Neuroblastoma - Digital Imaging and Staging Systems - Comprehensive Case-Based Review

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Learning objectives

Due to the great clinical and social significance of neuroblastomas in childhood, this work aims to present a succinct and comprehensive review of the diagnostic imaging features of this condition, as well as its up-to-date staging and risk stratification systems. The text is supplemented by images from a retrospective overview of 39 cases of neuroblastoma spanning up to 16 years back from the date of submission.

The primary imaging diagnostic modalities for neurofibroma include ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine. This work will focus primarily on CT and MRI, while also providing a succinct, yet sufficient, overview of ultrasonographic and nuclear medicine findings and guidelines.

General information is discussed in the Background section. Imaging applications, a quick breakdown of imaging characteristics, reporting tips, example protocols, staging systems, and specific clinical example cases are discussed in the Findings and procedure details section. Treatment, albeit sporadically mentioned, is not the focus of this work.
Neuroblastoma (NBL) was originally described by Virchow in 1863. [10] It is the most common embryonal tumor and the third most frequent malignant tumor in children (after leukaemia and brain malignancies). [1, 2, 10] NBL is the most frequent extracranial tumor before 18 years of age as it makes up 8-10% of pediatric neoplasms. It accounts for about 15% of childhood cancer deaths. [2] It stems from the primitive cells of the sympathetic nervous system and of the adrenal medulla. [1, 3, 5, 6, 8] Between 25% and 35% of cases manifest before the first year, while 75% manifest by the fourth. 90% of cases are diagnosed before 6 years of age. Only 3% of cases present after 10 years of age. Mean age of diagnosis is 2 years. Neuroblastoma yearly morbidity varies between 5-10 per million children. Most sources agree that boys are slightly more likely to be affected. [1, 9, 10] There are no racial differences in frequency, though such are described in tumor biology - African-Americans are more likely to have a fatal outcome. Mean age of diagnosis is about 18-22 months. [1, 2, 9, 10, 12] Approximately 40-70% of patients have metastatic disease at diagnosis. [1, 5, 6, 9] Survivability is highly dependant on the age at which diagnosis is established and the stage of disease - children below 1 year of age and at an early stage have the best prognosis. [1] NBLs have a variable course - some behave aggressively, while others (typically in infancy) can spontaneously regress. [6, 7, 8, 10, 31]

NBL is most frequently located in the abdomen - 65-70% of cases. The adrenal glands make up 35% of all cases as the most common site of origin, while the extraadrenal retroperitoneum (the paraspinal ganglia and, to a lesser degree, the organ of Zuckerkandl) primaries comprise 30% of cases. Mediastinal cases are 15%, cervical - 4%, spinal ganglia - 8%, pelvis - 2%, and olfactory apparatus - 1%. Multiple primary tumors can occur in up to 2% of cases, potentially with varying degrees of differentiation. [1, 2, 5, 7, 10, 12]

Newborns and infants can be affected (congenital and neonatal neuroblastoma). [1, 10] Neuroblastoma is the most common malignancy in the first month of life. Neonatal NBL is of adrenal origin. It has a very good prognosis, and despite metastatic spread present at diagnosis in almost half of patients, survival rates are over 90%. [10] Fetal NBL can be detected on antenatal ultrasonography or magnetic resonance tomography as early as 19 weeks (mean age of discovery 36 weeks gestation) - it is adrenal in origin in 90% of cases. [10] Its appearance is that of a complex mass with cystic components in the locus of the adrenal. It is possible to appear entirely solid or predominantly cystic. Color Doppler often shows diffuse vascularity instead of a single feeding vessel. [2] Fetal neuroblastoma also has a very good prognosis, treatment is conservative. [10]

I. CLINICAL MANIFESTATIONS
The clinical manifestations of the disease are quite varied and determined by the localization and size of the primary tumor, as well as the spread of any metastatic deposits. Initially clinical signs are scarce. Most frequently the presentation is by symptoms, associated with metastatic disease. [1, 4, 5, 6] The signs are generally categorized in three groups of symptoms.

Firstly, **specific symptoms**, related to the **site of the primary mass** - a direct result of organ compression / destruction by the initial tumor. Since neuroblastoma can arise in any structure of the sympathetic nervous system, clinical manifestations can be very diverse. Intraabdominal tumors can produce a sensation of focal weight, abdominal pain, abdominal distention or asymmetry, palpable abdominal mass, venous collaterals, and rarely ascites. Intrathoracic / cervical neuroblastomas manifest with cough, dyspnea, rarely cyanosis or palpable cervical mass. Primary neuroblastoma, arising from the olfactory organ (esthesioneuroblastoma), demonstrate dyspnea, olfactory dysfunction, and upper pharyngeal obstruction. [1, 6]

Characteristic of these tumors are neurological and neurovegetative symptoms: Claude Bernard-Horner syndrome (ptosis, myosis, and enophthalmus) on the affected side in cervical and mediastinal forms; temperature differences between facial halves, between upper or between lower limbs; spinal ganglia forms - urinary bladder and bowel incontinence, radicular signs, lower paraplegia due to spinal cord compression. [1, 6, 8, 9]

Secondly, **clinical manifestations of metastatic disease** - neuroblastoma can metastasize via hematogenous and lymphatic spread. The primary type of metastases at diagnosis are in bone (50-60%). Additional frequent locations of metastatic deposits are liver, skin, retrobulbar space. Lymphatic spread to mediastinal / peripheral lymph nodes is seldom. Sometimes, in advanced disease with a long evolution, rare pulmonary metastases can manifest. Meningeal deposits are exceptionally rare. In up to 5% of cases with neuroblastoma metastases the primary lesion cannot be identified. [1, 10]

