Observational Study

Medicine®

OPEN

Analysis of the risk factor for the poor prognosis of localized neuroblastoma after the surgical

Kai Zhou, MD[a,b], Xiao-lu Li, MD[a], Jian Pan, MD[a], Jian-zhong Xu, MD[b], Jian Wang, PhD[a,*]

Abstract

Neuroblastoma is a unique malignancy in infants often presenting with either localized or metastatic disease. The study was carried out to explore the risk stratification of the poor prognosis for patients underwent surgical treatment.

60 patients diagnosed with neuroblastoma were primarily enrolled in the study from April 2008 to April 2016. All the patients underwent surgical treatment and received 5-year follow-up. Clinical variables, including age, International Neuroblastoma Staging System (INSS) stage, tumor size and site, histology, and MYCN status were retrospectively analyzed, and EFS was chosen as the endpoint.

The median age of patients was 8.2 months and average follow-up period was 40.2 ± 8.6 months. Among 60 patients, complete remission was achieved in 35 patients and partial remission in 14 subjects. Poor prognosis including patient death and tumor progression were overserved in 11 patients. Cox multifactor regression analysis revealed that age, histology and MYCN status had significant prognostic effect on event-free survival (EFS) rate for neuroblastoma patients underwent surgical treatment.

In our study, we identified a series of prognostic factors including age, histology, and MYCN status predicting the prognosis of neuroblastoma patients after surgical treatment.

Abbreviations: AUC = area under curve, CR = complete remission, EFS = event-free survival, INRC = international neuroblastoma treatment response criterion, INSS = International Neuroblastoma Staging System, PD = patient death, PR = partial remission, ROC = receiver operating characteristic curve, SD = standard deviations, TP = tumor progression.

Keywords: neuroblastoma, prognosis, risk factors

1. Introduction

Neuroblastoma is a heterogeneous tumor rising from neural crest progenitor cells, which appears as the most frequently diagnosed extra-cranial solid tumor in children, accounting for nearly 10% of all childhood cancers.[1–3] It is a unique malignancy in that infants often present with either localized or metastatic disease which can spontaneously regress without intervention while elder children can succumb to the disease after months to years of arduous therapy.[4,5] There are studies showed that the over whole survival rates of patients with the most aggressive neuroblastoma are < 40%, even after intensive therapy.[6,7]

A lot of previous studies have investigated the NB as aspect of epidemiology, molecular mechanism, chemotherapy, radiotherapy and so on.[8,9] Over the past several decades, the outcome for childhood cancer has improved dramatically. However, the long-term outcome of children with NB that are classified as high risk remains poor.[10,11] The improved understanding of neuroblastoma biology and its impact on prognosis has relatively resulted in better tailoring of therapy. In clinical, the requirement for further surgical resection, chemotherapy, or radiotherapy is based upon a patient's risk stratification with general principles of therapy.[12] So far, several studies have published the potential risk factors which contributed to outcomes of NB patients.[13,14] But as far as we know, it is the first study which specifically focus on risk factors for outcomes of the patients underwent surgical treatment.

2. Methods and materials

2.1. Ethical considerations

This retrospective study was approved by the ethics committee of Children hospital, Soochow University. We acquired all the informed consent from the enrolled patients before the study. All the methods in the research were performed in accordance with the relevant guidelines and regulations.

2.2. Subjects selected for the study

Around 60 patients diagnosed with neuroblastoma were primarily enrolled in the study from April 2008 to April 2016. Strict inclusion and exclusion criteria were adopted to address potential sources of bias. Inclusion criteria of the enrolled subjects have been described below: pathological results proved to be neuroblastoma; the survival condition of the enrolled patients could be identified; all the patients enrolled in the study underwent surgical treatment and/or chemotherapy; patients ranged from 0 to 18 months old; absence of metastases, and no

Editor: Shihan He.

The authors have no conflicts of interest to disclose.

[a] Department of General Surgery, Children's Hospital of Soochow University, Suzhou, [b] Department of Pediatric Surgery, The First Affiliated Hospital of Bengbu Medical College, Bengbu, China.

[*] Correspondence: Jian Wang, Soochow University Affiliated Children's Hospital, Suzhou, 215025, Jiangsu, China (e-mail: wangjianszdx@sina.comjianwang0512@163.com).

Medicine (2018) 97:40(e12718)

Received: 22 May 2018 / Accepted: 13 September 2018

http://dx.doi.org/10.1097/MD.0000000000012718

previous chemotherapy. Exclusion criteria included patients received additional treatment before enrollment, incomplete data during follow-up. Clinical variables including International Neuroblastoma Staging System (INSS) stage, tumor histopathology, MYCN status, primary tumor sites and size, and type of tumor resection were collected and analyzed for all patients.

