EVIDENCE BASED MANAGEMENT FOR Nueroblastoma

Introduction:
Neuroblastoma and related neoplasms arise from those neural crest cells which differentiate in cells of the sympathetic ganglia and adrenal medulla. Neuroblastoma is the most common extracranial solid tumor in children. They account for 7-10% of the childhood cancer. Because neuroblastoma can arise from any site along the sympathetic nervous system chain, the locations of primary tumors at the time of diagnosis are varied and change with age. Metastatic extension of neuroblastoma occurs in lymphatic and hematogenous patterns. Hematogenous spread occurs most frequently to bone marrow, bone, liver and skin. Rare presentation with paraneoplastic syndromes such as opsoclonus myoclonus, Vasointestinal peptide (VIP) associated chronic diarrhea are known. Neuroblastoma represents one of the most challenging malignancies. For treatment decisions because of its unusual biological behavior which includes spontaneous regression at one end to maturation to ganglioneuroma and relentless treatment resistant progression at other end of spectrum. The main achievements in the management of Neuroblastoma during last two decades were the reduction of chemotherapy in-patients with low risk disease and the increased efficacy of chemotherapy in high-risk disease.

Evaluation of patient:
Primary site
X Ray, USG, CTScan/MRI
131I MIBG scan
24 hr-Urinary VMA

Metastatic disease
Bone marrow aspiration & trephine biopsy
Technetium Bone scan
131I MIBG scan

Diagnostic criteria:
Gold standard for the diagnosis of neuroblastoma is examination of tumor tissue by histopathology and immunohistochemistry.

International Neuroblastoma Diagnostic criteria (INDC) has been established for reliable diagnosis.

An unequivocal pathological diagnosis is made from tumor tissue by light microscopy, with or without immunohistology, electron microscopy and or increased urine catecholamines or metabolites (> 3 SD above the mean for age),

Or

Bone marrow aspirate or biopsy containing unequivocal tumor cells, and increased urine catecholamines or metabolites (> 3 SD above the mean for age).

Staging of Neuroblastoma:
Clinical staging as per Evans (CCSG) staging system is done if surgery is not done upfront. International neuroblastoma staging system (INSS) is used when surgical details are available & is one of the most important prognostic factor.
**INSS**

**Stage 1**
Localized tumor confined to the area of origin; complete gross excision with or without microscopic residual disease, identifiable ipsilateral and contralateral lymphnodes negative microscopically.

**Stage 2 A**
Unilateral tumor with incomplete gross excision; identifiable ipsilateral and contralateral lymphnodes negative microscopically.

**Stage 2 B**
Unilateral tumor with complete or incomplete gross excision; with positive ipsilateral lymph nodes, identifiable contralateral negative microscopically.

**Stage 3**
Tumor with metastases to midline with or without the involvement of regional lymph node or unilateral tumor with contralateral regional lymph node involvement or midline tumor with bilateral regional lymphnode involvement.

**Stage 4**
Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver and/or other organs.

**Stage 4-S**
Localised primary tumor as

**EVANS**

**Stage 1**
Tumor limited to origin or structure of origin.

**Stage II**
Tumor with regional spread that does not cross the midline; ipsilateral lymphnode may be involved.

**Stage III**
Regional tumor crossing the midline; bilateral lymph nodes may be involved.

**Stage IV**
Tumor with metastases to distant discontinuous sites such as lymph nodes, bone, bone marrow, organs and soft tissue.

**Stage IV-S**
Localized primary tumor and
Response Criteria

<table>
<thead>
<tr>
<th>Response CR</th>
<th>Primary No</th>
<th>Mets No</th>
<th>Markers No</th>
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<tbody>
<tr>
<td>VGPR</td>
<td>&gt; 90% but &lt; 100%</td>
<td>No (except bone)</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>PR</td>
<td>by 50% - 90%</td>
<td>by 50% - 90% at measurable site, No new lesions.</td>
<td>by 50% - 90%</td>
</tr>
<tr>
<td>NR</td>
<td>-</td>
<td>by &lt;50% at measurable site, No new lesions.</td>
<td>-</td>
</tr>
<tr>
<td>PD</td>
<td>-</td>
<td>New lesions, Previously neg marrow +ve.</td>
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Risk Stratification

Risk stratification depends upon many factors
Age
Stage
Pathology (Pre chemotherapy biopsy or specimen)

Favorable Histology
1. Neuroblastoma (NB) with low or Intermediate MKI in children < 1.5 yr.
2. Differentiating NB with low MKI in children 1.5 - 5 yrs.
3. Ganglioneuroblastoma (GNB) intermixed

Unfavorable Histology
1. All NB with high MKI.
2. NB with intermediate MKI
3. Undifferentiated & Poorly differentiated NB between 1.5 - 5 years.
4. All NB > 5 years.
5. GNB nodular.