Frequent and characteristic symptoms are bone pains with consequent limping - part of the Hutchinson syndrome in neuroblastoma. [1, 2] Bone marrow involvement results in marked anaemia, and less frequently in haemorrhagic syndrome and increased risk of infection. In some cases of advanced disease linear ecchymoses in the shape of glasses (raccoon eyes) can be seen periorbitaly or on the eyelids. [1, 7] Extensive hepatic metastases (Pepper syndrome) manifest as hepatomegaly. [1, 2] Retrobulbar metastatic deposits can result in bulbar protrusion. Small blue or purple subcutaneous metastases can manifest in infants under 12 months of age - they are dubbed "blueberry muffin" syndrome, also sometimes referred to as Smith syndrome. [1, 2, 7, 9, 10] Despite neuroblastoma being of neurogenous origin, brain metastases are rare. [1]
Lastly, **general clinical symptoms** - advanced cases can manifest overall weakness, loss of appetite, irritability, weight loss, pyrexia, sweating. Watery diarrhoeia with electrolyte loss (dehydration + hypokalemia) results from increased secretion of vasoactive intestinal polypeptide (VIP - vipoma syndrome) - it can be observed in 1% of abdominal neuroblastomas, more often in mature ganglioneuroblastomas. Increased secretion of catecholamines leads to tachycardia, headache, nausea/vomiting, red dermographism, intermittent arterial hypertension. [1, 7, 10] The clinical complex of myasthenia gravis is seldom observed. A characteristic symptom of neuroblastoma is the opsoclonus-myoclonus syndrome (also known as the "dancing eyes and dancing feet" syndrome); it's observed in only 2% of cases, usually in very young children. [1, 2, 7, 8, 9, 10, 11] Manifestations of catecholamine intoxication, as well as vipoma and opsoclonus myoclonus syndromes can also be classified under paraneoplastic symptoms, which are negated once the primary is excised. [1, 11]

II. GENETIC RISK

As with other tumors, neuroblastoma emerges as a result of genetic mutations in critical genes, which control cellular growth, proliferation and differentiation. This enables uncontrolled growth and division, forming a tumor mass. Most such mutations are acquired - somatic mutations, not heritable. Neuroblastoma resulting from somatic mutations is termed sporadic and requires at least two separate mutations to manifest. Much less frequently genetic mutations that increase the risk of neuroblastoma can be inherited via gamete (autosomal dominant pathway) - the resulting tumor is termed familial. The mutated allele is therefore present in every cell of the child's body, necessitating only a singular additional somatic mutation to trigger disease development. This explains the incomplete penetrance - not all carriers will develop neuroblastoma. [1]

Familial neuroblastoma is a rarity - 1-2% of cases. Characteristically diagnosed at a very early age (9 months) and multifocal (20% of primary familial neuroblastomas). Pathological variants of the ALK (the ALK gene is in close proximity to MYCN in the short arm of chromosome 2p) and PHOX2B genes are the most frequent causes of the familial type. Patients with neurofibromatosis 1 and Beckwith-Wiedemann disease are also more prone to develop neuroblastoma than the general population. [1] Additional associated conditions include DiGeorge syndrome and Hirschsprung disease. [2]

**Table 1. Genetic syndromes in which neuroblastoma is the primary associated tumor** [1]

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Name</th>
<th>Tumor syndrome</th>
<th>Way of inheritance</th>
</tr>
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<table>
<thead>
<tr>
<th>GPC3</th>
<th>Glypican 3</th>
<th>Simson-Golabi-Behmel syndrome</th>
<th>X-linked recessive</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRAS</td>
<td>v-Ha-ras (Harvey rat sarcoma viral oncogene homolog)</td>
<td>Costello syndrome</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>PALB2</td>
<td>Partner and localizer of BRCA2</td>
<td>Fanconi (N) anemia</td>
<td>Autosomal dominant (biallele mutations)</td>
</tr>
<tr>
<td>PHOX2B</td>
<td>Paired-like homeobox 2b</td>
<td>-</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>ATRX</td>
<td>Chromatin-remodeling complex</td>
<td>Alpha thalassemia and mental retardation</td>
<td>X-linked</td>
</tr>
</tbody>
</table>

It has been established that 60-76% of patients with thoracic NBL have increased levels of urinary catecholamines (vanillylmandelic acid, VMA). [1, 9, 10] Based on this, attempts have been made to screen for neuroblastoma in infants, however, this was not reported to lead to a significant improvement of therapeutic results. Conclusions drawn from these studies suggest that the "wait and see" strategy may prove optimal in many patients with incidentally found neuroblastomas. [1, 10, 13, 14, 15, 16]
Findings and procedure details

IMAGING METHODS

I. RADIOGRAPHY

Possibly the most widely spread method of diagnostic imaging. Unfortunately, it yields the smallest amount of information regarding the initial tumor. Neuroblastoma (NBL) has a very unspecific appearance - an intrathoracic / intraabdominal mass of soft tissue attenuation. Intrathoracic lesions are usually paraspinal, with a sharp pleural-pulmonary interface; they are often oriented along the vertical axis of the body - following the sympathetic chain. [8] Adjacent bones (ribs, vertebrae) may be eroded/remodelled by pressure from the lesion; potential widening of neural foramina and focal widening of the spinal canal could be appreciated on radiographs. [8] Between 30-50% may demonstrate calcifications. [2, 7, 10]

Skeletal metastases are usually lucent, with ill-defined borders, with or without periosteal reaction. [1, 2, 23] Metaphyseal lucency can be observed as a result of secondary tumor deposits in bone, mimicking leukaeic infiltration. Sclerotic metastases are uncommon. [2, 10]

II. ULTRASONOGRAPHY

Ultrasonography is a cheap and widely available tomographic imaging method with no ionizing radiation. It is recommended as the initial examination of choice when beginning to explore the patient. Ultrasound is very valuable for establishing the initial diagnosis and for staging malignant disease. The sonographic image gives information in regard to the location, size, internal echogenicity, contour, and signs of invasion. All of these must be considered, when building the differential diagnosis. [1]

In relation to size, neuroblastoma has been described to be asymptomatic at large sizes in some cases, while manifesting early symptoms at small sizes in others. [1]

Initial localization can be difficult to pinpoint with large lesions, due to their sheer size and encroachment upon several adjacent structures / spaces - thus complicating the differential. NBL can be situated in the adrenal / paravertebral region, or closely adherent to a kidney. Paravesical masses should have rhabdomyosarcoma included in their differential diagnosis, while hepatoblastoma should be considered in masses closely adherent to the liver. [1]
Echogenicity can vary between hypo- and hyperechogenicity, while internal structure is usually described as primarily heterogeneous with typical central high-amplitude echoes, corresponding to calcifications. The presence of calcification is regarded as one of the key imaging features of neuroblastoma. [6] Calcification appears as either coarse foci of echogenicity (usually without distinct acoustic shadowing) or is fine, resulting in diffusely increased tumor echogenicity. [10] NBL can also demonstrate hypo- to anechoic areas, relatively few in number, but quite large - these correspond to areas of internal tumor hemorrhage or necrosis. It is possible, albeit quite rarely, for a large central necrotic zone to form. In contrast, neuroblastoma’s primary differential condition - nephroblastoma (Wilms’ tumor) - demonstrates a polycystic pattern with hyperechoic septae and anechoic areas, smaller in size than the ones in NBL. Wilms’ also exhibits cystic anechoic areas much more commonly than neuroblastoma.[1, 2, 5, 7, 9, 10]

