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

# Standards and datasets for reporting cancers

# Dataset for peripheral neuroblastic tumours histopathology reports

**December 2010**

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| **Unique document number** | G104 |
| **Document name** | Dataset for peripheral neuroblastic tumours histopathology reports |
| **Version number** | 1 |
| **Produced by** | Dr Catherine Cullinane, Leeds Teaching Hospitals Trust |
| **Date active** | September 2010 |
| **Date for review** | September 2013 |
| **Comments** | In accordance with the College's pre-publications policy, this document was put on The Royal College of Pathologists' website for consultation from 2 September to 1 October 2010. Seven items of feedback were received and the authors considered them and amended the document as appropriate. Please email publications@rcpath.org if you wish to see the responses and comments.<br><br>Dr Peter Cowling<br>Director of Communications |

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## Contents

## Foreword

The cancer datasets are **guidelines.** Guidelines are systematically developed statements to assist the decisions of practitioners and patients about appropriate healthcare for specific clinical circumstances and are based on the best available evidence at the time the dataset was prepared. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed a failure of duty of care.

This dataset was reviewed by the Cancer Services Working Group and was placed on the College website for consultation with the membership between 2 September and 1 October 2010. All comments received from the Working Group and the membership will be addressed by the authors to the satisfaction of the Chair of the Working Group and the Director of the Professional Standards Unit, and the Director of Communications.

Each year, the authors of the dataset, in conjunction with the sub-specialty advisor to the College, will consider whether or not the dataset needs to be revised.

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

This dataset was developed without external funding to the dataset writing group or lead author. The remit of The Royal College of Pathologists is to promote the quality of pathology services through training and education. It has no remit to negotiate the terms and conditions of employment for pathologists.

The College requires the authors of datasets to provide a list of potential conflicts of interest and intellectual property deed of assignment; these are monitored by the Professional Standards Unit and are available on request.

## 1 Introduction

The management of peripheral neuroblastic tumours 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 British Isles every year.

The reporting pathologist should either be a core member of the paediatric oncology MDT or have access to a pathologist who is a core member for review purposes. The pathologists reporting these cases should ideally be paediatric histopathologists. The *Guidance on Cancer Services* issued by the National Institute of Health and Clinical Excellence (NICE) recommends that specialist paediatric pathologists should be involved with the pathological diagnosis of solid tumours in children.[1] Pathologists may also submit cases for further opinion and or rapid review to the chair of the Neuroblastoma Pathology Panel of the Childhood Cancer and Leukaemia Group (CCLG).

Neuroblastoma is the most common extracranial solid malignant tumour in childhood.[2] It is a member of a family of tumours, peripheral neuroblastic tumours (PNTs), which arise in the sympathetic system and are neural crest derived. PNTs encompass a spectrum of tumours ranging from the malignant neuroblastoma at one end to the completely benign ganglioneuroma at the other end. A heterogeneous disease, neuroblastoma exhibits a variable clinical course ranging from spontaneous regression, differentiation to benign tumour or progression to aggressive disease, which is often fatal in spite of intensive multi-modality therapy. Most infants have a good prognosis with complete regression with minimal treatment even in the presence of metastases, whereas older children frequently have

metastases and more aggressive disease. It usually presents in children less than two years old and in 90% of cases by five years of age. Prognosis and clinical management are dependent on age, staging, pathological findings, genetic and molecular biological profile and biochemical features.[3] Although the guidelines for The Royal College of Pathologists (RCPath) are primarily aimed at collecting core data in the reporting of cancers, the peripheral neuroblastic tumours include benign and malignant tumours and therefore all are included in the dataset proforma (Appendix D).

This dataset has been devised to include the data required for a careful assessment and adequate reporting of peripheral neuroblastic tumours. Evidence for the dataset was obtained from a review of relevant literature from the past decade, using the PubMed and MedLine databases. Selection of the information included is based on the author's own experience and discussion with colleagues. 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 and/or research requirements.

