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Clinical characteristics, treatment and prognosis of paediatric patients with metastatic neuroblastoma to the brain

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ABSTRACT

Objective: Neuroblastoma (NB) is the most common extracranial solid malignancy in children. Metastatic involvement of brain is rare in NB. This study was established to evaluate the clinical characteristics, treatment and prognosis of NB patients with brain metastases.

Patients and methods: From September 2005 to December 2016, the clinical data of 15 cases with brain metastases among 264 NB patients admitted to Beijing Tongren Hospital, Capital Medical University were collected and retrospectively analysed. The clinical features of the 15 patients were summarised, and the patients were grouped according to different treatment methods and followed up for a median time of 41 months. The survival curves were plotted, and the Log-rank test was performed to compare the effect of different treatment methods on the prognosis.

Results: The proportion of brain metastases in NB patients in our hospital is 5.68% (15/264). For the prognosis of 15 NB cases, the survival time of combined radiotherapy and/or autologous peripheral blood stem cell transplantation group was longer than that of simple operation and chemotherapy group (61.79 ± 9.59 vs. 30.00 ± 5.99 months, P = 0.03). Among the 15 patients, 4 cases underwent intracranial tumor resection, 4 cases received craniospinal irradiation, and the rest received maintenance chemotherapy. The 2-year survival rate was 82.2%, and the 5-year survival rate was 19.9%. The survival time of combined intracranial surgery and/or radiotherapy group was significantly longer than that of the chemotherapy group (46.67 ± 6.69 vs. 16.42 ± 1.42 months, P = 0.003).

Conclusions: The incidence of brain metastases NB in children is relatively small, but the prognosis is very poor. Active chemotherapy, radiotherapy and surgery-based comprehensive treatment can prolong the survival time.

1. Introduction

Neuroblastoma (NB) is the most common extracranial solid malignancy in children. NB is also the most common childhood tumor diagnosed before the age of 1 year [1]. Its prevalence is approximately one case per 7000 births [2]. The etiology of this malignancy is still obscure. Environmental influences or parental exposures have not been identified [3]. This tumor generally occurs sporadically [4]. Metastases are present in up to 70% of patients with NB, frequently involving bone, bone marrow and liver at the time of diagnosis [5] and confer a poor prognosis. Metastatic involvement of the head and neck is also commonly seen both at presentation and recurrence and manifests most often as osseous metastases involving the calvarium, orbit or skull base [6]. However, metastasis to the brain (parenchymal, intraventricular or leptomeningeal) is rare and a serious complication indicating poor prognosis [7].

In recent years, long-term survival rates in paediatric patients with advanced stage NB have gradually increased because of novel treatment protocols that include aggressive chemotherapy, surgery, radiation, autologous stem cell transplantation and immunotherapy [8,9], while the risk of brain metastases has risen [8,10]. Brain metastases may be present at the initial diagnosis, but in most cases, they develop later, during disease progression or relapse. The median time from initial diagnosis to brain metastases development is 13–22 months [11–13].

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Recurrent metastatic NB is difficult to cure, particularly in patients with central nervous system (CNS) disease [14]. The CNS has emerged as a sanctuary site leading to relapse. Among large series, the incidence of leptomeningeal (LM) or CNS parenchymal disease in relapsed patients is 6–8% [15,16]. The results of treatment of CNS metastases are particularly poor, as most of the children die due to disease progression [11,13,17]. Furthermore, CNS relapses have been almost always fatal [14–16], and hence, there is an increasing need for innovative treatments.

However, owing to the low incidence of NB with brain metastases, there are few reports on the prognosis of NB treated by different comprehensive treatments. This study was established to characterize the clinical characteristics, treatment and prognosis of NB patients with brain metastases.

