

## Pictorial Essay

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# Pediatric imaging of neuroblastoma-From classic to atypical

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## Abstract

Neuroblastoma (NB) is the most common extracranial solid tumour in children, accounting for approximately eight percent of paediatric cancer and fifteen percent of pediatric cancer deaths. Reaching a correct and timely diagnosis is extremely important, especially in aggressive NB. Prognosis and treatment are based on tumour biology and genetics, patient age and perhaps most importantly, disease stage. The current staging system relies heavily on imaging, and this pictorial essay provides a description of the radiological features of NB, from classic to atypical, and the modalities used to help confirm the diagnosis and staging of NB. Our aim is to provide radiologists with a comprehensive collection of presentations of NB, to help improve diagnostic accuracy and decrease time to diagnose.

**Keywords:** Neuroblastoma, Imaging, Pediatric, Radiology.

## Introduction

Neuroblastoma (NB) is the commonest extracranial solid tumour of the pediatric population [1,2], and the most common neonatal solid tumour [3]. The median age at diagnosis is about 16 months [1], and 90% of the cases are diagnosed by the age of six [2]. NB accounts for eight percent of pediatric cancers, but causes about fifteen percent of childhood cancer deaths [4]. It is mostly diagnosed as a painless abdominal mass; however, it is often metastatic and symptomatic [2]. As the name suggests, NB is derived from neural crest cells of the sympathetic nervous system; thus, it may be found in a sympathetic tissue anywhere in the body [2,4]. Almost half of the NB cases originate in the adrenal glands, and other common sites are sympathetic ganglions of the retroperitoneum and chest [1,5]. The factors influencing prognosis are tumour biology and genetics, the patient's age and, perhaps most importantly, the disease stage [1,2].

Reaching a correct and timely diagnosis is extremely important, especially in aggressive NB. Our aim is to provide radiologists with a comprehensive collection of imaging presentations of NB, to help improve diagnostic accuracy and decrease time to diagnose.

## Staging systems

Historically, NB staging was defined by the International Neuroblastoma Staging System (INSS) (Table 1) [1], and although since supplanted, INSS is still used and reported in the literature [3,6]. In 2009, an improved staging system was proposed by the International Neuroblastoma Risk Group (INRG), a conglomerate of investigators from major cooperative oncology groups from North America, Australia–New Zealand, Germany, Japan and China [1], which also includes the Children's Oncology Group (COG), Children's Cancer Group (CCG) and

Pediatric Oncology Group (POG) [7]. Their staging system, currently in use, is aptly named the INRG Staging System (INRGSS), and it relies heavily on imaging (Table 2) [1,4], specifically on the twenty image-defined risk factors (IDRF) of NB (Table 3) [1,2]. The IDRF serves as the basis for decisions regarding therapy, including surgical intervention, and together with clinical data, provides risk stratification and staging for NB [1,4]. It is also important to note that since 2009 COG has used a POG-CCG Intergroup Neuroblastoma Risk Classification System that includes age, INRGSS stage, MYCN status, histologic category, grade of differentiation, ploidy, and 11q status<sup>1</sup> all of which affect tumour aggressiveness, and that in 2021 a revision to include other indicators such as Shimada histology, mitosis karrhyohexis index, extent of primary tumour, segmental chromosomal aberrations and RNA expression signatures was underway [7]. Of all the tumour genetics mentioned above, MYCN requires specific attention because amplification of the MYCN gene is one of the most important poor prognostic factors. MYCN is associated with aggressive NB, and approximately 50% of high-risk patients have MYCN-amplified tumours [8].

**Table 1.** *International Neuroblastoma Staging System (INSS) Staging System [1].*

Tumour Stage	Description
1	Localized tumour with complete gross excision, with or without microscopic residual disease. Representative ipsilateral lymph nodes are negative for tumour microscopically. Nodes attached to and removed with the primary tumour may be positive.
2A	Localized tumour with incomplete gross excision. Representative ipsilateral nonadherent lymph nodes are negative for tumour microscopically.
2B	Localized tumour with or without complete gross excision, ipsilateral nonadherent lymph nodes are positive for tumour, and enlarged contralateral lymph nodes are negative microscopically.
3	Unresectable unilateral tumour that infiltrates across the midline, with or without regional lymph node involvement, or a midline tumour with bilateral extension via infiltration (unresectable) or lymph node involvement.
4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined in stage 4S).
4S	Localized primary tumour (as defined in stage 1, 2A, or 2B) with dissemination limited to the skin, liver and/or bone marrow in infants younger than 1 year, marrow involvement of less 10% of total nucleated cells, and MIBG* scan findings negative in the bone marrow.

\*Abbreviation MIBG, metaiodobenzylguanidine

**Table 2.** *International Neuroblastoma Risk Group (INRG) Staging System [1].*

Tumour Stage	Description
L1	Localized tumour not involving vital structures, as defined by the list of IDRFs*, and confined to one body compartment.
L2	Local-regional tumour with presence of one or more IDRFs*.
M	Distant metastatic disease (except as defined in stage MS).
MS	Metastatic disease in children younger than 18 months, with metastasis confined to the skin, liver and/or bone marrow.

\*Abbreviation IDRF, Image Defined Risk Factors. Please refer to Table 3 for a list of IDRF.

