ORIGINAL ARTICLE
Turk J Surg 2026;42(2):239-250

Neuroblastoma treatment in children: Single-center case series and review of the literature

Asmir Jonuzi[1], Ilhana Tinjak[2], Benjamin Kulovac[3], Predrag Ilic[4], Zlatan Zvizdic[1]

[1]Department of Pediatric Surgery, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[2]University in Sarajevo Faculty of Medicine, Sarajevo, Bosnia and Herzegovina
[3]Department of Urology, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[4]Department of Pediatric Urology, Institute for Mother and Child Health Care of Republic Serbia, Belgrade, Serbia

ABSTRACT

Objective: Description of the clinical presentation and tumor behavior, its general and pathological characteristics, diagnostic and therapeutic approaches, as well as treatment outcomes in children with neuroblastoma (NB) at a single-center. Special focus was placed on the duration of the diagnostic process and the correlation between disease stage, presence of metastases, and treatment outcomes. Given the small cohort, this report is presented as a descriptive case series complemented by a focused review of the literature NB.

Material and Methods: A retrospective study was conducted for the time period from January 1st, 2010, to December 31st, 2024. The study included 13 patients (7 males, 6 females; median age: 44 months; range, 0-114) diagnosed with NB who underwent surgery and were hospitalized at the Department of Pediatric Surgery, Clinical Center of the University of Sarajevo. Demographic, clinical, biochemical, radiological, and treatment data were extracted from medical records. A narrative review of major published NB cohorts was conducted to compare our observations with existing evidence.

Results: The median age at diagnosis was 44 months. The largest number of patients were in the age group of 2-4 years, and most presented with stage four disease (according to International Neuroblastoma Staging System classification). The tumor was located in the adrenal gland in 92.3% of cases. The median survival time was 36 months. Patients had elevated serum neuron-specific enolase, urinary vanillylmandelic acid, as well as blood ferritin and lactate dehydrogenase levels. The most common symptoms were loss of appetite, presence of a palpable mass, and abdominal pain. Metastases were present in 76.9% of patients, and stage four was associated with aggressive metastatic dissemination. A multimodal approach was used in treatment. The median time from symptom onset to primary care physician consultation was 12 days, and the median time from physician consultation to diagnosis was 14 days. Relapse occurred in 46.2% of cases, most frequently in patients with stage four disease. A total of 7 patients (46.2%) survived.

Conclusion: Advanced-stage disease at diagnosis, metastatic burden, and unfavorable outcomes, are dominating factors in our single-center experience. When compared with larger published cohorts, our findings align with global patterns. Due to inherent sample size limitations, these observations are hypothesis-generating and the need for larger, multicenter studies remains.

Keywords: Neuroblastoma, child, neoplasm staging, neoplasm metastasis, combined modality therapy

INTRODUCTION

Neuroblastoma (NB) is the most common malignant extracranial tumor in children, whose embryogenic origin rises from progenitor neural crest cells (1,2). That implies that it can develop anywhere in the sympathetic nervous system, but most commonly it is located in the adrenal gland. On this ground, and its high rate of spontaneous regression, the tumor exhibits specific behaviour, clinical characteristics, and prognostic parameters (1).

NB accounts for around 7% of all childhood cancers and about 15% of childhood cancer mortality worldwide. The median age at diagnosis is 17-18 months, and around 90% of cases occur in children younger than 5 years (3). NB can develop sporadically or be inhibited, where cases of inhibited NB are much rarer (1-4). Dysregulation of key oncogenes, important for tumor growth initiation and progression, is noted in its development (5). Sporadical cases of NB are connected to mutations in important regulatory genes, such as *ALK* or *PHOX2B* (4,6). The most important molecular anomaly found is MYCN oncogene amplification (1,6,7).

The histological classification, distinguishes the following types: NB (Schwannian stroma-poor), ganglioneuroblastoma, intermixed (Schwannian stroma-rich), ganglioneuroblastoma, nodular (with both stroma-rich and stroma-poor areas), and ganglioneuroma (Schwannian stroma-dominant) (8,9).

Cite this article as: Jonuzi A, Tinjak I, Kulovac B, Ilic P, Zvizdic Z. Neuroblastoma treatment in children: single-center case series and review of the literature. *Turk J Surg.* 2026;42(2):239-250

Corresponding Author
Asmir Jonuzi

E-mail: jonuziasmir@hotmail.com
ORCID ID: orcid.org/0000-0002-5637-9510

Received: 03.10.2025
Accepted: 16.04.2026
Epub: 04.05.2026
Publication Date: 04.06.2026

DOI: 10.47717/turkjsurg.2026.2025-9-34

Available at **www.turkjsurg.com**

Clinical presentation is diverse, due to differences in localisation and stage at the diagnosis (10). NB is most often found in the area of the adrenal gland, but may also appear in retroperitoneal space, mediastinum, spine, or pelvis (1). Metastases are present in up to 70% of patients at diagnosis, and most commonly include bone, bone marrow, liver, and skin (11,12).

Because of the origin of NB, several significant biochemical parameters can be identified. Characteristically, elevated levels of catecholamines and their metabolites -vanillylmandelic acid (VMA) and homovanillic acid- are found in serum and urine, along with increased levels of lactate dehydrogenase (LDH), ferritin, and serum neuron-specific enolase (NSE) (13). Most valuable diagnostic modalities include computed tomography and magnetic resonance (1). The diagnostic criteria for NB include either a positive histopathological finding, or the demonstration of bone marrow metastases in the presence of elevated catecholamine or metabolite levels in urine or serum (14). Advanced disease at presentation is the main factor leading to unfavorable outcomes (15). Prognosis depends on several factors, including age, stage, pathohistology, molecular features such as presence of MYCN amplification, but also genetic anomalies and biological markers (10,16,17). Most used classification system is the International Neuroblastoma Staging System (INSS), where NB is divided into Stages 1-4, with special stage marked as 4s, reserved for infants younger than 1 year (14,18).

Various therapeutic modalities are available for NB, due to the heterogeneity of this disease in terms of its forms and stages. The treatment approach may include different combinations of the following options: Surgical resection, chemotherapy, radiotherapy, and immunotherapy. Prior to initiating any therapeutic intervention, prognostic factors are carefully evaluated (14,19-21).

Despite extensive global research, data from single centers in low and middle income regions still remain limited. Institutional experience often reflects unique diagnostic pathways, resource availability, and patient characteristics, that are not adequately represented in literature. This study is explicitly framed as a descriptive single-center case series, accompanied by a focused narrative review of the literature, due to the small cohort size. The findings should be interpreted within the broader context of major international NB studies. Because inferential statistics are not feasible with a cohort of this size, the results from our center should be considered hypothesis-generating and exploratory.

The aim of this study was to analyze the clinical presentation, pathological and biological features, diagnostic and therapeutic approaches, and treatment outcomes of children with NB treated at the Clinical Center of the University of Sarajevo. Special attention was given to diagnostic delay, disease stage, presence of metastases, and their association with survival. Main focus lies on defining patterns and objectives relevant for future multicenter work.

