Original Article

Neuroblastic Tumours in Children: Outcome from a Referral Centre in India

Basant Kumar, Rajanikant Yadav[1], Vijai D Upadhyaya, Ashwani Mishra, Yousuf, Prabhakar Mishra[2], Punita Lal[3]

Departments of Pediatric Surgical Superspecialties, [1]Radiodiagnosis, [2]Biostatics and [3]Radiotherapy, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Abstract

Background: There is a paucity of uniform literature on the outcome of children with neuroblastic tumours from developing countries. This study aims to present the outcome in children having neuroblastic tumours. **Materials and Methods:** We retrospectively reviewed patients with neuroblastic tumours from January 2014 to March 2020. Data analysed were pertaining to the age, sex, presentation, site, stage, diagnostic evaluation performed, management and follow-up results, etc., The final outcomes were assessed as complete response; partial response (PR); no response (NR) and progressive disease. International Neuroblastoma Risk Group staging was used and patients were categorised on the basis of age, site and stage of tumour. Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up and event for OS was death. **Results:** Forty-seven patients were included with median age of 60 months (ranges of 2–180; mean = 61.87 ± 47.56). About 72.3% (n = 34) patients were males. Out of total, 6.4% (n = 3), 53.2% (n = 25) and 38.3% (n = 18) were in stage L1, L2 and M, respectively, whereas 2.1% (n = 1) patients were in stage MS. Surgery was performed in 25 (53.19%) patients, but gross total excision was achieved in 48.90% (n = 23) patients. Onlu 10.60% (n = 5) patients were referred, whereas 14.89% (n = 7) patients reported recurrences. Mean and median follow-up time of the patients was 24.64 ± 16.04 and 18 months (range: 3–60 months). Out of total, 53.2% (n = 25) and 29.8% (n = 14) patients had complete and PRs, respectively, whereas 17% (n = 8) patients had NR. Out of the total 47 patients, 8 (17%) achieved events (deaths), whereas the rest, 39 (83%) patients, were censored. Mean event-free OS time was 50.04 months. **Conclusion:** There was a significant difference in patient deaths in recurrence and non-recurred patients (4/7, 57.1% vs. 4/40/, 10%, P = 0.011). Survival time was significantly higher in patients with stages L1-L2 as compared to Stage 4. Stage and age were found predictors of survival.

Keywords: Gross total resection, neuroblastic tumours, neuroblastoma, survival, treatment

Introduction

Neuroblastic tumours are heterogeneous group of embryonic tumours derived from neural crest cells. It represents a spectrum of disease from undifferentiated, aggressive to differentiated and largely quiescent tumours.[1] Malignant peripheral neuroblastic tumours (PNTs), account for the most of PNTs, with nearly 50% of patients have a high risk phenotype. It is characterised by widespread disease dissemination and poor long-term survival. PNTs are responsible for 12% of deaths associated with cancer in children younger than 15 years of age.[1,2] Forty-eight per cent of patients have metastatic disease at the time of diagnosis.[2,3] Some tumours undergo spontaneous involution without any therapy, while others progress with a fatal outcome despite the implementation of maximal modern therapy.[4,5] Although the probability of survival for children with neuroblastoma has improved over time, even in the best-published literature, results do not parallel with those obtained for some other childhood malignancies such as Wilms tumours and germ cell tumours.[4,5]

There is a paucity of literature on the outcome of children with neuroblastic tumours from a developing country like India and also the available literature is not uniform.[5-11] Lack of awareness, illiteracy, low socioeconomic status and relatively

Received: 09-10-2021 **Revised:** 06-03-2022 **Accepted:** 16-03-2022 **Available Online:** 31-01-2023

Access this article online

Quick Response Code:

Website: www.afrjpaedsurg.org

DOI: 10.4103/ajps.ajps_152_21

Address for correspondence: Dr. Basant Kumar, Department of Pediatric Surgical Superspecialties, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raibareli Road, Lucknow - 226 014, Uttar Pradesh, India.
E-mail: drbkg75@rediff.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Kumar B, Yadav R, Upadhyaya VD, Mishra A, Yousuf, Mishra P, *et al*. Neuroblastic tumours in children: Outcome from a referral centre in India. Afr J Paediatr Surg 2023;20:34-9.

less referral centres are associated with late presentation, poor outcome and high dropout rate.[5-11] The aim of this study is to present our experience with neuroblastic tumours and their outcome in the patients treated at our centre.