2. Materials and methods

From September 2005 to November 2016, 15 cases with brain metastases among 264 NB paediatric patients admitted to Beijing Tongren Hospital, Capital Medical University were included in our study. At the time of the initial diagnosis, enhanced chest CT, abdominal and pelvic enhanced CT and B ultrasound, MRI, ECT bone scan, bone marrow cytology, minimal residual bone marrow neuroblastoma, superficial lymph node ultrasound and cranial imaging examination were all completed. Brain metastasis of NB was confirmed by central nervous system imaging or lumbar puncture cerebrospinal fluid cytological examination. Staging was carried out according to the International Neuroblastoma Staging System [18]. MRI was performed with a HDxT 3.0 T scanner (GE Medical System, Milwaukee, WI, USA), using a 8-channel phased array coil. Data were obtained from T2WI and FLAIR sequences. T2WI was performed with a repetition time of 3580 ms, an echo time of 80 ms, a field of view of 22 × 22 mm, a matrix number of 256 × 512, a slice thickness of 5 mm and an interslice gap of 1 mm. FLAIR was performed with a repetition time of 2500 ms, an echo time of 7 ms, a field of view of 22 × 22 mm and a matrix number of 256 × 512. 0.01 mmol/kg Gadopentetate Dimeglumine was used as the contrast agent. The MRI characteristics of brain metastases are markedly enhanced and may be ring-enhanced when accompanied by cystic necrosis and uniform nodular enhancement in the absence of cystic necrosis. MRI manifestations of meningeal metastasis can be divided into four types: 1) Hydrocephalus with or without meningeal or ependymal enhancement; 2) Dura-arachnoid enhancement is characterised by continuous, thick arc-shaped enhancement of the cerebral convex surface of the skull, which does not extend into the sulcus; 3) Pia mater-arachnoid, characterised by a thin line or nodular reinforcement that extends across the surface of the brain and extends into the sulci; 4) Subependymal enhancement.

Ethical approval was given by the Medical Ethics Committee of the Beijing Tongren Hospital, Capital Medical University. Written informed consent was obtained from all participants and their guardians.

Medical records were reviewed for patients' age, sex, symptoms at primary diagnosis and brain metastases, time interval between disease onset and brain involvement, treatment type before and after brain involvement and location of brain metastases.

2.1. Therapeutic regimen

After the definite diagnosis of NB, a detailed therapeutic regimen was followed (Table 1): 5 (33.33%) cases were treated with chemotherapy only; 2 (13.33%) cases were treated with chemotherapy and radiotherapy; 1 (6.67%) case was treated with chemotherapy, intracranial surgery and autologous peripheral hematopoietic stem cell transplantation; 4 (26.67%) cases were treated with chemotherapy and autologous peripheral hematopoietic stem cell transplantation; 2 (13.33%) cases were treated with chemotherapy, intracranial surgery and radiotherapy; 1 (6.67%) case was treated with chemotherapy and

Table 1
Clinical characteristics of NB paediatric patients with brain metastases.

Characteristic	Case (n, %)
Gender	
Male	11 (73.33%)
Female	4 (26.67%)
Age (Year)	
< 5	9 (60.00%)
5 ~ 10	5 (33.33%)
≥10	1 (6.67%)
Symptom at primary diagnosis	
Fever	9 (60.00%)
Leg pain	2 (13.33%)
Abdominal pain	6 (40.00%)
Lower limb pain	1 (6.67%)
Joint pain	1 (6.67%)
Low back pain	1 (6.67%)
Left back pain	1 (6.67%)
Weakness of the lower limbs	1 (6.67%)
Diarrhea	1 (6.67%)
Left eyeball protrusion	2 (13.33%)
Mass on the forehead	1 (6.67%)
The location of the lesion in the diagnosis of NB	
Left adrenal gland	4 (26.67%)
Right frontal lobe, parietal lobe	1 (6.67%)
Bone	13 (86.67%)
Bone marrow	12 (80.00%)
Retroperitoneal	8 (53.33%)
Lymph node	5 (33.33%)
Intracranial	2 (13.33%)
Left mediastinum	1 (6.67%)
Lung	2 (13.33%)
Middle cranial fossa	1 (6.67%)
Right renal portal	1 (6.67%)
Spine	2 (13.33%)
Right posterior mediastinum	1 (6.67%)
Posterior mediastinum	1 (6.67%)
Right adrenal gland	1 (6.67%)
Liver	1 (6.67%)
Skull, tibia	1 (6.67%)
Time duration (Month)	
0	5 (33.33%)
0~50	7 (46.67%)
≥50	3 (20.00%)
Symptoms of brain metastases	
Headache	9 (60.00%)
Paralysis of both lower extremities	3 (20.00%)
Convulsion	7 (46.67%)
Blurred vision	1 (6.67%)
Dizzy	1 (6.67%)
Vomit	1 (6.67%)
Bowel and bladder disturbances	2 (13.33%)
Location of brain metastases	
Left frontal lobe	4 (26.67%)
Right frontal lobe	4 (26.67%)
Left occipital lobe	1 (6.67%)
Left temporal lobe	4 (26.67%)
Left middle cranial fossa	1 (6.67%)
Pia enhancement and nodule of the whole brain	2 (13.33%)
Left parietal lobe	2 (13.33%)
Left cerebellum	1 (6.67%)
Left side of sella turcica	1 (6.67%)
Parietal lobe	3 (20.00%)
Thickening of spinal soft spinal meninges	1 (6.67%)
Right parietal lobe	2 (13.33%)
Contrast enhancement spinal cord membrane	2 (13.33%)
Treatment	
CHT	5 (33.33%)
CHT + RAT	2 (13.33%)
CHT + IS + SCT	1 (6.67%)
CHT + SCT	4 (26.67%)
CHT + RAT + IS	2 (13.33%)
CHT + IS	1 (6.67%)

