The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for histopathological reporting of peripheral neuroblastic tumours

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Contents

Foreword

The cancer datasets published by the Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items (see Appendices G and H) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were consulted for this document:

- Children's Cancer and Leukaemia Group (CCLG)
- National Cancer Research Institute Children’s Group, Neuroblastoma Subgroup
- National Reference Centre for Neuroblastoma Biology, Newcastle Cancer Cytogenetics Laboratory.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset.

The information used to develop this dataset was obtained by undertaking a systematic search of PubMed. Key terms searched included neuroblastic tumour, neuroblastoma, pathology, stage, infant and children, and genetics. Dates searched were between April 2019 to November 2023 to identify any relevant new publications. This dataset has been

devised to include the information required for a careful assessment and adequate reporting of peripheral neuroblastic tumours (PNTs). previous recommendations of the College and evidence based practice including local and international guidelines widely used, including information from the authors' own experience and discussion with colleagues. Recommendations of the Neuroblastoma Special Interest Group of the CCLG for patients with high-risk neuroblastoma and low/intermediate-risk neuroblastoma are included. The core data items have published evidence that indicates their value in optimal patient management and prognosis. Other non-core data items that fall outside the core definition are also described. These are included to provide a comprehensive report to meet local clinical, research and tumour registry requirements. Published evidence was evaluated using modified SIGN guidance (see Appendix K). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence were identified by College members via feedback received during consultation.

A formal revision cycle for all cancer datasets takes place on a 3-yearly basis. However, each year, the College will ask the authors of the dataset, in conjunction with the relevant sub-specialty adviser to the College, to consider whether the dataset needs to be revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken, whereby a short note of the proposed changes will be placed on the College website for 2 weeks for Fellows' attention. If members do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Professional Guidelines team, Working Group on Cancer Services and Lay Advisory Group and was placed on the College website for consultation with the membership from 12 March to 9 April 2024. All comments received from the Working Group and membership were addressed by the author to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest;

these are monitored by the Professional Guidelines team and are available on request. The authors have declared no conflicts of interest.

1 Introduction

The management of PNTs is the responsibility of the appropriately experienced paediatric oncology multidisciplinary team (MDT). These tumours are rare and predominantly identified in the paediatric age group. Approximately 100 new cases of neuroblastoma are diagnosed in the UK every year. The reporting pathologist should have access to a paediatric pathologist or paediatric pathology MDT. The pathologists reporting these cases should ideally be paediatric histopathologists.[1] Most neuroblastomas can be diagnosed by the presence of raised urinary catecholamine metabolites vanillylmandelic acid (VMA) and homovanillic acid (HMA) and, less frequently, elevated levels of dopamine.[2,3] However, it is mandatory that all suspected neuroblastomas (except in the case of neonatal adrenal masses) are biopsied (if safe for the patient) as the cytogenetic, molecular genetic profile and histopathological features contribute to risk stratification that influences treatment. It is particularly important in low/intermediate-risk tumours, as tumour biology is becoming increasingly important to stratify patients into relevant treatment groups.

Neuroblastoma is the most common extracranial solid malignant tumour in childhood.[4,5] It is a member of a family of tumours, PNTs, which arise in the sympathetic nervous system and are neural crest-derived. PNTs encompass a spectrum of tumours, ranging from malignant neuroblastomas at one end to completely benign ganglioneuromas at the other. Neuroblastomas are heterogeneous and exhibit a variable clinical course ranging from spontaneous regression, differentiation to benign tumour or progression to aggressive disease, which is often fatal despite intensive multimodality therapy. Most infants have a good prognosis with either observation alone or surgical or chemotherapy treatments, even in the presence of metastases, whereas older children frequently have metastases and more aggressive disease. It usually presents in children less than 2 years old and, in 90% of cases, by 5 years of age.[2,3]

The International Neuroblastoma Risk Group (INRG) classification system was developed to stratify patients into pre-treatment risk groups on the basis of prognostic risk factors and currently includes: patient age, INRG tumour stage (Appendix C), histopathological category, grade of tumour differentiation, presence or absence of *MYCN* amplification, segmental chromosomal abnormalities (SCA) or numerical chromosomal abnormalities

(NCA) and DNA ploidy.[6] All patients are assigned an internationally agreed risk group (very low, low, intermediate and high) as detailed in Appendix A.

Briefly, a number of genetic features are strongly associated with prognosis in neuroblastoma.[7–18] *MYCN* amplification is an adverse prognostic factor. SCA include deletion of 1p, 3p, 4p or 11q, or gain of 1q, 2p or 17q with or without numerical chromosomal alterations, which also have an adverse prognostic impact. Activating point mutations of ALK (~10% of sporadic cases) as well as gene amplification have also been described, making ALK a promising target for molecular therapy. Telomere abnormalities involving TERT and the alternative lengthening of telomeres (ALT) have been identified in neuroblastomas. Diploidy is an adverse prognostic factor. NCA in the absence of SCA are associated with a better prognosis. Mixed SCA and NCA are classified as SCA.

Prior to the INRG classification, there was no internationally agreed risk-group stratification in clinical trials and guidelines. The CCLG low/intermediate-risk neuroblastoma treatment guidelines are based on risk group assigned by INRG classification.

High-risk neuroblastoma represents the largest neuroblastoma subgroup. The prognosis of these patients has progressively improved over recent years through intensified multi-modality treatment. Patients diagnosed with high-risk neuroblastoma by INRG classification are treated according to SIOPEN high-risk neuroblastoma clinical trial protocol or guidelines.

1.1 Target users and health benefits of this guideline

The target users of the dataset are trainee and consultant paediatric pathologists, as well as surgeons, oncologists, cancer registries and the National Cancer Registration and Analysis Service. The collection of standardised cancer-specific data facilitates reporting of required pathological features and thus provides important prognostic information aiding the appropriate clinical management of patients. It also supports the collection of epidemiological data, research and provides accurate data for healthcare planning.

1.2 Role of the pathologist

The role of the pathologist includes:

- diagnosis
- identification of histological prognostic features
- establishing extent of tumour in loco-regional excisions

- selection of tissue for molecular genetic/biological analysis studies
- selection of tissue for research and tumour banking
- support of local, national and international collaborative research
- promotion of standardisation of terminology and classification.

