

Clinical characteristics and risk factors of 47 cases with ruptured neuroblastoma in children

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Abstract

Background: Neuroblastoma (NB) tumor rupture was a rare oncology emergency with poor prognosis. We aimed to evaluate clinical characteristics and risk factors for ruptured NB. **Methods:** A retrospective study was conducted on 47 confirmed ruptured NB patients in Beijing Children's Hospital between January 2009 and January 2019. To identify tumor rupture risk factors within high-risk NB, we included 93 consecutive nonruptured high-risk NB patients from January 2017 to January 2019. **Results:** Median age at presentation was 29 months (adrenal and retroperitoneum origin) for 47 ruptured NB patients. Spontaneous tumor rupture occurred in 22 cases; 18 developed tumor rupture during or after the first chemotherapy cycle, and 7 developed after core needle biopsy. Five patients died of tumor rupture, and 17 patients' parents refused further anti-tumor therapy. Among 25 remaining patients, 6 survived without disease, 5 remained under treatment with stable disease, and 14 died. According to multivariate logistic regression analysis, the maximum diameter of primary tumor > 13.20 cm and MYCN gene amplification were independent risk factors for tumor rupture within high-risk NB. **Conclusions:** Tumor rupture is an uncommon, life-threatening presentation among NB patients; these patients are most likely to have poor outcomes due to tumor recurrence or rapid progression. Several treatment modalities, including symptomatic support therapy and chemotherapy, are important for saving lives and creating conditions for subsequent treatment.

Background

In pediatric patients with neuroblastoma (NB), spontaneous tumor rupture has been documented in previous case reports [1]. Tumor rupture is an uncommon, life-threatening presentation among NB patients, and several studies have reported poor prognosis of patients with ruptured NB [2]. Some patients are diagnosed with NB following spontaneous tumor rupture as the initial symptom. However, accurate diagnosis may be difficult if a tumor is ruptured at initial presentation. In addition, some cases develop tumor rupture during or after chemotherapy and biopsy. Several treatment modalities, including symptomatic support therapy, emergency or staged surgery, and chemotherapy, have been described. In this study, we retrospectively evaluated the clinical characteristics, treatment, and prognosis of ruptured NB cases. Moreover, to identify clinical risk factors for tumor rupture among NB patients, we compared clinical characteristics between nonruptured and ruptured NB. Thus, we aimed to contribute to current knowledge of this rare disease and to aid the development of better treatment strategies.

Methods

Patient information

A total of 47 consecutive patients with ruptured NB who were diagnosed in Beijing Children's Hospital (BCH) between January 2009 and January 2019 were included in this retrospective study. To compare the clinical characteristics between nonruptured and ruptured high-risk NB, we included 93 consecutive patients with nonruptured high-risk NB in the abdomen and pelvis from January 2017 to January 2019 in

this retrospective study. Basic patient information was collected by referring to medical records. The initial diagnosis of NB was established according to the International Neuroblastoma Staging System (INSS) criteria [3]. In special cases of seriously ill patients without bone marrow metastasis, the initial clinical diagnosis was established by typical tumor localization with typical metastases (such as bone, liver, lymph node, and skin) detected by metaiodobenzylguanidine (MIBG) or fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) and combined with abnormal tumor marker levels. Patients were staged according to the International Neuroblastoma Risk Group Staging System (INRGSS) [4] and grouped by the INRG classification system [5]. Patients with ruptured NB were followed up to January 1, 2019. All methods were carried out in accordance with relevant guidelines and regulations, and the study was approved by the Medical Ethics Committee of BCH (2017-k-89). A waiver of consent was awarded to conduct analyses in this study.

Laboratory analysis

Laboratory analysis was performed prior to treatment, and the interval between laboratory tests and biopsy was less than 15 days. Urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) were analyzed by gas chromatography-mass spectrometry (GC/MS), and their concentrations were expressed as a ratio to urinary creatinine concentration. Lactate dehydrogenase (LDH), neuron-specific enolase (NSE), and ferritin were measured in serum using routine clinical chemistry laboratory methods. Bone marrow metastasis disease was evaluated by bone marrow aspiration and biopsy. Tumors were classified in accordance with the International Neuroblastoma Pathology Classification System (INPC) [6]. In this study, *MYCN* gene copy numbers and segmental chromosome aberration (1p and 11q) were analyzed using the fluorescence in situ hybridization (FISH) method.

Treatment

Patients were treated with multimodal therapy based on the BCH-NB-2007 protocol for intermediate-risk NB combined with chemotherapy and surgery [7]. According to the biological features of the tumor, patients received four or eight cycles of chemotherapy. Chemotherapy consisted of reduced doses of carboplatin and etoposide (CBVP) and cyclophosphamide, adriamycin and vincristine (CADO). In the BCH-NB-2007 protocol for high-risk NB (based on the Hong Kong N6 protocol), chemotherapy, surgery, and myeloablative therapy (carboplatin, etoposide and melphalan) were performed with autologous stem cell rescue, radiotherapy, and treatment of minimal residual disease with isotretinoin. Induction chemotherapy consisted of high-dose cyclophosphamide, adriamycin and vincristine (CAV) and high-dose cisplatin and etoposide (CVP). Chemotherapy was performed every 21 days. Surgical resection of residual primary tumor or sites of regional dissemination (nodal disease) was performed after cycle 4, and peripheral-blood stem cell harvest was performed after cycle 5.