With regard to stakeholders, this consultation dataset was reviewed by the Neuroblastoma Subgroup of the National Cancer Research Institute Childhood Cancer and Leukaemia Clinical Studies Group (NCRI CCL CSG) and the National Childhood Tumour Registry of the Childhood Cancer Research Group (CCRG), Oxford. Specialist paediatric and general histopathologists acting on behalf of the College also reviewed it.

**Role of the pathologist**

1. Diagnosis.
2. Selection of tissue for molecular genetic studies.
3. Selection of tissue for research.
4. Support of local, national and international collaborative research.
5. Identification of histo-prognostic features.
6. Promotion of standardisation of terminology and classification.

Peripheral neuroblastic tumours are classified according to the International Neuroblastoma Pathology Classification (INPC) (see Appendix A). The classification was established in 1999 and revised in 2003.[4–5] A prognostic classification, it is based on morphological features and age and defines four categories of tumour and two distinct prognostic groups ('favourable histology' and 'unfavourable histology'), based on grade of neuroblastic differentiation, Schwannian stromal development and mitotic karyorrhectic index.[6–8] The four 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 International Staging System (INSS) for neuroblastoma is based on extent of disease, surgical and radiological criteria including surgical extent of excision, margins, presence or absence of nodal metastases, extent of spread and bone marrow infiltration.[2–3] Recently the new International Neuroblastoma Risk Group (INRG) classification system was developed to establish an agreed international approach to pre-treatment risk stratification of neuroblastoma.[9] It is based on clinical criteria including age, adverse molecular factors such as MYCN amplification, as well as histological tumour category and grade of tumour

differentiation. The new INRG staging system is based on image-defined risk factors (IDRFs) and is not dependent on extent of surgery.[10] These surgical staging systems are outlined in Appendix B.

## 2 Clinical information required on the specimen request form

1. Presentation, signs and symptoms
2. Age of patient
3. Site and laterality of biopsy or excision
4. Site of lymph nodes
5. Urinary catecholamine result if pre-treatment biopsy
6. Previous treatment.

## 3 Specimen handling, description and block selection

Ideally, all specimens should be sent fresh to the laboratory for immediate examination by the pathologist. Good communication with the clinical and surgicals teams is a prerequisite.

The pathologist triages the fresh biopsy or resected tumour and selects the samples for molecular genetic investigation, and for future research and tumour banking if appropriately consented. A number of genetic features are strongly associated with prognosis in neuroblastoma.[11–16] The excised tumour is weighed and measured in three dimensions. The external surface of the resected fresh tumour should be inked prior to incision. A photographic record or diagram is very useful to record blocks. The tumour does not require opening in a particular way to facilitate fixation. It should be sliced along the greatest diameter and the cut surface should be carefully inspected and sampled for cytogenetic studies and for freezing in liquid nitrogen and storage at $-80^0$C. In addition, any distinct or haemorrhagic nodule(s) should be identified and counted. Each nodule should also be sampled for genetic studies and freezing. Corresponding adjacent blocks from the tumour mass and nodule(s) should also be formalin fixed. It is important to use a labelling scheme that clearly indicates these corresponding blocks as A, B, etc. to enable estimation of percentage and type of viable tumour cells, which is important in the quality control of the genetic data. If the facilities are available, touch preparations (at least five) should be made from these blocks prior to fixation, air-dried and unfixed, and stored at $-20^o$C for fluorescent in-situ hybridization (FISH). In the past, all nodular ganglioneuroblastomas were regarded as poor prognosis tumours. However, it is now clear that the prognosis is variable and is essentially that of the neuroblastoma in the nodule. If two or more nodules of neuroblastoma are present, the prognosis is that of the neuroblastoma with the worse prognostic features.[5,17]

It is recommended that all areas of the excised tumour be adequately sampled, usually one block per centimetre of greatest dimension.[18] The inked surface margin should be included. Any attached lymph nodes should be submitted. Small nodes may be submitted intact and large nodes sampled or submitted in their entirety. In the post-treatment resected tumour areas of necrosis and scarring may be estimated.