MATERIAL and METHODS

Study Design and Setting

This study is framed as a descriptive single-center case series with a focused narrative review of the literature. This clinical, retrospective study was conducted at the Clinic of Pediatric Surgery of the Clinical Center of the University of Sarajevo, covering the period from January 1, 2010 to December 31, 2024. The study included 13 patients (7 males, 6 females; median age: 44 months; range, 0-114) who were diagnosed with NB, who underwent surgery and were hospitalized at the Department of Pediatric Surgery, Clinical Center of the University of Sarajevo).

The data for the research were collected by reviewing the available medical documentation through the electronic database of the Clinical Center of the University of Sarajevo and the archives of the Clinic of Pediatric Surgery and Pediatric Clinic of the Clinical Center of the University of Sarajevo.

The study complied with the ethical principles of the Declaration of Helsinki and with all International Council for Harmonization and Good Clinical Practice Guidelines. The study was approved by the Local Institutional Review Board (Ethical Committee of the Clinical Center University of Sarajevo, protocol code: 51-45-1-6872/25, date: 24 February 2025).

The following features were reviewed: Gender, age at the time of diagnosis, history, clinical presentation, additional diagnoses, tumor localization and characteristics, diagnostic workup, time interval from symptoms appearance to physician checkup and from physician checkup to definite diagnosis, disease stage, presence and localization of metastases, immunohistopathological findings, treatment and surgical intervention performed, disease outcome, complications, and recurrence. The study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent was waived.

Institutional Pathway for NB Management – Diagnostic, Staging, and Treatment Pathway

Patients diagnosed with NB were evaluated and treated according to an institutional protocol designed and alligned according to the International Neuroblastoma Risk Group (INRG) guidelines.

Diagnosis and staging: The diagnostic criteria for NB included either histopathological confirmation of the primary tumor with or without elevated catecholamine levels or metabolites in urine or serum, or evidence of bone marrow metastases in the presence of elevated urinary or serum catecholamines or their

metabolites. Initial assessment included clinical examination, routine laboratories, and measurement of tumor biomarkers (urinary VMA, serum neuron-specific enolase, LDH, and ferritin) where feasible. Local disease was assessed with ultrasonography followed by cross-sectional imaging (computed tomography or magnetic resonance imaging of chest/abdomen/pelvis). Metastatic staging was evaluated with I123-meta-iodobenylguanidine (MIBG) scintigraphy, with involvement of bone marrow assessed by flow cytometry. Obtained tumor tissue was analyzed for MYCN status (FISH) and ploidy (DNA index). Pretreatment staging used the INRG Staging System (INRGSS). The post-surgical staging using INSS was also recorded.

Risk stratification: The treatment-assigning risk groups were determined using the INRG classification, integrating age, histology, and tumor biology (MYCN, ploidy, genomic profile).

Therapeutic modalities: Surgery, chemotheraphy, MIBG Therapy, myeloablative therapy with ASCT, and immunotherapy were noted as treatment options. Timing for surgical treatment was risk-adapted. Primary resection was the ultimate goal for low-risk patients, however, for intermediate and high-risk groups, surgery followed neoadjuvant chemotherapy. Indications and regimens for all forms (both neoadjuvant and adjuvant) of chemotherapy were strictly protocol-defined regarding the INRG risk group. For MIBG therapy, patients were referred to other reference centers. Myeloablative therapy with ASCT was part of our high-risk protocol until approximately 2018-2019. Its reinstatement is planned for 2026. Immunotherapy (anti-GD2) was not administered in our center, and patients were referred externally.

Follow-up and relapse: Follow-up included clinical assessment, imaging studies, and laboratory monitoring according to institutional practice. Time-intervals varied individually, according to the patients risk-group. In reference to the International Neuroblastoma Response Criteria (INRC), relapse was defined as appearance of new site(s) of disease or progression of existing disease - defined as tumor size growth of >25% relative to the best documented response - after initial response (including partial ones) to the treatment. It was ascertained during scheduled follow-up assesments.

Study Endpoints

The primary endpoint was to characterize treatment outcomes-overall survival (OS), as well as treatment efficacy within our cohort. OS was defined as the time from diagnosis to death from any cause, and was analyzed as median OS. Secondary endpoints included: 1) clinical and pathological characterization-clinical presentation, diagnostic work-up, therapeutic approach, and general and pathological characteristics of patients with NB in our institution; 2) quantification of time intervals from symptom onset to first physician consultation and from that consultation to definitive diagnosis; 3) association between key variables, specifically between disease outcome (OS, relapse) and both disease stage at presentation and the presence of metastases at diagnosis, as well as baseline biomarker profiles (MYCN status, ploidy); 4) report of the incidence and nature of postoperative complications; 5) report of incidence of relapse- defined per the INRC.

Statistical Analysis

The data were processed using Microsoft Excel software (version 16.0, Microsoft 365 Apps; Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics software (version 30.0; IBM Corp., Armonk, NY, USA). Given the small sample size (n=13), the analysis was restricted to descriptive statistics. Categorical variables are presented as counts and proportions (n, %). Continuous variables are summarized as medians with ranges. OS was visualized using the Kaplan-Meier method; however, no comparative hypothesis testing was performed.

The follow-up duration for the cohort was calculated from the date of diagnosis to the date of last known contact or death. For the patients that survived, follow-up times were right-censored at their last documented clinical assessment. The median follow-up time for the entire cohort was 25 months (range: 10-120 months).

Regarding missing data, the available-case approach was used. Analyses were performed based on number of patients with available data and no imputation was performed due to the retrospective design and small sample size. Naturally, denominators are reported explicitly where applicable. The results are presented in textual, numerical and tabular form.

RESULTS

Patient Characteristics

The median age was 44 months (range, 0-114), meaning most patients (53.8%, 7/13) were in the age group of 2-4 years old. Among 13 patients, all (100%, 13/13) had negative family history for NB. Twelve patients (92.3%, 12/13) had no family history of malignancy, while in one patient a positive family history of malignancy was noted, specifically Hodgkin lymphoma. In 5 patients, the tumor was of Stage 2 according to INSS classification (38.5%, 5/13), one patient had Stage 3 (7.7%, 1/13) and 7 patients had Stage 4 (53.9%, 7/13). No patients were identified with Stage 1 or 4s. Primary tumor sites were the adrenal gland in 12 cases (92.3%, 12/13; 4 right and 8 left) and the head and neck region in 1 case (7.7%, 1/13). First symptoms were recognized by the doctor in 3 patients (23.1%) and by the parents in 10 patients (76.9%, 3/13). The median time from the initial appearance of symptoms to the first visit with a primary care physician was 12 days (range: 1-45 days). The median time from that first doctor's visit to the confirmation of a diagnosis was 14 days (range: 6-20

days). Total of 5 patients (38.5%, 5/13) had other diagnoses upon initial presentation, where 3 (23.1%, 3/13) presented with anemia, and 2 (15.4%, 2/13) had amblyopia. One patient (7.7%, 1/13) had opsoclonus-myoclonus syndrome with ataxia and one patient (7.7%, 1/13) was initally presented with the diagnosis of polyarthralgia. Six patients had lethal outcome (46.2%, 6/13) (Table 1).

Stage and the Disease Outcome

A total of 2 patients (15.4%, 2/13) were in the 0-2 years age group (both with Stage 2 disease), 7 patients (53.8%, 7/13) were in the 2-4 years age group (2 with Stage 2, 1 with Stage 3, and 4 with Stage 4), and 4 patients (30.8%, 4/13) were in the 6-15 years age group (1 with Stage 2 and 3 with Stage 4).