**Table 3.** *Description of Image Defined Risk Factors (IDRF) [1].*

Anatomic Region	Description
Multiple body compartments	Ipsilateral tumour extension within two body compartments (i.e., neck and chest, chest and abdomen, or abdomen and pelvis)
Neck	Tumour encasing the carotid artery, the vertebral artery, and/or the internal jugular vein Tumour extending to the skull base Tumour compressing the trachea
Cervicothoracic junction	Tumour encasing the brachial plexus roots Tumour encasing the subclavian vessels, the vertebral artery, and/or the carotid artery Tumour compressing the trachea
Thorax	Tumour encasing the aorta and/or major branches Tumour compressing the trachea and/or principal bronchi Lower mediastinal tumour infiltrating costovertebral junction between T9 and T12 vertebral levels
Thoracoabdominal junction	Tumour encasing aorta and/or vena cava
Abdomen and pelvis	Tumour infiltrating the porta hepatis and/or the hepatoduodenal ligament Tumour encasing branches of the superior mesenteric artery at the mesenteric root Tumour encasing the origin of celiac axis and/or the origin of the superior mesenteric artery Tumour invading one or both renal pedicles Tumour encasing the aorta and/or vena cava Tumour encasing iliac vessels Pelvic tumour crossing the sciatic notch
Intraspinal tumour extension	Intraspinal tumour extension (whatever the location) provided that more than one-third of the spinal canal in the axial plane is invaded, the perimedullary leptomeningeal spaces are not visible, or the spinal cord signal intensity is abnormal
Infiltration of adjacent organs and structures	Pericardium, diaphragm, kidney, liver, duodenopancreatic block, and mesentery

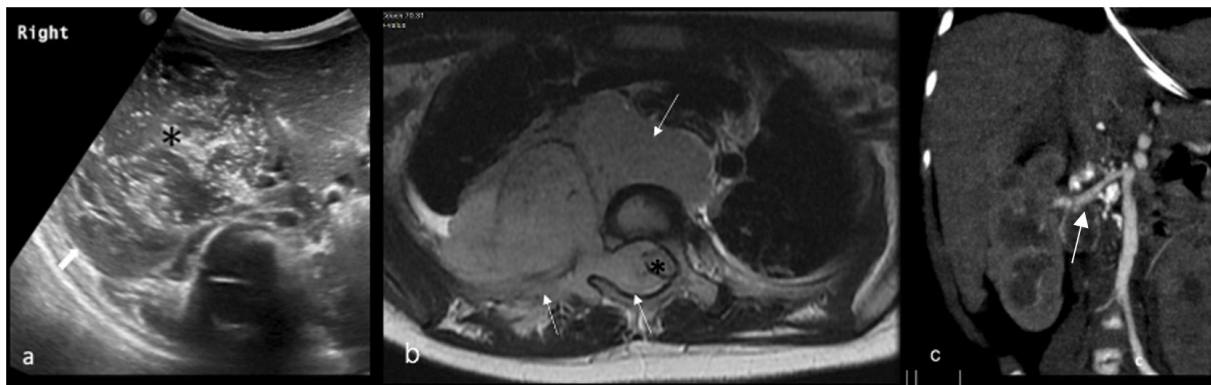
## Imaging of the primary tumour in neuroblastoma

The primary tumour is most often located in the adrenal gland (48%), the extra-adrenal retroperitoneum (25%) or the thorax (16–20%) [4]. Both magnetic resonance imaging (MRI) and computed tomography (CT) may be used in the diagnosis of NB [2,4]. It is generally accepted that MRI is superior because of its sensitivity in identifying the local IDRFs such as chest wall invasion, and spinal canal involvement, and in the detection of metastatic bone and bone marrow lesions [2,4]. Indeed, for the reasons stated above, and due to the principle of as low as reasonably achievable (ALARA) radiation exposure in pediatric oncology patients [8], MRI is the imaging of choice for the diagnosis of NB according to the guidelines [1].

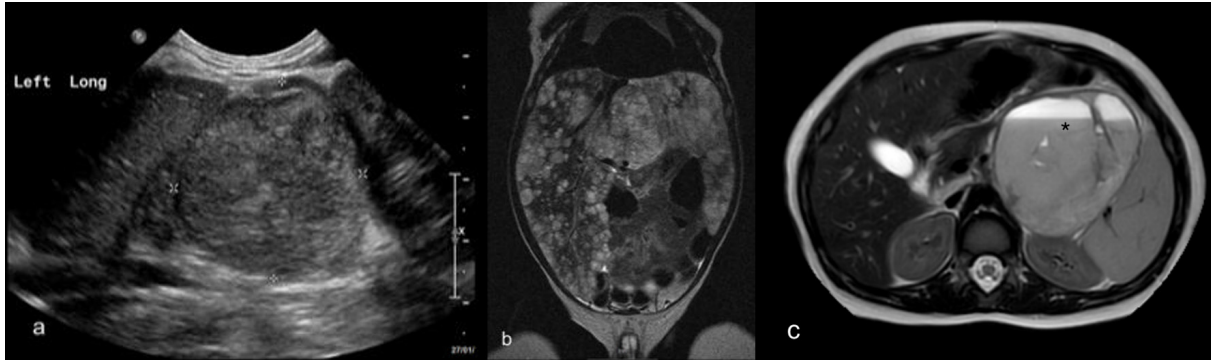
On imaging, NB typically appears as a solid, heterogeneous abdominal mass with calcification, that is poorly marginated and may cross the midline (Figure 1) [2,3]. NB has a tendency to encase and displace, rather than invade, anatomical structures [2,4]. On the initial diagnosis, MRI of NB follows the pattern of many solid abdominal malignancies, displaying low or intermediate intensity on T1-weighted sequences and high intensity on T2 [2,4]. There are areas within the tumour of variable contrast-enhancement [2], and NB also often shows restricted diffusion on diffusion weighted imaging [2,4]. MRI can detect areas of calcification and haemorrhage [2]. On CT, NB is characterized by poorly differentiated margins and heterogeneity, with calcification and possible extension across the midline and into adjacent cavities [2]. There may be areas of low density representing cystic necrosis [4].

