ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCE SCHOOL OF MEDICINE

DEPARTMENT OF RADIOLOGY

SENIOR RESEARCH PAPER

IMAGING FEATURES OF NEUROBLASTOMA AT INITIAL PRESENTATION ASSOCIATED WITH METASTATIC SPREAD AND POOR CLINICAL OUTCOME: A CROSS-SECTIONAL STUDY

Imaging Features of Neuroblastoma at Initial Presentation Associated with Metastatic Spread and Poor Clinical Outcome: A Cross-Sectional Study

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Abstract

Background: Neuroblastoma (NB) is a tumor of the sympathetic nervous system which represents one of the most common malignancies in early childhood; initial imaging gives important information on the diagnosis of NB.

Objective: This study aimed to assess imaging features of NB associated with metastatic disease at presentation and poor clinical outcome in a resource limiting setting.

Methods: A hospital-based cross-sectional study was conducted. Computed Tomography (CT) images were reviewed and imaging appearances were evaluated in all patients with pathology confirmed cases of neuroblastoma in Tikur Anbessa Specialised Hospital (TASH) radiology department from January 2023-December 2024. Using Statistical Package for Social Sciences version 27 (SPSS) software program, data was analysed. Association between imaging features variables like location, size and IDRFs with disease prognostic factor (metastasis) and clinical outcome were analysed using Fisher's exact test.

Results: Among 42 participants, 22 were male (52.4%). The participants' age ranged from 1 to 120 months, a median age is 33 months. Twenty four patients (57.1%) had tumor originating from the adrenal gland, followed by non-adrenal retroperitoneal in 13 (31%). Thirty-five cases (83.3 %) had a tumor size greater than 4 cm in longest diameter. Thirty-three cases (78.6%) had at least one image defined risk factor and intra-abdominal vascular encasement is seen in 27 cases (64.3%). Twenty-two cases (52.4%) had a metastatic disease at presentation and the most common single site of metastasis was bone in 8 patients (36.4%), followed by liver in 6 patients (27.3%). Nineteen cases (45.2%) had a metastatic NB. 6(14%) had improvement on follow up, 11(26%) were on palliative treatment, 5(12%) were lost on follow up and status unknown, and 20 (48%) patients died.

A statistically significant association was found between the primary tumor location and tumor size with tumor metastasis at initial presentation with a two sided Fisher's exact sig P-value of 0.045 and 0.027 respectively. There is an association between metastatic disease at presentation and clinical outcome (P-value of 0.006).

Conclusion: NB presents as a large intra-abdominal solid mass with calcification and roughly half of them having metastasis at initial presentation. Adrenal tumor origin and large tumors have more propensities to have metastatic disease at presentation. Metastatic spread at initial presentation has a poor clinical outcome.

Keywords: Adrenal tumor, CT scan, IDRFs, INGRSS, Neuroblastoma, Pediatric

Acronyms

Neuroblastoma (NB)

International Neuroblastoma Staging System (INSS)

Bone marrow aspirate or biopsy (BMA/B)

Metaiodobenzylguinide (MIBG)

International Neuroblastoma Risk Group system (INRGS)

Image Defined Risk Factors (IDRFs)

International Neuroblastoma Risk Group Staging System (INRGSS)

Computerized Tomography Scan (CT scan)

Statistical Package for Social Sciences version 27 (SPSS-27)

Interquartile Range (IQR)

Deoxyribo Nucleic Acid (DNA)

V-MYC myelocytomatosis viral related oncogene, neuroblastoma derived (MYCN)

Magnetic Resonance Imaging (MRI)

Tikur Anbessa Specialized Hospital (TASH)

Institutional Review Board (IRB)

Introduction

Neuroblastoma is a tumor of the sympathetic nervous system which represents one of the most common malignancies in early childhood. Age, stage and location of the tumor and biological behavior all affect clinical presentation. Infants and localized tumors have benign course [1]. Non-specific symptoms can be seen at the initial presentation and represent bone marrow involvement. Metastatic disease is present in 70% of children with neuroblastoma at initial stage of presentation [2]. Imaging plays a crucial role in differentiating NB from other solid intra-abdominal tumors. Initial imaging gives important information on the diagnosis of NB, its relation with vital organs and vessels, the stage of disease and surgical planning [1].