2.3. Treatment

The need for the preoperative chemotherapy was confirmed with the oncologists and surgeons based on the tumor size and sites and resectibility at presentation. Patients were offered chemotherapy if there were signs of organ dysfunction, life-threatening symptoms, or spinal cord compression. All the patients underwent surgical resection. The thoracic neuroblastomas were approached through a standard lateral thoracotomy. For cervical neuroblastomas, surgery was carried out with a transverse crease incision. Since most of the abdominal tumors are found in the upper abdomen, the thoracoabdominal approach was chosen in this situation. For patients underwent incomplete tumor resection, postoperative chemotherapy was performed.

2.4. Type of tumor resection

Complete excision was defined as excision of all visible tumor, including abnormal lymph nodes, which corresponds to INSS stage 1. Near-complete excision was considered as removal of the tumor with a minimal macroscopical residue, which related to INSS stage 2. Partial excision was defined as removal of the tumor with a macroscopic gross residue. This corresponds to INSS stage 3. Also partial excision is also related to the rare cases in which the tumor is resected completely, however the contralateral lymph nodes are infiltrated by the tumor.

2.5. Follow-up and grouping

All patients enrolled in the study were followed-up by outpatient service. All the patients received follow-up examinations every 3 months for 2 years after operation. After that patients received follow-up examinations twice a year for 3 to 5 years after operation. Lost follow-up was defined as losing contact with the medical staff more than 6 months during the follow-up period. All the enrolled patients were divided into good prognosis group and poor prognosis group. The outcomes include the state of disease evaluated based on the International Neuroblastoma Treatment Response Criterion (INRC): complete remission (CR) was defined as no residual tumor was found in CT, bone scan, bone marrow smear and physical examination for more than one month; partial remission (PR) was defined as the volume of the tumor is reduced by more than 50% for at least one month; tumor progression (TP) was defined as new metastatic lesion was found or the primary tumor becomes larger; patient death (PD) was defined as the enrolled died of the neuroblastoma during the follow-up period.[15] The good prognosis group consist of patients with the results of CR and PR, and the bad prognosis group consist of patients with the results of TP and PD. No potential confounders could be found in the present study.

2.6. Survival analyses

Event-free survival (EFS) was defined as time from diagnosis until time of first occurrence of relapse, secondary malignancy, death, or until time of last follow-up if none of these happened. Univariate analyses using a log-rank test, at a 5% significance level and without adjustment for multiple testing, were performed to identify factors statistically significantly predictive of EFS to be carried forward into the survival regression.

2.7. Statistical analysis

All the statistical analyses were carried out by using SPSS 21.0 (SPSS, Chicago, IL). Data are presented as mean ± standard deviations (SD). Cox multifactor regression analysis was performed to identify factors independently associated with the prognosis of the neuroblastoma after surgical treatment. Survival curve was also applied to compare the survival rate between different groups. ROC (receiver operating characteristic) curve was constructed and the area under curve (AUC) was calculated to identify which parameter is most sensitive at predicting the recrudescence of the neuroblastoma after the surgical treatment. Cut point value was acquired by calculating the maximum value of sensitivity plus specificity. Tests were performed using 2-tailed and $P < .05$ was considered significant difference.

3. Results

3.1. Patients characteristics

The average follow-up period was 40.2 ± 8.6 months. Of all enrolled patients, 32 were diagnosed before the age of 12 months. Thirty-six patients presented with abdominal primary and 24 patients were diagnosed with a head or neck primary. With regard to INSS stage system, 22 patients were found in stage 1, 20 patients in stage 2 and 18 patients in stage 3. Computed tomography (CT) defined the tumor location at the thoracic (n = 21), cervical (n = 12), and abdominal (n = 27). The histology and MYCN status were also determined in each patient. The characteristics of these patients are given in Table 1.

Table 1

Patients characteristics (n = 60).

	Values
Age, months	
Median	8.2
Range	0–18
Gender	
Male	26
Female	34
INSS stage	
1	22
2	20
3	18
Tumor size, cm	
≤5	39
>5	21
Tumor site	
Neck	12
Thorax	21
Abdomen	27
Histology	
Ganglioneuroblastoma	49
Neuroblastoma	11
MYCN status	
Nonamplified	45
Amplified	15

INSS = International Neuroblastoma Staging System.

Table 2

The type of tumor resection and chemotherapy.

