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Role of Multi-slice CT in Staging of Neuroblastoma

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ABSTRACT

Background: The International Neuroblastoma Risk Group Staging System (INRGSS) is a recent pretreatment staging system for neuroblastoma (NB), based on imaging by CT before surgery.

Purpose: this study aimed to stage NB cases using CT scan, in relation to available clinicopathologic data.

Patients and Methods: Twenty pathologically proven NB cases were included. All were reviewed for patients' characteristics, includingage; sex, clinical picture, LN status and metastatic spread. All cases underwent CT scan for diagnosis. Stagingwas done using IDRFs, LN status and metastatic spread according to the INRGSS and INSS when available. **Results**: an abdominal mass was found in 85% of cases and the suprarenal gland was the most common site of primary tumor (50% of cases). Concerning tumor grade, 85 % of cases were poorly differentiated. LNs were positive in 70%, and metastatic spread was found in 35% of patients respectively. Staging according to the INRGSS showed that L2 was the most common stage (45% of cases), followed by M stage (35%). L1 and MS stages were found in 15% and 5% of cases respectively. Only 7 cases had postsurgical CT scans, and were staged according to the INSS. **Conclusion**: it was concluded that the use of the INRGSS using CT scan, is a recent valuable pretreatment staging system, allowing accurate classification of neuroblastoma.

Keywords: Neuroblastoma (NB), Computed tomography (CT) scan, Image Defined Risk Factors (IDRFs), International Neuroblastoma Risk Group Staging System (INRGSS), International Neuroblastoma Staging System (INSS).

INTRODUCTION

Neuroblastoma is the commonest extracranial pediatric solid tumor and the most frequent solid neoplasm in the first year of life [(1)].It arises from the precursors of the sympathetic nervous system. The most common primary sites of neuroblastoma are the adrenal gland (40%), paraspinal ganglia in the retroperitoneum (25%), mediastinum (15%), neck (5%) and pelvis (3%) [(2,3)]. The natural history of NB is extremely heterogeneous, but is usually predictable from clinical and biologic features[(4)].Treatment and outcome of neuroblastoma depend on assessment of risk status and on stage of the disease [(3)].

Imaging by Computed Tomography (CT) plays an important role in diagnosis, staging and follow up of NB. Most protocols include regular CT assessment, to determine efficacy of therapy and thuspredict patient's prognosis [(5)].

For a long time; the International Neuroblastoma Staging System (INSS) was used for staging [(6)]. However, this post surgical staging system depends on surgical skill; it can't be applied uniformly in different centers, or used for pretreatment risk classification [(3)].

The International Neuroblastoma Risk Group Staging System (INRGSS) is a recent pre treatment staging system for NB, based on the imaging results taken by CT or MRI before surgery. It suggests that using a standardized nomenclature can facilitate international collaborative studies all over the world. The INRGSS broadly classifies NB into localized and metastatic cases [(7)].

Aim: This study aims to stage neuroblastoma cases using CT scan according to the INRGSS, in relation to available clinicopathologic data.

PATIENTS AND METHODS

Patients: This retrospective study included 20 pathologically provenneuroblastoma cases. All patients presented to the Medical or Surgical Oncology outpatient clinics of the National Cancer Institute (NCI) -Cairo Universityand underwent CT scan in the Radiodiagnosis department. Patients' data were collected from their medical records during the period from January 2017 to July 2017 and reviewed for clinicopathologic characteristics. Cases with poor quality CT or with incomplete data were

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excluded from the study. **The study was approved by the Ethics Board of Ain Shams University.**

METHODS

1- All patients were subjected to contrast enhanced CT scan using the General Electric light speed, volume computed tomography" VCT" 64 present in the National Cancer Institute, where axial cuts were obtained with additional sagittal and coronal reconstruction images. This whole body CT scanner features 40mm coverage of patient's anatomy per rotation and 64 slices at 0.625mm. The high image resolution is ideal for pediatric imaging. This system maintains outstanding image quality, while reducing the patient's radiation exposure up to 70%.

2- For accurate diagnosis and proper staging of the 20 studied cases, CT scans were revised and staged according to the International Neuroblastoma Risk Group Staging System [(7)] (INRGSS)as shown in table 1, which can be used for both pre or post treatment CT scans. Staging was done according to the various image defined risk factors (IDRFs) recorded.

The INRGSS broadly classifies NB into localized and metastatic cases. The localized disease is further divided into L1 and L2 stages. The metastatic group is defined as stage M when the tumor has spread to other parts of the body, and stage MS where the tumor has spread only to skin, liver and/or bone marrow in patients younger than 18 months [(7)].