Materials and Methods

We retrospectively reviewed the electronic hospital records including operation theatre and follow-up records from January 2014 to March 2020 of all patients with neuroblastic tumours treated in our department. Data analysed were pertaining to the age, sex, clinical presentation, site, stage, diagnostic evaluation performed, management (surgery/chemotherapy/radiotherapy), post-operative problems and follow-up results. Patients with adequate data were included in the study. Diagnoses were made either on the basis of histopathological examination of the tumour tissues taken through biopsy (open/trucut) or by fine-needle aspiration samples with or without immunohistochemistry or by the results of bone marrow examinations (aspirates and/or trephines) combined with elevated levels of urinary vanillylmandelic acid (VMA) and/or homovanillic acid (HVA). All patients were evaluated by contrast enhanced computed tomography (CT) scan, skeletal survey, bone scans along with complete haematology, liver and renal function tests, serum ferritin, serum lactate dehydrogenase, coagulation profile, etc., I^{131} MIBG scan and DOTONAC PET CT-scan were performed in patients depending on availability of radioisotopes (dye) at that time in our institute and financial condition of patients. MYCN evaluation was not available at our centre.

Inclusion criteria

All patients with diagnosis of Neuroblastic tumours who were treated in our institute from January 2014 to March 2020 and received at least three cycle of chemotherapy were included in the study.

Exclusion criteria

Patients with inadequate records or those who discontinued treatment before receiving <3 cycle of chemotherapy or died before diagnosis were excluded from the study.

Patients were categorised on the basis of 'age of the patients (<12 months and >12 months); 'sites' of the tumour (abdominal [adrenal, non-adrenal, pelvic] and extra-abdominal [thoracic, thoraco-abdominal, cervical, cervico-thoracic]) and 'stage' of the tumour as described by International Neuroblastoma Risk Group (INRG).[12] Treatment varied on the basis of clinical presentation and stage of the disease. All patients having Stage L-1 were primarily operated, while Stage L-2, M and MS patients were received neoadjuvant chemotherapy [Tables 1 and 2] followed by surgery when possible. Radiotherapy (15–35 Gy) to the primary site was given as per the clinical scenario. Surgical resection was attempted only when radiological findings suggested resectability without image-defined risk factors (IDRFs) either upfront or following week 17 of chemotherapy [Figure 1]. During surgery, resection of tumour was tried as complete as possible, but it was not possible in many patients. In such cases, Gross Total Resection (GTR) was performed which was defined as removal of more than 90% of tumour mass. Children with no response (NR) or progressive disease (PD) were referred to higher centres or for palliative care. MIBG therapy was offered only for progressive or relapsed PD as palliation. Myeloablative therapy and autologous stem cell transplantation (ASCT) facility is not available in our institute.

The final outcomes were assessed as Complete Response (CR); Partial Response (PR); NR and PD according to international criteria for response to treatment.[13] CR was defined as absence of tumour at the primary and metastatic sites as confirmed by radiological studies with or without histopathology of the resected specimen. Overall survival (OS) was calculated from the date of diagnosis to date of last follow-up and event for OS was death.

Statistical analysis

Continuous variables were presented in mean ± standard deviation and median (range). Categorical variables were presented in frequency (%). Test of the association between recurrences and mortality was assessed by Fisher's exact test. Kaplan–Meier method was used to estimate the mean and median survival time with a corresponding 95% confidence interval. Log-rank test was used to compare the survival time between stages. Cox proportional hazard model was used to identify the predictors of the survival time in univariate analysis and the variables with $P < 0.2$ (modified cut-off value) used to include the variables from univariate to multivariate analysis to find out the independent predictors of the survival time. $P < 0.05$ was considered as statistically significant. Data were analysed using the Statistical Package for the Social Sciences, version-23 (SPSS-23, IBM, Chicago, Illinois, USA).

