



# Optimizing the Outcome of Pediatric Metastatic Neuroblastoma in a Nontransplant Setting in a Developing Country: Retrospective Study from a Tertiary Cancer Center in India

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## Abstract

**Objective** This article estimates the survival of children over 1 year of age diagnosed with metastatic neuroblastoma (NB) and treated in a nontransplant facility and determines the factors affecting survival.

**Materials and Method** Case records of children aged 1 to 14 years treated for metastatic NB in our center from January 2008 to December 2017 were studied. Patients received conventional chemotherapy followed by surgery, radiotherapy, and metronomic maintenance chemotherapy.

**Results** Eighty-nine patients with metastatic NB received treatment. Mean age was 3.5 years and male:female ratio was 1.1:1. The most common primary site was suprarenal (55%) and the most common site of metastasis was bone marrow (76%). Forty percent patients had multiple metastatic sites. Mean baseline lactate dehydrogenase (LDH) was 3724 U/L (range 303–16609 U/L) and 65% patients had LDH > 750 U/L. Fifty-three patients (59.6%) had good response to chemotherapy as evidenced by clearance of metastatic disease, but out of them, 43 patients (81%) progressed subsequently. Twenty-six patients underwent surgery and 12 patients received maintenance therapy. Seventy-four patients (86%) developed recurrence and all but one died. Median time to recurrence and death were 9 months (range 0–120 months) and 10 months (range 1–123 months), respectively. At a median follow-up of 72 months (range 15–135 months), 16 patients are alive, with 5-year disease-free survival and overall survival of 17.6 and 18.4%, respectively. Age, baseline LDH, chemotherapy regimen, and response to treatment significantly affected survival.

**Conclusion** Younger age, lower baseline LDH, and good response to chemotherapy appear to confer survival advantage in pediatric metastatic NB, and may be used for optimization of treatment in the nontransplant setting in developing countries.

## Keywords

- ▶ pediatric
- ▶ metastatic neuroblastoma
- ▶ survival
- ▶ developing country
- ▶ India

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## Introduction

Neuroblastoma (NB), the most common pediatric extracranial solid tumor, is one of the most challenging childhood cancers to treat. In the developing countries, majority of children with NB present with high-risk and metastatic disease, with frustratingly low survival even after skillful use of multiple treatment modalities.<sup>1</sup> In the high-income countries, the use of advanced therapeutics like high-dose chemotherapy followed by autologous stem cell transplant (ASCT), surgery, radiotherapy, and immunotherapy is able to yield around 40% survival in high-risk NB.<sup>2</sup> Transplant facilities and anti-GD2 therapy, which form the standard of care in the developed countries, are not available to majority of the needful patients in the low-and-middle-income countries (LMICs). In the nontransplant setting like ours, metastatic NB is treated with conventional chemotherapy combined with local control modalities like surgery and/or radiotherapy.<sup>3</sup> We determined treatment outcome and factors affecting survival of children over 1 year of age with metastatic NB treated at our center with chemotherapy, surgery, and radiotherapy.

## Materials and Method

This is a retrospective study of case records of all children aged 1 to 14 years with stage 4 NB treated at our center over a 10-year period (January 1, 2008 to December 31, 2017). Disease evaluation was done clinically and by blood investigations including lactate dehydrogenase (LDH) and imaging of the primary site with ultrasound or computed tomography scan. Metastatic workup included skeletal X-rays and bone marrow biopsy. Assessment of bone metastases was dependent on skeletal X-rays, as MIBG (metaiodobenzylguanidine) scintigraphy was not available in our hospital and bone scan could be used only sparsely because of interruptions in availability of reagent. The diagnosis of NB was established by histopathology and immunohistochemistry of bone marrow or primary tumor tissue. N-myc studies were not available in the hospital.

### Inclusion and Exclusion Criteria

All patients over 1 year of age diagnosed with metastatic NB and received treatment at our center were included. Patients who received treatment elsewhere and those who expired before starting treatment were excluded.