Statistical analysis

Statistical analysis was performed by SAS 9.4. Continuous variables were presented as the mean with standard deviation or median and interquartile range if the normality hypothesis test rejected the null hypothesis of normal distribution. Categorical variables were reported as counts and percentages. Two independent samples t-tests and χ^2 tests were used to compare characteristics between the ruptured and nonruptured groups. Receiver operating characteristic (ROC) curve analysis was performed to determine the most appropriate cut-off values. Univariate and multivariate logistic regression analyses were conducted to select potentially useful characteristics for predicting tumor rupture. The area under the receiver operating characteristic (AUC-ROC) curves of the model were calculated (in this study, some tumor marker results were obtained after tumor rupture as some patients were admitted to the hospital with spontaneous tumor rupture. Thus, the tumor marker results were not included in the analysis). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

During the study period from January 2009 to January 2019, NB was diagnosed in approximately 1800 patients at our institute. A total of 47 ruptured NB patients (28 male and 19 female), with a median age at presentation of 29 months (range, 6 months to 8 years), were included in this study. Table 1 lists details regarding key patient characteristics. The median value of the maximum diameter of primary tumor was 13.20 (10.99, 15.50) cm (range, 4.3 cm to 27.7 cm). Thirty-five patients (35/47, 74.47%) had INRG stage M disease, and metastatic sites included bone marrow (22/35), bone (20/35), distant lymph nodes (19/35), liver (9/35), soft tissues (5/35), and brain (1/35).

Tumor rupture

Among the 47 ruptured NB patients, spontaneous tumor rupture occurred in 22 cases (46.81%); 18 cases (38.30%) developed tumor rupture during or after the first chemotherapy cycle (15 cases of CAV, 2 CBVP, and 1 CADO). From the first day of chemotherapy, the median duration of rupture was 5 (2, 6) days, and 7 cases (14.89%) developed rupture after core needle biopsy with a median duration of 6 (3, 7) days. Most patients experienced abdominal pain, abdominal distension, and drowsy mentality symptoms; all tumors were detected by ultrasound and/or CT scan (Figure 1), and these patients were ultimately diagnosed with tumor rupture. The laboratory data revealed anemia of varying degrees in most patients, with a median hemoglobin level of 74 (58, 88) g/L (range, 36 g/L to 130 g/L). After tumor rupture diagnosis, 5 patients (10.64%) received symptomatic support therapy with or without chemotherapy, and all of these patients died of hemorrhagic shock, disseminated intravascular coagulation (DIC), and multiple organ

dysfunction syndrome (MODS). Seventeen patients' parents (36.17%) refused further therapy, and these patients were discharged in unstable condition from the hospital against the advice of doctors. The remaining 25 patients (53.19%) were discharged in stable condition from the hospital after symptomatic support therapy with or without chemotherapy and surgery. Additionally, all 25 of these patients received further INRG risk-based therapy (Figure 2-4).

Treatment

Among the 25 patients discharged in stable condition from the hospital, 23 patients (23/25, 92%) with high-risk NB received induction chemotherapy (CAV alternated with CVP), and 2 patients (2/25, 8%) with intermediate-risk NB received chemotherapy of CBVP alternated with CADO. Furthermore, 19 (19/25, 76%) patients received macroscopically complete resection of the primary tumor, 4 (4/25, 16%) received gross total (> 90%) resection of the primary tumor, and 2 (2/25, 8%) did not receive operation on the primary tumor site because of disease progression. Six patients received myeloablative therapy, autologous stem cell transplantation and further radiotherapy, while 9 received only radiotherapy.

Prognosis

In this study, 5 patients died of tumor rupture, and 17 patients' parents refused any further anti-tumor therapy in our institute after the diagnosis of NB tumor rupture. Among the remaining 25 patients, 6 patients (6/25, 24%) survived until the end of follow-up (survival time was 11 months, 17 months, 23 months, 32 months, 42 months, and 46 months, respectively), 5 (5/25, 20%) remained in treatment with stable disease, and 14 (14/25, 56%) died (13 patients died of tumor recurrence or progression, and one died of renal failure after surgery) with a median time of 11 (7, 21) months (range, 2 months to 37 months).

In this study, 14 patients experienced tumor recurrence or progression, with a median time of 10 (6, 15) months (range, 2 months to 22 months) after diagnosis. Seven patients experienced tumor progression during therapy and died (4 cases of local progression and 3 cases of combined local and distant metastatic progression). Alternatively, 7 patients experienced tumor recurrence (4 cases of local recurrence, one case of distant metastatic recurrence, and 2 cases of combined local and distant metastatic recurrence), and 6 of these patients died. Only one patient survived for 46 months after chemotherapy and tumor resection.