Results

In the study, 47 patients were included with mean and median age of 61.87 ± 47.56 months and 60 months (range of 2–180 months). About 72.3% ($n = 34$) of patients were males. Out of total, 6.4% ($n = 3$), 53.2% ($n = 25$) and 38.3% ($n = 18$) patients were in Stage L-1, L-2 and 4, respectively, whereas 2.1% ($n = 1$) patient was in Stage MS [Tables 1 and 2]. Most common presentation was fever (>80%) followed by lump/pain/discomfort (>69%), bone pain (>30%), lower limb paresis (>6%), diarrhoea (>2%) and proptosis (>2%). Chemotherapy was given to all patients with malignant histology according to the risk group [Figure 1]. Out of total 47 patients, surgery was performed in 53.19% ($n = 25$), but gross total excision (GTR) was achieved in only 48.94% (23) patients. Only biopsy could be done in 4.26% (2) patients. Only 3 (6.38%) patients showed matured histology. Only 10.6% ($n = 5$) of patients were referred to other higher centres based on the parent/patient request during their course of chemotherapy. Only 17% ($n = 8$) patients died during the course of follow-up (event), whereas 14.9% ($n = 7$) of patients reported recurrences. There were significant differences in patients' deaths in recurrence and non-recurred cases (4/7, 57.1% vs.

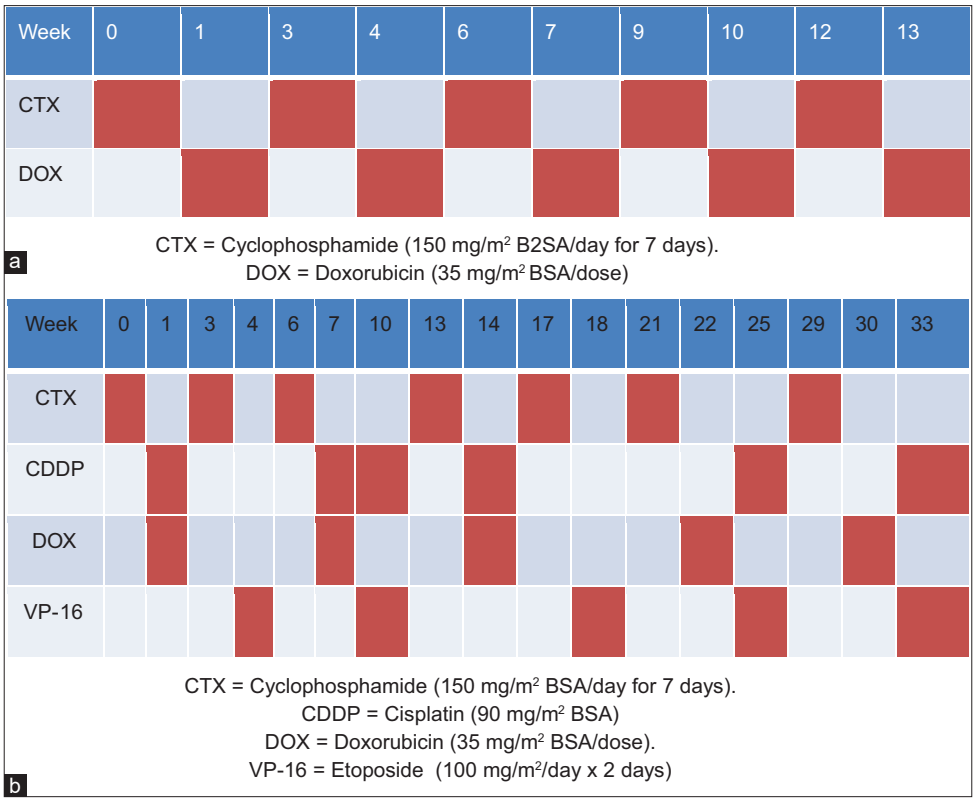


Figure 1: (a) Chemotherapy Regime for 'Low Risk' Patients. (b) Chemotherapy Regime for 'High Risk' patients

4/40/, 10%, $P = 0.011$). Mean ± SD and median follow-up time of the patients were 24.64 ± 16.04 and 18 months (range: 3-60 months). Out of total 47 patients, 53.2% ($n = 25$) of patients showed CR, 29.8% ($n = 14$) of patients had PR, whereas 17% ($n = 8$) had NR or had PD [Figure 2].