Neonates and infants require special consideration because NB may have a different disease course in this age group and a unique appearance (Table 2) [2,4]. In neonates, NB originates almost exclusively in the adrenal glands, appears cystic in approximately 50% of cases, although it may also be semi-solid or solid, it is less often calcified, and it carries a better prognosis (Figure 2) [3,6,9]. It is also important to note that cystic NB, when isolated to the adrenal gland, can be confused with an adrenal hematoma, especially as calcifications may be present

in an old hematoma and in NB [3,11]. To further obscure the matter, cystic NB may present with an intra-cystic haemorrhage (Figure 2c) [11]. Serial ultrasounds can differentiate between the two, as hematomas decrease in size more quickly than cystic haemorrhagic NB. In fact, it has been suggested in the literature that neonatal NB is evaluated equally as well by US, partially due to the fact that NB often appears cystic in this age group, and is more easily monitored with serial US examinations [3].



**Figure 1.** Typical presentations of NB. (a) Ultrasound of an adrenal NB in a 20-month-old boy. Right adrenal mass shown as a solid heterogeneous lesion with calcifications in abdominal US (black asterisk), and the right kidney is caudally displaced (white arrow). (b) A dumbbell lesion in a three-year-old girl with retroperitoneal and paravertebral NB lesions (white arrows) with extension through the neural foramina into the epidural space with severe mass effect on the spinal cord (black asterisk). Intraspinous tumour extension is an IDRF. (c) A one-year-old girl with a right adrenal NB and calcified lymph nodes surrounding the right renal artery (white arrow), shown in a coronal section of an abdominal CT with IV contrast.



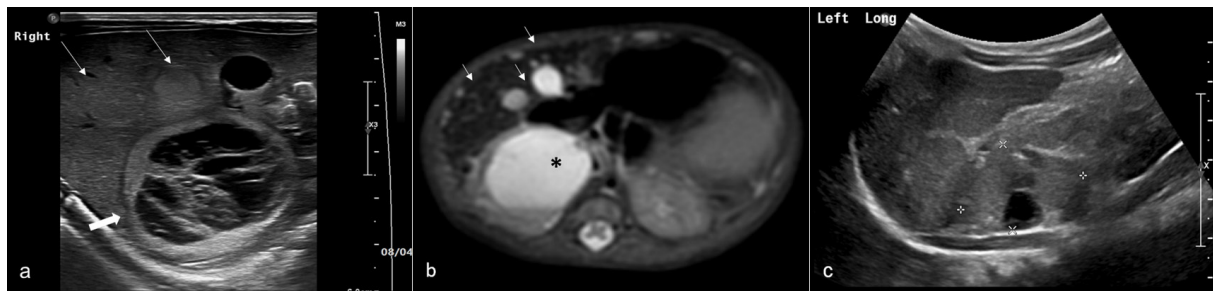
**Figure 2.** Typical presentation of NB in infants. (a) Ultrasound of an adrenal NB in a newborn, seen also prenatally. The left adrenal mass in the newborn shown as a solid heterogeneous lesion (between the cursors) in an abdominal US. (b) A one-month-old boy with an adrenal mass and multiple liver metastases (stage MS) shown here in a coronal T2W abdominal MRI. Note the enlarged liver with multiple T2W hyperintense lesions. (c) Cystic haemorrhagic NB in a twenty-two-month-old girl. Seen here is an axial T2W MRI image showing a cystic lesion with a fluid-fluid level (black asterisk), located in the upper left abdomen, anterior to the left kidney and the spleen. The lesion was resected and proven to be adrenal NB in pathology.

## Additional less common presentations of the primary tumour

### *Cystic neuroblastoma beyond the neonatal period*

Although cystic NB is more typical of neonatal NB, it also occasionally occurs in older pediatric age groups [2]. Cystic NB is defined as having one or more cysts within the tumour, and it may become more complex in appearance over time with solidification into a partially solid or solid lesion [3]. It is identifiable on US, CT or MRI [3]. Bilateral cystic NB is found in less than 10% of NB, and in 20% of familial NB [10]. Metastasis is less likely in cystic NB, and the most common site of metastases in cystic congenital NB is the liver (Figure 3) [6].

