GPOH Guidelines for Diagnosis and First-line Treatment of Patients with Neuroblastic Tumors, update 2025

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GPOH Guidelines for Diagnosis and First-line Treatment of Patients with Neuroblastic Tumors, update 2025

GPOH-Leitlinien für die Diagnose und Erstlinien-Behandlung von Patienten mit neuroblastischen Tumoren, update 2025

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ABSTRACT

The clinical course of neuroblastoma is more heterogeneous than any other malignant disease. Many low-risk patients experience regression after limited or even no chemotherapy. However, more than half of high-risk patients die from disease despite intensive multimodal treatment. Precise disease characterization for each patient at diagnosis is key for risk-adapted treatment. The guidelines presented here incorporate results from national and international clinical trials to produce recommendations for diagnosing and treating neuroblastoma patients in German hospitals outside of clinical trials.

ZUSAMMENFASSUNG

Der klinische Verlauf von Neuroblastomen ist sehr variabel. Bei Patienten mit günstigem Risikoprofil werden regelhaft Spontanregression der Tumoren beobachtet. Bei Hochrisiko-Neuroblastom können dagegen nur ca. 50 % der Patienten durch eine intensive multimodale Therapie geheilt werden. Eine exakte Risikoklassifizierung jedes einzelnen Patienten ist von entscheidender Bedeutung eine korrekte risikoadaptierte Therapie. Die hier vorgestellten Empfehlungen berücksichtigen Ergebnisse von nationalen und internationalen klinischen Studien und definieren den gegenwärtigen Standard für die Behandlung von Patienten mit Neuroblastomen in Deutschland außerhalb von klinischen Studien.

Introduction

Neuroblastoma presents either as low-risk disease capable of regression after mild or no treatment or as high-risk disease, often leading to death despite intensive multimodal treatment [1–3]. Many clinical and molecular factors have been associated with patient prognosis, but the molecular mechanisms explaining the divergent course remain incompletely understood. Telomere maintenance mechanisms appear to play a central role in high-risk neuroblastoma development [4]. Treatment decisions must consider the risk profile in each individual patient according to International Neuroblastoma Risk Group (INRG) classification to avoid overtreating low-risk and undertreating high-risk disease. Here, we update guidelines we first published in 2017 to define a current national standard for the diagnosis and treatment of patients with neuroblastic tumors not included in clinical trials. These guidelines are based on definitions and strategies from previous German clinical trials and take into account publications from other research groups. If patients are treated in prospective clinical trials, different recommendations may apply depending on the trial protocol. Significant changes compared to the 2017 guidelines are (1) routine assessment of *ALK* amplification and mutation status at diagnosis, (2) RNA expression array analysis for low- and medium-risk disease at diagnosis, (3) delay of complete staging up to 6 months in asymptomatic infants with suspected neuroblastoma, (4) routine assessment of supraclavicular lymph nodes in patients at diagnosis of high-risk neuroblastoma, (5) revised blood criteria for the start of chemotherapy cycles, (6) introduction of immune-chemotherapy prior to myeloablative chemotherapy for high-risk disease with incomplete metastatic response to induction chemotherapy, (7) external beam radiotherapy to the primary tumor site in all patients with high-risk neuroblastoma, (8) optional external beam radiotherapy to metastatic sites in patients with ≤ 3 active metastatic lesions after myeloablative chemotherapy and (9) an increase in the interval between radiotherapy of central body compartments and busulfan-containing myeloablative chemotherapy of 60 days.

Diagnosis of neuroblastoma

Clinical and laboratory assessment

Physical examination includes an evaluation for an abdominal mass, assessment of hepatomegaly and evaluation of all lymph nodes. High-risk neuroblastoma frequently involves the left supraclavicular lymph nodes in patients with intra-abdominal disease. Proptosis, Horner's syndrome or skull-based metastases should also be evaluated in the head and neck. A detailed neurological examination is necessary, and especially critical in young patients with paraspinal masses, to ensure early detection of evolving paralysis. Levels of neuron-specific enolase (NSE) and lactate dehydrogenase (LDH) are determined in the blood as non-specific markers of malignant disease, and catecholamine excretion into the urine is assessed by testing for vanillylmandelic and homovanilic acids (VMA and HVA). Similar sensitivity and specificity is achieved by spot urine analysis and 24-hour collection [5], making urine collection unnecessary.

Cross-sectional imaging

Magnetic resonance imaging (MRI) is considered the standard imaging technology for patients with neuroblastoma. Detailed guidelines have been published [6]. Initial staging requires MRI of the primary tumor site in all patients and skull/central nervous system in patients with high-risk disease. In high-risk cases with abdominal tumors, the cervical region should also be searched for supraclavicular lymph nodes at least by ultrasound, followed by MRI to confirm lesions or in case of equivocal findings. All sites involved at diagnosis must be re-assessed at regular intervals during treatment and follow-up. Prospective trials comparing whole-body MRI, [^{123}I]mIBG SPECT, [^{18}F]FDG PET/CT and bone marrow cytology are limited to date [7–10]. Whole-body MRI, however, can provide valuable information about tumor extent, and may be complemented by high-resolution local imaging [11]. The degree of neuroblastic tumor differentiation can be better predicted by diffusion-weighted imaging [12, 13], although visual assessment alone without quantifying diffusion restriction can increase the rate of false-positive lesion detection [14]. Computed tomography (CT) is an alternative to MRI for patients with ferromagnetic implants or for preoperative vasculature imaging in the tumor area. CT is not recommended for routine use due to radiation exposure.

^{123}I-labeled meta-iodobenzylguanidine scintigraphy ([^{123}I] mIBG)

[^{123}I]mIBG scintigraphy is the current gold standard for functional imaging in neuroblastoma patients and is internationally recommended [15]. Detailed guidelines have been published [16–19]. Scintigraphy requires 370 MBq [^{123}I]mIBG in adults, is dosage-reduced according to body weight in children, but should maintain at least 80 MBq [^{123}I]mIBG total activity despite discussions to reduce minimal activity to 37 MBq [^{123}I]mIBG [20]. Balancing image quality against radiation exposure remains a matter of debate, but considering that high noise and unfavorable scatter characteristics regularly limits [^{123}I]mIBG image interpretability, any reduction in

administered activity comes at the risk of further diminishing image quality. The scan must be performed 24 hours after [^{123}I]mIBG injection. Single-photon emission computed tomography (SPECT) of all relevant body parts is the clinical standard [21]. Whenever possible, SPECT should be combined with low-dose-CT (SPECT/CT) to overcome the limitations of SPECT alone to accurately anatomically localize lesions. Additional imaging at 4 hours post-injection is unlikely to provide additional information and can, therefore, be omitted [22]. Patients need preparation for [^{123}I]mIBG imaging, including voiding of the urinary bladder prior to each scan, to allow clear interpretation of pelvic organs particularly in patients with pelvic primary tumors. Thyroid blockage should begin before [^{123}I]mIBG injection and continue until the third day post-injection. The [^{123}I]mIBG scintigraphy report should include the semi-quantitative SIOPEN score. In brief, the score distinguishes 12 skeletal compartments, in which the extent of mIBG-positivity for each lesion is scored with a value between 1 and 6, then the lesion scores are added together, yielding a maximal score of 72 [23]. In the future, [^{123}I]mIBG scintigraphy may be gradually replaced by [^{18}F]meta-fluorobenzylguanidine ([^{18}F]mFBG) PET/CT, which has shown higher lesion detection rates than [^{123}I]mIBG imaging in small cohorts of patients with neuroblastoma [24–26]. Scan times are also much shorter, which can obviate general anesthesia [27]. However, [18F]mFBG is currently only available at a few sites, and [^{123}I]mIBG-derived response criteria [15] will need adapting for [^{18}F]mFBG in prospective comparative trials.

Positron emission tomography (PET)-CT and PET-MRI

About 15 % of neuroblastomas and the majority of ganglioneuromas fail to accumulate [^{123}I]mIBG. Positron emission tomography (PET) imaging is required for such mIBG-nonavid tumors [28, 29]. Several tracers are available. As a general rule, initial staging should always be done before the start of chemotherapy and follow-up assessments should always be done with the same tracer. With alternating tracers, it can be difficult to correctly assess the dynamics of the treatment response or to recognize progression. For neuroblastomas that only weakly or do not accumulate mIBG, [^{18}F]FDG PET-/CT is traditionally recommended as the alternative to [^{123}I]mIBG scintigraphy. [^{18}F]FDG PET-/CT can help resolve discrepancies between MRI and [^{123}I]mIBG scintigraphy, including suspected heterogeneous [^{123}I]mIBG uptake between the primary tumor and metastatic sites [30, 31]. High sensitivity, acceptable for neuroblastoma diagnostics, is achieved by [^{18}F]FDG PET/CT [32]. Comparison with MRI or, if available, PET-MRI is recommended, since bone marrow often intensively absorbs [^{18}F]FDG after recovery from chemotherapy, which may be misinterpreted as persistent or even progressive bone marrow infiltration [33]. Prospective clinical trials in small patient series demonstrated that [^{18}F]FDG PET/CT might substitute for [^{123}I]mIBG scintigraphy (if unavailable) at least for initial staging [34–37]. Other PET tracers targeting the somatostatin receptor ([^{68}Ga]Ga-DOTATATE and [^{68}Ga]Ga-DOTATOC) act independently from the NET transporter system [38] and have shown better diagnostic accuracy than [^{123}I]mIBG in prospective studies [39–41]. However, prospective clinical trials comparing [^{68}Ga]Ga-DOTATATE/DOTATOC PET/CT and [^{18}F]FDG PET/CT are not yet available. Therefore, before becoming the new clinical standard, these alternative PET tracers need more evaluation in prospective clinical trials. [^{18}F]DOPA, another commercially available PET, tracer has emerged with promising imaging results compared to [^{123}I]mIBG [42, 43]. While FDG-PET and [^{18}F]DOPA-PET are diagnostic imaging tools, mIBG and somatostatin receptor-based methods can also be adapted for radionuclide therapy using [^{131}I]mIBG or [^{177}Lu]Lu-DOTATATE.