### Chemotherapy

Two chemotherapy schemes were in use for treating pediatric NB in the hospital during this time. Chemo A was a moderately aggressive regimen consisting of vincristine 1.5 mg/m<sup>2</sup>, Adriamycin 40 mg/m<sup>2</sup> and cyclophosphamide 1500 mg/m<sup>2</sup> alternating with cisplatin 100 mg/m<sup>2</sup>, and etoposide 450 mg/m<sup>2</sup> every 3 weekly for 1 year (maximum cumulative dose of Adriamycin 360 mg/m<sup>2</sup>). Chemo B was the less intensive regimen consisting of six 3-weekly cycles of vincristine, Adriamycin 30 mg/m<sup>2</sup>, and cyclophosphamide 750 mg/m<sup>2</sup>. Patients were assigned to receive the chemotherapy

regimen by the treating consultant based on the general condition, extent of metastatic disease, logistic and social factors, and parental decision.

### Response to Chemotherapy

Response assessment was done after four cycles of chemotherapy with bone marrow examination and skeletal X-rays. MIBG was not available in the hospital and bone scan was not done universally due to erratic availability of reagent. Disappearance of disease from metastatic sites as evidenced by a normal bone marrow examination and absence of lytic bone lesions on skeletal X-rays was considered as good response. Imaging of the primary site for response assessment was done only for patients who cleared the disease from metastatic sites. Persistent metastatic disease was considered as poor response.

### Local Treatment and Maintenance Chemotherapy

Surgery was done if safe resection was feasible, followed by further chemotherapy according to the assigned regimen. Radiotherapy was given for unresectable/residual disease after completion of treatment regimen, followed by oral metronomic chemotherapy with cyclophosphamide 50 mg/m<sup>2</sup> and etoposide 50 mg/m<sup>2</sup> daily for 20 days per month for 6 to 8 months. Patients with disease progression at any time were assigned to palliative care.

### Primary and Secondary Outcome Measures

The primary outcome measure was to estimate the survival of children over 1 year of age treated for metastatic NB. The secondary outcome was to determine any clinical or biological factors affecting survival of these patients in the nontransplant setting.

## Statistical Methods

The descriptive analysis included the absolute and relative frequency for categorical variables. Comparison between groups was carried out using the chi-square test or Fisher's exact test. Variables for the survival analysis were age, primary site, metastatic site, baseline LDH, chemotherapy regimen, response to chemotherapy, and surgery. The survival curve was estimated for each variable using the Kaplan–Meier method. The comparison between curves was obtained by the log-rank test. The Cox regression model was used to assess the effect of the variables on survival (multivariate analysis to calculate hazard ratios), which included variables with the following characteristics according to the Kaplan–Meier analysis with a significant difference ( $p < 0.05$ ). The level of significance established for all analyses was 5%. All analyses were performed using the software SPSS 20.0 for Windows (Statistical Package for Social Sciences, IBM, United States).

## Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of

the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was carried out according to the regulations established by the Institutional Clinical Research Review Board and approved by Human Ethics Committee, Regional Cancer Centre Trivandrum (No. 02/2018/13, dated 22/02/2018, 2 p.m.). Consent for treatment and use of medical record data for scientific studies were routinely obtained for all patients.

## Results

### Patient Demographics

There were 119 children > 1 year of age with metastatic NB, forming 50.2% of the total noninfant NB patients. Mean age of

the patients was 3.5 years (range 1–14 years) and male: female ratio was 1.1:1. Eighty-nine patients consented for treatment and are included in the analysis. Out of these, 24 patients were aged < 18 months and 65 patients were older.

