高 雄 榮 民 總 醫 院
神經母細胞瘤診療原則

2019年02月26日 第一版

兒童癌症醫療團隊擬訂

注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如你是一個癌症病人，直接引用這個診療原則並不恰當，只有你的醫師才能決定給你最恰當的治療。

修訂指引

- 本共識依下列參考資料制定版本
  - 台灣兒童癌症研究群(TPOG)，TPOG_N2002_neuroblastoma

會議討論

上次會議：2018/02/22

本共識與上一版的差異

上一版	新版
1. 無治療流程圖。	1. 新增治療流程圖。

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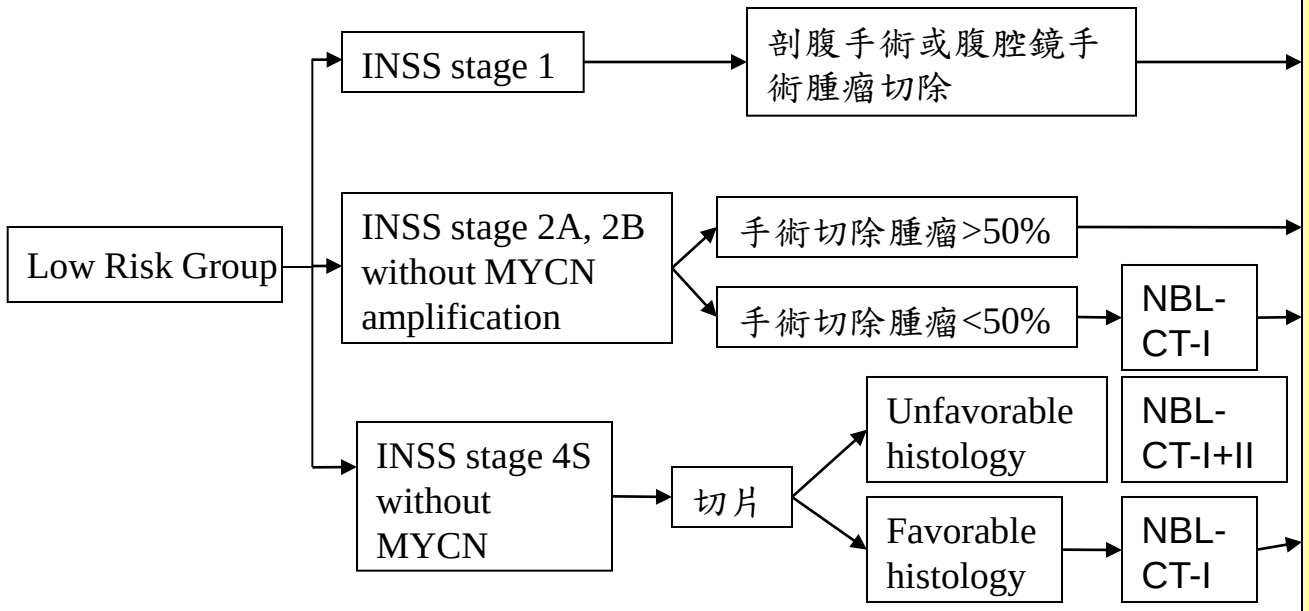
評估	診斷	治療	追蹤

- 病史，理學檢查
- 營養及日常體能狀態
- 身高體重，體表面積計算
- 血液常規
- 電解質及肝腎功能
- 凝血功能
- 腫瘤指標 (LDH, ferritin, 24hrs urine VMA)
- 心臟超音波檢查
- 腹部超音波
- 聽力檢查
- 骨髓抹片/切片檢查*
- 骨頭掃描*
- 胸腹部電腦斷層攝影 (CT)* or 核磁共振檢查(MRI)*(擇一)
- 腫瘤之N-myc檢測(外送國家衛生研究院)*

*與癌症期別相關之主要檢查



※ CBC/DC, original site CT or MRI
Every 3 months for 2 years
Every 6 months for 3-5years then annually
※ Whole body bone scan every 6 months for 5 years then annually
※ VMA (if initial positive)Every 3 months for 2 years
Every 6 months for 3-5years then annually

詳見APPENDIX I: International Neuroblastoma Staging System (INSS)
APPENDIX II: Assignment of Risk Group Protocol