Bone marrow assessment

Neuroblastoma does not homogenously infiltrate bone marrow. Collecting bone marrow aspirates from multiple sites reduces the false-negative rate [44]. Four aspirates from different sites or two aspirates and two trephine biopsies are mandatory [45]. The variability between observers is generally high in bone marrow cytology. In addition, the degree of bone marrow infiltration can only be reliably assessed in aspirates with a sufficient content of total nucleated cells [46]. Anti-GD2 immunocytology is currently centrally evaluated in bone marrow samples from all neuroblastoma patients treated in Germany [45, 47]. However, PCR-based bone marrow testing is expected to complement or potentially replace immunocytology in the future [48]. The assessment of bone marrow infiltration during therapy using molecular analyses is not yet standard and requires further investigation in prospective clinical studies [49–52].

Tumor biopsy, histology and assessment of molecular alterations

Tumor histology and molecular genetics are crucial for risk stratification for all neuroblastoma patients. Tumor biopsy is mandatory for all patients at initial diagnosis of the disease. The only exceptions are high-risk patients with massive bone marrow infiltration and infants under 6 months of age, in whom a delayed diagnosis is performed for suspected low-risk neuroblastoma. Definitions set in the International Neuroblastoma Pathology Classification (INPC [53]) system are used for tumor histology (▶ **Table 1**). Central reference histology by an experienced pediatric tumor pathology center is recommended. During biopsy, sufficient tumor material for histopathological evaluation as well as analyses of *MYCN* amplification, gene expression profiling, single-nucleotide variations, copy number aberrations, ploidy and other studies must be obtained because tumor-specific genetic markers are critical determinants for treatment planning.

Analysis of selected molecular tumor markers, including amplifications at the *MYCN* gene locus [54–56], chromosome 1p copy number [57, 58] and chromosome 11q copy number [58, 59] are accepted risk factors for patients with neuroblastoma. Recent studies suggest that risk assessment may be improved by more advanced biomarkers. Analysis of telomere maintenance mechanisms [4, 60], panel sequencing of risk-associated and/or actionable molecular alterations [4], gene expression profiling using microarrays [61] and assessment of overall copy number alterations [62] are systematically assessed in molecular and clinical trials. In particular, gene expression-based signatures and copy number alterations currently contribute to risk assessment in Germany and other European countries, respectively. Assessing *ALK* gene amplification and mutational status has become standard-of-care since it had been shown that patients with neuroblastomas harboring

▶ **Table 1** The International Neuroblastoma Pathology Classification (INPC, [53]).

Neuroblastoma (Schwannian stroma-poor)	
	Neuroblastoma, undifferentiated: Undifferentiated small- round-cell tumor without histological signs of neuroblastic differentiation, supplementary techniques (immunohistochemistry, and/or cytogenetics) are required to establish diagnosis.
	Neuroblastoma, poorly differentiated: Some tumor cells show a neuroblastic differentiation (≤ 5 % of tumor cell) within a background of (often focal) neuropil, ≤ 50 % Schwannian stroma.
	Neuroblastoma, differentiating: > 5 % of tumor cells have cytomorphologic features of differentiation toward ganglion cells (e. g. enlarged eccentric nucleus with vesicular chromatin pattern, broad, eosinophilic or amphophilic cytoplasm). Neuropil is usually present, ≤ 50 % Schwannian stroma.
Ganglioneuroblastoma, intermixed (Schwannian stroma-rich)	
	Ganglioneuromatous component is dominating (> 50 % of tumor), nests of neuroblastic cells are intermixed or randomly distributed in the ganglioneuromatous tissue and only microscopically visible, neuroblastic cells show variable stages of differentiation (differentiating neuroblasts and maturing ganglion cells), neuropil is prominent in the neuroblastic foci.
Ganglioneuroma (Schwannian stroma-dominant)	
	Ganglioneuroma, maturing: Ganglioneuromatous differentiation with minimal infiltration of scattered, evenly or unevenly distributed neuroblasts or maturing ganglion cells, no larger nests of neuroblasts.
	Ganglioneuroma, mature: Ganglioneuromatous differentiation with mature ganglion cells surrounded by satellite cells.
Ganglioneuroblastoma, nodular (Composite Schwannian stroma-rich/ stroma-dominant and stroma-poor)	
	Presence of macroscopical visible, usually hemorrhagic neuroblastic nodules (stroma-poor component) and sharply demarcated ganglioneuroblastomatous (stroma-rich intermixed) or ganglioneuromatous differentiation. The stromal component can predominate in the tumor, but (1) also can appear as thin or broad septa between stroma-poor neuroblastic nodules or (2) the tumor itself shows a ganglioneuroblastoma intermixed or ganglioneuroma histology and a lymph node metastasis is composed of a stromal-poor neuroblastoma ('atypical' Gangioneuroblastoma, nodular).
Neuroblastic tumor, unclassifiable	
Neuroblastoma, NOS (not otherwise specified)	
Ganglioneuroblastoma, NOS (not otherwise specified)	

ALK mutations or amplifications benefit from *ALK* inhibitor treatment [63–66]. Liquid biopsies are a new research field [67, 68]. For this reason, longitudinal blood and bone marrow collection (1–2 ml sampling volumes) and, if available, unfixed fresh-frozen tumor tissue are recommended during treatment.

Staging systems

Since its creation in the 1980's, neuroblastoma has been classified in patients according to the International Neuroblastoma Staging System (INSS, ▶ **Table 2**) at diagnosis and during the course of treatment [69]. Assessing the initial disease extent and completeness of frontline tumor resection are key factors in INSS staging. The International Neuroblastoma Risk Group (INRG) established a new staging system (▶ **Table 2**) that instead utilizes the presence

▶ **Table 2** The International Neuroblastoma Staging System (INSS, [69]) and International Neuroblastoma Risk Group Staging System (INRGSS, [70]).

INSS		**INRGSS**	
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph node negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive for the tumor). A grossly resected midline tumor without ipsilateral (with = stage 2A) or contralateral (with = stage 2B) lymph node involvement is considered stage 1.	L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment.
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.	L2	Locoregional tumor with presence of one or more image-defined risk factors.
2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph node positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically		
3	Unresectable unilateral tumor infiltrating across the midline with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement. The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.		
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or or other organs except as defined for stage 4S.	M	Distant metastatic disease (except stage MS).
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B) with dissemination limited to liver, skin and bone marrow (limited to infants < 1 year of age). Marrow involvement in stage 4S should be minimal, i. e., < 10 % of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The mIBG scan should be negative in the marrow.	MS	Metastatic disease in children younger than 18 months with metastasis confined to skin, liver and/or bone marrow.
Note: Multifocal primary tumors (e. g., bilateral adrenal primary tumors) should be staged according to the greatest extend of disease as defined and followed by a subscript letter M (e. g., 3M).		Note: Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined in the table.	

of anatomical conditions referred to as **image-defined risk factors** (IDRF) [1, 70, 71]. These factors indicate an increased surgical risk for frontline tumor resection, making complete low-risk tumor resection less likely (▶ **Table 3**) [70–73]. INRG staging distinguishes between localized L1 tumors without image-defined risk factors, localized L2 tumors with image-defined risk factors making initial complete resection unlikely, stage M metastatic disease and stage MS disease with metastases restricted to skin, liver and a limited grade of bone marrow infiltration in children diagnosed at 18 months or younger [70]. Both INSS and INRG staging should be recorded for patients, since it is not possible to infer one stage from the other. The INRG Working Group has also published consensus criteria for evaluating response to neuroblastoma treatment ([15], ▶ **Table 4**).

Low-risk neuroblastoma

Definition

If the patients are not included in a clinical trial with different criteria, the definitions of the NB2004 trial are applied. Neuroblastoma is defined as *low-risk* if one of the following applies: (1) INSS stage 1 without *MYCN* amplification, (2) INSS stage 2 lacking both *MYCN* amplification and chromosome 1p aberration, (3) INSS stage 3 lacking both *MYCN* amplification and chromosome 1p aberration in a patient under 2 years of age or (4) INSS stage 4S neuroblastoma with the modified upper age limit of 18 months, corresponding to INRG stage MS, without *MYCN* amplification (▶ **Fig. 1**).

Surgery

The primary goal of the first operation is to collect tumor tissue for histological and molecular analysis. Complete tumor resection should only be attempted if IDRF are absent. Minimal invasive surgery can be considered in tumors of limited size, without IDRF and not located in the abdominal midline [74–76]. Core needle (but *not* fine needle) biopsies are an alternative to open biopsy, as they usually provide tumor tissue in acceptable quantity and quality for pathological and molecular analyses [77, 78]. Delayed tumor resection should be considered for observation patients, who have non-progressing residual tumors and have reached the end of the 2nd year of life (patients diagnosed at < 1 year of age) or have been under observation for 1 year (patients diagnosed at ≥ 1 year of age) if the risk of surgery appears low. Otherwise, further observation by regular imaging is strongly recommended. Abnormal locoregional lymph nodes must also be removed if complete tumor resection appears feasible. Differentiating between the primary tumor and locoregional lymph node metastases is not always possible using imaging or during surgery, making histological assessment necessary.