All of the 5 patients (100%, 5/5) with Stage 2 disease survived. In contrast, 6 out of 7 patients (85.7%, 6/7) with Stage 4 disease had a lethal outcome, with one survivor who had a follow-up period of 10 months. The single patient with Stage 3 disease also survived.

Kaplan-Meier analysis was used to describe OS (Figure 1). Median OS was 36 months. Around 91.7% survived at 12 months and 45.8% at 36 months. Several patients were censored during follow-up. Survival curve showed a plateau in later months.

MYCN Amplification and the Disease Outcome

Data on MYCN amplification analysis were available for 8 patients (61.6%, 8/13), among whom MYCN amplification was present in 4 (30.8% of the total cohort, 4/13) and absent in 4 patients (30.8%, 4/13). Overall, among the patients with a lethal outcome (n=6), 4 had confirmed MYCN amplification, 1 had a negative MYCN status, and 1 had missing data. Among the survivors (n=7), 3 patients had a negative MYCN status, and 4 had missing data. The descriptive analysis indicated a mortality rate of 100% (4/4) in the patients with confirmed MYCN amplification, compared to 25% (1/4) in those with a confirmed non-amplified status. MYCN amplification was documented in 3 out of 7 patients (42.9%) with Stage 4 disease, and in 1 out of 5 patients (20%) with Stage 2 disease, suggesting a trend of more frequent amplification in advanced stages. This is clinically relevant for prognosis, as MYCN is a marker of aggressiveness in NB. However, further studies with a larger sample size are necessary to confirm these findings with greater reliability.

Biological Markers

Baseline biomarker levels, collected at diagnosis prior to any treatment, were analyzed. Data on the initial serum NSE levels were available for 7 patients. All 7 had elevated NSE levels, with a median value of 101.0 µg/L [interquartile range (IQR): 370-20.9; range: 18.10-939 µg/L; normal range: 0-13 µg/L]. Initial urinary VMA level results were available for 9 patients. Of these, 7 patients had elevated VMA levels, with a median value of 15.1 mg/g (IQR: 66.9-9.25; range: 3.2-535.9 mg/g of creatinine). The other two (2/9) had results within the normal reference range (1-10 mg/g). Blood ferritin data was available for 10 patients, showing a median value of 238.0 ng/mL (IQR: 895.06-195.44; range: 62.0-1090.0 ng/mL). Five of them (5/10) had elevated ferritin levels (the median for this group was 818 ng/mL), while the other five had values within the normal range (10-225 ng/mL). Blood LDH levels were available for 9 patients. The median value was 1826 U/L (IQR: 2277-618; range: 445-5566 U/L). Eight patients (8/9) showed LDH levels above the normal range (195-470 U/L), and one patient (1/9) had a value within the normal limits (Table 2).

Applied Therapeutic Modalities

In our cohort included pre- and postoperative chemotherapy, surgery, myeloablative therapy, MIBG therapy, and immunotherapy, either as single interventions or in various combinations, with surgical procedures (adrenalectomy and complete tumor resection with or without lymphadenectomy) performed at the clinic for pediatric surgery (Table 3).

Symptoms

The most frequently reported symptoms among our patients were loss of appetite, the presence of a palpable mass, and abdominal pain, each occurring in 53.8% of cases (n=7, 7/13). Fatigue was present in 30.8% of cases (n=4, 4/13), while paleness and joint pain each appeared in 23.1% of cases (n=3, 3/13). Symptoms such as fever, hip pain, dyspnea, vomiting, dysuria,

Table 1. Overview of the association between clinical variables and relapse

Variable	Without relapse (n=7)	With relapse (n=6)	Total (n=13)
Outcome			
Lethal Survived	1 (7.7%) 6 (46.2%)	5 (38.5%) 1 (7.7%)	6 (46.2%) 7 (53.8%)
INSS stage			
2 3 4	4 (30.8%) 1 (7.7%) 2 (15.4%)	1 (7.7%) 0 5 (38.5%)	5 (38.5%) 1 (7.7%) 7 (53.8%)

INSS: International Neuroblastoma Staging System.

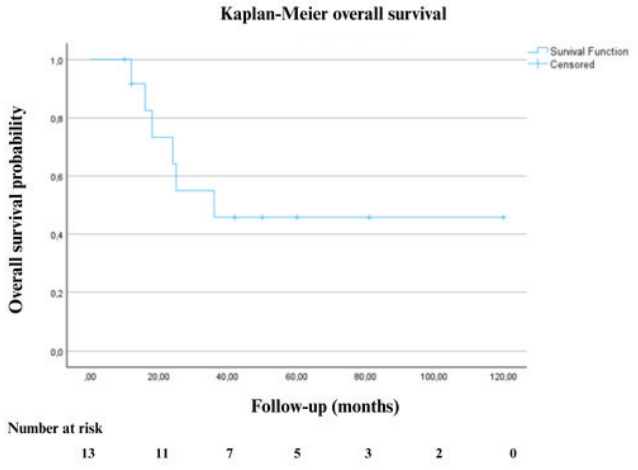

Figure 1. Kaplan-Meier curve describing overall survival of the study cohort. Median survival was 36 months. Estimated survival was 91.7% at 12 months and 45.8% at 36 months. Tick marks represent censored observations.

walking difficulties, constipation, prolonged crying, and groin pain were less common, each appearing in 15.4% of cases (n=2, 2/13). On the rare end, symptoms like the inability to bear weight on the legs, hand tremors, eyelid hematoma, and protrusion of the eyeball were each seen in only 7.7% of cases (n=1, 1/13). A large number of symptoms occurred only rarely (in just 1 or 2 patients), which may imply that the clinical presentation is significantly heterogeneous (Table 4).

Symptoms and the Disease Stage

In the Stage 2 (n=5), it is shown that the most common symptoms were a palpable mass (60%, 3/5), loss of appetite (60%, 3/5), abdominal pain (40%, 2/5), fatigue (40%, 2/5), and shortness of breath (20%, 1/5). The presentation was characterized by local symptoms with moderate systemic complaints. In Stage 4 (n=7), the most frequent symptoms were abdominal pain (71.4%, 5/7), a palpable mass (57.1%, 4/7), loss of appetite (42.9%, 3/7), joint pain (42.9%, 3/7), and paleness (42.9%, 3/7). Fever, difficulty walking, constipation, and hip pain were each present in 28.6% of cases (2/7). This stage also included specific, rarer symptoms like bulging eyeball, eyelid hematoma, prolonged crying, hand tremors, and the inability to bear weight (each at 7.7%, 1/13). A higher frequency of pain and systemic symptoms was observed in this advanced stage. In Stage 3 (n=1), only one patient was classified, providing insufficient data for a meaningful analysis. Certain clinical trends were observed, such as abdominal pain, joint pain, a palpable mass, and paleness being more common in Stage 4, potentially indicating disease progression. Loss of appetite was a symptom recorded across all Stages.

Metastases

Metastatic disease-including involvement of regional lymph nodes-was present in 10 patients (76.9%, 10/13). Only three patients (23.1%, 3/13) showed no evidence of metastasis. A detailed overview of the metastatic sites identified for each patient is provided in Table 3.