Molecular studies (Optional)
1. DNA Index
2. N myc amplification
3. Chromosome 1p deletion

Guidelines for risk adapted therapies and expected outcome
Risk factors | Recommendation | Expected Survival
--- | --- | ---
**Low**
A: All ages St I,2,4S
B: All ages St 1
< 1 yr St 2A, 2B
>1yr2A, 2B Nmyc NA/FH
St.4S Nmyc NA/FH/DI>1

Surgery alone

Surgery + Low dose Chemotherapy for >1yr St 2B Nmyc NA/FH & 4S with life threatening symptoms

70-90%

**Intermediate**
A: All age St 3
<1yr St 4
B: All age St 3 Nmyc NA/FH
< 1 yr St 4 Nmyc NA
St.4S Nmyc NA/FH/DI=1

Surgery + Moderately Intensive Chemotherapy ±Radiotherapy (Conventional and/or 131I MIBG Therapy)

50-75%

**High**
A: >1yr all St 4
B: >1yr St 2B Nmyc A/UH
All age St 3 Nmyc A/UH
> 1 yr. all St 4
St 4S Nmyc A`

**Induction**: Intensive chemotherapy+Local therapy with Surgery ± Radiotherapy (Conventional &/or 131I MIBG Therapy)

**Consolidation**: Myeloablative therapy with stem cell Rescue.

**Minimal Residual disease**: Differentiating agents/Immunotherapy

20-40%

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**Management Algorithm at Tata Memorial Hospital**

![Image of algorithm diagram](image-url)
Surgery
Surgery plays a pivotal role in the management of neuroblastoma, both for diagnosis and for treatment. Patients with tumors that are localized to one side of midline, or crossing the midline without encasement of major blood vessels, are candidates for primary surgical resection. Surgery alone is curative for stage I tumors. The goals of primary surgical procedures, performed before any therapy, are to establish the diagnosis, to provide tissue for biologic studies, to stage the tumor surgically, and to attempt to excise the tumor without injury to vital structures. In delayed primary or second-look surgery, the surgeon determines response to therapy and removes residual disease when possible. The importance of gross total resection in the management of disseminated neuroblastoma remains controversial.

RADIOTHERAPY
Indications:

Low-risk-patients with symptomatic life - or organ-threatening tumor that does not respond rapidly enough to chemotherapy.

Intermediate-risk patients whose tumor has responded incompletely to both chemotherapy and attempted resection and also has unfavorable biologic characteristics.

Radiation therapy to the primary site is recommended for high-risk patients even in cases of complete resection.

As part of preparatory regimen for bone marrow transplant. Palliative radiation therapy to sites of metastatic disease.

Principles of Radiation Therapy:
Target volume:
Clinical target volume (CTV) should include the primary tumor (gross/ microscopic) with adequate margins (no study till date on adequacy of margins). If the regional nodes are involved/ suspected to be involved – the region should also be included in the radiation field.
Routine inclusion of uninvolved next echelon of nodes is not advisable.

The entire vertebral body should be included in the radiotherapy portal to prevent scoliosis.

In 4S disease with liver involvement, it is not necessary to include the entire liver in the radiotherapy port to induce tumor regression. Portals can be modified to spare critical organs.

Recommendation: CTV + 1.5-2 cm margin from the tumor to the block edge.

**Total Dose:**
Neuroblastoma is a moderately sensitive tumor to radiation with a low repair capacity of radiation damage. Mild variability in radiosensitivity could be attributed to variations in oncogene genomic amplification e.g. n-myc amplification.

Data suggest an age-dependent dose response in neuroblastoma. Hypothetically explained by a difference in the proportion of clonogenic tumor cells.

Recommendation:
- **Age < 18 months:** Gross disease: 15Gy (Wide local field) + 10Gy (Boost)  
  Microscopic Disease: 15Gy (Wide local field) + 5Gy (Boost)
- **Age > 19 months:** Gross disease: 20Gy (Wide local field) + 10Gy (Boost)  
  Microscopic Disease: 15Gy (Wide local field) + 10Gy (Boost)

**Chemotherapy**

Chemotherapy plays pivotal role in the management of neuroblastoma. Alkylating agents - cyclophosphamide, cisplatin, doxorubicin, and the epipodophyllotoxins are the cornerstone of multi-agent regimens.