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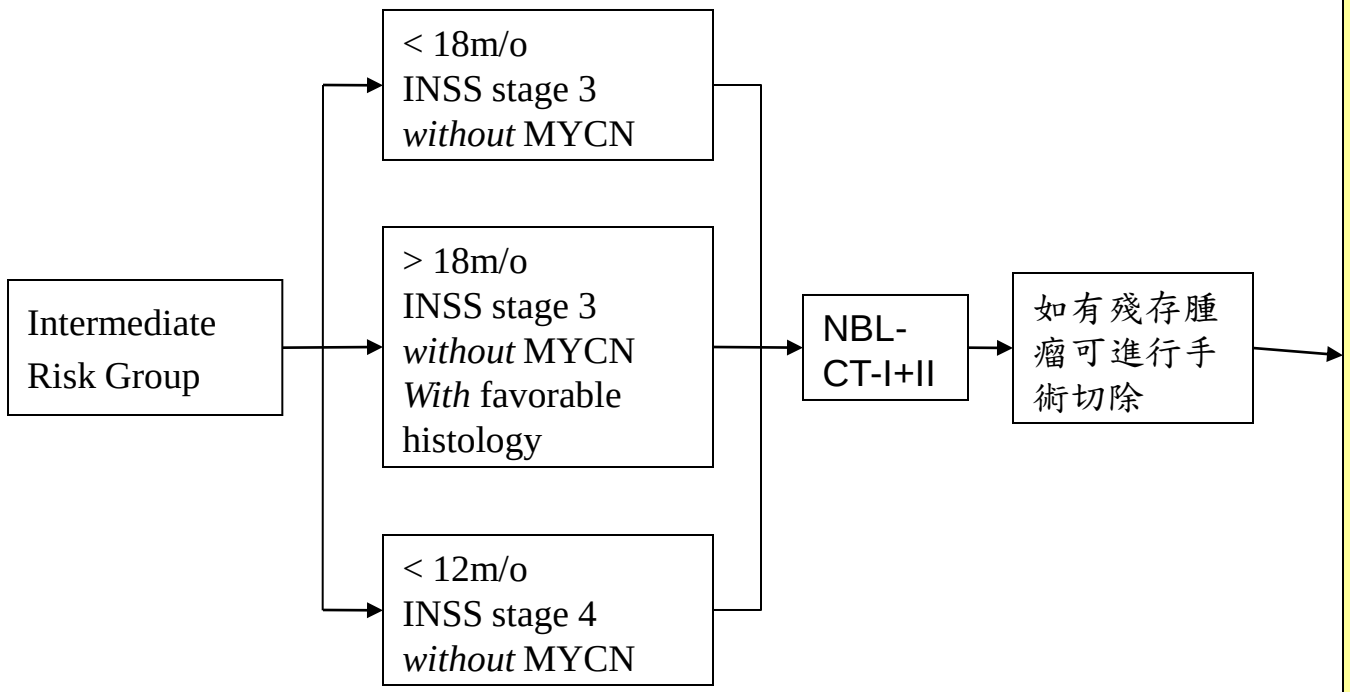

