Prevalence, clinical features and prognosis of malignant solid tumors in infants: a 14-year study

Tian Zhi #, Wei-Ling Zhang #, Yi Zhang, Yi-Zhuo Wang, Dong-Sheng Huang *

Department of Pediatrics, Beijing Tongren Hospital, Capital Medical University

* Corresponding author: Dong-Sheng Huang, Department of Pediatrics, Beijing Tongren Hospital, Capital Medical University, No. 1 Dongjiaominxiang Dongcheng District, Beijing 100176, China. Email: hds5180@sina.com

# These authors equally contributed

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Abstract

The onset of malignant solid tumors in infants is insidious and difficult to diagnose on time. The purpose of our study is to provide a theoretical basis for clinical diagnosis by retrospective analysis of the data in the past 14 years. Here, we retrospectively collected the clinical data of infants aged 0-12 months with malignant solid tumors in Beijing Tongren Hospital Affiliated to Capital Medical University from May 2005 to May 2019. The epidemiology, clinical characteristics, treatments and prognosis were statistically analyzed. A total of 496 infants (294 males and 202 females) with malignant solid tumors were analyzed. The main period of onset was 1-11 months. The most common tumor was retinoblastoma (RB, 51.8%), followed by hepatoblastoma (HB, 26.6%), neuroblastoma (NB, 10.5%), rhabdomyosarcoma (RMS, 3.4%), malignant renal tumors (3.2%), infantile fibrosarcoma (IFS, 1.6%), malignant teratoma (1.2%), Ewing’s sarcoma (ES, 0.8%), medulloblastoma (MB, 0.4%) and inflammatory myofibroblastic tumor (IMT, 0.4%). The median follow-up time was 32 months (range 2-162 months). The 1-year, 3-year, and 5-year overall survival of all patients were 97.3%, 89.2%, and 81.1%, respectively, and event-free survival was 94.7%, 84.8%, and 75.8%, respectively. In conclusion, as a special group, malignant solid tumors in infants are complex, heterogeneous, and relatively rare. The prognosis of RB, HB, NB, RMS, malignant renal tumors, IFS, malignant teratoma, ES, MB, and IMT, were excellent due to timely diagnosis and rational treatment.

Keywords: infants; malignant solid tumors; clinical features; prognosis.
Introduction

With the improvement of modern medical level, the prognosis of tumors has been dramatically improved, but tumors are still the second cause of childhood death following accidental injury. [1] In recent years, malignant solid tumors in infants have attracted the attention of researchers worldwide. [2] According to the data of Surveillance Epidemiology and End Results (SEER) in the US, the incidence rate of malignant tumors in infants has gradually increased in the past 30 years, and malignant solid tumors account for more than 2/3 of infant malignant tumors. [3] Most infant tumors occur within the first 28 days of life in a process fundamentally different from most other pediatric and adult tumors. [4] In addition, it has been reported that the age of onset of malignant solid tumors in children is getting lower and lower, especially in the first year after birth. [5] Notably, fetuses were found space-occupying lesions through B-ultrasound and confirmed as malignant solid tumor by pathology after birth. [4]

Malignant solid tumors in infants are different from tumors of the older children and knowledge gained from treating older children cannot be used to infants. [6] The histological types of infant tumors are mostly embryonal tumors or germ cell tumors. [7] Due to the growth and development characteristics of infants, their pathogenesis, treatment response, and prognosis are significantly different from those of older infants. [8, 9] Furthermore, the onset of infant malignant solid tumors is insidious and difficult to diagnose in time. In China, there are few studies on infant malignant solid tumors.

Therefore, we aimed to retrospectively analyze the clinical characteristics, treatment, and outcomes in some infant malignant solid tumors involvement in this study and provide valuable information for diagnosis and treatment.
Materials and methods

Patients
This single-center, retrospective study enrolled 496 infants with malignant solid tumors admitted by the Pediatric Department, Beijing Tongren Hospital Affiliated to Capital Medical University from May 2005 to May 2019.

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Clinical Research Ethics Committee Beijing Tongren Hospital, Capital Medical University (Ethical approval number: TRECKY2019-033). All relevant examinations and treatments have obtained the consent of their guardians and signed informed consent.

