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**Title:** Neuroblastoma – A Master of Disguise and a Challenge to Cure

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**Abstract**

Neuroblastoma is an embryonal tumour arising from primitive neural crest cells of the sympathetic nervous system. It is one of the commonest childhood cancers and typically affects very young children. It is characterised by a very broad spectrum of clinical presentation and outcome, driven by the biology of the tumour. This ranges from ‘low risk’ tumours, most commonly in infants, which may spontaneously regress and have an excellent prognosis with minimal or no treatment, to ‘high risk’ disease, which carries a poor prognosis despite intensive multi-modal treatment. Although particular presentations may be associated with favourable or unfavourable outcome, the clinical features may mask the underlying biology of the tumour and a full assessment of the clinical and biological features is required to determine appropriate treatment. The International Neuroblastoma Risk Group (INRG) classification, based on the age of the patient and the stage, grade and genetics of the tumour, is used to stratify treatment according to risk factors. This review provides an overview of current neuroblastoma management, focusing on how INRG classification is applied in practice, and how this is used to determine individual patient treatment. The challenges that remain, particularly in treating patients with high-risk disease, are discussed.

**Key words** Neuroblastoma, risk-stratification, *MYC-N,*metastatic, Image Defined Risk Factors (IDRF), International Neuroblastoma Risk Group (INRG) Segmental Chromosomal Abnormalities (SCA)

Neuroblastoma is an embryonal tumour arising from primitive neural crest cells of the sympathetic nervous system (SNS). It is one of the commonest childhood cancers, accounting for approximately 8% of all paediatric malignancies. There are around 100 new cases per year in the UK, the majority of whom are very young children, mostly under 5 years of age. It is characterised by a very broad spectrum of clinical presentation and outcome, driven by the biology of the tumour. This ranges from ‘low risk’ tumours, most commonly in infants, which may spontaneously regress and have an excellent prognosis with minimal or no treatment, to ‘high risk’ disease, which carries a poor prognosis despite intensive multi-modal treatment. In 2009, The International Neuroblastoma Risk Group (INRG) classification system was published, agreeing consensus risk factors and a pre-treatment risk grouping system (1). This was based on analysis of survival and potential risk factors of 8,800 patients, collected within the INRG database. Since then the INRG system has been used as a framework to stratify treatment for patients with neuroblastoma. This review provides an overview of current neuroblastoma management, focusing on how treatment is stratified depending on clinical and biological risk factors, and the challenges that remain, particularly in treating high-risk patients.

**How does neuroblastoma present?**

Neuroblastoma can arise anywhere within the SNS, most commonly in the adrenal gland or abdominal paraspinal ganglia, and less frequently in the thorax, cervical and pelvic ganglia. More than 50% of patients will have evidence of metastatic disease, typically in the bones or bone marrow. Presenting symptoms will depending on the location and extent of the primary tumour and on the presence of metastatic disease. In addition, patients will occasionally present with immune-mediated paraneoplastic phenomena or with symptoms resulting from hormone secretion by the tumour *(Table 1).*

**How is neuroblastoma diagnosed?**

In over 90% of patients with neuroblastoma, there will be elevated levels of catecholamine metabolites (e.g. homovanillic or vanillylmandelic acid) in the urine, and spot urine analysis demonstrating these is useful in making a rapid diagnosis. However, tissue biopsy is required to confirm a histological diagnosis and to ascertain biology of the tumour, as histological features and cytogenetic profile are key elements of risk stratification. Tissue should be obtained from the primary tumour, ideally by percutaneous, image-guided, biopsy if feasible, ensuring sufficient tissue is obtained for immunohistochemistry as well as genetic profiling.

**How is risk group determined?**

Although particular presentations may be associated with favourable or unfavourable outcome, the clinical features may mask the underlying biology of the tumour, and a full assessment of this is required to decide appropriate treatment. INRG stratification is based on the patient’s age, stage, histology and cytogenetics of the tumour *(Table 2):*