3- For cases having available post-surgical scans, the INSS was also used for staging [(6)], in addition to theINRGSS staging system (table 2).

4- The study was approved by the Ethics Board of Ain Shams University.

Table 1-International Neuroblastoma Risk Group Staging System (INRGSS)

Stage	Description
L1	Localized tumor not involving vital structures, as defined by the list of image-defined risk factors, and confined to one body compartment.
L2	Locoregional tumor with presence of one or more image-defined risk factors.
M	Distant metastatic disease (except stage MS tumor).
MS	Metastatic disease in children younger than 18 months, with metastases confined to skin,liver, and/or bone marrow.

Table 2- International Neuroblastoma Staging System (INSS)

Tumor Stage	Description
1	Localized tumor confined to area of origin; complete excision, with or without microscopic residual; ipsilateral and contralateral lymph nodes negative
2A	Unilateral tumor with incomplete excision; ipsilateral and contralateral lymph nodes negative
2B	Unilateral tumor with complete or incomplete excision; positive ipsilateral regional lymph nodes; contralateral lymph nodes negative
3	Unresectable tumor infiltrating across the midline with or without lymph node involvement;or, unilateral tumor with contralateral lymph node involvement; or midline tumor with bilateral lymph node involvement
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, and/or other organs
4S	Localized primary tumor as defined for stage 1 or 2 with disseminationlimited to liver, skin, and/or bone marrow(limited to infants less than 1 year of age)

RESULTS

I-Clinicopathologic Results

The age ranged from 1 to 10 years, with a mean of 3.40 (3.40 ± 2.21)and a median age of 3 years. Mostcases (18/20) were > 1 year (90%) and only 2/20 were aged 1year (10%).Out of the 20 patients, 10 were males (50%) and 10 were females (50%), with a M: F ratio of 1:1**.**

The Shimada classification for pathologic diagnosis and grading of NB was used (table 3). Among 20 cases, 17 were poorly differentiated (85%) and only 3 were well differentiated.

Immunohistochemical confirmation of diagnosis was also reported. All 20 cases were positive for synoptophysin and negative for Desmin and leucocyte common antigen (LCA).

Table 3: Shimada Classification of 20 Neuroblastoma patients

Grading	Number	Percent
Poorly differentiated:	**17**	**85.0**
Unfavorable histology	13	65.0
Favorable histology	4	20.0
Well differentiated-Favorable histology	**3**	**15.0**
Total	**20**	**100.0**

Presenting symptom was abdominal distension in the abdomen (15/20cases) noticed by parents. Fever and generalized weakness was reported in 3 and 2 cases respectively. The most common clinical finding was abdominal mass in 17 cases (85%). One case was a retroperitoneal mass, 1 presacral mass and one had a large hepatic mass, metastatic at initial presentation.

II- CT Radiologic Results

1-Site of Tumor

The suprarenal gland was the primary site of origin in 10 patients (50%), 6 were on the left. There were 5 cases of abdominal origin (25%).Site of all cases is shown in table 4.

Table 4: Site of tumor in 20 Neuroblastoma cases

Site	Number	Percent
Suprarenal Gland	10	50.0
Abdominal	5	25.0
Suprarenal, para-aortic and retroperitoneal	2	10.0
Paraaortic	1	5.0
Pelvi-abdominal	1	5.0
Presacral	1	5.0
Total	**20**	**100.0**

2- Tumor CT Criteria

As shown in table 5, 14/20 cases were heterogeneous (70%). There were 6hypodense masses (30%).

Table 5: CT Criteria of the 20 neuroblastoma cases.

CT Criteria	Number	Percent
Heterogeneous Mass	**14**	**70.0**
Not crossing midline/without calcifications	5	25.0
With internal calcifications.	7	35.0
Crossing the midline.	2	10.0
Hypodense Mass	**6**	**30.0**
Not crossing the midline/without calcifications.	3	15.0
Not crossing the midline /with internal calcification.	3	15.0
Total	**20**	**100.0**

3- Lymph Node Status

Positive lymph nodes were found in 14 /20 cases (70 %). The most commonly affected LNs were the para-aortic nodes (5 /14 cases). Six cases were negative for lymph node spread (30 %) (table 6).

Table 6: Lymph Node Status in 20 Neuroblastoma cases.

Lymph Node Status	Number	Percent
Positive	**14**	**70.0**
Para-aortic	5	25.0
Abdominal	4	20.0
DeepCervical	2	10.0
Cervical/Mediastinal	1	5.0
Hilar/subcarinal	1	5.0
PortaHepatis	1	5.0
Negative	**6**	**30.0**
Total	**20**	**100.0**

4-Metastatic Spread

It was found that 13 cases were free from metastatic spread (65%). Tumor metastasis was noted in7 cases (35%).

