CHILDREN’S CANCER AND LEUKAEMIA GROUP (CCLG)
NEUROBLASTOMA SPECIAL INTEREST GROUP

Treatment of Patients with
Low/Intermediate Risk Neuroblastoma

JANUARY 2015

Originally written by D Tweddle and K Wheeler August 2011
Updated by DA Morgenstern, F Herd and DT /KW January 2015

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The CCLG does not sponsor or indemnify the treatment detailed herein. These treatment recommendations are provided by the Neuroblastoma Special Interest Group to inform and for use at the sole discretion of treating clinicians who retain professional responsibility for their actions and treatment decisions. Treatment recommendations are based on current best practice and not what is necessarily proposed for any forthcoming clinical trial.
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Major updates from previous version

- New recommendation for observation only for infants with stage L2 tumours with no LTS, no MYCN amplification and NCA profile.
- New recommendation to consider treatment according to high-risk protocol for patients aged >5 years with stage L2 tumours without MYCN amplification with unfavourable histology. These patients should be discussed with the national coordinators.
- Clarification of advice regarding use of histopathology at diagnostic biopsy and surgical resection to stratify intermediate risk patients aged >18 months.
- Additional information added in appendices
Introduction

These guidelines are treatment recommendations for patients with low and intermediate risk Neuroblastoma in the UK. The European collaborative group SIOPEN currently has an open study for these patients (LINES, EudraCT 2010-021396-81). However, this study is not open in the UK and consequently it is recommended that patients be treated according to the following guidelines (which are largely, although not entirely, based on the SIOPEN LINES trial treatment recommendations and do not include the randomisations that form part of the trial).

All patients with neuroblastoma should have a diagnostic biopsy performed\(^1\) and genetic analyses undertaken in a national reference centre. Whilst it is acceptable for MYCN FISH to be undertaken in large centres, it is now very important that the more complex genetic investigations such as multiplex ligation dependent probe amplification (MLPA), array CGH or SNP array are performed in the Newcastle national reference centre (Northern Genetics Service Cytogenetics Laboratory) since this can have implications for treatment stratification as well as prognosis. We recommend that all UK centres send frozen neuroblastoma (NB) tissue to Newcastle from all neuroblastoma patients as this laboratory has undergone rigorous quality assurance in line with other European national reference laboratories as part of the European Neuroblastoma Quality Assurance Group (ENQUA) (Ambros et al, Clinical Cancer Research, 2011).

\(^1\) An exception may be made for neonates and young infants with adrenal masses diagnosed at age < 3 months in whom it may be appropriate to undertake a ‘watch and wait’ strategy rather than undertaking biopsy or surgical resection.
### Risk stratification approach

Risk stratification for all patients with neuroblastoma is crucial in determining treatment. The following criteria are used:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient age</strong></td>
<td>In general, patients aged ≤18 months at diagnosis have a better prognosis than those aged &gt;18 months. Note that patients with metastatic disease without MYCN amplification or segmental chromosomal abnormalities, aged 12-18 months are currently treated on the high-risk study, albeit with reduced treatment intensity.</td>
</tr>
<tr>
<td><strong>Tumour stage</strong></td>
<td>Under the new International Neuroblastoma Risk Group (INRG) staging system, localised disease is staged as L1 or L2 depending on the presence of image defined risk factors (IDRF). See Appendix 1 for more information.</td>
</tr>
<tr>
<td><strong>MYCN amplification</strong></td>
<td>MYCN amplification remains a critical risk factor in neuroblastoma and it is vital that MYCN status is determined by an accredited laboratory. Note that MYCN gain does not equate to MYCN amplification.</td>
</tr>
<tr>
<td><strong>Tumour histology</strong></td>
<td>For patients aged &gt;18 months with localised (L2) disease, treatment will be reduced for patients with International Neuroblastoma Pathology Classification (INPC) differentiating disease, compared to those with undifferentiated or poorly differentiated tumours. Generous biopsies should be taken on these patients at diagnosis so that the histology is representative. The initial chemotherapy approach can be the same for both subgroups.</td>
</tr>
<tr>
<td><strong>Chromosomal abnormalities</strong></td>
<td>There is increasing evidence for a prognostic impact of chromosomal abnormalities (see, for example, Schleiermacher 2011 and 2012) and, in particular, the presence of segmental (SCA) as compared to numerical chromosomal abnormalities (NCA). It is recommended that tissue from all neuroblastoma cases be sent to the Newcastle reference laboratory for analysis of SCA/NCA. See Appendix 3 for more information.</td>
</tr>
<tr>
<td><strong>Life-threatening symptoms</strong></td>
<td>See Appendix 4 for more information. Particular care should be taken in the management of neuroblastoma with intra-spinal extension.</td>
</tr>
</tbody>
</table>
Treatment groups and recommended treatment

