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Treatment and outcomes of 1041 pediatric patients with neuroblastoma who received multidisciplinary care in China

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ABSTRACT

Importance: Neuroblastoma is the most common extracranial malignant solid tumor in children. Multidisciplinary care is critical to improving the survival of pediatric patients with neuroblastoma.

Objective: To systematically summarize the clinical characteristics of children with neuroblastoma and evaluate their prognosis with multidisciplinary care provided in a single center.

Methods: This retrospective study analyzed the clinical data of 1041 patients with neuroblastoma who were diagnosed, treated, and followed-up in the Hematology-Oncology Center of Beijing Children's Hospital from 2007 to 2019.

Results: The median age at diagnosis was 34 months; 80.8% of the patients were younger than 5 years of age. Notably, 243 patients (23.3%) were classified as low-risk, 249 patients (23.9%) were classified as intermediate-risk, and 549 (52.7%) were classified as high-risk. Furthermore, 956 patients underwent surgical resections; 986 (94.7%) patients received chemotherapy; and 176 patients with high-risk neuroblastoma received hematopoietic stem cell transplantation. The 5-year event-free survival (EFS) rate was 91.3% and 5-year overall survival (OS) rate was 97.5% in low-risk group; in the intermediate-risk group, these rates were 85.1% and 96.7%, respectively, while they were 37.7% and 48.9% in the high-risk group ($P < 0.001$ for both). The 5-year EFS and OS rates were significantly higher in patients diagnosed between 2015 and 2019 than in patients diagnosed between 2007 and 2014 ($P < 0.001$). In total, 278 patients (26.7%) exhibited tumor relapse or progression; the median interval until relapse or progression was 14 months. Of the 233 patients who died, 83% died of relapse or progression of neuroblastoma and 4.3% died of therapy-related complications.

Interpretation: The 5-year OS rate was low in high-risk patients, compared with low-and intermediate-risk patients. Multidisciplinary care is critical for improvement of survival in pediatric patients with neuroblastoma. Additional treatment strategies should be sought to improve the prognosis of patients with high-risk neuroblastoma.

KEYWORDS

Neuroblastoma, Pediatric, Multidisciplinary care, Prognosis

INTRODUCTION

Neuroblastoma is an embryonal tumor that originates from undifferentiated neural crest cells and is the most common extracranial solid tumor in childhood; it constitutes 8%–10% of all childhood malignancies.[1,2] Neuroblastoma displays heterogeneity in terms of histology and genetics; thus, recommended treatments and expected outcomes are affected by age, histological variation, and genetic background. Multidisciplinary teams involved in treatment of patients with neuroblastoma include oncology, surgery, radiotherapy, transplantation, imaging, pathology, and psychology.[3] Multidisciplinary management has been successfully performed for many types of cancer, with the expectation of improving patient survival.[4,5] In 2007, we began to establish a multidisciplinary care approach for the diagnosis and treatment of solid tumors in the Hematology-Oncology Center of Beijing Children's Hospital. Importantly, we applied this comprehensive multidisciplinary care approach for management of neuroblastoma. In this study, we analyzed the clinical characteristics of children with neuroblastoma who underwent multidisciplinary care from 2007 to 2019 and evaluated their prognoses following receipt of multidisciplinary treatment.

METHODS

Ethical approval

The study was approved by the Ethics Committee of Beijing Children's Hospital and was conducted in accordance with the Helsinki Declaration. Written informed consent to participate in the study and for publication was obtained from all the patients' parents before their enrollment in this study.

Patients

From February 2007 to December 2019, 1148 pediatric patients with neuroblastoma were newly diagnosed at the Hematology-Oncology Center of Beijing Children's Hospital. Fifty-two patients who were discharged from our hospital without any treatment were excluded from this study. Fifty-five high-risk patients who did not complete 13-*cis*-retinoic acid maintenance treatment were also excluded. Finally, 1041 pediatric patients with neuroblastoma were enrolled in this retrospective study (Figure 1).

Diagnosis and staging

Diagnostic criteria were as follows: (1) Unequivocal pathologic diagnosis was made from tumor tissue by light microscopy (with or without immunohistochemistry,