Analysis of metastatic locations in the affected group (n=10) showed lymph nodes to be the most commonly involved site, present in all patients (100%, 10/10) with metastatic disease. Review of records showed that abdominal (50%, 5/10) and retroperitoneal lymph nodes (20%, 2/10) were most involved. Metastases were found in para-aortic/paracaval lymph nodes in 20% of cases, while parailiac, retrosternal, and cervical lymph nodes were less frequently involved (12.5% each, 1/8). Bone metastases were also frequent, occurring in 50% of patients with metastatic disease (5/10). Within this group, the vertebrae were the most commonly affected site (80%, 4/5), with pelvic and cranial bones each involved in a single case (10% of metastatic patients, 1/10 each). Other metastatic sites included the liver, pleura, and intracranial region (20% each, 2/10), as well as paravertebral muscles and bone marrow (30% each, 3/10). Subcutaneous tissue and the lungs were each affected in one case (10%, 1/10).

Metastases and Stages of the Disease

As expected, the prevalence of metastases varied significantly based on disease stage. In Stage 2, metastases were present in 2 out of 5 patients (40%, 2/5), implying that disease dissemination can occur even in earlier stages. In contrast, all patients in Stage 3 and Stage 4 had confirmed metastases, representing a 100% metastasis rate in these groups (8/8). Analysis of metastases in Stage 4 patients revealed aggressive dissemination: 100% (7/7) had lymph node involvement, and 71.4% (5/7) had bone metastases. Metastases in paravertebral muscles and bone marrow were present in 42.9% of these patients. In Stage 2,

Table 2. Range of baseline biological marker values in patients at diagnosis

Biological marker (unit)	Median (IQR)	Range in patients	Patients with data (n/total)	Reference values*
NSE (µg/L)	101.0 (20.9-370.0)	18.10-939	7/13	0-13
VMA (mg/g of creatinine)	15.1 (9.25-66.9)	3.2-535.9	9/13	1-10
Ferritin (ng/mL)	238.0 (195.44-895.06)	62.0-1090.0	10/13	10-225
LDH (U/L)	1826 (618-2277)	445-5566	9/13	195-470

*: Reference ranges and units adapted from Bolkar ST, et al. Indian J Clin Biochem 2008;23(3):293-295.
IQR: Interquartile range, NSE: Neuron-specific enolase, VMA: Vanillylmandelic acid, LDH: Lactate dehydrogenase.

Table 3. Demographics and other characteristics of patients with neuroblastoma		
Criteria	**n**	**%**
Sex		
Male	7	53.8
Female	6	46.2
Family history		
Negative	13	100
Positive	0	0
Disease stage (INSS classification)		
1	0	0
2	5	38.5
3	1	7.7
4	7	53.9
4s	0	0
Tumor localization		
Adrenal gland	12	92.3
Left	8	66.7*
Right	4	33.3*
Head and neck area	1	7.7
MYCN amplification		
Yes	4	30.8
No	4	30.8
No data available	5	38.5
Therapeutic approach		
Chemotherapy only	3	23.1
Surgery + chemotherapy	4	30.8
Surgery only	2	15.4
Multimodal therapy[§]	4	30.8
Metastases at diagnosis		
Yes	10	76.9
Lymph nodes	10	100[#]
Bone	5	50[#]
Bone marrow	3	30[#]
Other sites[±]		
No	3	23.1
Histopathology		
Neuroblastoma	12	92.3
Ganglioneuroblastoma	1	7.7
Postoperative complications		
Yes	1	7.7
No	12	92.3
Relapse		
Yes	6	46.2
No	7	53.8
Survival status		
Lethal	6	46.2
Survived	7	53.8

*: Percentage of adrenal gland tumors (n=12), [§]: Includes therapies with combination of MIBG, myeloablation, surgery, chemotherapy, or immunotherapy (n=4), [±]: Other sites include pleura, liver, intracranial region, paravertebral muscles, subcutaneous tissue, and lungs, [#]: Percentage of patients with metastases (n=10), INSS: International Neuroblastoma Staging System.

metastases were exclusively localized to regional lymph nodes (n=2), consistent with INSS Stage 2B classification.

Histopathology and Immunohistochemistry

The type of NB was determined by histopathological examination. A total of 12 patients (92.3%, 12/13) received a histopathological diagnosis of NB. For the majority of patients (69.2%, 9/13), the diagnosis was designated simply as "NB" without further specification. In three patients (30.8%, 3/13), the diagnosis included additional specifications: Nodular NB (7.7%, 1/13), poorly differentiated NB (7.7%, 1/13), and undifferentiated NB (7.7%, 1/13). Each of these specifications was reported in one patient. One case (7.7%, 1/13) was diagnosed as ganglioneuroblastoma.

Postoperative Complications

Of the 13 cases examined, postoperative complications occurred in only one patient (7.7%, 1/13). These complications involved intestinal obstruction and hypokalemia, which required the patient to be readmitted to the clinic for pediatric surgery. The remaining 92.3% (12/13) of patients experienced no postoperative complications.

Relapse, Outcome and the Disease Stage

Relapse was documented in 6 patients (46.2%, 6/13), while the remaining 7 patients (53.8%, 7/13) experienced no relapse. Among patients with a fatal outcome (n=6), 5 had experienced a relapse (83.3%, 5/6), and 1 had not (16.7%, 1/6). Descriptively, patients with a fatal outcome had a higher proportion of relapse (83.3%, 5/6) compared to those with a positive outcome (14.3%, 1/7).

No patients with Stage 2 disease experienced a relapse (0/5). Among the 7 patients with Stage 4 disease, 5 (71.4%, 5/7) had a documented relapse, while 2 (28.6%, 2/7) did not. The single patient with Stage 3 disease (1/1) did not experience a relapse. For descriptive analysis, stages were grouped into two categories: Lower stages (Stages 1 and 2, n=5) and higher stages (Stages 3 and 4, n=8). Patients with higher-stage disease experienced relapse more frequently (62.5%, 5/8) compared to those with lower-stage disease (20%, 1/5). The associations between outcome, relapse, and disease stage are shown in Table 1.

DISCUSSION

In our single-center case series, the vast majority of patients presented with advanced-stage NB, with already developed metastatic disease and elevated tumor biomarkers-thus, survival outcomes were unfavorable. As it is expected, delayed diagnosis appears to be connected to the poorer clinical and overall outcomes. Consistency with the patterns reported in larger published papers is present. However, due to study limitations, these findings are strictly descriptive and hypothesis-generating.

The management of unpredictable diseases such as NB, demands clear and guided assessment. Current international risk stratification systems depend primarily on patients age, disease stage and specific molecular markers. Contemporary analyses from large cohorts work on reinforcement of critical epidemiological and biological patterns. For context, findings in contemporary NB studies are summarized in Table 5.

Gender and Prognosis: Unlike earlier views that the gender was not relevant for prognosis, there is an evidence today that indicate a slight predominance of NB in males (22-24). Studies from the past (22) reported that gender has neither prognostic significance nor relevance for the incidence of NB. However, more recently, studies have focused on differences related to gender, showing a higher incidence in boys (23,24). According to research by Tas et al. (24), the incidence of NB is slightly higher in boys than in girls (51.7% versus 48.3%, respectively). Several contemporary studies (25,26) analyzing the correlation between gender and NB have concentrated on differences in outcomes and therapeutic success, noting that boys tend to have somewhat worse outcomes. A comprehensive study of global NB incidence and mortality from 2025 (3) reported the greatest gender difference in the 2-4 year age group, with a male-to-female ratio of 1.96:1. In our study, we have also observed a slightly higher incidence in boys (54%).