### Disease Characteristics

The most common site of primary tumor was suprarenal ( $n=66$ , 55.5%), followed by retroperitoneal ( $n=25$ , 21%), thoracic/mediastinal ( $n=7$ , 5.9%), cervical ( $n=8$ , 6.7%), and multifocal ( $n=3$ , 2.5%). Primary tumor was undetected in 6 patients (5%). The most common site of metastasis was bone marrow ( $n=68$ , 76.3%), followed by bone ( $n=14$ , 15.9%), lymph nodes ( $n=6$ , 6.2%), and liver ( $n=1$ , 1%). Thirty-six patients (40.4%) had multiple metastatic sites. Baseline LDH values were available for 79 patients, with mean value of

**Table 1** Prognostic variables on univariate analysis

Prognostic variable	DFS probability	p-Value	OS probability	p-Value	Hazard ratio	p-Value
Age						
< 2 y	19.8	0.96	23.3	0.92	1.02	0.927
> 2 y	15.3		15.2			
Primary site						
Adrenal	14.7	0.178	17.6	0.07	1.00	0.99
Cervical	30.0		30.0			
Posterior mediastinal	50.0		100.0			
Paraspinal	13.3		13.3			
Abdominal/retroperitoneal	33.3		33.3			
Multifocal	25.0		25.0			
Metastatic site						
Bone marrow	18.0	0.865	20.7	0.87	1.3	0.861
Bones	9.1		9.1			
Lymph nodes	25.0		25.0			
Multiple sites	16.3		15.9			
LDH						
< 750 U/L	50.0	0.028	46.9	0.032	2.29	0.013
> 750 U/L	18.6		16.2			
Chemotherapy						
Chemo A + Metronomic	55.6		55.6			
Chemo A	23.6	0.001	27.2	0.001	6.03	0.001
Chemo B	8.3		8.1			
Response						
Good	27.8	0.001	29.7	0.001	6.96	0.001
Poor	3.3		3.3			
Surgery						
No surgery	5.7	0.001	7.5	0.001	1.32	0.001
Biopsy only	0.0		0.0			
Debulking	66.7		66.7			
Excision	43.8		43.8			

Abbreviations: DFS, disease-free survival; LDH, lactate dehydrogenase; OS, overall survival.

**Table 2** Response and outcome by treatment regimen

Parameter	Chemo A (n = 38)	Chemo B (n = 51)
Metronomic chemo maintenance	9 (23.6%)	3 (5.8%)
RT	2 (5.2%)	1 (1.9%)
Good response	30 (78.9%)	23 (45%)
Poor response	6 (15.7%)	24 (47%)
Recurrence/relapse	27 (71%)	46 (90%)
Patients alive	11 (28.9%)	5 (9.8%)
5-year DFS	23.6%	5.0%
5-year OS	27.2%	8.1%

Abbreviations: DFS, disease-free survival; OS, overall survival; RT, radiotherapy.

3724 U/L (range 303–16609 U/L). Fifty-eight patients (65%) had LDH > 750 U/L and 21 patients (23.5%) had LDH < 750 U/L.

**Treatment and Response**

Thirty-eight patients (42.6%) received Chemo A, out of which 30 patients (78.9%) had good response to chemotherapy and 6 patients (15.7%) had poor response. Fifty-one patients (57.3%) received Chemo B, out of which 23 patients (45.09%) had good response and 24 patients (47.05%) had poor response (►Table 1). In 6 patients, response assessment could not be done because of early clinical progression or death. Surgery could be attempted in 26 patients (29.2%), with excision in 16

patients, debulking in 6 patients, and biopsy alone in 4 patients. Only 3 patients received radiotherapy and 12 patients received metronomic maintenance chemotherapy (9 patients after Chemo A and 3 patients after Chemo B).

►Table 2 shows patient outcome by treatment regimen.

**Relapse and Death**

Overall, 74 patients (86%) developed recurrence/progression of disease. Out of the 53 patients who had good initial response to chemotherapy, 43 patients (81%) relapsed. The median time to recurrence/progression was 9 months (range 1–120 months). Seventy-three patients (85.9%) died, the median time to death being 10 months (range 1–123 months). Cause of death was disease progression in 71 patients and toxicity-related deaths in 2 patients. Three relapsed patients are lost to follow-up.