*Stage:* The INRG Staging System (INRGSS) provides a pre-surgical staging system, based on whether the primary tumour is considered resectable or unresectable, as defined by agreed Image Defined Risk Factors (*Table 3*) and whether there is evidence of metastatic disease (2). Tumours are categorised as localised resectable (L1) or unresectable (L2) or metastastic (M). In addition, a special category of metastatic disease (Ms) occurring in infants is recognised, which is typically characterised by bulky liver disease and skin nodules, but without evidence of bony, lung or CNS disease. In order to fully stage patients, cross-sectional imaging of the primary tumour site (MRI or CT) is required to ascertain resectability and 131-Iodine meta-iodo-benzyl-guanidine (131-I MIBG) imaging and bilateral bone marrow aspirate with trephine biopsies are needed to assess for metastatic disease. MIBG is taken up by most neuroblastomas, and in most cases will identify metastatic sites. However, if the primary tumour does not demonstrate evidence of MIBG uptake, FDG-PET imaging should be used as an alternative. CNS imaging should be considered in infants and patients with high-risk disease. Ideally, staging should be completed prior to starting treatment, but if there is clinical urgency to start chemotherapy (e.g. spinal cord compression) then it may be done as soon as feasible.

*Histology:* Neuroblastoma is a small round blue cell tumour. Histology may display typical pseudorosettes or evidence of neuronal differentiation, but immunohistochemical staining for specific markers (e.g. PHOX2B, NSE) is needed to confirm diagnosis and to distinguish from other embryonal tumours. There is a spectrum of differentiation, from undifferentiated neuroblastoma (composed entirely of neuroblasts with no ganglion cell differentiation) to mature ganglioneuroma, composed entirely of mature ganglion cells. In between these extremes, are poorly differentiated (<5% mature ganglion cells) and differentiating (> 5% mature ganglion cells) neuroblastoma, and ganglioneuroblastoma (intermixed or nodular). The International Neuroblastoma Pathology Classification (INPC) is used to categorise histology as ‘favourable’ or ‘unfavourable’, depending on the age of the patient, the degree of differentiation (undifferentiated, poorly differentiated or differentiating) and the mitosis-karyorrhexis index (low, intermediate or high).

*Cytogenetics:* Neuroblastoma is a genetically complex disease with abnormalities ranging from changes in numbers of copies of whole chromosomes (ploidy) to single gene changes including mutations or gene amplification. One of the first genetic abnormalities to be discovered in neuroblastoma was amplification of the *MYCN* oncogene*.* This is associated with rapid disease progression and inferior outcome, and assigns the patient to a high-risk category of disease in most cases. Consequently, this is the most important genetic test to be undertaken on all neuroblastoma tumours at diagnosis and can be performed rapidly by fluorescent *in situ* hybridisation. The presence of additional chromosomes (numerical chromosomal abnormalities (NCA)) is associated with a favourable outcome. As well as gain and loss of whole chromosomes, parts of chromosomes can also be affected (segmental chromosomal aberrations (SCA)). There are seven typical SCA which have been associated with poor outcome in neuroblastoma (1p loss, 1q gain, 2p gain, 3p loss, 4p loss, 11q loss and 17q gain) and the presence of any of these may require intensification of treatment, depending on other risk factors. NCA and SCA can be detected by single nucleotide polymorphism (SNP) arrays. In addition, all neuroblastoma should be tested for mutations or amplifications in the *ALK* (anaplastic lymphoma kinase) oncogene. ALK mutations are the commonest cause of hereditary neuroblastoma (1-2% of all neuroblastoma) and can occur in all risk groups. *ALK* aberrations are associated with inferior outcome in patients with high risk neuroblastoma and in the next European high risk neuroblastoma trial, patients with *ALK* aberrations will receive treatment with an ALK inhibitor, in addition to standard treatment, to try and improve survival. In the future, all of these molecular investigations will be replaced using a whole genome sequencing, but validation of this in comparison to current gold standard techniques, as well as improvement in turnaround times, is requirement before this is adopted. In view of the importance of genomic analysis in the risk stratification of patients, is it essential that it is performed robustly in national reference laboratories.

**How does neuroblastoma treatment depend on INRG risk group?**

Once tumours have been fully staged and the biology characterised, patients can be assigned to an INRG risk group and treatment then given according to national practice. In the UK, the Children’s Cancer and Leukaemia Group treatment recommendations are in in line with the most recent European Neuroblastoma Research network (SIOPEN) trials *(Table 4).*