Table 4. Presentation of symptoms by disease stage

Symptom	Stage 2 (n=5)	Stage 3 (n=1)	Stage 4 (n=7)
Localized symptoms			
Palpable mass	3 (60%)	0 (0%)	4 (57.1%)
Dysuria	0 (0%)	1 (100%)	1 (14.3%)
Pain in abdomen	2 (40%)	0 (0%)	5 (71.4%)
Systemic symptoms			
Loss of appetite	3 (60%)	1 (100%)	3 (42.9%)
Fatigue	2 (40%)	1 (100%)	1 (14.3%)
Elevated body temperature	0 (0%)	0 (0%)	2 (28.6%)
Metastatic symptoms			
Paleness	0 (0%)	0 (0%)	3 (42.9%)
Joint pain	0 (0%)	0 (0%)	3 (42.9%)
Dyspnea	1 (20%)	0 (0%)	1 (14.3%)

Table 5. Summary of key large cohort studies in neuroblastoma

Study/cohort (year)	Sample size (n)	Key stage distribution	MYCN status rates	Primary treatment strategy	Reported OS/EFS	Relapse rate
Tas et al. (Netherlands, 2020)	593	52% Stage 4	NA	High dose chemotherapy followed by autologous stem cell transplant and anti GD2 based immunotherapy	5-yr OS: all patients – increase of OS from 44 +/- 5% to 61 +/- 4%; Stage 4: from 19 +/- 6% to 44 +/- 6% (1990-2014); EFS - NA	NA (implied high in Stage 4)
Liu et al. (China, 2023)	1 224	48.9% with distant mets	20-25%	Multimodal standard	Without bone metastases 5-yr OS: 87.2%; bone metastasis 5-yr OS: 66.9%; EFS NA	Implied high with metastases
Lucena et al. (Brazil, 2018)	258	46% Stage 4	Test was performed in 17%; 25% of tested had *MYCN* amp	Risk-adapted, per INRG	5-yr OS: 62% (all); 5-yr EFS: 52%	72%
Al-Tonbary et al. (Egypt, 2015)	142	76.7% Stage 4;	Test available in 17%; NA	Risk-based chemotherpy	2-yr OS: males- 47.6 +/-14.0%, females – 10.4% +/- 9.8%	NR
Current study (Sarajevo, 2025)	**13**	**53.9% Stage 4**	**30.8% (of tested)**	**Multimodal, per INRG**	**Median OS: 36 mo; Stage 4 survival: 14.3%**	**46.2% (all); 62.5% (Stage 3 and 4)**

OS: Overall survival, EFS: Event-free survival, NR: Not reported, NA: Not applicable, INRG: International Neuroblastoma Risk Group.

Age Distribution: Approximately 90% of NB occurs in children <5 years, with a median age at diagnosis of 17-18 months (4,14). Older age (>18 months) at diagnosis is a poor prognostic factor, especially when combined with advanced disease (24). In the study conducted by Williams and Williams Spector (25), there were approximately 50% of patients within the 1-4 year age group. According to a study by Ting et al. (23), the median age at diagnosis of malignant tumors in children was 4 years. Considering that 18 months represents an important prognostic cut-off (according to the - INRGSS), some studies have shown that about 45% of patients are diagnosed before this age (24). We have noted that most patients (53.8%) belonged to the 2-4 year age group, with a median age of 44 months.

Family History and Predisposition: Family predisposition for NB development is very rare–with only 1-2% of patients reported to have positive family history for NB (27). Moreover, no exogenous factors have been associated with NB development (28). In our study, none of the patients had a family history of NB. In 12 patients (92.3%), the family history was negative for malignancies, while in one patient a positive family history of malignancy was noted, specifically Hodgkin lymphoma.

Patterns of Time Intervals Relevant for Diagnostics: It is very commonly reported that a majority of NB patients had experienced a diagnostic delay (29,30). A paper from Beijing (29) reported a median diagnostic interval of 1 month (range, 0.2-24 months). In that cohort, 52 out of 62 patients experienced a diagnostic delay, with time interval between symptom onset to diagnosis longer than 2 weeks. In another study of patients with NB presenting with intracranial metastases (30), the median time from the first symptoms to diagnosis was 4.2 months. In our cohort, the distribution of the interval from symptom/sign onset to the first physician visit was asymetrical–which implies that some parents sought medical attention later than others. The time from the first physician visit to the diagnosis was also asymetrically distributed, with 75% of cases diagnosed within 15 days, and only a few outliers extending up to 20 days.

Primary Tumor Location: Primary NB tumors mostly originate in the adrenal gland and abdominal cavity (24). They are far less common in the neck, chest, or pelvis (11). In our cohort, twelve (92.3%) patients had NB localized in the adrenal gland, while one patient (7.7%) presented with NB in the head and neck region, thus our findings support the notion of the predominant primary site of NB in children.

Stage at Presentation: Advanced-stage (INSS Stage 4) disease accounts for 50-70% of presentations in unselected cohorts and is the primary factor contributing to mortality (24,30). Based on definitive histopathological diagnosis, most of the patients from our cohort (53.9%) were classified as Stage 4. Liu et al. (30) reported that 74.4% of NB cases are diagnosed at an advanced age, while Tas et al. (24) stated that the most patients had Stage 4 upon diagnosis (52%). Our research is consistent with these observations, confirming that a substantial proportio of patients present when the stage of NB is advanced.

Presenting Symptoms: The presenting symptoms at the moment of diagnosis of NB in the vast majority of cases are abdominal pain, a palpable mass, as well as systemic signs such as fever and weight loss (23,31). In our cohort of thirteen patients, the most frequently observed presenting symptoms were loss of appetite, a palpable abdominal mass, and abdominal pain, each occurring in 58.8% of cases. These findings are in line with previous reports. A recent study from China (23) analyzed common symptoms of pediatric solid tumors, and it has reported that the most frequent ones are palpable masses in 34.9% of cases, abdominal pain in 21.1%, and fever in 6.3%. Nonetheless, literature emphasizes the great clinical significance of systemic symptoms such as fever, appetite loss, and weight loss (31). Other reported symptoms in our patients included fatigue, pallor, joint pain, fever, dyspnea, vomiting, dysuria, difficulty walking, constipation, prolonged crying, and groin pain, whereas less common findings included inability to bear weight, hand tremors, eyelid hematomas, and proptosis. In our study, the "raccoon eyes" phenomenon was observed in 7.7% of cases. Paper from Ghosh et al. (32) reports this phenomenon in up to 20% of cases, hence, its presence is consistent with the one in our cohort. Specific symptom patterns often correlate with metastatic spread: bone metastases typically manifest as musculoskeletal pain or impaired mobility, and bone marrow involvement is usually associated with anemia or thrombocytopenia (31). Similarly, studies from Brazil (29) noted fever, abdominal pain, abdominal mass, and bone pain as the most common presenting features, confirming that our findings align with established patterns in NB. Overall, the variability in symptom presentation is important for maintaining a high index of suspicion for NB across a broad spectrum of clinical signs.

