Clinical characteristics and prognosis of 40 patients with periorbital metastasis of neuroblastoma

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Abstract

Background

This study was performed to summarize the clinical characteristics of patients with periorbital metastasis of neuroblastoma (NB) and analyze the short-term prognosis.

Methods

This study included 40 patients with periorbital metastasis of NB from March 2007 to March 2018. The patients' clinical characteristics and short-term prognosis were retrospectively analyzed.

Results

The 40 patients comprised 25 boys and 15 girls with a median age at onset of 31 months (range, 8–132 months). The patients' symptoms included a periorbital mass and eye bruising (n = 37, 92.5%), limb pain (n = 14, 35.0%), a head and neck mass (n = 8, 20.0%), fever (n = 8, 20.0%), an abdominal mass (n = 4, 10.0%), weakness (n = 3, 7.5%), abdominal pain (n = 2, 5.0%), anemia (n = 2, 5.0%), and others (n = 3, 7.5%). All 40 patients had stage IV, high-risk NB. Various auxiliary structures of the eye were involved: ocular muscles (n = 11, 27.5%), lacrimal glands (n = 4, 10.0%), optic nerve (n = 2, 5.0%), and eyelid (n = 1 2.5%). Fifteen patients (37.5%) had tumor invasion in a periorbital sinus cavity. All patients had bone marrow and bone metastasis. Of 38 patients with a known MYCN gene status, 17 patients (44.7%) had MYCN amplification. The median follow-up duration was 19 months (range, 4–144 months). The 5-year event-free survival rate was 6%, and the 5-year overall survival rate was 16%.

Conclusions

Patients with periorbital metastasis of NB often have multi-organ metastases, extremely high rates of MYCN amplification and bone marrow metastasis, and a poor short-term prognosis.

Background

Neuroblastoma (NB) is one of the most common pediatric extracranial solid tumors[1] and has a high rate of malignancy. Most patients have distant metastases at the time of the initial diagnosis. These metastases are most frequently observed in the bone and bone marrow[2, 3], and periorbital soft tissue involvement is more common than in other non-periorbital tumors. Harreld[4] reported that 30% of pediatric patients with NB developed periorbital metastasis over an 18-month period. In the present study, we collected the clinical data of patients with periorbital metastasis of NB admitted to the Hematology-Oncology Center of Beijing Children's Hospital affiliated to Capital Medical University from March 2007 to March 2018. The patients' clinical characteristics were summarized, and the correlations between the MYCN gene status and periorbital metastasis were analyzed.

Methods

Patients

The medical records of patients who were diagnosed with high-risk NB and periorbital metastasis were reviewed. The data collected included sex, age, clinical manifestations, laboratory examination findings (including the concentrations of lactate dehydrogenase [LDH], neuron-specific enolase [NSE], and vanillylmandelic acid [VMA]), N-myc, and chromosome status. Periorbital metastasis was defined as involvement of one or more of the following structures: periorbital bone (ethmoid bone, frontal bone, lacrimal bone, palatal bone, maxilla, sphenoid bone, or zygomatic bone), soft tissue around the orbit, or eyeballs and their auxiliary structures (lacrimal glands, vessels, nerves, intraorbital soft tissue, and eyelid). Each patient with NB was staged according to the International Neuroblastoma Staging System and assigned a risk group according to the International Neuroblastoma Risk Group and the Children's Oncology Group[5, 6].

Treatment

The BCH-HR-NB-2007 protocol was used in all patients and included the following four main components, which lasted about 18 months: (1) induction chemotherapy, (2) local control, (3) consolidation, and (4) maintenance therapy with isotretinoin (13-cis-retinoic acid). Local control treatment included surgical resection, generally after four to six cycles of induction chemotherapy, and external beam radiation to the primary site and other sites of active residual disease. Consolidation therapy included myeloablative chemotherapy, autologous stem cell rescue, and radiation therapy.