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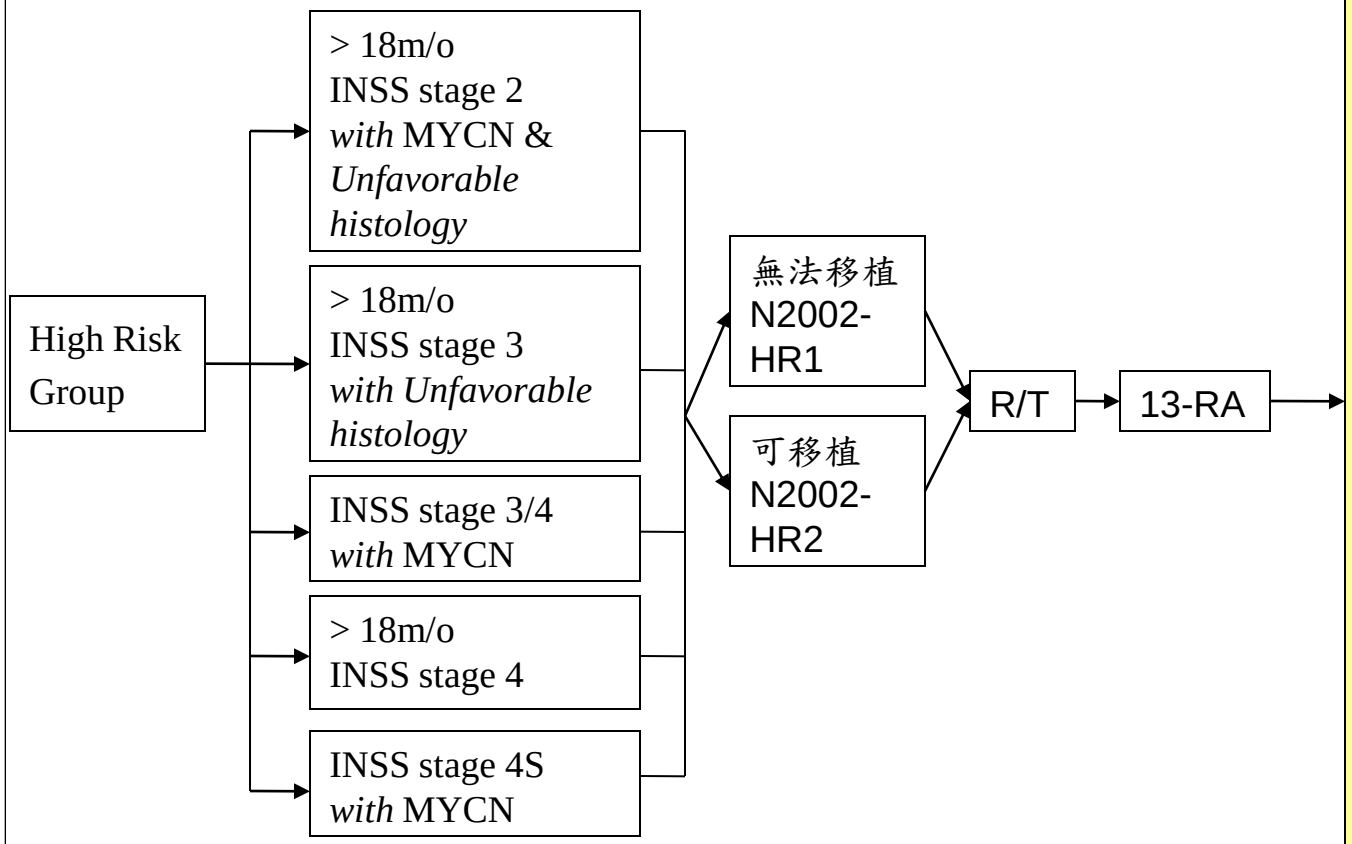

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化學治療處方建議表:NBL-CT-I

Chemotherapy	**Reference**
Cycle 1 **Day 0** Carboplatin 560mg/m^2 (18mg/kg)* for 1 hour Etoposide 120mg/m^2 (4mg/kg)* for 2 hours **Day 1&2** Etoposide 120mg/m^2 (4mg/kg)* for 2 hours	COG A3961 SCHEMA
Cycle 2 **Day 0** Carboplatin 560mg/m^2 (18mg/kg)* for 1 hour Cyclophosphamide 1000mg/m^2 (33mg/kg)* for 1 hour Doxorubicin 30mg/m^2 (1mg/kg)* for 1 hour	

* For children less than 365 days of age or who are ≦ 12kg in weight

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化學治療處方建議表:NBL-CT-I (con.)

Chemotherapy	Reference
Cycle 3 **Day 0** Cyclophosphamide 1000mg/m^2 (33mg/kg)* for 1 hour Etoposide 120mg/m^2 (4mg/kg)* for 2 hours **Day 1&2** Etoposide 120mg/m^2 (4mg/kg)* for 2 hours	COG A3961 SCHEMA
Cycle 4 **Day 0** Carboplatin 560mg/m^2 (18mg/kg)* for 1 hour Etoposide 120mg/m^2 (4mg/kg)* for 2 hours Doxorubicin 30mg/m^2 (1mg/kg)* for 1 hour **Day 1&2** Etoposide 120mg/m^2 (4mg/kg)* for 2 hours	

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化學治療處方建議表:NBL-CT-II

Chemotherapy	Reference
Cycle 5 **Day 0** Cyclophosphamide 1000mg/m^2 (33mg/kg)* for 1 hour Etoposide 120mg/m^2 (4mg/kg)* for 2 hours **Day 1&2** Etoposide 120mg/m^2 (4mg/kg)* for 2 hours	COG A3961 SCHEMA
Cycle 6 **Day 0** Carboplatin 560mg/m^2 (18mg/kg)* for 1 hour Cyclophosphamide 1000mg/m^2 (33mg/kg)* for 1 hour Doxorubicin 30mg/m^2 (1mg/kg)* for 1 hour	

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化學治療處方建議表:NBL-CT-II (con.)

