Taiwan has been rapidly eliminated since the nationwide vaccination of newborn infants for hepatitis B virus began in 1984.[77] Currently, HB has become the most common infant and childhood hepatic tumor in Taiwan. The differential diagnosis of HB in children includes hepatocellular carcinoma, sarcomas, metastatic cancer, benign neoplasms such as hemangioma, and other masses such as congenital cysts or abscesses.[78] HCC, sarcomas, and metastatic cancer do not usually present in infancy. HB usually presents as abdominal distension, but may also be asymptomatic and detected incidentally with increased AFP. Familial adenomatous polyposis coli and overgrowth syndromes such as Beckwith-Wiedemann syndrome are associated with a genetic predisposition to HB.[79]

The histology of HB is heterogeneous, probably reflecting distinctive phases of hepatogenesis as the origin of different HBs. Although the well-differentiated "pure" fetal type HB with low mitotic activity has an excellent prognosis and can be treated by surgery alone if completely resectable, chemotherapy is indicated in all other types of HB.[80]

The major cooperative study groups use the PRETEXT (Pre-treatment Extent of disease) clinical guidelines based on the segmental anatomy of liver imaging to predict surgical resectability and to stratify patients into risk groups.[78] Patients with high-risk HB based on this analysis should receive neoadjuvant chemotherapy, definitive surgical resection, and adjuvant chemotherapy postoperatively. Cisplatin and doxorubicin is an effective regimen.[81] For HBs that are multifocal, large, and unresectable, or have vascular invasion, initial chemotherapy followed by liver transplantation is a promising strategy that may eventually cure the disease.[82]

### 4.8. Neuroblastoma

NB and its more differentiated variant, ganglioneuroblastoma, are derived from the sympathoadrenal lineage of neural crest precursor cells.[83] This is the most common solid tumor in infancy (Figure 1). The clinical course of NB is highly heterogeneous and age-dependent. Although children older than 1.5 years often present with high-risk metastatic disease, most infants with NB show low-risk features and some tumors may even spontaneously regress or differentiate into a benign tumor.[84] Given its great diversity in cancer biology and clinical behavior, NB has been referred to as a "clinical enigma"[85] as well as a "model disease",[86] indicating that studying NB would help to elucidate not only cancer biology, but also neurobiology and neuronal differentiation.

Although the majority of primary NB tumors originate from the adrenal gland, some tumors may be found along the sympathetic nervous ganglia, forming a paraspinal mass in the neck, posterior mediastinum, retroperitoneum, or pelvis.[83] In infants, NBs are usually asymptomatic and present as an incidental tumor that is palpated by a caregiver, usually in the abdomen, or as an unexpected finding during an imaging study ordered for other medical illnesses. Occasionally, locally advanced NB may compress nearby structures, especially nerves, causing Horner syndrome due to sympathetic trunk compression (cervical and high thoracic mass) or lower extremity weakness due to spinal cord compression (thoracic and abdominal tumors). To distinguish benign conditions such as neonatal adrenal hemorrhage from NB, neural crest-specific molecular imaging with $^{123}$I-metaiodobenzylguanidine scintigraphy or $^{18}$F-fluorodihydroxyphenylalanine positron emission tomography may be very helpful.[87]

The risk-directed treatment of infants with NB is determined by both tumor biology and the clinical characteristics, with the most important parameters including age, stage, imaging, histology, *MYCN*, ploidy, and chromosomal alterations.[88] For localized NB, primary gross total resection can usually be achieved and serve as sufficient treatment, although some NBs with image-defined risk factors, chromosome 11q aberrations, and amplification of the *MYCN* oncogene still require adjuvant chemotherapy.[88] Intriguingly, if left untreated, 47% of localized NBs in infants have shown spontaneous, complete regression in 4–20 months.[89] Therefore a wait-and-see strategy without cytotoxic treatment may be justified in a subset of patients and is currently undergoing clinical trials in the USA and Europe.

In contrast, chemotherapy is still needed for the vast majority of metastatic NBs (stage 4 or stage M) in infants. Of note, a special subtype of metastasis, designated as stage "4S" or "MS", has only limited spread to the skin, liver, and bone marrow (with tumor cells $<$10% and must be negative on MIBG scintigraphy).[90] Most cases of stage MS have no *MYCN* amplification and can be cured with minimal treatment. Because extensive liver disease may infrequently cause respiratory distress and adverse hepatic effects, limited treatment can be used in these complications of tumor presentation. This can be a significant clinical challenge.[91]

### 4.9. Wilms tumor (nephroblastoma)

WT, also called nephroblastoma, accounts for 4–6% of cancers in infancy. WT almost always arises from the kidney; approximately 10% of patients have both kidneys affected.[92] Common presenting features may include an incidental abdominal mass, hypertension, or hematuria. The differential diagnosis of a renal mass in infancy includes: congenital mesoblastic nephroma, a benign tumor requiring only surgery; rhabdoid tumor, a highly malignant tumor with a much poorer prognosis than WT, which often also involves the brain; clear cell sarcoma of the kidney, which requires different chemotherapy from WT; primitive neuroectodermal tumor, a tumor that may arise at any site in infants including the kidney and which is treated like Ewing's sarcoma; rhabdomyosarcoma, most commonly the embryonal type; renal cysts; and, occasionally, severe hydronephrosis.