International Neuroblastoma Staging System (INSS) states that the diagnosis of NB is established when bone marrow aspirate or biopsy (BMA/B) contains unequivocal tumor cells with increased urine or serum catecholamine metabolites. Cross-sectional imaging with CT or MRI is recommended to evaluate the abdomen, while Metaiodobenzylguinide (MIBG) to scan bone metastasis and differentiate active lesions from scar tissue, and BMA/B for marrow involvement. Post-surgical tumor staging has a grading system of I-IV with a special group categorized as IVS who have a localized primary tumor with disseminated disease limited to skin, liver and/or bone marrow (only in infants less than 1 year, marrow involvement less than 10% on biopsy and MIBG negative marrow) [3,4].

A consensus on pre-treatment risk classification was established in 2009 with the development of the International Neuroblastoma Risk Group (INRG) system. Surgical risk factors are predicted based on the radiographic images, and hence the term Image Defined Risk Factors (IDRFs) is used. Although the International Neuroblastoma Risk Group Staging System (INRGSS) and IDRFs are intended to be used at the time of initial diagnosis, they may also be used for treatment follow up. It is advised that all patients (including those with

metastatic disease) have their primary tumor's IDRFs status documented, even if it is not required for staging patients with disseminated disease; so that the impact of IDRFs on surgical resection, surgical complications, and outcome can be prospectively evaluated in all patients [4, 5].

L1 is a single-compartment tumor that does not affect any critical structures.
A Loco-regional tumor with the presence of one or more IDRF is L2. M is for distant metastatic tumor, with the exception of (Metastasis-Special) MS. Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow is MS [5].

To the best of our knowledge, there is no published study which correlates specific imaging features of NB with disease prognostic factors like metastatic spread at presentation in Ethiopia. This study aims to describe the imaging features of NB at presentation and to investigate imaging factors associated with NB metastasis and poor clinical outcome. This provides a base line study on common imagining features of NB at presentation and association with NB prognostic factors.

Methods and Materials

A hospital-based cross-sectional study design was conducted. All children with confirmed neuroblastoma who have pre-treatment CT scan images from January 2023 to December 2024. Exhaustive sampling technique was employed and all cases available during the study period (42 cases) were included. Patient data were accessed and images were reviewed on the hospital web-med system.

Eligibility criteria

Inclusion criteria

- All confirmed cases of neuroblastoma obtained in the study period.
- Initial CT scan

Exclusion criteria

- Cases who don't have initial CT scan image
- Incomplete and inadequate images for evaluation
- Children with equivocal diagnosis

Study Variables

- Age, sex
- Size of the mass
- Location of the mass
- Presence of calcification
- IDRFs, Metastastatic disease

- Stage of the disease
- Clinical outcome

Data collection strategy

Using patient Identification number patient medical records were accessed from the hospital Medweb system. CT scan images of patients' with pathology proven NB were identified and evaluated. Size of the lesion, site, enhancement pattern, presence of calcification, IDRFs and metastasis were recorded using structured questioner and transcribed to the excel spread sheet.

Data analysis

Using Statistical Package for Social Sciences version 27 (SPSS) software program, data was analysed and described using tables, graphs and figures and association between variables were analysed using Fisher's exact test and Pearson's correlation test.

Results

Among 42 participants, 22 were male (52.4%). The participants' age ranged from 1 to 120 months, with median age of 33 months and IQR 45 months.

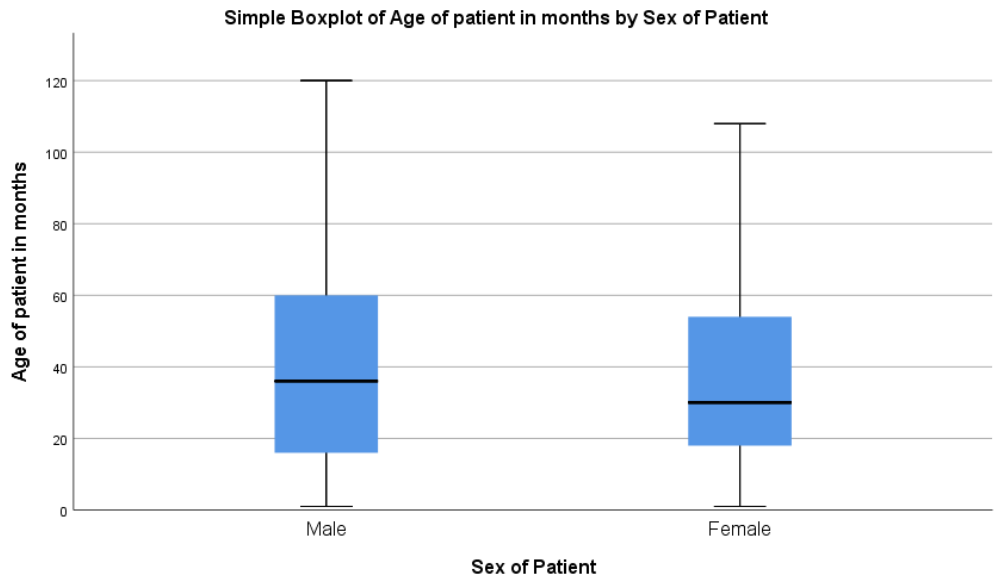
Table 1: Participants' sex distribution.