PNTs are classified according to the International Neuroblastoma Pathology Classification (INPC; see Appendix B). The classification was established in 1999 and revised in 2003.[19,20] It is a prognostic classification based on morphological features and age. It defines 4 categories of tumour and 2 distinct prognostic groups ('favourable histology' [FH] and 'unfavourable histology' [UH]) on the basis of grade of neuroblastic differentiation, Schwannian stromal development and mitosis–karyorrhexis index (MKI).[21–23] The prognostic groups' FH and UH are currently not used for patient management in the UK. For risk stratification, patient's age and tumour histology are independent entities.

The 4 categories of tumour are:

- neuroblastoma (Schwannian stroma poor)
- ganglioneuroblastoma intermixed (Schwannian stroma rich)
- ganglioneuroblastoma nodular (composite, Schwannian stroma rich/stroma dominant and stroma poor)
- ganglioneuroma (Schwannian stroma dominant), maturing or mature).

The INRG staging system uses image-defined risk factors (IDRFs) and is not dependent on extent of surgery, as in the previous International Neuroblastoma Staging System.[24] The INRG staging system is a clinical staging system and is outlined in Appendix C. TNM staging is not applicable for PNTs.

2 Clinical information required on the request form

This includes:

- presentation, signs and symptoms
- age of patient
- site and laterality of biopsy or excision
- site of lymph nodes

- urinary catecholamine result if pre-treatment biopsy
- previous treatment
- family history.

3 Pre-treatment tumour biopsy and excision

In the UK, most PNTs encountered in children are neuroblastomas and most patients have disseminated or unresectable disease at presentation. Biopsies are, therefore, more common than primary excisions. The majority are needle core biopsies. Sometimes metastases are biopsied, e.g. a skin nodule that may provide more diagnostic tissue. Open surgical biopsies are uncommon. The handling of the tumour tissue should always be performed by the pathologist who, apart from making the histological diagnosis, should choose the relevant tumour areas for molecular-genetic/biological analysis.

For primary excisions the pathologist should assess:

- the representability of the chosen areas and estimate the percentages of viable tumour tissue, necrosis and preserved non-tumour tissue (i.e. fibrosis)
- the tumour cell content, i.e. the percentage of tumour cell nuclei compared to all preserved nuclei. This procedure will enable reliable interpretation of the molecular-genetic results. The information obtained from small biopsies may be limited by a minimal amount of viable tumour, crush artefact, and the presence of necrosis and calcification. The pathologist is expected to confirm the diagnosis of neuroblastoma and exclude other small round blue cell paediatric tumours. Immunohistochemistry (IHC) is therefore essential in many of these cases. The antibodies useful for diagnosis of PNTs include paired-like homeobox 2b (PHOX2B),[25] synaptophysin, neuron-specific enolase, PGP9.5, tyrosine hydroxylase, CD56 (N-CAM), chromogranin A and S100.

The number of biopsies required is not established but, in practice, at least 4 (preferably more) are needed to establish the diagnosis, achieve molecular genetic profile and facilitate tumour banking and research. Biopsies with at least 5,000 viable tumour cells are required for MKI assessment. Very limited tumour samples could be classified as neuroblastoma not otherwise specified (NOS) or ganglioneuroblastoma NOS.

4 Tumour handling and block selection

All specimens should be sent fresh to the histopathology laboratory for immediate examination by the pathologist. Good communication with the clinical and surgical teams is a prerequisite.

The pathologist triages the fresh biopsy or resected tumour and selects the samples for diagnosis, which are formalin fixed. Molecular genetic/biology work up, whole genome sequencing (WGS) and tumour banking (if appropriately consented) are performed on snap frozen material.

Fresh frozen tumour samples from the UK and Ireland for cytogenetic and molecular genetic testing should be sent to the National Reference Centre for Neuroblastoma Biology in Newcastle (see Appendix D).

The reference laboratory will perform MYCN FISH, SNP array and targeted pathogenic Alk variant analysis and then submit tumour DNA for paediatric tumour NGS panel sequencing.

The reference laboratory will submit any surplus frozen tumour to the Vivo Biobank once they have confirmation that consent has been obtained by the referring centre.

Patients with neuroblastoma are eligible for the Genomics England WGS programme. Samples (tumour and germline blood sample) are submitted with the record of discussion through usual pathways for the relevant local Genomic Laboratory Hub (GLH). If the neuroblastoma centre reference laboratory has sufficient surplus DNA, then this can be submitted as tumour DNA to the North East and Yorkshire GLH. This would require clinicians to communicate with the reference laboratory and coordinate germline samples being sent via the local GLH.

It is advised that patients are biopsied at relapse when possible to assess relapse tissue for any genomic evolution. As per diagnostic samples, these should be submitted to the national reference laboratory and are also eligible for WGS programme. Relapse tissue may also be submitted to any relevant biology or genomic relapse studies or as biological samples for any relevant clinical trial.

The formalin fixed biopsies for histological diagnosis should be submitted in 2 paraffin blocks if there is sufficient material, so that 1 block can be made available for trial or research purposes.

The excised fresh tumour can be weighed and is measured in 3 dimensions. The external surface of the resected tumour is inked prior to sampling. It should be thinly sliced. The cut surface of each slice is carefully inspected. The tumour is sampled for genetic molecular and biological studies, research and tumour banking. Stroma-poor tumour is of most interest for molecular analysis and often presents a soft, gelatinous or friable consistency with a grey, brown or red discolouration of the surface due to bleeding between tumour cells. Very firm, light yellow or whitish areas usually represent Schwann cell stroma or fibrosis and are of less molecular genetic interest but should be sampled for histological confirmation.

Nodules with a cut surface darker than the surrounding tissue must always be sampled. A careful examination to exclude or confirm nodules of neuroblastoma is necessary, as clonal evolution on the background of such tumours characterises ganglioneuroblastoma nodular; any distinct or haemorrhagic nodule(s) should be identified and counted. Each nodule should be sampled for molecular genetic studies, research and banking, if of sufficient size, since they may have different histological and genetic features. Corresponding adjacent blocks from the tumour mass and nodule(s) should be formalin fixed for correlation.

Prognosis in nodular ganglioneuroblastoma is essentially the same as the prognosis for nodules of neuroblastoma. If 2 or more nodules of neuroblastoma are present, prognosis is based on the neuroblastoma with the worst prognostic features.[20,26]

Ganglioneuroblastoma intermixed and ganglioneuroma are rarer than neuroblastoma and can be diagnostically and clinically challenging.[27,28]

It is recommended that all areas of the excised tumour be adequately sampled, usually 1 block per centimetre of greatest dimension.[29] Lymph nodes with obvious tumour deposits should have representative samples taken; smaller lymph nodes should be sampled in their entirety.