Metastatic Patterns: Metastatic disease at diagnosis is very common in NB, and it involves regional lymph nodes, bone, bone marrow, and liver most frequently (11,12,33). Previous studies have shown that up to 70% of patients with NB present with metastases at diagnosis (11). A large Chinese cohort which included 1224 patients reported distant metastases in 48.9% of cases, results that are consistent with other similar studies (12,33). Most common secondary tumor sites for NB are regional lymph nodes, bones, bone marrow and liver (11). Our results are in line with these observations, as metastases were identified in 76.9% of patients, with lymph node involvement present in all cases. Bone metastases were observed in 50% of patients, compared to 33% reported in a study from Sao Paulo (34). As expected, we have also observed an association between advanced stages (3 and 4) and the presence of metastases. That confirmed current

knowledge that high-risk patients exhibit greater mortality and more aggressive NB behavior (4,16).

Due to the activity of immune system, 2-3% of children with NB develop opsoclonus-myoclonus syndrome (35). In our cohort, this diagnosis was identified in 7.7% of patients. Anemia is also a common manifestation of NB, which explains why 23.1% of our patients had been diagnosed with anemia prior to the confirmation of NB (31). In total of 38.5% of our patients, additional diagnoses were recorded prior to NB, including, apart from those previously mentioned, amblyopia and polyarthralgia.

Diagnostic Biomarkers: Serum NSE, LDH, ferritin, and urinary catecholamine metabolites (VMA) are well established diagnostic and prognostic markers. In a paper published by Bolkar et al. (13) which analyzed biochemical parameters in children with NB, it was reported that urinary VMA, serum NSE, ferritin, and LDH were significantly elevated in histologically confirmed cases compared to healthy controls. The relevance of these parameters has long been recognized in the literature (36), with several studies making an emphasize on their importance in prognosis of the disease, particularly NSE and LDH, but also LDH and ferritin (19,29). In our study, all patients had elevated serum NSE levels, while 88.9% had high LDH values. Additionally, 77.8% of patients had increased VMA in urine, and ferritin was elevated in 50% of cases. Our results confirm importance of these paramters, named in previous studies. These markers have great clinical value-they are good diagnostic indicators but also useful for monitoring progression of the disease. Considering that more than 90% of children with NB present with high levels of catecholamines and their metabolites (19), biochemical testing is crucial component of monitoring of patients with NB.

Treatment Modalities: Therapy modality is dependent on risk-group (18). Low-risk disease often requires surgery alone, while high-risk disease demands a multimodal approach: Intensive induction chemotherapy, surgical resection of the primary tumor, myeloablative therapy with autologous stem cell transplant, chemotherapy, radiotherapy, and immunotherapy (anti-GD2 antibodies). This paradigm has improved survival for high-risk patients (3). All of our patients underwent multimodal therapy, adjusted to the stage of their disease.

Histopathological Classification: Literature most frequently identifies NB as the most common histopathological type of this disease, but it is not the only one. Other variants, such as ganglioneuroblastoma and ganglioneuroma are also described, as well as their own subtypes (9). A study from the United States (37) that included 145 children reported histopathological diagnosis NB in 130 cases (80.7%), which is consistent with our findings, where it was defined in 92.3% of patients.

Relapse Patterns and Outcomes: Many studies have examined the relationship between the characteristics of NB and outcomes of treatments following disease relapse. The INRC defines relapse as the occurrence of a new disease site or a tumor increase of at least 25% after initial response to treatment (38). According to the research based on the INRG data base, which included 8 800 patients younger than 21 years of age diagnosed between 1990 and 2002, 2 266 experienced a first relapse, progression of the disease or development of a secondary tumor. More than half of patients with high-risk NB either fail to respond to treatment or eventually relapse (39). Although relapse can occur in intermediate-risk groups, it is reported in only 20% of cases. Survival after relapse in high-risk NB remains less than 10% (40). Our results further underscore the connection between relapse and lethal outcomes -46.2% of our patients had relapse, and it was more common in those with advanced stages (3 and 4). Based on these results, questions can be raised on developing new therapeutic strategies aimed at reducing relapse rates and improving OS in patients with advanced stages or high-risk NB.

Postoperative complications after NB treatment were reported in 44.7% of cases in one study from China (41). In our study, only one experienced a postoperative complication, which was intestinal obstruction. Minimally invasive surgery is generally recommended for reducing the risk of postoperative ileus and adhesion formation (42).

Survival Outcomes and Mortality: Long-term survival in NB in localized stages (1-3) still remains excellent (>90%), but in advanced Stage 4 disease, it is persistently poor (3,16,24,43,44). In our study, 46.2% of patients had a lethal outcome. NB is a tumor characterized by high mortality rates, with 10-year survival reaching 91% for Stages 1-3, and only 38% for Stage 4 (16). A more recent study from 2025 (3) reported that high-risk NB has mortality rates of 50%, whereas low-risk and intermediate-risk NB has mortality rate lower than 10%. Our results are limited by the fact that mortality was not analyzed separately according to disease stage and risk-group, the aggressive nature of the tumor was once again evident.

A paper published by Berthold et al. (43) reported that 10-year survival in children with Stages 1-3 has consistently been high, whereas for Stage 4 it has remained lower, increasing from 2% to 38% between 1979 and 2015. Our findings are consistent with these observations -85.7% of children with Stage 4 had lethal outcomes, while all children with Stage 2 survived.

The median survival time in our study is 36 months, with the Kaplan-Meier curve showing a steep decline in the early phases: 1-year survival was 91.7%, and 3-year survival is 45.8%. Similarly, a study from Egypt (44) reported a 2-year survival of 19.0±16.8% in children with NB and poor prognosis, in contrast to 71.4±17.1% in those with favorable prognosis. Another study from the Netherlands (24) found a 5-year survival rate 35±3% for Stage 4, and 93±2% for Stages 1-2. Although our analysis was not

stratified by stage, the observed survival trends are consistent with global data. Once again, the aggressive nature of advanced NB is a central concern.

Molecular Landscape: MYCN amplification, present in around 20% of cases, is a well-established marker of tumor aggressiveness and poor prognosis, particularly in advanced-stage disease (45). Its presence is the most relevant piece of data, regarding genetic material, that influence prognosis of disease. The association between *MYCN* gene amplification and disease stage was observed and described descriptively in our cohort. The MYCN amplification was more frequently present in patients with advanced-stage NB.

Our study aimed to examine the impact of early diagnosis of NB at the initial stage of the disease on treatment outcomes. We followed thirteen patients treated at the clinic for pediatric surgery KCUS. The predominance of advanced-stage disease at diagnosis, commonly present metastatic involvement, adrenal localization, elevated tumor biomarkers and poor survival outcomes in advanced stages are similar to observations from international registries and population-based studies. In contrast, some differences were present–the proportion of patients presenting with Stage 4 disease, the high relapse rate, and the elevated mortality in our cohort appear higher than those present in other studies. That can be the result of several limitations of the study. For comparing mentioned findings with our institutional experience, refer to the Table 6.