Sex	Frequency	Percent
Male	22	52.4
Female	20	47.6
Total	42	100

Table 2: Participants' age distribution

Age (months)	Mean	38.5
	Median	33
	Maximum	120
	Minimum	1
	Range	119
	IQR	45

The median age for males was 36 months; slightly higher than that for females which was 30 months.



Twenty four patients (57.1%) had tumor originating from the adrenal gland, followed by non-adrenal retroperitoneal origin in 13 (31%). Four patients had thoracic NB and one case had multicompartment thoracoabdominal involvement.

Location of the tumor

		Frequency	Percent
Valid	Left suprarenal	15	**35.7**

	right supra renal	9	21.4
	retroperitoneal	13	**31.0**
	thoracic paravertebral	4	9.5
	Multicompartment (thoraco abdominal)	1	2.4
	Total	42	100.0

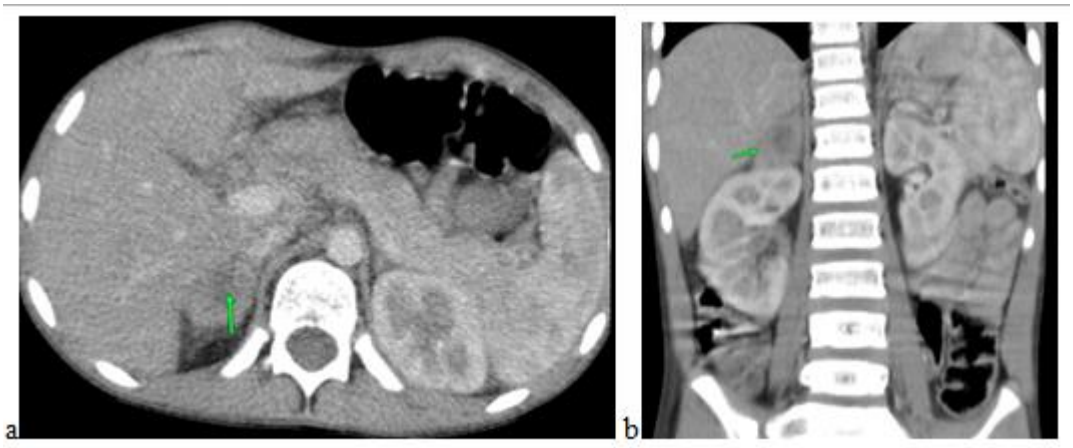


Fig 1 a&b axial and coronal post contrast abdominal CT scan show 2x2x3 cm right adrenal NB without any IDRF

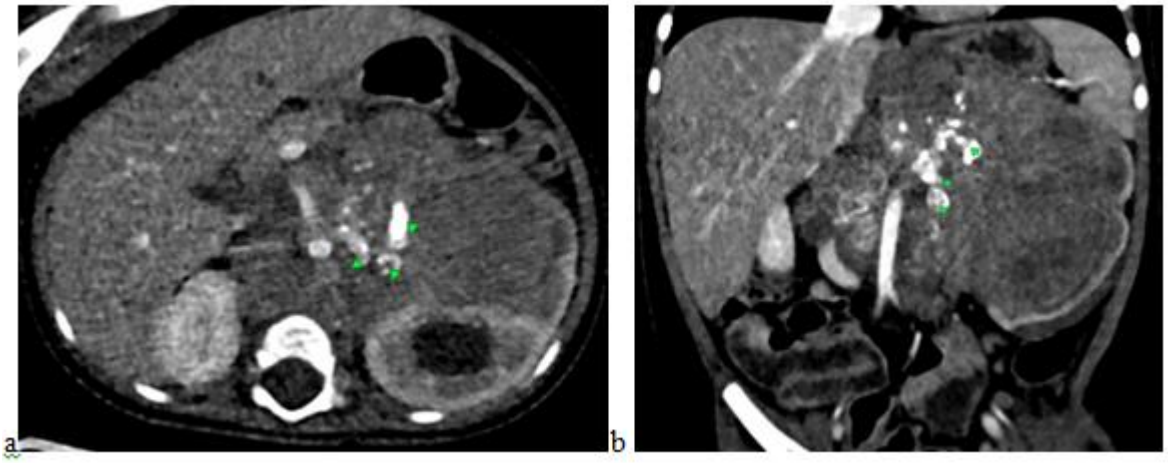


Fig 2 a&b Axial and Coronal abdominal CT scan of a 1 yr old patient show a retroperitoneal mass with chunky calcification (arrow head) encasing and elevating aorta and its branches.