Identification of an ipsilateral displaced kidney further drives the differential towards NBL. Additional potentially displaced structures include the aorta and inferior vena cava - ventral rearrangement of the latter two is appreciable with sonography. They, along with the mesenteric and renal vessels can be demonstrated to have been surrounded by the lesions. Patency can be confirmed with color Doppler. [10]

In terms of contour solitary masses are usually smooth and sharply demarcated, while secondary deposits tend to be multilobulated. Invasiveness / infiltration as well as compression of adjacent structures are crucial factors in determining the optimal treatment strategy - all of these can be (at least partially) identified via ultrasonography. Typically, liver invasion by an adjacent NBL mass can be manifested by absence of differential movement between them. [10]

III. COMPUTED TOMOGRAPHY(CT) AND MAGNETIC RESONANCE IMAGING (MRI)

Imaging is at the base of diagnosing, staging, and monitoring solid tumors, including neuroblastoma. NBL’s structure is unspecific and quite similar to the other abdominal neoplasms in children - Wilms’ tumor, ganglioneuroblastoma, and ganglioneurinoma. Imaging on its own is insufficient to identify the histological nature of solid tumors. Two separate strata of tumor evaluation exist in characterizing neuroblastoma - primary tumor and metastases. The choice of imaging modality is dictated based on the location of the primary mass. [1] In a study among 31 children with abdominal NBL Hugosson C., et al. report no significant difference between CT and MRI when evaluating tumor location and size. However, the same study notes MRI’s superiority for evaluating intraspinal invasion. Both methods surpass ultrasonography in assessment of local invasion. In terms of appraisal of metastases scintigraphy and bone marrow biopsy perform en par with CT and MRI. [1, 17] Initial masses in the cervical region are recommended to be
evaluated with MRI; when inapplicable, a suitable substitute would be contrast-enhanced CT (CECT), accompanied by ultrasound. Thoracic localizations are recommended to be imaged with MRI; when impossible - CECT. Abdominal localizations - CT or MRI, either of which accompanied by sonography. [1, 18]

On CT, neuroblastoma is typically heterogeneous. [2, 9, 10] Once again, calcifications are an important hallmark - they are seen in up to 80-90% of cases (note that only 50% of thoracic cases calcify), and can appear sand-like, curvilinear, or globular. [1, 2, 7, 8, 9, 10] Low attenuation necrotic or hemorrhagic areas may be evident. [1, 2, 9, 10] The lesions show heterogeneous or little enhancement. [10] NBL can develop beneath the aorta, consequently lifting it off the vertebral column. [2] Neuroblastoma is described as a poorly demarcated, lobulated mass that can insinuate itself around (surround), and eventually engulf abdominal structures. [2, 7, 10] It has a characteristic tendency to encase vessels and compress/displace adjacent organs (displacing the renal axis for example). [2, 7] However, much less frequently, in more aggressive lesions infiltrative growth has been reported, most often invading the kidney or psoas muscle - in such cases, the differential with Wilms' tumor is challenging. [2]

NBL can often extend across the midline, and even into the thorax. [1, 7]

Lymph node enlargement is often present. [2]
MRI is superior to all other modalities in establishing the organ of origin, as well as intracranial/intraspinal/epidural/leptomeningeal/paraspinal and bone marrow disease. [2, 6, 10] All children with paraspinal masses should undergo MRI. [10] On T1 weighted images neuroblastoma appears hypointense, retaining its heterogeneity as also seen on ultrasound and CT. On T2 weighted images it is once more heterogeneous, but hyperintense. T2 demonstrates cystic/necrotic areas with high signal intensity. Signal voids may be evident (representing calcification). [2, 8, 9, 10] Most often, NBL is approximately isointense to nervous tissue on T1, and mildly hyperintense to it on T2.
[8] Post contrast (Gadolinium), enhancement is variable and heterogeneous, much like in contrast enhanced CT. [2, 8, 10]

Diffusion weighted imaging (DWI) demonstrates areas of restricted diffusion - where there is lack of free random motion of water protons. Such areas correspond to soft tissue with cells packed more tightly than normal - namely tumors. Ergo, NBL demonstrates as a high signal lesion on DWI. [6]

There are three crucial tumor characteristics that a radiologist must evaluate - localization, size, and Image Defined Risk Factors (IDRFs, discussed in further detail below - see Staging). [1, 21]

1. **Tumor location** - neck, thorax, abdomen, pelvis, para-/intraspinal.

In paraspinal NBL the location and size are determined in relation to a neighbouring vertebra. For abdominal NBL their relation to the sagittal plane has to be evaluated - midline or lateral location (according to INSS - see Staging below). Midline tumors are characterized according to their relation to the great vessels - aorta and vena cava, while lateral tumors - according to their relation to the aorta, vena cava, and ipsilateral kidney. Tumors crossing the midline into the contralateral side are considered stage 3 (INSS - see Staging). By definition, if the mass crosses the contralateral aspect of the vertebral body of the same level, it has crossed the midline. Tumor relations to vital structures (structures that cannot be sacrificed without impairment of normal function) must be evaluated for optimal surgical strategy, where applicable. [1, 19, 22]

**Fig. 8**: Case 05

*References:* Diagnostic Imaging, University Hospital Saint Marina - Varna/BG
2. Tumor size - in well-demarcated lesions it is to be measured in three planes.