Tumor rupture risk factors

Since NB tumor rupture mainly occurs in children with high-risk NB (40/42, 95.24%) we further analyzed 93 cases of INRG high-risk NB patients with primary nonruptured tumors in this study. By comparing the clinical characteristics between nonruptured (n = 93) and ruptured (n = 40) high-risk NB (Table 2), we found significant differences in age, primary site, maximum diameter of the primary tumor, most tumor markers, pathological characteristics, and the *MYCN* gene ($P < 0.05$).

According to the maximum joint sensitivity and specificity values, the stratification value of age and maximum diameter of the primary tumor were calculated by ROC curve analyses. The cut-off values for the above characteristics were 29 months and 13.2 cm, respectively (Supplementary Figure 1). In this study, some tumor marker results were obtained after tumor rupture as some patients were admitted to the hospital with spontaneous tumor rupture. Thus, the tumor marker results were not included in multivariate analysis

In multivariate logistic regression analysis, the maximum diameter of primary tumor > 13.20 cm and *MYCN* gene amplification were two independent risk factors for high-risk NB tumor rupture, with adjusted odds ratios (ORs) of 6.401 (1.986, 20.626) and 7.874 (2.520, 24.603), respectively (Supplementary Table 1). The AUC-ROC of the model was 0.827, and the sensitivity and specificity were 96.2% and 66.2%, respectively (Supplementary Figure 2).

Discussion

Tumor rupture is an uncommon, life-threatening presentation among NB patients. Due to the rarity of NB tumor rupture, the previous literature mainly comprises case reports, and large-series reports are lacking. To our knowledge, the current case series of patients with NB tumor rupture is the largest reported series to date from a single institution. The results affirm that 1) the main causes of NB tumor rupture include spontaneous rupture, tumor rupture during or after the first cycle of chemotherapy, and tumor rupture after core needle biopsy. 2) Tumor rupture occurs mostly in patients with high-risk NB. 3) After NB tumor rupture, symptomatic support treatment and chemotherapy are the main treatment, whereas surgery and interventional therapy are not usually the first choices. 4) NB tumor rupture is highly aggressive, disease progression or recurrence occurs early, and patients are susceptible to tumor recurrence with diffuse intraperitoneal lesions. 5) Finally, the value of maximum diameter of primary tumor > 13.20 cm and *MYCN* gene amplification are independent risk factors for high-risk NB tumor rupture.

Spontaneous NB rupture is very rare in infants or children. This condition is more common in neonates, which can be explained by the trauma of delivery, especially when a congenital adrenal mass is crushed between the spine and liver [8-10]. Generally, the mechanism of spontaneous NB rupture is not fully understood. In terms of anatomic position, neonatal adrenal NB, which originates from the right side and is located between the spine and liver, is more prone to rupture [1, 11]. Regarding tumor size, a larger tumor is more likely to rupture. In a previous report, the risk of rupture significantly increased when the maximum diameter of the tumor exceeded 10 cm [12, 13]. Regarding tumor components, tumors with solid components are less likely to rupture, while tumors with obvious cystic components and

liquefaction necrosis are more likely to rupture. With regard to predisposing causes, some patients experience tumor rupture due to external forces, such as trauma, delivery and tumor biopsy, while chemotherapy could induce tumor necrosis and might lead to altered blood flow to the capsule or surrounding tissue of the original tumor, resulting in coagulopathies that damage the tissue [11]. Since 2013, our institute has carried out core needle biopsy for NB patients. Thus far, this procedure has been performed in more than 500 cases. In the present study, only 7 cases of tumor rupture were caused by core needle biopsy (7/500, 1.4%). Regarding the molecular biological characteristics of the tumor, 5 cases of spontaneously ruptured NB were reported in previous studies, and *MYCN* amplification was positive in 3 of 4 examined cases, suggesting that the aggressive behavior of *MYCN*-amplified NB might predispose the tumor to spontaneous rupture [1].

Previous studies have confirmed that *MYCN* gene amplification plays an important role in promoting angiogenesis and the proliferation, invasion, and metastasis of NB cells to inhibit cell differentiation and apoptosis [14-16]. Targeting *MYCN* has significant potential for the treatment of highly vascularized NB. The structure of blood vessels in malignant tumors was also considered fragile compared with that of blood vessels in normal tissues, which could cause the infarction of the vessels and the necrosis of the tumor capsule [16]. The above molecular biological basis is helpful to explain the relationship between *MYCN* gene amplification and NB tumor rupture, but the specific mechanism still needs further study in the future.

The operative indication for spontaneous rupture of NB should be thoroughly considered. Evaluating imaging-defined risk factors (IDRFs) plays an important role in judging whether upfront surgery can be performed. For stable patients with resectable tumors (without IDRFs), complete resection is the best choice to completely arrest the bleeding. In cases of unstable states or unresectable tumors (with IDRFs), interventional embolization or laparotomy for hemostasis as damage-control surgery might be applicable. Interventional embolization is an effective treatment for organ-origin tumors such as liver tumors and kidney tumors when spontaneous rupture occurs [17-20]. However, NB originates from the retroperitoneum and usually has no definitive blood supply. Thus, interventional embolization was usually ineffective. Considering the imaging characteristics of the patients in this study, most of the ruptured NB tumors were huge. Additionally, the tumors always encased important intraperitoneal blood vessels, and seriously infiltrated adjacent organs or structures. Thus, IDRFs were present in most of the ruptured NBs, and upfront surgical resection was extremely difficult. In this study, 3 patients with spontaneously ruptured NB underwent upfront surgery. During the operation, we found that the tumors were huge, fragile and bled easily; they also seriously invaded the adjacent organs and blood vessels. Therefore, an appropriate surgical treatment must be discussed according to the patient's general state in addition to the tumor features (such as INRG staging, the origin, and local invasiveness). Exploration, hemostasis, and biopsy were the primary purpose if surgery was performed, and emergent removal of tumors was unnecessary when hemostasis was achieved.