The dominant CT scan imaging appearance was solid density in 35 patients (83.3%) with a homogeneous enhancement in 30 patients (71.4%). Thirty patients (71.4%) had tumor calcification while twelve (28.6%) had no calcification.

Thirty five cases (83.3 %) had a tumor size greater than 4 cm in longest diameter. Seven cases (16.7%) had a tumor size less than or equal to 4 cm.

Table 3: Tumor size in the longest diameter

Tumor size	Frequency	Percent
<=4cm	7	16.7
4-8 cm	14	33.3
8-12cm	15	35.7
12-16cm	6	14.3
Total	42	100

Thirty three cases (78.6%) had at least one image defined risk factor. Intra-abdominal vascular encasement was seen in 27 cases (64.3%); seven had a renal vessel encasement, four had renal hilum invasion**.** Three cases had vertebral canal invasion while one case was a left thoracoabdominal NB.

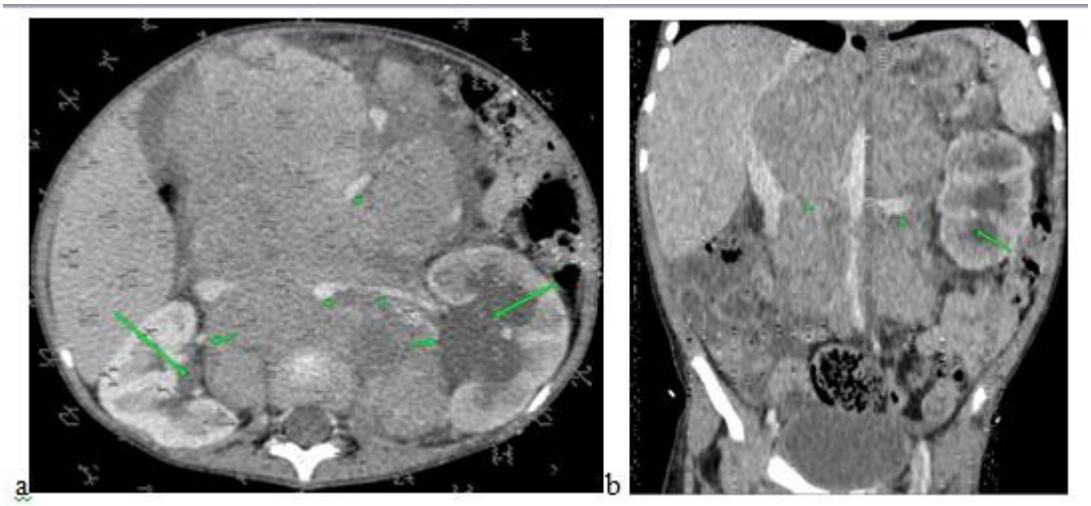


Fig 3 a&b: Abdominal CT scan of a 2 yr old Female show 8.5x9x12 cm retroperitoneal solid homogeneously enhancing mass with lobulated outline. There is encasement and elevation of the aorta and renal vessels (arrow head) and invasion of the renal hilum with mild right hydronephrosis and moderate left hydronephrosis (short and long arrows).

Twenty two cases (52.4%) had metastatic disease at presentation, while twenty cases (47.6%) had no metastases. The most common single site of metastasis was bone in 8 patients (36.4%), followed by liver in 6 patients (27.3%). Multiorgan metastasis was seen in 7 cases (31.8 %); while one case had a distant metastasis to a lymph node (4.5%).