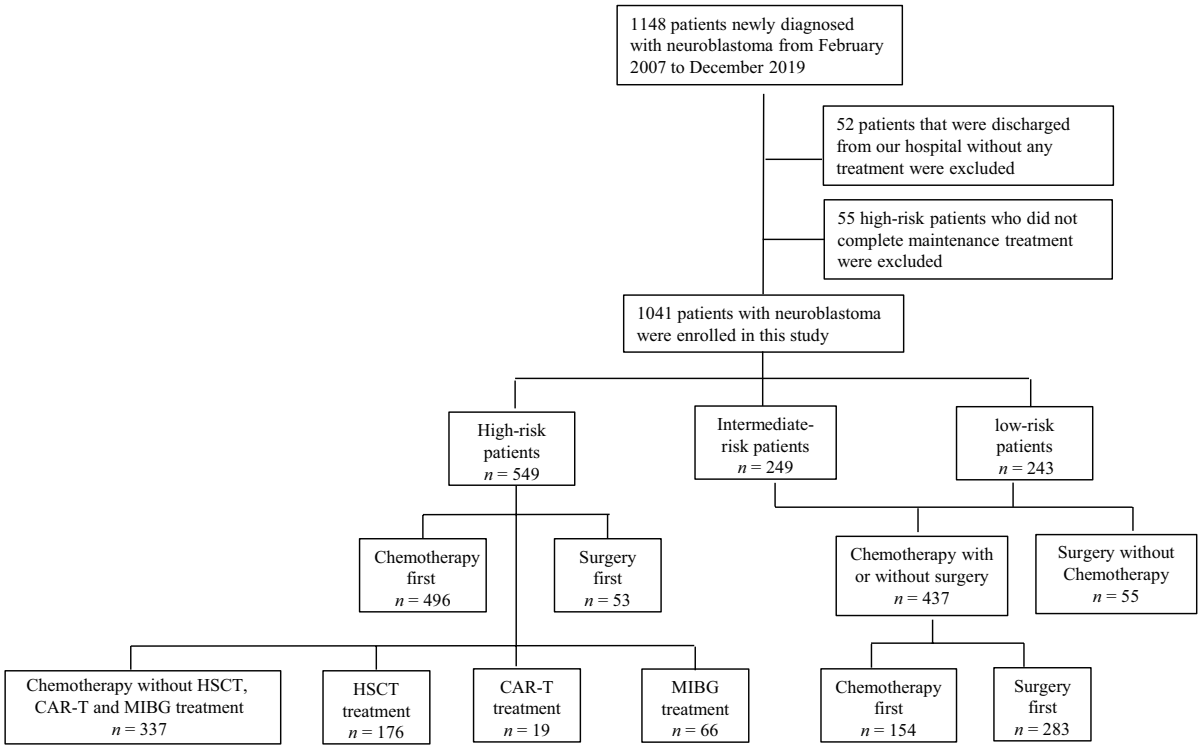

FIGURE 1 Flow diagram of patient enrollment and treatment in this study. HSCT, Hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor modified T-cells; MIBG, metaiodobenzylguanidine.

electron microscopy, and increased urine (or serum) catecholamines or metabolites); or (2) Bone marrow aspirate or trephine biopsy showed unequivocal tumor cells and increased urine (or serum) catecholamines or metabolites.[6]

Clinical stage and risk group: Positron emission tomography-computed tomography, metaiodobenzylguanidine (MIBG) scan, bone scan, bone marrow aspirate and trephine biopsy, enhancement computed tomography, ultrasonic examination of primary and metastatic tumors, and cranial magnetic resonance imaging were performed to confirm the Image-Defined Risk Factors and determine the clinical stage, in accordance with the International Neuroblastoma Risk Group Staging System. In this study, risk group classification criteria were based on the Children's Oncology Group before 2011 and on International Neuroblastoma Risk Group after 2011.[7,8]

Treatment strategies

A multidisciplinary treatment model was implemented with the participation of surgery, radiotherapy, and transplantation teams, under the management of the oncology team.

***Chemotherapy*:** Alternating chemotherapy regimens of CADO and CBVP were applied to patients in low- and intermediate-risk groups. The CADO protocol was applied as follows: cyclophosphamide, 750 $mg \cdot m^{-2} \cdot d^{-1}$, days 1 and 2; adriamycin, 25 $mg \cdot m^{-2} \cdot d^{-1}$, days 1 and 2; vincristine, 1.5 $mg \cdot m^{-2} \cdot d^{-1}$, day 1. The CBVP protocol was applied as follows: carboplatin, 200 $mg \cdot m^{-2} \cdot d^{-1}$, days 1 to 3; etoposide, 150 $mg \cdot m^{-2} \cdot d^{-1}$, days 1 to 3. The dose of cyclophosphamide in the CADO regimen for low- and intermediate-risk groups was 30 $mg \cdot kg^{-1} \cdot d^{-1}$ in infants younger than 12 months of age. Alternating chemotherapy regimens of CAV and CVP were applied to patients in the high-risk group. CAV was applied as follows: vincristine, 1 $mg \cdot m^{-2} \cdot d^{-1}$, days 1 to 3; adriamycin, 25 $mg \cdot m^{-2} \cdot d^{-1}$, days 1 to 3; cyclophosphamide, 70 $mg \cdot m^{-2} \cdot d^{-1}$, days 1 and 2. The CVP protocol was applied as follows: cisplatin, 50 $mg \cdot m^{-2} \cdot d^{-1}$, days 1 to 4; etoposide, 200 $mg \cdot m^{-2} \cdot d^{-1}$, days 1 to 3. For patients with body weight below 12 kg, the dose of cyclophosphamide in the CAV regimen was reduced by 25%–33%.

***Surgery*:** High-risk neuroblastoma patients without surgical resection at the time of diagnosis were able to undergo surgery after three to four courses of chemotherapy when tumor markers had decreased, bone marrow metastases had become clear, and other metastatic sites were limited.

Patients with low- or intermediate-risk neuroblastoma underwent resection of the primary tumor at the time of diagnosis, or after three to four courses of chemotherapy.

According to the tumor site, the departments in our hospital that were involved in the surgery of neuroblastoma included neurosurgery, otorhinolaryngology head and neck surgery, thoracic surgery, and surgical oncology. The otorhinolaryngology head and neck surgery department was responsible for the resection of neck tumors; the surgical oncology department was responsible for the resection of abdominal and pelvic tumors; and the thoracic surgery department was responsible for the resection of thoracic neuroblastoma. Thoracic surgical approaches in this study mainly included thoracoscopy and open thoracotomy. Laminectomy was performed by the neurosurgery department as an initial procedure for patients with serious spinal cord compression caused by tumor invasion.