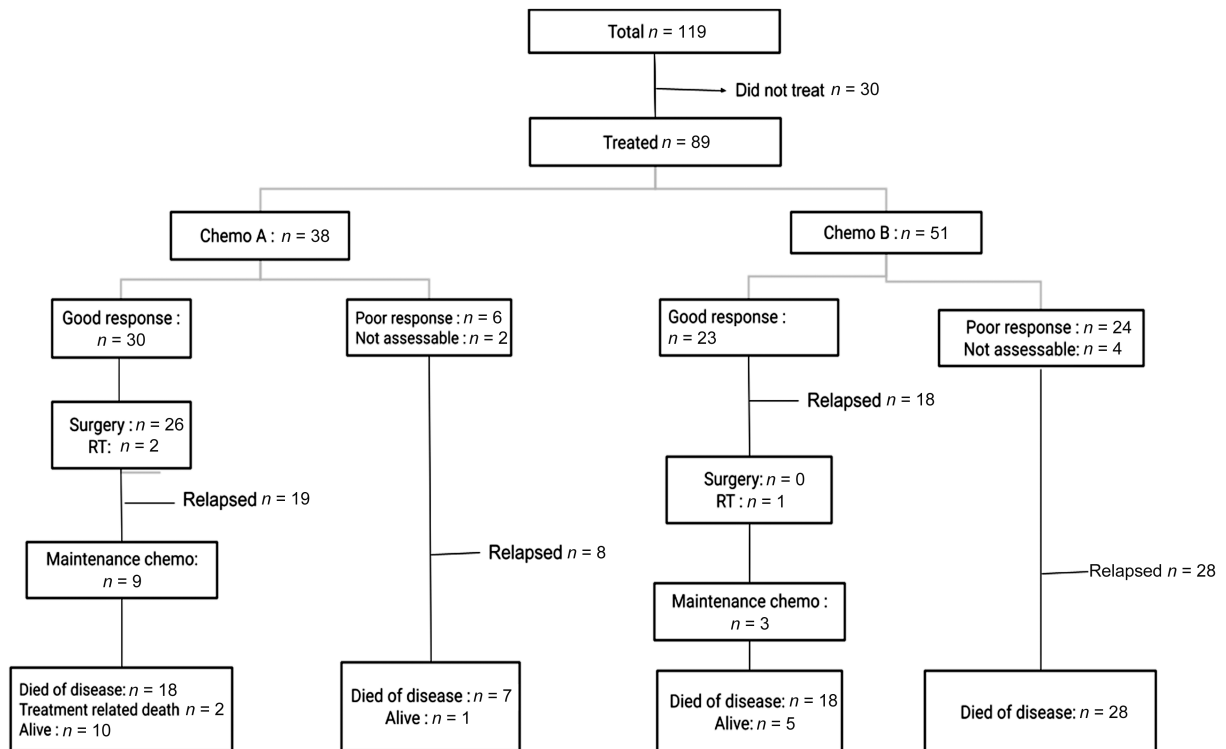
►Fig. 1 depicts the summary of patient treatment and outcome.