*Low Risk neuroblastoma*

Low risk neuroblastoma comprises around 30% of patients, and has an excellent outcome (overall survival > 95%).Patients under the age of 18 months withunresectable (L2) tumours without unfavourable genetic features or life or organ threatening symptoms *(Table 2, group 1)* may be safely be safely observed in the anticipation that spontaneous regression may occur. Regression can begin any time up to 18 months of age; tumours may initially get larger, and may take many years to completely regress. Where there are life or organ-threatening features, or if there are SCA, chemotherapy *(Table 2, group 2 and 3 respectively)* must be given without delay to relieve these symptoms, and continued until there is tumour shrinkage and resolution of life-threatening symptoms or the tumour becomes resectable. Similarly patients with Ms disease, may either be observed *(Table 2, group 4)* or treated with 2-4 cycles of chemotherapy if there are life-threatening or adverse genetic features *(Table 2, groups 5 and 6 respectively).* Patients with opsoclonus myoclonus syndrome (OMS), often have low risk neuroblastoma. Immunosuppression is required to treat the OMS, and the neuroblastoma should be managed according to the INRG risk group. Although low risk and good biology may require no treatment, surgical resection of L1 tumours may improve the OMS symptoms.

*Intermediate Risk neuroblastoma*

Intermediate risk neuroblastoma comprises around 20% of patients, and overall survival for this group is approximately 80%. It includes patients > 18 months old with L2 disease and infants < 12 months old with metastatic disease involving either bone, lung or CNS metastases (Stage M). In both groups *MYCN* amplification is absent.

Intermediate risk disease which is unresectable L2 disease in patients >18 months of age has a variable clinical course and outcome which is strongly dependent on histology and biology. If the tumour shows differentiating histology *(Table 2, group 7),* 4 cycles of conventional chemotherapy are given followed by surgery if feasible. However if the histology shows undifferentiated or poorly differentiated neuroblastoma *(Table 2, group 8),* treatment is intensified with 6 cycles of chemotherapy, followed by surgery, radiotherapy to the site of primary tumour and 13 cis retinoic acid treatment. With this treatment there is a 63% chance of progression free survival. Recent unpublished data suggests prognosis of this group is also influenced by the presence of SCA and together with age > 5 years (previously shown to be of prognostic importance), current UK recommendation is that such patients are treated as high risk. Patients with stage M disease < 12 months, without MYCN amplification *(Table 2, group 10)* have a very good prognosis with > 90% chance of long-term progression free survival with a limited number of courses of conventional chemotherapy with or without surgical resection of the primary tumour.

*High-Risk Neuroblastoma*

High-risk neuroblastoma compromises approximately 50% of patients and is associated with long-term survival of <50%, despite advances in treatment. In Europe, the current standard of care is based on evidence and outcomes from the SIOPEN-HR-NBL1 trial which completed patient accrual in 2017 and included 5 randomisations across three of the 5 standard modalities of treatment. The multi-modality treatment is given over 14-18 months and includes:

*Induction chemotherapy:* a number of induction chemotherapy regimens are used across the world, but since 2002 the European standard is a regimen termed Rapid COJEC. This is a dose intensive platinum-based regimen in which patients receive 8 courses of chemotherapy at 10 day intervals with granulocyte colony stimulating factor (G-CSF) support between courses. Metastatic response at the end of induction chemotherapy is important, with poor response strongly associated with reduced long-term survival. Poor response is defined as patients with significant mIBG uptake in bone (SIOPEN score >3) and / or persistent bone marrow involvement. Approximately 25% of patients do not achieve these response criteria and rather than proceed with the other treatment modalities should be considered for alternative second line induction regimens, including relevant clinical trials.

Patients aged 12 -18 months with MYCN non-amplified metastatic disease are initially classified as high-risk, but if the tumour has NCA only, and no evidence of SCA, they may be considered as having intermediate risk disease, and stop treatment after induction chemotherapy and surgery.

At the end of induction chemotherapy, a peripheral stem cell mobilisation and collection should be performed. The combination of chemotherapy and high dose of G-CSF is used mobilise CD34+ve stem cells from the bone marrow into the peripheral circulation and these are collected by attaching the patient to a cell separator via an appropriate double lumen central line. These cells are cryopreserved for re-infusion following high-dose chemotherapy treatment

*Surgery:* Once a good metastatic response has been achieved, surgical excision of the primary tumour should be considered, with the aim of achieving as complete a resection as is safely feasible, as there is evidence that incomplete resection of the primary tumour is associated with poorer survival. The risks of surgery include intra-operative bleeding, organ damage and particularly kidney and nerve damage and Horner’s syndrome. If surgery is likely to involve a nephrectomy then surgery can be delayed until after high-dose chemotherapy treatment to preserve renal function for nephrotoxic chemotherapy treatment.