Kaplan–Meier method was used to compute the mean and median event (death)-free survival time of the treated patients. Out of the total 47 patients, 8 (17.39%) achieved events (deaths), whereas rests 39 (82.61%) were censored. Results showed that the overall mean event-free OS time was 50.04 months [Table 3]. Survival time was significantly higher in patients with Stages L1-L2 as compared to Stage M (58.36 months vs. 16.58 months, $P < 0.001$) [Table 4]. Twenty-seven (58.69%) patients are still alive and under regular follow-up, but five patients have active disease.

In this cohort, out of the available patients` demographic characteristics (age and gender) and clinical findings (stages, type of interventions), age ($P = 0.047$) and stage ($P = 0.003$) were found as statistically significant, whereas gender ($P = 0.114$) and site ($P = 0.700$) of tumour were statistically insignificant (each $P > 0.05$) for OS. In multivariate analysis, both the significant variables have been included. Results showed that only stage was statistically significant ($P = 0.008$) and independent predictor of the mortality after adjusting age that was not statistically significant ($P = 0.381$). There was an insignificant difference in survival probability of the cancer patients between Stages L-1 and L-2, and the result was found to be statistically insignificant [Table 3 and Figure 3].

Table 1: Patients' profile ($n = 47$)

Patient category	Cases, *n* (%)
Gender	
Male	34 (72.34)
Female	13 (27.66)
Age of diagnosis (months)	
<12	7 (14.89)
>12	40 (85.11)
Site of primary tumour	
Abdominal	39 (82.98)
Adrenal	25 (53.19)
Para spinal	12 (25.53)
Pelvic	2 (4.26)
Extra-abdominal	8 (17.02)
Cervical	1 (2.13)
Thoracic	4 (8.51)
Thoraco-abdominal	3 (6.38)
Stage	
L1	3 (6.38)
L2	25 (53.19)
M	18 (38.30)
MS	1 (2.13)
Surgery	25 (53.20)
Gross total resection	23 (48.94)
Biopsy only	2 (4.26)
Histopathology	
Ganglioneuroma	3 (6.38)
Ganglioneuroblastoma	8 (17.02)
Neuroblastoma	36 (76.60)

Table 2: Tumour stage according to age and sites

Stage	Age		Site	
	≤12 months, *n* (%)	>12 months, *n* (%)	Abdominal, *n* (%)	Extra-abdominal, *n* (%)
L1	0	3 (6.38)	2 (4.26)	1 (2.13)
L2	4 (8.51)	21 (44.68)	19 (40.43)	6 (12.77)
M	2 (4.26)	16 (34.04)	17 (36.17)	1 (2.13)
MS	1 (2.13)	0	1 (2.13)	0
Total	7 (14.89)	40 (85.11)	39 (82.98)	8 (17.02)

Table 3: Predictors of the survival (*n*=47)

Predictors of the survival of the cancer patients (*n*=47)						
Variable's	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	5.09	1.02-25.39	0.047	2.11	0.40-11.33	0.381
Sex	3.08	0.76-12.40	0.114	-	-	-
Stages	30.89	3.27-291.79	0.003	22.37	2.23-224.68	0.008
Sites	1.51	0.19-12.27	0.700	-	-	-

Cox proportional hazard model, $P<0.05$ significant. HR: Hazard ratio, CI: Confidence interval

Table 4: Event (death) free survival time (*n*=47)

Event (death)-free survival time of the cancer patients (*n*=47)					
Stage	Mean		Median		*P*
	Value	95% CI	Value	95% CI	
L1-L2	58.36	55.23-61.50			<0.001
M	16.58	12.58-20.60	18.00	10.69-25.30	
Total	50.04	43.80-56.28			

Kaplan-Meier method with log-rank test used. Median survival time was not available when patients did not have survival time below 50%. $P<0.05$ significant. CI: Confidence interval