Infants aged ≤12 months were eligible for this study if they were diagnosed as malignant solid tumors by pathology or clinical diagnosis. Several malignant solid tumors were included as follows: retinoblastoma (RB), hepatoblastoma (HB), neuroblastoma (NB), rhabdomyosarcoma (RMS), malignant renal tumors (nephroblastoma, clear cell sarcoma of the kidney (CCSK), renal RM), infantile fibrosarcoma (IFS), inflammatory myofibroblastic tumor (IMT), germ cell tumors (TGCTs), Ewing’s sarcoma (ES) and medulloblastoma (MB). Patients with unclear clinical or pathological diagnosis, non-infancy, and non-new onset solid tumors were excluded from this study.

Diagnosis and treatment regimes
The primary tumor foci, tumor markers, imaging examinations were considered as the methods for clinical diagnosis. The International Intraocular Retinoblastoma Classification (IIRC) was used for RB staging. [10] The diagnoses of HB were based on the Children’s Hepatic tumors International Collaboration (CHIC), [11] PRETEXT, pathological diagnosis,
and alpha-fetoprotein (AFP). The stage of NB was determined according to the International Neuroblastoma Staging System (INSS). [12] RMS Intergroup Rhabdomyosarcoma Study (IRS) was used as the basis for RMS staging. [13] Genetic testing was used for testing the genetic susceptibility.

Surgery, chemotherapy, radiotherapy, interventional therapy, and new treatments were adopted in our study. The formulation of the chemotherapy regimen was based on the advice of the Children's Oncology Group (COG) and the experience of our hospital. Pre-surgical chemotherapy was sustained for 3-5 cycles. Post-surgical chemotherapy was sustained for 4-6 cycles. 21 to 28 days were one cycle of chemotherapy. The conventional first-line chemotherapy regimens were recommended for most patients. For cases with poor first-line chemotherapy prognosis, individualized chemotherapy regimens could be used. Laser treatment, vitrectomy, intraocular injection and interventional therapy were recommended for infants with refractory solid tumors.

**Efficacy evaluation and follow-up**

The patients were followed up to May 2020, which was completed by returning to the hospital for reexamination and telephone. Survival analysis was evaluated by overall survival (OS) and event-free survival (EFS). OS was defined as the time from admission to death due to any causes. EFS was defined as the time from admission to the first tumor recurrence/metastasis or death due to any reason.

**Statistical analysis**

All statistical analyses were conducted using SPSS 19.0 software (SPSS Institute. IL,USA). Normal distribution data were expressed as mean ± standard deviation (SE), and non-normal distribution data as the median and interquartile range (IQR). Survival data were analyzed by the Kaplan-Meier survival analysis method. Statistical significance was set at p<0.05.
Results

Patient characteristics
From May 2005 to May 2019, 496 infants with diagnosed infantile malignant solid tumors from our center were enrolled in this analysis. There were 294 (59.3%) males and 202 (40.7%) females, with a median age of onset of 6.23 months (range 0-12 months). The majority onset of patients were 1-11 months (Figure 1).

The most common type were RB (257/496, 51.8%) followed by HB (132/496, 26.6%), NB (52/496, 10.5%), RMB (17/496, 3.4%), malignant renal tumors (16/496, 3.2%), IFS (8/496, 1.6%), malignant teratoma (6/496, 1.2%), ES (4/496, 0.8%), MB (2/496, 0.4%), IMT (2/496, 0.4%). 9 patients had a family history of malignant tumors in their lineal consanguinity. During pregnancy, 5 cases (1.0%) were found space-occupying lesions through B-ultrasound and confirmed as malignant solid tumors by pathology after birth.

Prevalence
As shown in Figure 2, over the past 14 years, the number of RB cases increased every year and reached a peak in 2013 (50/496, 10.1%). The incidence of malignant solid tumors in other types also showed an increasing trend every year, but the peak was slightly later than RB, concentrated in 2017 (45, 9.1%). In terms of patients’ distribution, the enrolled infants were widely distributed, mainly in north China. The top 4 regions were Hebei (65, 13.1%), Shandong (58, 11.7%), Henan (41, 8.3%), and Beijing (38, 7.6%), respectively.

Baseline characteristics, treatments and outcomes
Baseline characteristics and treatments of all the following diseases were shown in Table 1.