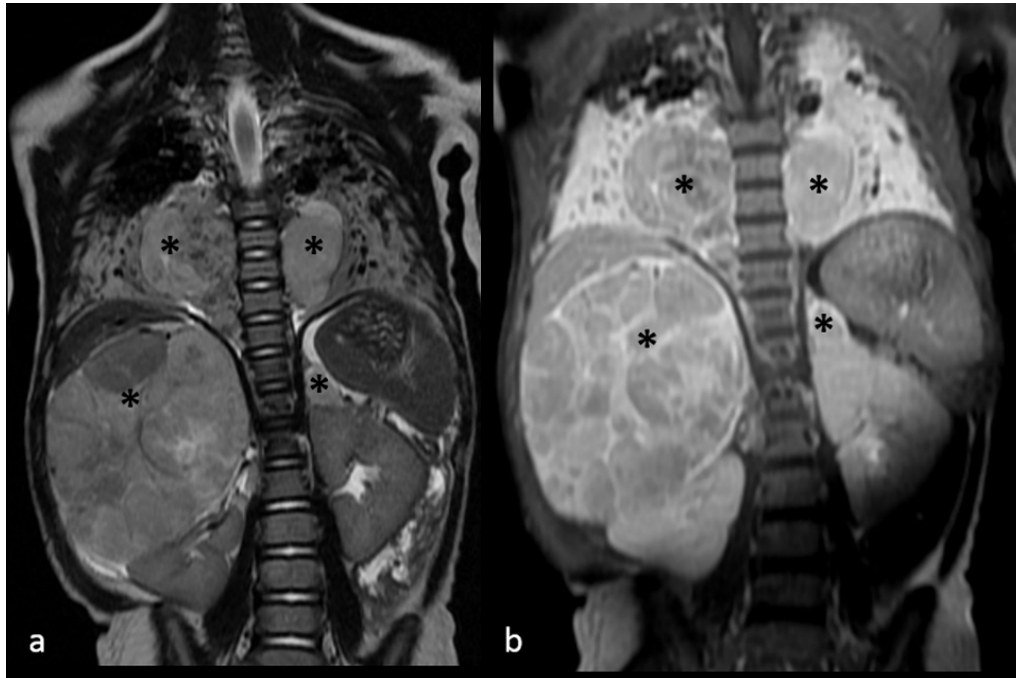




**Figure 3.** Bilateral adrenal cystic NB with liver metastases in a newborn. (a) Transverse US of the upper right abdomen showing a right adrenal cystic mass with thin septa and a fluid-fluid level (thick arrow), and liver metastasis seen as round isoechoic or slightly hyperechoic lesions in the liver (thin arrows). (b) An axial T2W MRI image showing a haemorrhagic cystic adrenal lesion (black asterisk) and multiple small liver metastases of varying sizes (thin white arrows). (c) Left adrenal mass with cysts within the cursors on a longitudinal US of the upper left abdomen.

### ***Multifocal primary neuroblastoma***

Multifocal primary NB is rare, but due to improvements in both our understanding and diagnosis of this disease, the incidence may increase [11,12]. Of note, although most NB is sporadic, multifocal primary NB is most often familial [13]. It is important to distinguish between multifocal primary NB and metastatic NB because multifocal primary NB is associated with more favourable biological features, and aggressive treatment can be avoided [11,12]. Indeed, multifocal NB might regress without any treatment [11]. Imaging findings that favor the diagnosis of multifocal primary NB over metastatic NB, are tumours on opposite sides of the body without distant lymph node, and bone or bone marrow metastases (Figure 4) [12]. Interestingly, it is thought that bilateral adrenal NB and stage 4S NB (similar to INRGSS stage MS), might actually be multifocal primary NB [11].

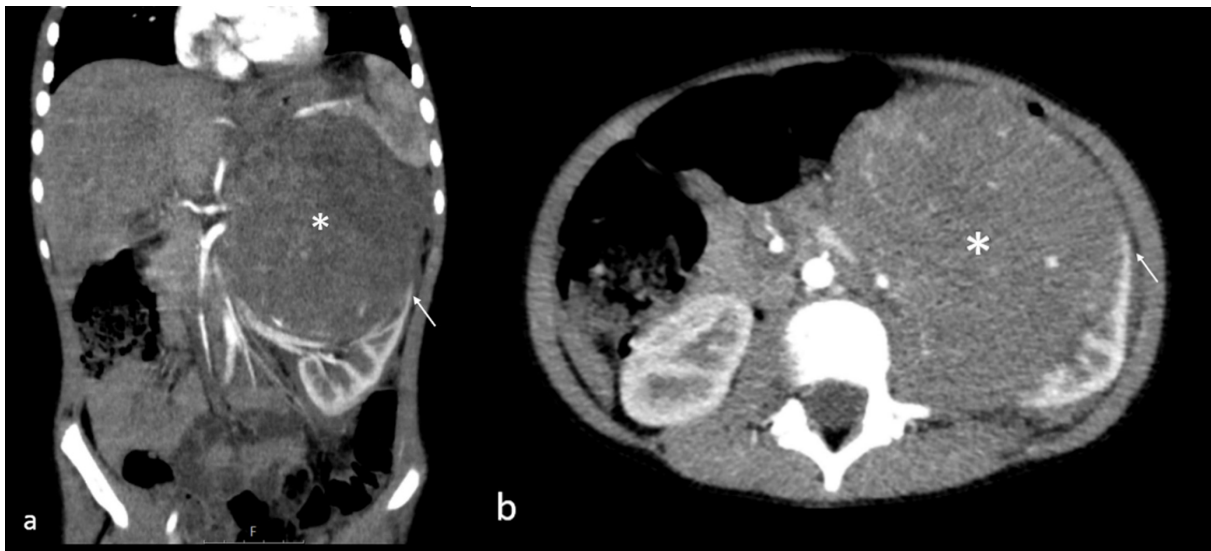


**Figure 4.** Multifocal NB at presentation in a four-year-old girl. (a) Coronal T2W MRI and (b) coronal T1W MRI with contrast are images of the chest and abdomen showing four discrete locations of NB (black asterisks); paravertebral lesions in the chest, one on each side of the spine, and bilateral adrenal lesions, larger on the right.

### ***Renal neuroblastoma***

Renal invasion of NB is fairly common due to the close proximity of the kidney to the adrenal gland, and indeed infiltration of the kidney is an IDRF. Renal NB (Figure 5), however, is extremely rare, and on imaging alone, it can easily be confused with Wilms tumour [14]. Key differences that may help distinguish between the two are calcifications, best seen on CT and typical of NB, and cystic components that are more likely in Wilms tumour [2]. NB is more likely to be a poorly marginated mass that may extend into the chest while Wilms is usually well

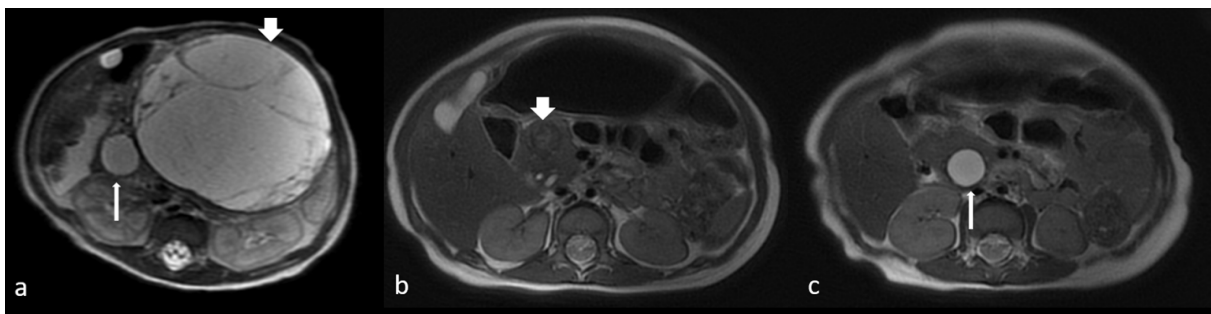
circumscribed [2]. NB is generally more likely to encase and displace anatomical structures including vessels, in contrast to Wilms tumour that often invades vasculature, especially the renal vein and IVC [2]. The most common metastatic sites of the tumours also differ; NB tends to metastasize to the bone and bone marrow while Wilms tumour most often metastasizes to the lung [2]. However, metastatic sites do overlap, including the lung, and liver metastases are fairly common to both tumours [2]. Another important difference is that MIBG is usually sensitive and specific for NB, while Wilms tumour is MIBG negative [2].