Time duration: Duration of time diagnosed as NB to brain metastases (months); CHT: chemotherapy, RAT: radiotherapy, SCT: stem cell transplantation, IS: intracranial surgery.

intracranial surgery. Brain metastases were all diagnosed by imaging. 2 cases underwent biopsy confirmation, and 1 case underwent CSF examination. After the diagnosis of brain metastasis, 4 cases (case 1, case 10, case 13 and case 14) were treated with intracranial surgery. The reasons of intracranial surgery were as follows: 3 cases (case 1, case 13 and case 14) have single BM and total resection of intracranial metastatic tumor can be performed. 1 case (case 10) had multiple BM, and subtotal resection was performed to alleviate the symptoms for the obvious supratentorial space occupying. In addition, the parents of all 4 patients hoped to achieve a complete cure through surgery. All of them were confirmed by pathology with intracranial metastasis of NB. Whether to perform intracranial surgery depends on the situation of intracranial metastatic lesions. When a single intracranial metastatic occurs or intracranial metastatic lesion is clearly causing dysfunction or affecting vital signs, the operation shall be performed with the consent of the family members or the parents of the children according to their financial status. All the children in this study were stage IV and high-risk, and all patients were treated with standard international protocols and the specific program referred to the chemotherapy program of the high-risk group agreed by Chinese neuroblastoma diagnosis and treatment experts [19]. The surgical indication for surgical resection was single brain metastasis with mass effect. The surgical indication for radiotherapy was multiple metastases, important functional areas metastasis, brain stem metastases and meninges metastases. The adverse effects of radiotherapy and chemotherapy were evaluated according to CTCAE [20]. Symptoms such as headache, vomiting and intracranial hypertension were treated with mannitol dehydration and intracranial pressure reduction. Once secondary epilepsy occurs, symptomatic treatment such as anti-epilepsy was given.

2.2. Follow up and clinical evaluation

Follow-up was performed by telephone, by mail and in the clinic. The patients were divided into a combined radiotherapy and/or autologous peripheral blood stem cell transplantation group and a simple operation and chemotherapy group. The prognosis of NB between combined and single therapeutic method was compared. After the diagnosis of brain metastases, the patients were divided into a combined intracranial surgery and/or radiotherapy group and a chemotherapy alone group based on the presence or absence of intracranial tumour resection and whole brain and total spinal cord radiotherapy, and the effects of different treatment methods on the prognosis of brain metastases were compared.

2.3. Statistical analysis

Quantitative data were expressed as means ± standard deviation (SD) and compared using the independent sample t-test. Statistical analysis was determined by SPSS 21.0 software (SPSS Inc.,US). The survival curve of children with brain metastases were plotted with Kaplan-Meier curves. Log-rank test was adapted to compare the effect of different treatment methods on the prognosis. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics

In this study, a total of 264 patients with NB were included, among which 15 patients (5.7%; eleven males, four females) were identified with IV stage brain involvement. The proportion of brain metastases in stage IV NB in our study was 7.5% (15/200). Median age of the patients at the time of primary tumour diagnosis was 3.75 years (range: 0.25–15.58 years). Among the 15 NB patients with brain metastases, 5 cases were clearly identified with brain metastases at the time of initial diagnosis, the remaining 10 cases were identified with brain metastases during treatment and follow-up. Median time interval between initial tumour diagnosis and brain involvement was 29.5 months (range: 3–100 months).