**Prognostic Factors**

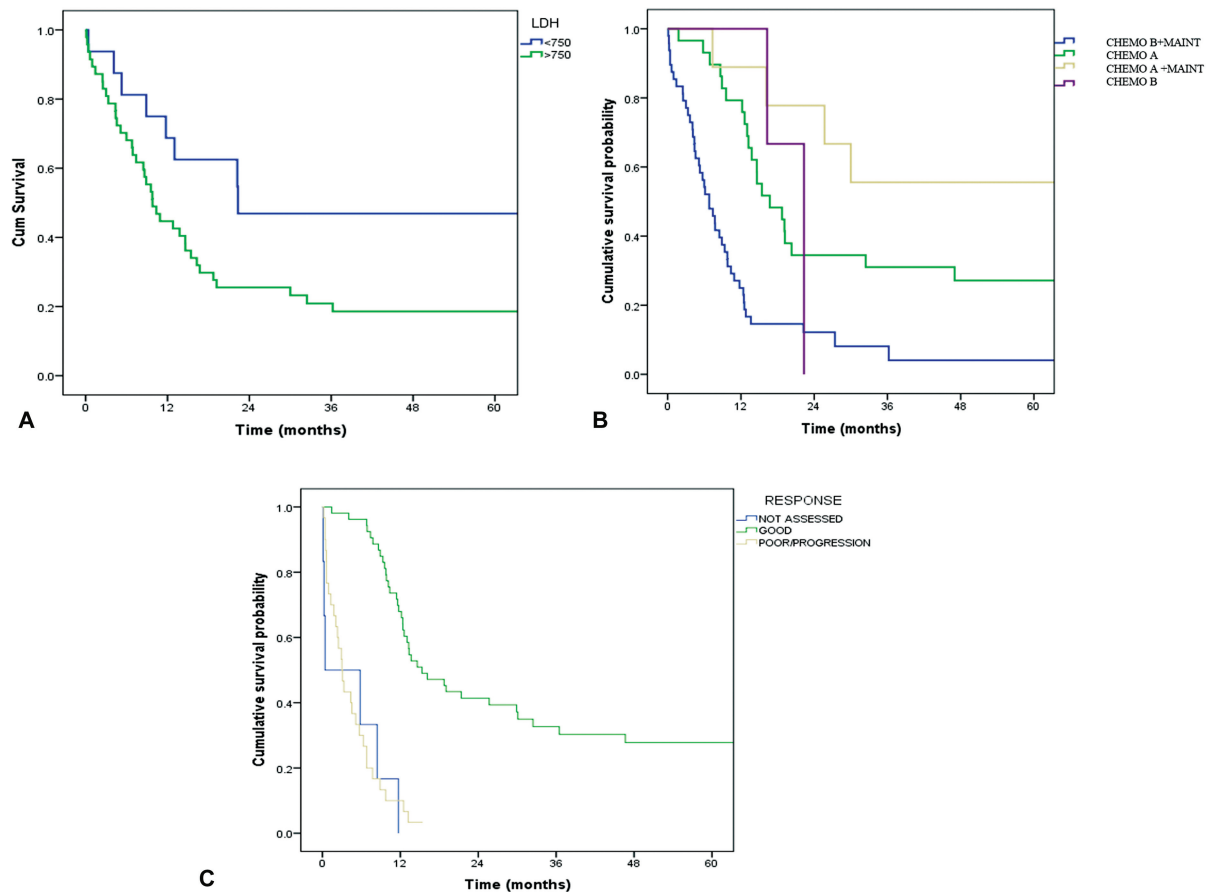
In univariate analysis, age < 18 months, LDH > 750 U/L, type of chemotherapy regimen, response to initial chemotherapy, number of chemotherapy cycles received, and surgery were found to be statistically significant factors for disease-free survival (DFS) and overall survival (OS).

Details of prognostic factors on univariate analysis are given in ►Table 1.

On multivariate analysis, age > 18 months, LDH > 750U/L, less aggressive Chemo B regimen, and poor response to chemotherapy were statistically significant poor prognostic factors.



**Fig. 1** Flowchart depicting treatment course and outcomes.



**Fig. 2** Kaplan–Meier survival curves of (A) overall survival (OS) by lactate dehydrogenase (LDH) > 750 U/L and < 750 U/L. (B) OS by type of chemotherapy regimen. (C) OS by response to chemotherapy.

### Survival

At a median follow-up of 72 months (range 15–135 months), there were 16 survivors. Five-year DFS was 17.6% and OS was 18.4%. Children < 18 months had significantly better DFS and OS (35.1 and 38.6%, respectively). Eleven patients out of 38 (28.9%) who received Chemo A and 5 patients out of 51 (9.8%) who received Chemo B survived. Twelve patients (9 on Chemo A and 3 on Chemo B) received metronomic chemotherapy, and 5 out of those 12 patients (41.6%) are alive.

►Fig. 2 shows the survival curves by the relevant prognostic factors where 9 out of 16 patients (56.2%) who survived were aged < 18 months at diagnosis. Mean age of survivors was 2.3 years (range 1–9 years) and their mean LDH at presentation was 728 U/L (range 303–1747 U/L).

Details of survival cohort are depicted in ►Table 3.