**Figure 5.** A five-year-old boy with a large left renal mass, treated with nephrectomy, with pathology proven primary renal NB. CT of the abdomen with contrast shows the kidney to be the origin of the large mass (white asterisk); cortical beak sign of the kidney can also be seen (thin white arrows), further affirming that the kidney is the origin of the mass in both (a) coronal and (b) axial images. Please note that invasion of the tumor into the renal pedicle is an IDR is clearly seen in both the coronal and axial images.

### ***Pancreatic neuroblastoma***

This unusual presentation of NB may arise from neural-crest derived precursors to the enteric nervous system that assists in the formation of pancreatic ganglia or neural crest signals that regulate the proliferation of pancreatic beta cells [15]. As of the year 2020, fewer than ten cases of pancreatic NB were identified in the literature (Figure 6) [15]. Despite its rarity, radiologists must remain alert to pancreatic NB, because NB is of the most common childhood cancers [16]. Imaging alone may not distinguish between pancreatic NB and other findings such as cystic teratoma, requiring further diagnostic workup that should include pathology.



**Figure 6.** A 17-day old girl, was referred to US due to abdominal distention. She was diagnosed with NB, proven by pathology, and followed by the MRI studies presented and did not undergo treatment or intervention. (a) An axial T2W MRI image showed two cystic lesions in the central mid abdomen, the larger a multi septate mass (arrowhead) and the smaller a simple cyst (arrow), diagnosed as NB. Only in follow up imaging, at the age of 7 months, was it clear that the lesions were located in the pancreas. Axial T2W MRI images showed two distinct pancreatic lesions in the uncinated process (arrowhead in b) and within the pancreatic head (arrow in c). The larger mass shrank and coarse calcifications appeared. No other mass was seen, and the adrenals appeared normal (not shown). Urine dopamine and neuron-specific enolase B (NSE-B) levels remained elevated until she was 12 months old.

### ***Olfactory neuroblastoma***

Olfactory NB (ONB) or esthesioneuroblastoma is believed to arise from basal neural cells of the olfactory mucosa in the superior nasal cavity [17], in close proximity to the cribriform plate (Figure 7) [17,18]. It usually appears in the fifth and sixth decades of life, less commonly in children [17]. ONB has its own staging system, Kadish staging, but it lacks standardized treatment protocols. The natural history of the disease varies and it is often in a challenging location for surgery [18]. Radiological evaluation for staging often includes a combination of MRI, CT and PET/CT. ONB typically appears as a soft tissue mass with its focal point at the superior olfactory recess, and it frequently demonstrates localized invasion, especially into the ethmoid sinuses. Extension through the cribriform plate may give the mass a “dumbbell” appearance, and cervical lymph node metastasis is present in approximately 20-30% of the patients [17].



**Figure 7.** A 16-year-old boy presented with vomiting and behaviour change proceeding several months of headache, with laboratory results significant for hyponatremia due to SIADH. He was later diagnosed with NB. (a) Axial and (b) coronal T2W MRI showing an intermediate signal intensity mass filling the left superior nasal cavity and middle meatus with extension into the maxillary sinus. (c) Sagittal T1W MRI showing contrast enhancement of the same mass.

## Other documented locations of neuroblastoma

Other locations of NB include bladder NB (8 cases reported by 2020) [19], sacrococcygeal NB (8 cases reported by 2020 [20], orbital NB [21], and NB within a teratoma, observed in ovarian teratomas [22], and an orbital teratoma [23].

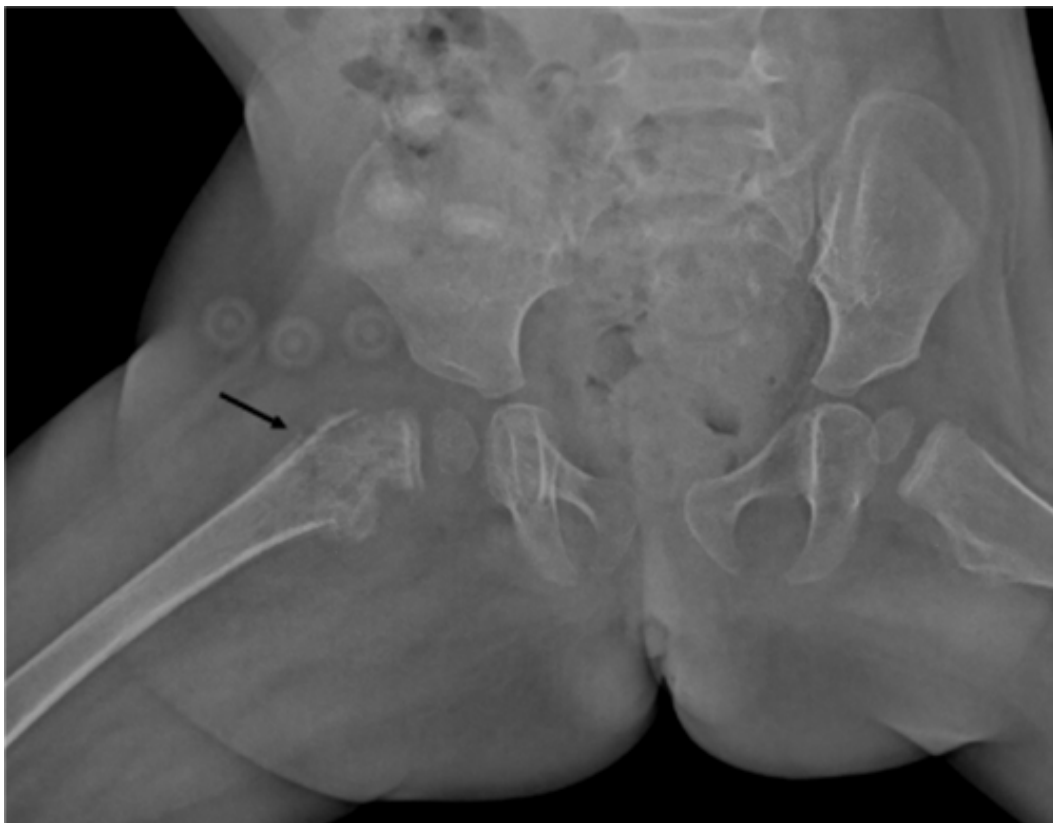
## Imaging of metastases in neuroblastoma