Table 2
Characteristics of neuroblastoma brain metastasis.

Characteristics	Analysis
Maximum diameter (cm, Mean ± SD)	3.09 ± 0.89
Number of BM (n, Mean ± SD)	1.67 ± 1.35
Edema (n, %)	
Yes	14 (93.33%)
No	1 (6.67%)
Enhancement (n, %)	
Homogeneous enhancement	4 (26.66%)
Heterogeneous enhancement	10 (66.67%)
None	1 (6.67%)

BM, brain metastasis.

The clinical characteristics of NB patients with brain metastases are listed in Tables 1 **and** 2 . The most common initial signs and symptoms of brain metastases were headaches in 9 cases, convulsions in 7 cases and vomiting in 1 case. Paralysis of both lower extremities in 3 cases, bowel and bladder disturbances in 2 cases occurred in patients with spinal cord involvement. Of the 15 patients with brain metastases, 14 cases had parenchymal brain metastases, 2 cases had meningeal enhancement with nodule formation (Fig. 1) and 3 cases had simultaneous brain metastases and meningeal metastases (Fig. 2).

3.2. Prognosis

By the end of 31 December 2017, the median followed-up period was 41.0 months (range, 17–103 months). The comprehensive treatment plan and prognosis of 15 cases are shown in Tables 1 and 3. During follow-up, 10 cases were dead of disease and 5 cases were alive. The median survival time after diagnosis of brain metastases was 40 months (range, 17–60 months), the 2-year survival rate was 82.2% and the 5-year survival rate was 19.9%. The survival curve of 15 patients with brain metastases of NB is shown in Fig. 3.

3.3. Survival analysis of different treatment methods for NB prognosis

As shown in Fig. 4, the median survival time of simple operation and chemotherapy group was 28 months (range: 17–46 months), and the average survival time was 61.79 ± 9.59 months. The median survival time of combined radiotherapy and/or autologous peripheral blood stem cell transplantation group was 58 months (range: 20–103 months), and the average survival time was 30.00 ± 5.99 months. Log-rank test result showed that the survival time in combined radiotherapy and / or autologous peripheral blood stem cell transplantation group was significantly longer than that in simple operation and chemotherapy group ($P = 0.03$).

3.4. Survival analysis of different treatment methods for NB brain metastases

As shown in Fig. 5, the median survival time in combined intracranial surgery and/or radiotherapy group and simple chemotherapy group was 41 months (average survival time: 46.67 ± 6.69 months) and 14 months (average survival time: 16.42 ± 1.42 months), respectively. And Long-Rank test result showed that the survival time in combined intracranial surgery and/or radiotherapy group was significantly longer than that in simple chemotherapy group ($P = 0.003$).

4. Discussion

NB is the most common extracranial solid tumour in children.