Study Limitations

This study has several limitations. The small size of this cohort (n=13), due to single-center, retrospective nature of this analysis, remains biggest limitation. It limits external validity, and contributes to the possibility of selection and information bias. Furthermore, statistical power is restricted, due to the limited sample size. Limited availability of MYCN status should also be noted, as well as limited and heterogeneous follow-up time interval. Therefore, the findings should be considered hypothesis-generating and exploratory.

Mentioned study limitations show why the need for larger, prospective, multicenter studies persists, which-within current research setting in Bosnia and Herzegovina, remain difficult to conduct. Nonetheless, this report is initial step toward structured data collection and further research, in the field of pediatric oncology.

Table 6. Comparison of current study findings with major series

Outcome parameter	Current Sarajevo cohort (n=13)	Findings from large series	Interpretation & divergence
Stage distribution	53.9% Stage 4 (INSS)	46-80% Stage 4/metastatic	**Aligned.** High proportion of advanced-stage disease at presentation is consistent globally.
Age at diagnosis	Median: 44 months	Median: 17-18 months	**Divergent.** Our cohort is significantly older. This likely has contribution to the observed poor prognosis, as age >18 months is one of the prognostic factors in metastatic NB.
MYCN amplification	30.8% of tested (4/13); 100% mortality in amplified	Around 25-40% overall; strong poor prognostic factor	**Trend aligned, rate higher.** Proportion with *MYCN* amp is descriptively higher. The 100% mortality in amplified cases (though n=4) brings out the importance of developing bigger studies regrading this trend.
Metastasis at Dx	76.9% (10/13)	Between 50-70%	**Aligned.** Our rate is at the upper end of reported ranges, consistent with the high stage distribution. Lymph node (100%) and bone (50%) involvement patterns are typical.
Biomarker elevation	NSE: 100% (7/7); LDH: 88.9% (8/9); VMA: 77.8% (7/9)	>90% elevation in catecholamines and its metabolites;	**Aligned.** High rates of biomarker elevation confirm diagnostic utility.
Treatment approach	Multimodal (Surgery, Chemo, MIBG, Immuno)	Risk-stratified multimodal standard (per INRG)	**Aligned.** Multimodal approach was applied.
Relapse rate	46.2% overall; 62.5% in Stage 3 and 4	40-60% in high-risk	**Aligned for Stage 4.** Our overall rate is product of the high proportion of advanced-stage patients. The pattern (relapse concentrated in Stage 4) is expected.
Survival (Stage 4)	14.3% (1/7) survived	5-yr OS: 35-60% in modern series	**Divergent/lower.** Our Stage 4 survival appears lower. Potential contributors: older age at diagnosis and small sample size.
Diagnostic intervals	Symptom to MD: median 12 days; MD to Dx: median 14 days	Often weeks to months; delay of around 2 weeks is common	**Aligned.** Our diagnostic timelines appear relatively efficient and are not excessively prolonged compared to literature reports.

INSS: International Neuroblastoma Staging System, LDH: Lactate dehydrogenase, VMA: Vanillylmandelic acid, NSE: Neuron-specific enolase, OS: Overall survival, INRG: International Neuroblastoma Risk Group, MIBG: Meta-iodobenylguanidine, MD: Medical doctor, Dx: Diagnosis.

CONCLUSION

In our single-center series of 13 patients with NB, the most common clinical signs and symptoms were loss of appetite, a palpable abdominal mass, and abdominal pain. The majority of patients had a primary tumor localized in the adrenal gland. Disease relapse was confirmed in 46.2% of patients, with relapse occurring more frequently in those diagnosed at advanced stages. The OS rate in our cohort was 53.8%. All patients with stage 2 disease survived, while 85.7% of patients with stage 4 disease had a fatal outcome. Elevated tumor biomarkers, including NSE, LDH, ferritin, and VMA, were noted in patients with advanced-stage disease, which is consistent with international observations. Disease stage at diagnosis was observed relating to the outcomes: Patients who presented with low stages have survived, while the ones with high stages were connected with high mortality and frequent relapses.

Upon these findings, we can state that the early recognition is one of the most important factors defining the outcomes of children with NB. Early recognition is associated with lower disease stages at diagnosis, hence, patients have more favorable outcomes. There is a need for multimodal, risk-adapted therapy and more structured follow-up protocols for high-risk patients, to address their higher likelihood of relapse.

For improving OS in children with NB-especially in low and middle income countries-future studies should focus on multicenter designs including patients with comprehensive molecular profiling, standardized staging, and uniform follow-up. That could better refine prognostic assessment and therefore contribute to the better outcomes in patients with NB.

Ethics

Ethics Committee Approval: The study was approved by the Local Institutional Review Board (Ethical Committee of the Clinical Center University of Sarajevo, protocol code: 51-45-1-6872/25, date: 24 February 2025).

Informed Consent: Due to the retrospective nature of the study, informed consent was waived.

Footnotes

Author Contributions

Surgical and Medical Practices - A.J., I.T., B.K., Z.Z.; Concept - A.J., I.T., B.K., P.I., Z.Z.; Design - A.J., I.T.; Data Collection or Processing - A.J., I.T., B.K., P.I., Z.Z.; Analysis or Interpretation - A.J., I.T., B.K., P.I., Z.Z.; Literature Search - A.J., I.T.; Writing - A.J., I.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. *Mahapatra CK, Mahapatra S. Neuroblastoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jul 23 [cited 2025 Apr 2]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448111/*
2. *Zhang Y, Huang D, Zhang W, Tang S, Han T, Zhu X, et al. Clinical characteristics of infant neuroblastoma and a summary of treatment outcome. Oncol Lett. 2016;12:5356-5362.*
3. *Nong J, Su C, Li C, Wang C, Li W, Li Y, et al. Global, regional, and national epidemiology of childhood neuroblastoma (1990–2021): a statistical analysis of incidence, mortality, and DALYs. eClinicalMedicine. 2025;79:102964.*
4. *Sainero-Alcolado L, Sjöberg Bexelius T, Santopolo G, Yuan Y, Liaño-Pons J, Arsenian-Henriksson M. Defining neuroblastoma: from origin to precision medicine. Neuro Oncol. 2024;26:2174-2192.*
5. *Van Groningen T, Koster J, Valentijn LJ, Zwijnenburg DA, Akogul N, Hasselt NE, et al. Neuroblastoma is composed of two super-enhancer-associated differentiation states. Nat Genet. 2017;49:1261-1266.*
6. *Ponzoni M, Bachetti T, Corrias MV, Brignole C, Pastorino F, Calarco E, et al. Recent advances in the developmental origin of neuroblastoma: an overview. J Exp Clin Cancer Res. 2022;41:92.*
7. *Izumi H, Kaneko Y, Nakagawara A. The role of MYCN in symmetric vs. asymmetric cell division of human neuroblastoma cells. Front Oncol. 2020;10:570815.*
8. *Davidoff AM. Neuroblastoma. Semin Pediatr Surg. 2012;21:21-24.*
9. *Shimada H, Ikegaki N. Genetic and histopathological heterogeneity of neuroblastoma and precision therapeutic approaches for extremely unfavorable histology subgroups. Biomolecules. 2022;12:79.*
10. *Dumba M, Jawad N, McHugh K. Neuroblastoma and nephroblastoma: a radiological review. Cancer Imaging. 2015;15:5.*
11. *Ara T, DeClerck YA. Mechanisms of invasion and metastasis in human neuroblastoma. Cancer Metastasis Rev. 2006;25:645-657.*
12. *Liu S, Yin W, Lin Y, Huang S, Xue S, Sun G, et al. Metastasis pattern and prognosis in children with neuroblastoma. World J Surg Oncol. 2023;21:130.*
13. *Bolkar ST, Ghadge MS, Raste AS. Biochemical parameters in neuroblastoma. Indian J Clin Biochem. 2008;23:293-295.*
14. *Bagatell R, Park JR, Acharya S, Aldrink J, Allison J, Alva E, et al. Neuroblastoma, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2024;22:413-433.*
15. *Whittle SB, Smith V, Doherty E, Zhao S, McCarty S, Zage PR. Overview and recent advances in the treatment of neuroblastoma. Expert Rev Anticancer Ther. 2017;17:369-386.*
16. *Li Q, Wang J, Cheng Y, Hu A, Li D, Wang X, et al. Long term survival of neuroblastoma patients receiving surgery, chemotherapy, and radiotherapy: a propensity score matching study. J Clin Med. 2023;12:754.*
17. *Meany H. Non-high-risk neuroblastoma: classification and achievements in therapy. Children (Basel). 2019;6:5.*
18. *Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG task force report. J Clin Oncol. 2009;27:298-303.*
19. *Fati F, Pulvirenti R, Paraboschi I, Martucciello G. Surgical approaches to neuroblastoma: review of the operative techniques. Children (Basel). 2021;8:446.*
20. *Colon NC, Chung DH. Neuroblastoma. Adv Pediatr. 2011;58:297-311.*
21. *Anderson J, Majzner RG, Sondel PM. Immunotherapy of neuroblastoma: facts and hopes. Clin Cancer Res. 2022;28:3196-3206.*
22. *Coldman AJ, Fryer CJ, Elwood JM, Sonley MJ. Neuroblastoma: influence of age at diagnosis, stage, tumor site, and sex on prognosis. Cancer. 1980;46:1896-1901.*
23. *Ting L, Kong X, He D. Epidemiology and clinical features of childhood malignant solid tumors in a single center in southwest China over 24 years. BMC Pediatr. 2025;25:12.*