Approximately fifty percent of NB presentations are complicated by metastases [2], which are most frequently found in the bone and bone marrow [4], typically in the long bones of the extremities, in the skull and in the bony orbit [24]. Skull bone metastasis in NB is also known as Hutchison's syndrome, and a limping gait with irritability is also a feature attributed to this syndrome [27]. NB is of the more common childhood cancers [2], and considering the high percentage of bone metastasis, aggressive bone lesions should raise the question of NB (Figure 8). It is also important to note that in cystic congenital NB, metastasis is less likely, and if it occurs, it is most commonly in the liver [6]. Congenital NB is also associated with skin and cutaneous lesions, appearing as a 'blueberry muffin syndrome' that has a broad differential diagnosis including congenital infections and other underlying malignancies [28].

Functional imaging is crucial for assessing NB metastases, and the most commonly used are metaiodobenzylguanidine (MIBG) scintigraphy, fluorodeoxyglucose combined with Positron Emission Tomography (FDG-PET), and 8F-3,4-dihydroxyphenylalanine (F-DOPA) PET/CT [24,25]. MIBG is sensitive and specific in the detection of NB [1], but a small percentage of NB tumours do not uptake MIBG [4]. In MIBG negative tumours as well as stage 1 and 2 tumours, FDG-PET is considered superior [2,4]. Nonetheless, MIBG has a higher tumour to non-tumour uptake ratio than FDG-PET, minimizing the number of false negatives [4]. F-DOPA PET/CT has been shown to be more sensitive than MIBG in some studies and may also be recommended in MIBG negative tumours [25]. The current guidelines state that MIBG is the functional imaging of choice for NB [1].

Other scans can be considered when the presentation requires further analysis, as will be discussed in the following sections when applicable [1].

MRI is the cornerstone imaging modality for assessing both primary tumours and metastases; it is especially sensitive in the detection of metastatic bone and bone marrow lesions and spinal canal involvement [2,4].

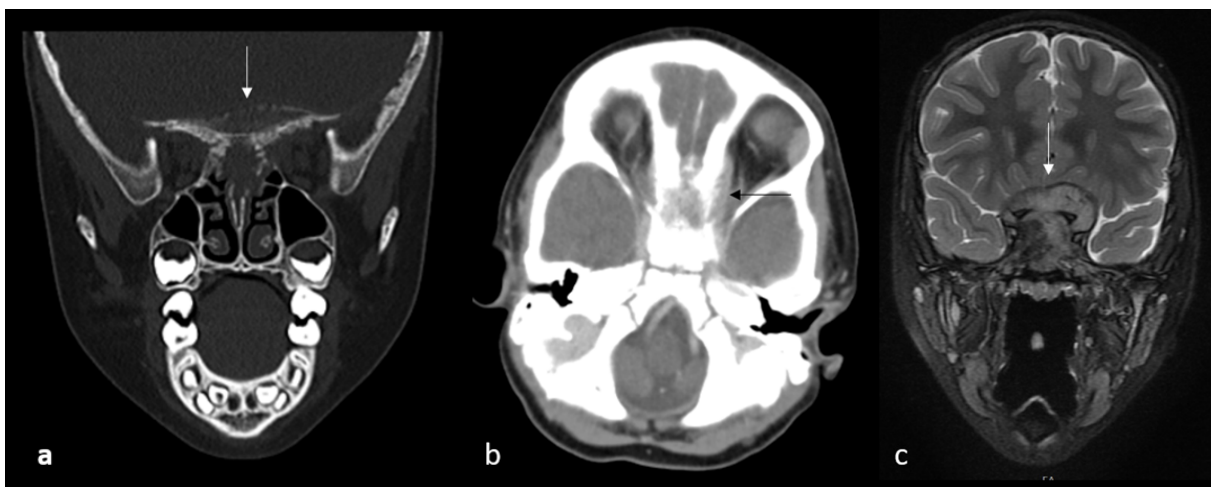


**Figure 8.** Femur fracture on the right in a 2-year-old girl, which was found to be metastatic NB.

## Other less common metastatic presentation of neuroblastoma

### *Orbital metastases without a primary lesion*

NB metastases to the skull, including orbital metastases (Figure 9), might be observed often because the skull represents a high proportion of the skeleton in young people [26]. A common clinical presentation of orbital invasion, for NB and other cancers, is ecchymotic orbital proptosis, but other symptoms include vision loss, edema, and restricted eye movement [27]. The radiological presentation of orbital NB usually includes thickened bones, in the sphenoid or the bones of the orbit itself, as well as periosteal reactions and lytic lesions. On MRI, orbital NB is characterized by low signal intensity on T1 and high signal intensity on T2-weighted images [27].