The table below summarises the risk stratification, treatment groups and recommended treatment approach based on the risk factors outlined above (and detailed further in the appendices). See Appendix 1 for larger format version.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Age (mo.)</th>
<th>MYCN</th>
<th>Grade</th>
<th>CA</th>
<th>LTS</th>
<th>Risk group</th>
<th>Courses</th>
<th>Treatment</th>
<th>LINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>all</td>
<td>Non-amp</td>
<td>Low</td>
<td>0</td>
<td>Surgery/observation only</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td>all</td>
<td>Amp</td>
<td>Intermediate</td>
<td>6</td>
<td>Carbo/etop and CADO x6 cycles total ± surgery + radiotherapy ± cis-RA</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>&lt;18</td>
<td>Non-amp</td>
<td>NCA</td>
<td>no LTS</td>
<td>Low</td>
<td>0</td>
<td>Observation ± surgery</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>≤18</td>
<td>Non-amp</td>
<td>NCA</td>
<td>LTS</td>
<td>Low</td>
<td>2-4</td>
<td>Carbo/etop x2 ± CADO x2 ± surgery</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>&gt;18</td>
<td>Non-amp</td>
<td>Diff [2]</td>
<td>Intermediate</td>
<td>4</td>
<td>Carbo/etop x2 + (CADO x2 or carbo/etop x2) ± surgery</td>
<td>7</td>
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<td></td>
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</tr>
<tr>
<td>L2</td>
<td>&gt;5 yrs</td>
<td>Non-amp</td>
<td>Undiff</td>
<td>Intermediate</td>
<td>Particular consideration should be given to these patients, high-risk therapy may be warranted. Please discuss with national coordinators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>All</td>
<td>Amp</td>
<td>High</td>
<td>High-risk study</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>M</td>
<td>&lt;12</td>
<td>Non-amp</td>
<td>Intermediate</td>
<td>4-8</td>
<td>Carbo/etop x2 ± CADO x2 ± surgery</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>12-18</td>
<td>Non-amp</td>
<td>NCA</td>
<td>Intermediate</td>
<td>High-risk study but receive only COJEC and surgery [4]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>M</td>
<td>&gt;18</td>
<td>Non-amp</td>
<td>SCA</td>
<td>High</td>
<td>High-risk study</td>
<td></td>
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<td>High-risk study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[1] The LINES column gives the group number that accords to the current SIOPEN LINES study and is provided for reference only.
[2] Caution is advised that the decision regarding differentiated vs. undifferentiated/poorly differentiated tumour should be confirmed on the resection specimen at the time of surgery and not solely on the basis of the original biopsy. For patients initially deemed to have a differentiated tumour on biopsy, but that then have undifferentiated/poorly differentiated histology at resection, it is recommended to escalate their treatment to high-risk (although these patients are not eligible for the SIOPEN High Risk study). Discussion with the national coordinators is strongly advised.
[3] Particular caution is advised in treating patients aged >5 yrs with poor risk histology and consideration should be given to escalating treatment to high-risk (although these patients are not eligible for the SIOPEN High Risk study). Discussion with the national coordinators is strongly advised.
[4] These patients aged 12-18 months are thought to have outcomes similar to infants aged <12 months and hence will be eligible for treatment reduction if there are NCA only. They should, however, be treated as part of the high-risk study, albeit receiving only rapid COJEC and surgery. If SCA are present these patients should receive full high risk treatment.

Low Risk
- Infants aged ≤ 18 months with localised unresectable non-MYCN amplified tumours
- Infants aged ≤ 12 months with stage Ms pattern of disease

Intermediate Risk
- Infants aged ≤ 12 months with metastatic (non-Ms) disease without MYCN amplification
- Children aged >18 months with localised unresectable non-MYCN amplified tumours (note that consideration should be given to escalating treatment for patients aged >5 yrs, see below)

NCA profile: Numerical Chromosomal Abnormalities see appendix 3
SCA profile: Segmental chromosomal abnormalities see appendix 3
LTS: Life threatening symptoms see appendix 4
IDRF: Image defined risk factors see appendix 2
Low Risk

Stage L1 tumours in infants see appendix 5

Stage L2, aged ≤ 18 months, MYCN non-amplified

a) NCA profile, no LTS (LINES group 1)
Observation with 3 monthly imaging
Chemotherapy may be indicated if tumour increases in size during period of observation
Consider surgery if image defined risk factors become negative (see Appendix 2).