24. *Tas ML, Reedijk AM, Karim-Kos HE, Pieters R, Tytgat GA, Van Noesel MM, et al. Neuroblastoma between 1990 and 2014 in the Netherlands: increased incidence and improved survival of high-risk neuroblastoma. Eur J Cancer. 2020;124:47-55.*
25. *Williams LA, Spector LG. Survival differences between males and females diagnosed with childhood cancer. JNCI Cancer Spectr. 2019;3:pkz032.*
26. *Djos A, Svensson J, Gaarder J, Umapathy G, Nilsson S, Ek T, et al. Loss of chromosome Y in neuroblastoma is associated with high-risk disease, 11q-deletion, and telomere maintenance. Genes Chromosomes Cancer. 2024;63:e23260.*
27. *Kamihara J, Diller LR, Foulkes WD, Michaeli O, Nakano Y, Pajtler KW, et al. An update from the 2023 AACR Childhood Cancer Predisposition Workshop. Clin Cancer Res. 2024;30:3137-3143.*
28. *Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014;64:83-103.*
29. *Fang X, Wang H, Ma X, Guo Y, Yang W, Hu S, et al. Clinical features of children with retinoblastoma and neuroblastoma. J Ophthalmol. 2020;2020:9315784.*
30. *Liu Y, Huo L, Zhang J, Liu Y. Intracranial metastases tend to be overt and predict poor prognosis in children with neuroblastoma. Front Pediatr. 2021;9:716880.*
31. *Pudela C, Balyasny S, Applebaum MA. Nervous system: embryonal tumors: neuroblastoma. Atlas Genet Cytogenet Oncol Haematol. 2020;24:284-290.*
32. *Ghosh SK, Dutta A, Basu M. Raccoon eyes in a case of metastatic neuroblastoma. Indian J Dermatol Venereol Leprol. 2012;78:740-741.*
33. *Mota EB, Penna CRR, Marchiori E. Metastatic dissemination of a neuroblastoma. J Pediatr. 2017;189:232–232.e1.*
34. *Lucena JN, Alves MT, Abib SC, Souza G, Neves RP, Caran EM, et al. Clinical and epidemiological characteristics and survival outcomes of children with neuroblastoma: 21 years of experience at the Instituto de Oncologia Pediátrica, in São Paulo, Brazil. Rev Paul Pediatr. 2018;36:254-260.*
35. *Meena JP, Seth R, Chakrabarty B, Gulati S, Agrawala S, Naranje P. Neuroblastoma presenting as opsoclonus-myoclonus: a series of six cases and review of literature. J Pediatr Neurosci. 2016;11:373-377.*
36. *Schleiermacher G, Rubie H, Hartmann O, Bergeron C, Chastagner P, Mechinaud F, et al. Treatment of stage 4s neuroblastoma-- report of 10 years experience of the French Society of Pediatric Oncology (SFOP). Br J Cancer. 2003;89:470-476.*
37. *Mina AS, Nashed GN, Hermina AM, Schauwecker SM, Phelps HM, Benedetti DJ, et al. Outcomes and histological variations of neuroblastoma and ganglioneuroblastoma with paraneoplastic syndromes. Am Surg. 2023;89:3745-3750.*
38. *Brodeur GM, Pritchard J, Berthold F, Carlsen NL, Castel V, Castelberry RP, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol. 1993;11:1466-1477.*
39. *London WB, Castel V, Monclair T, Ambros PF, Pearson AD, Cohn SL, et al. Clinical and biologic features predictive of survival after relapse of neuroblastoma: a report from the International Neuroblastoma Risk Group Project. J Clin Oncol. 2011;29:3286-3292.*
40. *Canete A, Gerrard M, Rubie H, Castel V, Di Cataldo A, Munzer C, et al. Poor survival for infants with MYCN-amplified neuroblastoma despite intensified treatment: the International Society of Paediatric Oncology European Neuroblastoma Experience. J Clin Oncol. 2009;27:1014-1019.*
41. *He M, Cai JB, Wu X, Tang YB, Wang JY, Mao JQ, et al. Perioperative complication incidence and risk factors for retroperitoneal neuroblastoma in children: analysis of 571 patients. World J Pediatr. 2024;20:250-258.*
42. *Jacobson JC, Clark RA, Chung DH. High-risk neuroblastoma: a surgical perspective. Children (Basel). 2023;10:388.*
43. *Berthold F, Spix C, Kaatsch P, Lampert F. Incidence, survival, and treatment of localized and metastatic neuroblastoma in Germany 1979-2015. Pediatr Drugs. 2017;19:577-593.*
44. *Al-Tonbary YB, Mohamed M, Ahmed E, Usama S, Shebl H, Tamer E. Clinico-epidemiology of neuroblastoma in North East Egypt: a 5-year multicenter study. Oncol Lett. 2015;10:1054-1062.*
45. *Agarwal P, Glowacka A, Mahmoud L, Bazzar W, Larsson LG, Alzrigat M. MYCN amplification is associated with reduced expression of genes encoding γ-secretase complex and NOTCH signaling components in neuroblastoma. Int J Mol Sci. 2023;24:8141.*