**Risk AdaptedChemotherapy Regimens**

<table>
<thead>
<tr>
<th>Country</th>
<th>Study</th>
<th>Regimen</th>
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<tbody>
<tr>
<td><strong>Low</strong></td>
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</table>
| 1. U.S.A | POG 8104                   | CTX 150 mg/m2/d PO d1-7  
  DOX 35 mg/m2 IV d8  
  Every 3wks x 6cycles |
| 2. Japan | JINCS 9405 for infant      | VCR 1.5 mg/m2 IV d1  
  CTX 300mg/m2 IV d8  
  Every 2wks x 6cycles |
| **Intermediate** |                     |                                              |
| 1. U.S.A NB | 84 (St Jude)            | Course 1, 3, 5:  
  CTX 150 mg/m2/d d1-7  
  CDDP 90 mg/m2 d8  
  DOX 35 mg/m2 d10  
  Course 2, 6:  
  CTX 150 mg/m2/d d1-7 |
VM-26 150 mg/m2/d d8-10
CI
Course 4 : CDDP 90 mg/m2
d1
VM-26 150 mg/m2/d d3-5
CI

2. Spain  N-I-87
Course 1, 3, 5 :
CTX 150 mg/m2/d d1-7
DOX 45 mg/m2 d8
Course 2, 4, 6 :
CDDP 50 mg/m2/d d1, 2,4,5
VM-26 90 mg/m2/d d3 & 6

High
1. U.S.A  N – 7 (MSKCC)
Course 1, 2, 4, 6 :
CTX 70 mg/m2/d 6hr inf. d1-2
DOX 25 mg/m2/d CI d1-3
VCR 0.33 mg/kg/d CI d1-3
VCR 1.5 mg/m2 IV d9
Course 3, 5, 7 :
CDDP 50 mg/m2/d d1-4
VP-16 200 mg/m2/d d1-3

Country  Study  Regimen

High
2. U.S.A.  CCG
2. U.S.A. CCG CDDP 60 mg/m2 6hr inf. d1
DOX 30 mg/m2 d2
VP-16 100 mg/m2/d d2 & 5
CTX 1000 mg/m2/d d3 & 4
Every 4wks x 5 cycles

3. French  NB-87
Course 1, 3 :
CTX 300 mg/m2/d IV d1-5
(CADO) VCR 1.5 mg/m2/d d1&5
DOX 60 mg/m2 d5
Course 2, 4 :
CDDP 40 mg/m2/d d1-5
(CVP) VP-16 100 mg/m2/d d1-5

4. Europe  ENSG
CTX 600 mg/m2 d1
(OPEC) VCR 1.5 mg/m2 d1
CDDP 80 mg/m2 CI d1
VP-16 200 mg/m2 d2
Course 2, 4, 6 :
CTX 600 mg/m2 d1
(OJEC) VCR 1.5 mg/m² d1
VP-16 200 mg/m² d1
Carbo 500 mg/m² d1

5. Japan  JNSG
CTX 1200 mg/m² d1
VCR 1.5 mg/m² d1
Pirarubicin 40 mg/m² d3
CDDP 90 mg/m² d5
A1; A1, A1, A1, A1,
Sx RT, A1 x 6 cycles
CTX 1200 mg/m² d1
Pirarubicin 40 mg/m² d3
VP-16 100 mg/m² d d1-5
CDDP 90 mg/m² d5
A3 : CTX 1200 mg/m² d1
Pirarubicin 40 mg/m² d3
VP-16 100 mg/m² d d1-5
CDDP 25 mg/m² CI d 1-5
New A1; A3, A3, A3, A3,
Sx RT, A3

MIBG T/t

It is considered for curative or palliative intent. It is given in a single sitting at 100-300 mCi dose, every 10 to 12 weeks. It is given as intravenous infusion over 2-3 hours. Certain drugs are to be avoided (labetolol, reserpine, tricyclic antidepressants and sympathomimetics). Lugol’s solution should be administered by mouth 3 times a day one day prior of therapy for thyroid blockade.

ABMT
Pre conditioning with high dose melphalan as below:
Inj. Melphelan 180 mg/m² in 500ml NS over 30 min infusion to start after 3 litres of hydration on day 0
Hyperhydration with 6 litres of IV fluids over 24 hours (3 days before and 3 days after Melphelan)
Inj. Chlorpromazine 10 mg/m² IV before Melphelan
Inj. Metaclopromide 30 mg/m² IV before Melphelan
Inj. Ondansetron 8 mg/m² at 30 min after Melphelan
Inj. Dexamethasone 8 mg/m² at 30 min after Melphelan
Maintenance of acid-base balance

Differentiating Agents
13-Cis retinoic acid is given 160 mg/m²/day into two divided doses orally for 14 days in 28 days cycle, such 6 cycles.