b) NCA profile + LTS (LINES group 2)
Rx 2- 4 courses of chemotherapy
VP/Carbo x 2 – if LTS then negative and IDRF negative proceed to surgical resection or if IDRF persist proceed with observation
VP/Carbo x 2 – if LTS remain positive for CADO x 2 and then if IDRF negative proceed to surgical resection or if IDRF persist proceed with observation. No indication for further chemotherapy

c) SCA profile ± LTS (LINES group 3)
4 courses of chemotherapy
Rx when LTS not present
VP/Carbo x 4
Rx when LTS present
VP/Carbo x 2 – if LTS resolve for further VP/Carbo x 2
VP/Carbo x 2 – if LTS persist CADO x 2
Surgery after 4 courses of chemotherapy if IDRF negative
When IDRF persist discuss with national surgical coordinator

2 In the SIOPEN LINES study, this group will be randomised between chemotherapy and observation only
Stage Ms, aged ≤ 12 months, MYCN non-amplified

a) NCA profile, no LTS (LINES group 4)
Rx Observation only

b) NCA profile + LTS (LINES group 5)
Rx 2-4 courses of chemotherapy
VP/Carbo x 2 – if LTS then negative proceed with observation, if LTS persist proceed with CADO x 2
Surgical resection of primary tumour not indicated in this group

c) SCA profile, ± LTS (LINES group 6)
4 courses of chemotherapy
Rx when LTS not present
VP/Carbo x 4
Rx when LTS present
VP/Carbo x 2 – if LTS resolve for further VP/Carbo x 2, if LTS persist for CADO x 2
Proceed with a surgical resection of the primary tumour if IDRF negative and if IDRF present discuss with the national surgical coordinator.

Note: If a genomic profile cannot be obtained at diagnosis, patients should be treated as follows:

- Stage L2, ≤ 18 months, MYCN non-amplified
  o Treat as per LINES group 2 (2-4 courses of carbo/etop) ³

- Stage Ms, ≤ 12 months, MYCN non-amplified
  o No LTS: observation only (LINES group 4); have a low threshold for treating if patient becomes symptomatic
  o With LTS: treat as per LINES group 5 (2-4 courses of carbo/etop)

³ Note that this guidance is slightly different from that in the LINES protocol
Intermediate risk

Stage L2, non-MYCN amplified, age 18 months - ≤ 10 years

a) Histology: INPC differentiating (LINES group 7) ⁴

Rx 4 courses of chemotherapy

VP/Carbo x 2 – if tumour responds continue with further VP/Carbo x 2, if no response continue with CADO x 2 then:

If IDRF negative for surgical resection
If IDRF still present discuss with surgical coordinator

b) Histology: INPC undifferentiated or poorly differentiated <5 yrs of age (LINES group 8)

Rx 6 courses of chemotherapy, surgery, radiotherapy and cis-retinoic acid

VP/Carbo x 2, CADO x 2

Followed by:

- If tumour response and IDRF then negative: surgical resection followed by VP/Carbo x 1, CADO x 1 if there was response to initial VP/Carbo, or CADO x 2 if no initial response to VP/Carbo
- If no tumour response and IDRF persist: surgical resection after discussion with surgical coordinator followed by CADO x 2
- If tumour response but IDRF persist: VP/Carbo x 1, CADO x 1 if there was response to initial VP/Carbo, or CADO x 2 if no initial response to VP/Carbo then surgical resection

If IDRF persist and cause concern, discuss with national surgical coordinator
Surgery should be followed by radiotherapy + 6 courses of 13 cis-retinoic acid. ⁵

If > 5 years with undifferentiated or poorly differentiated tumour histology, consider treatment according to high-risk protocol.

These older patients had a particularly poor outcome (5 yr EFS 35% vs 72% for 18-60 months age group) in the SIOPEN NB2009 study (Kohler 2013) and therefore treatment escalation to high-risk protocol should be considered. Note however that these patients are not eligible

⁴ Caution is advised that the decision regarding differentiated vs. undifferentiated/poorly differentiated tumour should be confirmed on the resection specimen at the time of surgery and not solely on the basis of the original biopsy. For patients initially deemed to have a differentiated tumour on biopsy, but that then have undifferentiated/poorly differentiated histology at resection, it is recommended to escalate their treatment to that for undifferentiated/poorly differentiated histology. However, treatment should not be reduced for patients with tumours that were initially undifferentiated/poorly differentiated but show differentiation at resection after chemotherapy. If in doubt, external review of pathology is advised.

⁵ Doses as for high-risk neuroblastoma study. These patients should also be discussed with UK Low and Intermediate risk NB leads, K Wheeler and/or D Tweddle
for the SIOPEN HR-NBL trial and, at present, are not eligible for immunotherapy as part of the HR-NBL trial or other studies. Discussion of individual patients with the national coordinators is strongly recommended.

**Stage L1, MYCN amplified age ≤ 10 years (LINES group 9)**

Rx 6 courses of chemotherapy
VP/Carbo x 2, CADO x 2, VP/Carbo x 1, CADO x 1
Surgery
Radiotherapy + 6 courses of 13 cis-retinoic acid.