Tumor response criteria

The treatment response was evaluated using the International Response Criteria for NB. Briefly, a complete response was defined as no identifiable tumor with a normal catecholamine level. A very good partial response was defined as a reduction of the primary tumor by 90 to 99% with a normal catecholamine level with or without residual 99Tc bone changes. A partial response was defined as a reduction of the primary and metastatic tumors by > 50%. A mixed response was defined as a reduction of any measurable lesion by > 50% with a reduction of any other lesion by < 50%. Stable disease was defined as no new lesion and an increase in any existing lesion by < 25%. Progressive disease was defined as any new lesion or an increase of any measurable lesion by > 25%.

Statistical methods

Event-free survival (EFS) was calculated from the date of diagnosis until the date of relapse, progression, secondary malignancy, or death, whichever occurred first. Overall survival (OS) was calculated from the date of diagnosis until death of any cause. Survival rates and standard errors were estimated using the Kaplan–Meier method. Differences in survival rates between the two groups were compared using the log-rank test. P-values of < 0.05 were considered statistically significant.

Results

General information

A total of 47 patients who were diagnosed with high-risk NB met the study inclusion criteria, but 7 patients discontinued treatment or were transferred to other hospitals. Therefore, 40 patients were involved in the final study and followed up. Their median age at onset was 30.5 months (range, 8–132 months), and their median disease course was 1.5 months (range, 6 days to 8 months). The clinical data of these 40 patients are shown in Table 1.

Table 1
Clinical characteristics of 40 patients with periorbital metastasis of neuroblastoma

Clinical features	Case	Percentage(%)
Gender		
Male	25	62.5
Female	15	37.5
Age		
≤ 18 months	7	17.5
18 months	33	82.5
Accompanied symptom		
Periorbital mass and bruising	37	92.5
Limb pain	14	35
Head and neck mass	8	20
Fever	8	20
Abdominal mass	4	10
Weak	3	7.5
Bellyache	2	5
Anemia	2	5
Others	3	7.5
Primary sites		
Retroperitoneum and adrenal area	37	92.5
Mediastinum	2	5
Skull base	1	2.5
INSS stage: IV	40	100
Risk grouping: High risk	40	40

INSS, International Neuroblastoma Staging System

Periorbital metastasis

Periorbital metastasis includes the orbital bone, surrounding soft tissue, eyeball and its auxiliary structures, and periorbital sinuses. All 40 patients in this study had orbital bone metastasis. Lateral soft tissue metastasis of the orbital bone was present in 38 patients, intraorbital soft tissue metastasis was present in 30, one or more metastases to the eyeballs with involvement of one or more eyeball auxiliary structures were present in 14 patients, and involvement of one or more sinus cavities near the orbit was present in 14 patients (Table 2).

Table 2
Sites of periorbital metastasis of neuroblastoma

Sites	Case	Percentage(%)
Lateral soft tissue of the orbit bone	38	95
Soft tissue of intra-orbit	30	75
Eyeball and its auxiliaries		
Extraocular muscles	11	27.5
Optic nerve	2	5
Eyeball	1	2.5
Eyelid	1	2.5
Sinus adjacent to orbit		
Maxillary sinus	8	20
Ethmoid sinus Frontal sinus Sphenoid sinus	6 2 2	15 5 5

Systemic metastasis

All 40 patients in this study had systemic metastasis. All 40 had bone (besides the orbital bone) and bone marrow metastasis, 13 (32.5%) had distant lymph node metastasis, 11 (27.5%) had dura mater metastasis, 10 (25.0%) had epidural metastasis, 6 (15.0%) had intraspinal metastasis, 3 (7.5%) had brain parenchymal metastasis, 10 (25.0%) had skin and soft tissue (besides the orbital soft tissue) metastasis, 6 (15.0%) had liver metastasis, 2 (5.0%) had pleural metastasis, and 1 (2.5%) had spleen metastasis.