Chemotherapy

Most low-risk neuroblastomas regress spontaneously and do not require systemic treatment. Chemotherapy is only necessary in the presence of threatening tumor-related symptoms at the time of diagnosis or later during observation. The main aim of chemotherapy for low-risk disease is to relieve threatening symptoms and not to achieve complete tumor regression (▶ **Fig. 2**). Threatening symptoms may include (1) an impaired general condition, (2) serious feeding difficulties leading to weight loss, (3) respiratory failure defined by oxygen requirement or carbon dioxide retention, (4) hypotension or hypertension according to age-related blood

▶ **Table 3** Image-Defined Risk Factors (IDRF) in neuroblastic tumors [70–72].

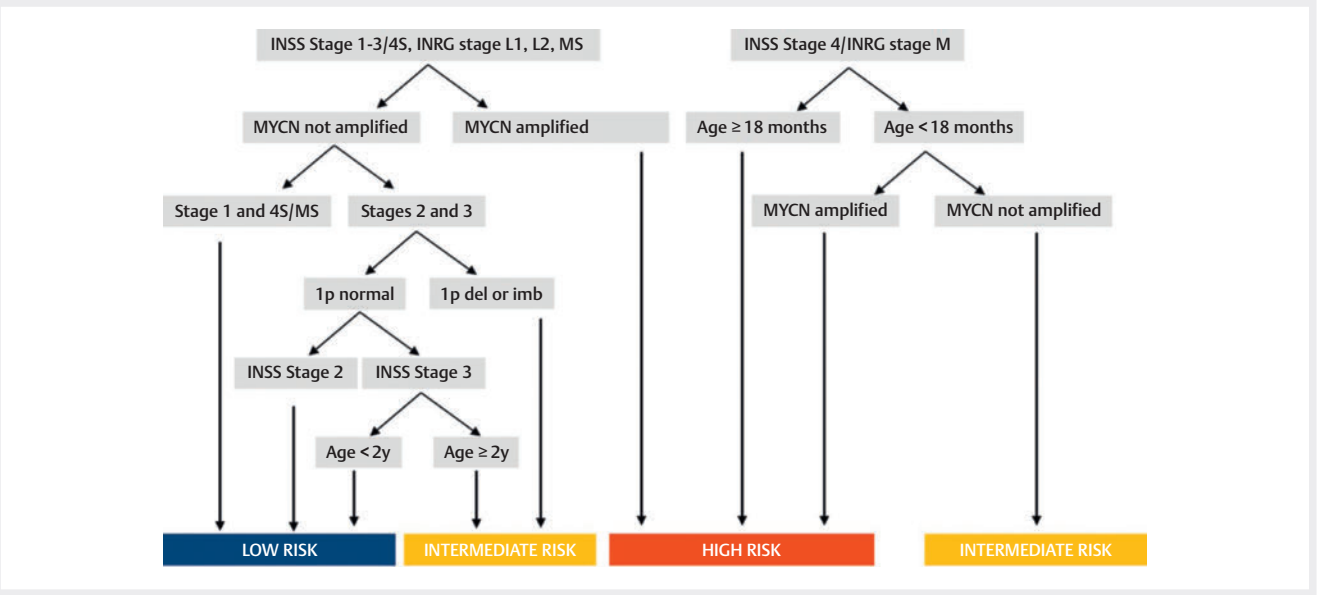
Ipsilateral tumor extension within two body compartments: Neck-chest, chest-abdomen, abdomen-pelvis	
Neck	Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
	Tumor extending to base of skull
	Tumor compressing the trachea
Cervico-thoracic junction	Tumor encasing brachial plexus roots
	Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
	Tumor compressing the trachea
Thorax	Tumor encasing the aorta and/or major branches
	Tumor compressing the trachea and/or principal bronchi
	Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12
Thoraco-abdominal	Tumor encasing the aorta and/or vena cava
Abdomen/pelvis	Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
	Tumor encasing branches of the superior mesenteric artery at the mesenteric root
	Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
	Tumor invading one or both renal pedicles
	Tumor encasing the aorta and/or vena cava
	Tumor encasing the iliac vessels
	Pelvic tumor crossing the sciatic notch
Intraspinal tumor extension whatever the location provided that: More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal.	
Infiltration of adjacent organs/structures	Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery
Conditions to be recorded, but not considered IDRFs	Multifocal primary tumors
	Pleural effusion, with or without malignant cells
	Ascites, with or without malignant cells

▶ **Table 4** Revised International Neuroblastoma Response Criteria [15].

Status	Primary tumor	Metaststic soft tissue and bone site	Bone Marrow	Overall
CR	<10 mm residual soft tissue at primary site AND Complete resolution of MIBG or FDG-PET uptake (for MIBG-nonavid tumors) at primary site	Resolution of all sites of disease, defined as: Nonprimary target and nontarget lesions measure < 10 mm AND Lymph nodes identified as target lesions decrease to a short axis <10 mm AND MIBG uptake or FDG-PET uptake (for MIBG-nonavid tumors) of nonprimary lesions resolves completely	Bone marrow with no tumor infiltration on reassessment, independent of baseline tumor involvement	All components meet criteria for CR
PR	≥30% decrease in longest diameter of primary site AND MIBG or FDG-PET uptake at primary site stable, improved, or resolved	≥30% decrease in sum of diameters of nonprimary target lesions compared with baseline AND all of the following: Nontarget lesions may be stable or smaller in size AND No new lesions AND ≥50% reduction in MIBG absolute bone score (relative MIBG bone score ≥0.1 to ≤0.5) or ≥50% reduction in number of FDG-PET–avid bone lesions	not applicable	PR in at least one component and all other components are either CR, MD (bone marrow), PR (soft tissue or bone), or NI; no component with PD
MD	not applicable	not applicable	Any of the following: (1) Bone marrow with ≤5% tumor infiltration and remains >0 to ≤5% tumor infiltration on reassessment OR (2) Bone marrow with no tumor infiltration that has ≤5% tumor infiltration on reassessment OR (3) Bone marrow with >20% tumor infiltration that has >0 to ≤5% tumor infiltration on reassessment	not applicable
MR	not applicable	not applicable	not applicable	PR or CR in at least one component but at least one other component with SD; no component with PD
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site	Neither sufficient shrinkage for PR nor sufficient increase for PD of nonprimary lesions	Bone marrow with tumor infiltration that remains positive with >5% tumor infiltration on reassessment but does not meet CR, MD, or PD criteria	SD in one component with no better than SD or NI in any other component; no component with PD
PD	>20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND Minimum absolute increase of 5 mm in longest dimension	Any of the following: (1) Any new soft tissue lesion detected by CT/MRI that is also MIBG avid or FDG-PET avid, (2) Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be neuroblastoma or ganglioneuroblastoma, (3) Any new bone site that is MIBG avid, (4) A new bone site that is FDG-PET avid (for MIBG-nonavid tumors) AND has CT/MRI findings consistent with tumor OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma, (5) >20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND minimum absolute increase of 5 mm in sum of diameters of target soft tissue lesions, (6) Relative MIBG score ≥1.2	Any of the following: (1) Bone marrow without tumor infiltration that becomes >5% tumor infiltration on reassessment OR (2) Bone marrow with tumor infiltration that increases by >twofold and has >20% tumor infiltration on reassessment	Any component with PD

CR, complete response; MD, minimal disease; MR, minor response; NI, not involved; PD, progressive disease; PR, partial response; SD, stable disease.

pressure reference values, (5) hepatic failure defined by CTCAE grade 3 bilirubin toxicity or impaired coagulation, (6) renal failure defined by impaired blood urea or creatinine, (6) a newly developed or a deteriorating pre-existing hydronephrosis, (7) newly developed MRI-documented intraspinal involvement regardless of symptoms or (8) any other organ system failure. Of note is that progression of hepatic metastases in patients with INSS stage 4S/INRG stage MS neuroblastoma can cause increased intra-abdominal pres-



▶ **Fig. 1** Treatment stratification for patients with neuroblastic tumors [rerif].

sure leading to respiratory and renal failure. Continuous trans-bladder monitoring of intra-abdominal pressure may help to predict this complication. An intra-abdominal pressure > 10 mm Hg associated with new or worsening organ dysfunction is defined as abdominal compartment syndrome in children [79]. This condition requires immediate chemotherapy start, and if intra-abdominal hypertension develops or worsens despite chemotherapy, operative herniation of the abdominal wall must be considered [80–82].