**Stage M, MYCN non-amplified, age < 12 months, any histology (LINES group 10)**

Rx 4-8 courses of chemotherapy
VP/Carbo x 2 then

- If response shown for further VP/Carbo x 2 and if metastatic remission achieved for surgical resection of primary, if metastatic remission not achieved continue with CADO x 2-4 courses to achieve metastatic remission
- If no response after initial VP/Carbo for CADO x 2 -4 to achieve metastatic remission

NOTE: metastatic remission is all sites other than the liver
Surgical resection when metastatic remission achieved and no further chemotherapy
Contacts

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Fax: 0191 241 8713
Email: Nick.Bown@nuth.nhs.uk or cancer.cytogenetics@nuth.nhs.uk

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Appendix 1: Clinical staging

For non-metastatic neuroblastoma, the INRG Staging System will be used.

**Stage L1:** Locoregional tumour not involving vital structures as defined by the list of Image Defined Risk Factors (IDRF; Appendix 2).

**Stage L2:** Locoregional tumour with presence of one or more IDRFs.

Within Stage L1 tumours with MYCN amplification there are very occasionally INSS stage 1 localised tumours with complete gross excision, with or without microscopic residual disease, who have representative ipsilateral lymph nodes microscopically negative for tumour (nodes attached to and removed with the primary tumour may be positive). This group of tumours (in contrast to any other stage of patient with MYCN amplification who are all treated as a high risk patients) are included in this study as intermediate risk patients.

For metastatic neuroblastoma, the INRG Staging system will be used but modified so that it is in accordance with the staging used in the previous trial for this group of patients INES 99.2-99.3.

**Stage M:** Distant metastatic disease with positive mIBG (except Stage Ms). In infants <12 months, mIBG or technetium scintigraphy uptake in the skeleton must be confirmed with a bone abnormality demonstrated on Plain X-ray and/or CT scan.

**Stage Ms:** Metastatic disease confined to skin and/or liver and/or bone marrow (or even other sites such as lymph nodes and/or testes), but NOT bone, lung, pleura or CNS, in infants <12 months. mIBG or technetium scintigraphy uptake to the skeleton may occur but there should be NO X-Ray or CT evidence of bone involvement.
# Neuroblastoma Risk Stratification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Age (mo.)</th>
<th>MYCN</th>
<th>Grade</th>
<th>CA</th>
<th>LTS</th>
<th>Risk group</th>
<th>Courses</th>
<th>Treatment</th>
<th>LINES [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>all</td>
<td>Non-amp</td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
<td>0</td>
<td>Surgery/observation only</td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td>all</td>
<td>Amp</td>
<td></td>
<td></td>
<td></td>
<td>Intermediate</td>
<td>6</td>
<td>Carbo/etop and CADO x6 cycles total ± surgery + radiotherapy + cis-RA</td>
<td>9</td>
</tr>
<tr>
<td>L2</td>
<td>≤18</td>
<td>Non-amp</td>
<td>NCA</td>
<td>no LTS</td>
<td>Low</td>
<td>0</td>
<td>Observation ± surgery</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>≤18</td>
<td>Non-amp</td>
<td>NCA</td>
<td>LTS</td>
<td>Low</td>
<td>2-4</td>
<td>Carbo/etop x2-4 ± CADO x2 ± surgery</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>≤18</td>
<td>Non-amp</td>
<td>Amp</td>
<td></td>
<td></td>
<td>Low</td>
<td>4</td>
<td>Carbo/etop x2-4 ± CADO x2 ± surgery</td>
<td>3</td>
</tr>
<tr>
<td>L2</td>
<td>&gt;18</td>
<td>Non-amp</td>
<td>Diff [2]</td>
<td></td>
<td>Intermediate</td>
<td>4</td>
<td>Carbo/etop x2 + (CADO x2 or carbo/etop x2) ± surgery</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>&gt;5 yrs [3]</td>
<td>Non-amp</td>
<td>Undiff</td>
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<td>All</td>
<td>Amp</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td>High-risk study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>&lt;12</td>
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<td>Intermediate</td>
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[1] The LINES column gives the group number that accords to the current SIOPEN LINES study and is provided for reference only.

[2] Caution is advised that the decision regarding differentiated vs. undifferentiated/poorly differentiated tumour should be confirmed on the resection specimen at the time of surgery and not solely on the basis of the original biopsy. For patients initially deemed to have a differentiated tumour on biopsy, but that then have undifferentiated/poorly differentiated histology at resection, it is recommended to escalate their treatment to that for undifferentiated/poorly differentiated histology. However, treatment should not be reduced for patients with tumours that were initially undifferentiated/poorly differentiated but show differentiation at resection after chemotherapy.

[3] Particular caution is advised in treating patients aged >5 yrs with poor risk histology and consideration should be given to escalating treatment to high-risk (although these patients are not eligible for the SIOPEN High Risk study). Discussion with the national coordinators is strongly advised.