Follow up
After completion of therapy, the patients are re-evaluated and are followed up every three monthly in the first year, every six monthly in the second year and annually thereafter in the Late effect clinic for long term survivors of childhood cancers to monitor growth and development and late effects of therapy.
Suggested Reading:

**Neuroblastoma - Diagnosis, Staging & Pathology**

**Revisions of the international criteria for Neuroblastoma diagnosis, staging, and response to treatment.**
Brodeur GM, Pritchard J, Berthold F et al.

PURPOSE AND METHODS: Based on preliminary experience, there was a need for modifications and clarifications in the International Neuroblastoma Staging System (INSS) and International Neuroblastoma Response Criteria (INRC). In 1988, a proposal was made to establish an internationally accepted staging system for neuroblastoma, as well as consistent criteria for confirming the diagnosis and determining response to therapy (Brodeur GM, et al: J Clin Oncol 6:1874-1881, 1988). A meeting was held to review experience with the INSS and INRC and to revise or clarify the language and intent of the originally proposed criteria. Substantial changes included a redefinition of the midline, restrictions on age and bone marrow involvement for stage 4S, and the recommendation that meta-iodobenzylguanidine (MIBG) scanning be implemented for evaluating the extent of disease. Other modifications and clarifications of the INSS and INRC are presented. In addition, the criteria for the diagnosis of neuroblastoma were modified. Finally, proposals were made for the development of risk groups that incorporate both clinical and biologic features in the prediction of prognosis. The biologic features that were deemed important to evaluate prospectively included serum ferritin, neuron-specific enolase (NSE), and lactic dehydrogenase (LDH); tumor histology; tumor-cell DNA content; assessment of N-myc copy number; assessment of 1p deletion by cytogenetic or molecular methods; and TRK-A expression. RESULTS AND CONCLUSION: Modifications of the INSS and INRC made at this conference are presented. In addition, proposals are made for future modifications in these criteria and for the development of International Neuroblastoma Risk Groups.

**Terminology and morphologic criteria of neuroblastic tumors: recommendations by the International Neuroblastoma Pathology Committee.**
Shimada H, Ambros IM, Dehner LP. et al.

BACKGROUND: As part of the international cooperative effort to develop a complete set of International Neuroblastoma Risk Groups, the International Neuroblastoma Pathology Committee (INPC) initiated activities in 1994 to devise a morphologic classification of neuroblastic tumors (NTs; neuroblastoma, ganglioneuroblastoma, and ganglioneuroma). METHODS: Six member pathologists (H.S., I.M.A., L.P.D., J.H., V.V.J., and B.R.) discussed and defined morphologically based classifications (Shimada classification; risk group and modified risk group proposed by Joshi et al.) on the basis of a review of 227 cases, using various pathologic characteristics of the NTs. The classification-grading system was evaluated for prognostic significance and biologic relevance. RESULTS: The INPC has adopted a prognostic system modeled on one proposed by Shimada et al. It is an age-linked classification dependent on the differentiation grade of the neuroblasts, their cellular turnover index, and the presence or absence of Schwannian stromal development. Based on morphologic
criteria defined in this article, NTs were classified into four categories and their subtypes: 1) neuroblastoma (Schwannian stroma-poor), undifferentiated, poorly differentiated, and differentiating; 2) ganglioneuroblastoma, intermixed (Schwannian stroma-rich); 3) ganglioneuroma (Schwannian stroma-dominant), maturing and mature; and 4) ganglioneuroblastoma, nodular (composite Schwannian stroma-rich/stroma-dominant and stroma-poor). Specific features, such as the mitosis-karyorrhexis index, the mitotic rate, and calcification, were also included to allow the prognostic significance of the classification to be tested. Recommendations are made regarding the surgical materials to use for an optimal pathobiologic assessment and the practical handling of samples. CONCLUSIONS: The current article covers the essentials and important points regarding the histopathologic evaluation of NTs. Using the morphologic criteria described herein, the INPC is proposing the International Neuroblastoma Pathology Classification. It is reported in a companion article in this issue (Cancer 1999; 86:363-71).

Prognostic factors and risk stratification

A systematic review of molecular and biological tumor markers in Neuroblastoma.
Riley RD, Heney D, Jones DR et al.
Clin Cancer Res. 2004 Jan 1; 10 (1 Pt 1): 4-12.