	Patients (n = 60)
Cervical neuroblastoma	
Complete resection	12
Near-complete resection	0
Partial resection	0
Thoracic neuroblastoma	
Complete resection	10
Near-complete resection	5
Partial resection	6
Abdominal neuroblastoma	
Complete resection	12
Near-complete resection	7
Partial resection	8

3.2. Type of tumor resection

The type of excision varied significantly according to tumor location and size. There are 12 cases of cervical neuroblastoma extending to the thoracic inlet. They all underwent complete excision using a cervical approach. Sixteen of the twenty-one thoracic neuroblastomas were completely or near-completely resected via thoracotomy. The remaining 6 patients with encasement of vessels received partial resection. For 8 out of 27 abdominal neuroblastomas, the initial surgical approach was limited to partial resection. Complete tumor resection was achieved in 12 patients and near-complete tumor resection in 7 patients. The type of surgery used in each case is presented in Table 2.

3.3. Outcomes

Among 60 patients, CR was achieved in 35 patients, while PR was 14 subjects. Good prognosis group included the patients with the CR and PR results. Poor prognosis group included subjects with TP and PD. Among 60 patients, the cumulative EFS rates were 88.3% at 1 year, 83.3% at 2 year, and 81.7% at 5 years. EFS rate improved significantly in patients under INSS stage 1 and 2, compared to those under stage 3 (1 year, 92.9% vs 77.8%; 5 years, 90.5% vs 61.1%). Patients with smaller tumor size had better EFS rate than those with larger tumor size (1 year, 90.9% vs 85.2%; 5 years, 84.8% vs 77.8%).

3.4. Prognostic factors for the Event-free survival

Univariate analysis revealed that 6 risk factors, including age, INSS stage, tumor size, histology, and MYCN status had significant prognostic effect on EFS. On multivariate analysis, only 3 were independent predictors for EFS. Age more than 12 months, neuroblastoma subtype and amplified MYCN status were associated with worse overall survival (Table 3). Good predictive values were obtained for the significant parameters with the AUC of 0.82 (age), 0.84 (neuroblastoma subtype), 0.85 (amplified MYCN) (Fig. 1).

3.5. Survival analysis

Consistent with prior studies, age was a key factor which determined EFS. As Figure 2 showed, patients under 12 months had higher EFS rates than that of patients more than 12 months ($P < .01$). Figure 3 showed the Kaplan–Meier survival curves for patients with different histological types. Patients with neuroblastoma had worse EFS, with recurrence occurring earlier than patients with ganglioneuroblastoma. EFS declined precipitously during first year of follow-up, subsequent a slowing in the decline after one year of follow-up. In link with previous results, MYCN status was another prognostic factors associated with patients EFS periods after primary surgery. Amplified MYCN status group showed an early decline over the first 1.5 years with a more gradual decline after 2 years of follow-up. The non-amplified MYCN status group showed a higher EFS than the amplified MYCN group ($P < .01$) (Fig. 4).

Table 3

Univariate and multivariate analysis of poor prognosis (n = 60).

Factor	Poor prognosis group (n = 11)	Good prognosis group (n = 49)	Univariate analysis *P*	Multivariate analysis (HR 95%)	*P*
Age, months					
≤12	3 (27.3%)	44 (89.8%)			
>12	8 (72.7%)	5 (10.2%)	.00	23.4, 4.6–118.2	.00
INSS stage					
1	2 (18.2%)	20 (40.8%)			
2	2 (18.2%)	18 (36.7%)			
3	7 (63.6%)	11 (22.5%)	.02	1.05, 0.45–2.12	.13
Tumor size, cm					
≤5	4 (36.4%)	35 (71.4%)			
>5	7 (63.6%)	14 (28.6%)	.03	1.23 0.15–2.31	.16
Tumor site					
Neck	2 (18.2%)	12 (24.5%)			
Thorax	3 (27.3%)	18 (36.7%)			
Abdomen	6 (54.5%)	19 (38.8%)	.63		
Histology					
Ganglioneuroblastoma	2 (18.2%)	20 (40.8%)			
Neuroblastoma	9 (81.2%)	29 (59.2%)	<.001	40.8 6.9–239.1	.00
MYCN status					
Nonamplified	2 (18.2%)	43 (87.8%)			
Amplified	9 (81.8%)	6 (12.2%)	<.001	32.3 5.6–183.2	.00

INSS = International Neuroblastoma Staging System.