RB
RB was the most enrolled patients in this study (257 cases, 51.8%), including newborns (22, 8.6%) and infants aged 2-12 months old (235, 91.4%).

Leukocoria and yellow-white pupillary reflection (80.9%) were the most common first symptoms. 5 cases had a family history of RB, and among them, 2 cases had intraocular
space occupation in fetal period. Unilateral RB (118, 45.9%) and bilateral RB (139, 54.1%) were found in patients. There were 396 eyes in 257 patients with RB, including intraocular RB (225, 358 eyes, 90.4%), extraocular RB (25, 31 eyes, 7.8%), and metastatic RB (7, 7 eyes, 1.8%). The number of neonatal with metastatic RB were predominant. According to the IIRC, [10] intraocular RB were divided into stage A-E, stage D (172, 43.4%) was predominant. Among extraocular RB, 20 cases invaded the optic nerve and/or the optic nerve stump, and 5 cases invaded the orbital tissues such as eye muscles. The patients with metastasis RB were unilateral lesions, and slightly more patients with the left eye (5 cases), including 1 patient with bone metastasis, 3 patients with intracranial metastasis, and 3 patients with cerebrospinal fluid metastasis.

With regard to treatment, 73 patients underwent surgery, 1 underwent radiotherapy, and 257 underwent chemotherapy (carboplatin [CAR]/etoposide [ETO] or teniposide [TEN]/vincristine [VIN]). In addition, 44 cases received new treatments (laser treatment 12, vitrectomy 23, intraocular injection 9). 39 patients underwent transcatheter ophthalmic artery chemotherapy. A total of 114 eyeballs were removed from 396 affected eyes and diagnosed with RB; the eye-preserving rate was 71.2%.

The OS of RB was 88.7%, with 29 deaths (intraocular RB, 11, extraocular RB, 11 and metastatic RB, 7). Among them, the OS of newborns and infants aged 2-12 months old was 86.4% and 88.9%, respectively. The survival rates of intraocular RB, extraocular RB, and metastatic RB were 95.1% (214/225), 56.0% (14/25), and 0 (7/7), respectively. There was statistically significant among them (p=0.015). It suggested that earlier at stage correlated with better prognosis.

HB
132 cases with HB, consisted of 8 newborns and 124 infants aged 2-12 months old, were enrolled (132/496, 26.6%). At the first diagnosis, abdominal distension was found to be the most prevalent (75.0%), followed by poor appetite, vomiting and diarrhea. In this study, 2 cases had a family medical history. 3 cases had liver space occupying lesions during
pregnancy (gestational weeks: 32-36 weeks), and were diagnosed as HB by pathology after birth; all of them were low birth weight infants.

All patients were diagnosed by pathological diagnosis and AFP (reference interval, 0-20 ng/ml). In our study, the mean AFP level of 132 cases with HB was 127.41 ± 7.23 μg/ml (range, 0.04-484.0 μg/ml) at the first diagnosis. According to the CHIC, [11] all pathological tissues were classified as epithelial type (76/132, 57.6%) or mixed type (56/132, 42.4%). The epithelial type included fetal type (51/76, 67.1%), embryonic type (21/76, 27.6%), giant beam type (2/76, 2.6%), and small cell undifferentiated type (2/76, 2.6%). All infants were divided into stage I (8/132, 6.1%), stage II (45/132, 34.1%), stage III (72/132, 54.5%) and stage IV (7/132, 5.3%) referring PRETEXT. [14] There were 45 cases with distant metastasis (newborns/infants aged 2-12 months old, 5/40), and the most common site of metastasis was lung (39/45, 86.7%), followed by intracranial metastasis (6 cases), bone metastasis (4), right atrial tumor thrombus (2), intestinal and mesenteric metastasis (1), and intraspinal metastasis (1). This study included tumor rupture (5/132, 3.8%) and multiple intrahepatic lesions (26/132, 19.7%).

All patients received platinum-based chemotherapy, including cisplatin (CIS)/fluorouracil (FLU)/VIN, CIS/FLU/VIN/doxorubicin (DOX), CIS/DOX, CAR/DOX, ifosfamide (IFO)/CAR/ETO. 78 cases received surgery, the complete resection rate was 59.1%. After the first operation, 16 patients underwent a second operation due to recurrence, and 26 patients underwent resection of the metastatic tumor. There was a patient had complete remission with liver transplantation. 8 patients were administrated with bevacizumab, with therapeutic efficiency of 88%. Patients with PRETEXT stage III or IV, who still have unresectable lesions after standard treatment, were assigned to interventional therapy. Among them, 21 cases died with OS of 84.1%. The OS of newborns and infants aged 2-12 months old were 50% and 86.3%, respectively.