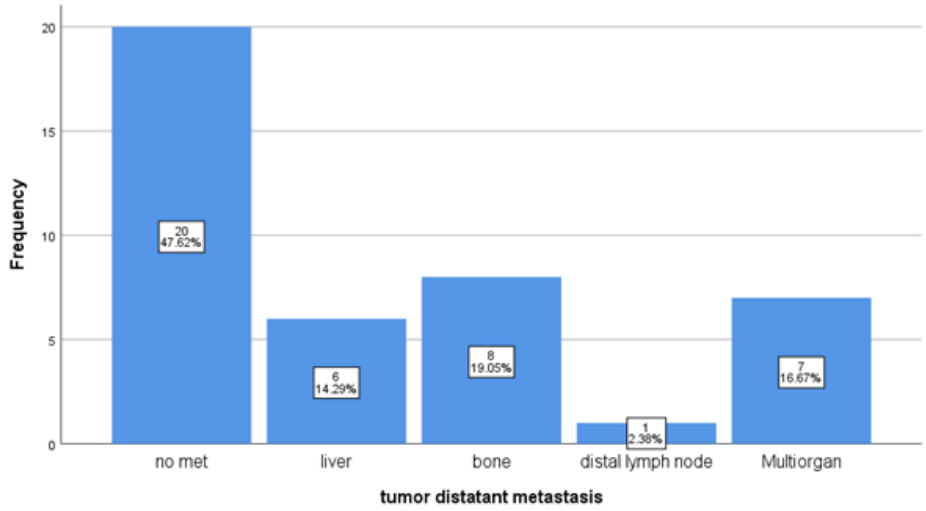


Figure 4: Bar chart of frequency of tumor metastasis

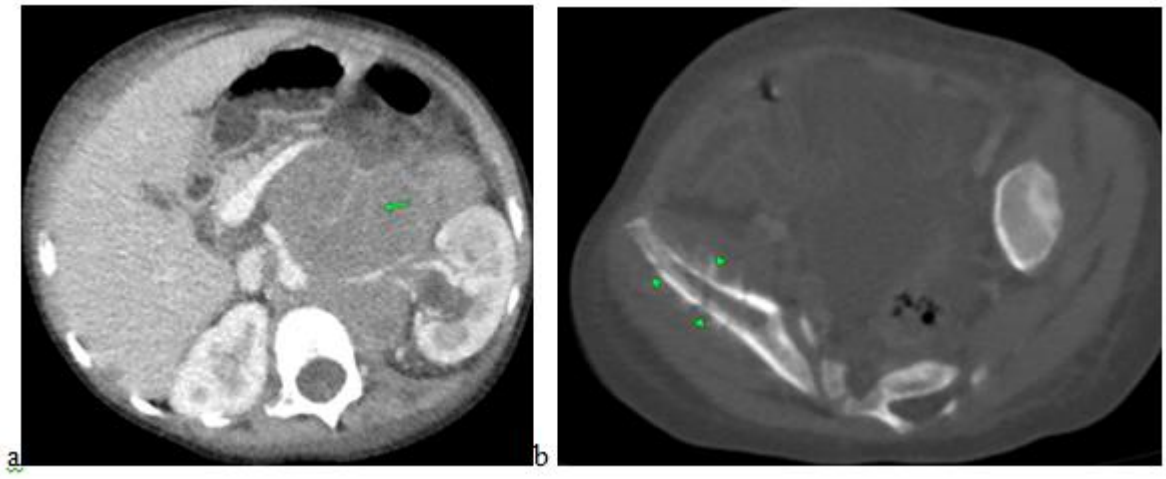
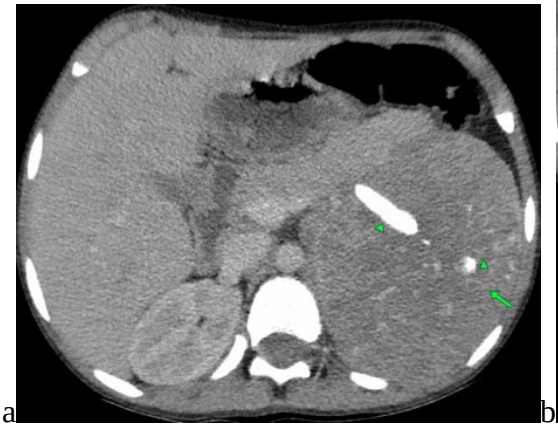
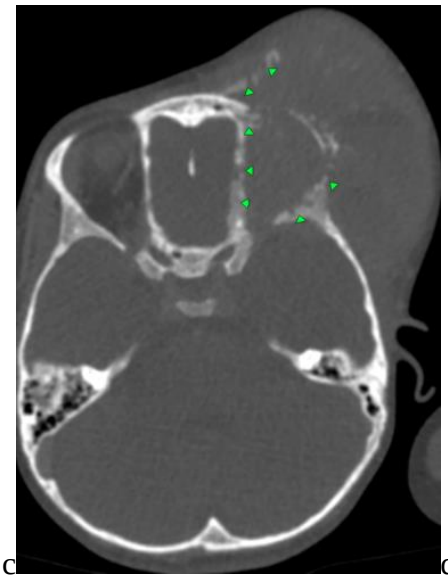
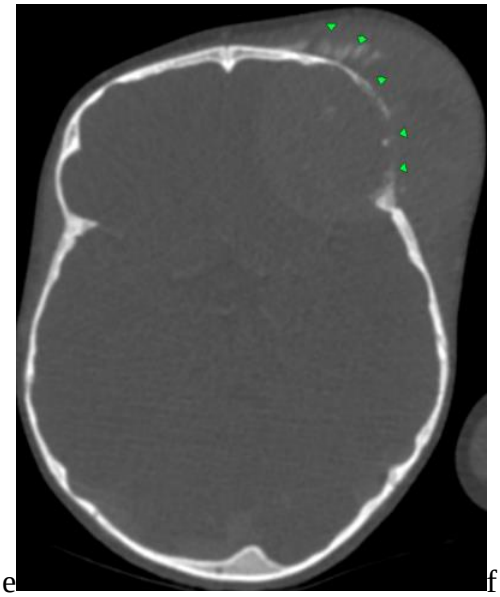
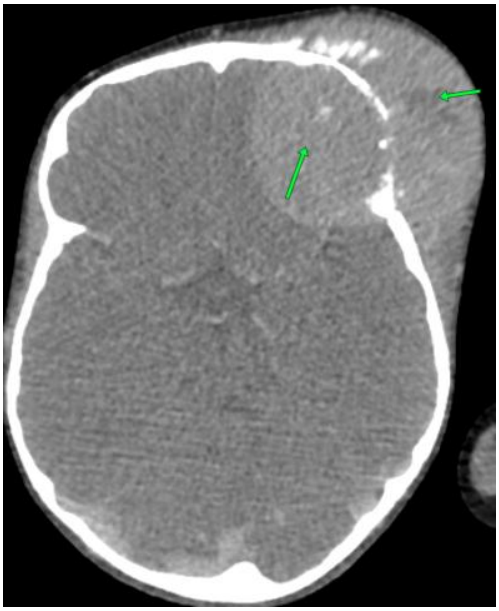