Due to the complex geometry of neuroblastoma the three-dimensional orthogonal approach is preferrable to RECIST. Pre-operative volume is calculated by the formula V = D1 x D2 x D3 x 0.52. The maximum transverse measurements (D1 and D2) are measured in the axial plane, while the height (D3) is measured in the sagittal or coronal plane. [1, 22]

Measuring complex tumor masses or masses with a multitude of adjacent lymph nodes is harder. It is recommended that adjacent lymph nodes be measured as part of the primary mass. [1, 10] The results from the measurement can be reported as a sum of the axial dimensions (D1 + D2), as a product of multiplication (D1 x D2), or as a volume (see above for formula). An adequate answer to treatment is considered a more than 30% reduction in the sum, or over 50% reduction in the product, or over 65% reduction in volume. Progression is defined as an over 20% increase in the sum, or over 25% increase in the product, or as over 40% increase in volume. [1]
3. **Image Defined Risk Factors** (IDRF, see Staging below) - the majority pertain to abdominal NBLs, due to their usual close relationship with major abdominal vessels and organs.

The tumor's relationship to adjacent structures is best appreciated in the imaging plane perpendicular to the plane of contact between NBL and said structure. Relationship to vessels is appreciated in two planes - perpendicular and longitudinal to the vessel of interest. There are several degrees of interrelation: separation, contact, encasement, and infiltration. [1, 22]

Separation - visible layer of fat between tumor and neighbouring structure. [1,22]

Contact - no visible layer present between mass and adjacent structure, but also no visible invasion. Less than 50% of the circumference of an arterial vessel is in contact with the mass. Contact is NOT an IDRF, except for renal vessels - attempts to dissect them from a mass holds a high risk of renal infaction / nephrectomy. [1, 22]

Encasement - surrounding of neighbouring structure by neuroblastoma. IDRF: at least 50% of an arterial vessel's circumference must be in contact with the mass; venous vessels should be compressed by the tumor with complete obliteration of their lumen. [1, 22]
Compression - tumor in contact with AIRWAY, reducing its short axis, thus - IDRF. [22]

Infiltration - ill-defined margins between tumor and adjacent structure - IDRF. Infiltration of vessels cannot be appreciated on imaging. [1, 22]

Fig. 2: Contact vs encasement - differentiating features.

References: Georgi Valchev MD


**Fig. 6:** Case 04a

**References:** Diagnostic Imaging, University Hospital Saint Marina - Varna/BG
Fig. 7: Case04B

References: Diagnostic Imaging, University Hospital Saint Marina - Varna/BG

- MRI coronary series
- Evident compression of inferior vena cava
- 4 year old patient
- Axial CT venous
- Calcified retroperitoneal mass
- Small area of hypodense necrosis within mass
- Mass elevates inferior vena cava from spine

Fig. 12: Case 09
References: Diagnostic Imaging, University Hospital Saint Marina - Varna/BG
IDRFs are specific in accordance to tumor site - neuroblastoma originating from the paraspinal sympathetic chains may extend through the neural foramina, and into the spinal canal - dubbed "dumb-bell" tumors. [1] They are seen in 10% of abdominal, 28% of thoracic and occasionally in some cervical NBLs. [10] Cord compression is a common
symptom among dumb-bell lesions. [1] The spinal cord and nerve roots in the region of neuroblastoma are usually displaced, but not frankly invaded - the lesion typically remains extradural. With marked compression, the involved myelon may appear edematous. [8] MRI demonstrating more than 1/3 of the spinal canal diameter is invaded or loss of the leptomeningeal spaces is considered an IDRF. [1, 22] Note that tumor extension below L2 causes radicular involvement, however, that is not a contraindication for excision of the extraspinal tumor component. [22] Meningeal involvement is best appreciated on MRI. [1]

Fig. 4: Case 02

References: Diagnostic Imaging, University Hospital Saint Marina - Varna/BG
Mediastinal masses involving the costovertebral junction between T9 and T12 may result in spinal cord ischaemia during excision, due to damage to the artery of Adamkiewicz. This should be considered and IDRF, however, often a sufficient collateral web has developed due to the slow growth of NBL, which could compensate for the potential loss of Adamkiewicz. [22]

Additional location-based characteristics of neuroblastoma can aid in narrowing the differential diagnosis. Primary cervical localization is unusual - only 2-3% of cases - most commonly manifesting as a well demarcated mass in the parapharyngeal space, with displacement of the common carotid artery, its internal and external branches, and the jugular vein. The differential of a cervical NBL includes lymphoma, metastatic deposits,
and other neurogenic tumors, especially neurofibromas, early neuroectodermal tumors (PNETs) and rhabdomyosarcoma. Paraspinal intraabdominal NBL can be found both inside and outside of the spinal canal; infiltration into the paraspinal musculature can be observed. Mediastinal neuroblastoma is almost always paravertebral in the posterior mediastinum; it can manifest rib and vertebral erosions, as well as destructive changes in the costovertebral joints; most frequently mediastinal NBL does not result in changes in the myelon at diagnosis due to slow growth; the lesion may extend directly into mediastinal lymph nodes or into the abdomen via the retrocrural space; the differential includes teratoma, inflammatory pseudotumor, and thymic tumors. [1, 8] Adrenal neuroblastoma can manifest cystic and hemorrhagic zones, calcifications, substantially aiding the differential with Wilms' tumor; infiltration into paraspinal musculature is easily identified; post-contrast adrenal NBL shows absence or minimal to moderate enhancement; the differential includes adrenal masses, resulting from hemorrhage, non-Hodgkin lymphoma, teratoma, rhabdomyosarcoma, anterior meningocele, and PNET. [1] Presacral masses are an unusual manifestation of NBL, accounting for about 5% of all cases. Presacral neuroblastoma commonly demonstrates characteristic amorphous, irregular calcifications. They are also associated with a better prognosis than the ones arising in the upper abdomen. [5]
Fig. 18: Case 14a  
**References:** Diagnostic Imaging, University Hospital Saint Marina - Varna/BG

- Axial CT (arterial+venous)  
- Total encasement of left renal artery and hypoperfusion of left kidney  
- Left hydronephrosis due to mass  
- Ventrally displaced left renal vein  
- Compressed inferior vena cava

Fig. 19: Case 14b  
**References:** Diagnostic Imaging, University Hospital Saint Marina - Varna/BG
In terms of metastatic disease, the liver is the primary focus of NBL in children under 1 year of age - 60% present with metastatic disease; [1, 2, 4, 5] NBL, followed by Wilms' tumor, are the most common primaries to metastasize to the liver in children; [1, 4, 5] the secondary liver changes manifest as multiple discrete focal lesions or diffuse parenchymal infiltration (infants at stage 4S), which could also be multifocal and with areas of low density ± calcification; [1, 4, 5, 10] regardless of the locus of the primary, the liver needs to be evaluated for metastatic deposits.