Brain metastasis was present in 2. Other metastatic sites are shown in table 7, including liver, skull and skin.

Table 7: Metastatic Spread in 20 Neuroblastoma patients

Metastatic Spread	Number	Percent
Negative	**13**	**65.0**
Positive	**7**	**35.0**
Brain	2	10.0
Face (mandible, maxillary, infraorbital)	1	5.0
Liver, skull, dura, skin.	1	5.0
Mandibular Ramus	1	5.0
Multiple hepatic focal lesions	1	5.0
Skull, dural metastasis	1	5.0
Total	**20.0**	**100.0**

5-Image Defined Risk Factors

To allow accurate staging according to the INRGSS, cases were analyzed for presence or absence of the different IDRFs.

Vascular encasement was noted in 11 (55%). Infiltration to nearby vital structures was present in 5 cases (25%). Invasion to one or both renal pedicles was evident in 10/20 cases (50%). Contact to head of pancreas was found in only 1 case (5%). However, compression to airways was not applicable in all studied cases (table 8, fig1).

Table 8- Frequency of Image Defined Risk Factors in 20 Neuroblastoma Cases

IDRF	Positive Nº	%	Negative Nº	%	Total Nº	%
Contact	1	5.0	19	95.0	20	100.0
Encasement	11	55.0	9	45.0	20	100.0
Infiltration	5	25.0	15	75.0	20	100.0
Invasion	10	50.0	11	55.0	20	100.0
Compression to airway	NA		NA		NA	

NA: Not Applicable

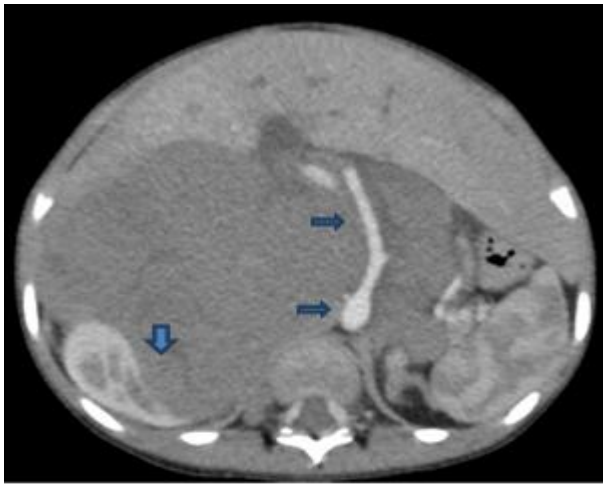

Figure 1. Axial CT showing encasement of the aorta and celiac trunk as well as invasion of the right renal pedicle and infiltration to the liver.

6-CT Staging according to the INRGSS

Among the 20 cases, 9 were classified as L2 (45%), having locoregional tumor with presence of 1 or more IDRFs. Stage M tumors with distant metastasis included 7/20 cases (35%). L1 stage with localized tumor not involving vital structures was present in 3cases (15%), and only 1 case was stage MS with skin metastasis (table 9).

Table 9: Frequency of INRGSS stages by CT in 20 neuroblastoma patients.

Stage	Number	Percent
L1	3	15.0
L2	9	45.0
M	7	35.0
MS	1	5.0
Total	**20**	**100.0**

7- CT Staging according to the INSS:

Only 7 cases had available postoperative CT scans allowing staging according to the INSS in addition to the INRGSS (table 10).

Table 10: CT Staging according to INSS in 7 neuroblastoma patients

INSS Stage	Number	Percent
IIA	1	14.29
IIB	2	28.57
III	2	28.57
IV	2	28.57
Total	**7**	**100.0**

8- Correlation between INGRGSS and INSS

Comparison of staging for the 7 cases with available staging by both INSS and INGRSS was done. One stage IIA case was staged L2, 2 stage IIB cases included 1 L1 and 1 L2. Both stage III cases were stage L2 and both stage IV cases were M stage by the INGRSS.

DISCUSSION

The International Neuroblastoma Risk Group Staging System [7] (INRGSS) is a recent staging system for NB, based on the imaging results taken before surgery or any other treatment.

The present study was conducted on 20 neuroblastoma cases in the pediatric age group. Staging for all cases was done according to the INRGSS. The INSS was also used to stage 7 cases having available postsurgical CT scans.

Regarding the clinicopathologic characteristics of the 20 studied cases, the age ranged from 1 to 10 years with a mean age of 3.4 years and a median of 3 years. This in accordance with other studies [8]. The majority of cases in the present work were > 1 year (90%) and none of the cases was above 10 years. It was reported that 98% of NB cases were less than 10 years[9].Also, in Egyptian studies, it was found that 77.4% and 95% of NB cases were > 1 year respectively [8] [10].There were 10 males and 10 females, with a M: F ratio of 1:1. Other studies reported that NB was slightly more common in males than females with a ratio of 1.1:1[8,9].