MYCN gene and chromosome

At the initial diagnosis, 38 patients underwent MYCN gene detection and 17 (44.7%) had MYCN amplification. Fourteen patients underwent chromosome G banding detection; among these patients, 4 had a normal karyotype and 10 had chromosomal abnormalities. The structural chromosomal abnormalities mainly involved 1p, 3p, and 1q, and the chromosome number abnormalities mainly involved deletion of chromosomes 11, 21, and 10 and gain of chromosomes 6 and 2.

Biological features

Table 3 lists the patients' characteristics. At the initial diagnosis, the median LDH concentration was 1095 U/L (range, 366–7799 U/L), and the LDH concentration was > 1500 U/L in 35% of the patients. No significant difference was found between the patients with an LDH concentration of > 1500 or < 1500 U/L according to 5-year EFS (χ^2 = 1.159, P = 0. 282) or 5-year OS (χ^2 = 1.156, P = 0. 282). Additionally, the NSE concentration at the initial diagnosis was increased in all 40 patients, and 23 patients had a concentration of > 370 ng/ml. The survival rate was not significantly different between the patients with an NSE concentration of > 370 and < 370 ng/ml according to 5-year EFS (χ^2 = 1.924, P = 0.165) or 5-year OS (χ^2 = 1.392, P = 0. 238). Among all 40 patients, 32 had a urinary VMA concentration higher than the normal range, with a median of 62.6 mg/24 h (range, 18.2–638 mg/24 h).

Table 3. Biological features of the initial tumors of 40 patients with periorbital metastasis of neuroblastoma

	Number (case)	Percentage (%)	EFS	OS
Objective			χ2P	χ2P
LDH(U/L)				
240 ~ 1500	26/40	65.0	1.159 0.282	1.156 0.282
> 1500	14/40	35.0		
NSE(ng/ml)				
16.3 ~ 370	17/40	42.5	1.924 0.165	1.392 0.238
> 370	23/40	57.5		
VMA(mg/24 h Urine)				
> 13.6	32/32	100.0	-	-

EFS, event-free survival; OS, overall survival; LDH, lactate dehydrogenase; NSE, neuron-specific enolase; VMA, vanillylmandelic acid

Reference ranges: LDH, 50–240 U/L; NSE, 0.0–16.3 ng/ml; urinary VMA, 0.0–13.6 mg/24 h urine

Treatment and prognosis

All 40 patients were treated regularly in our department and followed up according to the BCH-NB-2007-HR protocol. Six patients (15%) maintained a complete response. One patient was lost after 5 years of follow-up. The other 33 patients (82.5%) developed tumor progression or recurrence. The median follow-up duration was 19 months (range, 4–144 months). Twenty-three patients (57.7%) exhibited tumor progression during treatment with a median progression time of 9 months (range, 4–18 months). One patient developed bone marrow progression and showed a partial response after additional

chemotherapy. The other 22 patients died during the initial stage of tumor progression. Ten patients developed tumor progression at 3 to 22 months after treatment; five of them died within 3 months with no further treatment, four received further chemotherapy and also died within 3 months, and one maintained a partial response after further treatments such as chemotherapy, radiotherapy, metaiodobenzylguanidine therapy, and chimeric antigen receptor T-cell therapy. The survivorship curve of the 40 patients was analyzed by the Kaplan–Meier method, which showed that the 5-year EFS rate was 6% and 5-year OS rate was 16% (Fig. 1A, B). Affiliations involvement showed no significant difference in the 5-year EFS and OS ($\chi^2 = 0.314$, $P = 0.574$; $\chi^2 = 0.043$, $P = 0.836$). An adjacent sinus cavity lesion was present in 35% of patients. There was no significant difference in the 5-year EFS and OS rates between patients with and without adjacent sinus cavity involvement ($\chi^2 = 0.429$, $P = 0.513$; $\chi^2 = 1.395$, $P = 0.238$). MYCN gene amplification was present in 44.7% of the 38 patients who underwent MYCN gene detection. However, there was no significant difference in the 5-year EFS and OS rates between patients with and without MYCN amplification ($\chi^2 = 0.147$, $P = 0.702$; $\chi^2 = 11.328$, $P = 0.532$).