Chemotherapy	Reference
Cycle 7 **Day 0** Carboplatin 560mg/m^2 (18mg/kg)* for 1 hour Etoposide 120mg/m^2 (4mg/kg)* for 2 hours **Day 1&2** Etoposide 120mg/m^2 (4mg/kg)* for 2 hours	COG A3961 SCHEMA
Cycle 8 **Day 0** Cyclophosphamide 1000mg/m^2 (33mg/kg)* for 1 hour Doxorubicin 30mg/m^2 (1mg/kg)* for 1 hour	

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化學治療處方建議表: N2002-HR1 flowchart

Day 1-7 Cy, Day 8 DDP, Day 10 Ep
↓
Day 22-28 Cy, Day 29-31 VP
↓
Day 43-49 Cy, Day 50 DDP, Day 52 Ep
↓
Day 72 DDP, Day 73-75 VP
↓
Day 92-98 Cy, Day 99 DDP, Day 101 Ep
↓
Day 120-126 Cy, Day 127-129 VP
↓
Surgery
↓
After wound healing
Day 1-7 Cy, Day 8 Ep
↓
Day 21 DDP, Day 22-24 VP
↓
Day 41-47 Cy, Day 48 Ep
↓
Day 60 DDP, Day 61-63 VP
↓
R/T 3500 cGy
↓
13-RA

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化學治療處方建議表: N2002-HR1 (con.)

Chemotherapy
Cy **Cyclophosphamide** 150mg/m^2/day IV or PO
DDP **Cisplatin** 90mg/m^2/day IV for 2 hours
Ep **Epirubicin** 35mg/m^2 IVP
VP **Etoposide** 225mg/m^2/day for 2 hours

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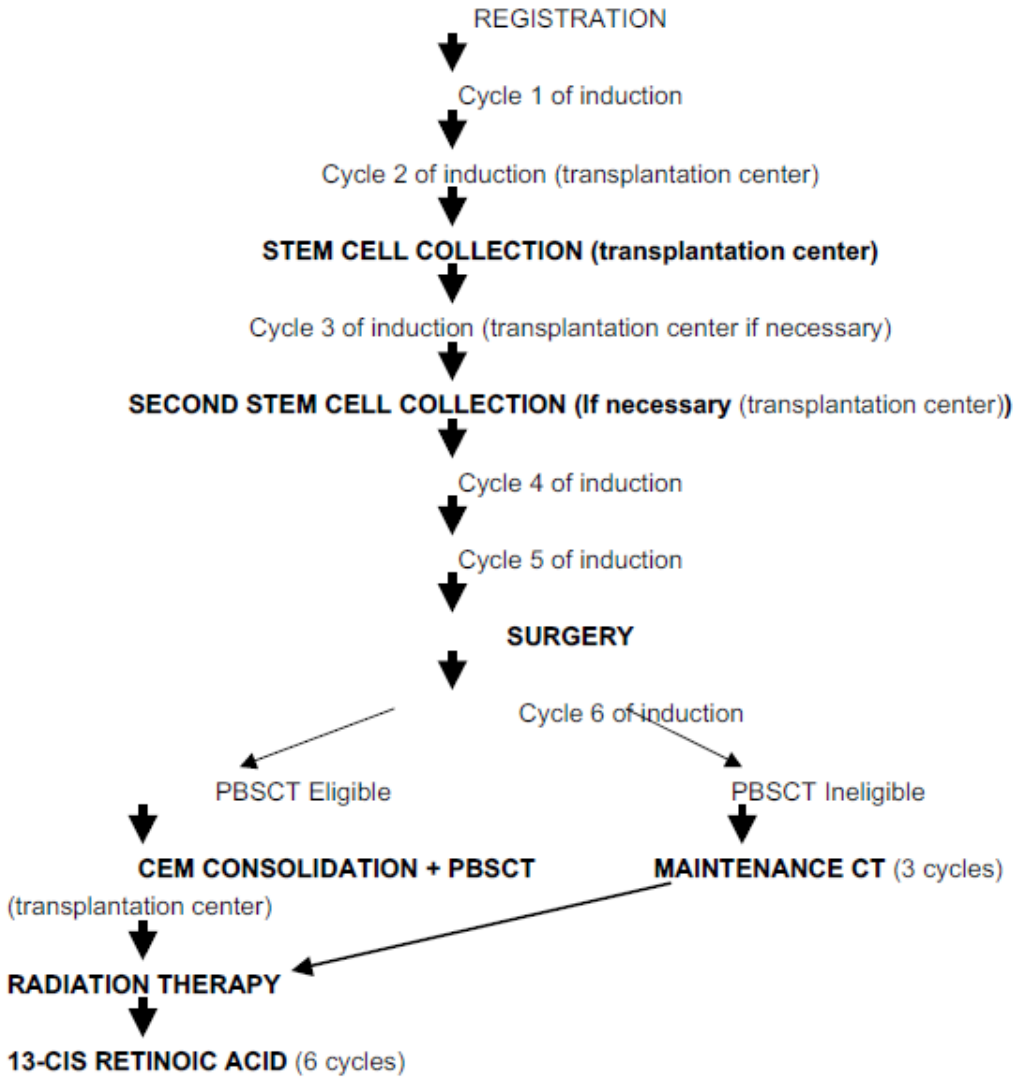
化學治療處方建議表: N2002-HR2 flowchart