[4] These patients aged 12-18 months are thought to have outcomes similar to infants aged <12 months and hence will be eligible for treatment reduction if there are NCA only. They should, however, be treated as part of the high-risk study, albeit receiving only rapid COJEC and surgery. If SCA are present these patients should receive full high risk treatment.

The Image Defined Risk Factors (IDRF) have been designed to guide surgical management of neuroblastoma at diagnosis, in particular to indicate whether biopsy or attempted resection is recommended as the first surgical procedure.

The same system of risk factors can be applied later during the course of treatment and follow-up, although it is not designed for this purpose. If a tumour remains IDRF positive after chemotherapy this is not an absolute contraindication to surgery. Resection may still be recommended if evaluation of the primary tumour suggests that the risk to life, or of major functional loss, is less than the risk from leaving residual disease.

Ipsilateral tumour extension within two body compartments:
- Neck-chest, chest-abdomen, abdomen-pelvis

Neck
- Tumour encasing carotid and/or vertebral artery and/or internal jugular vein
- Tumour extending to base of skull
- Tumour compressing the trachea

Cervico-thoracic junction
- Tumour encasing brachial plexus roots
- Tumour encasing subclavian vessels and/or vertebral and/or carotid artery
- Tumour compressing the trachea

Thorax
- Tumour encasing the aorta and/or major branches
- Tumour compressing the trachea and/or principal bronchi
- Lower mediastinal tumour, infiltrating the costo-vertebral junction between T9 and T12

Thoraco-abdominal
- Tumour encasing the aorta and/or vena cava

Abdomen/pelvis
- Tumour infiltrating the porta hepatis and/or the hepatoduodenal ligament
- Tumour encasing branches of the superior mesenteric artery at the mesenteric root
- Tumour encasing the origin of the celiac axis, and/or of the superior mesenteric artery
- Tumour invading one or both renal pedicles
- Tumour encasing the aorta and/or vena cava
- Tumour encasing the iliac vessels
- Pelvic tumour crossing the sciatic notch

Intraspinal tumour extension whatever the location provided that:
- More than 1/3 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, duodenopancreatic block and mesentery.

Conditions recommended to be recorded, but NOT considered IDRFs:
- Multifocal primary tumours
- Pleural effusion (with or without malignant cells)
- Ascites (with or without malignant cells)
Appendix 3: Definitions of genomic profile

Segmental chromosomal abnormalities SCA is the presence of any SCA observed recurrently in neuroblastoma not including MYCN e.g. deletion of 1p, 3p, 4p or 11q or gain of 1q, 2p or 17q with or without numerical chromosomal alterations.

Numerical Chromosomal Abnormalities NCA: Numerical chromosome abnormalities only.

Mixed SCA and NCA are classified as SCA
Appendix 4: Life threatening symptoms

The presence of any of these symptoms is an indication for chemotherapy.

- **Intraspinal neuroblastoma**
  Patients who either have symptoms of spinal cord compression or have a spinal tumour component that occupies more than one third of the spinal canal on the axial plane and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal.

- **Systemic upset**
  - Pain requiring opiate treatment
  - **Gastrointestinal**
    - Vomiting needing nasogastric/IV support
    - Weight loss >10% body weight
    - NB: diarrhoea with VIP does not respond to chemotherapy and is a definite indication for surgery
  - **Respiratory**
    - Respiratory distress without evidence of infection
    - Tachypnoea >60
    - Oxygen need
    - Ventilatory support
  - **Cardiovascular System**
    - Hypertension
    - IVC compression +/- leg oedema
  - **Renal**
    - Impaired renal function, creatinine increased x2 ULN
    - Poor urine output, less than 2mL/kg/hour
    - Hydroureter/hydronephrosis
  - **Hepatic**
    - Abnormal liver function >2 ULN
    - Evidence of DIC
    - Platelets <50 x 10^9/L
  - **Bladder/Bowel dysfunction** secondary to a mass effect.

- **A very large tumour volume causing concern of possible tumour rupture and/or the possible rapid development of systemic upset.**

NOTE: Some of these symptoms will require immediate treatment with chemotherapy. In these cases the definitive biopsy to obtain material for the genomic profile should be delayed until the patient is fit enough to have a biopsy which is likely to be either within 7 days of the chemotherapy administration or just before the second course of chemotherapy is given.