Discussion

NB is an embryonal tumor that originates from neural crest cells and accounts for 7–8% of all pediatric tumors and 15% of deaths caused by pediatric malignancies[7]. The peak age of NB is 2 to 4 years, and > 80% of children are diagnosed at > 5 years of age[8]. The median age of the 40 patients in our study was 30.5 months, and only 1 patient was older than 10 years; this is similar to previous studies.

As reported by Kieuhoa[9], the primary tumor site was in the posterior mediastinum in about 15% of patients with NB, and this site was associated with a better prognosis. In our study, the primary tumor site was in the posterior mediastinum in only 5% of patients, which might have influenced the poor prognosis. The primary tumor was in the retroperitoneal and adrenal areas in 92.5% of patients, which was related to the fact that most patients in our study had stage IV tumors according to the International Neuroblastoma Staging System.

Additionally, 92.5% of the patients in our study were diagnosed with an orbital mass and bruising in the initial stage of the disease. Therefore, 65.0% (26/40) of the children were initially treated in an ophthalmology clinic. One of the patients presented with periorbital bruising at the beginning of the disease course, and after 2 weeks of local treatment with eye drops in the ophthalmology clinic, the periorbital bruising was aggravated. A head computed tomography (CT) examination subsequently revealed a periorbital mass, and the patient was then sent to the oncology department. Another patient was also diagnosed in an ophthalmology clinic. This patient had swelling and ecchymosis of the eyes and was suspected to have kidney disease; however, NB was diagnosed in the oncology department after a head CT examination revealed a periorbital mass. A third patient with a right periorbital mass underwent biopsy in an ophthalmology clinic, and the pathological diagnosis was NB. The remaining children with both a periorbital mass and ecchymosis were diagnosed and treated in the hematology department after a CT or magnetic resonance imaging examination. Therefore, the possibility of NB

should be considered in children with a periorbital mass and bruising. Imaging examinations including CT, magnetic resonance imaging, ultrasound, positron emission tomography/CT are required to achieve a diagnosis of head and facial soft tissue metastasis.

Approximately 60% of NB can reportedly metastasize to the bone, bone marrow, lymph nodes, and liver. Among these sites, bone marrow and bone metastases are most frequently observed (about 70.5% and 55.7% of cases, respectively), and all sites are strongly associated with a poor prognosis[10]. In the present study, all patients had three or more sites of metastasis. Periorbital metastasis is one component of multiple metastases throughout the body. All patients in this study had bone and bone marrow metastasis. Based on the above findings, infiltration of local soft tissue through bone marrow and bone metastasis is believed to be a route of tumor cell metastasis to the head and facial soft tissue. Harreld[4] reported that 30% of children with NB older than 18 months with distant metastasis had periorbital bone and soft tissue metastasis; among them, children with manifestations of soft tissue metastasis such as periorbital bruising had a worse prognosis. Children with central nervous system and intracranial metastases of NB also had a poor prognosis, showing a high mortality rate. Single-center data from another study showed that among patients with NB, about 1.9% had central nervous system metastasis and 14.0% had intracranial metastasis[11]. In the present study, about 22.5% of patients had central nervous system metastasis (including brain parenchymal and spinal metastasis), and the rate of intracranial metastasis was as high as 60%. Therefore, the high rate of intracranial metastasis was another factor related to the poor prognosis in this study.