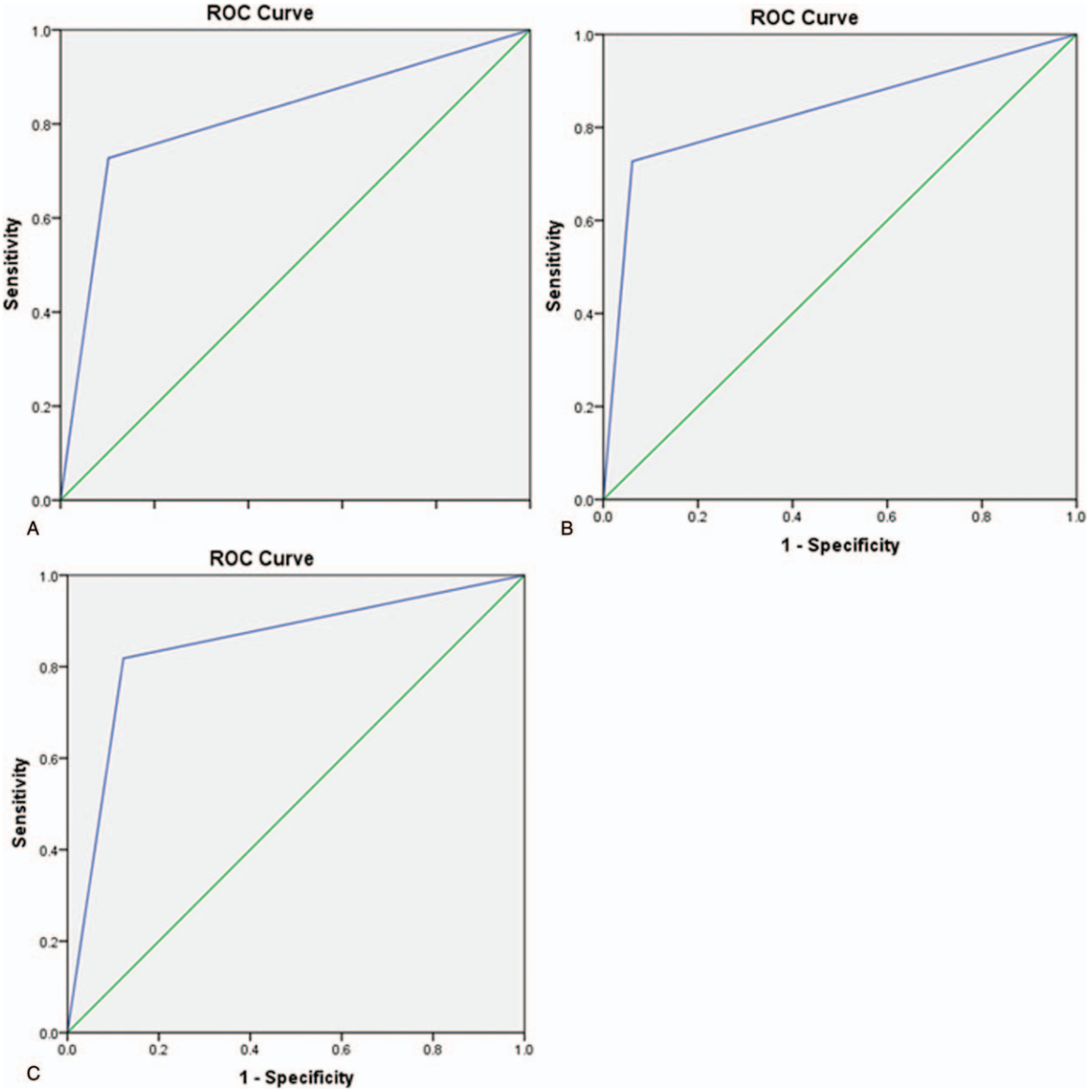

Figure 1. ROC for the significant parameters; (A) indicates ROC of age with the AUC of 0.82, (B) indicates ROC of neuroblastoma subtype with the AUC of 0.84, (C) indicates the amplified MYCN with the AUC of 0.85. ROC = receiver operating characteristic curve.

4. Discussion

Previous studies have demonstrated that the outcome of recurrent high-risk neuroblastoma was much worse than those of primary intermediate-risk tumors.[16,17] The role of surgery in the treatment of neuroblastoma is no doubt the mainstay of therapy for the majority of patients with localized neuroblastoma.[18,19] However, there is no convincing evidence which could predicts the outcome of neuroblastoma patients underwent tumor resection. Given that tumor resection may be acceptable for most low- and intermediate-risk patients, the need to determine prognostic factors after surgical treatment has become increasingly apparent. In our study, the prognostic factors of 6 variables were analyzed, and EFS was chosen as the endpoint. Our data showed that 3 of 6 variables were highly statistically significant and also considered clinically relevant.