Discussion

Neuroblastic tumours are different in its various clinical and biological characteristics, and prognosis mostly depends on genetic and molecular markers. Results of treating these tumours improved over time, and survival rate increased from <25% to 96%.[4-11,14-17] Our data also confirm this improving trend in India, in spite of lack of resources and unavailability of facilities of genetic and molecular markers detection. In current practice, the treatment of malignant PNTs depends on 'risk groups'. This risk group is determined by various factors including patient age, tumour stage, presence or absence of IDRF, histopathological appearance and molecular biological factors.[4,18,19]

The standard stratification of patients into risk group as defined by INRG classification could not be done in this cohort, but we modified it according to our availability of resources. In absence of molecular biological markers, we categorised the risk group on the basis of patient age, tumour stage, presence or absence of IDRF, histopathology, serum markers (serum lactate dehydrogenase and serum ferritin) and urinary VMA and HVA and its ratio. Children above 12 month with Stage L-2, Stage M and having high serum LDH/ferritin level and high HVA/VMA ratio were considered as high risk.

In this study, the median age of diagnosis was 60 months that is quite more as compared with previous studies.[5,16,20] Cooperative group studies of POG and CCG[20] from 1986 to 2001 showed a median age at diagnosis of about 19 months, while a study from India[5] having 144 cases showed the median age at diagnosis of 36 months. The late presentation in developing countries like ours is related with poor healthcare facilities in rural areas, illiteracy, low socioeconomic status and lack of awareness about childhood malignancies among population and primary healthcare workers resulting in late referral. Only 14.89% (7) of patients were presented before age of 1 year in this cohort.

Univariate analysis showed that the age at which the diagnosis was made had a significant impact on OS (P = 0.047; hazard ratio [HR] 5.09; 95% confidence interval [CI] 1.02–25.39), while in multivariate analysis, age at diagnosis did not show any significant difference on OS. In this cohort, only 27.66% (13) of patients were female. A preponderance of male sex (2.6:1) in the study is related with gender bias in our society and we also observed about comparative more dropouts in female children during treatment because of it. This male sex predominant was similar with previous study from India[5,7,10] but higher than the observations from European population-based registry.[21] In this study, gender did not show any significant difference on OS (P = 0.114; HR: 3.08; 95% CI: 0.76–12.40).

Location of most of the tumours in this cohort was abdominal (82.98%; 39) and adrenal gland constituted 53.19% (25) of all tumours. Previous studies also reported the similar frequency of adrenal site.[5,16,17] Worst prognosis reported in tumours arises primarily from abdominal sympathetic chain site followed by the adrenal gland as primary site.[5,22] Massad, *et al*.[23] reported that the site of the primary