NB
There were 52 patients with NB (52/496, 10.5%), including newborns (6, 11.5%) and infants aged 2-12 months old (46, 88.5%). 40 cases of primary tumors occurred in the adrenal gland, most of them were onset of unilateral, only one case was bilateral adrenal space occupying lesions, and primary tumors of 12 cases originated from the mediastinum. According to the INSS, all infants were divided into stage I (3/52, 5.8%), stage II (9/52, 17.3%), stage III (15/52, 28.9%), stage IV (14/52, 26.9%) and stage IVs (11/52, 21.1%) in our study. [12] Furthermore, there were 25 cases with distant metastasis, including lymphatic metastasis (9, 34.6%), hepatic metastasis (6, 21.1%), osseous metastases (4, 17.3%), intraspinal metastasis (3, 13.7%) and subcutaneous metastasis (3, 13.3%).

All patients received surgery and chemotherapy. The chemotherapy regimens were cyclophosphamide (CYC)/DOX/VIN, ETO/CIS, CYC/VIN/CIS/DOX or ETO, CYC/topotecan (TOP). 9 patients underwent second surgery due to recurrence or metastasis.

2 cases with higher expression of GD-2 received cellular immunotherapy of CAR-T.

The mean neuron specific enolase (NSE) level of 52 cases with NB was 103.9±52.7 ng/ml (range, 22.4-370 ng/ml; reference interval, 0-16.3 ng/ml). Besides, 7 (7/36, 19.4%) cases carried the positive variant in the N-myc gene with a survival rate of 71.4% (5/7). 5 cases died and the OS was 90.4% (newborns, 83.3%; infants, 91.3%).

**RMS**

A total of 17 cases (17/496, 3.4%) with RMS were included. One patient had a family medical history. The majority of RMS (14/17, 82.4%) originated in the head and neck, preponderant in orbital space-occupation. The most common pathological type was embryonic (15/17, 88.2%). According to IRS staging, all patients were divided into stage I (2/17, 11.8%), stage II (4/17, 23.5%), stage III (6/17, 35.3%), and stage IV (5/17, 29.4%).

17 patients underwent surgery, 14 underwent radiotherapy, and 2 underwent chemotherapy (DOX/VIN/CYC/CIS, IFO/VIN/ETO, dactinomycin [DAC]/ETO/VIN). Due to the younger age of this group, except for surgery and chemotherapy, they were not treated with
radiotherapy at the initial diagnosis. 2 patients were treated with radiotherapy (seed implantation, external irradiation) after recurrence, and eventually, all died. Three death were reported, with an OS of 82.4%.

Malignant renal tumors
In our analysis of 16 infants (16/496, 3.2%) with malignant renal tumors, one patient had a family medical history. There were kind of pathological types: nephroblastoma (14/16, 87.5%), renal RMS (1/16, 6.2%) and CCSK (1/16, 6.2%). No distant metastasis was reported in this population. They were treated with surgery and chemotherapy. The chemotherapy regimens were VIN, VIN/DAC or pirarubicin (PIR), CYC/VIN/PIR/ETO, CAR/IFO/ETO. After the first operation, 3 patients underwent nephrectomy due to recurrence of the tumor. The OS of malignant renal tumors was 87.5%.

IFS and IMT
10 cases were enrolled. 8 cases (8/10, 80.0%) were diagnosed with IFS, including hand/foot mass, back mass, and retroauricular mass. In addition, 3 patients were EVT6 gene positive by FISH testing. 2 cases (2/10, 20.0%) were IMT. The primary tumors were located in the abdominal mesentery. All the patients underwent chemotherapy and 70% of the patients had surgery. The chemotherapy regimens were vindesine (VIND)/CYC/DAC, VIND/PIR/CYC/CIS. No death was reported, and the OS was 100%.