Survival analysis confirmed that the predictive ability of age was continuous in nature for neuroblastoma. However, inconsistent with some previous publications, our study found that the optimal age cut-off is 12 months. While London et al[20] reported statistical support existed for an age cut-off of 460 days. This discrepancy might reflect the different inclusion criteria of patients, with previous article include patients under INSS stage 4 and therefore postponing the cut-off age. Susan et al[21] support for an optimal "cut-off" between 15 and 19 months. They found that children younger than 18 months had EFS and OS rates of 63% ± 2% and 68% ± 2%, respectively. Children of 18 months of age or older had EFS and OS rates of 23% ± 1% and 31% ± 1%, respectively. Besides, they also analyzed the EFS rates for patients in stage 4 tumors younger than 12 months and found there was no statistically different between patients of 12 months or older and patients younger than 12 months. In addition, they

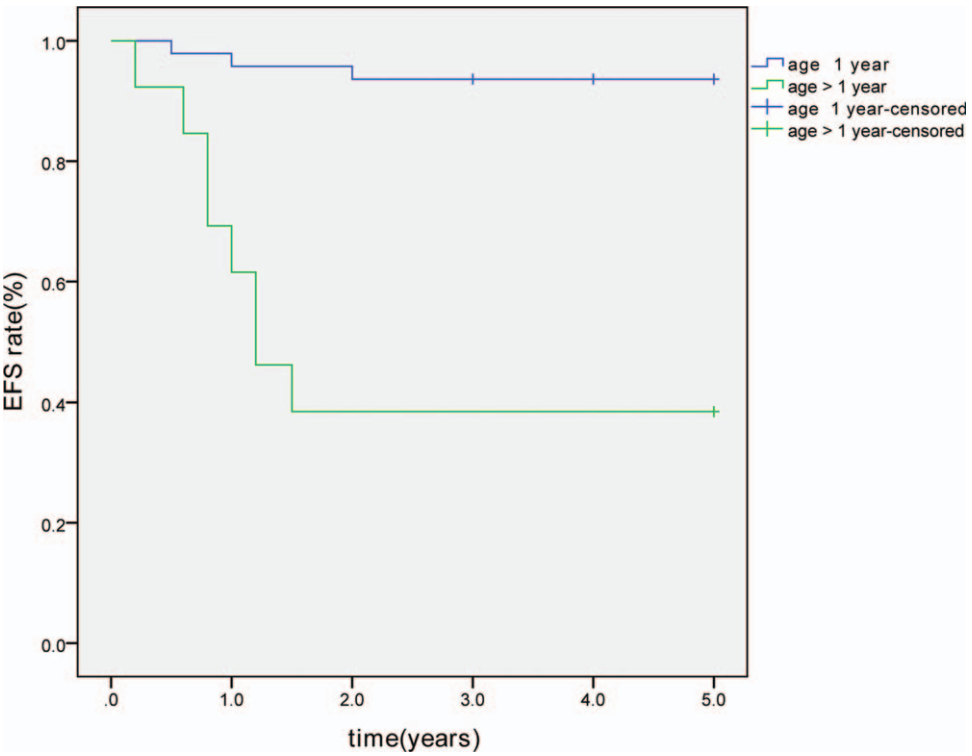

Figure 2. Kaplan–Meier survival curves of patients with age under 12 months or more than 12 months.

also claimed that for patients with diploid, stage M, MYCN non-amplified tumors, the more conservative age cut-off of 12 months might be more acceptable. Our results elucidated that patients with age under 12 months had a significantly higher EFS rate than those more than 12 months. Taken together, INSS stage should be taken into consideration when select the optimal cut-off age.

Tumor histology is another well-established prognostic variable in neuroblastoma.[22,23] Our data were in accordance