Standard chemotherapy is the N4 cycle used in previous prospective German neuroblastoma protocols (chemotherapy details in ▶ **Table 5**). Of note is that no chemotherapy-induced hearing loss, cardiomyopathy or kidney damage occurred in the 214 patients younger than 18 months at diagnosis who were treated with N4 cycles within the NB97 and NB2004 trials (unpublished results). A carboplatin and etoposide combination can be considered as an alternative to N4 [83]. Each chemotherapy cycle starts 21 days after day 1 of the preceding cycle unless bone marrow recovery is delayed, as determined by ≥ 500/µl neutrophils without granulocyte colony-stimulating factor (G-CSF) and ≥ 50,000/µl platelets without platelet transfusions. Chemotherapy should be halted when tumor-associated symptoms are resolved. Additional N4 cycles are recommended if symptomatic local tumor growth is observed after initial response to less than four N4 chemotherapy cycles. Intensified chemotherapy, according to intermediate-risk treatment, is strongly recommended if symptomatic local tumor growth continues after a total of four N4 chemotherapy cycles. If tumor regrowth is observed during follow-up after successful initial N4 chemotherapy, a tumor biopsy should be considered, as neuroblastic tumors can undergo maturation to ganglioneuroblastoma intermixed or ganglioneuroma. These mature neuroblastic tumors do not respond to chemotherapy and always require surgical resection. Systemic chemotherapy is only justified if an immature neuroblastic tumor is growing. If patients with low-risk neuroblastoma develop metastatic progression or relapse, treatment according to intermediate-risk (patients < 18 months with progression to INSS stage 4 / INRG stage M) or high-risk strategy (patients > 18 months with progression to INSS stage 4 / INRG stage M) is strongly recommended.

Radiotherapy and [^{131}I]mIBG therapy

The excellent prognosis of patients with low-risk neuroblastoma [2, 83] must be balanced against the potential long-term effects of radiation exposure (second malignancies and growth impairment) from external beam radiotherapy and [^{131}I]mIBG therapy [84–87]. For this reason, external beam radiotherapy and [^{131}I]mIBG therapy are not routinely scheduled for patients with low-risk neuroblastoma.

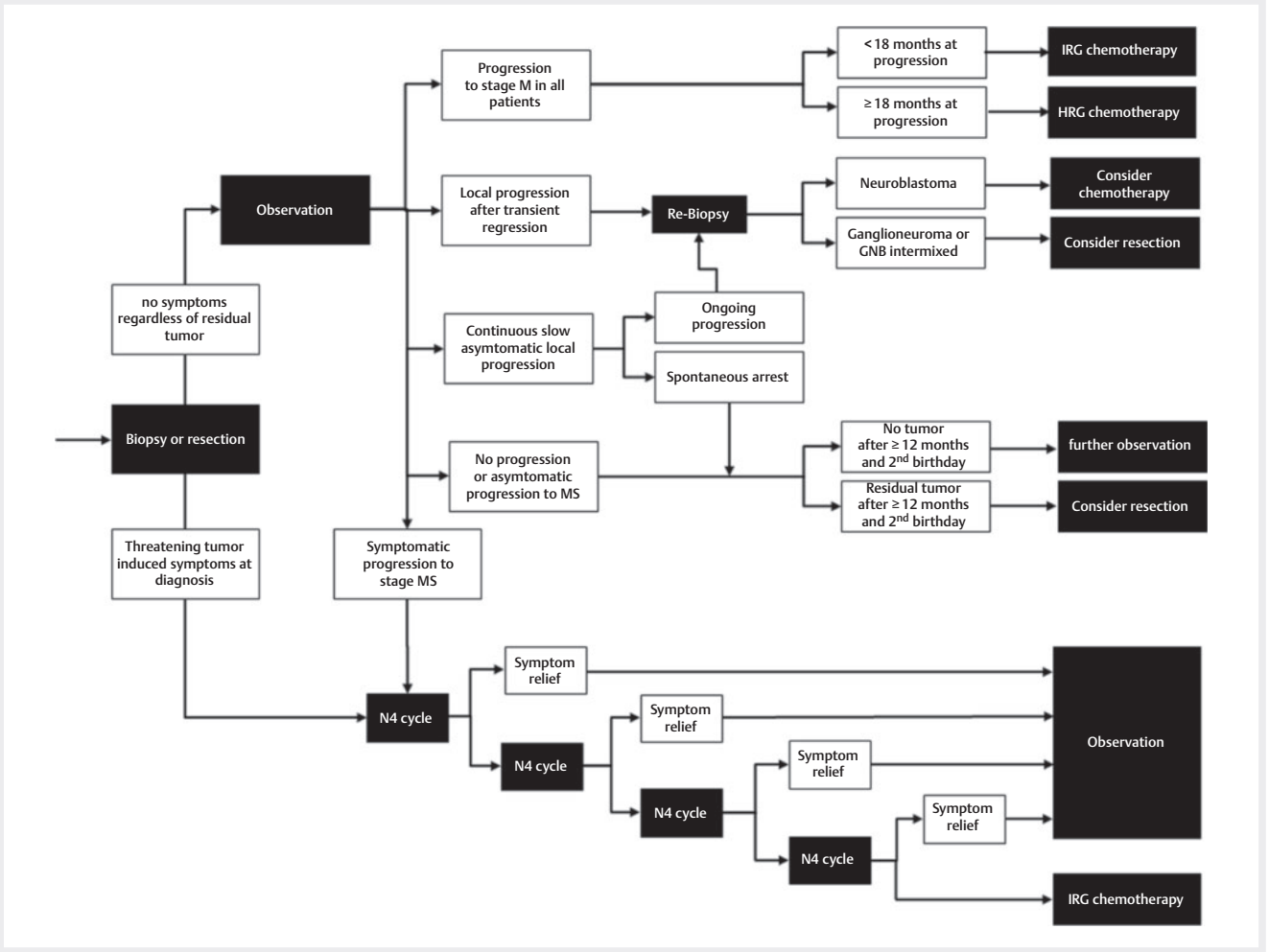
Intermediate-risk neuroblastoma

Definition

Unless the clinical trial protocol followed applies different criteria, neuroblastoma patients are defined as having *intermediate risk* if one of the following applies: (1) INSS stage 2 tumor with chromosome 1p deletion or imbalance but no *MYCN* amplification in patients of any age, (2) INSS stage 3 tumor with chromosome 1p deletion or imbalance but no *MYCN* amplification in patients < 2 years at diagnosis, (3) INSS stage 3 tumor without *MYCN* amplification in patients ≥ 2 years at diagnosis or (4) INRG stage M or INSS stage 4 tumor lacking *MYCN* amplification from patients < 18 months at diagnosis (▶ **Fig. 1**).

Surgery

Initial complete primary tumor resection should be attempted in the absence of image-defined risk factors. If image-defined risk factors are present at diagnosis, complete resection should be delayed until after chemotherapy. Delayed surgery in intermediate-risk patients older than 18 months with localized neuroblastoma should aim for gross total resection of the residual tumor, which if achieved, is associated with better outcome [88]. External beam radiation is an alternative local treatment if complete resection can



▶ **Fig. 2** Observation and treatment algorithm for low-risk neuroblastoma [rerif].

only be achieved with substantial damage to vital organs or structures. However, all measures should be taken to avoid the necessity of external beam radiotherapy for post-surgery residual tumor tissue whenever possible. It should be noted that the presence of image-defined risk factors does not automatically rule out complete resection during the course of treatment. However, tumor resection in patients with image-defined risk factors requires an experienced surgeon and surgical team [73].

Chemotherapy

Limited chemotherapy in patients with localized intermediate risk has unsatisfactory cure and survival rates [89]. Intensified chemotherapy was tested for patients with localized intermediate-risk in the NB2004 trial, in which 60 % and 76 % of these patients achieved 10-year event-free and overall survival, respectively (unpublished data). Of patients < 18 months of age and treated within GPOH NB90, NB97 and NB2004 trial protocols for INSS stage 4/INRG stage M neuroblastoma, 73 % and 86 % achieved 10-year event-free and overall survival, respectively [90]. Although patient numbers were limited, intensified treatment by myeloablative chemotherapy or immunotherapy in this cohort was not associated with improved outcome [90, 91]. Substituting carboplatin for cisplatin is recommended to avoid ototoxicity [92]. The recommended state-of-the-art intermediate-risk induction chemotherapy consists of alternating N5c and N6 cycles (▶ **Table 5**) in a total of six chemotherapy cycles (▶ **Fig. 3**). If vindesine is not available, 1.5 mg/m² vincristine (maximum total dose 2 mg) is recommended as an infusion over 1 hour instead [93]. This six-cycle induction chemotherapy is followed by four N7 cycles of oral cyclophosphamide. Each chemotherapy cycle starts 21 days after day 1 of the preceding cycle unless bone marrow functional recovery is delayed, as determined by ≥ 500/µl neutrophils without G-CSF support and ≥ 50,000/µl platelets without platelet transfusions.

Radiotherapy

The role of radiotherapy in patients with intermediate-risk neuroblastoma has not yet been established. It must be considered on an individual basis. Considering the high local failure rate in this patient group, especially in the presence of residual tumor, radiotherapy must be considered in patients who were older than 18 months at the time of diagnosis and have an inoperable vital residual tumor. It is strongly recommended to transfer these patients to specialized centers for pediatric radiotherapy. Radiation treatment must be planned using the most recent CT and/or MRI scan and can be

▶ **Table 5** Chemotherapy cycles for patients with neuroblastic tumors.