*High-dose chemotherapy and autologous stem cell transplant:* Patients have consolidation high-dose chemotherapy treatment with myeloablative doses of busulfan and melphalan. The bone marrow is then rescued with re-infusion of the previously harvested stem cells which usually results in engraftment by 10-14 days post stem cell re-infusion. Particular risks from high dose chemotherapy include severe life threatening infections, veno-occlusive disease, pulmonary toxicity and infertility. This period of treatment usually includes a 3-6 week in-patient hospital stay with supportive care in appropriate protective isolation.

*Radiotherapy:* In addition to surgery as local tumour control, it is standard practice to also treat the primary tumour bed with external beam radiotherapy at a dose of 21Gy in 14 fractions, regardless of the degree of surgical resection.

*Immunotherapy and differentiation therapy:* The final 6 months of treatment consists of 6 courses of treatment with oral *cis*-retinoic acid alternating with 5 courses of immunotherapy. The *cis*-retinoic acid causes neuronal differentiation of the neuroblastoma cells, resulting in a more mature cellular phenotype. The addition of anti-GD2 monoclonal antibody treatment to treatment is based on the seminal study by US Children’s Oncology group, which demonstrated a 20% improvement in 2 year event free survival in patients receiving anti-GD2 (Dinutuximab), given with GM-CSF and IL-2, in addition to standard treatment (3). In Europe, SIOPEN have demonstrated similar outcome with a different anti-GD2 antibody (dinutuximab beta), given as a 10 day continuous infusion, without cytokines, given every 5 weeks for 5 cycles. Immunotherapy is initially delivered as an in-patient, but if patients tolerate this well then they can receive a component of the immunotherapy at home via a continuous infusion device. The potential side-effects of immunotherapy include allergic or anaphylactic reactions, neuropathic pain, capillary leak syndrome and neuro-toxicity including ophthalmoplegia and occasionally myelitis, which can show a variable degree of recovery.

Despite these intensive treatments, outcomes for high-risk patients remain poor. The SIOPEN European consortium have recently opened the HR-NBL2 trial with the aim of improving outcome. This trial will compare the efficacy and toxicity of Rapid COJEC compared to the German Oncology and Haematology Group induction regimen, the addition of an extra course of high dose chemotherapy and boosting radiotherapy doses (additional 14.4 Gy) to any significant post-surgical tumour residuum

**Relapsed Neuroblastoma**

Over 50% of patients with high-risk neuroblastoma will relapse or have disease which is refractory to standard treatments. The outcome for these patients is extremely poor, with long-term survival less than 10%. The optimal therapy for relapsed high-risk neuroblastoma is not clearly defined. The overall approach is similar between Europe and North America but the choice of drugs might be different depending on the local clinical trials as well as drug availability. Biopsy of relapsed tumour is paramount to understand tumour evolution at relapse and moreover to identify potential novel targets for which small molecules are available such as ALK, MAPK pathway and CDK4/6 alterations. There is an overall agreement that the first line of treatment for relapsed neuroblastoma is the use of some form a chemotherapy-based regimen but it is unclear which combination of chemotherapy is the most efficacious and various schedules have demonstrated similar results.

Recently the addition of anti-GD2 to chemotherapy has shown promising results in patients with relapsed disease. The COG ANBL1221 study combined temozolomide and irinotecan with dinutuximab plus GMCSF regimen, and demonstrated significant anti-tumour activity irrespective of prior anti-GD2 antibody treatment. Overall, 41.5% of the patients showed objective responses and a further 41.5% had stable disease (4). As a result of this, chemoimmunotherapy is currently the standard of care in North America for children with relapsed or refractory neuroblastoma and ongoing clinical trials are investigating strategies to further improve the efficacy of such combination.

In Europe, the BEACON-Neuroblastoma trial (NCT02308527) has shown that addition of bevacizumab to irinotecan/temozolomide has promising effects on progression free survival.