Fig 5 abdominal CT scan with contrast in a 2yr old male with stage M retroperitoneal NB disease; axial image shows 8x7x8.6 cm retroperitoneal mass encasing and elevating aorta and renal vessels and invasion of the left renal hilum(a). Right iliac bone sclerotic lesion and aggressive periosteal reaction (b)suggestive of metastatic bone disease.

a  b 

c  d 

e  f 

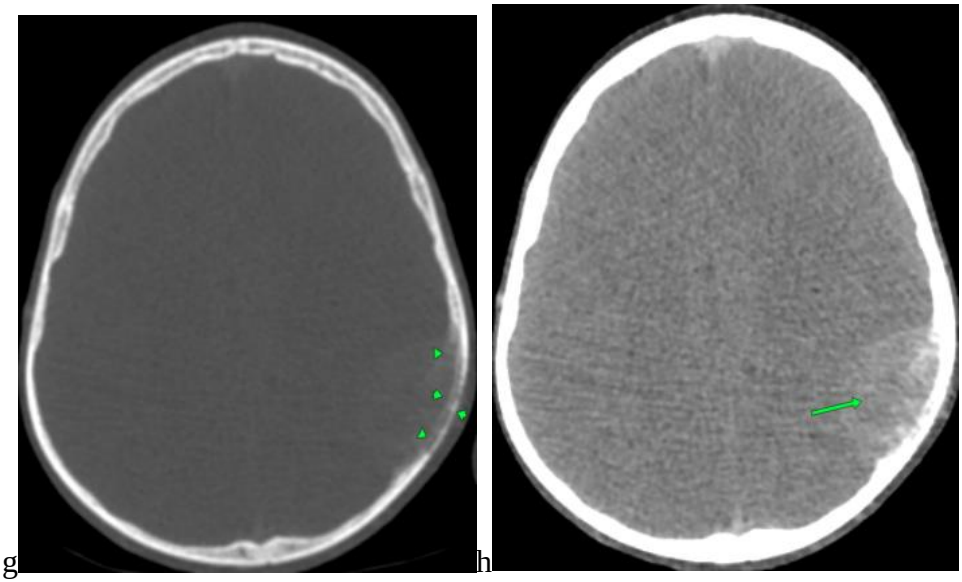
g  h

Fig 6:post contrast Abdominal and head CT scan (a&b) of a 10 yr old male child 9x10.5x12.5 cm left suprarenal homogeneously enhancing mass(arrow) with centre calcification(arrow heads); displaces pancrease and splenic vessel anteriorly.(c&d)Bone and soft tissue window of the brain CT scan show a bone lesion (arrow head)with cortical destruction and aggressive periosteal reaction involving the left orbital bone and soft tissue(arrow).e,f,g&h are bone and soft tissue window brain CT scan images at a higher section showing left frontal and parietal bone lesion (arrow head) with scalp and epidural soft tissue lesion(arrow);findings in keeping with NB metastatic disease.