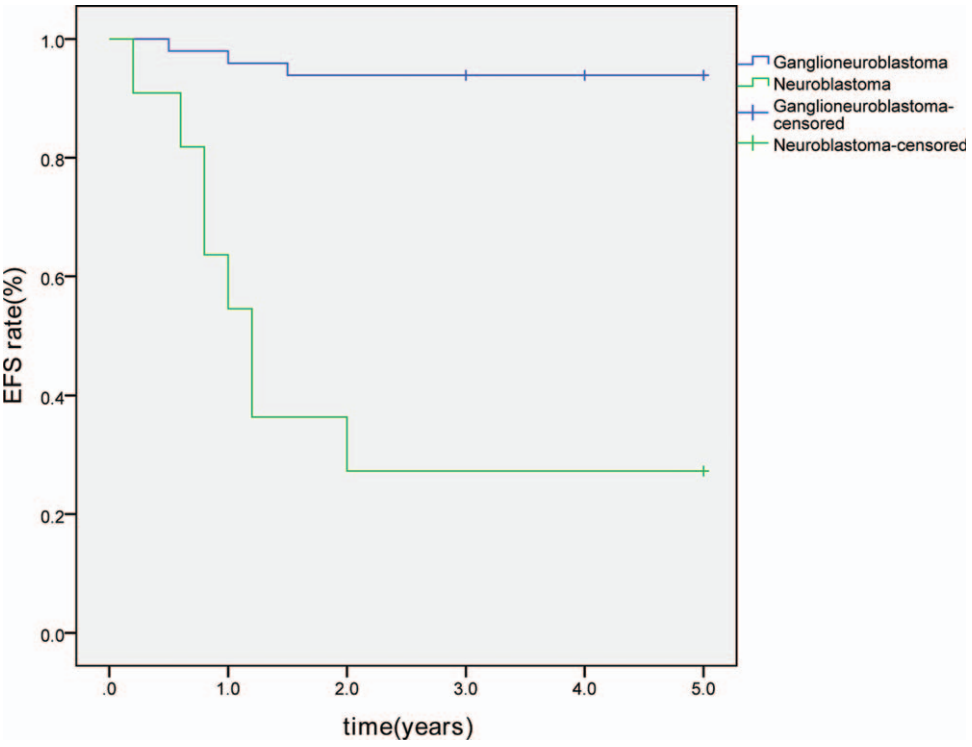

Figure 3. Kaplan–Meier survival curves for patients with different histological types.

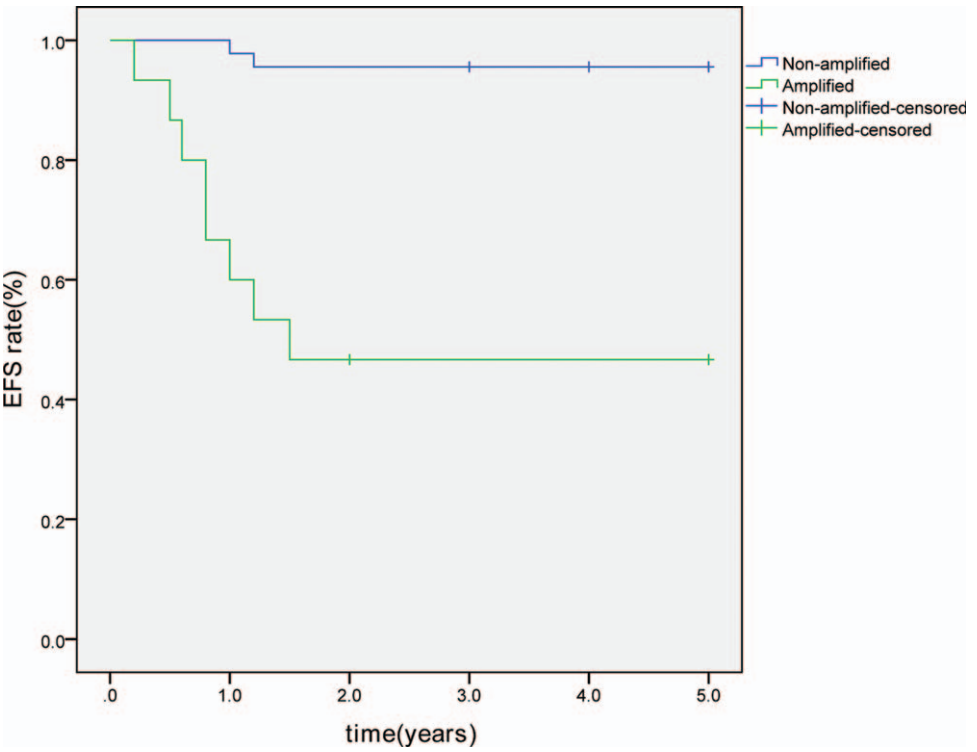

Figure 4. Kaplan–Meier survival curves for patients with non-amplified MYCN status or amplified MYCN status.

with previous studies showing the better prognosis in ganglioneuroblastoma than in neuroblastoma.[23] We found that a better EFS rate in patients with ganglioneuroblastoma than that in neuroblastoma. In the spectrum of differentiation of neuroblastic tumors, ganglioneuroblastoma, nodular subtype, occupies a unique position. The International Neuroblastoma Pathology Classification (INPC) defines it as a stroma-dominant or stroma-rich tumor, surrounding by one or more macroscopic nodules of stroma-poor neuroblastoma.[24] Angelini et al[25] found that patients with ganglioneuroblastoma were older, a larger proportion had unfavorable INPC pathology, and rarely had MYCN amplified status when compared with those with neuroblastoma. However, they determined that the 5-year EFS in ganglioneuroblastoma was 70% ± 1% (vs 81.8 ± 1%), a slight lower compared with our results. This discrepancy of EFS rates can be explained by different selected patients. In Angelini's study, they included patients in INSS stage 4, which have worse EFS rate. However, even in this situation, this 5-year EFS rate was higher than patients with neuroblastoma in our study (70% vs 54.5%).