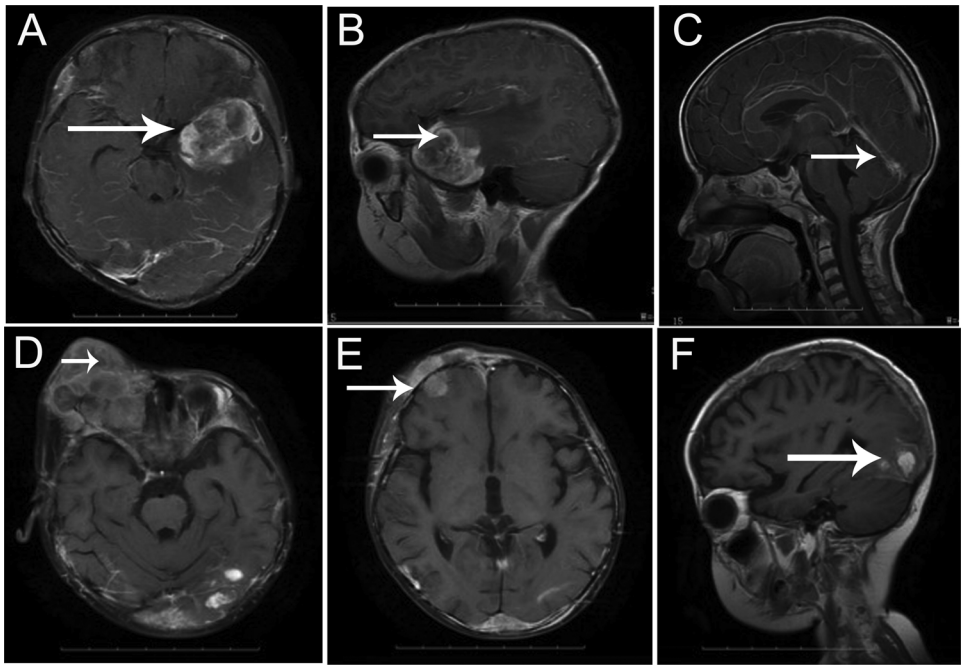

Fig. 1. Imaging of neuroblastoma with intracranial metastasis.
A-C: Cranial enhanced MRI of case No. 4 showed a large mass on the left temporal lobe with clear cerebral edema around the lesion. Tortuous vessels can be seen around the lesion with thickened and enhanced meningina. The diploe of right parietal bone was partially enhanced with thickened and enhanced dura mater adjacent to the parietal regions.
D-F: Cranial enhanced MRI of case No. 2. Irregular masses were seen in the right orbit and around the orbit, and the lesions extended forward to the outside of the orbit.

Tumour spontaneous regression or differentiation happens in patients with low-risk disease, and surgery with little or no adjunctive therapy is effective for these patients [21,22]. While for patients with high-risk diseases, chemo-resistance and metastasis are the two main problems. Patients may initially respond to chemotherapy, but chemoresistance would develop soon. Multiple metastasis usually occurs at diagnosis. Despite multimodality chemotherapy and stem cell transplantation, satisfactory response still could not be achieved. The long-term survival rate of these patients is less than 40% [1,21–23]. Current treatments for CNS relapses are inadequate, carrying a high morbidity and mortality rate [24]. Therefore, more effective treatments are urgently needed.

The 15 cases reported in our current study were all over 1 year old, and all of them were diagnosed with stage IV NB. The proportion of brain metastases in stage IV NB in our study was 7.5% (15/200), which was consistent with a previous study [25]. The median interval from the initial diagnosis to the development of brain metastasis (18 months,