Malignant teratoma
6 patients (6/496, 1.2%) with malignant teratoma were enrolled. The primary tumor originated from the gonad (left testis), extragonadal, mostly in sacrococcygeal. One of them had S3 level intraspinal metastasis and died due to tumor progression. All of them received surgery and chemotherapy; the chemotherapy regimens were VIN/bleomycin (BLE)/CIS; BLE/ETO/CIS. The OS of malignant teratoma was 83.3%.
ES
Among 4 cases with ES. 2 cases had EWSR1 gene test but no positive results were found. The primary tumor of 4 cases originated from the eye socket, nasal wing and pelvic cavity. All patients underwent surgery, chemotherapy with an OS of 75%.

MB
There were 2 patients (2/496, 0.4%) were enrolled. All of them were classic MB. The primary site was the fourth ventricle. No distant metastasis was found. All received effective treatments, such as surgery and chemotherapy, and one received radiotherapy. In addition, intrathecal injection is also an effective adjuvant therapy. 1 patient died of respiratory and cardiac arrest due to tumor compression of the brain stem. The OS was 50%.

Survival analysis
As of May 2019, the median follow-up time was 32 months (range, 2-162 months). Among 496 cases, 63 cases were reported dead and the survival rate was 87.3%. Kaplan-Meier survival analysis showed that 1-year, 3-year, and 5-year OS of included patients were 97.3%, 89.2%, and 81.1%, respectively. 1-year, 3-year, and 5-year EFS was 94.7%, 84.8% and 75.8%, respectively (Figure 3). As shown in Figure 4-5, we analyzed OS and EFS for each disease, The estimated 3-year EFS of RB was 88.0% ± 2.2%, HB was 88.0% ± 2.2%, 86.9% ± 3.5%, NB was 85.2% ± 6.0%, RMS was 77.8% ± 11.4%, malignant renal tumors was 81.6% ± 10.8%, malignant teratoma was 80.0% ± 17.9%, ES/primitive neuroectodermal tumor (PNET) was 75.0% ± 21.7%, and MB was 50.0% ± 35.4%.

Discussion
To our knowledge, this is the first long-term study of infant malignant solid tumors in China. We reported our observations over the past 14 years and found that the malignant solid tumors in infants are complex and changeable. With timely diagnosis and rational treatment, the prognosis of them was excellent.
Infant tumors are mostly embryonic-derived tumors, and their pathogenesis involves developmental biology, genetics, environmental factors and others. [15] It has been shown that genetic predisposition is one of the important causes of infant tumors. [16] RB, NB and HB all have obviously genetic susceptibility. Notably, N-myc, WT1 and RB1 genes are associated with NB, nephroblastoma, RB and other tumors, respectively. In the process of fetal development, activation or inhibition of these genes can lead the normal development of embryos disordered, and even transformed into cancer. [17-19] In our study, 9 (1.8%) infants had a family history of malignancies in their immediate family, including 5 cases of RB, 2 cases of HB, 1 case of RMS, and 1 case of nephroblastoma.

A report analyzed the incidence of childhood cancers in the past 29 years; the incidence of males and females were 0.155‰ and 0.136‰, respectively. [20] Similarly, in this study, most of the cases were male. The tumors in infants were mainly embryonic solid tumors. Another institution demonstrated that the top three incidence rate of tumors were RB (44%), leukemia (19%) and NB (10%). [21] Our result showed that RB accounted for 51.8% of all malignant solid tumors in infants, higher than previously reported. The possible reason was that our hospital is specialized in ophthalmology. Many patients with infant malignant solid tumors went to our hospital for treatment before 2013. However, after 2013, with the changes of treatment patterns in our hospital, the maturity of treatment technology in local hospitals and the support of Medical Insurance Policy, most patients prefer to choose a local hospital for treatment. The incidence trend of other solid tumors also showed an increasing trend. In addition, we found that the number of HB was lower than that of RB (26.6%), but the incidence rate is significantly higher than that of other articles. Interestingly, it was consistent with the study by Hung GY et al. in which the incidence rate of HB in China's Taiwan region is 2-5 times that of the European and American countries. [15] It is speculated that gene variation may be a risk factor for HB in Han nationality. [22]

In terms of regional distribution, the patients’ residence covers more than 30 provinces and cities in China. However, due to the geographical location of our center, the source of
patients was still mainly in North China. In this study, the incidence of RB in infancy was mostly in intraocular RB (90.4%). Among them, stage D (80.3%) was dominant. Few cases died with metastatic RB. Previously study showed that stage E (80.3%) was preponderated in intraocular RB of older children. [23] Importantly, we found that stage of RB in infants was early than that in older children, and metastatic RB was rare. We speculated that the reason for this difference may be related to the young age of onset, the early detection of the disease, and the tumor has not yet metastasized. However, once the tumor breaks through the eyeball and has distant metastasis, the prognosis is often poor.