***Radiation therapy*:** In the intermediate-risk group, patients older than 18 months of age with unfavorable histology were administered radiotherapy on the primary tumor bed at the end of chemotherapy. Radiotherapy was performed on both the primary tumor bed and the sites of persistent metastases in patients with high-risk neuroblastoma at the end of intensive chemotherapy. The radiation dose to primary tumors was 20–25 Gy, while the dose to metastatic tumors was a maximum of 20 Gy.

***Hematopoietic stem cell transplantation (HSCT)*:** High-risk patients could be administered myeloablative chemotherapy, followed by autologous hematopoietic stem cell rescue as consolidation treatment. The myeloablative regimen contained carboplatin, 300 $mg \cdot m^{-2} \cdot d^{-1}$, days 6 to 3 before transplantation; etoposide, 160 $mg \cdot m^{-2} \cdot d^{-1}$, days 6 to 3 before transplantation; melphalan, 140 $mg \cdot m^{-2} \cdot d^{-1}$, day 5 before transplantation; melphalan, 70 $mg \cdot m^{-2} \cdot d^{-1}$, day 4 before transplantation.

***^{131}I-MIBG and chimeric antigen receptor modified T-cells (CAR-T) therapy*:** High-risk patients with relapsed or refractory neuroblastoma with MIBG-avid tumors could be administered ^{131}I-MIBG therapy. Patients with relapsed or refractory neuroblastoma after intensive chemotherapy, surgery, and radiotherapy, with or without HSCT, could be administered CAR-T therapy.

Evaluation

All patients were evaluated by assessment of tumor markers (serum lactate dehydrogenase (LDH), serum neuron specific enolase (NSE), urinary vanillylmandelic acid, urinary homovanillic acid and tumor size, according to risk group and treatment stage. Patients with bone marrow metastasis at the time of diagnosis underwent review of bone marrow aspirate. Patients with MIBG-avid tumors underwent MIBG scans at the end of intensive therapy. MIBG scans were performed at 6-month intervals in high-risk patients receiving maintenance treatment. The evaluation criteria were established with reference to the Response Evaluation Criteria In Solid Tumors (RECIST) and International Neuroblastoma Response Criteria (INRC).[9,10]

Follow-up

After discontinuation of drug treatment, patients were followed up at 3-month intervals in years 1 and 2, at 6-month intervals in years 3–5, and at 12-month intervals thereafter. The patients were evaluated with respect to tumor markers, imaging of primary and metastatic tumors and bone marrow aspirate (solely for patients with prior bone marrow metastasis). The evaluation also included monitoring of therapeutic toxicity, such as hepatic and renal function, cardiac function, and audition. Event-free survival (EFS) was defined as the interval from the day of diagnosis to an event or date of last follow-up (if no event occurred). An event was defined as the first occurrence of relapse or progression of neuroblastoma, secondary malignancy, or death for any reason. Overall survival (OS) was defined as the interval from the day of diagnosis to death for any reason or date of last follow-up (if no death occurred). Early death was defined as death within 1 month after diagnosis of neuroblastoma. The final follow-up cutoff date was April 30th, 2020.

Statistical methods

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). Data with non-normal distributions are expressed as medians (ranges); the Wilcoxon signed-rank test was used for comparisons of these data between groups. Qualitative data are presented as counts (percentages); the chi-squared (χ^2) test was used for comparisons of these data between groups. Log-rank tests were used to compare differences in survival estimates between variables. Cox proportional hazards regression analysis was used to investigate risk factors that might influence OS. Survival plots were constructed using the Kaplan–Meier method. $P < 0.05$ was considered as statistical significance.

RESULTS

Clinical data

The 1041 patients with neuroblastoma in this study comprised 541 boys and 500 girls with a median age of 34 months (range, 0–191 months). Children younger than 5 years of age comprised 80.8% of the patients, while children older than 10 years of age comprised only 1.6% of the patients. The median largest primary tumor diameter was 7.9 cm (range, 0.9–29.0 cm), the median level of serum LDH was 388.5 U/L (range, 117.0–17324.0 U/L), and the median level of serum NSE was 89.5 ng/mL (range, 5.1–2370.0 ng/mL).

The primary tumor sites of 665 patients were located in the retroperitoneal or adrenal region, including 445 (66.9%) in the high-risk group and 220 (33.1%) in the low- and

intermediate-risk groups. Moreover, 109 (16.4%) patients with primary tumor sites in the retroperitoneal or adrenal region exhibited *MYCN* amplification. The primary tumor sites of 307 patients were located in the thorax, including 82 (26.7%) in the high-risk group and 225 (73.3%) in the low- and intermediate-risk groups; furthermore, five patients with primary tumor sites in the thorax exhibited *MYCN* amplification. Among patients with primary tumors outside the retroperitoneal and thoracic regions, 22 were in the high-risk group and 47 were in the low- and intermediate-risk groups; no patients with primary tumors outside the retroperitoneal and thoracic regions exhibited *MYCN* amplification. The clinical characteristics of the 1041 patients are shown in Table 1.