Neuroblastoma frequently disseminates to the skull base and orbits; skull metastases demonstrate distention of the sutures due to underlying nodular dural metastases (dural mets can be diffuse or nodular). [1, 2, 7] Cerebral secondary deposits are very rare and tend to have a very variable appearance when present; their differential includes chronic
anaemias (thalassemia major, iron deficiency anemia, spherocytosis, histiocytosis). [1, 2, 7]

**Bone** metastases manifest in 60% of cases; they are osteolytic, with/without periosteal reaction. [1, 23] Bone marrow disease usually demonstrates as diffuse infiltration, but it may also present a nodular pattern (with areas of low signal on T1 and high signal on T2). [10] **Pulmonary** metastases are rare - 1-3%; usually reported as bilateral multiple small nodules. [1, 10] Most frequently there are additional secondary deposits outside of these areas - MIBG-scintigraphy is best for their discovery and evaluation (see below) - said examination is to be performed prior to surgery. The role of whole body MRI for bone examination is still uncertain; initial publications report high sensitivity. A combination of a native and Gadolinium-enhanced T1 scan is considered to be optimal. [1, 9] Due to a low sensitivity of CT to small areas of cortical destruction, it is possible to under-stage stage 4 disease. Because of that, some studies suggest that MRI with whole body short time inversion recovery (STIR) imaging can replace the CT + bone scintigraphy combination for overall assessment of stage 4 NBL, reducing the radiation exposure and number of sedation procedures requires. [10]
- 4 year old patient
- Right abdominal inhomogeneous mass
- Axial CT (arterial) demonstrates total encasement of right renal artery
- Axial CT (venous) demonstrates total encasement of a ventrally displaced inferior vena cava

- Coronary MRI IR shows high signal bone marrow metastases in both femurs, both acetabula, and left iliac wing
- MIBG scintigraphy - high captation in primary adjacent to liver and in both femurs

**Fig. 15:** Case 12

**References:** Diagnostic Imaging, University Hospital Saint Marina - Varna/BG
- 2 year old patient
- Axial CT native and venous
- Mass stemming from right adrenal
- Calcification evident on native phase
- Encasement of right renal artery

**Fig. 14:** Case 11

**References:** Diagnostic Imaging, University Hospital Saint Marina - Varna/BG

NBL post conservative treatment can become fibrotic, and calcify additionally. [6, 10]

**Differential diagnosis**

A list of common conditions that mandate consideration in patients with suspected neuroblastoma is provided below:
Table 2. [2]

For intrathoracic NBL consider:
- Intrathoracic lymphoma
- Extralobar pulmonary sequestration
- Round pneumonia
- Ganglioneuroma
- Ganglioneuroblastoma

For intraabdominal NBL consider:
- Ganglioneuroma
- Ganglioneuroblastoma
- Rhabdomyosarcoma
- Wilms' tumor

Widening of the inferior paravertebral soft tissues may be due to thoracic discitis - discitis, however, will also manifest narrowing of the affected disc space as well as loss of definition of the vertebral endplates. [9] Mediastinal masses in children under 3 years of age are to be considered a neuroblastoma until proven otherwise. When said mass demonstrates air bronchograms, parapneumonic effusion, and a lack of rib erosion/intraspinal extension, posterior round pneumonia could be considered. Lymphoma usually presents as an anterior mediastinal mass. Ganglioneuroma is the most common mediastinal mass in adolescents and young adults - it is a benign lesion, with imaging features similar to NBL. [9]

The primary differential of abdominal neuroblastoma is Wilms' tumor - both occur in early childhood and present as large abdominal masses, closely related to the kidneys. Below is a full list of useful distinguishing features:

Table 3. [2, 5]

<table>
<thead>
<tr>
<th>NBL</th>
<th>Calcification - very common (90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Encases vascular structures without invading them</td>
</tr>
<tr>
<td></td>
<td>Younger age group (&lt;2 years)</td>
</tr>
<tr>
<td></td>
<td>Poorly marginated</td>
</tr>
<tr>
<td></td>
<td>More common to have extension into thorax</td>
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<tr>
<td></td>
<td>Can elevate the aorta off the vertebral column</td>
</tr>
</tbody>
</table>
More commonly crosses the midline, especially behind the aorta

More aggressive variants can invade the kidney (rarely)

Wilms' Calcification - uncommon (10-15%)

Displaces adjacent structures without enveloping them / without insinuating between them

Well demarcated

Claw sign with the kidney

Slightly older group (peak incidence 3-4 years)

Extension into inferior vena cava / renal vein

Example CT protocol

Prepatation - prior to the procedure, the scanning conditions should be adapted for neonates / infants - appropriate temperature, immobilization, anesthesia, and sedation. The use of multidetector CT (MDCT) reduces the need for sedation with proper immobilization. There is no consensus regarding the use of oral contrast - it would be an impediment to proper anesthesia (the latter can be applied in no less than 4 hours after peroral intake of liquids). No enema is required. [1]

Technique - 1. Frontal topogram/localizer/scout - no diagnostic value, used for planning. 2. Native scan of the area of interest - initial attenuation values of tissues, good recognition of calcification. 3. Post contrast scans in arterial and portal venous phases: use non-ionic low-osmolar contrast with iodine concentration in the range of 300-350 mg/l; contrast volume - 1,5-2 ml/kg of patient weight; infusion speed adapted to the patient’s age - usually 0,8-2 ml/sec; scan time is specific for each examination - dependent on available scanner hardware and patient size; scan delay in contrast enhanced studies - 22-25 sec for neck/thorax, 35 and 60 sec for abdomen and pelvis (arterial and portal venous phases respectively); slice thickness - 1-1,5 mm, Pitch 1; tube voltage - 80-100 kV in neonates and babies, 100-120 kV in older children (minimize dose). [1]

Example MRI protocol
Preparation, sedation, monitoring. Image quality is heavily susceptible to motion artifacts. The latter can severely reduce diagnostic value. Sedation is mandatory and all patients need to be connected to adapted monitoring devices. Different sedation protocols can be used, depending on local strategies. Hearing protection is mandatory. [1]