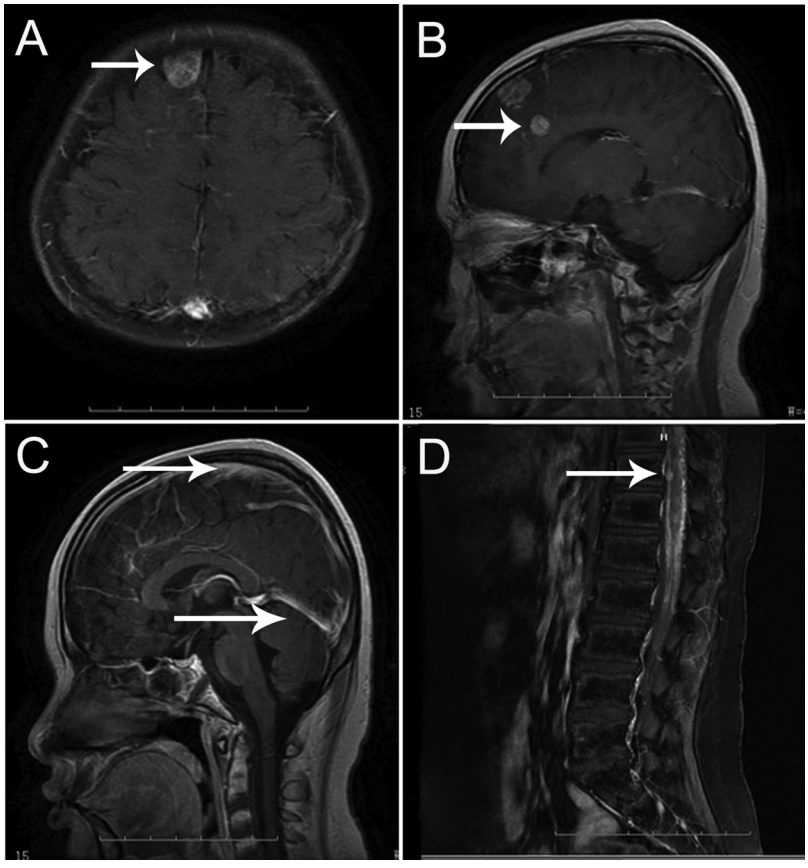

Fig. 2. Imaging of NB with intracranial and spinal cord metastasis.
A-B: Cranial enhanced MRI of case No. 14. Post-operative state of the left temporoparietal. The top of the left iliac crest was incomplete, and the iliac crest of the cranial plate showed flake-like signals. After enhancement, the left temporal lobe softened and communicated with the lateral ventricles; abnormal signals and intensification were seen on the right frontal and subcortical areas.
C-D: enhanced MRI of lumbar spine due to defecation disorders 7 months after treatment. Sagittal scan showed thickening of the spinal meninges and enhanced after enhancement.

Table 3
Demographic data and outcome of the study population.

Characteristic	Case (n, %)
Follow up time (Month)	
17~46	10 (66.67%)
47~103	5 (33.33%)
Fate	
Dead	10 (66.67%)
Alive	5 (33.33%)
Survival time after brain metastasis (Month)	
0~20	9 (60%)
21~60	6 (40%)

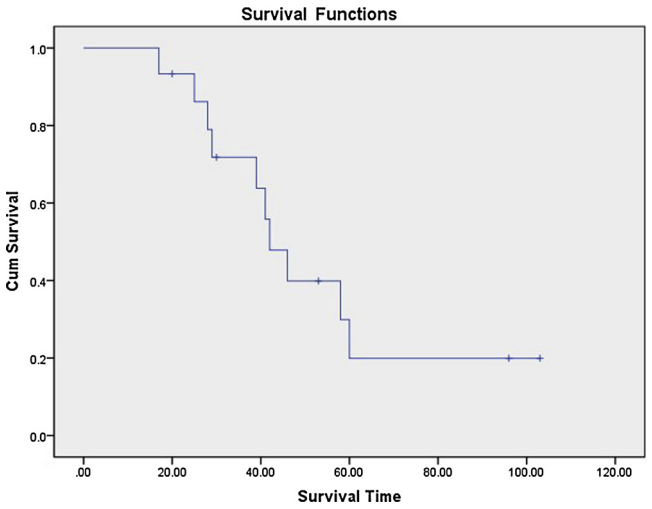

Fig. 3. Survival curves of 15 cases with brain metastases and neuroblastoma.

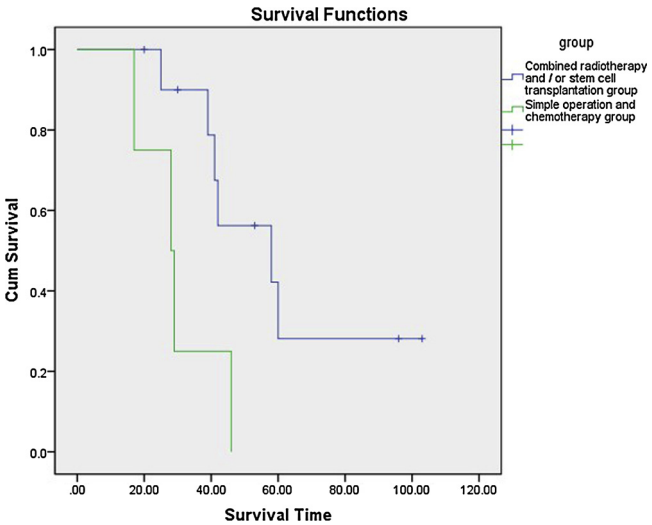

Fig. 4. Survival curves of combined radiotherapy and/or autologous peripheral blood stem cell transplantation group and surgery plus chemotherapy group. The survival time and cumulative survival rate of children with neuroblastoma in combined radiotherapy and/or autologous peripheral blood stem cell transplantation group were better than those of simple surgery and chemotherapy.

range 6–32 months) in a previous study [26] was shorter than the current study. It has been reported that age and bone marrow involvement at initial diagnosis were associated with the subsequent development of brain metastasis in stage IV NB [26]. All 15 cases reported in this article had bone and/or bone marrow metastases, of which 5 cases were initially diagnosed with brain metastases.