If tumour material for the genomic profile is obtained after the initiation of chemotherapy, the genomic profile will be considered non-informative (no genomic profile result) and the patient will not be eligible for a genomic profile result treatment stratification.
Appendix 5: Management of adrenal masses in infants

Infants diagnosed < 3 months old with localised adrenal masses suspicious of neuroblastoma do not necessarily require biopsy or surgical resection and may be appropriately managed with observation alone. Such patients should have serial ultrasound measurement of the lesion and measurement of urine VMA/HVA and an increase in the size of the lesion or urine VMA/HVA should prompt surgical resection. For young infants/neonates, formal staging investigations (e.g. bone marrow aspirates, mIBG scintigraphy) may be deferred until the age of 3 months provided there is no increase in lesion size or urine VMA/HVA levels.
Appendix 6: Management of spinal cord compression

Diagnosis and evaluation

Early detection of spinal cord compression can be difficult especially in younger children. The most common symptoms are back pain, reduced mobility of the legs and/or arms, sensory and sphincter dysfunction.

The presence of a motor deficit is particularly important since children who develop complete motor loss usually experience little or no recovery. Infants with congenital dumbbell tumours have a particularly poor outcome with regards to neurological recovery.

Evaluation: urgent MRI is mandatory if spinal cord compression is suspected. Myelography and lumbar puncture are of no diagnostic use, and are absolutely contraindicated.

It may be difficult to accurately assess the volume of the intraspinal tumour due to the half-moon configuration it commonly takes in that particular site. Intraspinal tumour extension should be considered as IDRF provided that more than 1/3 of the spinal canal in the axial plane is invaded, and/or the leptomeningeal spaces are not visible, and/or the spinal canal is abnormal.

Treatment of spinal cord compression

Spinal cord compression without symptoms

The regular use of MRI has increased the number of cases with documented infiltration of foramina (with or without invasion of the spinal canal). However, in the majority of cases, especially when the intraspinal component is modest (less than 33% of the diameter), there are no neurological symptoms.

There is very little, if any, evidence that an asymptomatic intraspinal tumour will grow any more after a resection of an extraspinal component. Information related to the few, well-documented cases suggests that the intraspinal neuroblastoma in patients with no neurological symptoms tends to remain stable or even regress without specific treatment.

If the spinal cord component occupies greater than 33% of the spinal canal, and/or the leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal it is recommended to treat these patients with chemotherapy even in the absence of signs or symptoms of spinal cord compression.

Spinal cord compression with neurologic signs

Patients with localised neuroblastoma who present with signs of spinal cord compression require urgent specific treatment. If neurological deficits are present and if there is clinical progression rapid therapeutic decisions must be made in a matter of hours or at most within 1–2 days. The decision regarding whether to administer emergency chemotherapy to these infants with a neurological deficit should be taken after urgent discussions between the oncologist and the neurosurgeon.

6 Adapted from SIOPEN LINES study protocol
Laminectomy or laminotomy is preferable only in infants showing a very rapid neurologic deterioration. This however occurs infrequently.

Once it has been decided that urgent chemotherapy is needed it should never be delayed in order to obtain a pre-chemotherapy biopsy sample. There is no urgent indication to remove the extraspinal tumour (which is likely to be unresectable, and surgery runs the risk of worsening the neurological deficit). The tumour should be biopsied (by Tru-cut, fine needle, or open biopsy), when the patient is stable within 7 days of starting chemotherapy. Initial chemotherapy in this situation should never be postponed in order to try and obtain a biopsy.

**Medical treatment of Spinal Cord Compression is as follows:**

Dexamethasone 0.5 mg/kg I.V. bolus followed by 0.2 mg/kg/day I.V. in 3 divided daily doses.

Chemotherapy is given using VP/Carbo. A second course should be given 21 days after the beginning of the first course. (See Appendix 7 for more details of chemotherapy)

A further MRI scan should be obtained following the first course of chemotherapy. If either no improvement occurs or if deterioration of the neurological signs are observed, and the intraspinal component has shown no response to treatment i.e. has not shrunk in size, laminotomy and an excision of the intraspinal component should be considered.

If the symptoms persist and the tumour remains unresectable on reassessment with MRI after 2 courses of VP/Carbo, then alternative chemotherapy should be given according to the protocol, CADO (see Appendix 7).

Some patients can have persistent neurological signs and symptoms from neurological damage caused at initial presentation of the SCC. If these neurological signs are stable over 2 courses of chemotherapy and the reassessment imaging does NOT show progressive disease it is generally not appropriate to continue on with extra courses of chemotherapy.
Appendix 7: Chemotherapy details

Depending on patient weight, the final drug dose is calculated on:
Body surface area (BSA) for patients weighing > 10 kg or
Weight for patients weighing ≤ 10 kg

For infants weighing below 5 kg, chemotherapy drug doses should be reduced by a further 33%.

Chemotherapy courses should be given at the indicated intervals (see below) provided the absolute neutrophil count (ANC) is >1.0 x10⁹/L and the platelet count (PLT) is >100 x 10⁹/L.

If the count has not recovered from the previous course of chemotherapy, treatment should be delayed for a week, and the count checked again.