TABLE 1 Clinical characteristics of pediatric patients with neuroblastoma (n = 1041)

Characteristics	Number of patients, *n* (%)	Characteristics	Number of patients, *n* (%)
Gender		*MYCN* status	
Male	541 (52.0)	Amplified	114 (11.0)
Female	500 (48.0)	Non-amplified	887 (85.2)
Age at diagnosis (months)		Unknown	40 (3.8)
<18	277 (26.6)	Years of treatment	
18–60	564 (54.2)	2007–2010	67 (6.4)
60–120	183 (17.6)	2011–2014	212 (20.4)
≥120	17 (1.6)	2015–2019	762 (73.2)
Primary tumor site		Surgery	
Retroperitoneal/adrenal	665 (63.9)	In our hospital	824 (79.1)
thoracic	307 (29.5)	Surgical Oncology	530 (50.9)
Neck	27 (2.6)	Thoracic Surgery	237 (22.7)
Pelvic	20 (1.9)	Head and Neck Surgery	22 (2.1)
Two body compartments	12 (1.1)	Neurosurgery	3 (0.3)
†Others	10 (1.0)	Two surgery departments	32 (3.1)
NSE (ng/mL)		In other hospital	132 (12.7)
<100	546 (52.4)	No surgery	85 (8.2)
≥100	495 (47.6)	Chemotherapy	
LDH (U/L)		Yes	986 (94.7)
<500	644 (61.9)	No	55 (5.3)
500–1500	272 (26.1)	Radiation therapy	
≥1500	125 (12.0)	Yes	525 (50.4)
Bone marrow metastasis		No	516 (49.6)
Yes	438 (42.1)	HSCT	
No	603 (57.9)	Yes	176 (16.9)
Bone metastasis		No	865 (83.1)
Yes	417 (40.1)	MIBG therapy	
No	624 (59.9)	Yes	66 (6.3)
Distant lymph node metastasis		No	975 (93.7)
Yes	375 (36.1)	CAR-T therapy	
No	665 (63.9)	Yes	19 (1.8)
		No	1022 (98.2)

†Others: skull base, intraspinal canal, no primary foci. NSE, neuron specific enolase; LDH, lactate dehydrogenase; HSCT, hematopoietic stem cell transplantation; MIBG, metaiodobenzylguanidine; CAR-T, chimeric antigen receptors modified T-cells.

Treatment

In total, 956 patients underwent surgical resection of primary tumors or metastases; of these, 824 underwent surgical resections in our hospital, while the remaining 132 patients underwent surgeries in other hospitals. In three subdivisions of the study period (2007–2010, 2011–2014, and 2015–2019), the proportions of patients with neuroblastoma who underwent surgery in our hospital were 70.0%, 76.8%, and 80.5%, respectively. Of 307 patients with primary thoracic tumor, 237 (77.2%) underwent surgical resection in the thoracic surgery department in our hospital. Thoracoscopic resections were performed in 166 patients, open thoracotomy approaches in 68 patients, and resections from the neck in three patients. Of 691 patients with primary abdominal and pelvic tumors, 530 (76.7%) underwent surgical resection in the surgical oncology department in our hospital. Of 27 patients with primary tumors located in the neck, 22 (81.5%) underwent surgical resection in the otorhinolaryngology head and neck surgery department in our hospital. Thirty-two patients underwent surgery involving two surgical departments; of these 32 patients, 28 (87.5%) had severe spinal cord compression caused by tumor invasion into the spinal canal. For these 28 patients, spinal canal decompression was performed in the neurosurgery department, followed by chemotherapy and resection of primary tumors in the surgical oncology or thoracic surgery departments.

In total, 986 patients received chemotherapy; 55 patients with very low- or low-risk neuroblastoma only underwent surgery and subsequent observation. Notably, 437 patients with low- or intermediate-risk neuroblastoma received chemotherapy, with a median of five courses of chemotherapy (range, 2–9 courses) (Figure 1).

Prognosis

The median follow-up period for all 1041 patients was 22.0 months (range, 0.2–154.0 months) until April 30, 2020. The 3-year OS rate was 72.1%, while the 5-year OS rate was 66.4%. The 3-year EFS rate of 1041 patients was 63.1%, while the 5-year EFS rate was 57.3% (Figure 2). The 5-year EFS rates were 91.3%, 85.1%, and 37.7% when patients were stratified into low-risk, intermediate-risk, and high-risk groups, respectively. The 5-year OS rates were 97.5%, 96.7%, and 48.9% when patients were stratified into low-risk, intermediate-risk, and high-risk groups, respectively (EFS: χ^2=195.772, $P < 0.001$; OS: χ^2=158.055, $P < 0.001$) (Figure 3A, B). The 5-year EFS rates were 47.4%, 47.4%, and 62.9% in patients who were diagnosed and treated in the following subdivisions of the study period: 2007–2010, 2011–2014, and 2015–2019, respectively. The respective 5-year OS rates were 55.4%, 54.8%, and 71.1% in patients who were diagnosed and treated in those three subdivisions of the study period (Figure 4A, B). The EFS and OS rates of patients who were diagnosed and treated in the 2015–2019 subdivision were significantly higher than patients who were diagnosed and treated in the prior subdivisions (EFS: $\chi^2 = 20.277$, $P < 0.001$; OS: $\chi^2 = 31.924$, $P < 0.001$).

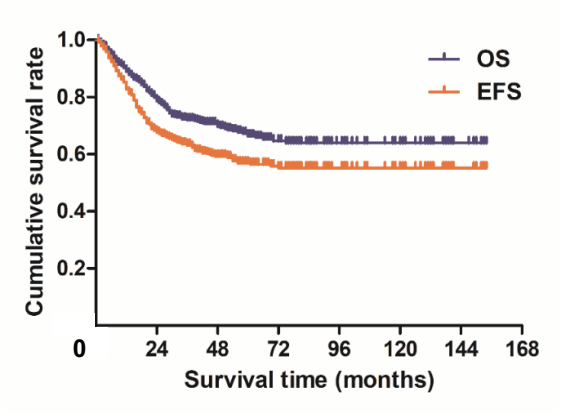

FIGURE 2 Event-free survival (EFS) and overall survival (OS) curves for 1041 patients with neuroblastoma.