In symptomatic support treatment, when a patient had a ruptured tumor, it was necessary to monitor the vital signs by ECG monitoring, recording urine volume, improving oxygenation by inhaling oxygen,

correcting shock by intravascular fluid therapy, obtaining blood samples for blood product preparation, and fully sedating and immobilizing the patient. Moreover, laboratory examinations and emergency imaging examinations should be performed immediately. According to the relevant tests and examinations, blood products such as erythrocytes, plasma, platelets and fibrinogen should be transfused to correct anemia, coagulation disorder and thrombocytopenia. Additionally, empirical anti-infective therapy, symptomatic myocardial protection, diuresis, correction of water and electrolyte disorders, and nutritional support therapy should be performed.

To perform anti-tumor therapy, imaging examinations, nuclear medical examinations, and laboratory examinations should be performed as soon as possible. NB-related tumor markers, bone marrow aspiration and biopsy, MIBG or PET-CT, and cranial CT/MRI should be performed to determine the tumor burden and tumor stage. Histopathological biopsy specimens of primary or metastatic lesions should be obtained as soon as the patient is in a stable condition. Molecular biology tests of the *MYCN* gene, 1p36, 11q23 and DNA ploidy should also be carried out. If a patient's condition is too poor to apply general anesthesia and surgery, core needle aspiration biopsy under local anesthesia might be a more appropriate way to obtain tumor tissue with less impact on the patient. Through the above examinations, we determined the diagnosis of NB, INRG stage and risk group. Alternatively, in extreme cases, evidence of pathological histology could not be obtained in some patients who were highly clinically suspected of NB without bone marrow metastasis. As a result, oncologists needed to communicate with the patients' parents that clinical diagnosis of NB and empirical chemotherapy were necessary to save the patients' lives. However, when a patient is in stable condition, pathological histology and molecular biology tests should be performed as soon as possible to correct the NB staging and grouping. For preventing tumor lysis syndrome, adequate hydration and alkalization played important roles in controlling tumor burdens and improving the overall conditions of patients. For high-risk NB patients in very poor condition who could not tolerate high-intensity chemotherapy, dose-induced chemotherapy could be performed in the first cycle of therapy, followed by standard protocols in the following cycles.

The results of this study showed that the prognosis of NB with tumor rupture was very poor. A few patients died directly due to MODS manifestations, such as hemorrhagic shock, heart failure, respiratory failure, and severe infection caused by tumor rupture. However, most patients could be discharged in stable condition after symptomatic support treatment and chemotherapy and received further stratified treatment according to their risk grouping. Through intensive preoperative induction chemotherapy, the majority of patients' conditions were stabilized, the levels of tumor markers decreased, tumors shrank, and metastasis disease was relieved or disappeared. Patients usually had the opportunity for delayed surgery, but most patients were susceptible to progression or early recurrence. The median time of tumor progression or recurrence was 10 (6, 15) months in this study. Only one patient survived after tumor recurrence, whereas all other patients died. Researchers analyzed the clinical and prognostic information of 2266 patients with NB recurrence or progression in the INRG database [21]. The median time of NB progression or recurrence was 13.2 months. The median recurrence time of patients with *MYCN* amplification was 11 months in 562 cases and 14.5 months in 1141 patients with no *MYCN* amplification, with a significant difference between the two groups ($P < 0.05$). The 5-year overall survival

(OS) rate of 2266 patients with recurrence was only $20\% \pm 1\%$, and patients who relapsed between 6 and 18 months after diagnosis had the highest risk of death (the peak value was approximately 12 months), which also supported the results of our study [21]. According to previous clinical studies, the most common recurrence sites in high-risk NB patients are bone and bone marrow, while the 5-year local recurrence rate of the primary site is only $11.9\% \pm 2.2\%$ [22]. In this study, among 14 patients with disease progression or recurrence, 13 patients experienced intraperitoneal progression or recurrence, and these patients often presented with diffuse intraperitoneal lesions. These lesions strongly suggested that progression and recurrence were related to implant metastasis caused by tumor rupture.

Conclusions

Tumor rupture is an uncommon, life-threatening presentation among NB patients, and patients with ruptured NB are most likely to have a poor outcome due to rapid progression or recurrence of the tumor. Several treatment modalities, including symptomatic support therapy and chemotherapy with/without emergency surgery, are important for saving lives and creating conditions for subsequent risk-based treatment. Additionally, the maximum diameter of primary tumor > 13.20 cm and *MYCN* gene amplification are two independent risk factors for high-risk NB tumor rupture. Thus, we can predict the early possibility of tumor rupture among NB patients and intervene as soon as possible, ultimately improving the prognosis of these patients.