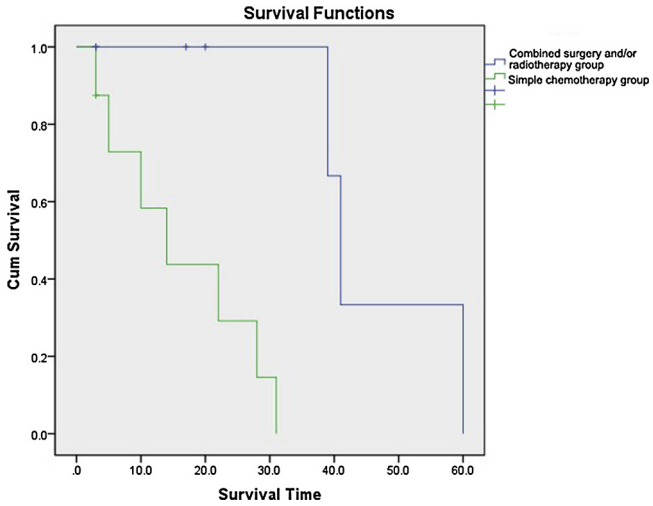

Fig. 5. The survival curves of combined chemotherapy and intracranial surgery and/ or radiotherapy group and simple chemotherapy group in brain metastases NB. The survival time and cumulative survival rates of patients with brain metastases NB treated by combined chemotherapy and intracranial surgery and/or radiotherapy were significantly better than those of simple chemotherapy.

Therefore, during the follow-up of IV NB, especially in children with bone and bone marrow metastasis, the head and spinal imaging examination and cerebrospinal fluid examination should be carried out regularly so as to diagnose brain metastases as soon as possible.

The clinical symptoms of brain metastases are similar to those of other solid tumour metastases, mainly intracranial hypertension and secondary epilepsy. Headache, vomiting and convulsions are the main manifestations of brain metastases. However, paralysis of both lower extremities, bowel and bladder disturbances (sphincter dysfunction) may occur when the spinal cord is involved. The proportion of NB with spinal cord involvement in previous reports [27] was higher than that in the current study (4.09%, 28/685 vs. 1.14%, 3/264). The imaging features of brain metastases NB varies from single brain lesion to diffuse meningeal involvement [16,28–30]. Metastases in the frontal and temporal lobes are the most common imaging features of brain metastases [31]. The 15 cases of brain metastases reported in this paper were mainly parenchymal brain metastases (14/15), mainly with frontal, temporal and parietal metastases, followed by spinal membrane and meningeal enhancement.

At present, NB is mainly treated by surgery, chemotherapy, radiotherapy and autologous peripheral blood stem cell transplantation [32]. In addition to traditional treatments, immunotherapy has also been used to treat the NB and have a promising effect [33,34]. A previous study had shown that monoclonal antibodies combined with immunotherapy can effectively treat NB [35]. In our study, the survival time in combined radiotherapy and/or autologous peripheral blood stem cell transplantation group was significantly longer than that in simple operation and chemotherapy group ($P = 0.03$); the survival time in combined intracranial surgery and/or radiotherapy group was significantly longer than that in simple chemotherapy group ($P = 0.003$). This demonstrated that combined radiotherapy and / or autologous peripheral blood stem cell transplantation can prolong the survival time of NB. Active intracranial surgery and craniocerebral radiotherapy can also prolong the survival time of NB patients with brain metastases. Surgical resection causes significant neuro-functional improvement in the majority of BM patients. Resection should be considered as a valid option to increase neurological function and quality of life for patients with BM [36]. Increasing evidence supports efforts at gross-total resection when this can be performed without risking increased morbidity or organ loss [37].

Our study provided evidence that active chemotherapy, radiotherapy and surgery-based comprehensive treatment can prolong the survival time of NB patients with brain metastases. Such a combined multi-modality approach to improve survival may be applicable to other solid tumours metastasizing to the brain.

5. Conclusions

The incidence of brain metastases NB in children is relatively small, but the prognosis is very poor. Stage IV NB with bone and marrow metastases increases the risk of brain metastases. Active chemotherapy, radiotherapy and surgery-based comprehensive treatment can prolong the survival time.

Competing interests

The authors declare that they have no conflict of interests.

Conflict of interest statement

The authors declare that they have no conflict of interests.

Ethical review committee statement

This study was approved by the ethic committee of Beijing Tongren Hospital, Capital Medical University and followed the Declaration of Helsinki. Informed consent were received from all patients.

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