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化學治療處方建議表:N2002-HR2 (con.)

Chemotherapy

Cycle 1, 2, 4, 6 of induction: CDV

Day 0&1

Cyclophosphamide 2100mg/m^2 (70mg/kg)* for 6 hours

Oncovin# 0.67mg/m^2 for 24 hours

Adrimycin 25mg/m^2 (0.83mg/kg)* for 24 hours

Day 2

Oncovin# 0.67mg/m^2 for 24 hours

Adrimycin 25mg/m^2 (0.83mg/kg)* for 24 hours

* For children less than 365 days of age or who are ≦ 12kg in weight

0.022mg/kg if < 12kg, 0.017mg/kg if < 12 months

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化學治療處方建議表:N2002-HR2 (con.)

Chemotherapy
Cycle 3, 5 of induction: CiE **Day 0, 1&2** Etoposide 200mg/m^2 (6.67mg/kg)* for 2 hours Cisplatin 50mg/m^2(1.66mg/kg)* for 1 hour **Day 3** Cisplatin 50mg/m^2(1.66mg/kg)* for 1 hour

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化學治療處方建議表:N2002-HR2 (con.)

Chemotherapy

Consolidation

Day -7 to -5

Carboplatin 425mg/m^2 (14.2mg/kg)* for 24 hours

Etoposide 338mg/m^2(11.3mg/kg)* for 24 hours

Melphalan 70mg/m^2(2.3mg/kg)* bolus

Day -4

Carboplatin 425mg/m^2 (14.2mg/kg)* for 24 hours

Etoposide 338mg/m^2(11.3mg/kg)* for 24 hours

Day -3 to -1 Rest

Day 0

Stem cell infusion

13-cis-Retinoic Acid therapy

13-cis-RA 160mg/m^2/day (5.33mg/kg/day)* for BID, for 14 days, followed by 14 days rest per cycle

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化學治療處方建議表:N2002-HR2 (con.)

Chemotherapy with *abnormal renal function*
Carboplatin using modified Calvert formula or 10mg/kg if ≦ 12kg total dose (mg/day) = (CCR x BSA/1.73 + 15 x BSA) x 4.1 **Etoposide** 200mg/m^2(6.7mg/kg)* for 24 hours **Melphalan** 60mg/m^2(2mg/kg)* bolus

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放射治療處方建議表

Indication：

1) Symptomatic NBL-LR patients that have not responded rapidly enough to chemotherapy.
2) Viable residual disease after completion of chemotherapy and“second look” surgery.
3) Recurrent local/regional disease of unfavorable biology who achieved a PR after treatment with NBL-CT-I and NBL-CT-II with or without a subsequent operation.
   (Note) Free of ileus, ANC > 1,000/μL, Hemoglobin > 10 g/dL before RT
4) ***All*** NBL-HR at the end of conventional chemotherapy or >28 days post-HSCT and fulfill the following: (1) APC > 1,000/μl; (2) No requirement for PLT transfusion; (3) Mucositis nearly resolved; (4) ALT < 80 U/L, Bil < 1.5 mg/dl, No VOD (if liver in the field); (5) No respiratory distress on room air (if lung or trachea in the field); (6) Alb > 3 g/dl without albumin infusion for 1 week (if abdominal irradiation); (7) Cre < 1.5 mg/dl (if kidney in the field); (8) No hematuria (if kidney or bladder in the field)