In recent years, research has showed that the MYCN gene is an indicator of NB with aggressive progression and a poor prognosis[12, 13]. Wang[14] reported that 12% of children with NB had MYCN amplification. The MYCN amplification rate of the patients treated in our center during the same period was 16.0%[15], while the rate in our study cohort was 44.7%. Therefore, the children in our study showed an extremely poor prognosis. We found no significant difference in the survival rate between the children with and without MYCN amplification in this study, which was probably due to the concurrence of multiple poor prognostic factors including the high rate of bone and marrow metastasis, high rate of intracranial metastasis, and high serum levels of tumor factors, resulting an overall poor prognosis. Many tumor suppressor genes are present in chromosome 1p, and changes in the regulatory sequence or coding of the gene or complete deletion of the gene will lead to loss of the cell's anti-cancer effect, which will also lead to the progression of tumor cells[16]. Some investigations have suggested that chromosomal structural abnormalities in the 1p and 17q regions are closely related to the MYCN gene status[17].

LDH is an enzyme that plays an important role in glycolysis and can be used as an indicator of the systemic tumor burden. NSE is also an enzyme takes part in the glycolysis process; it exists in neurons and nerve-derived cells and is a highly specific and sensitive indicator of NB[18]. An LDH concentration of > 1000 U/L and NSE concentration of > 100 ng/ml are poor prognostic factors[19]. In the present study, 35% of children had an LDH concentration of > 1500 U/L, while 57.5% of children had an NSE

concentration of > 370 ng/ml (detection maximum), indicating a poor prognosis. NB originates from neural crest or primitive nerve cells that synthesize and secrete catecholamines. The catecholamine metabolite VMA in urine is a specific tumor index that can be used as an important diagnostic clue[20]. In the initial stage, all children in the present study exhibited an increased level of urine VMA. Thus, the children with orbital metastasis of NB had a large tumor load and adverse factors resulting in a poor prognosis.

In this study, 40 children were treated, evaluated, and followed up based on the BCH-NB-2007-HR protocol. Other single-center analyses showed that the 5-year EFS of NB was 64.3%[21] and the 5-year EFS of NB with bone marrow metastasis was 36.1%[22]; in the present study, however, the 5-year EFS of NB with periorbital metastasis was only 6% and the 5-year OS was only 16%. Therefore, NB with periorbital metastasis is characterized by aggressive progression, early death after progression, a low retreatment response rate, and an extremely low survival rate.

Conclusion

This research shows that patients with periorbital metastasis of NB often have extensive systemic metastasis. Most patients have bone and bone marrow metastasis, with an extremely high rate of central nervous system and intracranial metastasis. The MYCN amplification rate is high and the serum levels of tumor biological factors in the early are high. Moreover, the survival rate of children with periorbital metastasis of high-risk NB is significantly lower than other NB patients. Therefore, patients with periorbital metastasis of NB are at high risk of death and have a poor prognosis. To improve the survival rate, it is necessary to find out the further biological characteristics and strengthen the efficacy of local treatment combined with systemic treatment.

Abbreviations

NB: neuroblastoma; LDH: dehydrogenase ; NSE: neuron-specific enolase ; VMA: vanillylmandelic acid; BCH-NB-2007-HR protocol: Beijing children's hospital neuroblastoma-2007-high-risk protocol; EFS: event-free survival; OS:overall survival; INSS, International Neuroblastoma Staging System;

Declarations

Ethics approval and consent to participate: This research and the BCH-NB-2007 protocol were approved by the Beijing Children's Hospital Institutional Ethics Committee. Informed consent was obtained from the parents or guardians of each patient according to the Declaration of Helsinki.

Consent for publication: Not applicable

Availability of data and materials: On an aggregated level, the BCH hematology-oncology center may share aggregated data upon reasonable request. The manual for the intervention is free to use for any

other research team after information and education from the BCH hematology-oncology center research team.