Abbreviations

Abbreviation	Full term or phrase
NB	Neuroblastoma
BCH	Beijing Children's Hospital
INSS	International Neuroblastoma Staging System
MIBG	metaiodobenzylguanidine
¹⁸ F-FDG PET/CT	fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography
INRGSS	International Neuroblastoma Risk Group Staging System
VMA	vanillylmandelic acid
HVA	homovanillic acid
GC/MS	gas chromatography-mass spectrometry
LDH	lactate dehydrogenase
NSE	neuron-specific enolase
INPC	International Neuroblastoma Pathology Classification System
FISH	fluorescence in situ hybridization
CBVP	carboplatin and etoposide
CADO	cyclophosphamide, adriamycin and vincristine
CAV	cyclophosphamide, adriamycin and vincristine
CVP	cisplatin and etoposide
ROC	receiver operating characteristic
AUC-ROC	area under the receiver-operating-characteristic
DIC	disseminated intravascular coagulation
MODS	multiple organ dysfunction syndrome
ORs	odds ratios
IDRFs	imaging-defined risk factors
OS	overall survival

Declarations

Ethical approval and consent to participate

All methods were carried out in accordance with relevant guidelines and regulations, and the study was approved by the Medical Ethics Committee of BCH (2017-k-89). A waiver of consent was awarded to conduct analyses in this study.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interest

The authors declare that they have no competing interests.

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Not applicable.

Authors' contribution

Study concept and design: HMW, XLM and SY. Acquisition and interpretation of data: WH, WY and HYC. Drafting of the manuscript: SY and HQ. Statistical analysis: SYC and QHR.

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Tables

Table 1. Clinical characteristics of 47 patients with neuroblastoma tumor rupture

Variables		Results ^{1,2}
Gender	Female	19 (40.43)
	Male	28 (59.57)
Age (months)		29 (24, 46)
Primary site	Adrenal	29 (61.70)
	Retroperitoneum	18 (38.30)
NSE (ng/mL) ³	≤ 370	8 (17.02)
	> 370	39 (82.98)
Ferritin (ng/mL)		261.10 (161.70, 519.50)
LDH (U/L)		2978 (1772, 4120)
Urinary VMA (%)		17.04 (10.71, 72.06)
Urinary HVA (%)		17.70 (4.80, 32.45)
Maximum diameter of primary tumor (cm)		13.20 (10.99, 15.50)
INRG stage	L1	2 (4.26)
	L2	10 (21.28)
	M	35 (74.47)
	MS	0 (0)
INPC	Favorable	0 (0)
	Unfavorable	20 (100.00)
	Unknown	27
MYCN status	Not amplified	9 (31.03)
	Amplified	20 (68.97)
	Unknown	18
1p	Normal	8 (50.00)
	Aberration	8 (50.00)
	Unknown	31
11q	Normal	18 (85.71)
	Aberration	3 (14.29)
	Unknown	26
INRG risk	Very low	1 (2.38)

Low	0 (0)
Intermediate	1 (2.38)
High	40 (95.24)
Unknown	5

¹ Continuous variables are presented as median and interquartile range;

² Classification variables are presented as numbers (percent);

³ Reference ranges of tumor markers: serum NSE ≤ 25 ng/mL; serum ferritin 6 ng/mL-159 ng/mL; serum LDH 110 U/L-295 U/L; urinary VMA 3.4%-51.4%; urinary HVA 0.2%-4.3%.

NSE, neuron-specific enolase; LDH, lactate dehydrogenase; VMA, vanillylmandelic acid; HVA, homovanillic acid; INRG, International Neuroblastoma Risk Group; INPC, International Neuroblastoma Pathology Classification.

Table 2. Comparison of clinical characteristics between ruptured and nonruptured high-risk neuroblastoma groups

Variables		Nonruptured neuroblastoma ^{1,2}	Ruptured neuroblastoma	Results ³	<i>P</i>
		(n = 93)	(n = 40)		
Gender	Female	39 (41.94)	16 (40.00)	0.043	0.8353
	Male	54 (58.06)	24 (60.00)		
Age (months)		43 (32,59)	29 (24,47)	-3.397	0.0007
Primary site	Adrenal	85 (91.40)	25 (62.50)	18.445	<
	Retroperitoneum	7 (7.53)	15 (37.50)		0.0001
	Pelvic	1 (1.08)	0 (0.00)		
Maximum diameter of primary tumor (cm)		10.35 (7.30, 12.60)	13.60 (11.70, 16.00)	4.910	<
NSE (ng/mL) ⁴		369.50 (228.83, 370.00)	370.00 (370.00, 599.25)	3.430	0.0006
Ferritin (ng/mL)		232.40 (132.00, 481.15)	290.10 (207.30, 615.70)	1.448	0.1477
Urinary VMA (%)		191.99 (44.73, 537.60)	16.67 (10.56, 67.05)	-4.365	<
Urinary HVA (%)		26.60 (12.74, 75.30)	17.70 (5.10, 32.13)	-2.135	0.0328
LDH (U/L)		723.00 (538.00, 1475.00)	3148.50 (2055.75, 4316.00)	6.912	<
INPC categories	NB	58 (63.04)	25 (100.00)	19.823	<
	GNBi	1 (1.09)	0 (0.00)		0.0001
	GNBn	33 (35.87)	0 (0.00)		
Grade of neuroblastic differentiation	Undifferentiated	1 (1.16)	1 (4.55)	4.603	0.1001
	Differentiating	24 (27.91)	2 (9.09)		