## 4 Microscopic report

The microscopic features linked with age are prognostic in the INPC classification.[4–5] The morphological features are well described in the literature.[2–8] Neuroblastoma (Schwannian stroma poor) has three grades. Undifferentiated neuroblastoma consists of undifferentiated tumour cells with no neuropil and requires immunohistochemistry 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 two subtypes. Mature ganglioneuroma has a Schwann cell stroma with scattered mature ganglion cells with 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 one or more discrete expansile nodules of neuroblastoma. A biopsy may include both components of the tumour, but often only one component is apparent on the biopsy. Clinical pathological 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 histology and genetic profiles of the tumours have also shown correlation. [19–20] Unfavourable histology in INPC classification is more often associated with MYCN oncogene amplification in the tumour and high stage. The classification into favourable histology (FH) and unfavourable histology (UH) had prognostic value in patients with low stage (INSS stages 2A and 2B) non-MYCN amplified tumours, a group with an overall good prognosis, as an increased relapse rate of 32% at 60 months was found in the UH group compared to 13.4% in the FH group.[21] The INRG Task Force's report found that grade of tumour, mitosis karyorrhexis index (MKI) and age each had independent prognostic ability.[9] Similar findings were reported recently by Shimada's group.[21] Within the patients with INSS stages 1, 2, 3 and 4S, histologic category (ganglioneuroma maturing and ganglioneuroblastoma intermixed) was the most powerful prognostic factor.[9] These tumours were only very rarely MYCN amplified. In non-stage 4 patients with neuroblastoma and ganglioneuroblastoma nodular, MYCN status was the most significant prognostic factor.

There are treatment recommendations on the Children's Cancer and Leukaemia Group (www.cclg.org.uk) for patients with non-high-risk neuroblastoma. Patients with high-risk neuroblastoma are eligible for the SIOPEN High Risk Study 1 (HRNBL@trials.bham.ac.uk). Pathology guidelines on handling of biopsy and resection specimens, bone marrow aspirates and trephines are included in the trial protocol.

The morphology in neuroblastoma – including cellularity, number of mitoses and karyorrhectic cells – may vary in different fields. MKI is a useful prognostic indicator in neuroblastoma (Schwannian stroma poor) tumours. It is the number of karyorrhectic nuclei and mitoses in 5000 tumour cells. Low MKI is <2% (<100 per 5000 cells), intermediate MKI is 2–4% (100–200 per 5000 cells) and high MKI is > 4% (>200 per 5000 cells). It is determined as an average made after examination of all sections and or all representative viable areas of the tumour. A case of composite neuroblastoma with histologically distinct clones has been reported with FH and UH patterns which were also biologically distinct with MYCN amplification demonstrated by FISH on paraffin section in the UH clone but not in the FH clone.[22] Large red nucleoli have been associated with MYCN-amplified tumours.[23] A large cell variant of neuroblastoma associated with more aggressive behaviour is reported.[24]

Formal criteria for size and colour of nucleoli as well as nuclear size are not available, but are currently the subject of research, as are other morphological features such as nuclear and cellular pleomorphism and anaplasia.

## 5 Core data items

**Clinical information:**

a) site of specimen

b) pre or post treatment

c) site(s) of separate lymph nodes.

**Macroscopic information:**

a) type of specimen – biopsy (needle or open/surgical) or resection

b) fresh tissue for genetic studies or paraffin block

c) fresh tissue for research

d) resection – nodule(s) present or absent

e) resection – number of nodules

f) lymph nodes attached – yes or no.