PURPOSE: The aim of this study was to conduct a systematic review, and where possible meta-analyses, of molecular and biological tumor markers described in neuroblastoma, and to establish an evidence-based perspective on their clinical value for the screening, diagnosis, prognosis, and monitoring of patients. Experimental Design: A well-defined, reproducible search strategy was used to identify the relevant literature from 1966 to February 2000. RESULTS: A total of 428 papers studying the use of 195 different tumor markers in neuroblastoma were identified. Small sample sizes, poor statistical reporting, large heterogeneity across studies (e.g., in cutoff levels), and publication bias limited meta-analysis to the area of prognosis only; MYCN, chromosome 1p, DNA index, vanillylmandelic acid:homovanillic acid ratio, CD44, Trk-A, neuron-specific enolase, lactate dehydrogenase, ferritin, and multidrug resistance were all identified as potentially important prognostic tools. CONCLUSIONS: This systematic review forms a knowledge base of the tumor markers studied thus far in neuroblastoma, and has identified some of the most important prognostic markers, which should be considered in future research and treatment strategies. Importantly, the review has also highlighted some general problems across primary tumor marker studies, in particular poor and heterogeneous reporting. These need to be addressed to allow better clinical interpretation and enable more appropriate evidence-based reviews in the future. In particular, collaboration of cancer research groups is needed to enable bigger sample sizes, standardize methods of analysis and reporting, and facilitate the pooling of individual patient data.

Long-term results and risk profiles of patients in five consecutive trials (1979-1997) with stage 4 neuroblastoma over 1 year of age.
Berthold F, Hero B, Kremens B et al.

During the last two decades new diagnostic and therapeutic tools have been utilized to improve the poor survival chances of children with stage 4 neuroblastoma. This
study reviews the risk profiles and the long-term outcome of patients from five consecutive German neuroblastoma trials. A total of 96% of all German patients registered at the German childhood cancer registry with neuroblastoma stage 4 over 1 year of age at diagnosis entered one of the trials during 1979-2001. Eight hundred and twenty-eight consecutive children were analyzed retrospectively. In spite of having significantly improved diagnostic tools like bone marrow superstaging and mIBG scintigraphy the stage 4 incidence did not increase after reaching completeness of the registry (5.4 cases/100,000 children at 1-14 years of age; P=0.52). The distribution of the primary tumors and of metastases was constant over the periods. The amount of bone marrow infiltration did not change with time. The risk factors lactate dehydrogenase, ferritin and MYCN, and the clinical risk groups 4A, 4B, 4C also remained constant over the trials with a few exceptions for NB97. The 5-year event free survival increased from 0.01+-0.01 (NB79) to 0.14+-0.03 (NB85), 0.16+-0.04 (NB82), 0.27+-0.02 (NB90), and 0.33+-0.04 (NB97). The overall survival rates improved similarly from 0.04 (NB79) to 0.44 (NB97). In conclusion, the improved survival was associated with better treatment and not caused by lower risk profiles in stage 4 neuroblastoma patients.

**Neuroblastoma - Surgery**

**Therapeutic significance of surgery in advanced neuroblastoma: a report from the study group of Japan.**

Tsuchida Y, Yokoyama J, Kaneko M et al.


The role of surgery was evaluated in 19 stage III and 102 stage IV neuroblastoma patients, all of whom were treated with intensive induction chemotherapy by the Study Group of Japan between January 1985 and March 1990. For stage III neuroblastoma, surgical intervention at the primary site was performed in 18 of the 19 patients, 9 during and 9 after the first three cycles of A1 regimen, consisting of high-dose cyclophosphamide, vincristine, THP-adriamycin, and cis-platinum. Gross complete resection of primary tumor and regional lymph nodes was feasible in 17 of the 19 patients (89%), and the survival rate for the 17 patients were 79%, 70%, and 70% at 2 years, 3 years, and 4 years, respectively. For stage IV, surgical intervention at the primary site was performed in 92 of the 102 patients (90%): 30 cases during the first 3 cycles of A1 chemotherapy and 62 cases after that, with gross complete resection accomplished in 81 of the 102 patients (79%). The 81 patients with gross complete resection achieved had a better prognosis than those 11 patients with partial resection (P less than .05). Overall survival rate was 62% at 2 years for 27 patients who underwent complete resection after 3 cycles of A1 when resolution of all metastases was obtained, whereas the survival was 52% at 2 years for 31 patients who similarly underwent complete resection but when evidence of persistent metastases was present. Patients in whom the ipsilateral kidney was preserved at surgery had an outcome superior to that of those with associated nephrectomy (P less than .05)