Technique - MRI always requires personalization of scan settings for each patient and the zone of interest. Currently, there is no consensus as to an optimal protocol in patients with NBL. Every protocol must be adapted to compensate for any motion, breathing, and cardiac activity artifacts. Pixel size varies between 0.5 and 1 mm and slice thickness - 3-6 mm for 2D images, 1-3mm for 3D images. The examination must be conducted in three planes - axial, sagittal, and coronal; sagittal and coronal images are mandatory in paravertebral and spinal localization for evaluation of foraminal and intraspinal extension. Adequate sequences are T2 and T1, with T2 preferably augmented with fat supression (fat saturation). The use of whole body MRI for bone marrow evaluation is underrepresented due to underperformance in comparison to metaiodobenzylguanidine (MIBG) scans - MIBG has higher specificity. Whole body MRI is also deficient as a means of controlling response to treatment - abnormal signal persists for months, despite proven good treatment response. [1]

Signal intensity of neuroblastoma is unspecific. Diffusion techniques could be of use for better demarcation of the mass, however, their contribution has yet to be sufficiently evaluated. [1]

The amount of Gadolinium used should not exceed 0.1 ml/kg. Intravenous contrast should be avoided in children with impaired renal function for fear of secondary nephrogenic systemic fibrosis. [1]

Successful planning of individual therapy demands precise imaging demarcation of the primary NBL mass, as well as thorough evaluation of proximal and distant metastatic deposits. CT and MRI are the initial examinations for staging. Protocols can vary between institutions. Ultrasonography is primarily used as an in-between evaluation method. MRI is superior for paraspinal lesions - it is crucial for the evaluation of foraminal and intraspinal spread, as well as spinal cord compression. MRI also surpasses CT when evaluating epidural space involvement, leptomeningeal metastases, and bone metastases. [1]

IV. NUCLEAR MEDICINE

Nearly 40% of children diagnosed with neuroblastoma are at stage 4 (INSS, see below) at diagnosis with distant metastases present. An assiduous search for all primary
and secondary deposits is mandatory for proper staging, which directly correlates to prognosis and affects the amount and type of therapeutic procedures. To ensure that all lesions are found the span of available diagnostic procedures is as wide as possible - it is supplemented by some specific nuclear medicine tests, such as 131I/123I-metaiodobenzylguanidine (MIBG) scintigraphy, as well as more general use nuclear medicine tests, namely bone scintigraphy and FDG positron emission tomography with CT (PET/CT). [1, 2, 10]

1. 131I/123-metaiodobenzylguanidine scintigraphy and single-photon emission CT (SPECT)

The radiopharmaceutical MIBG is a functional noradrenaline analogue, synthesized on the basis of neuronal blockers bretillium and guanethidine. Its transport pathway and intracellular biodistribution are analogous to the biogenic amines. MIBG, as a marked compound, is used in the visualization of tumors of neuroectodermal origin, which have retained their capacity to recapture extracellular noradrenaline - NBL, pheochromocytoma, and to a lesser degree - paraganglioma, medullary thyroid carcinoma, Merkel-cell carcinoma. The radiopharmaceuticals are marked with Iodine-123 and Iodine-131, respectively 123I-MIBG and 131I-MIBG. Since 123I-MIBG has significantly better imaging characteristics and lower dose, 123I-MIBG is preferred for pediatric use. 131I-MIBG is an acceptable alternative only if there is no logistic access to 123I-MIBG, although it is chosen for dosimetric planning prior to 131I-MIBG therapy. Approximately 90% of NBLs uptake MIBG. No more than 4% of pediatric tumors (with the exception of nephroblastoma/pheochromocytoma) are detected using MIBG scans, ergo MIBG has a very high specificity for neuroectodermal tumors and can be used for initial (pre-operative) confirmation of this type of histology. Tomographic visualization with SPECT or SPECT/CT gives certain advantages in localizing smaller soft-tissue foci, increasing the sensitivity of the method from 80-90% to 98%. The benefit of using SPECT alone is finding small tumor formations in close proximity to organs of high physiological MIBG fixation. The advantage of using the hybrid technique SPECT/CT is the potential clarification of equivocal findings from CT or MRI, as well as interpreting false positive and false negative findings. The role of SPECT alone has yet to be established in the context of the following point-based treatment response evaluation systems. [1, 2, 5, 8, 9, 10]

Currently 123I-MIBG is a routine element in staging neuroblastoma patients. The primary advantage of the method is a combination of high sensitivity and high specificity, respectively 86-95% and 83-100%. [1, 24, 25] This is greatly beneficial for evaluation of bone and bone marrow involvement, and assessment of therapeutic results as well. Several systems have been established for appraising initial involvement and correlating it with posttherapeutic states - Curie, Frappaz, SIOPEN. [1, 26] They encompass skeletal involvement and the presence of soft tissue lesions and are all based on segmenting the skeleton to anatomic sectors, each receiving its own point score based on intensity and
spread of malignant involvement. The score systems also have a prognostic significance - initial score in Curie or SIOPEN respectively 2 and 4 correlates with better survivability. [1, 26] Patients who are MIBG negative (score 0) after four cycles of induction chemotherapy are also expected to have better survival rates. [1] Scores over 5 correlate with a significantly lower survivability. The exact time of the initial staging, respectively first IMBG scan, is not set in stone - pre-operative scans are preferred, as they demonstrate the MIBG status of the initial mass. When logistically impossible, post-surgical scanning could be performed. A more than 50% decrease in spread score post treatment is considered partial response (PR). Only a score of 0 post treatment is defined as complete remission (CR) according to scintigraphic criteria. Routine MIBG scintigraphic follow-up is not recommended. [1, 10]

2. Other radiopharmaceuticals in neuroblastoma

When MIBG-scintigraphy is unavailable or in the rare cases of MIBG-negative neuroblastoma, the only way to evaluate skeletal involvement is **bone scintigraphy with 99mTc-marked compounds**. This examination is difficult to interpret in children due to the high physiological activity in the metaepiphysial zones, which, unfortunately, have a predilection to be affected by metastatic NBL. [1] Uptake is demonstrated in both cortical and marrow lesions. [9] The combination of "hot" and "cold" vertebral lesions is characteristic of metastatic neuroblastoma. [8] Bone scintigraphy is inapplicable for treatment response evaluation due to low specificity and slow recovery of the bone changes. [1, 5]