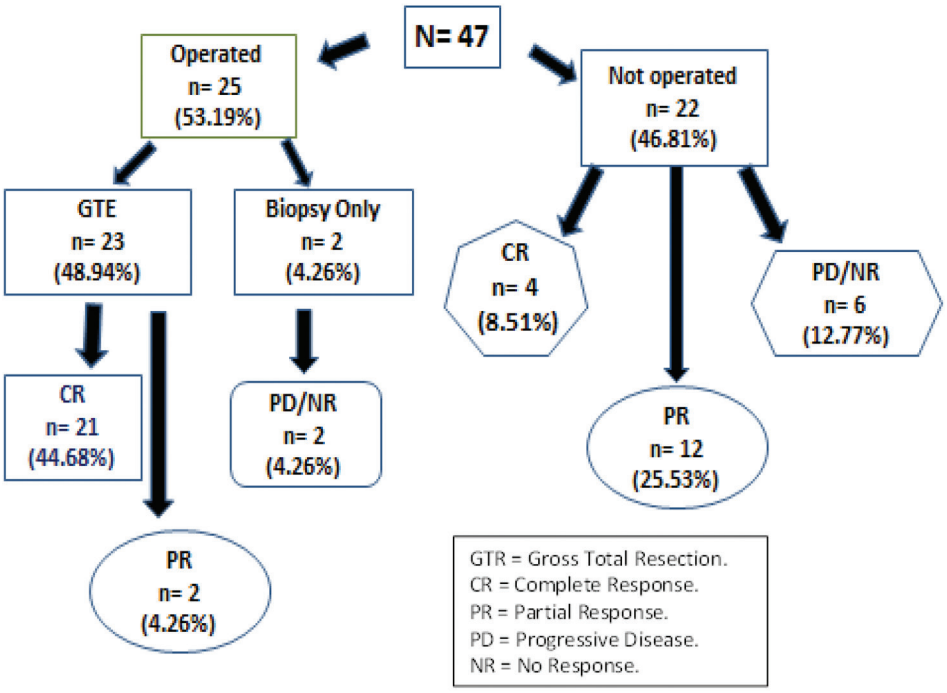


Figure 2: Overall outcome

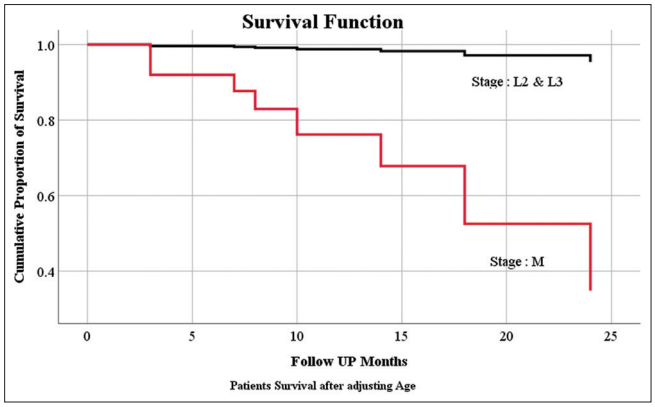


Figure 3: Event (death) survival time curve of patients after adjustment of age

tumour as an independent significant factor affecting OS in children with neuroblastoma, but in our study, we could not found the site of the tumour as a significant factor affecting OS (P = 0.700; HR: 1.51; 95% CI 0.19–12.27). We also observed that the presentation of extra-abdominal tumours was relatively early because of early symptoms due to tumour mass.

Most of the patients presented with locally advanced disease (Stage L-2; 53.19%) followed by disease with metastasis (Stage M; 38.30%). Only 3 (6.38%) patients had Stage L-1 disease, while stage MS was found in only one (2.13%) patient in this cohort. Presentation with advanced diseases (Stage L-2 and M) constitutes >91% of cases in this series. Delayed presentation is related with late referral, lack of awareness (delayed visit to healthcare facilities) and low socio-economic conditions. Similar advanced stage diseases at the time of diagnosis are reported in various studies from India, Malaysia, Turkey and Hong Kong which ranged from 70% to 88% of cases.[5,6,10,16,21,24-27] Both univariate and multivariate analyses of data showed stage of tumour as a significant predictor on OS ([univariate – P = 0.003; HR: 30.89; 95% CI: 3.27–291.79]; [multivariate – P = 0.008; HR: 22.37; 95% CI: 2.23–224.68]). This study also confirms the relationship of stage of tumour to prognosis of the disease as confirmed by various previous studies.[4-6,10]

Chemotherapy is quite effective in malignant PNTs and CRs were shown in metastatic disease. Low-risk patients received three-weekly courses of cyclophosphamide and doxorubicin for 5 weeks, while high-risk patients received cyclophosphamide, doxorubicin, cisplatin and etoposide [Figure 1]. Only by use of chemotherapy in non-operated group of patients, CR was achieved in 8.51% (4) of patients, while PR was found in 25.53% (12) of patients. Severe immunosuppression required prolonged hospitalisation observed in 11.36% (5; n = 44) of patients.