	Poorly differentiated	61 (70.93)	19 (86.36)		
MKI	< 2%	37 (49.33)	0 (0.00)	20.486	< 0.0001
	2% - 4%	28 (37.33)	11 (64.71)		
	> 4%	10 (13.33)	6 (35.29)		
INPC	Favorable	16 (19.75)	0 (0.00)	7.076	0.0078
	Unfavorable	65 (80.25)	18 (100.00)		
<i>MYCN</i> status	Not amplified	65 (73.03)	6 (23.08)	21.259	< 0.0001
	Amplified	24 (26.97)	20 (76.92)		
INRG stage	L1	1 (1.08)	1 (2.50)	6.090	0.1073
	L2	6 (6.45)	8 (20.00)		
	M	85 (91.40)	31 (77.50)		
	MS	1 (1.08)	0 (0.00)		

¹ Continuous variables are presented as the median and interquartile range;

² Classification variables are presented as numbers (percent);

³ Results represent the z value of the Mann-Whitney test and the χ^2 value of the chi-square test, respectively;

⁴ Reference ranges of tumor markers: serum NSE \leq 25 ng/mL; serum ferritin 6 ng/mL-159 ng/mL; urinary VMA 3.4%-51.4%; urinary HVA 0.2%-4.3%; serum LDH 110 U/L-295 U/L.

NSE, neuron-specific enolase; VMA, vanillylmandelic acid; HVA, homovanillic acid; LDH, lactate dehydrogenase; INPC, International Neuroblastoma Pathology Classification; NB, neuroblastoma; GNBi, ganglioneuroblastoma, intermixed; GNBn, ganglioneuroblastoma, nodular; MKI, mitosis-karyorrhexis index; INRG, International Neuroblastoma Risk Group.

Figures

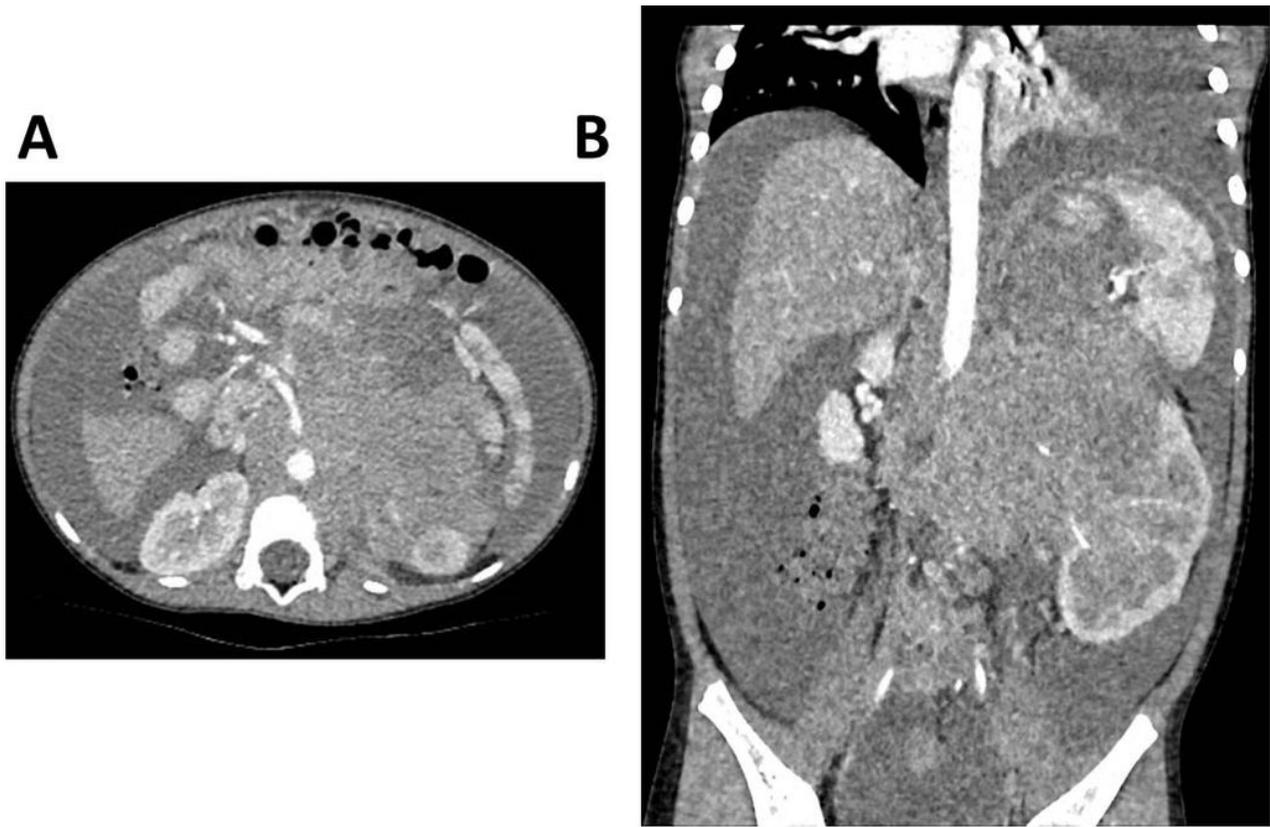


Figure 1

Abdominal enhanced computed tomography (CT) imaging findings of ruptured neuroblastoma. (A) Transverse section image; (B) 3-dimensional reconstruction image.