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References

1. Louis CU, Shohet JM. Neuroblastoma: molecular pathogenesis and therapy. Annu Rev 2015;66:49-63.
2. Wezel E M V, Decarolis B, Stutterheim J, et al. Neuroblastoma messenger RNA is frequently detected in bone marrow at diagnosis of localised neuroblastoma patients[J]. European Journal of Cancer, 2016, 54:149.
3. Burchill S A, Beiske K, Shimada H, et al. Recommendations for the standardization of bone marrow disease assessment and reporting in children with neuroblastoma on behalf of the International Neuroblastoma Response Criteria Bone Marrow Working Group[J]. Cancer, 2017, 123(7):1095.
4. Harreld J H, Bratton E M, Federico S M, et al. Orbital Metastasis Is Associated With Decreased Survival in Stage M Neuroblastoma.[J]. Pediatric Blood & Cancer, 2015, 63(4):627-633.
5. Sidhu SK,Ramalingam K,Goyal S;Poonia M, et al. Comparing the Efficacy of Leishman-Giemsa Cocktail Stain, Giemsa Stain, and Papanicolaou Stain in Potentially Malignant Oral Lesions: A Study on 540 Cytological Samples. [J] JCytol.2018.Ape-Jun;35(2):105-109.DOI:10.4103/joc.joc-249-16
6. Kuldeep Singh, Shalija Kotwal. Importance of image guided fine needle aspiration in diagnosis of benign and malignant lesions. [J]. Int J Res Med Sci. 2016 Feb;4(2):512-518
7. Maris J.M. Recent advances in neuroblastoma . N. Engl. J. Med.2010362: 2202–2211.
8. Panagopoulou P, Georgakis M K, Baka M, et al. Persisting inequalities in survival patterns of childhood neuroblastoma in Southern and Eastern Europe and the effect of socio-economic development compared with those of the US[J]. European Journal of Cancer, 2018, 96:44-53.
9. Vo K T, Matthay K K, Neuhaus J, et al. Clinical, Biologic, and Prognostic Differences on the Basis of Primary Tumor Site in Neuroblastoma: A Report From the International Neuroblastoma Risk Group Project[J]. Journal of Clinical Oncology, 2014, 32(28): 3169-3176.

10. Morandi F, Corrias M V, Pistoia V. Evaluation of bone marrow as a metastatic site of human neuroblastoma.[J]. Ann N Y Acad Sci, 2015, 1335(1):23-31.
11. Mei J, Dawei Z, Wen Z, et al. Clinical characteristics and prognosis of 42 patients with high-risk neuroblastoma with central nervous system and intracranial invasion, Shandong Medical Journal 2016 56(20)38-40.
12. Corredor J C, Nicole R, Karen B, et al. N-Myc expression enhances the oncolytic effects of vesicular stomatitis virus in human neuroblastoma cells:[J]. Molecular Therapy Oncolytics, 2016, 3(C):16005.
13. Brockmann M, Poon E, Berry T, et al. Small Molecule Inhibitors of Aurora-A Induce Proteasomal Degradation of N-Myc in Childhood Neuroblastoma[J]. Cancer Cell, 2013, 24(1):75-89.
14. Pei W, Dandan G Pin Y ,et al. Copy number variations and its clinical significance of N-MYC gene in children with neuroblastic tumors, 2017(11):2339-2344.
15. Yue Z X Huang C Gao C et al. MYCN amplification predicts poor prognosis based on interphase fluorescence in situ hybridization analysis of bone marrow cells in bone marrow metastases of neuroblastoma. Cancer Cell International 2017 17 (1)
16. Schramm A, Koster J , Assenov Y,et al.Mutational dynamics between primary and relapse neuroblastomas.[J].Nat Genet,2015,47(8):872-877.DOI:10.1038/ng.3349.
17. Ho N ,Peng H , Mayoh C,Liu PY, et al. Delineation of the frequency and boundary of chromosomal copy number variations in paediatric neuroblastoma.[J].Cell Cycle .2018 .17.6,749-758,DOI:1080/15384101.2017.1421875
18. Abbasoglu A, Sarialioglu F, Yazici N, et al. Serum neuron-specific enolase levels in preterm and term newborns and in infants 1-3 months of age.[J]. Pediatrics & Neonatology, 2015, 6(2):114-119.
19. Tomasik T Risk factors of hearing impairment in premature infants [J] Przegl Lek 2008,65 9 375-384
20. Clark Z D, Cutler J M, Pavlov I Y, et al. Simple dilute-and-shoot method for urinary vanillylmandelic acid and homovanillic acid by liquid chromatography tandem mass pectrometry[J]. Clinica Chimica Acta, 2017, 468:201-208.
21. Xiaoli M, Mei J, Dawei Z, et al. Clinical features and recent treatment effect analysis of 91 neuroblastoma patients with multidisciplinary treatment. J Appl Clin Pediatr. 2013;28:178–82.
22. Hongjun F, Cheng H, Yan S, et al. Clinical characteristics and prognosis of high-risk neuroblastoma with bone marrow metastasis in children. Chin J Pediatr,2019, 57 863-869