Künkele A et al reported that the current globe salvage rate of RB could reach 62-75% (stage A-C of IIRC, 100%; stage D-E of IIRC, 50%-80%) in the world. [24] The eye salvage rate of our study was 71.2%, including 100% in stage A, B and C stage, 80.2% in stage D and 44.8% in stage E, which were consistent with other literature reports.

Through statistical analysis of great data, Piotr Czauderna pointed out that the HB in infancy was mainly pure embryonic type with relatively good differentiation, which had better EFS time. [25] From the distribution of pathological tissues in this study, the major type of HB in infancy was an epithelial type. Among the epithelial type, the fetal-type with good prognosis was the most, which was consistent with the literature report. According to the data of SIOPEL, PRETEXT staging can predict the resectability of the tumor, which is very crucial for the prognosis. [26] Data from this study showed that there were more infants in PRETEXT III and less in IV. The complete tumor resection rate was 59.1%, close to the level of international. [27] Systemic metastasis can occur in the early stage of HB, as in older children with HB, the lung is the most common site of metastasis. [28] Our result showed that among the 45 cases with distant metastasis, 86.7% had lung metastasis, which was consistent with the literature.

NB originates from the adrenal medulla to the sympathetic nervous system. The prognosis of infants with NB is better than that of older children, and even some children with IVs stage of NB can appear spontaneous regression in the first few months after birth. [29] The positive
variant in N-myc gene is closely related to the poor prognosis of NB. Notably, it's reported that the incidence of e positive variants in N-myc in infants with NB is about 10%, with a survival rate of 34.3%. \[17, 30\] In this study, the incidence accounted for 19.4% (7/36), and the survival rate was 71.4%, which was higher than that reported in the literature. It may be related to the small sample size.

Soft-tissue sarcoma in children is composed of a series of malignant connective tissue, RMS accounts for more than half of them. The RMS could be found in the head, neck, limbs, genitourinary system and other parts. \[26\] In this study, the primary tumors of 14 cases (82.4%) originated in the head and neck, which was higher than that reported in the literature. \[31\] The possible reason was that the level of Otorhinolaryngology, Head and Neck Surgery in our hospital ranked among the top in China, so the source of patients was relatively large.

The histological classification of infant RMS was mainly embryonal and the prognosis was better than other types. \[32\] In this data, 88.2% of the RMS were embryonal, which was consistent with relevant reports. IFS occurs at an early age, with 35% occurring after birth, but the long-term survival rate is close to 90%. \[33\] 8 children were included in this study had earlier onset age than other diseases. We treated them according to the treatment protocol of the European Pediatric Soft-Tissue Sarcoma Study. All patients survived and achieved excellent prognosis. In this study, nephroblastoma accounted for 87.5%, with no distant metastasis, and its prognosis was better than that of CCSK and renal RMS, which supported the previous publications. \[34\]

Based on the international classification of pediatric cancer, infant malignant tumors are highly aggressive high-grade tumors, whereas their prognosis is much better than that of older children and adults. \[35\] Alfar AS et al. studied 615 newborns with malignant tumors from the SEER database in the United States and found that the 5-year OS of malignant solid tumors was 71.2%. \[36\] One French study showed that the 5-year OS for malignant solid tumors in newborns was 83.8%. \[4\] In this study, the 5-year OS of infants with malignant solid tumors was 81.1%, which was basically consistent with reference reports.
Here, we found the OS of RB, NB, malignant renal tumors and IFS were more than 85% in our study. Nevertheless, in some low-income countries, the OS of infants with RB was 30%-60%. [37] The reason may be the patients were given good eye service in our hospital. A long-term survival result based on 409 patients showed the OS of pediatric RMS was 33%, which less than our research. [38] We speculated the considerable disparity result from the small sample size. For the same reason, we cannot adequately compare newborns with infants aged 2-12 months old. We only found that the proportion of neonatal tumors were higher than the previous study, and the OS in RB, HB of neonatal were lower than older infants. [39] Newborns have immature physiology, and their hematopoietic and immune systems are not fully developed and the response to therapy is unpredictable. [40] Thus, a larger sample size are needed to fully explore the difference in clinical features and outcomes among newborns and older infants.

