# Neuroblastoma - Disease State

Neuroblastoma is a malignant tumor of neural crest cells (the cells that give rise to the sympathetic nervous system) observed in children. It is usually seen as mass lesions in the neck, chest, abdomen, or pelvis.[1,2]

## Epidemiology[1,2]

**10%** **of pediatric malignancies**

it is the most common extracranial solid tumor in children

## Ultra-orphan disease[3]

Overall, it is estimated to affect approximately

**1/10,000** **live births[2]**

*Orphan disease designation ceiling: 5 in 10,000 people*

In the US:[4]

**700-800** **new cases annually**

**50%** **high-risk NB[5]**

***50% of high-risk NB have R/R***

## Estimated annual incidence of ~1/100,000 children

under the age of 15 years[6]

## Signs and Symptoms

**Median age** of neuroblastoma patients **at diagnosis** is 573 days, or roughly **18 months**[7-9]

**The majority (65%) of tumors are located in the abdomen**[8,9]

- Within the abdomen, tumors are commonly found in the **adrenal gland medullary region and along the abdominal sympathetic nerve chain**[8]

**Most patients (~50%) have metastatic disease at diagnosis**[8,10]

### General symptoms:[11]

- Fatigue
- Loss of appetite
- Bone pain

vs

### Specific symptoms:[11]

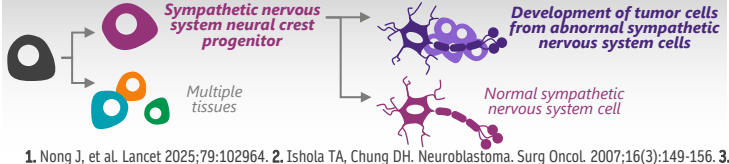
- Swollen abdomen
- Breathlessness and difficulty swallowing
- Lump in the neck
- Blueish lumps in the skin and bruising, particularly around the eyes
- Weakness in the legs and unsteady walk
- Severe watery diarrhea
- Jerky muscle movements

## Pathology

### How does neuroblastoma develop?[10,12]

**Multipotent neural crest cells** migrate throughout the embryo forming different tissues

It is likely that **neuroblastoma occurs when mutations lead to developmental abnormalities** in neural crest progenitors of the sympathetic nervous system lineage




### Most important mutations

- Inherited mutations in key predisposition genes (e.g., **ALK, PHOX2B**) increase the risk of developing neuroblastoma[13]
- **MYCN is used as a prognostic biomarker in neuroblastoma**[10]

**MYCN amplification or aberrations is found in ~25% of cases, and is correlated with poor prognosis, progression-free survival, and metastatic behavior**[10]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# Diagnostic Pathway for Neuroblastoma

## Initial clinical assessment

- **History and symptoms**
  Look for common symptoms or signs of catecholamine excess[14] (e.g., hypertension, sweating)
- **Physical exam**[2]
  Focus on finding palpable masses, lymphadenopathy, hepatomegaly[15], or neurologic deficits (e.g., from spinal cord compression)

## Laboratory tests[2]

- **Urinary catecholamines**
  Elevated VMA (vanillylmandelic acid) and HVA (homovanillic acid) are classic markers
- **Blood tests**
  CBC (anemia or cytopenias if marrow involved); Liver and renal function tests; LDH and ferritin (may be elevated in advanced disease); NSE can also be elevated

## Imaging studies[2]

- **Ultrasound**
  Often the first step if an abdominal mass is suspected
- **MRI or CT scan (CAP)**
  Detailed evaluation of the primary tumor and involvement of nearby structures
- **mIBG scan**
  Highly specific for NB, used to detect both primary and metastatic disease
- **PET scan**
  Sometimes used in mIBG-negative tumors

## Bone marrow evaluation[2]

- **Bone marrow aspirate and biopsy**
  Done bilaterally to assess metastatic involvement

## Pathologic confirmation

- **Biopsy of tumor**[2,9]
  Histologic confirmation is required; look for small, round, blue cells typical of neuroblastoma
- **Immunohistochemistry**[16,17]
  Positive for markers like synaptophysin, chromogranin, and NB84
- **Genetic testing**[2,8-10,13]
  MYCN amplification (key prognostic marker); Chromosomal aberrations like 1p and 11q deletions, 17q gain; ALK mutation (especially in familial or relapsed cases)

## Staging and risk stratification[18]

- **INRG Staging System**
  Based on imaging and presence/absence of image-defined risk factors; Categories: L1, L2, M, MS
- **Risk Groups: low, intermediate, or high-risk**
  Based on age, stage, histology, MYCN status, ploidy
- **INSS**
  Based on tumor removal; Categories: 1, 2A, 2B, 3, 4, 4S

## Risk Stratification[19]

***Risk stratification helps to predict clinical outcomes and optimize therapy for patients with neuroblastoma***

The **INRG classification**, which uses seven clinical and biological factors associated with the outcome at diagnosis to classify neuroblastoma into four risk categories: **very low, low, intermediate, and high-risk**

**50%** **children diagnosed with high-risk neuroblastoma**[5]

**Only 50% of these patients reach long-term survival**[5]

*Patients diagnosed with intermediate- or low-risk neuroblastoma have better outcomes, achieving ≥95% OS*

## Treatment High-risk Patient[5,20]

***Whole treatment duration approximately 18 months***[20]

**1 Induction therapy** → **2 Consolidation therapy** → **3 Maintenance therapy**

Induction therapy + ASCR → Surgery → High-dose chemotherapy* + SCT → Radiation therapy → Immunotherapy + Differentiation therapy (retinoid)

**High risk of relapse if no or ineffective maintenance therapy**

*50% patients still relapse, without available SOC*[5]

## R/R Disease

- **Relapse**: when neuroblastoma **re-emerges** after complete remission or very good partial response
- **Refractory**: disease that **responds incompletely** to treatment and is still evident in macroscopic amounts after several months of adequate therapy, but is **stable or slightly reduced**

**R/R has a poor prognosis**[4,20]
5-year OS = ~20% prior to immunotherapy, and it remains very difficult to treat

## Treatment R/R Patient[5,21]

- Chemotherapy
- Chemotherapy + Immunotherapy
- Tandem transplant
- Anti-GD2 antibody immunotherapy
- Cell-based therapy
- Clinical trials
- CAR-T and NK-cells investigational therapies

***Without SOC, treatment will vary based on severity, risk, mutations, R/R nature of the disease, age, available and approved therapies***

*Myeloablative chemotherapy.
ASCR, autologous stem cell rescue; CAP, chest/abdomen/pelvis; CBC, complete blood count; CT, computed tomography; IDRF, image-defined risk factor; INRG, International Neuroblastoma Risk Group; INSS, International Neuroblastoma Staging System; LDH, lactate dehydorgenase; mIBG, meta-iodobenxylguanidine; MRI, magnetic resonance imaging; NB, neuroblastoma; NSE, neuron-specific enolase; OS, overall survival; PET, positron emission tomography; R/R, relapsed/refractory; SCT, stem cell transplant; SOC, stndard of care.


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