5 Histology of pre-treatment biopsies and tumour excisions (see Appendix E)

Primary surgical excisions of neuroblastoma are uncommon. The microscopic features linked with age are prognostic in the INPC.[2–5,19–23] Briefly, neuroblastoma (Schwannian stroma poor) has 3 grades:

- undifferentiated neuroblastoma consists of undifferentiated tumour cells with no neuropil and requires IHC to establish the diagnosis
- poorly differentiated neuroblastoma has neuroblasts with variable amounts of neuropil, <5% ganglion cell differentiation and scanty Schwann cells in the fibrovascular septa
- differentiating neuroblastoma has >5% differentiated ganglion cells and <50% Schwann cells.

Ganglioneuroblastoma intermixed (Schwannian stroma rich) has >50% Schwann cells with randomly distributed nests containing neuroblasts, maturing and mature ganglion cells, and neuropil and/or nests of naked neuropil.

Ganglioneuroma (Schwannian stroma dominant) has 2 subtypes:

- mature ganglioneuroma has a Schwann cell stroma with scattered mature ganglion cells with surrounding satellite cells
- maturing ganglioneuroma has a Schwann cell stroma with scattered small nests of differentiating neuroblasts and maturing ganglion cells without satellite cells or neuropil, as well as mature ganglion cells.

Nodular ganglioneuroblastoma is a composite tumour of different clones, consisting of either ganglioneuroma or ganglioneuroblastoma intermixed with 1 or more discrete expansile nodules of neuroblastoma. A biopsy may include both components of the tumour, but often only 1 component is apparent. Clinicopathological correlation is important, as the biopsy of the primary tumour may show only ganglioneuroma or ganglioneuroblastoma intermixed without the neuroblastoma, which may have disseminated. If metastatic sites, such as bone marrow, were positive for neuroblastoma, the tumour would be classified as ganglioneuroblastoma nodular variant subtype. Rarely, no residual neuroblastoma is identified in the resected mass even when extensively sampled. If the neuroblastoma nodule was biopsied, then the ganglioneuroma or ganglioneuroblastoma intermixed component would only become apparent when the primary tumour mass was resected.

The morphology in neuroblastomas, including cellularity, and number of mitoses and karyorrhoectic cells, may vary in different fields. MKI is a useful prognostic indicator in neuroblastoma (Schwannian stroma-poor) tumours. MKI is calculated using the number of karyorrhoectic nuclei and mitoses in 5,000 tumour cells. A low MKI is defined as <2% (<100 per 5,000 cells), an intermediate MKI is defined as 2–4% (100–200 per 5,000 cells)

and a high MKI is defined as >4% (>200 per 5,000 cells).[30] It is determined as an average made after examination of all sections and/or all representative viable areas of the tumour. In a report, a patient presented with a composite neuroblastoma composed of 2 histologically distinct clones, 1 of which had a FH and the other a UH. Fluorescent in-situ hybridisation on the paraffin sections demonstrated that *MYCN* was only amplified in the UH clone and not the FH clone.[31] Tumours with genotype–phenotype discordance have also been described.[32]

It should be noted that the MKI and the classification of neuroblastomas as FH and UH may be determined locally but these are not required for current treatment protocols in the UK.

Large red nucleoli have been associated with *MYCN*-amplified tumours.[33,34] A large cell variant of neuroblastoma associated with more aggressive behaviour was reported.[35]

Formal criteria for size and colour of nucleoli, as well as nuclear size, nuclear and cellular pleomorphism and anaplasia, have not yet been established.

6 Reporting bone marrow specimens

Bone marrow is the most common site of metastasis in neuroblastomas. Metastatic disease at the time of diagnosis is a powerful predictor of poor outcome and is used in the INRG staging system for treatment stratification. For recommended sample collection, see Appendix F.

The persistence of neuroblastoma disease (minimal or overt) in bone marrow after treatment is predictive of poor outcome and provides a means with which to assess disease response, without having to wait for the development of greater tumour burden.[36,37] Morphology on bone marrow aspirates and trephine biopsies have been used for bone marrow assessment for many years. However, these methods have limited sensitivity when neuroblastoma infiltration is <10% and could underestimate the prevalence of bone marrow infiltration. Therefore, the revised International Neuroblastoma Response Criteria (INRC) require assessment of bone marrow aspirates and trephines for neuroblastoma cells using morphologic criteria in conjunction with appropriate antibodies to confirm the identity of neuroblastoma cells by immunocytology (if available) and/or IHC.[38] The revised INRC now include quantitative assessment of bone marrow involvement. Criteria defining minimal disease, stable disease and progressive disease are included in Appendix G.

A summary of recommendations for the standardised bone marrow disease assessment and reporting in children with neuroblastoma is included in Appendix G. Although the INRC Bone Marrow Working Group has recommended reverse transcription quantitative polymerase chain reaction (RTqPCR), it has not been incorporated in revised INRC. Currently, RTqPCR on bone marrow is only used in the UK in research as part of a trial and samples are collected for registered tumour banks. Immunocytochemistry on cytospin is also not mandatory.[38,39]

An optimal bone marrow core needle biopsy should preferably contain red bone marrow parenchyma at a minimum length of 1 cm.[39,40] The amount of haematopoietic and tumour tissue within the biopsy should be recorded in millimetres; cortical bone, cartilage, soft tissue, blood clots or areas that are crushed are excluded from the measurement.

Bone marrow trephine should be reported based on at least 6 haematoxylin and eosin (H&E) sections and 2 neuroblastoma IHC markers on 3 sections each. Bone marrow infiltration is estimated as the surface area occupied by the PNT, as a percentage of the evaluable bone marrow spaces on each biopsy (0–≤5%, 5–20%, and >20%).[38]

Importantly, tumour histology should be classified as poorly differentiated, undifferentiated or differentiating. In the case of small tumour aggregates, IHC for synaptophysin can help to discriminate undifferentiated and poorly differentiated neuroblastoma. In rare cases in which stroma-rich and stroma-poor histology are present within a single biopsy, the amount of stroma-rich and stroma-poor tumour should be recorded separately as a percentage of the surface area occupied by the tumour. The MKI is not warranted.