Cycle	Drug	single dose (patients <1 year or <10 kg)	single dose (patients ≥1 year and ≥10 kg)	application
N4	Doxorubicine	0.5 mg/kg	15 mg/m²	30-min-infusion day 1, 3, and 5
	Vincristin	0.025 mg/kg	0.75 mg/m², max 0.7 mg/dose	iv push day 1, 3, and 5
	Cyclophosphamid	10 mg/kg	300 mg/m²	30-min-infusion day 1 to 7
	MESNA	2 mg/kg	60 mg/m²	iv push 0, 4, and 8 hrs after each cyclophosphamide
	Hydration	50 ml/kg	1500 ml/m²	24-hrs-infusion day 1 to 7
N5c	Vindesine	0.1 mg/kg	3 mg/m², max 6 mg	1-hr Infusion day 1
	Carboplatin	5.2 mg/kg	160 mg/m²	24-hrs-infusion day 1 to 4
	Etoposide	4.2 mg/kg	100 mg/m²	24-hrs-infusion day 1 to 4
	Hydration	100 ml/kg	3 000 ml/m²	24-hrs-infusion day 1 to 7
	G-CSF	5 µg/kg	5 µg/kg	subcutaneously, starting day 9 until neutrophil recovery
N5	Vindesine	0.1 mg/kg	3 mg/m², max 6 mg	1-hr Infusion day 1
	Cisplatin	1.3 mg/kg	40 mg/m²	24-hrs-infusion day 1 to 4
	Etoposide	4.2 mg/kg	100 mg/m²	24-hrs-infusion day 1 to 4
	Hydration	100 ml/kg	3 000 ml/m²	24-hrs-infusion day 1 to 7
	G-CSF	5 µg/kg	5 µg/kg	subcutaneously, starting day 9 until neutrophil recovery
N6	Vincristine	0.05 mg/kg	1.5 mg/m², max. 2 mg	1-hr-infusion day 1 and 8
	Dacarbacine	6.7 mg/kg	200 mg/m²	1-hr-infusion day 1 to 5
	Ifosfamide	50 mg/kg	1 500 mg/m²	23-hrs-infusion day 1 to 5 (pause for Dacarbacine)
	Doxorubicine	1 mg/kg	30 mg/m²	4-hrs-infusion days 6 and 7
	Hydration	100 ml/kg	3 000 ml/m²	24-hrs-infusion day 1 to 7
	MESNA	30 mg/kg	900 mg/m²	24-hrs-infusion day 1 to 7
	G-CSF	5 µg/kg	5 µg/kg	subcutaneously, starting day 10 until neutrophil recovery
N7	Cyclophosphamid	5 mg/kg	150 mg/m²	single daily oral dose
	MESNA	1 mg/kg	30 mg/m²	singe oral dose 0, 4, and 8 hrs after cyclophosphamide
IT-dB	Irinotecan	n. a.	50 mg/m²	1-hr Infusion day 1 to 5
	Temzolomide	n. a.	100 mg/m²	Orally or as 90-min-Infusion days 1 to 5
	Dinutuximab beta	n. a.	20 mg/m²	10 (20)-hrs-infusion day 2 to 6
	Hydration	n. a.	1 500 ml/m²	24-hrs-infusion day 1 to 6
BU/MEL	Busulfan	<9 kg 1.0 mg/kg, 9-<16 kg 1.2 mg/kg, 16-23 kg 1.1 mg/kg, >23-34 kg 0.95 mg/kg, >34 kg 0.8 mg/kg	<9 kg 1.0 mg/kg, 9-<16 kg 1.2 mg/kg, 16-23 kg 1.1 mg/kg, >23-34 kg 0.95 mg/kg, >34 kg 0.8 mg/kg	2-hrs-infusion every 6 hrs days -6 to -3
	Melphalan	140 mg/m²	140 mg/m²	30-min-infusion day -2
	Hydration	100 ml/kg	3 000 ml/m²	24-hrs-infusion day -7 to 0
	Clonazepam	0.025 mg/kg	0.025 mg/kg	every 24 hrs day -7 to -1
	Stem cells	≥2 Mio/kg CD34+ cells	≥2 Mio/kg CD34+ cells	day 0
	G-CSF	5-10 µg/kg	5-10 µg/kg	subcutaneously, starting day +2 until neutrophil recovery

scheduled in parallel to the oral N7 cycles. A total dose of 36 Gy should be delivered to the tumor volume in daily fractions of 1.8 Gy. The target volume includes the residual tumor and the preoperative tumor, whenever considered feasible. For the clinical target volume (CTV), 0.5 cm margins should be added and adapted to anatomical barriers. The margin for the planning target volume (PTV) will be determined according to institutional guidelines, typically 0.5 to 1 cm. Proton beam irradiation is emerging as an alternative to photon beam radiotherapy, and is particularly preferable for very young children and children with tumors near critical organs [94–99]. Patients should be discussed in the national neuroblastoma tumor board with the reference radiation oncologist for radiotherapy planning.

Maintenance therapy

Maintenance therapy following chemotherapy is not standard treatment for intermediate-risk patients. Isotretinoin (13-cis-retinoic acid) was only administered to patients with INSS stage 3 neuroblastoma and an unfavorable risk profile within the CCG3891 trial [100–102], and data for efficacy in this particular group of patients are not yet available. However, isotretinoin (13-cis-retinoic acid) was not found to be effective in treating patients with high-risk neuroblastoma [101, 103, 104]. Data for the efficacy of anti-GD2 antibodies to treat intermediate-risk patients are also not available to date. No maintenance therapy is, therefore, currently recommended for intermediate-risk patients after the end of N7 chemotherapy.

▶ **Fig. 3** Treatment algorithm for intermediate-risk neuroblastoma. N5c: carboplatin, etoposide, and vindesine, N6: ifosfamide, dacarbacin, vincristine, and doxorubicine, N7: oral cyclophosphamide, OP: tumor resection, RT: radiotherapy, mIBG: mIBG therapy [rerif]

High-risk neuroblastoma

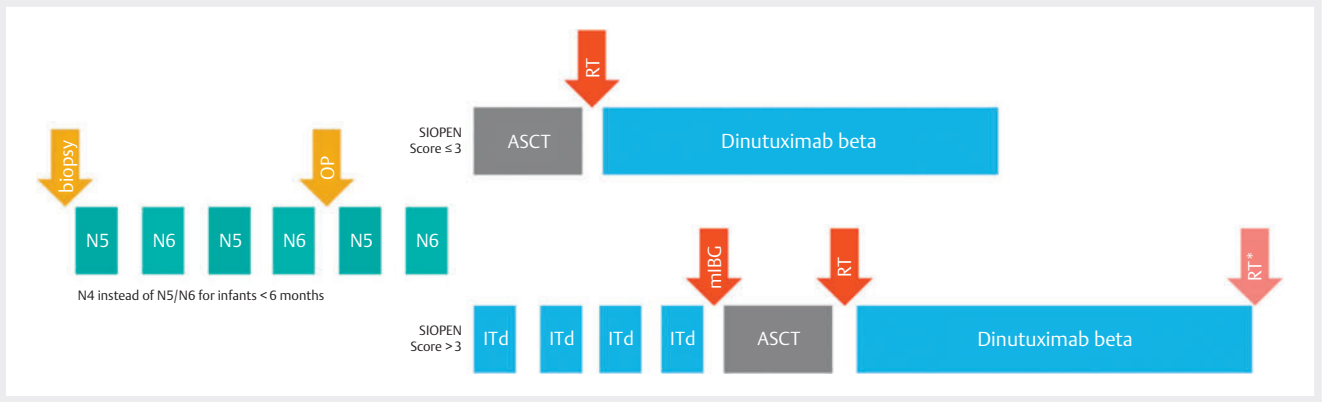
Definition

High-risk neuroblastoma includes all patients with INSS stage 4 / INRG stage M tumors, who are ≥ 18 months of age at diagnosis and all patients with neuroblastomas harboring a *MYCN* amplification (▶ **Fig. 1**).

Surgery

The primary aim of initial surgery is to collect tumor tissue for histology and molecular analysis even in patients with high-risk neuroblastoma. Initial complete primary tumor resection can be attempted in the absence of image-defined risk factors. In patients in poor condition or who had image-defined risk factors at diagnosis, complete primary tumor resection should be postponed until after (2-)4 chemotherapy cycles. Primary tumor resection, however, should not be further postponed even in case of persisting image-defined risk factors. Tumor resection during or after induction chemotherapy is standard-of-care worldwide for high-risk neuroblastoma. The impact of complete versus incomplete tumor resection remains a matter of debate in high-risk neuroblastoma treatment [105]. In line with other reports, retrospective data analysis did not demonstrate an advantage of either complete or gross total resection of the primary tumor in patients of any age diagnosed between 1985 and 1999 and treated for INSS stage 4 neuroblastoma in Germany or patients enrolled in the NB97 trial and > 18 months at diagnosis of INSS stage 4 neuroblastoma [106–113]. Other authors reported better overall survival at least after > 90 % resection as compared to < 90 % [114], better outcome if gross total tumor resection was achieved at the time of diagnosis [111], or after complete or gross total tumor resection [115–122]. In contrast, complete resection was clearly associated with better outcome in patients with localized high-risk neuroblastoma [88].

Taken together, the impact of tumor resection on the final outcome of this intensively treated patient group appears to be limited. The intraoperative techniques may also vary substantially be-



▶ **Fig 4** Treatment algorithm for high-risk neuroblastoma. N5: cisplatin, etoposide, and vindesine, N6: ifosfamide, dacarbacin, vincristine, and doxorubicine, ITd: irinotecan, temozolomide, and dinutuximab beta, ASCT: busulfan and melphalan, OP: tumor resection, RT: radiotherapy, mIBG: mIBG therapy (*Radiotherapy can be given after immunotherapy in patients with significant residual metastases after ASCT, severe toxicity from ASCT or at a very young age) [rerif]

tween the published series. Unpublished data from the GPOH neuroblastoma trials indicate that precise pre-operative imaging, case discussion between oncologists and surgeons and appropriate intra-operative exposure of the tumor region might also impact the operation result. Taking all the above into account, complete tumor resection should always be aimed for in patients with high-risk neuroblastoma unless the procedure is likely to cause permanent functional and cosmetic damage. The disadvantage of incomplete resection may be compensated by intensified local radiotherapy [123]. Considering the low incidence of high-risk neuroblastoma, patients should be referred for complex tumor surgery to centers with proven experience in neuroblastoma surgery. It is recommended to discuss the need for transfer prior to operation in a national neuroblastoma board video conference together with the reference surgeons.