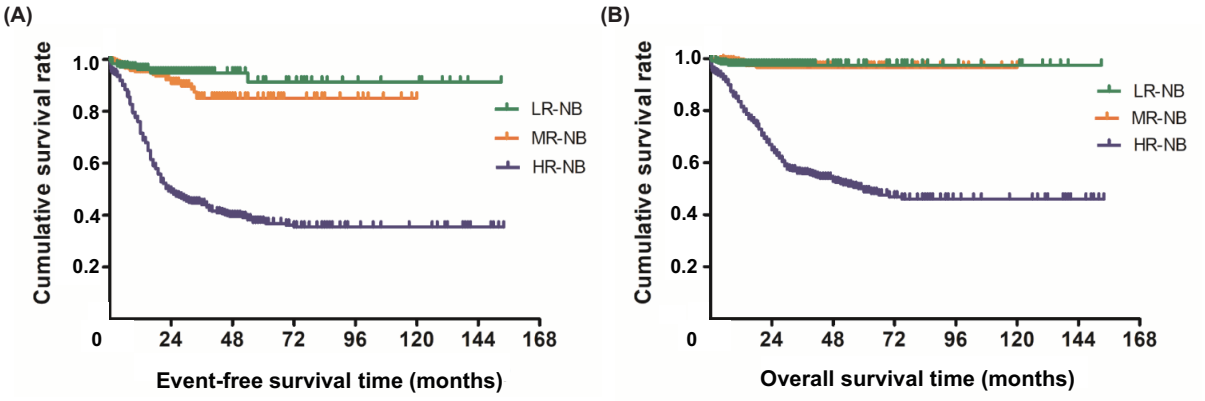

FIGURE 3 Event-free survival (A) and overall survival curves (B) for patients with low-risk (LR), intermediate-risk (MR), and high-risk (HR) neuroblastoma (NB).

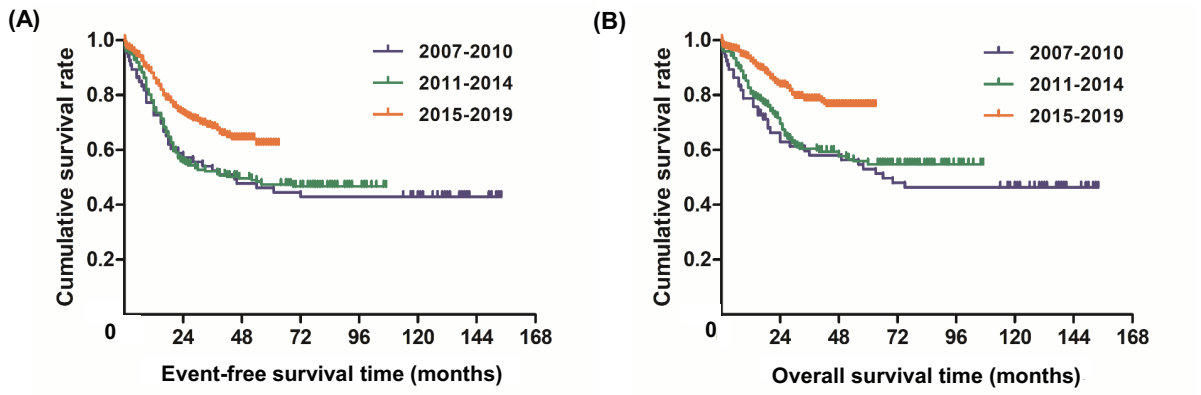

FIGURE 4 Event-free survival (A) and overall survival curves (B) for patients in each of three subdivisions of the study period.

Univariate survival analysis showed that retroperitoneal/adrenal tumors, NSE ≥ 100 ng/mL, LDH ≥ 1500 U/L, largest primary tumor diameter ≥ 7.9 cm, bone metastasis, bone marrow metastasis, and distant lymph node metastasis were associated with poor prognosis in patients with low- and intermediate-risk neuroblastomas (all $P < 0.05$) (Table 2). Bone marrow metastasis (*HR*: 4.730; 95% *CI*: 1.290–17.335; $P < 0.05$) and LDH ≥ 1500 U/L (*HR*: 3.801; 95% *CI*: 1.470–9.828; $P < 0.05$) were poor prognostic factors for survival of patients with low- and intermediate-risk neuroblastomas, according to Cox regression models. Univariate survival analysis showed that NSE ≥ 100 ng/mL, LDH ≥ 1500 U/L, bone metastasis, bone marrow metastasis, and *MYCN* amplification were associated with poor prognosis in patients with high-risk neuroblastoma (all $P < 0.05$) (Table 3). Bone marrow metastasis, LDH ≥ 1500 U/L, and *MYCN* amplification were poor prognostic factors for survival of patients with high-risk neuroblastoma, according to Cox regression models (*HR*: 1.812, 1.712, and 1.754, respectively; 95% *CI*: 1.272–2.582, 1.424–2.059, and 1.426–2.157, respectively; all $P < 0.05$).