Highly specific target antigens for which IHC is unambiguous include synaptophysin, tyrosine hydroxylase, chromogranin A, CD56 (N-CAM) and PHOX2B. Any 2 of these markers can be used (the INRC Bone Marrow Working Group endorsed the use of chromogranin A or synaptophysin along with PHOX2B[39]). When suspected, Schwann cells can be reliably detected by morphology and IHC for the S100 protein. NSE and NB84 labelling is not recommended because both lack specificity; NB84 expression can be limited in metastatic NB in bone marrow specimens.[39]

A bone marrow biopsy is regarded as negative for tumour in the absence of neuroblastoma cell nests detected by H&E staining and IHC, using a minimum of 2 antibodies.

7 Post-treatment specimens

Many high-risk neuroblastomas are excised following initial chemotherapy. The INPC classification is not used in post-treatment cases and the tumours are not reclassified. However, it is worth commenting on the morphology.

These tumours show varying degrees of response to cytotoxic therapy, with necrosis, calcifications and scarring. It is recognised that both chemo- and radiotherapy can induce significant histological changes, including cytodifferentiations with areas of neuroblastoma-like, ganglioneuroblastoma-like and ganglioneuroma-like differentiation, i.e. the development of Schwannian stroma. If a tumour originally diagnosed as differentiating neuroblastoma on biopsy shows undifferentiated or poorly differentiated tumour on post-treatment resection, then it is recommended that treatment is escalated.

Residual tumour similar to the biopsy (e.g. poorly differentiated, differentiating and undifferentiated neuroblastoma) may be seen in the primary tumour and in lymph nodes.

Regional lymph node biopsy is recommended. The histology report should state the site and number of positive lymph nodes, with the extent of metastatic deposits including micrometastases (<2 mm) and extracapsular extension of tumour.

Treating clinicians may be interested in the excision margins and need to know if viable tumour is present in lymph nodes and the site of these nodes, as this detail is relevant to radiotherapy planning. Another reason for examining the resected specimen is to allay clinical concerns. There may be no apparent clinical or radiology evidence of a response to treatment. This may be due to refractory or progressive disease. However, it may also be observed in less aggressive tumours because of extensive differentiation with increased amount of Schwannian stroma that is non-responsive to chemotherapy. The extent or degree of tumour necrosis and calcifications should be stated.

[Level of evidence – GPP.]

8 Core data items

8.1 Clinical information

The following are core clinical data items:

- site of specimen

  - clinical presentation may be diverse and differential diagnoses including other metastatic or primary paediatric malignancies may require exclusion. It is important for clinicians to correlate gross and histological findings with the pre-treatment image defined risk factors as described in the radiology reports, in particular where imaging data are uncertain and organ invasion will be relevant for radiotherapy planning.

[Level of evidence – GPP.]

- pre- or post-treatment
  - INPC is not applied to post-treatment tumours. The morphology of PNTs can change significantly over time or rapidly as a response to cytotoxic chemotherapy (usually inducing differentiation and an increase in Schwannian stroma).

[Level of evidence – GPP.]

- site(s) of separate lymph nodes
  - in post-treatment resected high-risk tumours, the radiotherapy field will extended to include sites with residual viable tumour from the histology report. In the INRG, nodal status is not applied to differentiate between L1 and L2 disease status.

[Level of evidence – GPP.]

8.2 Macroscopic information

The following are core macroscopic data items:

- type and size of specimen – biopsy (needle or open/surgical) or resection. The sample size/number of needle cores provide an estimate on tumour representation and how cellular the biopsy is for molecular studies.

[Level of evidence – GPP.]

- fresh tissue for genetic studies

[Level of evidence – A.]

- resection: number of nodule(s) present
  - nodular variant subtype

[Level of evidence – B.]

- lymph nodes attached – yes or no

[Level of evidence – GPP.]

- adequate bone marrow trephine biopsy – yes or no.

[Level of evidence – GPP.]

8.3 Microscopic information

The following are core microscopic data items:

- tumour category according to INPC
  - neuroblastoma (Schwannian stroma poor)
  - ganglioneuroblastoma intermixed (Schwannian stroma rich)
  - ganglioneuroblastoma nodular (composite, Schwannian stroma rich/stroma dominant and stroma poor)
  - ganglioneuroma (Schwannian stroma dominant)

[Level of evidence – A.]

- neuroblastoma – grade of differentiation
  - NOS
  - undifferentiated
  - poorly differentiated
  - differentiating
    - for patients aged >18 months with localised (L2) disease, treatment will be reduced for patients with differentiating neuroblastoma compared with those with undifferentiated or poorly differentiated tumours (according to current treatments guidelines for low/intermediate-risk tumours)

[Level of evidence – B.]

- IHC profile
  - positive for one or more of the commonly used neural markers (PHOX2B, synaptophysin, NSE, PGP9.5) if morphology on H&E is equivocal
  - establishes diagnosis in small or crushed biopsies and in undifferentiated neuroblastoma

[Level of evidence – GPP.]

- necrosis and/or calcification – present or absent
  - may limit the data, both histopathological and molecular genetic, that can be obtained from the specimen

[Level of evidence – GPP.]

- lymph node metastases – present or absent
- extent of confirmed metastases, sites for radiotherapy

[Level of evidence – GPP.]

- bone marrow infiltration – present or absent
- bone marrow infiltration – % involvement (left, right)
- neuroblastoma differentiation
  - undifferentiated
  - poorly differentiated
  - differentiating.

[Level of evidence – B.]

9 Non-core data items

These data items do not impact directly on patient management in the UK. However, they may be collected as part of pathological data required to support trials, to facilitate consensus in identification of morphological criteria and to permit comparison between centres.

9.1 Macroscopic information

Macroscopic information includes the following:

- size in 3 dimensions
- number of lymph nodes
- frozen/fixed tissue for research/tumour banking with valid consent.

9.2 Microscopic information

Microscopic information includes the following:

- MKI
- nuclear pleomorphism, anaplasia, nuclear size
- nucleolar size and colour
- post-treatment changes.

10 Reporting frozen sections

Frozen sections are not routinely used in the diagnosis or management of patients with PNTs but are required to determine tumour cell content in molecular genetic/biological tests and research studies.

11 SNOMED codes

Tumours should be coded using SNOMED codes (Appendix H). It is noted, however, that SNOMED is now in a practical transition phase, as part of the intended full implementation of SNOMED CT by the NHS and Public Health England. SNOMED ceased to be licensed by the International Health Terminology Standards Development Organisation from 26 April 2017.