Dose modification
If significant infective problems occur (CTCAE Grade 4), consider reducing the doses of myelosuppressive therapy by 20% for subsequent courses.

If an allergic reaction occurs during the administration of Etoposide, appropriate measures should be taken. However, the drug should be tried again with the next course at a slower rate and with steroid premedication.

In the case of marked ptosis or other neurological deficit (other than loss of tendon reflexes), consider reducing or omitting the next vincristine dose. In the case of CADO chemotherapy, the second vincristine of CADO should be postponed by one week.

If there is CTCAE Grade 2 renal toxicity repeat GFR and modify the dose of Carboplatin.
VP/Carbo (Etoposide [VP16] and carboplatin)

Courses of VP/Carbo are given at 21 day intervals

<table>
<thead>
<tr>
<th>DAY</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Etoposide</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Both these drugs are given on days 1-3 of each course.
It is advisable that a central line is inserted for chemotherapy.
In those patients where treatment is given via a peripheral line, great care should be taken to avoid extravasation.
Additional hydration is not required in the absence of vomiting, as long as oral intake is satisfactory.
If this is not the case, then intravenous fluids at "maintenance" rates (depending on the age and weight of the child) should be given for the duration of chemotherapy.

CADO (Cyclophosphamide, doxorubicin and vincristine)

Courses of CADO are given at 21 day intervals

<table>
<thead>
<tr>
<th>DAY</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>X</td>
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<td>X</td>
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A central line is suggested for the administration of doxorubicin.
Appendix 8: Surgical Guidelines

Aims of surgery

- To achieve complete excision of localised neuroblastoma with minimal morbidity.
- To provide sufficient tissue for histological and biological studies by biopsy in those children where resection would be hazardous.
- To remove residual tumour after chemotherapy or natural involution only in those situations where the benefit is likely to outweigh the risk.

Surgical procedures at presentation

At presentation this group of tumours fall into one of three broad categories, which guide the initial surgical approach.

- Tumours suitable for resection at presentation:
  - L1 by INRG definition (localised tumour: IDRF negative)

- Tumours suitable for biopsy only at presentation:
  - L2 by INRG definition (localised tumour: IDRF positive)
  - M and MS tumours by INRG definition (metastatic disease)*

- Tumours suitable for observation only (no resection or biopsy):
  - Adrenal mass in selected infants under 90 days of age at presentation (see Appendix 5 for further details)

*Excision of the primary tumour may be an alternative diagnostic procedure to biopsy in metastatic tumours, provided the primary tumour is IDRF negative.

Since pathological diagnosis, MYCN status and other biological parameters remain central to the management of neuroblastoma, biopsy or resection at presentation is mandatory in all children, except those less than 90 days at presentation with an adrenal mass less than 5 cm in diameter.

Subsequent/secondary surgical procedures

Following chemotherapy or natural involution the criteria for attempting delayed resection are influenced by the age of the child, and also sometimes by the IDRF. The IDRF have been designed to guide surgical management of neuroblastoma at diagnosis, in particular to indicate whether biopsy or attempted resection is recommended as the first surgical procedure.

The same system of risk factors can be applied later during the course of treatment and follow-up, although it is not designed for this purpose. If a tumour remains IDRF positive after chemotherapy this is not an absolute contraindication to surgery. Resection may still be recommended if evaluation of the primary tumour suggests that the risk to life, or of major functional loss, is less than the risk from leaving residual disease.

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7 Extracted from SIOPEN LINES study protocol
• Excision of primary mass should be attempted for:
  o Persistent suprarenal mass in infants under 90 days at presentation, following period of observation, provided the tumour is IDRF negative.
  o Enlarging suprarenal mass in an infant under 90 days of age at presentation, according to the study guidelines, provided the tumour is IDRF negative
  o L2 tumours in children less than 18 months at presentation, where the IDRF have become negative following chemotherapy or natural involution.
  o Ms tumours in children less than 12 months at presentation with segmental chromosomal alteration, provided the tumour is IDRF negative.
  o Metastatic (M) tumour in children under 12 months at presentation (bone, lung, and/or CNS metastases), with no evidence of residual metastatic disease (liver excluded), irrespective of IDRF status.
  o L2 tumours in children over 18 months of age at presentation with a differentiating tumour that has become IDRF negative following chemotherapy.
  o L2 tumours in children over 18 months of age at presentation with undifferentiated or poorly differentiated tumours, irrespective of IDRF status.

• Excision of primary mass should be considered and potentially a surgical second opinion should be obtained for:
  o Persistent or enlarging suprarenal mass in infants under 90 days at presentation, which is IDRF positive at the time when the guidelines suggest that resection should be carried out.
  o L2 tumours in children less than 18 months at time of presentation, with segmental alterations, where the IDRF remain positive after chemotherapy.
  o Ms tumours in children less than 12 months at time of presentation, with segmental alterations, where the IDRF remain positive after chemotherapy.
  o L2 tumours in children over 18 months at presentation with a differentiating tumour which remain IDRF positive.
  o Tumours that remain IDRF positive, and are causing persistent symptoms at the end of the chemotherapy schedule.