In total, 278 patients (86.8%) experienced tumor relapse or progression at a median of 14 months (range, 1–72 months). Relapse or progression occurred in 31 patients (11.2%) with low- or intermediate-risk groups; of these, 21 patients (67.7%) exhibited relapse or progression at primary tumor sites. The 5-year OS rates were 22.7% in patients with relapse or progression who underwent MIBG treatment and 17.1% in patients with relapse or progression who did not undergo MIBG treatment ($\chi^2 = 5.541$, $P = 0.019$). The 5-year OS rates were 32.0% in patients with relapse or progression who underwent CAR-T treatment and 16.8% in patients relapse or progression who did not undergo CAR-T treatment ($\chi^2 = 3.610$, $P = 0.057$). Three patients in high-risk group developed secondary malignant neoplasms, comprising acute leukemia, thyroid cancer, and Ewing's sarcoma of the leg at 54 months, 20 months, and 69 months after the diagnosis of neuroblastoma, respectively.

TABLE 2 Univariate survival analysis of 492 patients with low- and intermediate-risk neuroblastoma

Characteristics	Number of patients, *n* (%)	5-year OS (%)	*P*
Gender			0.231
Male	227 (46.1)	97.9	
Female	265 (53.9)	96.2	
Age at diagnosis (months)			0.186
<18	246 (50.0)	95.9	
≥18	246 (50.0)	98.2	
Risk group			0.865
Very low/low	243 (49.4)	97.5	
Intermediate	249 (50.6)	96.7	
Primary tumor site			0.047
Retroperitoneal/adrenal	220 (44.7)	94.9	
thoracic	225 (45.7)	98.4	
†Others	47 (9.6)	100	
NSE (ng/mL)			<0.001
<100	400 (81.3)	98.6	
≥100	92 (18.7)	89.8	
LDH (U/L)			<0.001
<500	446 (90.7)	98.0	
500–1500	43 (8.7)	92.3	
≥1500	3 (0.6)	0	
The longest diameter of primary tumor (cm)			0.032
<7.9	356 (72.4)	98.2	
≥7.9	136 (27.6)	93.9	
Bone marrow metastasis			<0.001
Yes	29 (5.9)	82.2	
No	463 (94.1)	98.0	
Bone metastasis			0.028
Yes	35 (7.1)	89.9	
No	457 (92.9)	97.6	
Distant lymph node metastasis			0.005
Yes	43 (8.7)	89.5	
No	449 (91.3)	97.7	

†Others: primary tumor sites except retroperitoneal/adrenal and thoracic sites. OS, overall survival; NSE, neuron specific enolase; LDH, lactate dehydrogenase.

TABLE 3 Univariate survival analysis of 549 patients with high-risk neuroblastoma

Characteristics	Number of patients, *n* (%)	5-year OS (%)	*P*
Gender			0.269
Male	314 (57.2)	46.8	
Female	235 (42.8)	51.5	
Age at diagnosis (months)			0.591
<18	31 (5.6)	51.3	
≥18	518 (94.4)	48.6	
Primary tumor site			0.059
Retroperitoneal/adrenal	44 (81.1)	45.5	
thoracic	82 (14.9)	62.1	
†Others	22 (4.0)	67.7	
NSE (ng/mL)			0.010
<100	146 (26.6)	59.4	
≥100	403 (73.4)	44.6	
LDH (U/L)			<0.001
<500	198 (36.1)	61.4	
500–1500	229 (41.7)	50.3	
≥1500	122 (22.2)	24.8	
The longest diameter of primary tumor (cm)			0.426
<7.9	173 (31.5)	50.1	
≥7.9	376 (68.5)	48.2	
Bone marrow metastasis			<0.001
Yes	409 (74.5)	41.4	
No	140 (25.5)	68.7	
Bone metastasis			0.009
Yes	382 (69.6)	43.3	
No	167 (30.4)	61.8	
Distant lymph node metastasis			0.385
Yes	332 (60.5)	49.4	
No	217 (39.5)	48.2	
MYCN status			<0.001
Amplified	114 (20.8)	30.5	
Non-amplified	397 (72.3)	55.5	
Unknown	38 (6.9)	29.6	
HSCT			0.543
Yes	176 (32.1)	45.3	
No	373 (67.9)	52.4	
MIBG therapy			0.970
Yes	66 (12.0)	38.8	
No	483 (88.0)	50.9	
CAR-T therapy			0.734
Yes	19 (3.5)	46.1	
No	530 (96.5)	49.3	

†Others indicate primary tumor sites except retroperitoneal/adrenal and thoracic sites. OS, overall survival; NSE, neuron specific enolase; LDH, lactate dehydrogenase; HSCT, hematopoietic stem cell transplantation; MIBG, metaiodobenzylguanidine; CAR-T, chimeric antigen receptors modified T-cells.