A list of applicable T and M SNOMED and SNOMED CT codes is provided in Appendix H.

Mapping SNOMED CT terminology is provided.

12 Criteria for audit

The following are recommended by the College as key assurance indicators:[41]

- cancer resections should be reported using a template or proforma, including items listed in the English COSD, which are, by definition, core data items in RCPath cancer datasets. English trusts are required to implement the structured recording of core pathology data in the COSD
  - standard: 95% of reports must contain structured data.

13 Acknowledgements

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Appendix A Risk stratification table

For further information on tumour category please see Appendix B and for International Neuroblastoma Risk Group (INRG) stage please see Appendix C.

Table 1: International Risk Group stratification.

Tumour category	INRG stage	Age	Tumour grade	MYCN amplification	SCA	Risk group
GN, GNBi	L1/L2	Any				Very low
NB, GNBn	L1	Any		Not amplified		Very low
				Amplified		High
NB, GNBn	L2	<18 months		Not amplified	No	Low
				Not amplified	Yes	Intermediate
		>18 months	Differentiating	Not amplified	No	Low
				Not amplified	Yes	Intermediate
			Poorly differentiated	Not amplified		Intermediate
			Undifferentiated	Not amplified		Intermediate
		Any		Amplified		High
NB, GNBn	M	<12 months		Not amplified		Intermediate
		12–18 months		Not amplified	No	High*
		>12 months		Not amplified	Yes	High
		Any		Amplified		High
NB, GNBn	MS	<12 months		Not amplified	No	Low**
				Not amplified	Yes	Low
				Amplified		High

*Receive less intense treatment if respond well.
**Observation only.

Abbreviations:
GN: ganglioneuroma; GNBi: ganglioneuroblastoma intermixed; GNBn: ganglioneuroblastoma nodular; NB: neuroblastoma; SCA: segmental chromosomal abnormalities.

Blank cells indicate that these factors are not relevant to decision making.

Appendix B International Neuroblastoma Pathology Classification of peripheral neuroblastic tumours[19,20]

Table 1: International Neuroblastoma Pathology Classification tumour categories and grades for PNTs.

Tumour grade	Tumour category
Neuroblastoma (Schwannian stroma poor) • Undifferentiated • Poorly differentiated • Differentiating	NB
Ganglioneuroblastoma intermixed (Schwannian stroma rich)	GNBi
Ganglioneuroblastoma nodular (composite Schwannian stroma rich/stroma dominant and stroma poor)	GNBn
Ganglioneuroma (Schwannian stroma dominant) • Maturing • Mature	GN
Abbreviations: GN: ganglioneuroma; GNBi: ganglioneuroblastoma intermixed; GNBn: ganglioneuroblastoma nodular; NB: neuroblastoma.	

Table 2: Favourable and unfavourable histologies.

INPC histology category and grade	Age	MKI	Favourable/unfavourable histology
Ganglioneuroma mature/maturing	Any	Any	Favourable
Ganglioneuroma intermixed	Any	Any	Favourable
Neuroblastoma undifferentiated	Any	Any	Unfavourable
Neuroblastoma poorly differentiated	Any	>4%	Unfavourable
	>18 months	Any	Unfavourable
	<18 months	<4%	Favourable
Neuroblastoma differentiating	>5 years	Any	Unfavourable
	<18 months	<4%	Favourable
	<18 months	>4%	Unfavourable
	18 months–5 years	<2%	Favourable

	18 months–5 years	>2%	Unfavourable
Ganglioneuroblastoma nodular	Favourable/unfavourable based on the morphology of the neuroblastoma nodule		
Abbreviations: MKI: mitosis-karyorrhexis index.			

Table 3: Mitosis–karyorrhexis index.

MKI level	**Expressed as a percentage**	**Expressed as cell count**
Low MKI	<2%	<100/5,000 cells
Intermediate MKI	2–4%	100–200/5,000 cells
High MKI	>4%	>200/5,000 cells
Note: Category and tumour as described in Table 1 remain important for risk stratification and management. MKI and INPC classification of PNTs as favourable and unfavourable has become less relevant. Tables 2 and 3 are included in this appendix for historical reasons and some trials may still require this information. Abbreviations: MKI: mitosis–karyorrhexis index.		

Appendix C Clinical staging system

International Neuroblastoma Risk Group Staging System[24]

L1 Localised tumour defined by image-defined risk factors (IDRFs) in one body compartment, not involving vital structures.

L2 Locoregional tumour with one or more IDRF.

M Metastatic tumour (not MS).

MS Metastatic tumour limited to skin, liver and bone marrow in children under 18 months old.

Appendix D Referral form for the National Reference Centre for Neuroblastoma Biology, Newcastle

Referral of material to National Reference Centre for Neuroblastoma Biology, Newcastle

Patient name:

Date of birth:

Address:

Referring hospital

Hospital number:

Pathology reference:

Consultant paediatric oncologist:

Consultant pathologist:

Clinical information (including stage of NB)

Date of biopsy:

Sent by: Date:

Phone number: Email address:

(Please provide contact number or email address so we can confirm receipt)

Please send a sample of frozen tumour labelled with at least 2 patient identifiers. Samples should be sent on dry ice, using the attached label (see sample label below).

Please phone or email the Newcastle Cancer Cytogenetics lab to pre-warn of sample arrival (0191 2418703, nuth.cancer.genomics@nhs.net).

Newcastle histopathology lab use only

Pathology RVI: please prepare 6 touch imprint slides for cytogenetics and an H&E section for Dr Katrina Wood. Send the imprint slides along with a ~2 × 2 × 2 mm piece of frozen tissue to Cancer Cytogenetics, Northern Genetics Service, Institute of Genetic Medicine, Central Parkway, Newcastle upon Tyne. Any remaining tissue to be stored in tissue bank.

Date sample received in RVI histopathology:

Sample size:

Remaining tissue stored in tissue bank: YES / NO

Sample label

For the urgent attention of Neuroblastoma team.