MYCN status played an important role in predicting prognosis of neuroblastoma patients. Amplification of MYCN was found in 25% of neuroblastoma patients and regarded as a biomarker for poor prognosis. Currently, MYCN amplification remains the best-characterized genetic marker of risk in neuroblastoma.[26] Previous study showed MYCN status was the most powerful prognostic factor within non–stage 4 neuroblastoma patients.[21] They found that patients with MYCN non-amplified status had EFS of 87% ± 1% and OS of 95% ± 1%, and 46% ± 4% and 53% ± 4% for patients with MYCN-amplified status. Canete et al[27] enrolled 46 infants with MYCN amplification and found 2-year EFS was 29%. Many studies also reported other genetic markers such as DNA ploidy, neurotrophin receptors could be used as prognostic factors.[28–30] Unlike other studies, we decided to only consider MYCN status because this formed a clear biologic subgroup with a well-known and well-described aggressiveness.

Neuroblastoma is a heterogeneous malignancy with prognosis ranging from near uniform survival to high risk for fatal demise. Neuroblastoma serves as a paradigm for the prognostic utility of biologic and clinical data and the potential to tailor therapy for patient cohorts at low, intermediate, and high risk for recurrence.[31] Studies have demonstrated that patients with low risk disease can be treated with surgery alone and supported a role for >90% resection of the primary tumor in high-risk patients.[32] Although overall survival is excellent for patients who have low- and intermediate-risk neuroblastoma with a general trend toward minimization of therapy, mortality rate is still high for high-risk patients.[33] Thus it is of importance to identify the characteristics which could predict the outcomes of patients. In our study, we found that surgical treatment to patients with localized neuroblastoma has good outcomes. Besides, our results also elucidated that several variables including younger age, ganglioneuroblastoma and MYCN nonamplified status correlated with good prognosis after surgery. We consider these prognostic factors will help in predicting outcomes of surgical treatment in clinical practice in the future.

One limitations of this study was relatively small sample groups, larger group studies need to be performed to firmly establish the conclusions; the second limitation of the study is the retrospective study, as in so many similar published study, may induce selection bias; thirdly, the limited number of enrolled patients may result in the selective bias.

From our series, we found that surgical treatment for patients with localized neuroblastoma had favorable outcomes. Besides, our results also elucidated that several variables including younger age, ganglioneuroblastoma and MYCN non-amplified status correlated with good prognosis after surgery. We hope that these prognostic factors will help in predicting outcomes of surgical treatment in the future.

5. Conclusion

In our study, we identified a series of prognostic factors including age, histology and MYCN status predicting the prognosis of neuroblastoma patients after surgical treatment.

Author contributions

Conceptualization: Jian Wang.
Data curation: Kai Zhou, Jianzhong Xu.
Funding acquisition: Jian Wang.
Investigation: Kai Zhou, Jianzhong Xu.
Methodology: Kai Zhou, Xiaolu Li, Jian Pan.
Resources: Jian Pan, Jianzhong Xu.
Software: Xiaolu Li.
Writing – original draft: Kai Zhou, Xiaolu Li, Jian Pan.
Writing – review & editing: Jian Wang.
Jian Wang: 0000-0002-5909-6372.