### Discussion

It is well known that the burden of high-risk and metastatic NB is high in the LMICs with suboptimal survivals. A previous study of 91 pediatric NB patients from our hospital some years back had reported around 60% stage 4 disease, with long-term survivors as low as 9% after multimodality treatment.<sup>1</sup> A recent compilation of studies from LMICs which includes several studies from India, describes survivals of 0 to 45% world-over without ASCT and anti-GD2 antibody.<sup>4</sup>

Single-institution studies from other developing countries like Brazil and countrywide outcomes from Turkey have reported 17 and 45% five-year survival, respectively, for stage 4 NB.<sup>5,6</sup> The overall poor results in LMICs are likely multifactorial such as inadequate diagnostic facilities, less intense chemotherapy protocols, inability to resect the primary tumor, limited availability, expertise, and prohibitive cost of transplant facilities and unavailability of monoclonal antibodies.<sup>2</sup> Treatment refusal and abandonment are also high in resource-challenged nations<sup>1,3</sup> as was noted in our study, likely because of social, health system-related, and financial reasons. Optimization of available resources thus becomes important while treating these patients in the LMICs.

The significance of clinical and biological prognostic factors like age, metastatic burden, and LDH in metastatic NB patients treated without transplant was explored in this study. Data from the International Neuroblastoma Risk Group (INRG) reveals that older age, involvement of bone marrow, bone, and multiple metastatic sites are associated with worse outcome.<sup>7</sup> The better prognostic value of younger age in noninfant metastatic NB has been proved historically by the Children's Cancer Group and the European registries.<sup>8</sup> Age cutoff of 18 months is utilized as standard for risk stratification of noninfant NB, but the earlier Children's Oncology Group study has shown that prognostic effect of age is continuous in nature.<sup>9</sup> In our study, children < 18

**Table 3** Characteristics of the survivor cohort ( $n = 16$ )

Variable	Value
Age	
Mean	2.3 y
Range	1–7 y
Gender	
Female	10
Male	6
LDH	
Mean	728 U/L
Range	303–1747 U/L
Primary site	
Adrenal	6
Abdominal	5
Cervical	2
Thoracic	1
Paraspinal	1
Multifocal	1
Metastatic site	
Limited metastases	14
Multiple metastases	2
Chemotherapy regimen	
Chemo A	12
Chemo B	4
Metronomic chemo	5
Response to treatment	
Good	15
Poor	1
Surgery/RT	
Debulking/excision	10
No surgery/biopsy only	6
RT	2

Abbreviations: LDH, lactate dehydrogenase; RT, radiotherapy.

months had significantly better event-free survival (EFS) and OS in a nontransplant setting. We understand that some of them would have had biologically favorable disease and would be considered as nonhigh-risk by the current international standards had they been properly risk-stratified using N-myc. Because of lack of facility in the hospital, N-myc study, MIBG scintigraphy, and bone scans could not be done in all our patients. Under these limitations, the significance of biomarkers like LDH and ferritin becomes important in risk stratification and prognostication of these patients. LDH is considered as a surrogate marker for N-myc amplification, and the International Society for Pediatric Oncology–Pediatric Oncology Developing Countries has recommended an arbitrary LDH value of 750 U/L as a prognostic marker when N-myc status is not known.<sup>2</sup> In the recently published

INRG study, higher LDH at presentation was independently prognostic for worse DFS and OS in metastatic NB.<sup>10</sup> In our study, patients with LDH > 750 U/L demonstrated markedly inferior survival than those with LDH < 750 U/L (18.2% vs. 46.9%), suggesting that those patients may have had biologically adverse tumors.

Treatment-related factors analyzed in this study were intensity of chemotherapy, response to chemotherapy, and impact of surgery. Dose-intensive short-duration chemotherapy incorporating cisplatin and etoposide is associated with better clinical outcomes in metastatic NB, and utilized in different chemotherapeutic regimens.<sup>11</sup> In the earlier study by Kusumakumary et al from our hospital in a group of NB patients treated with heterogeneous chemotherapy protocols, one of the reasons explained for poor outcome of stage 4 NB patients was the less aggressive palliative intent chemotherapy.<sup>1</sup> In our study, survival of patients who received the cisplatin-containing regimen A was far better than those who received the regimen without cisplatin (28.9% vs. 9.8%). Our results may have been confounded by a selection bias, as patients with multiple metastases and poor general condition were not expected to tolerate aggressive treatment and inadvertently received the less intensive regimen.