**18F-Fludeoxyglucose (FDG) PET/CT.** There is no significant correlation between MIBG status and FDG captation, which is unhelpful in pre-selection of patients, who could benefit from FDG PET. In general, the method is less reliable in comparison to MIBG in terms of bone/bone marrow involvement, and can be especially misleading after chemotherapy. FDG PET exceeds CT in terms of nodal involvement detection, which gives it an advantage in localized resectable NBL. [1, 10]

**18F-F-dihydroxyphenylalanine (18F-F-DOPA) PET/CT.** The method uses a promising marker to diagnose neuroblastoma, with initial studies showing better sensitivity and specificity than MIBG. [1, 27, 28] Data is so far scarce, primarily derived from pilot studies, with the radiopharmaceutical not having been validated as either a diagnostic or prognostic marker. A substantial drawback is the inability to use scan data for planning therapeutic regimens, based on 131I-MIBG. [1]

**STAGING SYSTEMS**

The treatment and prognosis of NBL are determined by the disease’s stage at diagnosis. Currently there are two methods of staging - one based on post-operative patients, and one for pre-treatment patients.
The **International Neuroblastoma Staging System** (INSS) is for post-operative patients and its main purpose is prognosis of outcome. It was established in 1986 and revised in 1988. [1, 2, 10, 19]

**Stage 1**
- Localised tumor with complete gross excision with or without microscopic residual disease
- Contralateral and representative ipsilateral regional lymph nodes negative for disease (nodes attached to and removed with primary tumor may be positive)

**Stage 2a**
- Localised tumor with incomplete gross excision
- Ipsilateral and contralateral nodes negative for tumor

**Stage 2b**
- Localised tumor with complete or incomplete resection
- Positive ipsilateral (non-adherent) nodes
- Contralateral nodes negative for tumor

**Stage 3**
- Unresectable lateral tumor that crosses the midline or
- Localised tumor with contralateral regional lymph node involvement
- Midline tumor with bilateral extension by infiltration or by lymph node involvement

**Stage 4S ("special")**
- <1 year of age
- Localised tumor (stage 1, 2A or 2B)
- Distant metastases confined to skin, liver and/or bone marrow

**Stage 4**
- Distant metastases not fulfilling stage 4S [2, 10, 19]
In 2008 the International Neuroblastoma Risk Group (INRG) introduced a clinical system for pretherapeutic (including preoperative) staging, based on imaging-determined risk factors - the **International Neuroblastoma Risk Group Staging System** (INRGSS). [1, 20] Two stages of localized disease are identified - L1 and L2, as well as two stages of metastatic disease - M and MS. INRGSS evaluates whether the primary tumor is affected by one or more of nearly 20 specific **Image Defined Risk Factors** (IDRF). Neither the midline, nor the lymph node status are included in the staging criteria of INRGSS. Naturally, resection lines are not an applicable criterion for INRGSS due to its pre-treatment nature. Metastatic disease is staged similarly in both INRGSS and INSS, however, it must be stipulated that the upper age limit of INRGSS stage MS is 18 months, while the age limit for stage 4S in INSS is 12 months. [1, 20]

**Stage L1**

- Localised tumors confined to one body cavity and not involving IDRFs

**Stage L2**

- Locoregional tumors involving one or more IDRFs

**Stage M**

- Distant (remote) metastases (i.e. excludes metastases to local lymph node groups)
- Excludes stage MS

**Stage MS**

- Metastases in patients <18 months (some centres <12 months) confined to skin, liver and/or bone marrow [1, 2, 20]

**Table 4. Image Defined Risk Factors (IDRFs) in neuroblastic tumors** [2, 10, 20]

<table>
<thead>
<tr>
<th>Ipsilateral tumor extension within two bodily compartments:</th>
<th>Neck-chest, chest-abdomen, abdomen-pelvis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck:</td>
<td>Tumor encasing carotid and/or vertebral artery and/or internal jugular vein</td>
</tr>
<tr>
<td></td>
<td>Tumor extending to base of skull</td>
</tr>
<tr>
<td></td>
<td>Tumor compressing the trachea</td>
</tr>
<tr>
<td>Cervico-thoracic junction:</td>
<td>Tumor encasing brachial plexus roots</td>
</tr>
<tr>
<td>Thorax:</td>
<td>Tumor encasing subclavian vessels and/or vertebral and/or carotid artery</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Tumor compressing the trachea</td>
</tr>
<tr>
<td></td>
<td>Tumor encasing the aorta and/or major branches</td>
</tr>
<tr>
<td></td>
<td>Tumor compressing the trachea and/or principal bronchi</td>
</tr>
<tr>
<td>Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12</td>
<td></td>
</tr>
<tr>
<td>Thoraco-abdominal:</td>
<td>Tumor encasing the aorta and/or vena cava</td>
</tr>
<tr>
<td>Abdomen/pelvis:</td>
<td>Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament</td>
</tr>
<tr>
<td></td>
<td>Tumor encasing branches of the superior mesenteric artery at the mesenteric root</td>
</tr>
<tr>
<td></td>
<td>Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery</td>
</tr>
<tr>
<td></td>
<td>Tumor invading one or both renal pedicles</td>
</tr>
<tr>
<td></td>
<td>Tumor encasing the aorta and/or vena cava</td>
</tr>
<tr>
<td></td>
<td>Tumor encasing the iliac vessels</td>
</tr>
<tr>
<td></td>
<td>Pelvic tumor crossing the sciatic notch</td>
</tr>
</tbody>
</table>

| Intraspinal tumor extension:        | Intraspinal tumor extension (any level) provided that more than one-third of spinal canal in axial plane is invaded, the perimedullary leptomeningeal spaces are not visible, or the spinal cord intensity is abnormal |
| Infiltration of adjacent organs/structures: | Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block and mesentery |

**Table 5. Conditions to be recorded, but NOT considered IDRFs** [20]
Multifocal primary tumors
Intraspinal tumors (with or without symptoms of spinal cord compression)
Pleural effusion (with or without malignant cells)
Ascites (with or without malignant cells)

INRGSS and INSS are used in unison, complementing each other.