Overall, 233 patients (22.4%) died, of whom 194 (83.3%) died of neuroblastoma relapse or progression, 12 (5.2%) died of tumor rupture, 17 (7.3%) died of extensive metastases or critical disease, and 10 (4.3%) died of therapy-related complications. Of the 10 patients who died of therapy-related complications, eight died of severe infection during transplantation or chemotherapy and two died of operation-related complications. The median age at diagnosis of the 12 patients who died of tumor rupture was 31 months (range, 19–103 months). Among these 12 patients, 11 exhibited high-risk neuroblastoma and the primary tumor sites were located in the retroperitoneal or adrenal region. The median interval until tumor rupture was 5 days after diagnosis of neuroblastoma (range, 0–20 days). Rupture occurred after chemotherapy in two patients and before chemotherapy in 10 patients. All patients with tumor rupture were treated with chemotherapy and coagulation factor support therapy, without surgical intervention. The age at diagnosis, the largest primary tumor diameter, and LDH level were compared among patients with different causes of death. The median age was lowest in patients with therapy-related death (15.5 months; range, 8.0–55.5 months; $P < 0.001$). The median primary tumor diameter was largest in patients who died of tumor rupture (14.5 cm; range, 10.8–26.0 cm; $P = 0.006$). The median level of LDH was highest in patients who died of tumor rupture (2785 U/L; range, 1087–8356 U/L; $P < 0.001$). Patients who died of extensive metastases or critical disease also had higher LDH and larger primary tumor diameter, compared with patients who died of relapse or progression and therapy-related complications (Figure 5A–C). Twenty-seven patients died within one month of diagnosis; of these, 12 died of tumor rupture and 15 died of extensive metastases or critical conditions.

DISCUSSION

The Hematology-Oncology Center of Beijing Children's Hospital began to systematically diagnose and treat neuroblastoma in 2007. With improved management experience and extensive multidisciplinary collaboration, the OS of patients with neuroblastoma has been improved each year. Following comprehensive cooperation with surgery, transplantation, and radiotherapy departments beginning in 2015, the treatment flow of patients has become increasingly efficient. The 5-year EFS rate and 5-year OS rate were significantly improved after 2015, compared with previous periods ($P < 0.05$). Notably, the follow-up duration for some patients treated after 2015 is relatively short; additional follow-up time is needed to confirm the long-term effects in these patients.

Treatment for neuroblastoma includes chemotherapy, surgery, radiotherapy, hemopoietic stem cell transplantation, immunotherapy, and other treatment modalities. Surgery plays an important role in the treatment of neuroblastoma.[11] The surgical teams involved in neuroblastoma comprehensive treatment in our hospital mainly include the surgical oncology team, thoracic surgery team, otorhinolaryngology head and neck surgery team, and neurosurgery team. In this study, 69.1% of patients with primary thoracic tumors underwent thoracoscopic resections in the thoracic surgery department in our hospital. Guye et al[12] showed

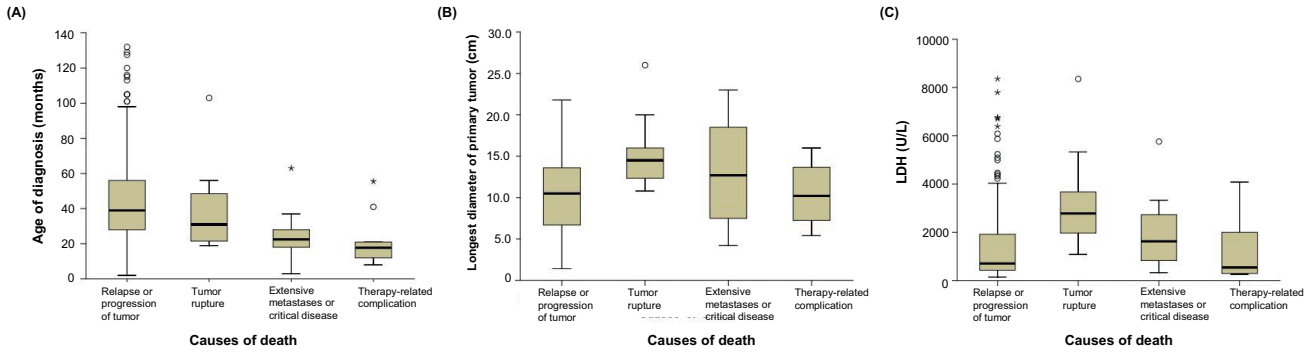

FIGURE 5 Correlation analysis of (A) Age at diagnosis; (B) Largest primary tumor diameter; (C) LDH level in patients with different causes of death. LDH, lactate dehydrogenase.

that thoracoscopy was a safe, effective approach for the resection and biopsy of solid lung tumors in a study of 134 children with solid thoracic tumors. Malek et al[13] compared the outcomes of thoracoscopic resection and open thoracotomy in 36 patients with thoracic neuroblastoma. They showed that thoracoscopic resection could facilitate shorter length of stay, milder pain, and less blood loss. There were no significant differences in complications, recurrence, survival, or disease-free survival between the two groups.[13] Notably, 7%–15% of patients with neuroblastoma will experience spinal cord compression, due to giant tumors that extend into the spinal canal. These patients present with neurological motor deficits or sphincter dysfunction. Long-term or severe compression may lead to permanent neurological dysfunction. Patients with severe spinal cord compression have been shown to benefit from neurosurgical intervention.[14] In the present study, 28 patients with intraspinal extension of abdominal or thoracic neuroblastoma underwent spinal canal decompression surgery by the neurosurgery department in our hospital. Following chemotherapy and subsequent primary tumor resection, 90% of the patients exhibited complete recovery of neurological motor deficit and sphincter dysfunction.