Induction chemotherapy

The number of available cytotoxic drugs effective against neuroblastoma is limited. Induction therapy schedules for high-risk neuroblastoma worldwide consist of drug combinations that include cisplatin, carboplatin, cyclophosphamide, ifosfamide, doxorubicin, etoposide, teniposide, topotecan, vincristine and vinblastine [100, 124–138]. Irinotecan and temozolomide are added to this list for patients with relapsed high-risk neuroblastoma [139–145]. The most effective induction chemotherapy combination is not yet known. One European randomized phase III trial compared rapid COJEC induction chemotherapy, which administers cytotoxic drugs every 10 days, to standard COJEC chemotherapy cycles administered every 21 days. In detail, rapid COJEC consists of course A (vincristine, carboplatin, etoposide), course B (vincristine, cisplatin) and course C (vincristine, etoposide, cyclophosphamide) given within 70 days in the sequence, A-B-C-B-A-B-C-B. While outcome determined by log-rank testing was similar, 5-year event-free survival was better in the group receiving rapid COJEC. However, infections and time spent in the hospital were greater in the rapid treatment arm [134, 146]. Another randomized trial demonstrated a similar outcome but less toxicity of rapid COJEC compared to MSKCC N5 induction chemotherapy, consisting of CAV (cyclophosphamide, doxorubicine, vincristine) and PE (cisplatin, etoposide) cycles administered in the sequence, CAV-CAV-PE-CAV-PE [137]. The prospective randomized GPOH NB2004-HR trial compared the standard GPOH induction chemotherapy with six N5/N6 cycles to an intensified induction chemotherapy with two additional N8 cycles, consisting of topotecan, etoposide and cyclophosphamide. Outcome was the same in both treatment arms, but patients in the intensified arm experienced more side effects during/after the additional chemotherapy cycles [138]. The randomized prospective SIOPEN HR-NBL2 trial (clinical trials identifier NCT04221035) is currently comparing rapid COJEC induction chemotherapy to the GPOH six cycle N5/N6 induction chemotherapy.

Until SIOPEN HR-NBL2 trial results become available, the GPOH recommends induction chemotherapy of alternating N5 and N6 cycles in a total of six chemotherapy cycles (**Fig. 4**). If vindesine is not available, 1.5 mg/m² vincristine (maximum total dose 2 mg) is recommended as an infusion over 1 hour instead [93]. Each chemotherapy cycle starts 21 days after day 1 of the preceding cycle (drug doses and infusion regimens in chemotherapy cycles, ▶ **Table 5**) unless bone marrow functional recovery is delayed, as determined by ≥ 500/µl neutrophils without G-CSF and ≥ 50,000/µl platelets without platelet transfusions. Potential target organ (i. e. heart, kidney and hearing) function must be assessed prior to each chemotherapy cycle. Patients should receive G-CSF after each chemotherapy cycle, as it lowers the frequency of febrile neutropenia in patients with high-risk neuroblastoma [147]. G-CSF can stimulate growth of neuroblastoma cell lines *in vitro*, but no evidence currently exists that this effect has an impact on outcome in patients undergoing intensive multimodal treatment for high-risk neuroblastoma [148–150]. Although global prolongation of induction chemotherapy did not improve high-risk neuroblastoma cure rates in patients [137, 138], additional alternative chemotherapy prior to high-dose chemotherapy can improve remission status in patients with an inadequate response to chemotherapy [151]. In view of the encouraging results of immuno-chemotherapy with irinotecan, temozolomide and dinutuximab (IT-dB) in patients with relapsed and refractory neuroblastoma [152–155], 2-4 additional IT-dB cycles should be considered for high-risk disease inadequately responding to induction treatment before proceeding to myeloablative chemotherapy. In line with SIOPEN criteria [151], insufficient response is defined as a SIOPEN score > 3 and/or persistent bone marrow infiltration.

Consolidation by myeloablative chemotherapy and stem cell transplantation

In general, patients should only proceed to stem cell collection and myeloablative chemotherapy after they have achieved an adequate response to induction chemotherapy. Although high tumor cell content in peripheral blood stem cell harvests has been reported to impair patient outcome, purging peripheral blood stem cell harvests of contaminating tumor cells by negative selection did not improve patient outcome [156]. CD34 positive selection should be considered at least for patients with significant residual bone marrow infiltration at the time of stem cell collection. The additional use of plerixafor could be an option for patients with insufficient stem cell mobilization [157–159].

Better outcome after myeloablative chemotherapy with autologous stem cell transplantation (ASCT) has been demonstrated in three randomized clinical trials [100, 101, 131, 132, 160]. Different myeloablative chemotherapies have been reported. One retrospective analysis [161] indicated that myeloablative chemotherapy with a combination of busulfan and melphalan (BU/MEL) is associated with better outcome and lower toxicity than alternative myeloablative chemotherapy regimens. This was confirmed by a prospective randomized SIOPEN trial with BU/MEL consolidation chemotherapy [162]. The German Neuroblastoma Trial Group recommends BU/MEL as consolidation chemotherapy based on the international evidence for this regimen, although the combination of the GPOH N5/N6 induction chemotherapy and BU/MEL for myeloablative chemotherapy has never been evaluated in prospective clinical trials. Special care should be taken when combining [^{131}I]mIBG therapy and BU/MEL. The administration of busulfan shortly after the administration of [^{131}I]mIBG has been associated with an increased risk of veno-occlusive disease (sinusoidal obstruction syndrome), transverse myelopathy and gastrointestinal toxicity in small patient series [163–166]. In contrast, a retrospective analy-

sis of 28 patients revealed no increased toxicity if BU/MEL was started at a median of 17 days (IQR 14–25 days) after [^{131}I]mIBG [167]. A 6-week interval between [^{131}I]mIBG therapy and chemotherapy is considered safe. The randomized ANBL0532 trial demonstrated that tandem myeloablative chemotherapy achieves a better patient outcome than single myeloablative chemotherapy [168]. The randomized prospective SIOPEN HR-NBL2 trial (clinical trials identifier NCT04221035) is currently comparing single and tandem transplant for high-risk neuroblastoma in patients with an adequate induction chemotherapy response. Total body irradiation as part of the myeloablative regimen has been abandoned due to poor patient outcome, an increase in growth deficiencies and other side effects [161, 169]. The value of allogeneic stem cell transplantation in high-risk neuroblastoma first-line treatment has not yet been demonstrated, although long-term remissions have been achieved by haplo-identical stem cell transplantation in patients with relapsed high-risk neuroblastoma [170–173].

[^{131}I]mIBG therapy

Most neuroblastoma cells express the norepinephrine transporter system and actively incorporate norepinephrine and its radio-iodinated derivate, [^{131}I]mIBG, which exposes the surrounding cells to radiation. [^{131}I]mIBG therapy has been shown to be effective against refractory or relapsed neuroblastoma as a single agent [28, 174–177] or in combination with radiosensitizing cytotoxic agents [178, 179]. Frontline [^{131}I]mIBG therapy resulted in manageable bone marrow toxicity in patients newly diagnosed with high-risk neuroblastoma [180–182]. According to previous GPOH protocols to treat high-risk neuroblastoma, patients with residual lesions detected in [^{123}I]mIBG scintigraphy after completing induction chemotherapy were scheduled for [^{131}I]mIBG therapy prior to myeloablative chemotherapy and stem cell transplantation [165, 183–185]. However, results of prospective comparative trials for patients treated with [^{131}I]mIBG therapy during multimodal first-line treatment are not yet available. [^{131}I]mIBG therapy can be considered for all patients with mIBG-positive residual disease after induction chemotherapy, additional IT-dB cycles and tumor resection. It should be scheduled prior to myeloablative chemotherapy (**Fig. 4**). A single [^{131}I]mIBG dose of 444 MBq/kg = 12 mCi/kg infused over 2 hours is recommended, and corresponds to a whole-body dose of ~ 2 Gy. It has been reported that higher response rates can be achieved with higher activities, such as 666 MBq/kg = 18 mCi/kg, but bone marrow toxicity may require infusion of autologous hematopoietic stem cells after [^{131}I]mIBG therapy [186]. According to radiation protection regulations, most hospitals are legally approved to handle 11.1 GBq = 300 mCi [^{131}I]mIBG at any one time maximally, making the maximal single activity for children >25 kg, 11.1 GBq = 300 mCi. Whole-body dosimetry should be carried out for all patients and tumor dosimetry whenever possible following published standards [187]. Possible short-term side effects of [^{131}I]mIBG include adrenergic stimulation with nausea, vomiting, oral mucositis, sialadenitis, thyroid dysfunction (despite thyroid blockage), thoracic pain, fever and interstitial pneumonia [188, 189]. Paravenous [^{131}I]mIBG infusion can cause severe local necrosis. Bone marrow toxicity may become symptomatic if the interval between [^{131}I]mIBG therapy and myeloablative chemotherapy exceeds 2–4 weeks. As already mentioned above, an interval of ~6 weeks should be maintained between [^{131}I]mIBG therapy and chemotherapy with busulfan.