Discussion is essential in these cases, because the advantage of excision depends upon careful assessment of risks vs. benefits.

• Excision of primary mass is not recommended for:
  o L2 tumours in children less than 18 months at the time of presentation, where the IDRF remain positive following chemotherapy or natural involution, unless there are segmental alterations.
  o Metastatic (Ms) tumours in children under 12 months at presentation, with no segmental chromosomal alterations irrespective of IDRF status
  o M tumours in children less than 12 months at presentation, who still have metastatic disease at sites other than the liver at the end of the chemotherapy schedule.
Timing of subsequent procedures (where applicable)

- Neonatal suprarenal masses managed on observation protocol
  - Enlarging tumour - excise (or biopsy) immediately
  - Persisting tumour - excise at 1 year of age providing IDRF negative
- Low risk tumours
  - Children receiving chemotherapy - excision of a localised tumour is recommended as soon as the tumour becomes IDRF negative in order to keep the chemotherapy load to a minimum
  - Children managed by observation only - excision is recommended at 1 year from diagnosis provided that IDRF are negative
- Intermediate risk tumours
  - Please refer to guidance on pages 8/9, or discuss with national surgical coordinator

Surgical approach for tumour resection

Abdominal tumours

- For abdominal lesions a transverse laparotomy incision is recommended.
- If necessary this can be extended to a thoracoabdominal approach

Pelvic tumours

- For a pelvic lesions a midline incision may be preferable to Pfannenstiel
- A combined laparotomy and posterior sagittal approach may be required for some low lesions.

Thoracic/cervical tumours

- Large thoracic lesions may require a double thoracotomy at a distance of 2-3 intercostal spaces, using the same soft tissue incision, or a thoracoabdominal approach if just above the diaphragm.
- For lesions in the dome of the thorax, and thoracic inlet, alternative approaches may be considered:
  - A ‘trap-door’ incision including neck, clavicle and sternum.
  - A trans-manubrial approach provides similar surgical access to the ‘trap-door’ incision, with less disruption of bones and muscle.
- In some instances, a combined surgical approach is required which may need more than one operating session. Examples include:
  - approach through cervicotomy and thoracotomy in cervico-mediastinal or upper-mediastinal neuroblastoma
  - bilateral thoracotomy in some cases of mediastinal NB extending beyond the midline (bilateral thoracotomies can be carried out synchronously or with an interval between the procedures)
  - laparotomy combined with a sacrococcygeal/posterior sagittal approach
  - laminotomy associated with thoracic or abdominal operation. Resection of large paravertebral tumours may result in vertebral instability. In these situations consider advice from spine/orthopaedic surgeons. A laparoscopic approach is acceptable provided oncological principles are strictly adhered to.
Lymph Node Evaluation

- To accurately INSS stage a localised tumour it is necessary to ascertain involvement of non-adherent lymph nodes. Therefore, if possible, non-adherent lymph nodes should be sampled during complete resections, even if the lymph nodes appear macroscopically normal. Depending on the site of the primary tumour, lymph nodes from the following regions should be examined and removed if they appear abnormal:
  - Lateral cervical region: jugular chain and supraclavicular area;
  - Chest: mediastinal lymph nodes above and below the tumour;
  - Abdomen: coeliac nodes (infra-diaphragmatic), mid-aortic (at renal level) and iliac region (bilaterally).

Intraspinal Extension

- In patients with no IDRF the extraspinal mass should be removed even though intraspinal disease remains. Macroscopic disease may be left in the intervertebral foramina, especially when there is a risk of leakage of spinal fluid and/or jeopardising the blood supply of the spinal cord.

Intraspinal disease with neurological symptoms

- The urgent need in this situation is relief of pressure on the spinal cord rather than excision of the primary. Operation is not usually the best strategy. See appendix 6.

Nephrectomy

- Nephrectomy does not confer a survival advantage so should be avoided wherever possible, and is not acceptable as part of immediate excision.

Tumour Relation with Great Vessels

- In order to gain further information on the accuracy of the pre-operative imaging, the intra-operative findings should be described in detail. Particular attention should be given to the technical difficulties encountered when the tumour is in contact with the vessels.

Risk factors encountered at operation

- If risk factors are encountered unexpectedly during operation, serious consideration should be given to abandoning the procedure.

Clips

- Titanium or absorbable clips should be used if necessary to avoid interference with subsequent imaging.
References


Hero et al, Localized Infant Neuroblastomas Often Show Spontaneous Regression: Results of the Prospective Trials NB95-S and NB97 J Clin Oncol 2008 Mar; 26(9):1504-10