In this study, 17.39% (8) of patients achieved events (death), whereas the rest, 82.61% (39) patients, were censored. Survival rate was found 58.69%, with a mean event-free survival time of 50.04 months. Largest series of 144 children with neuroblastoma from India by Agarwala *et al*.[5] reported 3-year OS of 60.7%. Qureshi *et al*.[11] reported 4-year OS of 91.5% in 54 children with neuroblastoma, but this study includes only intermediate-risk patients. Other studies by Kusumakumari *et al*.[6,7] (survival rate: 27% for Stage 3 and 9% for Stage 4) and Bansal *et al*.[10] reported very poor outcome in children with advanced disease. More than 90% patients in our study had advanced disease (stage L2 and M), and in spite of limited resources, our results are

fairly comparable with these studies. Our data also confirm that OS s in stage-M are still significantly less (16.58 months) than other stages. Even in developed countries, reported OS is approximately 40% in high-risk patients (>18 months, Stage III, IV or any stage with MYCN amplification).[4]

This study has certain limitations because of its retrospective nature. There might be selection bias due to irregular follow-up of patients. Many times we had telephonic conversation with patients/parent only for follow-up because of their remote location. We do not have genetic and molecular markers evaluation facilities at our centre for correct categorisation of risk group according INRG. Furthermore, we do not have facility of immunotherapy/myeloablative therapy with ASCT, and all patients with advanced stage and progressive/non-responsive disease need to referral at higher centres having these facilities. These referred patients usually lost during follow-up. We have facility of MIBG therapy from the past 1 year, but it is used only for palliation.

Conclusion

PNTs are biological tumours and prognosis depends on various factors. Our study showed stage of tumour and age of patient at diagnosis; both are significant predictors of survival [Table 3], whereas gender ($P = 0.114$) of patient and site ($P = 0.700$) of tumour were statistically insignificant (each $P > 0.05$) for OS. Mean survival time was significantly higher in patients with Stage L-1, L-2 as compared to Stage M (58.36 months, 95% CI: 55.23–61.50 vs. 16.58 months, 95% CI: 12.58–20.60). There was a significant difference in patients` death in recurrence and non-recurred cases (4/7, 57.1% vs. 4/40, 10%; $P = 0.011$). Scheduled chemotherapy is quite effective in malignant neuroblastic tumour. High mortality and large dropout rate is related with delayed referral, late presentation, advanced disease, lack of awareness and low socio-economic status.