External beam radiotherapy (EBRT)

EBRT is an integral part of multimodal treatment for high-risk neuroblastoma [190]. While single-arm studies have demonstrated the feasibility of different radiotherapy concepts, prospective randomized trials have not yet been designed to directly compare the efficacy of incorporating radiotherapy into high-intensity multimodal treatment protocols for patients with high-risk neuroblastoma [191–196]. Important questions remain to be answered about EBRT optimal target volume, dosing concept and timing. This uncertainty is reflected in the range of EBRT recommendations from various international trial groups [190]. The U.S. American CCG-3891 randomized trial compared targeting the gross residual tumor with 10-20 Gy EBRT alone (in patients scheduled for continuation chemotherapy) to the same EBRT protocol combined with 10 Gy total body irradiation during myeloablative chemotherapy and ASCT (in patients scheduled for ASCT). EBRT provided no benefit for either randomized group in separate analyses [197]. A retrospective analysis of the German NB97 trial demonstrated that intensified EBRT (36-40 Gy) improved both event-free and overall survival in patients with mIBG-avid residual tumors compared to patients receiving no radiotherapy despite the presence of active residual tumor [123]. This is in line with reports by other groups [198–200]. In contrast, the U.S. American Children's Oncology Group (COG) could not confirm an improved outcome after additional boost to residual tumors when comparing patients from the ANBL0532 and A3973 clinical trials [201]. In the GPOH NB97 and NB2004-HR trials, only patients with active residual tumor received tumor region radiotherapy (36.0 to 40.0 Gy). In contrast, all patients in the SIOPEN HR-NBL1 trial received radiotherapy to the primary tumor region (21.0 Gy), regardless of residual tumor presence at the time of EBRT. In an unpublished comparison, local control rates for patients without residual tumor who received EBRT in the SIOPEN trial appeared to be better than for patients (not offered radiotherapy) in the GPOH trial. Given this, albeit limited, evidence, EBRT of the pre-operative tumor extent is recommended for all patients.

EBRT is scheduled after myeloablative chemotherapy and ASCT. The interval between radiotherapy of central body compartments and busulfan-containing myeloablative chemotherapy should be at least 60 days to avoid cumulative toxicity and, particularly, myelitis and veno-occlusive disease (**Fig. 4**) [163]. Since radiation-induced myelitis may occur after paraspinal EBRT during subsequent immunotherapy [202], a 28-day interval between radiation and immunotherapy is recommended. The order of EBRT preceding immunotherapy could also be changed in selected patients, for example, if ASCT achieves no complete metastatic remission or produces severe toxicity or if patients are too young for EBRT at the time it is scheduled. In these cases, immunotherapy should be completed before radiotherapy begins. There should be a minimum period of 4 weeks between the end of immunotherapy and the start of EBRT. The standard clinical target volume (CTV) includes the pre-operative tumor adapted to current anatomy and a 0.5 cm CTV-margin that is adapted to anatomical boundaries. A dose of 21.6 Gy is to be delivered to the target volume in daily fractions of 1.8 Gy, considering the age of the patient, size of irradiated volume and

tolerance doses of surrounding critical organs. If residual unresectable macroscopic tumor is present at the time of radiotherapy, an additional boost of 14.4 Gy can be delivered to the residual tumor (total cumulative dose: 36 Gy). In addition to any CTV, a planning target volume (PTV) margin of 0.5–1.0 cm has to be added. The advantage of hyper-fractionation over conventional fractionation has never been demonstrated, and most patients require general anesthesia for radiotherapy sessions. Thus, conventional fractionation is recommended. Intra-operative radiotherapy was found to be effective in a small series, but was associated with a considerable frequency of late effects, such as vascular stenosis and is, therefore, not recommended [203–205]. A retrospective SIOPEN study demonstrated a relevant number of deviations from radiotherapy protocol requirements, indicating the need for a centralized radiotherapy reference center giving advice for individual patients [206]. Before high-dose chemotherapy, all patients should be discussed in the national neuroblastoma tumor board with reference radiation oncologists for radiotherapy planning. Modern, image-guided, risk-adapted radiation therapy planning requires appropriate imaging studies and information on side-specific renal function.

The value of radiotherapy for residual **metastatic lesions** is controversial [194, 207, 208]. Jazmati et al. were not able to demonstrate a better outcome in 18 patients from the GPOH NB97 and NB90 trials, who underwent radiotherapy of metastatic lesions [209]. Notably, the outcome of this high-risk cohort was as good as the outcome of the entire trial population. Still, it seems contradictory to perform local radiotherapy of the primary tumor region in complete local remission, while MIBG-avid metastatic lesions are not irradiated. For reasons of feasibility, however, radiotherapy of metastatic lesions should be restricted, particularly in the absence of clear evidence. EBRT of the metastatic sites with a target dose of 36 Gy should be considered in patients with a limited number of residual osteomedullary or soft tissue mIBG-avid oligometastatic lesions [209].

Proton beam irradiation is emerging as an alternative to photon beam radiotherapy, and is particularly preferable for very young children and tumors near critical organs, since proton beam therapy can reduce the irradiated body volume, thus, better protecting adjacent organs from ionizing radiation [94–97, 99, 210]. According to recent publications, organs at risk are better spared and fewer secondary malignancies arise in patients treated with proton therapy compared to patients receiving modern conformal photon treatments [98, 210, 211].

Post-consolidation therapy

In contrast to published early results from the CCG-3891 trial, single-agent isotretinoin (13-cis retinoic acid) treatment does not improve long-term outcome in patients with high-risk neuroblastoma [101, 103], and is no longer recommended. Murine and chimeric anti-GD2 antibodies have been assessed in single-arm trials for many years [212–216]. The randomized ANBL0032 trial showed that administering ch14.18/SP2/0 anti-GD2 antibody (dinutuximab) to patients in first remission from high-risk neuroblastoma impressively improved 2-year outcome [217]. Although follow-up showed a decreasing survival benefit for patients who underwent immunotherapy [218], the combination of dinutuximab, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 2 (IL2) and isotretinoin is considered standard of care in the USA for first-line high-risk neuroblastoma treatment [217]. The ch14.18/CHO anti-GD2 antibody (dinutuximab beta) was developed in Europe, but has differences in activity and pharmacokinetics to ch14.18/SP2/0 [219, 220]. Implementing dinutuximab beta in high-risk neuroblastoma treatment also improved patient outcome [221]. Emerging data suggest co-administering cytokines is of no value. Two sequential prospective SIOPEN clinical trials investigated IL2 administration with ch14.18/CHO short-term [222] and long-term infusion [223]. IL2 did not improve outcome in either trial, but did result in more frequent side effects [222, 223]. Prospective clinical trial data assessing the impact of GM-CSF in high-risk neuroblastoma are not available. Since IL2 did not improve outcome after dinutuximab beta immunotherapy and GM-CSF is not available on the European market, single-agent immunotherapy with dinutuximab beta is the current standard post-consolidation therapy.

Common side effects of dinutuximab beta are pain, fever, hypotension, fluid retention, cytokine release syndrome and pupillotony. Rare side effects are severe allergic reactions, respiratory failure, peripheral neuropathy and spinal transverse myelitis [202, 224]. Dinutuximab beta should preferentially be administered as long-term continuous infusion over 10 days. At the start of the first cycle, analgesic prophylaxis consisting of morphine, metamizol, and gabapentin is strongly recommended [225]. In almost all patients, pain medication can be reduced during subsequent cycles of dinutuximab beta [225, 226], so that patients could even receive dinutuximab beta infusions on an outpatient basis. However, the drug is currently only approved for inpatient use. Dinutuximab and naxitamab are alternative anti-GD2 antibodies currently approved in the USA for first-line treatment of patients with high-risk neuroblastoma (dinutuximab) and refractory/relapsed neuroblastoma (naxitamab). Direct comparative studies between dinutuximab and dinutuximab beta are not available. Naxitamab is not yet approved for first-line high-risk neuroblastoma therapy. Patient outcomes achieved with naxitamab were no different to dinutuximab and dinutuximab beta in non-controlled retrospective datasets [227].

In December 2023, the US Food and Drug Administration (FDA) granted marketing authorization for eflornithine (difluoromethylornithine, DFMO) for the treatment of high-risk neuroblastoma patients who have successfully completed first-line multimodality multiagent therapy including anti-GD2 immunotherapy [228]. Eflornithine is an inhibitor of the enzyme ornithine decarboxylase (ODC), which is the first enzyme in the biosynthesis of polyamines, and a transcriptional target of MYCN. The FDA's decision was based on the encouraging results of the single-arm Beat Childhood Cancer (Trial NMTRC003/003B) [229] and case-control studies comparing patients from the NMTRC003/003B and ANBL 00032 trials [230], although the results of prospective comparative randomized trials are not available. Eflornithine appears to improve long-term survival in high-risk neuroblastoma patients with few side effects. The most important toxicity is hearing loss. This is relevant because patients with high-risk neuroblastoma often suffer from hearing loss after chemotherapy with platinum compounds. Other manageable side effects included otitis media, fever, pneumonia, diarrhea, elevated liver enzymes, neutropenia and anemia [228]. The

drug is currently not available in Germany but becomes an additional treatment option after receiving market authorization by the European Medicines Agency.