Nineteen cases (45.2%) have a metastatic NB according to INRG staging system, while three cases (7.1%) are MS with diffuse liver metastasis on CT scan. Sixteen cases (38.1%) L2 and four cases (9.5%) are L1.

		Frequency	Percent
Valid	L1	4	9.5
	L2	16	38.1
	MS	3	7.1
	M	19	45.2
	Total	42	100.0

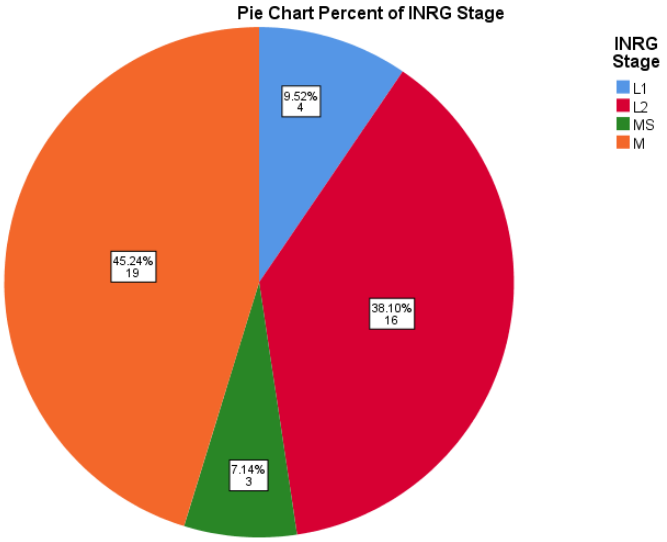


Fig 7 pie chart percent of INRG NB stage

Out of 42 cases, 6(14%) had improvement on follow up, 11(26%) were on palliative treatment, 5(12%) were lost on follow up and status unknown, and 20 (48%) patients died primarily because of the NB or related complications.

Association between the location of primary tumor and tumor size with tumor metastasis at initial presentation is statistically significant with a two sided Fisher's exact test P-value of 0.045 and 0.024 respectively. No association between IDRFs and tumor metastasis. Association between metastatic disease at presentation and clinical outcome had a P-value of 0.006

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	24.422[a]	16	.081	.072
Likelihood Ratio	25.831	16	.056	.036
Fisher's Exact Test	23.253			**.045**
Linear-by-Linear Association	.012[b]	1	.914	.917
N of Valid Cases	42			

		Tumor size in longest diameter	tumor distatant metastasis
Tumor size in longest diameter	Pearson Correlation	1	.349*
	Sig. (2-tailed)		.024
	N	42	42
tumor distatant metastasis	Pearson Correlation	.349*	1
	Sig. (2-tailed)	.024	
	N	42	42

*. Correlation is significant at the 0.05 level (2-tailed).

Discussion

The result showed that NB is slightly more common in males 22 patients (54.2%) with male-to-female ratio of 1.1:1. The median age at diagnosis is 33 months females presenting slightly at earlier age. (30 months vs 36 months) This agrees with a study conducted by Anissi Eddaibouni, Aroua et al. and Van Heerden, J., et al. in South Africa [6, 7].

The commonest site of origin of NB is the adrenal gland (57.1%) followed by extra-adrenal retroperitoneal (31%). A study by Gbadamosi, Hafisatu et al. [8] showed the commonest site of tumor origin of NB was extra-adrenal retroperitoneum (60%) followed by adrenal gland (30%). The difference in the result can be explained by the study setting; where only small number (10) of patient with NB were included by Gbadamosi, Hafisatu et al. However, a large-scale study by Cohn, S.L., et al. [9] showed the adrenal NB accounting for 48% followed by extra-adrenal retro-peritoneum (25%), findings are in keeping with our study.

We found that the majority of cases (69 %) tumor size greater than 4cm, in its widest diameter. This finding indicates a larger proportion of the patients had a large-sized tumor at presentation; similar to the study conducted in Ghana [8]. This can be explained by late presentation; as most clinical presentation of NB is asymptomatic intra-abdominal mass.