According to the Shimada classification, the majority of cases were poorly differentiated (17/20cases, 85%). Immunohistochemical confirmation of NB diagnosis showed that all cases were positively stained for synaptophysin, indicating presence of neurofilaments, and negative for desmin and LCA excluding diagnosis of rhabdomyosarcoma and lymphoma respectively [1].

The most common clinical presentation in this study (17/20 cases, 85%) was an abdominal mass. As demonstrated in CT scans, the majority of tumors were in the adrenal gland (10/20 cases, 50%) and abdomen (5/20 cases, 25%). This is similar to results of other studies [3] [11].However, another study reported that 70% of cases were of abdominal origin [12]. In the present study, 14/20 cases (70%) were seen on CT scans as heterogeneous masses, 7 of which having calcifications (35%). This is in accordance to previous studies describing NB as large lobulated heterogeneous mass [5]. The presence of calcifications favors the diagnosis of NB; it was reported in 85% of abdominal cases [13]. This higher percentage than the present study is due to larger number of cases studied.

In this study, 14/20 cases (70%) had positive nodal affection including regional and distant LNs. Distant metastasis was present in 7/20 cases (35%) including brain, hepatic, skull, dural and skin metastasis. About 50-60% of neuroblastomas were reported to have nodal or distant metastasis [9].Also; another study reported that regional LN affection and metastatic spread was found in 35% and 50 % of studied cases respectively [14].

IDRFs are important, as they define the anatomic extent of NB, and its relation to adjacent vital structures (vessels and nerves) or organs [12] [15].
In this work, only 1/20 cases (5%) showed contact with the head of pancreas, with no visible layer between the tumor and pancreas. Contact is not considered an IDRF.
Encasement was found in 11/20 cases (55%). In these cases, contact between the affected vessels and the tumor involved more than 50% of its circumference [15].
Infiltration of neighboring structures was detected in 5/20 cases (25%). It affected the pancreas, the liver, the hepatoduodenal ligament or diaphragm. An infiltrating tumor extends into an adjacent organ, with absence of margins between them [15].
Invasion of one or both renal pedicles was evident in 10/20 cases (50%).Due to difficult dissection of the renal pedicle during surgery; this risk factor was considered present even with presence of contact only between the tumor and the renal vessels [15]. All these IDRFs are similar to those of previous studies, but with much higher frequency which is explained by late stage presentation and lower number of cases included in this work. Other studies reported vascular encasement in 21% and 13%, invasion of renal pedicles in 5 % and 9% and infiltration of adjacent organs in 7% and 9% respectively[16] [17].
In this study, Stage L2 was the most commonly found, 9/20 cases (45%) had locoregional tumor with presence of 1 or more IDRFs. Stage M followed, 7/20 cases (35%) involved distant metastasis. L1 was found in 3 cases (15%), with localized tumor confined to 1 body compartment without any IDRFs, LNs or metastatic spread. Only 1 case was stage MS with liver and skin metastasis aged less than 18 months as mentioned in the

INRGSS. Staging according to the INSS was possible in only 7/20 cases, having available post operative CT scans. Stages IIB, III and IV included 2 cases each, while only 1/7 cases was stage IIA. Comparing the 7 cases by both staging systems in the present work, showed that the stage IIA case was restaged as L2.The 2 stage IIB included 1 L1 and 1 L2.Both stage III cases were also L2, and both stage IV cases were M stage according to the INRGSS. This is in accordance with the results of another work, where stages I, II and III of the INSS were restaged into L1 or L2 in the INRGSS. Stage IV cases were stage M, and Stage IV S was stage MS [(18)]. It was reported in several studies that INRGSS is a standardized approach, facilitating collaborative studies between different centers and comparison of patient outcome of different treatment protocols, which was not possible when using the INSS [(17) (19)]. Both INSS and INRGSS were found to be highly prognostic. The INRGSS is much more reliable in comparison to the risk based clinical trials. The limitation of this staging system is that it cannot be applied post-treatment [(7)].

CONCLUSION

The use of the INRGSS is a recent valuable pretreatment staging system for neuroblastoma, allowing accurate classification depending on the presence or absence of IDRFs. It is not intended to replace the INSS but can be used in parallel. Imaging by CT scan plays an important role in diagnosis and staging of neuroblastoma.

However, further researches on a larger scale are needed to allow more accurate and detailed information about the value of the INRGSS in Egyptian neuroblastoma cases, with correlation to patient outcome.

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