**Neuroblastoma - Radiotherapy**

**A) RADIOTHERAPY TARGET VOLUME**

We have evaluated the role of radiotherapy in providing local control of primary tumors and to palliate metastases from neuroblastoma (NB). Fifty-five children with histologically verified NB were evaluated and treated from 1967 to 1984. In univariate analysis, the actuarial survival of eight children with thoracic primaries (85%) was significantly better than the survival of 39 children with intra-abdominal primaries (35%, p = 0.0287). The survival of 28 children less than or equal to 18 months of age at diagnoses was 73%, whereas 27 children older than 18 months had a survival probability of 10% (p = 0.0001). The survival by Evans stage was: I 100% (2 patients), II 85% (7), III 60% (13), IV 4% (27) and IV-S 100% (6). According to the Pediatric Oncology Group (POG) staging system, the survival was: A 100% (3), B 66% (9), C 66% (9), D 23% (34). A multivariable analysis indicated that the Evans staging system was a more powerful indicator of prognosis than the POG system. The analysis also indicated that Evans stage and patient age were independent determinants of survival. The primary tumor site did not add significant prognostic information beyond these two factors. Children with Stage I disease were treated with surgery alone. Most children with Stages II and III disease were treated with surgery, irradiation, and Cyclophosphamide or Cyclophosphamide plus Vincristine. All seven patients with Stage II disease received post-operative irradiation to the primary tumor and were locally controlled with doses of 4.8 to 26.5 Gy. Eleven of the 13 patients with Stage III disease were irradiated post-operatively. Seven of these 11 patients were locally controlled with doses of 12 to 48.4 Gy. The four Stage III patients with in-field recurrences were older children with large radiotherapy fields and/or low doses administered. The Radiation Therapy Oncology Group pain score system was used to evaluate response of painful bony metastases to irradiation. A response was observed in 65% of the sites irradiated. A response was observed at 67% of the soft tissue seven patients. All patients responded with doses ranging from 5 to 24.4 Gy. Five of the 17 children who survived for more than 5 years following treatment had significant scoliosis or kyphosis secondary to vertebral body abnormalities in irradiated bones. All five children were irradiated at a young age with megavoltage equipment.

**Long-term results of therapy for stage C neuroblastoma.**

Halperin EC.


BACKGROUND: The appropriate therapy for Stage C neuroblastoma (NB) is uncertain. Because of the need for information applicable to the development of new randomized trials, we deemed it appropriate to investigate the patient characteristics, survival, patterns of failure, and complications of therapy in these children. METHODS: Search of the medical records of Duke University Medical Center from 1/1/60 to 3/1/95 disclosed 146 patients with NB, which included 13 Stage C patients. RESULTS: Mean age at diagnosis was 3.6 years. Twelve patients had primary abdominal tumors (92%) and one had a thoracic primary (8%). Twelve (92%) of the patients received chemotherapy including cyclophosphamide. 11 (85%). Adriamycin, 6 (46%), cisplatinum, 4 (30%), and VP 16, 4 (30%). All patients received radiotherapy (RT, mean dose administered 22.6 +/- 8 Gy). With a mean follow-up of 8 years, the 10-year overall survival was 54% and the relapse-free survival was 46%. Four patients relapsed in the primary operative tumor bed and primary RT field, two relapsed in mediastinal or left supraclavicular lymph nodes as
well as distantly following treatment of upper abdominal primaries, and in one the site of relapse is unknown. Long-term complications of therapy included two children who developed secondary malignancies associated with RT, two girls who developed primary ovarian failure, five children with clinically significant kyphosis and scoliosis, and one who suffered postoperative wound dehiscence following RT. CONCLUSIONS: Although this study did not include modern techniques of staging with n-myc amplification and DNA index, the occurrence of next echelon nodal failures gives credence to the continuation of the dialogue concerning the appropriate role of “prophylactic” irradiation to mediastinal and left supraclavicular nodes in locally advanced upper abdominal NB. Documentation of significant long-term ill effects reinforces the need to critically evaluate the indications for RT.

Spinal deformity in children treated for neuroblastoma.
Mayfield JK, Riseborough EJ, Jaffe N et al.

Of seventy-four children who were treated at a mean age of seventeen months for neuroblastoma and survived more than five years, fifty-six (76 per cent) had spinal deformity due either to the disease or to the treatment after a mean follow-up of 12.9 years. Of these fifty-six, 50 per cent had post-radiation scoliosis (mean, 18 degrees; range, 5 to 79 degrees), and 16 per cent had post-radiation kyphosis, most frequently at the thoracolumbar junction (mean, 39 degrees; range, 13 to 61 degrees), at the time of follow-up. Two kyphotic thoracolumbar curve patterns were identified: (1) an angular kyphosis with a short radius of curvature and its apex at the twelfth thoracic and first lumbar vertebrae, and (2) a thoracic kyphosis with a long radius of curvature that extended into the lumbar spine. The post-radiation deformity—both the scoliosis and the kyphosis—progressed with growth, the scoliosis at a rate of 1 degree per year and the kyphosis at a rate of 3 degrees per year. Epidural spread of the neuroblastoma was associated with most of the cases of severe scoliosis and kyphosis. The deformity was due either to the laminectomy or to the paraplegia acting in conjunction with the radiation. Eighteen per cent of 419 children with this malignant disease survived more than five years, and of the survivors, 20 per cent had spinal deformity severe enough to warrant treatment. The factors associated with the development of spinal deformity in patient treated for neuroblastoma were: (1) orthovoltage radiation exceeding 3000 rads, (2) asymmetrical radiation of the spine, (3) thoracolumbar kyphosis, and (4) epidural spread of the tumor.