High-risk neuroblastoma is routinely treated with intensive chemotherapy, surgery, radiotherapy, and 13-*cis*-retinoic acid maintenance in China. Some patients receive myeloablative chemotherapy, followed by autologous hematopoietic stem cell rescue as consolidation therapy. However, survival remains poor for children with neuroblastoma relapse or progression. Survival of patients with relapsed high-risk neuroblastoma is currently <10%. At the time of first relapse, 60% of patients have been reported to relapse within 18 months, while 80% have been reported to relapse within 24 months of diagnosis.[15] In the present study, the median interval until tumor relapse or progression was 14 months; 88.8% of patients exhibited high-risk neuroblastoma. This time was the later period of maintenance treatment or just termination of therapy in high-risk neuroblastoma. In the present study, patients with tumor relapse or progression received further intensive chemotherapy, MIBG treatment, or CAR-T treatment. CAR-T therapy for patients with relapsed or refractory neuroblastoma has been considered safe and feasible since the early 2000s. There are currently many open clinical trials of CAR-T therapy for patients with relapse or progression neuroblastoma.[16] Our data showed that CAR-T therapy was well tolerated; it provided a short-term therapeutic effect for patients with refractory and recurrent neuroblastoma. However, it did not improve the long-term survival rate. Tumor relapse and progression are the major challenges in treatment of patients with high-risk neuroblastoma. This is a therapeutic limitation for patients with high-risk neuroblastoma in China. In recent years, immunotherapy involving the anti-GD2 antibody has further improved the survival of patients with high-risk neuroblastoma. A phase 3 randomized clinical trial of the Children's Oncology Group showed that immunotherapy with ch14.18 was associated with a significantly improved outcome, compared with standard therapy, in patients with high-risk neuroblastoma. Immunotherapy was superior to standard therapy with respect to rates of 2-year EFS (66% *vs*. 46%, $P = 0.01$) and 2-year OS (86% *vs*. 75%, $P = 0.02$).[17] Another phase 3 randomized clinical trial of SIOPEN showed that the 5-year EFS rate was 53% and 5-year OS rate was 63% in patients with high-risk neuroblastoma who received anti-GD2 antibody ch14.18/CHO treatment.[18]

The prognoses of patients with low- and intermediate-risk neuroblastoma are much better than those of patients with high-risk neuroblastoma. In the present study, 31 patients with low- or intermediate-risk neuroblastoma exhibited tumor relapse or progression; of these 31 patients, 67.7% exhibited relapse or progression at the primary tumor site. The causes of relapse or progression were related to the biological characteristics of the tumor (e.g., unfavorable histology), extensive metastases in some infants, and partial resection of the tumor in patients with large residual lesions. SIOP reports showed that gross resection or subtotal resection was an important factor for cure in patients with localized neuroblastoma who did not exhibit *MYCN* amplification. However, patients older than 18 months of age with unfavorable histopathology and elevated LDH exhibited a high number of relapses.[19,20]

Therefore, the surgeon's technique and the degree of surgical resection of the primary tumor are important factors in the prognosis of low- and intermediate-risk neuroblastoma.

Treatment advances have led to significantly improved outcomes for children with neuroblastoma; consequently, the number of survivors is increasing. During the past four decades, high-risk patients have been treated with increasingly intensive and multi-modal approaches. Neuroblastoma survivors are at enhanced risk of developing secondary malignant neoplasms, compared with the general population. In this study, three patients with high-risk neuroblastoma developed secondary malignant neoplasms, including acute leukemia, thyroid cancer, and Ewing's sarcoma; notably, the sites of secondary solid tumors were not the radiotherapy sites of neuroblastoma. Applebaum et al[21] analyzed 2801 neuroblastoma patients and found that 34 (1.2%) developed secondary malignant neoplasms, including renal cell carcinoma, thyroid cancer, acute myeloid leukemia, sarcoma, and lymphoma. Furthermore, 14.7% of secondary malignant neoplasms occurred at the site of radiotherapy for the primary neuroblastoma tumor.[21] The incidence of secondary malignancy was relatively low in the present study, presumably because of the shorter treatment time for patients with neuroblastoma in our center and the shorter follow-up interval for our patients.

The risks of early death due to acute leukemia, hepatoblastoma, or brain tumor are significantly greater than the risk of death due to neuroblastoma in children. Age younger than 1 year was considered to be a risk factor for early death in patients with solid tumors.[22] The early death in this study mainly occurred in patients with tumor rupture, extensive metastases, or critical diseases. Moreover, the primary tumor diameter and LDH level were significantly greater in patients with tumor rupture, extensive metastases, or critical diseases. Qin et al analyzed 47 cases with tumor rupture, which revealed that a primary tumor diameter >13.2 cm was an independent risk factor for tumor rupture in children with neuroblastoma. The LDH level was significantly higher in patients with tumor rupture than in patients without tumor rupture.[23] Clinicians should carefully monitor patients with high LDH and large tumors to reduce the risk of death due to tumor rupture and critical diseases. In the present study, the median age was lowest among patients with therapy-related death (15.5 months), compared with other causes of death. Because infants are less able to tolerate aggressive treatment, clinicians should perform careful management of young patients with neuroblastoma. Tumor relapse and progression remain the primary causes of death in patients with neuroblastoma. With respect to death caused by tumor relapse or progression, more comprehensive multidisciplinary care approaches and more effective therapeutic methods are essential to improve the prognosis of patients with neuroblastoma.

The management of neuroblastoma by a multidisciplinary care approach in Hematology-Oncology Center of Beijing Children's Hospital has been ongoing for more than 10 years. In this study, the 5-year OS rates of low-, intermediate- and high-risk patients were 97.5%, 96.7%, and 48.9%, respectively. Moreover, the therapy-related mortality rate was 4.3%. Notably, 80% of the surgeries were performed by surgical teams in our hospital. Multidisciplinary cooperation is an important approach for improving the survival of patients with neuroblastoma. More effective therapeutic methods should be designed to improve the prognoses of these patients.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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