**PROGNOSIS**

Patients with stage 1, 2 or 4S have a better prognosis. [2, 10] The majority of patients (40-60%), however, present at stages 3 or 4. [2, 29] For advanced disease, the age of the patient is the most important prognostic factor. [2, 30] Prognosis is best for younger patients and those with a nonabdominal primary tumor. [2, 6, 7]

**Table 6. Survival rates**

<table>
<thead>
<tr>
<th>Stage</th>
<th>3 year survival</th>
<th>1 year event free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1, 2 or 4S</strong></td>
<td>75-90%</td>
<td>80-90%</td>
</tr>
<tr>
<td><strong>Stage 3</strong></td>
<td>&lt;1 year</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>&gt;1 year</td>
<td>60-75%</td>
</tr>
<tr>
<td><strong>Stage 4</strong></td>
<td>&lt;1 year</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>&gt;1 year</td>
<td>15%</td>
</tr>
</tbody>
</table>

Accurate prediction of each patient's individual risk at the time of diagnosis is key for planning the optimal personalized treatment. To this end, risk stratification systems have been developed - for example, the German Neuroblastoma Trial NB2004 divides patients into three groups - low (50% of patients), intermediate (10%), and high risk (40%), depending on age, tumor stage, tumor biological characteristics, etc. [6, 31] Low risk patients have a survival rate of >95%. The intermediate and high risk groups have survival rates of 90-95% and 40-50% respectively. [6] The NB2004 criteria are listed below. [32]
Lower patient age and early tumor stage are both favorable prognostic factors. [31] Genetic markers are currently employed in risk stratification. These include genomic amplification of the MYCN oncogene on chromosome 2p24, allelic deletion of the short arm of chromosome 1, and allelic deletion of the long arm of chromosome 11. [31] MYCN in particular is a highly specific predictor of a poor outcome. [2, 31]

Table 7. Prognostic factors [2, 31]

<table>
<thead>
<tr>
<th>Poor prognostic factors</th>
<th>Favorable prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Later age of onset (&gt;18 months)</td>
<td>TRK-A expression</td>
</tr>
<tr>
<td>Higher stage (particularly with metastases)</td>
<td></td>
</tr>
<tr>
<td>MYCN mutation</td>
<td></td>
</tr>
<tr>
<td>Chromosome 1p deletion</td>
<td></td>
</tr>
<tr>
<td>Unfavorable Shimada histology index</td>
<td></td>
</tr>
</tbody>
</table>

Despite all this, at times risk stratification fails to determine the best initial treatment strategy, resulting in under- and overtreatment. [31]
Infants and children with low-risk abdominal or pelvic neuroblastoma and no significant risk of intraspinal extension should be monitored with ultrasound. Sonography can also monitor abdominal tumors pre- and post-resection, as well as those at stage 4S not necessitating resection. Monitoring in children with high-risk neuroblastoma post-radiotherapy can be performed with either CT or MRI in addition to ultrasound. Relapse or progression should be sought for and evaluated with a multimodality approach - imaging (sonography, CT, MRI, MIBG), clinical assessment, and tumor markers (VMA). [10]
Fig. 2: Contact vs encasement - differentiating features.

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Fig. 20: NB2004 Risk stratification.

© German Neuroblastoma Trial NB2004
- 21 month old patient
- Axial CT arterial phase
- Large left adrenal mass + extensive necrosis
- Liver metastases

Fig. 3: Case 01

© Diagnostic Imaging, University Hospital Saint Marina - Varna/BG
- 2 year old patient
- Axial CT and sagittal T2 MRI demonstrate neuroforaminal invasion of a left paravertebral mass - foramina between Th2 and Th4 affected

**Fig. 4:** Case 02

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- 21 month old patient
- Axial CT of thorax (arterial) shows lymph node involvement + bilateral small effusions
- Axial CT of abdomen (venous) shows primary mass from left adrenal:
  - the primary crosses the midline
  - encasement of left renal vessels
  - invasion into left kidney

**Fig. 5:** Case 03

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Fig. 6: Case 04a

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Fig. 7: Case 04B

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Fig. 8: Case 05

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Fig. 9: Case 06

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Fig. 10: Case 07

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Fig. 11: Case 08

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- 4 year old patient
- Axial CT venous
- Calcified retroperitoneal mass
- Small area of hypodense necrosis within mass
- Mass elevates inferior vena cava from spine

Fig. 12: Case 09

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Fig. 13: Case 10

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Fig. 14: Case 11

- 2 year old patient
- Axial CT native and venous
- Mass stemming from right adrenal
- Calcification evident on native phase
- Encasement of right renal artery

Metastasis in right fibula:
- Moth eaten lesion
- Codman triangle

© Diagnostic Imaging, University Hospital Saint Marina - Varna/BG
- 4 year old patient
- Right abdominal inhomogeneous mass
- Axial CT (arterial) demonstrates total encasement of right renal artery
- Axial CT (venous) demonstrates total encasement of a ventrally displaced inferior vena cava

- Coronary MRI IR shows high signal bone marrow metastases in both femurs, both acetabula, and left iliac wing
- MIBG scintigraphy - high captation in primary adjacent to liver and in both femurs

**Fig. 15:** Case 12

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Fig. 16: Case 13a

- 3 year old patient
- Axial and coronal CT (arterial)
- Inhomogeneous mass arising from right adrenal
- Invasion into right kidney and liver

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Fig. 17: Case 13b

- Axial and coronal CT (venous)
- Severe progression evident
- Liver infiltration significantly increased with marked hepatomegaly
- New retrocrural involvement
- Sagittal CT (venous)
- Compression of aorta and inferior vena cava

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Fig. 18: Case 14a
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- 5 year old patient
- Chest film demonstrates paravertebral mass behind heart
- Axial/sagittal CT (arterial+venous) show paravertebral inhomogeneous mass
- Associated effusion
- Upper mediastinal lymph node packets with necrosis
- Sagittal CT shows total encasement of left renal artery

Fig. 19: Case 14b
Conclusion

Neuroblastoma's clinical significance is substantial, and its manifestations varied. Therefore, it is paramount to maintain a high degree of awareness of up-to-date diagnostic and staging guidelines. NBL requires multimodality imaging, with MRI and MIBG bearing the highest significance in regard to current guidelines: MRI + contrast for evaluating neural foraminal extension and bone marrow metastases, whole MIBG for determining disease extent.
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