**Microscopic information:**

a) 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)

Neuroblastoma – grade of differentiation:
Not otherwise specified (NOS)
Undifferentiated
Poorly differentiated
Differentiating

Ganglioneuroblastoma nodular:
Number of nodules of neuroblastoma
Grade of neuroblastoma differentiation in each nodule
Variant subtype

Ganglioneuroblastoma:
Not otherwise specified (NOS)

Ganglioneuroma subtype:
Maturing
Mature

b) Mitosis karyorrhexis index (MKI) in neuroblastoma (and each neuroblastoma nodule in ganglioneuroblastoma nodular):

Tissue not suitable for determination
Low
Intermediate
High

c) Surgical margin involvement if excision either pre-treatment or post-treatment:

Positive
Negative

d) Immunohistochemistry profile

Positive for one or more of commonly used neural markers (synaptophysin, NB84, NSE, PGP9.5)

Establishes diagnosis in small or crushed biopsies and in undifferentiated neuroblastoma

e) Necrosis – present or absent (included here as it may limit the data, both histopathological and genetic, that can be obtained from the specimen)

f) Calcification – present or absent (included here as may limit the data, both histopathological and genetic, that can be obtained from the specimen)

g) Lymph node metastases – present or absent

h) Extranodal spread – present or absent

i) INPC prognostication category

Favourable
Unfavourable
Not suitable (if neuroblastoma diagnosed but insufficient tissue to determine INPC and or MKI, depending on age)

j) Tumour evaluation in paraffin blocks adjacent to areas sampled for genetic studies and research as important for quality control in genetic results and also aids determination of suitability of the tissue samples stored for future research. The information is given as percentages of viable neuroblasts, viable ganglion cells, viable Schwann cells, viable other cells and also percentage necrosis.

## 6 Non-core data items

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

**Macroscopic information:**

a) size in three dimensions

b) weight of excised tumour

c) number of lymph nodes.

**Microscopic information:**

a) nuclear pleomorphism, nuclear size

b) nucleolar size and colour

c) vascular (venous/lymphatic) invasion

d) post-treatment changes.

## 7 SNOMED coding

See Appendix C.

## 8 Reporting of small biopsies

Most paediatric peripheral neuroblastic tumours encountered in UK are neuroblastomas and most are high stage and disseminated at presentation. Biopsies are therefore more common than primary excisions. Most biopsies are needle cores. Sometimes metastases are biopsied, e.g. skin nodule, and may provide more diagnostic tissue. Open surgical biopsies are uncommon today. The information gleaned from small biopsies may be limited by minimal amount of viable tumour, presence of necrosis, crush artefact and calcification. The pathologist is expected to confirm the diagnosis of neuroblastoma and exclude other tumours (see below). Immunohistochemistry is essential in many of these cases. It is usually not possible to use the INPC classification on such limited specimens. Such tumours would be classified as neuroblastoma NOS (not otherwise specified) or ganglioneuroblastoma NOS (not otherwise specified). Large biopsies, in practice greater than at least $1cm^3$, or biopsies with at least 5000 viable tumour cells are required to attempt INPC classification. When tissue is limited, touch imprints or paraffin sections can be sent for genetic study by FISH.

Undifferentiated neuroblastoma also, by definition, requires immunohistochemistry to make the diagnosis. It is a small blue cell tumour. A variety of neural markers may be used, depending on local practice. The tumour cells are synaptophysin and NB84 positive. NSE and PGP 9.5 are less specific. A panel of antibodies may be required, depending on presentation and site of biopsy, to exclude other tumours such as rhabdomyosarcoma, lymphoma/leukaemia, Wilm's tumour and peripheral primitive neuroectodermal tumour, etc.[3]