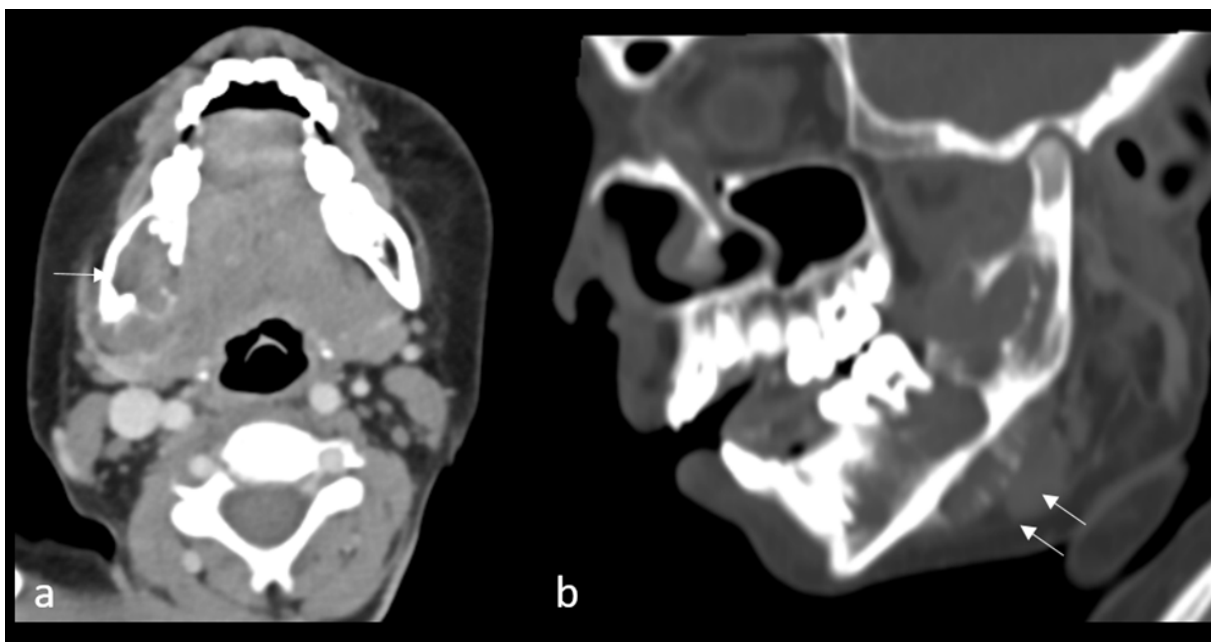


**Figure 9.** A CT was performed on a girl aged two years and seven months who presented with a one-month history of torticollis, neck pain and intermittent strabismus. (a) Coronal CT in bone filter revealed a bony sphenoid lesion (thin arrow). (b) Axial image shows the soft tissue window of the same sphenoid bone lesion (thin arrow). (c) Coronal T2W MRI image shows the sphenoidal lesion surrounding both pre-chiasmatic optic nerves (thin arrow).



### ***Mandibular metastasis***

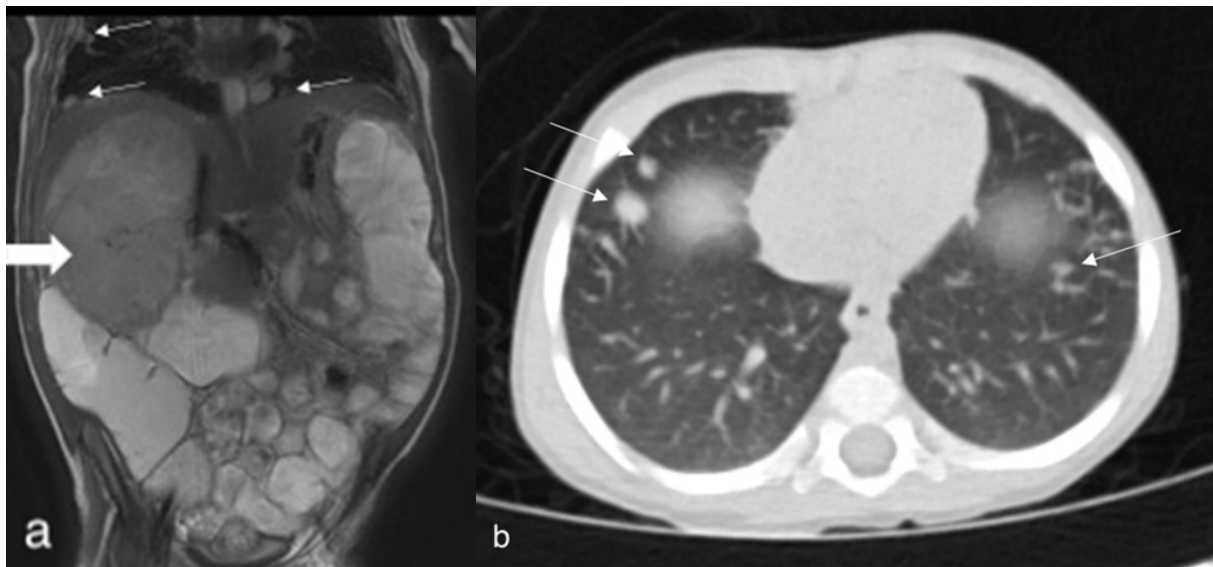
Mandibular metastases (Figure 10) warrant a broad differential diagnosis that may include lymphoma, soft tissue sarcoma, osteosarcoma, primitive neuroectodermal tumour (PNET), a central malignancy of the odontogenic origin, or a metastatic tumour [28]. In such cases histopathologic evaluation of tumour tissue or the analysis of bone marrow aspirate for the presence of tumour cells is crucial for diagnosis, as well as standard laboratory tests for NB [28].