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放射治療處方建議表

Dosage：

1) For NBL-LR children other than stage 4S, total 2,100 cGy (e.g. 150 cGy x 14 fractions).
2) For NBL-IR children other than stage 4S, total 2,400 cGy (e.g. 150 cGy x 16 fractions).
3) For children with stage 4S disease, 150 cGy x 3 fractions for the liver
4) For NBL-HR: total 3,500 cGy for those with conventional therapy and 2,160 cGy (e.g. 180 cGy x 12 fractions) for those with myeloablative therapy over primary site and metastatic sites.

Critical Organs：

1) Peritoneal cavity: < 1,50/0 cGy for contralateral kidney.
2) Thorax: < 1,500 cGy for 2/3 or more of the lung volume.
3) Liver: < 1,500 cGy for 2/3 or more of the liver volume.

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癌症藥物停藥準則

影像學檢查，若腫瘤反應為NR或PD (定義請見APPENDIX III「反應標準」)，應停止或改變治療方式。

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APPENDIX I. International Neuroblastoma Staging System (INSS)

STAGE	Description
Stage 1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).
Stage 2A	Localized tumor with incomplete gross excision; representative ipsilateral non-adherent lymph nodes negative for tumor microscopically.
Stage 2B	Localized tumor with or without complete gross excision, with ipsilateral non-adherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumor infiltrating across the midline[1], with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for Stage 4S).
Stage 4S	Localized primary tumor (as defined for Stage 1, 2A or 2B) with dissemination limited to skin, liver, and/or bone marrow[2] (limited to infants <1 year of age).
Stage X_M	Multiple primary tumors (e.g., bilateral adrenal primary tumors) should be staged according to the greatest extent of disease, as defined above, and followed by a subscript "M" (e.g. 3_M).

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APPENDIX II. Assignment of Risk Group Protocol

Table 1. Assignment of Risk Group Protocol After Biology Study

INSS Stage	Age	MYCN Status	Shimada Histology	TPOG-NBL Assignment
1	0 – 21 y	Any	Any	LR
2A, 2B	< 365 d	Any	Any	LR
	≥ 365 d – 21 y	Non-Amp	Any	LR
	≥ 365 d – 21 y	Amp	Fav	LR
	≥ 365 d – 21 y	Amp	Unfav	HR
3	< 365 d	Non-Amp	Any	IR
	< 365 d	Amp	Any	HR
	≥ 365 d – 21 y	Non-Amp	Fav	IR
	≥ 365 d – 21 y	Non-Amp	Unfav	HR
	≥ 365 d – 21 y	Amp	Any	HR
4	< 365 d	Non-Amp	Any	IR
	< 365 d	Amp	Any	HR
	≥ 365 d – 21 y	Any	Any	HR
4S	< 365 d	Non-Amp	Fav	LR
	< 365 d	Non-Amp	Unfav	IR
	< 365 d	Amp	Any	HR

Table 2. Assignment of Symptomatic Patients Before Biology Study

Age	2A, 2B	3	4	4S
< 365 d	Low	Intermediate	Intermediate	Low
≥ 365 d – 21 y	Low	Intermediate	High	-

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APPENDIX III. International Neuroblastoma Response Criteria反應標準

Response	Criteria
Complete Response (CR)	Total disappearance of tumor, with no evidence of disease; urine catecholamines are normal.
Very Good Partial Response (VGPR)	Primary tumor has decreased by 90-99%, no evidence of metastatic disease; urine catecholamines are normal; residual bone scan changes are allowed.
Partial Response (PR)	> 50% decrease in the size of all measurable lesions; the number of positive bone sites is decreased by > 50%; no more than one positive bone marrow site allowed; if this represents a decrease in the number of positive sites at diagnosis.
Mixed Response (MR)	No new lesions, > 50% reduction of any measurable lesion (primary or metastasis) with < 50% reduction in other lesions and < 25% increase in any lesion.
No Response (NR)	No new lesions, < 50% reduction and < 25% increase in any lesion.
Progressive Disease (PD)	Any new lesion; increase in any measurable lesion by > 25%; previous negative bone marrow positive for tumor.

Reference

1. TPOG_N2002_neuroblastoma., http://www.ccfroc.org.tw/content_sub_page.php?level1ID=12&level2ID=2