Bone marrow trephine biopsies and bone marrow aspirates are taken for clinical staging, risk assessment at diagnosis and monitoring response to treatment. The larger the deposit of tumour in the marrow cavity, the easier it is to reach a diagnosis. Immunohistochemistry is helpful in detection and confirmation of small clusters of neuroblastic cells. NB84 is less useful in trephine biopsies.[25] CD56 is useful but will also react with rhabdomyosarcoma. Synaptophysin, chromogranin and β-Catenin are also valuable in detecting low-level disease.[26] A variety of techniques have been used to detect tumour cells in bone marrow aspirates, especially single cells, not detectable by standard cytomorphology, including immunocytology panels, flow cytometry and RT-PCR, but their reliability and quantification have been controversial. An international standardised protocol for tumour cell detection by immunocytochemistry has been developed and will facilitate multicenter trials in minimal residual neuroblastoma detection.[27]

## 9 Reporting of frozen sections

Frozen sections are not routinely used in the diagnosis or management of patients with PNTs, unless there is a desire to confirm that tumour tissue is present in the specimen as an aid in triaging for diagnostic, molecular genetic studies or research and to determine tumour cell content in molecular or genetic research studies.

## 10 Specific aspects of individual tumours not recorded elsewhere

Many neuroblastomas are removed following therapy. The INPC classification is not used on post-treatment cases. These tumours show varying degrees of response to therapy, with necrosis, scarring and ganglioneuromatous differentiation. The surgeons are usually interested in the excision margins and presence or absence of viable tumour in lymph nodes and extranodal spread into surrounding tissues. The INSS staging system is a post surgical

system (see Appendix B). The number of lymph nodes with metastatic disease is not important but the location of the involved nodes, ipsilateral or contralateral, is important. Some tumours, including ganglioneuroblastoma intermixed, are not resectable and are observed. If the latter continue to grow, chemotherapy may be given to control growth and symptoms. Ganglioneuroblastoma intermixed and ganglioneuroma are rarer than neuroblastoma and can be diagnostically and clinically challenging.[28–29] A careful examination to exclude or confirm nodules of neuroblastoma is necessary, as clonal evolution on the background of such tumours characterises the ganglioneuroblastoma nodular. Other reasons for examining the resected specimen are to allay clinical concerns. There may be no apparent clinical response to treatment. This may due to progression of an aggressive tumour. 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 necrosis is not of prognostic importance as described in other paediatric tumours, e.g. Ewing's sarcoma.

## 11 Audit criteria

The following standards are suggested as some criteria that might be used in periodic reviews of the peripheral neuroblastic tumours diagnostic service.

a. Completeness of histopathology reports expressed as average proportion of the core data items recorded.

b. Number and type of biopsy cases with sufficient tumour to determine International Neuroblastoma Pathology Classification (INPC) and Mitotic Karyorrhectic Index (MKI).

c. Number and type of biopsy cases with insufficient tumour to determine International Neuroblastoma Pathology Classification (INPC) and Mitotic Karyorrhectic Index (MKI).

d. Number of cases with sufficient needle biopsies to submit portions for cytogenetic analysis and freezing for research purposes; number of cases with genetic studies done on paraffin block or sections.

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## Appendix A International Neuroblastoma Pathology Classification (INPC) of peripheral neuroblastic tumours[4–5]

**Neuroblastoma (Schwannian stroma poor)** NB
Undifferentiated
Poorly differentiated
Differentiating

**Ganglioneuroblastoma intermixed (Schwannian stroma rich)** GNBi

**Ganglioneuroblastoma nodular**
**(composite Schwannian stroma rich/stroma dominant and stroma poor)** GNBn

**Ganglioneuroma (Schwannian stroma dominant)** GN
Maturing
Mature

**Favourable histology (FH) criteria**

| Category | Grade | Age | MKI |
|---|---|---|---|
| **Neuroblastoma** | Poorly differentiated | <18 months | Low or intermediate |
| | Differentiating | <18 months | Low or intermediate |
| | Differentiating | 18 months to 5 years | Low |
| **Ganglioneuroblastoma nodular** | As per neuroblastoma in nodule(s) with age and MKI | | |
| **Ganglioneuroblastoma intermixed** | | Any age | |
| **Ganglioneuroma** | | Any age | |