The commonest imaging appearance of neuroblastoma in this study was solid density in 83.3%, with a homogeneous enhancement, and calcification was seen in 71.4% of patients. Neuroblastoma can be suspected based on imaging patterns [10]. The appearance of neuroblastoma on CT or MRI is a large, lobulated, heterogeneous solid mass displacing the nearby organs [11].

We found that majority (52.4%) had metastatic disease at presentation. The most common single site of metastasis was the bone which was seen in 8 patients (36.4%), followed by liver

in 6 patients (27.3%). Multiorgan metastasis was seen in 7 cases (31.8 %); while one case has a distant metastasis to a lymph node (4.5%). This finding is in agreement with a study by Liu, Shan et al. revealed that 48.9% of NB patients had distant metastases at the time of diagnosis [12] and also a study by Anissi Eddaibouni, A., et al. showed bone as the commonest site of metastasis accounting for 54.2% cases [8,14].

In addition, we found a significant statistical (P=0.045) association between the origin of the tumor and distant metastasis at presentation. This can be explained by the findings of (13) Stating NB arising in the adrenal gland is more likely to harbour structural DNA aberrations including MYCN amplification.

We found statistical significant association between the size of the tumor at initial presentation and metastasis (P=0.024). This is consistent with (14) which conclude tumor size is a key prognostic factor of NB patients and a cut-off value >4 cm might predict poor prognosis.

Staging is crucial to assess risk and to choose appropriate treatment plan. The new International Neuroblastoma Risk Group (INRG) classification of localized NB depends on the presence of Image-Defined Risk Factors (IDRFs). IDRFs can be identified during initial diagnosis (12). The most commonly encountered IDRFs in our study were intra-abdominal vascular encasement, which was seen in 27 cases (64.3%).

We found that 45.2% of cases have a stage M, followed by stage L2 in 38.1%, L1 in 9.5% and MS in 7.1%. This is similar to the study by Anissi Eddaibouni, Aroua et al., where majority of the patients had stage M peripheral neuroblastoma at their initial presentation.(6) Statistical association between metastatic spread at initial presentation and clinical outcome was significant (P=0.006).

Strength of this study is all are pathology proven cases of NB and is a tertiary centre study where most pediatric oncology cases referred. Limitation of this study include a single centre study with small number of study population and only CT scan images were evaluated for consistency as only few patients had MRI evaluation.

Conclusion

Neuroblastoma presents as a large intra-abdominal solid mass with calcification and roughly half of them having metastasis at initial presentation. Adrenal tumor origin and large tumors have more propensities to have metastatic disease at presentation. Metastatic spread at initial presentation has a poor clinical outcome.

Statements and Declarations

Funding

This research has received a financial support from Addis Ababa University, college of health science, TASH.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

This study was approved by the Institutional Review Board (IRB) of College of Health Sciences, Addis Ababa University (Approval Number: 2612/24) and all procedures performed were in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to Participate

Not applicable

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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Originality Report

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by Professor Daniel Zewdneh

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Annexes

IMAGE DEFINED RISK FACTORS (IDRFs):

a. Encasement: arteries, veins or airways; > 50% circumferential tumor contact of artery or airway, or vein flattened by tumor with no visible lumen

b. Flattening: veins only; narrowed but patent

c. Compression: airways only; mass effect due to tumor

d. Infiltration: organs and vital structures; loss of margins due to tumor

e. Invasion: renal pedicle only; surgically critical area

b1. Infiltration of the porta hepatis: Yes/No

b2. Infiltration of the hepatoduodenal ligament region: Yes/No

b3. Encasement of celiac origin: Yes/No

b4. Encasement of SMA origin: Yes/No

b5. Encasement of proximal SMA branches: Yes/No

b6. Invasion of renal pedicle: Yes/No (contact or encasement)

b7. Encasement of aorta below the thoraco-abdominal junction: Yes/No

b8. Encasement of IVC below the thoraco-abdominal junction: Yes/No

f. Intraspinal Invasion -

This exam is not intended for full diagnostic evaluation of the spine. > 1/3 canal invasion is considered positive. Spine MR may be considered if clinically indicated.

g. Infiltration of Adjacent Organs or Structures -

Pericardium: Yes/No

Diaphragm: Yes/No

Kidney: Yes/No

Liver: Yes/No

Adjacent infiltration of duodenopancreatic block: Yes/ No

Adjacent infiltration of mesentery: Yes/No