Histopathology Reception

Cellular Pathology

Level 3, New Victoria Wing

Royal Victoria Infirmary

Queen Victoria Road

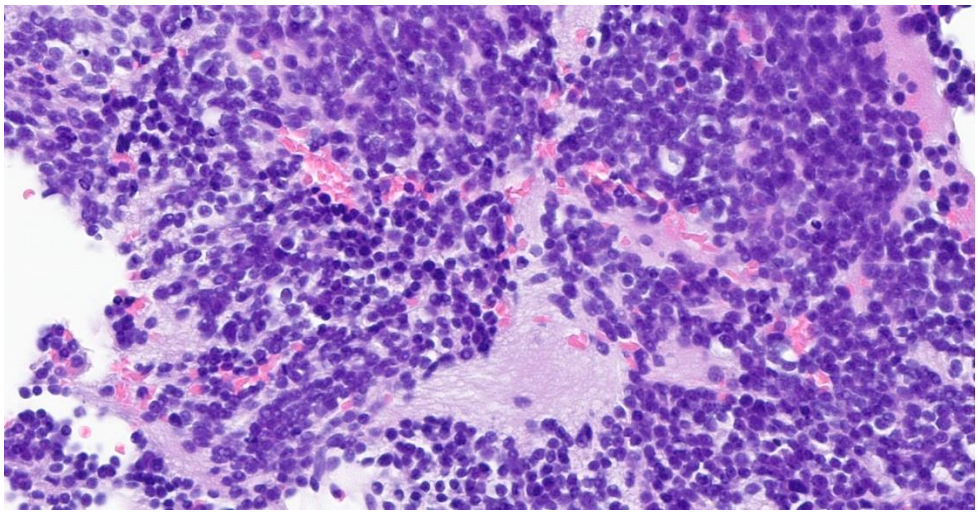
Newcastle upon Tyne

NE1 4LP

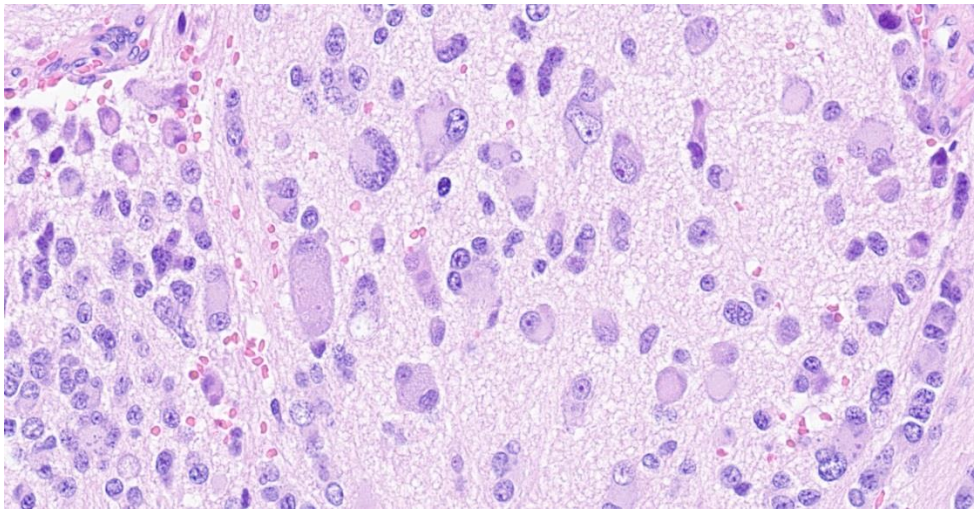
URGENT – FROZEN TISSUE ENCLOSED

Appendix E Histomorphological features of peripheral neuroblastic tumours

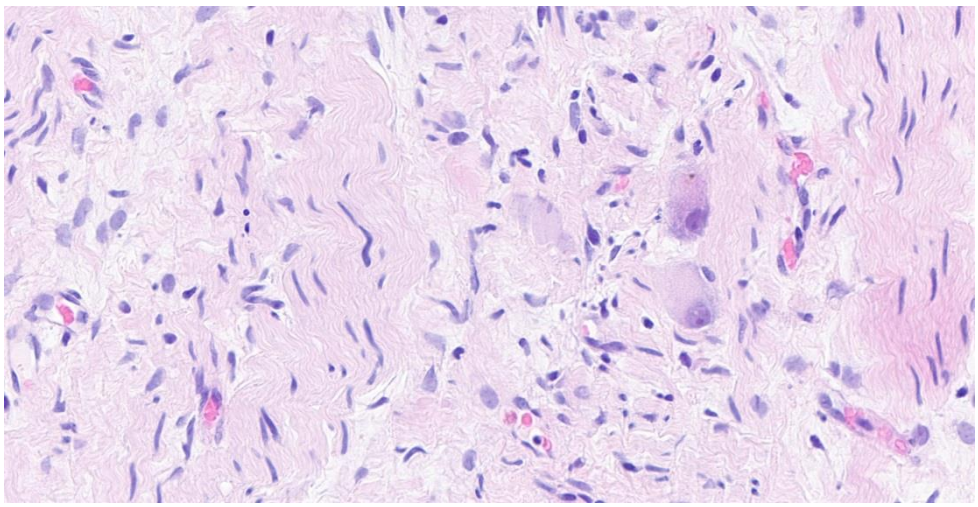
All microphotographs by Dr Jens Stahlschmidt.



A. Poorly differentiated NB: A classical small round blue cell tumour. The nests of tumour cells are partly dissected by vascular septa. The cytoplasmic extensions form a fibrillar, frothy mesh known as neuropil. Ganglion cells are rare (< 5%). Undifferentiated NB lacks neuropil and ganglion cells and requires immunolabelling for pathological diagnosis (H&E, x800).