**Unfavourable histology (UH) criteria**

| Category | Grade | Age | MKI |
|---|---|---|---|
| **Neuroblastoma** | Undifferentiated | Any age | |
| | Poorly differentiated | <18 months | High |
| | | >18 months | Any |
| | Differentiating | <18 months | High |
| | | 18 months to 5 years | Intermediate or high |
| **Neuroblastoma** | Any | > 5years | Any |
| **Ganglioneuroblastoma nodular** | As per neuroblastoma in nodule(s) with age and MKI | | |

## Appendix B Clinical staging systems

### International Staging System for Neuroblastoma (INSS)[2–3]

Stage 1 Localised tumour, complete macroscopic excision, +/– microscopic residual disease, and ipsilateral and contralateral lymph nodes negative for tumour microscopically.

Stage 2A Localised tumour, incomplete macroscopic excision, ipsilateral and contralateral lymph nodes negative for tumour microscopically.

Stage 2B Localised tumour +/– complete macroscopic excision, ipsilateral lymph nodes positive for tumour microscopically.

Stage 3 Unresectable tumour, crosses midline, +/– regional lymph node metastases; localised unilateral with contralateral lymph nodes positive for metastases, or midline tumour with bilateral spread or lymph node metastases.

Stage 4 Disseminated tumour with metastases in distant lymph nodes, bone, bone marrow, liver, and/or other organs (except as defined in Stage 4s)

Stage 4s Localised primary tumour (Stage 1 or 2) with disseminated tumour limited to liver, skin and/or bone marrow, in infants <1 year old.

### International Neuroblastoma Risk Group (INRG) staging system[10]

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 C SNOMED codes for peripheral neuroblastic tumours

### T codes

| | |
|---|---|
| Adrenal gland NOS | T-93000 |
| Right adrenal gland | T-93010 |
| Left adrenal gland | T-93020 |
| Abdomen NOS | T-Y4100 |
| Abdomen, peritoneum, retroperitoneum NOS | T-Y4000 |
| Abdominal cavity | T-Y4500 |
| Thorax, NOS | T-Y2100 |
| Right thorax | T-Y2110 |
| Left thorax | T-Y2120 |
| Lymph node NOS | T-08000 |
| Lymph node of abdomen, NOS | T-08400 |
| Aortic lymph node | T-08480 |
| Liver, NOS | T-56000 |
| Soft tissues, NOS | T-1X000 |
| Orbit soft tissue | T-XX00Y |
| Skin, NOS | T- 01000 |
| Bone, NOS | T-1X500 |

### M codes

| | |
|---|---|
| Neuroblastoma, NOS | M 95003 |
| Neuroblastoma, metastatic, NOS | M95006 |
| Ganglioneuroblastoma | M94903 |
| Ganglioneuroma | M94900 |

## Appendix D Proforma for peripheral neuroblastic tumours histopathology reporting

Surname: ..... Forenames: ..... Date of birth: ..... Sex: M / F

Hospital: ..... Hospital no: ..... NHS/CHI number:.....

Date of surgery: ..... Date of report: .....Report no: .....

Date specimen received: ..... Pathologist: ..... Surgeon: ..... Oncologist.....

---

**Core data**

**Site of specimen ……...**

**Nature of specimen**

| | | | | | | |
|---|---|---|---|---|---|---|
| Needle biopsy | Yes □ | No □ | Open biopsy | Yes □ | No □ |
| Resection | Yes □ | No □ | Post treatment | Yes □ | No □ |
| Fresh tissue/imprint for genetic studies | | | Yes □ | No □ | |
| Paraffin block/section for genetic studies | | | Yes □ | No □ | |
| Fresh tissue for research | | | Yes □ | No □ | |