B) RADIOTHERAPY DOSE
The effect on human neuroblastoma spheroids of fractionated radiation regimes calculated to be equivalent for damage to late responding normal tissues.
Wheldon TE, Berry I, O'Donoghue JA et al.

Multicellular tumour spheroids (MTS) are a useful in vitro model of human cancer. An experiment was designed to assess the likely therapeutic advantage of hyperfractionation—a proposed strategy in radiotherapy. A cell line (NB1-G) derived from human neuroblastoma was grown as MTS. This MTS line is radiosensitive with low capacity for repair of sublethal radiation damage. These properties make NB1-G a suitable line to test the theoretical advantage of hyperfractionation. MTS were irradiated using alternative fractionated regimens, with fraction sizes varying from
0.5 to 4 Gy. In each experiment, the total dose was chosen to make the regimens theoretically isoeffective for damage to late-responding normal tissues (calculated using the linear-quadratic mathematical model with alpha/beta = 3 Gy). The radiation responses of MTS were evaluated using the end-points of regrowth delay and "proportion cured". Regimens using smaller doses per fraction were found to be markedly more effective in causing damage to neuroblastoma MTS, as assessed by either end-point. These experimental findings support the proposal that hyperfractionation should be a therapeutically advantageous strategy in the treatment of tumours whose radiobiological properties are similar to those of the MTS neuroblastoma line NB1-G.

Dose response analysis of pediatric neuroblastoma to megavoltage radiation.

Children with neuroblastoma treated in Salt Lake City from 1966 through 1982 were analyzed in an attempt to develop guidelines for external beam radiation. Particular attention was addressed to time-dose relationships in those patients with residual disease post-resection (Stages II and III). Altogether, 76 patients were analyzed and survival rates were: Stage I–100%; Stage II–84%; Stage III–69.2%; Stage IV–14.3%; Stage IV-S–71.4%.

Survival rates were correspondingly better in younger children and in infants. Indications for postoperative radiation therapy in this population were: unresectable or gross remaining tumor; residual tumor in neural foramina; tumor spill during surgery; positive regional lymph nodes or positive surgical margins. Local control was achieved in a majority of patients undergoing surgery and radiation for limited disease. In children younger than 1 year of age, no local failures were observed at doses above 1200 rad. In children between 1-2 years of age, no local failures were observed with doses as low as 1440 rad. In children older than 3 years, local failures were observed up to 4500 rad.

Hyperfractionated low-dose radiotherapy for high-risk neuroblastoma after intensive chemotherapy and surgery.

PURPOSE : To assess prognostic factors for local control in high-risk neuroblastoma patients treated with hyperfractionated 21-Gy total dose to consolidate remission achieved by dose-intensive chemotherapy and surgery. PATIENTS AND METHODS : Patients with high-risk neuroblastoma in first remission received local radiotherapy (RT) totaling 21 Gy in twice-daily 1.5-Gy fractions. RT to the primary site followed dose-intensive chemotherapy and tumor resection; the target field encompassed the extent of tumor at diagnosis, plus 3-cm margins and regional lymph nodes. RT to distant sites followed radiologic evidence of response. Local failure was correlated with clinical factors (including other consolidative treatments) and biologic findings. RESULTS : Of 99 consecutively irradiated patients followed for a median of 21.1 months from RT, 10 relapsed in or at margins of RT fields at 1 to 27 months (median, 14 months). At 36 months after RT, the probability of primary-site failure was 10.1% +/- 5.3%. No primary-site relapses occurred among the 23 patients whose tumors were excised at diagnosis, but there were three such relapses among the seven patients who were irradiated with evidence of residual disease in the
primary site. Four of 18 patients with MYCN-amplified disease and serum lactate dehydrogenase greater than 1,500 U/L had local failures (23.4% +/- 10.7% risk at 18 months). Acute radiotoxicities were insignificant, but three of 35 patients followed for > or = 36 months had short stature from decreased growth of irradiated vertebra. CONCLUSION: Hyperfractionated 21-Gy RT is well tolerated and, together with dose-intensive chemotherapy and surgery, may help in local control of high-risk neuroblastoma. Extending the RT field to definitively encompass regional nodal groups may improve results. Visible residual disease may warrant higher RT dosing. Patients with biologically unfavorable disease may be at increased risk for local failure. RT to the primary site may not be necessary when tumors are excised at diagnosis.

The Changing Role of Radiation Therapy in the Treatment of Neuroblastoma.
Marcus KC, Tarbell NJ.