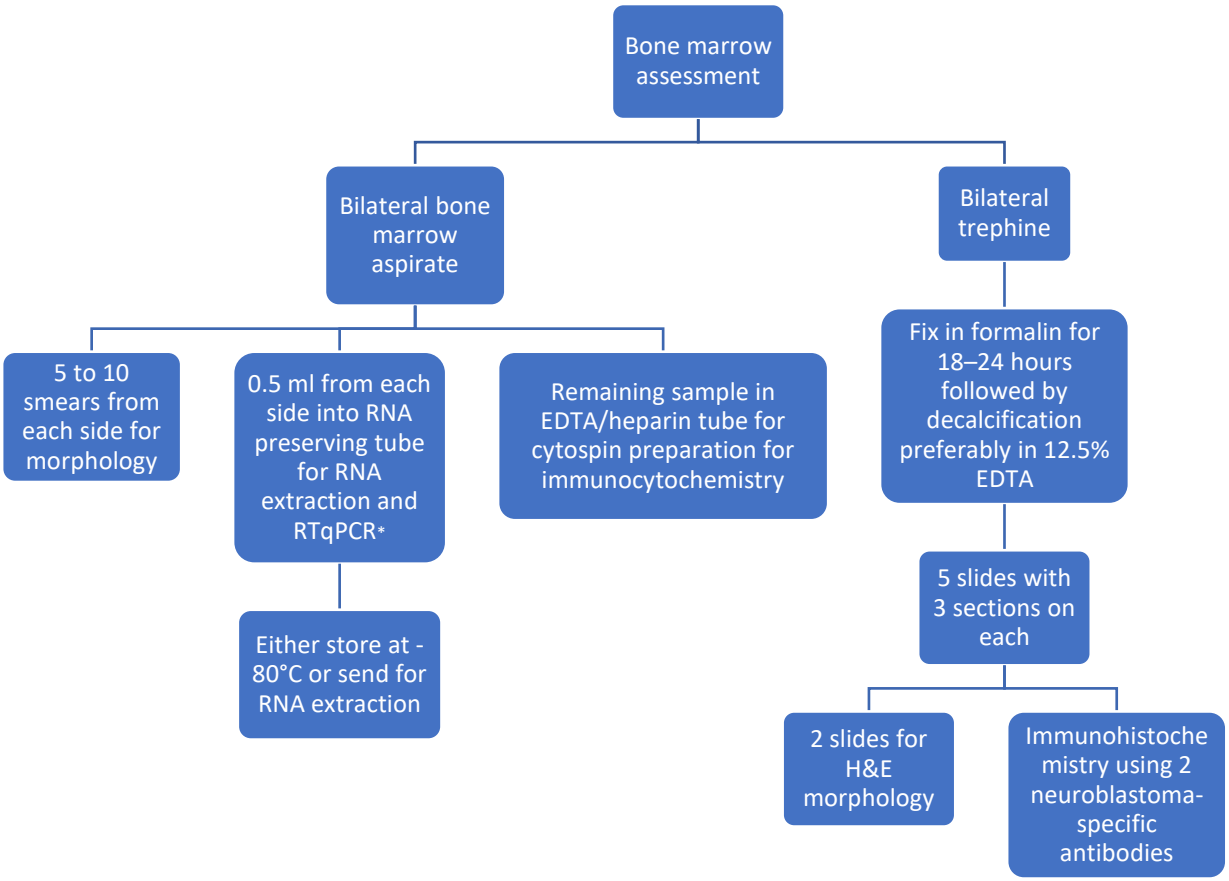


B. Differentiating NB: This lesion is stroma-poor (less than 50% Schwann cells) and shows more than 5% ganglion cell differentiation in a background of neuroblasts and abundant neuropil (H&E, x800).



C. Ganglioneuroma: Ganglioneuroma represents the most differentiated end of the spectrum of neuroblastic tumours. Sparse ganglion cells focally with satellite cells are embedded in abundant Schwann cells/stroma forming fascicles (stroma rich) (H&E, x800).

Appendix F Bone marrow assessment



EDTA: ethylenediaminetetraacetic acid; H&E: haematoxylin and eosin; RTqPCR: reverse transcription quantitative polymerase chain reaction.

*RTqPCR is currently used in research trials and samples are collected for registered tumour banks.

Appendix G Interpretation and reporting of reassessment bone marrow examination[38,39]

Baseline/previous bone marrow findings	Reassessment marrow findings	Interpretation
Infiltration	No infiltration	CR
≤5% infiltration	>0% and ≤5% infiltration	MD
No infiltration	>0% to ≤5% infiltration	
>20% infiltration	>0% to ≤5% infiltration	
No infiltration	>5% infiltration	PD
Infiltration	>2-fold of previous involvement and is >20% infiltration	
Infiltration	≥5% and dos not meet the criteria of CR, MD or PD	SD
No infiltration	No infiltration	Not involved
Infiltration/no infiltration	Inadequate for assessment	Not evaluable
Abbreviations: CR: complete response; MD: minimal disease; PD: progressive disease; SD: stable disease.		

Appendix H SNOMED coding

SNOMED T codes

Topographical codes	SNOMED code (SNOMED 3.5/ SNOMED 2)	SNOMED CT terminology	SNOMED CT code
Adrenal gland, NOS	T-B3000/T-93000	Entire adrenal gland (body structure)	181127006
Right adrenal gland	T-B3010/T-93010	Entire right adrenal gland (body structure)	281625001
Left adrenal gland	T-B3020/T-93020	Entire left adrenal gland (body structure)	281626000
Abdomen, NOS	T-D4000/T-Y4100	Entire abdomen (body structure)	302553009
Abdomen, peritoneum, retroperitoneum, NOS	T-D4000/T-Y4000	Entire abdomen, peritoneum and retroperitoneum (combined site) (body structure)	277050003
Abdominal cavity	T-D4010/T-Y4500	Entire abdominal cavity (body structure)	361294009
Thorax, NOS	T-D3000/T-Y2100	Entire thorax (body structure)	302551006
Right thorax	T-D3010/T-Y2110	Entire right thorax (body structure)	362682009
Left thorax	T-D3020/T-Y2120	Entire left thorax (body structure)	362683004
Lymph node, NOS	T-C4900/T-08000	Entire lymph node (body structure)	181756000
Lymph node of abdomen, NOS	T-C4400/T-08400	Entire abdominal lymph node (body structure)	245342005
Aortic lymph node	T-C4480/T-08480	Entire aortic lymph node (body structure)	731061004
Liver, NOS	T-62000/T-56000	Entire liver (body structure)	181268008
Soft tissues, NOS	T-1A000/T-1X000	Entire soft tissues (body structure)	727285002
Orbit soft tissue	T-AA00B/T-XX00Y	Entire soft tissues of orbit (body structure)	362501007
Skin, NOS	T-01000	Entire skin (body structure)	181469002
Bone, NOS	T-11001/T-1X500	Entire bone (organ) (body structure)	90780006
Bone marrow, iliac crest	T-C1002/T-06002	All iliac bone marrow (body structure)	732089003

Bone marrow, NOS	T-C1000/T-06000	All bone marrow (body structure)	279729006

SNOMED M codes

Morphological codes	SNOMED code (SNOMED 3.5/ SNOMED 2)	SNOMED CT terminology	SNOMED CT code
Neuroblastoma, NOS	M95003	Neuroblastoma (morphologic abnormality)	87364003
Neuroblastoma, metastatic, NOS	M95006	Neuroblastoma, metastatic (morphologic abnormality)	704147007
Ganglioneuroblastoma	M94903	Ganglioneuroblastoma (morphologic abnormality)	69515008
Ganglioneuroma	M94900	Ganglioneuroma (morphologic abnormality)	53801007

Procedure codes (P)

Local P codes should be recorded. At present, P codes vary according to the SNOMED system in use in different institutions.