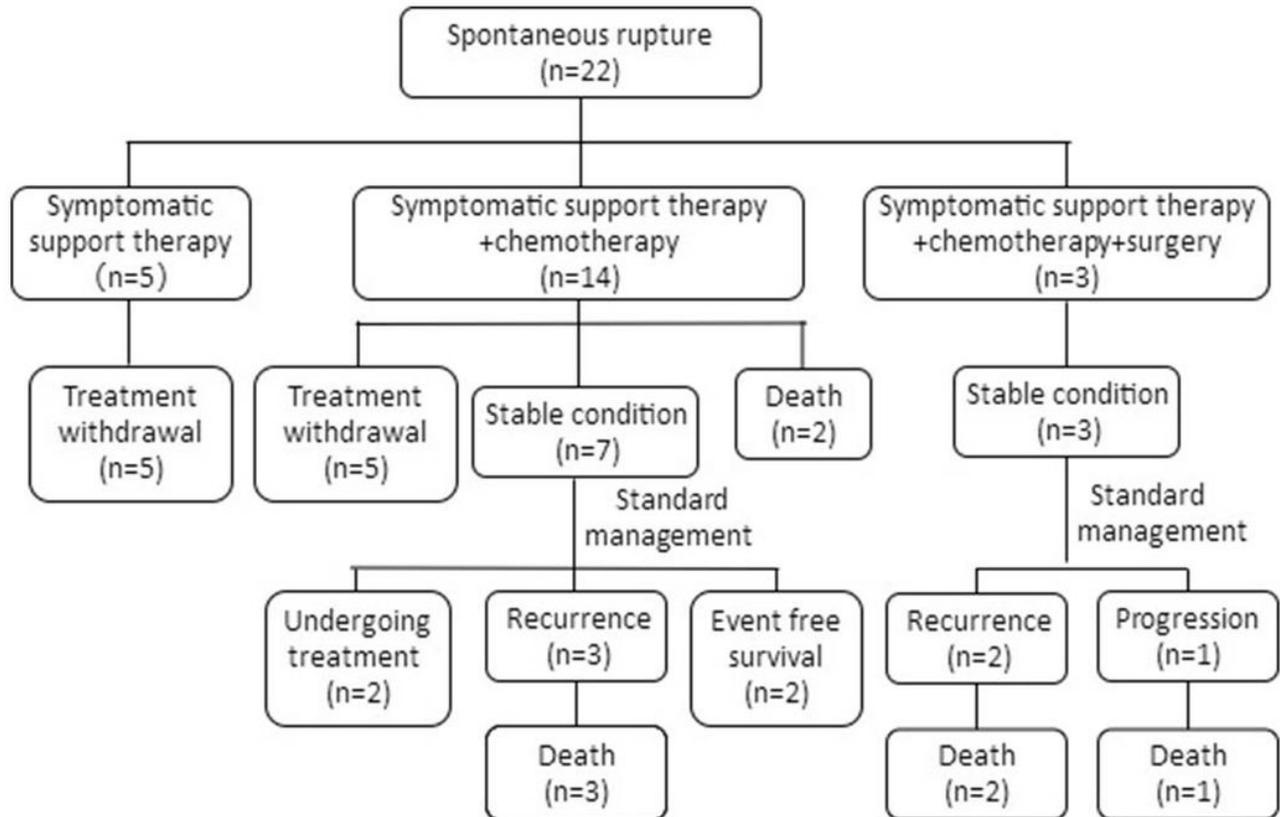


Figure 2

Treatment and prognosis of 22 patients with spontaneous NB rupture.