References

[1] Matthay KK, Maris JM, Schleiermacher G, et al. Neuroblastoma. Nat Rev Dis Primers 2016;2:16078.
[2] Tolbert VP, Matthay KK. Neuroblastoma: clinical and biological approach to risk stratification and treatment. Cell Tissue Res 2018;372:1–5.
[3] Cheung NV, Dyer MA. Neuroblastoma: developmental biology, cancer genomics and immunotherapy. Nat Rev Cancer 2013;13:397–411.
[4] Maris JM, Hogarty MD, Bagatell R, et al. Neuroblastoma. Lancet 2007;369:2106–20.
[5] Nuchtern JG, London WB, Barnewolt CE, et al. A prospective study of expectant observation as primary therapy for neuroblastoma in young infants: a Children's Oncology Group study. Ann Surg 2012;256:573–80.
[6] Esposito MR, Aveic S, Seydel A, et al. Neuroblastoma treatment in the post-genomic era. J Biomed Sci 2017;24:14.
[7] Aksoylar S, Varan A, Vergin C, et al. Treatment of high-risk neuroblastoma: national protocol results of the Turkish Pediatric Oncology Group. J Cancer Res Therap 2017;13:284–90.
[8] Heck JE, Ritz B, Hung RJ, et al. The epidemiology of neuroblastoma: a review. Paediatr Perinat Epidemiol 2009;23:125–43.
[9] Poremba C, Scheel C, Hero B, et al. Telomerase activity and telomerase subunits gene expression patterns in neuroblastoma: a molecular and immunohistochemical study establishing prognostic tools for fresh-frozen and paraffin-embedded tissues. J Clin Oncol 2000;18:2582–92.
[10] London WB, Castel V, Monclair T, 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;29:3286–92.
[11] Pearson AD, Pinkerton CR, Lewis IJ, et al. High-dose rapid and standard induction chemotherapy for patients aged over 1 year with stage 4 neuroblastoma: a randomised trial. Lancet Oncol 2008;9:247–56.
[12] Park JR, Eggert A, Caron H. Neuroblastoma: biology, prognosis, and treatment. Pediatr Clin North Am 2008;55:97–120. x.
[13] Baker DL, Schmidt ML, Cohn SL, et al. Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. N Engl J Med 2010;363:1313–23.
[14] Vermeulen J, De Preter K, Naranjo A, et al. Predicting outcomes for children with neuroblastoma using a multigene-expression signature: a retrospective SIOPEN/COG/GPOH study. Lancet Oncol 2009;10:663–71.
[15] Cangelosi D, Blengio F, Versteeg R, et al. Logic Learning Machine creates explicit and stable rules stratifying neuroblastoma patients. BMC Bioinformatics 2013;14:S12.
[16] Bagatell R, Rumcheva P, London WB, et al. Outcomes of children with intermediate-risk neuroblastoma after treatment stratified by MYCN status and tumor cell ploidy. J Clin Oncol 2005;23:8819–27.
[17] Simon T, Berthold F, Borkhardt A, et al. Treatment and outcomes of patients with relapsed, high-risk neuroblastoma: results of German trials. Pediatric Blood Cancer 2011;56:578–83.
[18] La Quaglia MP. Surgical management of neuroblastoma. Semin Pediatr Surg 2001;10:132–9.
[19] Jrebi NY, Iqbal CW, Joliat GR, et al. Review of our experience with neuroblastoma and ganglioneuroblastoma in adults. World J Surg 2014;38:2871–4.
[20] London WB, Castleberry RP, Matthay KK, et al. Evidence for an age cut-off greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. J Clin Oncol 2005;23:6459–65.
[21] Monclair T, Brodeur GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG) Staging System: an INRG Task Force Report. J Clin Oncol 2009;27:298–303.
[22] Shimada H, Ambros IM, Dehner LP, et al. The International Neuroblastoma Pathology Classification (the Shimada system). Cancer 1999;86:364–72.
[23] Kubota M, Suita S, Tajiri T, et al. Analysis of the prognostic factors relating to better clinical outcome in ganglioneuroblastoma. J Pediatr Surg 2000;35:92–5.
[24] Peuchmaur M, d'Amore ES, Joshi VV, et al. Revision of the International Neuroblastoma Pathology Classification: confirmation of favorable and unfavorable prognostic subsets in ganglioneuroblastoma, nodular. Cancer 2003;98:2274–81.
[25] Angelini P, London WB, Cohn SL, et al. Characteristics and outcome of patients with ganglioneuroblastoma, nodular subtype: a report from the INRG project. Eur J Cancer (Oxford, England: 1990) 2012;48:1185–91.
[26] Huang M, Weiss WA. Neuroblastoma and MYCN. Cold Spring Harb Perspect Med 2013;3:a01441.
[27] Canete A, Gerrard M, Rubie H, et al. Poor survival for infants with MYCN-amplified metastatic neuroblastoma despite intensified treatment: the International Society of Paediatric Oncology European Neuroblastoma Experience. J Clin Oncol 2009;27:1014–9.
[28] Ikeda H, Iehara T, Tsuchida Y, et al. Experience with International Neuroblastoma Staging System and Pathology Classification. Brit J Cancer 2002;86:1110–6.
[29] Brodeur GM, Minturn JE, Ho R, et al. Trk receptor expression and inhibition in neuroblastomas. Clin Cancer Res 2009;15:3244–50.
[30] Park JR, Eggert A, Caron HN. Neuroblastoma: biology, prognosis, and treatment. Pediatric Clin North Am 2008;55:97–120.
[31] Schilling FH, Spix C, Berthold F, et al. Neuroblastoma screening at one year of age. N Engl J Med 2002;346:1047–53.
[32] Ferris MJ, Danish H, Switchenko JM, et al. Favorable local control from consolidative radiation therapy in high-risk neuroblastoma despite gross residual disease, positive margins, or nodal involvement. Int J Radiat Oncol Biol Phys 2017;97:806–12.
[33] Rich BS, McEvoy MP, LaQuaglia MP, et al. Local control, survival, and operative morbidity and mortality after re-resection, and intraoperative radiation therapy for recurrent or persistent primary high-risk neuroblastoma. J Pediatr Surg 2011;46:97–102.