WT may also present in the context of concomitant abnormalities due to an underlying genetic syndrome, such as hemihypertrophy (overgrowth syndromes), aniridia, and genitourinary anomalies. Deletion, loss of function mutation, or uniparental disomy of the tumor suppressor genes, *WT1* or *WT2* (H19), are the major genetic abnormalities found in most WTs.

The prognosis for patients with WT is usually excellent. The prognostic factors include histology (poor prognosis is associated with the presence of anaplasia if there is more than focal anaplasia

present), the extent of local disease (stage of the disease), the presence of metastatic disease (stage 4 disease), and cytogenetic abnormalities in the tumor. Although surgical excision is mandatory in the management of WT, adjuvant chemotherapy is indicated in all tumors except very small tumors that have been completely removed; chemotherapy may be avoided in infants with small tumors less that 500 g and with good biology. Radiation treatment should be added only for locally advanced Stage 3 disease and metastatic (Stage 4) disease. In bilateral (Stage 5) WTs, preoperative chemotherapy followed by renal parenchymal-sparing surgery can cure the majority of patients.[93] The prognostic biological factors for bilateral WT are similar to those for unilateral WT: the presence of anaplastic histology and cytogenetic factors. Care must be taken to reduce the rate of end-stage renal failure, an important issue in this unique group of patients.[93]

### 4.10. Germ cell tumors

Yang et al have described a high incidence of extracranial GCTs in Taiwan and in other East Asian countries, accounting for 16% of cancers in infancy (Figure 2B).[15] Whether the high rate is due to different definitions of the disease, genetic background, or environmental factors remains to be elucidated. Both gonadal and extragonadal GCTs may be seen in infants, with extragonadal sites including the mediastinum, retroperitoneum, or pelvis. Sacrococcygeal GCT (SGCT) is the most common fetal neoplasm (1 in 27,000 live births).[94] Most cases are diagnosed prenatally, although some may be discovered incidentally after birth during imaging studies for other reasons. Histologically, GCTs may include mature teratoma, immature teratoma, and malignant tissues. Initial evaluation with AFP and beta-human chorionic gonadotropin tumor markers is mandatory.

A complete tumor resection is mandatory for the treatment of SGCT. Nevertheless, if the preoperative image shows an extensive lesion, which might indicate a high possibility of malignancy with a high surgical risk of functional sequelae, then an intra-operative frozen section biopsy sample may guide subsequent surgical planning. The pure mature and immature teratomas are benign tumors and complete excision should be attempted as they do not respond to chemotherapy and confer a 5-year relapse rate of 17–28% after incomplete excision.[95] However, if the frozen section shows a malignant GCT component, an initial tumor biopsy sample followed by platinum-based neoadjuvant chemotherapy facilitates delayed, but complete, tumor resection and a better treatment outcome.[96] Occasionally, sarcomas may arise in benign teratomas and are treated according to their histological type.[97]

### 4.11. Sarcomas

Although rhabdomyosarcomas originating from skeletal muscle comprise nearly half of all childhood soft tissue sarcomas, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) is the most common type of sarcoma in infancy.[8] The surgeon plays a key part in the initial diagnosis and staging of sarcomas in infants. The NRSTSs are a heterogeneous group of diseases. In the first year of life, benign fibroblastic proliferations and low-grade fibrosarcomas occur more commonly, and many occur at birth. Some infantile fibrosarcomas carry an *ETV6-NTRK3* translocation with a very poor prognosis. The tumors can occur at any site and approximately one-third of the tumors occur on the trunk.

Embryonal rhabdomyosarcoma may occur in infancy and can often be treated with limited chemotherapy without long-term sequelae using vincristine and dactinomycin. However, when alveolar rhabdomyosarcoma and primitive neuroectodermal tumors are present in infancy, they are often locally extensive and present with metastatic disease. Although responsive to chemotherapy, the prognosis for these tumors is guarded. The combinations of vincristine, cyclophosphamide and doxorubicin and of ifosfamide and etoposide are effective in these high-risk tumors.[98] Importantly, granulocyte-colony stimulating factor is required to give the intensity of treatment that is required.[99]

## 5. Conclusions

Infants with cancer are a unique population in which the tumorigenesis is strongly associated with genetic abnormalities and treatment has to be adapted to the special needs of young infants. The percentage distribution of cancer types in infants is different from that in older children and there are also racial differences. Successful diagnosis of cancer in infancy requires a high index of suspicion, careful taking of the clinical history and physical examination, and prompt referral to a pediatric oncologist when there is a suspicion of a neoplasm.

Treatment is directed by the risk and extent of the disease, with the avoidance of extensive surgery and radiation treatment whenever possible. To improve the cure rate and diminish the late effects of treatment, it is critical that further translational research into the biology of these tumors, and into biomarker discovery that facilitates better risk stratification, are carried out, as well as meticulously designed cooperative clinical trials that efficiently test the safety and efficacy of novel treatments using a small sample size.

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