**Figure 10.** *Mandibular metastasis in an eight-year-old both with proven retroperitoneal NB. Axial (a) and sagittal (b) CT images of the mandible. Note the lytic lesion with an aggressive periosteal reaction (arrows).*

### ***Lung metastasis***

Lung and pleural metastases on presentation of NB are extremely rare, and are only seen in children presenting with other distant metastases, considered stage M [6, 29-31]. Lung metastases are present at diagnosis in approximately 3.6% of stage 4 NB [1,29], and are independently associated with a worse prognosis (Figure 11) [29,30]. Although CT is not a routine screening tool in the diagnosis of NB, it is the most sensitive imaging tool for the assessment of lung metastasis, and therefore should be used when lung nodules are suspected [1]. On imaging, NB lung metastases have non-specific patterns [1], but the most common finding on CT is multiple nodules of varying sizes and distributions, noncalcified, some smooth and some spiculated [31]. Calcified lung nodules have also been observed [6]. The non-specific nature and rarity of NB lung metastases, as well as the current imaging protocols, make it a challenge to find these metastases [6].



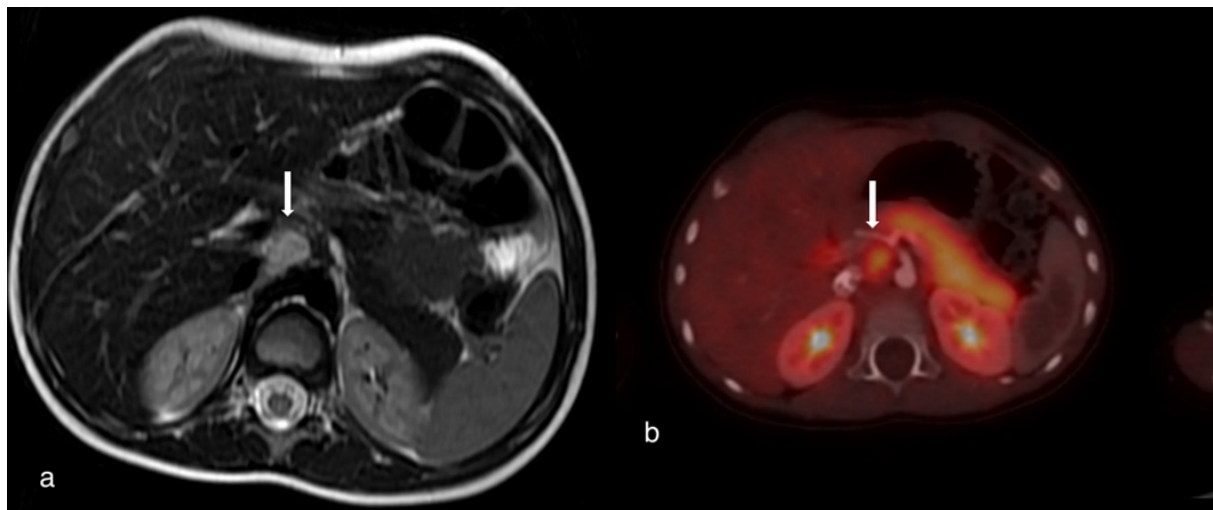
**Figure 11.** A fifteen-month-old boy with right adrenal NB. Initially, an MRI of the primary lesion in the right adrenal was performed. (a) A coronal T2W MRI of the primary tumour in the right adrenal (thick arrow) revealed lung lesions suspected to be metastases at presentation (thin arrows), necessitating a chest CT. (b) An axial chest CT without contrast in the lung window that showed multiple bilateral nodules, some with coarse calcifications, a characteristic of lung metastases (thin arrows).

### ***Other documented metastatic sites***

Other atypical metastases at presentation are bone marrow metastases with no primary tumour,<sup>24</sup> central nervous system metastases [26,32], pancreatic metastasis and ovarian metastasis [33].

## **Opsoclonus-myoclonus syndrome in neuroblastoma**

Opsoclonus-myoclonus ataxia syndrome (OMAS) is a rare inflammatory disorder, often with a paraneoplastic etiology, specifically associated with NB [34]. Only about 2-3% of children with NB have OMAS, but it is suspected that approximately 50% of pediatric OMAS cases are precipitated by an underlying NB [34]. OMAS is associated with low-risk NB and favorable oncological outcomes, but the neurological sequelae, such as relapsing OMAS, is more challenging to treat [35]. Tumour resection is important to the treatment of OMAS, even if the low-risk nature of the tumour would otherwise allow for a 'wait and see' approach [35]. OMAS may be associated with a miniscule, difficult to detect, NB tumour (Figure 12) [34], underscoring the importance of searching well for NB in children who present with OMAS. In addition, NB is known to appear as long as six months after the onset of OMAS; therefore, long-term monitoring is required, including follow-up urine, serum, and MRI studies [35]. Interestingly, research that retrospectively analyzed 38 children with OMAS, suggested that <sup>68</sup>Ga-labelled DOTANOC PET/CT might be more sensitive than MIBG for the detection of very small NB tumours [34]. Also, a larger study showed no MIBG uptake in non-primary NB tumour sites in children and adults with OMAS [36], suggesting that functional imaging alternatives should be considered.



**Figure 12.** A five-month-old girl who presented with opsoclonus myoclonus ataxia syndrome. (a) axial T2W showed a small solid retroperitoneal lesion adjacent to the celiac trunk on the right (white arrow) with high attenuation. (b) an 18F-DOPA PET/CT shows the same solid lesion (white arrows) in a fused image.

## Conclusion

The diagnosis and staging of NB are heavily reliant on imaging, and though this pediatric tumour is common, the broad range of possible imaging presentations continues to be a challenge for radiologists.

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