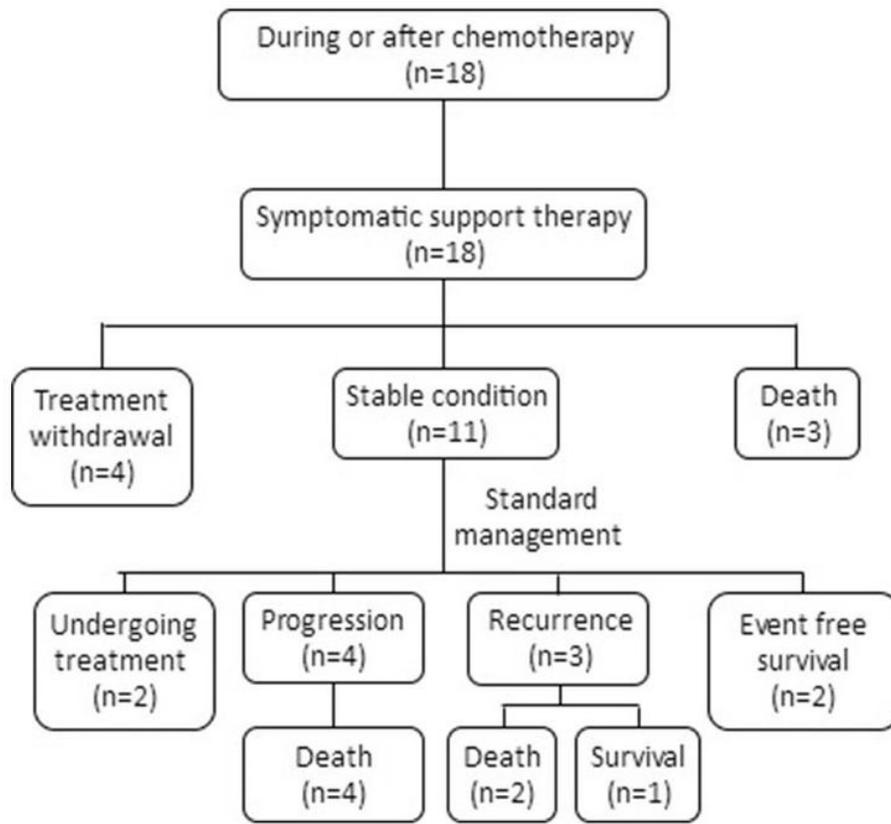


Figure 3

Treatment and prognosis of 18 patients with NB tumor rupture during or after chemotherapy.

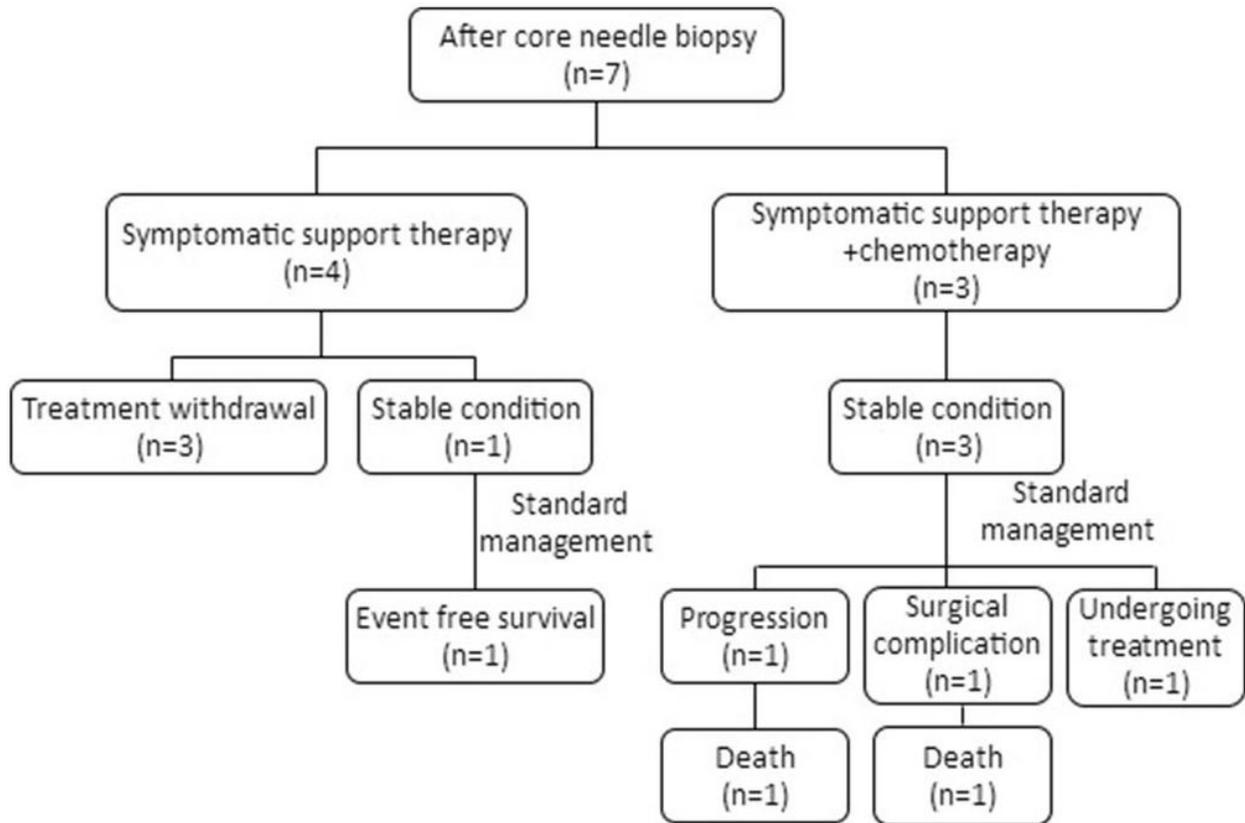


Figure 4

Treatment and prognosis of 7 patients with NB tumor rupture after core needle biopsy.

Supplementary Files

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