We noted an unusually high response to chemotherapy in our patients, probably because response evaluation was done with bone marrow examination and skeletal X-rays only. If MIBG would have been used, the number of responders would have been lesser. However, good response to initial chemotherapy did not translate to proportionately good EFS or OS in our patients, because of early relapses, suggesting that conventional chemotherapy is not able to maintain the remission status. In an earlier analysis from our own center, 15 out of 17 children with metastatic NB treated with multiagent chemotherapy had a good initial treatment response, but their 2-year survival was only 11.7%.<sup>11</sup> Whether further intensification of chemotherapy in good responders should be considered in the setting of nonavailability of transplant facility is a question to be addressed. Recently, Jain et al have reported improved survivals in high-risk NB patients treated without ASCT or dinutuximab using an intensive consolidation regimen with topotecan, vincristine, and doxorubicin in India.<sup>4</sup> We also observed that patients who underwent tumor excision or debulking had better outcome, but surgery and radiotherapy could be offered to very less number of patients, hence the impact of such a finding is doubtful.

Of interest are the characteristics of our survivor cohort. We observed that they were younger, mostly females, presented with lower baseline LDH, mostly had limited metastases, received moderately intensive cisplatin-containing chemotherapy, all but one were good responders, and most underwent excision or debulking. Very few patients in our cohort were able to reach the maintenance phase of treatment, but this group had the best survival of 41%.

The limitations of our study are that it is a retrospective study of a cohort of patients treated with nonuniform chemotherapy protocols. Nonavailability of N-myc testing and MIBG, selection bias in treatment protocol, and

limitation of clinical facilities and resources for treatment may also be considered as a limitation. Most patients who attend our center for treatment come from poor socio-economic status and are not able to afford costly treatments. Treatment costs were met partially by the center with the help of government aids and there was always shortage of human resources. Given the poor prognosis of metastatic NB, during the earlier time period many parents opted out of the cisplatin-containing regimen because they could not afford to stay in and around the hospital for frequent monitoring and management of subsequent complications. Over the years, because of increased government initiatives and support from new voluntary organizations, new treatment assistance schemes and staff support for pediatric cancer patients in the hospital were provided, resulting in increase in clinical facilities and improvements in supportive care, so that overall more number of pediatric patients could afford cancer treatments. The increased trend in survival may be a reflection of more number of patients being able to take the aggressive protocol.

Future prospective study may be proposed based on our findings from the present study. Younger patients and those with lower LDH at presentation may be treated with moderately intensive platinum-containing chemotherapy and response of metastatic sites after first few cycles of chemotherapy may be utilized to guide further treatment. Patients with clearance of metastases may preferably receive intensified chemotherapy, followed by surgery of primary, radiotherapy to residual tumor, and maintenance chemotherapy. On the other end of the spectrum, identification of patients with multiple adverse factors like older age, very high baseline LDH, multiple metastatic sites, or poor response to chemotherapy which portend poor outcome may allow the focus to be directed on early provision of palliative care along with less intensive cancer-directed treatment aiming at reducing the symptom burden, improving the quality of life, and smooth transition toward end-of-life care.

## Conclusion

Our study reveals that improvement in clinical services like chemotherapy and supportive care can result in a trend toward better survivals in children with metastatic NB in a resource-limited setting. Selected stage 4 NB patients may survive even without transplant or immunotherapy, and they can be identified based on simple and affordable investigations like baseline LDH, ferritin, and good response to initial chemotherapy. Stratification of these patients on the basis of clinical and biological factors can facilitate justified allocation of available resources while planning treatment for metastatic NB patients in the LMICs.

## Patient Consent

Consent for treatment and use of medical record data for scientific studies were routinely obtained for all patients.

## Funding

None.

## Conflict of Interest

None declared.

## Acknowledgments

None.

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