Acknowledgement

The authors would like to thank all residents, staffs, patients and parents for their help and cooperation during the management of these patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Shimada H, Ambros IM, Dehner LP, Hata J, Joshi VV, Roald B. Terminology and morphologic criteria of neuroblastic tumors: Recommendations by the International Neuroblastoma Pathology Committee. Cancer 1999;86:349-63.
2. Yang S, Cai S, Ma X, Zeng Q, Qin H, Han W, *et al.* Discrimination of histopathologic types of childhood peripheral neuroblastic tumors based on clinical and biological factors. Sci Rep 2018;8:10924.
3. Irwin MS, Park JR. Neuroblastoma: Paradigm for precision medicine. Pediatr Clin North Am 2015;62:225-56.
4. Parikh NS, Howard SC, Chantada G, Israels T, Khattab M, Alcasabas P, *et al.* SIOP-PODC adapted risk stratification and treatment guidelines: Recommendations for neuroblastoma in low- and middle-income settings. Pediatr Blood Cancer 2015;62:1305-16.
5. Agarwala S, Mandelia A, Bakhshi S, Srinivas M, Bajpai M, Gupta AK, *et al.* Neuroblastoma: Outcome over a 14 year period from a tertiary care referral centre in India. J Pediatr Surg 2014;49:1280-5.
6. Kusumakumary P, Ajithkumar TV, Ratheesan K, Chellam VG, Nair MK. Pattern and outcome of neuroblastoma. A 10 year study. Indian Pediatr 1998;35:223-9.
7. Kusumakumari P, Ajithkumar TV, Hariharan S, Varma RR, Chellam VG, Nair R, *et al.* Intensive chemotherapy in children with stage IV neuroblastoma. Indian J Pediatr 1999;66:867-72.
8. Rao SR, Iyer RS, Nair CN, Kurkure PA, Pai SK, Advani SH. Infantile neuroblastoma: 10 year TMH experience. Indian J Cancer 1993;30:85-7.
9. Biswas G, Kurkure P, Banavali S, Achrekar S, Kulkarni P, Bhagwat R, *et al*. Challenges in management of advanced neuroblastoma: Experience at Tata Memorial Hospital, Mumbai, India. J Clin Oncol, 2004; 22:8562
10. Bansal D, Marwaha RK, Trehan A, Rao KL, Gupta V. Profile and outcome of neuroblastoma with convertional chemotherapy in children older than one year: A 15-years experience. Indian Pediatr 2008;45:135-9.
11. Qureshi SS, Bhagat M, Harris C, Chinnaswamy G, Vora T, Kembhavi S, *et al.* Outcomes and complications of surgery in patients with intermediate-risk neuroblastoma: Experience from an Indian tertiary Cancer Centre. Pediatr Surg Int 2018;34:435-42.
12. 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.
13. Park JR, Bagatell R, Cohn SL, Pearson AD, Villablanca JG, Berthold F, *et al.* Revisions to the international neuroblastoma response criteria: A consensus statement from the national cancer institute clinical trials planning meeting. J Clin Oncol 2017;35:2580-7.
14. Wilson LM, Draper GJ. Neuroblastoma, its natural history and prognosis: A study of 487 cases. Br Med J 1974;3:301-7.
15. Bernstein ML, Leclerc JM, Bunin G, Brisson L, Robison L, Shuster J, *et al.* A population-based study of neuroblastoma incidence, survival, and mortality in North America. J Clin Oncol 1992;10:323-9.
16. Spix C, Aareleid T, Stiller C, Magnani C, Kaatsch P, Michaelis J. Survival of children with neuroblastoma. Time trends and regional differences in Europe, 1978-1992. Eur J Cancer 2001;37:722-9.
17. Schroeder H, Wacher J, Larsson H, Rosthoej S, Rechnitzer C, Petersen BL, *et al.* Unchanged incidence and increased survival in children with neuroblastoma in Denmark 1981-2000: A population-based study. Br J Cancer 2009;100:853-7.
18. Irtan S, Brisse HJ, Minard-Colin V, Schleiermacher G, Galmiche-Rolland L, Le Cossec C, *et al.* Image-defined risk factor assessment of neurogenic tumors after neoadjuvant chemotherapy is useful for predicting intra-operative risk factors and the completeness of resection. Pediatr Blood Cancer 2015;62:1543-9.
19. Brisse HJ, McCarville MB, Granata C, Krug KB, Wootton-Gorges SL, Kanegawa K, *et al.* Guidelines for imaging and staging of neuroblastic tumors: Consensus report from the International Neuroblastoma Risk Group Project. Radiology 2011;261:243-57.
20. Brodeur GM, Maris JM. Neuroblastoma. In: Pizzo PA, Poplack DG, editors. Principles and Practice of Pediatric Oncology. 5th ed. Philadelphia: Lippincott Raven; 2006. p. 933-70.
21. Gatta G, Capocaccia R, Stiller C, Kaatsch P, Berrino F, Terenziani M, *et al.* Childhood cancer survival trends in Europe: A EUROCARE Working Group study. J Clin Oncol 2005;23:3742-51.
22. Angstman KB, Miser JS, Franz WB 3rd. Neuroblastoma. Am Fam Physician 1990;41:238-44.
23. Massad M, Slim MS, Mansour A, Dabbous I, Firzli S, Issa P. Neuroblastoma: Report on a 21-year experience. J Pediatr Surg 1986;21:388-91.
24. Schüz J, Kaletsch U, Meinert R, Kaatsch P, Spix C, Michaelis J. Risk factors for neuroblastoma at different stages of disease. Results from a population-based case-control study in Germany. J Clin Epidemiol 2001;54:702-9.
25. Ng SM, Abdullah WA, Lin HP, Chan LL. Presenting features and treatment outcome of 78 Malaysian children with neuroblastoma. Southeast Asian J Trop Med Public Health 1999;30:149-53.
26. Olgun N, Kansoy S, Aksoylar S, Cetingul N, Vergin C, Oniz H, *et al.* Experience of the Izmir pediatric oncology group on neuroblastoma: IPOG-NBL-92 protocol. Pediatr Hematol Oncol 2003;20:211-8.
27. Leung CK. Fifteen years' review of advanced childhood neuroblastoma from a single institution in Hong Kong. Chin Med J (Engl) 1998;111:466-9.