Appendix I Reporting proforma for peripheral neuroblastic tumours

Surname: ……Forenames:……Date of birth: ……Sex:……

Hospital……..……Hospital No:……..……NHS No:……

Date of surgery:……Date of report authorisation: ……Report No:……

Date of receipt:……...Pathologist:……..……Clinician:……....

Site of specimen ……

Nature of specimen

Needle biopsy □ Open biopsy □

Pre-treatment primary tumour resection □ Post-treatment primary tumour resection □

Fresh tissue/imprint for genetic studies Yes □ No □

Paraffin block/section for genetic studies Yes □ No □

INPC tumour category

Neuroblastoma

NOS □ Poorly differentiated □ Undifferentiated □ Differentiating □

Ganglioneuroblastoma

NOS □ Intermixed □ Nodular □ Number of nodules ……

Variant subtype Yes □ No □

Ganglioneuroma

Maturing □ Mature □

Immunohistochemistry profile (on morphological undifferentiated tumours only)

Synaptophysin	Positive	□	Negative	□	Not done	□
PGP9.5	Positive	□	Negative	□	Not done	□

PHOX2B	Positive	□	Negative	□	Not done	□
NSE	Positive	□	Negative	□	Not done	□
S100	Positive	□	Negative	□	Not done	□
Other (specify):……	Positive	□	Negative	□	Not done	□

Necrosis

Present □ Absent □

Calcification

Present □ Absent □

Lymph nodes

Not received □

Metastasis present □ Metastasis absent □

Site …….

Bone marrow trephine biopsies

Adequate trephine

Yes □ No □ Not known □

Infiltration

Present □ Absent □

Percentage involvement (each site) Left …… Right ……

Grade of neuroblastoma

NOS □ Poorly differentiated □ Undifferentiated □ Differentiating □

Molecular genetics

MYCN amplification

Present □ Absent □ Not done □

Segmental chromosomal abnormalities

Present □ Absent □ Not done □

List…….

Numerical chromosomal abnormalities

Present □ Absent □ Not done □

List……

Other molecular abnormalities

Present □ Absent □

List……

SNOMED code(s)

T…… M……

T…… M……

Signature…… Date……...……..

Appendix J Reporting proforma for peripheral neuroblastic tumours in list format

Element name	Values	Implementation notes
Site of specimen	Free text	
Nature of specimen	Single selection value list: • Needle biopsy • Open biopsy • Pre-treatment primary tumour resection • Post-treatment primary tumour resection	
Fresh tissue/imprint for genetic studies	Single selection value list: • Yes • No	
Paraffin block/section for genetic studies	Single selection value list: • Yes • No	
INPC tumour category	Single selection value list: • Neuroblastoma, NOS • Neuroblastoma, undifferentiated • Neuroblastoma, poorly differentiated • Neuroblastoma, differentiating • Ganglioneuroblastoma, NOS • Ganglioneuroblastoma, intermixed • Ganglioneuroblastoma, nodular • Ganglioneuroma, maturing • Ganglioneuroma, mature	
Number of nodules	Integer	To be completed if 'INPC tumour category, Ganglioneuroblastoma, Nodular' is selected.
Variant subtype	Single selection value list: • Yes • No	To be completed if 'INPC tumour category, Ganglioneuroblastoma, Nodular' is selected.

Immunohistochemistry profile, Synaptophysin	Single selection value list: • Positive • Negative • Not done	
Immunohistochemistry profile, PGP9.5	Single selection value list: • Positive • Negative • Not done	
Immunohistochemistry profile, PHOX2B	Single selection value list: • Positive • Negative • Not done	
Immunohistochemistry profile, NSE	Single selection value list: • Positive • Negative • Not done	
Immunohistochemistry profile, S100	Single selection value list: • Positive • Negative • Not done	
Immunohistochemistry profile, Other	Single selection value list: • Positive • Negative	
Immunohistochemistry profile, Other, specify	Free text	
Necrosis	Single selection value list: • Present • Absent	
Calcification	Single selection value list: • Present • Absent	
Lymph nodes	Single selection value list: • Not received • Metastasis present • Metastasis absent	
Lymph nodes, Metastasis present, Site	Free text	To be completed if ‘Lymph nodes, Metastasis present’ is selected.

Lymph nodes, Metastasis absent, Site	Free text	To be completed if 'Lymph nodes, Metastasis absent' is selected.
Adequate bone marrow trephine biopsies	Single selection value list: • Yes • No • Not known	
Presence of bone marrow infiltration	Single selection value list: • Present • Absent	
Bone marrow infiltration, Percentage involvement, Left	Integer	To be completed if 'Presence of bone marrow infiltration, Present' is selected.
Bone marrow infiltration, Percentage involvement, Right	Integer	To be completed if 'Presence of bone marrow infiltration, Present' is selected.
Grade of neuroblastoma in bone marrow	Single selection value list: • NOS • Poorly differentiated • Undifferentiated • Differentiating	
MYCN amplification	Single selection value list: • Present • Absent • Not done	
Segmental chromosomal abnormalities	Single selection value list: • Present • Absent • Not done	
Segmental chromosomal abnormalities, List	Free text	
Numerical chromosomal abnormalities	Single selection value list: • Present • Absent • Not done	
Numerical chromosomal abnormalities, List	Free text	
Other molecular abnormalities	Single selection value list:	

	• Present • Absent	
Other molecular abnormalities, List	Free text	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix K Summary table – Explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008; 337:1832)

Grade (level) of evidence	**Nature of evidence**
Grade A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target population or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high- quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix L AGREE II guideline monitoring sheet

The guidelines of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this guideline that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	1
2 The health question(s) covered by the guideline is (are) specifically described	1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword, 1
12 There is an explicit link between the recommendations and the supporting evidence	1–11
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	1–11
16 The different options for management of the condition or health issue are clearly presented	1–11
17 Key recommendations are easily identifiable	1–11
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword

19	The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–K
20	The potential resource implications of applying the recommendations have been considered	Foreword
21	The guideline presents monitoring and/or auditing criteria	12
Editorial independence		
22	The views of the funding body have not influenced the content of the guideline	Foreword
23	Competing interest of guideline development group members have been recorded and addressed	Foreword