Targeted molecular therapies are becoming increasingly important although the number of actionable molecular targets in neuroblastoma is limited. *ALK* somatic mutations are the most common aberration affecting about 10 % of neuroblastomas [65, 231]. *ALK* amplifications occur in ~2–3 % of neuroblastomas, mutually limited to *MYCN*-amplified tumors [231]. ALK inhibitors such as crizotinib, ceritinib and lorlatinib are available on the market for lung cancer and lymphoma treatment. Single-agent ALK inhibitor treatment has been demonstrated to achieve responses even in heavily pretreated patients with refractory and relapsed neuroblastoma [64, 66, 232]. However, the value and toxicity profile for *ALK* inhibitor treatment within multimodal first-line treatment protocols is as yet unknown. The use of ALK inhibitors should be strictly limited to patients with neuroblastomas harboring known *ALK* aberrations, preferentially, within the respective clinical trials. A transatlantic clinical trial combining standard induction chemotherapy with an *ALK* inhibitor for first-line treatment of high-risk neuroblastomas harboring *ALK* mutations will start enrollment soon.

Other molecular treatments including inhibitors for the aurora A or CDK4 kinases are currently under evaluation in early clinical trials in patients with relapsed and refractory neuroblastoma. Except ALK inhibitors, targeted therapies are currently reserved for second-line treatment of relapsed/refractory neuroblastoma, because their superiority over standard multimodal treatment has not yet been demonstrated. Although treatment of refractory and relapsed neuroblastoma is not the focus of this publication, we must point out here that in case of a relapse, tissue sampling for histological and molecular characterization must always be attempted.

Follow-up after treatment completion

Treatment completion is defined as first diagnosis in low-risk patients without any treatment, since these patients only undergo tumor operation, and end of multimodal treatment in intermediate- and high-risk patients. Regular follow-up visits are recommended to detect disease relapse and late developing toxicities from treatment. The recommended assessment intervals are shorter in the first five years following treatment and lengthen after the 5-year mark, since the event rate decreases ≥ 5 years after diagnosis irrespective of the risk group. Tumor markers detect about 25-50 % of relapses or progressions, but more events are diagnosed by clinical examination and imaging [233]. All patients should, therefore, be clinically assessed, receive imaging of the primary tumor site and have catecholamine metabolite excretion assessed in the urine every 6 weeks in the first year after completing treatment. Serum NSE and other blood tests should be combined with each MRI, because intravenous access is required to administer MRI contrast. Bone marrow aspiration and [^{123}I]mIBG scintigraphy should be repeated every 6 months until no abnormalities are detected by either. Intervals between visits can be increased to every 3 months in years 2-5 following treatment completion and further extended to every 6-12 months after reaching the 5-year mark. The primary tumor site should be assessed by ultrasound during every visit and by MRI at least every 3 months during the first three years. Thoracic neuroblastoma cannot be detected by ultrasound, and requires either chest x-ray or more frequent MRI instead. In low-risk patients, routine MRI can be discontinued if no residual tumor is detected or once complete regression is demonstrated by MRI. Complete disease staging based on MRI, [^{123}I]mIBG scintigraphy, [^{18}F]FDG PET-/CT (for [^{123}I]mIBG-nonavid neuroblastoma) and bone marrow assessment is required if relapse or progression is suspected.

Late effects

Follow-up is also important for detecting late effects since long-term neuroblastoma survivors face several treatment-induced chronic health conditions. Platinum compound-related hearing impairment (grade > 2) has been reported in 12-14 % of long-term survivors, who were treated for different pediatric malignancies [234, 235]. Moderate to severe hearing deficits affect more than 50 % of high-risk neuroblastoma survivors [92, 236, 237]. Hearing impairment has also been strongly associated with impaired quality of life, academic learning problems and psychosocial difficulties [238]. Accordingly, health-related quality of life assessment among long-term neuroblastoma survivors revealed a clear pattern of poor emotional health compared to healthy, previously untreated individuals [239]. Hypothyroidism has been observed in 24 % of long-term survivors of high-risk neuroblastoma [237], and is most likely due to the use of radio-iodinated mIBG for neuroblastoma diagnosis and therapy. The frequency of hypothyroidism appears to be even higher in patients who received not only [^{123}I]mIBG scintigraphy, but therapy with [^{131}I]mIBG or radio-iodinated antibodies [240–242]. Focal nodular hyperplasia in the liver has been increasingly detected in survivors of high-risk neuroblastoma since more patients have become long-term survivors who received intensive multimodal treatments [243]. The emergence of a survivor group with this late effect is too new yet to tell whether focal nodal hyperplasia in the liver could lead to subsequent morbidity decades after treatment for high-risk neuroblastoma. To detect such late effects, long-term follow-up must include annual ECG/echocardiography, audiometry, kidney function testing, thyroid function testing and growth and puberty assessments for the first 5 years of follow-up and every 2 years thereafter. It is strongly recommended that patients are seen by the pediatric oncologist at least until the 18th birthday. Long-term follow-up in adult survivors of childhood neuroblastoma requires specialized care, which as yet, is unfortunately not available in most care centers. Long-term follow-up guidelines by the International Guideline Harmonization Group are available under www.ighg.org.

Spinal cord compression in patients with neuroblastoma

Neuroblastomas develop from sympathetic tissue, and have the potential to cause spinal cord compression by invading the spinal canal. Symptoms of spinal cord compression develop in about 5 % of all patients with neuroblastoma [244]. Prolonged compression of the spine is well known to lead to irreversible loss of motor neurons [245]. Optimal management of neuroblastoma-induced spinal cord compression is, however, still controversial. While neurosurgery can achieve immediate decompression, it can also lead to collateral tissue alteration [246]. Chemotherapy is another alter-

native to reduce the intraspinal tumor volume within a few days. Retrospective comparison of neurosurgery and chemotherapy to treat spinal cord compression in patients with neuroblastoma has shown that early and late symptom relief and late effects were not statistically different [247–249]. The recommended strategy is to assign neurosurgery or chemotherapy based on the remaining neuroblastoma treatment the patient is to receive. Patients who are likely to be classified in the observation group should be prioritized for neurosurgical treatment. Patients who are likely to need chemotherapy anyway should start with chemotherapy instead of undergoing emergency neurosurgery. Radiotherapy can be considered in palliative situations after balancing short-term benefit and long-term toxicity [250, 251].

Infants <6 months of age in good clinical condition with suspected neuroblastoma

Newborns and infants with neuroblastoma have an excellent prognosis even without treatment. A suprarenal mass detected by routine ultrasound in a clinically healthy child could either be neuroblastoma or a suprarenal hemorrhage. Suprarenal bleeding does not require treatment. A suprarenal mass or small cervical, thoracic, abdominal or pelvic paravertebral tumors in infants are very likely infant neuroblastoma. The vast majority of these tumors have favorable characteristics, and are very likely to undergo spontaneous regression. Therefore, initial staging should be divided into two steps. All infants should initially receive a clinical examination that includes assessment of the entire integument and ultrasound of the neck, abdomen (particularly liver), pelvis and brain. Blood should also be collected at this examination for liver and kidney function tests, blood count, lactate dehydrogenase (LDH), ferritin and neuron-specific enolase (NSE) levels in serum. Urinary catecholamine excretion (vanillymandelic acid and homovanillic acid) should also be initially assessed. Ultrasound should be repeated at least weekly during the first weeks of observation to detect rapid progression. Infants with tumor-associated symptoms or with a tumor persisting beyond 3-6 months of age should undergo complete staging with MRI of the involved regions, [^{123}I]mIBG scintigraphy combined with SPECT/CT reconstruction, bone marrow assessment from aspirates collected from at least 4 different sites and open or core needle tumor biopsy to confirm the diagnosis and to assess molecular risk factors.

Ganglioneuroma and ganglioneuroblastoma intermixed

Ganglioneuromas are benign mature neuroblastic tumors, which can display mIBG uptake and cause increased excretion of catecholamine metabolites in the urine [28]. The treatment of choice is surgical resection, even though surgery-related complications are frequent due to invasive ganglioneuroma growth [252, 253]. Ganglioneuroblastoma intermixed (GNBI) tumors have previously been considered malignant. However, case reports and analysis of a patient series revealed that postoperative progression was highly unlikely after incomplete resection and that chemotherapy was ineffective against both ganglioneuromas and ganglioneuroblastoma intermixed tumors [1, 28, 29, 253–256]. Patients with either ganglioneuromas or ganglioneuroblastoma intermixed tumors should only receive surgical resection that aims for incomplete tumor resection if complete resection would require mutilating neighboring organ systems and should not receive chemotherapy.

Adults with neuroblastoma

Neuroblastoma is rarely diagnosed in adults. It is controversially discussed whether the tumors of these patients might have other molecular characteristics than young children [257, 258]. No data from prospective trials are available from this patient subgroup because this occurs so rarely. The extremely low patient numbers prevent prospective trial organization now or in the future [257, 259–261]. Tumor biopsies must undergo central re-assessment by pathologists experienced in diagnosing and staging pediatric tumors. If the histological diagnosis is confirmed by central review, patients must undergo complete staging according to GPOH standards, including bone marrow assessment at four different sites, MRI of the primary tumor region and brain, whole-body [^{123}I]mIBG scintigraphy. [^{18}F]FDG PET/CT should be added for cases with [^{123}I]mIBG-nonavid neuroblastomas or conflicting results from MRI and [^{123}I]mIBG scintigraphy that indicate heterogeneity in mIBG uptake. Treatment should follow the guidelines for pediatric patients, but dose reduction of the first two induction cycles to 80 % should be considered, depending on the performance status and general condition of the patient. Molecular analysis of potential actionable targets is highly recommended for this special subgroup.

Contributor's Statement

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Conflict of Interest

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