Molecular radiotherapy is another form of treatment available for relapsed/refractory neuroblastoma. In a meta-analysis of more than 1100 patients with neuroblastoma receiving 131I-mIBG therapy, 131I-mIBG therapy showed a mean response of 32%. Various trials are currently looking at ways of improving the therapeutic advantages of 131-I-MIBG, in particular the MiNivAN study (NCT02914405) is exploring the toxicity and efficacy of 131I-mIBG therapy in combination with nivolumab (anti PD-1 antibody) and dinutuximab beta (anti GD2 antibody). In addition, a US New Approaches to Neuroblastoma Therapy (NANT) trial recently found that patients receiving MIBG with vorinostat had the highest response rate compared to Vincristine/Irinotecan and MIBG or MIBG alone (NCT01019850). Despite the efficacy of 131I-MIBG therapy in children with relapsed neuroblastoma, the low number of institutions able to administer radioactive treatment limits its widespread use. Studies evaluating other radioactive agents targeting the somatostatin receptor (e.g 177Lu-DOTATATE) have been performed but a definite role is yet to be established.

Options for further progressions or relapses depend on alternative regimens if toxicities allow, or enrolment into early clinical trials investigating the use of molecular targeted agents with or without a backbone chemotherapy. Some of these clinical trials do not use any biomarker for patient selection but others do and therefore sampling of relapse tumours for the identification of potential therapeutic target becomes paramount. Although neuroblastomas at diagnosis show a relative paucity of genetic alterations in therapeutically relevant gene targets, relapsed neuroblastoma tumors have an increased number of mutations that could be actioned in the context of clinical trials.

ALK mutations are a target of particular interest, and the incidence of ALK aberrations in higher at relapse than at initial diagnosis. Although an initial phase I trial of crizotinib (a first generation ALK inhibitor) did not show promising results in ALK-mutated neuroblastoma, further studies have shown that ALK inhibitors might be effective only in patients with specific ALK mutations. For example, the phase 2 trial showed that crizotinib had activity in a subset of ALK–mutated neuroblastomas (Arg1275Gln), but not in neuroblastomas harbouring other ALK mutations or amplification. Ceritinib, a second generation ALK inhibitor showed preliminary limited response against neuroblastoma but complete study results are awaited. The results of the phase I study of single agent lorlatinib report that patients over 18 years had a better response compared to the group of younger patients. Further combinational studies trials are ongoing, such as the NANT phase I study of lorlatinib in combination with cyclophosphamide and topotecan (NCT03107988).

Many other targets are being explored and have been prioritized by the neuroblastoma community, including Aurora A, BCL2, MDM2, CDK4/6, ODC1, WEE1 and CHK1, and clinical trials are being performed, however their role in the relapsed setting, as well as a strong selection strategy, are yet to be established. Combinatorial trial designs are being explored to reduce the number of single agent clinical trials and to promote the combination of small molecules based on a strong preclinical rationale with or without a backbone chemotherapy. Clinical trials remain, nevertheless, the best possible treatment for patients with relapsed neuroblastoma.

**Conclusions:**

* **Neuroblastoma has a very broad spectrum of clinical presentation, tumour biology and prognosis.**
* **Risk stratification based on patient age, tumour stage and biology is vital to identifying appropriate treatment plans.**
* **Some patients with low risk disease can be safely observed, as spontaneous regression is common, but high risk patients require intensive multimodal therapy**
* **Relapsed high risk neuroblastoma is particularly challenging and novel, targeted, approaches are being explored to improve outcome**

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**Suggested further reading**

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**Table legends:**

**Table 1:** **Clinical presentations of neuroblastoma**

**Table 2: International Neuroblastoma Risk Group stratification;** taken from Cohn et al (1). Tumours are stratified based on stage (L1/L2/M/Ms), age, histology (ganglioneuroma (GN), ganglioneuroblastoma (GNB)), grade of differentiation, MYCN amplification (AMP) or non-amplified (NA) and presence of 11q aberration.

**Table 3: Image Defined Risk Factors in neuroblastoma:** Adapted from The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report (2).

**Table 4: Risk-stratified treatment of neuroblastoma:** The UK Children’s Cancer and Leukemia Group treatment recommendations according to INRG. Treatment is stratified based on stage (L1/L2/M/Ms), age in months (mo.), *MYCN* amplification (amp or non-amp), grade (differentiating (diff.) or undifferentiated) and chromosomal abnormalities (CA) and the presence of life-threatening symptoms (LTS). Treatment include chemotherapy with carboplatin/etoposide or CADO (cyclophosphamide, doxorubicin, vincristine), surgery, radiotherapy and cis-retinoic acid (cis-RA). Groups refer to those in the SIOPEN Low and Intermediate Risk Neuroblastoma (LINES) trial (NCT01728155)