Figures

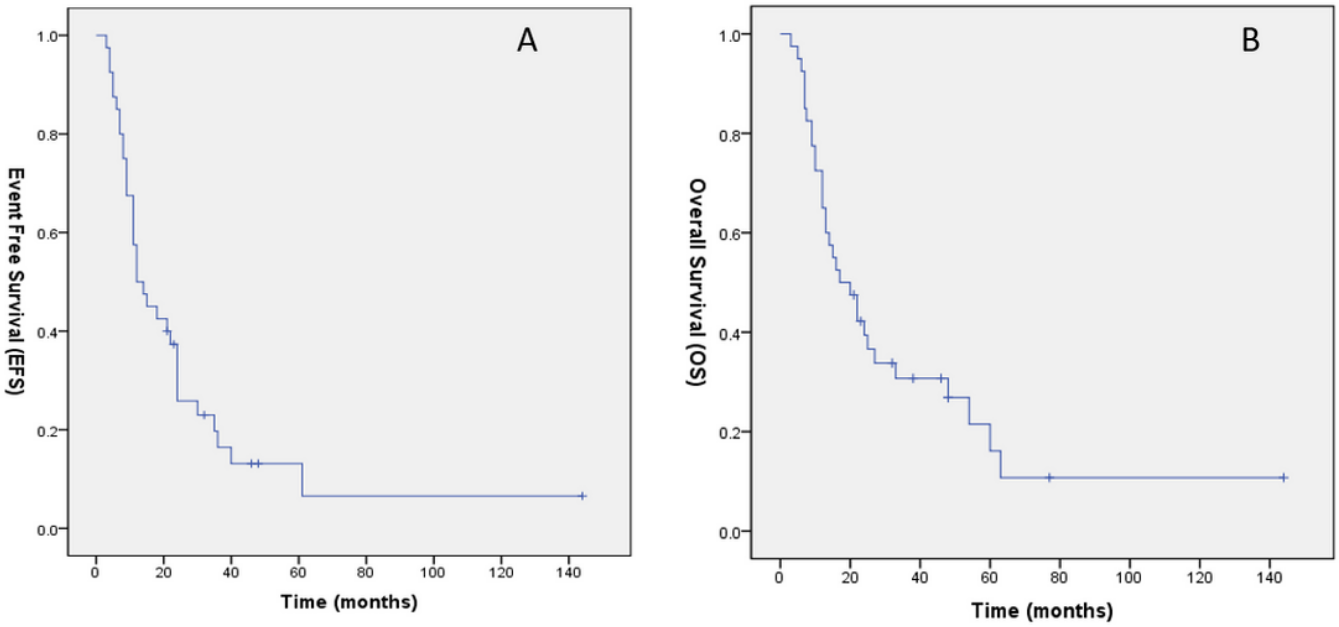

Figure 1

Survival rates of the 40 patients with periorbital metastasis of NB. (A) Event-free survival rate. (B) Overall survival rate.