| **Neuroblastoma** | □ | **Ganglioneuroblastoma** | □ | **Ganglioneuroma** | □ |
|---|---|---|---|---|---|
| NOS | □ | NOS | □ | Maturing | □ |
| Undifferentiated | □ | Intermixed | □ | Mature | □ |
| Poorly differentiated | □ | Nodular | □ | | |
| Differentiating | □ | – Nodule number | □ | | |
| | | – Variant subtype | □ | | |

| **Mitotic karyorrhectic index** | | **Immunohistochemistry** | | **Necrosis** | |
|---|---|---|---|---|---|
| Not suitable | □ | Synaptophysin | □ | Present | □ |
| Low | □ | NB84 | □ | Absent | □ |
| Intermediate | □ | NSE | □ | **Calcification** | |
| High | □ | PGP9.5 | □ | Present | □ |
| | | | | Absent | □ |

| **Surgical margins** | | **Lymph node(s)** | | **INPC prognostic group** | |
|---|---|---|---|---|---|
| Positive for tumour | □ | Not received | □ | Favourable | □ |
| Negative for tumour | □ | Metastasis present | □ | Unfavourable | □ |
| | | Site…… | | Not suitable | □ |
| | | Metastasis absent | □ | | |
| | | Site…… | | | |
| | | **Extranodal spread** | Yes □ | No □ | |

| **Tumour in paraffin blocks adjacent to fresh portions sent for biological study** | **A** | **B** |
|---|---|---|
| % viable neuroblastic tumour cells | □ | □ |
| % viable ganglion cells | □ | □ |
| % viable Schwann cells | □ | □ |
| % viable other cells | □ | □ |
| % necrosis | □ | □ |

**SNOMED code(s)** **T…… M……**

**T…… M……**

**Signature……** **Date……...……..**

## Appendix E Peripheral neuroblastic tumours dataset monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE standards for good quality clinical guidelines (www.agreecollaboration.org). The sections of this dataset that indicate compliance with each of the AGREE standards are indicated in the table.

| AGREE Standard | Section of dataset |
|---|---|
| SCOPE AND PURPOSE | |
| 1. The overall objective(s) of the guideline is (are) specifically described | 1 |
| 2. The clinical question(s) covered by the guidelines is (are) specifically described | 1 |
| 3. The patients to whom the guideline is meant to apply are specifically described | 1 |
| STAKEHOLDER INVOLVEMENT | |
| 4. The guideline development group includes individuals from the relevant professional groups | 1 |
| 5. The patients' views and preferences have been sought | N/A |
| 6. The target users of the guideline are clearly defined | 1 |
| 7. The guideline has been piloted among target users | Yes |
| RIGOR OF DEVELOPMENT | |
| 8. Systematic methods were used to search for evidence | 1 |
| 9. The criteria for selecting the evidence are clearly described | 1 |
| 10. The methods used for formulating the recommendations are clearly described | 1 |
| 11. The health benefits, side effects and risks have been considered in formulating the recommendations | 1 |
| 12. There is an explicit link between the recommendations and the supporting evidence | 3, 4, 11 |
| 13. The guideline has been externally reviewed by experts prior to its publication | 1 |
| 14. A procedure for updating the guideline is provided | Foreword |
| CLARITY OF PRESENTATION | |
| 15.The recommendations are specific and unambiguous | 3, 4 |
| 16. The different options for management of the condition are clearly presented | 3, 4 |
| 17. Key recommendations are easily identifiable | 3, 4 |
| 18. The guideline is supported with tools for application | Appendix D |
| APPLICABILITY | |
| 19.The potential organizational barriers in applying the recommendations have been discussed | 1, 3 |
| 20.The potential cost implications of applying the recommendations have been considered | N/A |
| 21.The guideline presents key review criteria for monitoring/or audit purposes | 3–5, 7–10 |
| EDITORIAL INDEPENDENCE | |
| 22. The guideline is editorially independent from the funding body | Foreword |
| 23. Conflicts of interest of guideline development member have been recorded | Foreword |