This study also has several limitations. First, in some malignant solid tumors, the sample size is small. There is not enough sample size to compare newborns with older infants. Second, the follow-up in some patients was relatively short. In future research, large-scale, long-term follow-up investigations are needed.

**Conclusion**

As a unique group, malignant solid tumors in infants are complex, heterogeneous, and relatively rare. Excitedly, the prognosis of kind of malignant solid tumors in infants is often better with comprehensive treatment. How to accurately diagnose, evaluate, and treatment is still a big challenge. This study has provided evidence for the diagnosis and treatment of malignant solid tumors in infants. However, it is still necessary to establish an infant's tumor database by a collaboration of multiple centers to make joint efforts to better improve the survival and prognosis of malignant solid tumors in infants.
References


Table 1. Baseline characteristics and treatments of different tumor types

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>RB</th>
<th>HB</th>
<th>NB</th>
<th>RMS</th>
<th>Malignant renal tumors</th>
<th>IFS and IMT</th>
<th>Malignant teratoma</th>
<th>ES</th>
<th>MB</th>
<th>All patients</th>
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<tbody>
<tr>
<td>Number (%)</td>
<td>257</td>
<td>132</td>
<td>52</td>
<td>17</td>
<td>16 (3.2%)</td>
<td>10 (2.0%)</td>
<td>6 (1.2%)</td>
<td>4</td>
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<td>496</td>
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<td>Male/female-no (%)</td>
<td>155</td>
<td>74</td>
<td>30</td>
<td>11</td>
<td>9 (56.3%)</td>
<td>8 (80.0%)</td>
<td>3 (50.0%)</td>
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<td>294 (59.3)</td>
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<td>Age at onset, median (range)</td>
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<td>8.40</td>
<td>6.40</td>
<td>5.60</td>
<td>6.88</td>
<td>9.57</td>
<td>7.73</td>
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<td>Follow-up time-months, median (range)</td>
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<td>46</td>
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<td>66</td>
<td>34</td>
<td>43</td>
<td>43</td>
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<tr>
<td>Overall survival</td>
<td>88.7%</td>
<td>84.1%</td>
<td>90.4%</td>
<td>82.4%</td>
<td>87.5%</td>
<td>100.0%</td>
<td>83.3%</td>
<td>75.0%</td>
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<td>87.3%</td>
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<td>Treatments</td>
<td>257</td>
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<td>17</td>
<td>16</td>
<td>10</td>
<td>6</td>
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<td>Surgery</td>
<td>73</td>
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</tbody>
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RB, retinoblastoma; HB, hepatoblastoma; NB, neuroblastoma; RMS, rhabdomyosarcoma; Malignant renal tumors; IFS/IMT, infantile fibrosarcoma and inflammatory myofibroblastic tumor; Malignant teratoma; ES, Ewing’s sarcoma; MB, medulloblastoma.
Figure 1. Sex and age distribution of solid tumors in infants
Figure 2. Epidemiology of malignant solid tumors in infants
Figure 3. Overall survival and event free survival of 496 infants with malignant solid tumors
Figure 4. Overall survival curve of different tumor types

1 retinoblastoma (RB), 2 hepatoblastoma (HB), 3 neuroblastoma (NB), 4 rhabdomyosarcoma (RMS), 5 malignant renal tumors, 6 infantile fibrosarcoma and inflammatory myofibroblastic tumor (IFS/IMT), 7 malignant teratoma, 8 Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET), 9 medulloblastoma (MB)
Figure 5. Event free survival curve of different tumor types

1 retinoblastoma (RB), 2 hepatoblastoma (HB), 3 neuroblastoma (NB), 4 rhabdomyosarcoma (RMS),
5 malignant renal tumors, 6 infantile fibrosarcoma and inflammatory myofibroblastic tumor
(IFS/IMT), 7 malignant teratoma, 8 Ewing’s sarcoma/primitive neuroectodermal tumor (ES/PNET), 9
medulloblastoma (MB)