Neuroblastoma (NBL) is the fourth most common pediatric malignancy. With a median age at diagnosis of 2 years, it represents half of all malignancies that present in the first month of life and one third of those that are diagnosed in the first year of life. NBL is unique among human cancers in its ability to undergo spontaneous differentiation and permanent tumor regression. This phenomenon is particularly characteristic of disseminated disease with liver, skin, and limited bone marrow involvement and involving a limited primary and presenting in children under 1 year of age. Advances in the understanding of the biologic behavior of NBL coupled with the clinical presentation have led to a risk-based approach to treatment, minimizing the treatment to some patients and supporting the need for more aggressive treatment to others. A new international staging system has been adopted that has allowed better comparisons among treatment reports from varying centers and cooperative groups. This article reviews the risk-related approach to the treatment of NBL and the changing role of radiation therapy.

Dose response analysis of pediatric neuroblastoma to megavoltage radiation.
Jacobson GM, Sause WT, O'Brien RT.

Children with neuroblastoma treated in Salt Lake City from 1966 through 1982 were analyzed in an attempt to develop guidelines for external beam radiation. Particular attention was addressed to time-dose relationships in those patients with residual disease post-resection (Stages II and III). Altogether, 76 patients were analyzed and survival rates were: Stage I–100%; Stage II–84%; Stage III–69.2%; Stage IV–14.3%; Stage IVS–71.4%. Survival rates were correspondingly better in younger children and in infants. Indications for postoperative radiation therapy in this population were: unresectable or gross remaining tumor; residual tumor in neural foramina; tumor spill during surgery; positive regional lymph nodes or positive surgical margins. Local control was achieved in a majority of patients undergoing surgery and radiation for limited disease. In children younger than 1 year of age, no local failures were observed at doses above 1200 rad. In children between 1-2 years of age, no local failures were observed with doses as low as 1440 rad. In children older than 3 years, local failures were observed up to 4500 rad.

Neuroblastoma: the Joint Center for Radiation Therapy/Dana-Farber Cancer
Institute/Children’s Hospital experience.
Rosen EM, Cassady JR, Frantz CN et al.

The treatment results for 118 patients with neuroblastoma seen at the Joint Center for Radiation Therapy/Dana-Farber Cancer Institute/Children’s Hospital from 1970 to 1980 were analyzed. Patients were treated with a combination of surgery, radiation therapy, and chemotherapy depending on stage and age. Disease-free survival was excellent in all patient groups except those over one year of age with stage IV disease, a group for which currently available therapy cures only a small proportion of patients. Patients with stage III disease and older patients with stage II disease did extremely well (survival of 81% and 89%, respectively) and may have benefited from intensive treatment with all three modalities. Survival for infants (under one year) with stage IV neuroblastoma (90%) has clearly improved with intensive combination chemotherapy. With combination approaches and newer, more effective systemic regimens, a real impact on survival appears to have been made in the last decade. Better approaches will be necessary to cure more than an occasional older patient with stage IV disease.

C) RADIOThERAPY WITH BONE MARROW TRANSPLANTATION (BMT)

Patterns of failure following total body irradiation and bone marrow transplantation with or without a radiotherapy boost for advanced neuroblastoma.
Sibley GS, Mundt AJ, Goldman S et al.

PURPOSE: To evaluate the patterns of failure and outcome of patients undergoing high-dose chemotherapy, total body irradiation (TBI), and bone marrow transplantation (BMT) for advanced/relapsed pediatric neuroblastoma, with emphasis on the impact of a radiotherapy boost to primary and metastatic sites. METHODS AND MATERIALS: Between May 1986 and June 1993, 26 patients with advanced neuroblastoma underwent high-dose chemotherapy and TBI followed by BMT at our institution. The majority of patients were over the age of 2 years (73%) and were Stage IV at diagnosis (81%). Multiple metastatic sites were involved including bone (17), bone marrow (15), distant nodes (11), liver (5), lung (4) and brain (1). Twenty patients (77%) received cyclophosphamide (50 mg/kg x 4 days) and TBI as consolidation therapy. TBI was delivered to a total dose of 12 Gy given in 2 Gy twice daily (b.i.d.) fractions over the 3 days preceding bone marrow infusion. A local radiotherapy boost of 8-24 Gy was given to 13 out of 26 patients (50%) to the primary and/or metastatic sites immediately prior to or following induction chemotherapy according to physician judgement. Sites not amenable to a radiotherapy boost included the bone marrow, diffuse/bilateral lung involvement, and multiple bone metastases (> four sites). RESULTS: The actuarial overall survival of the 26 patients was 40.4% at 3 and 5 years, with a progression-free survival at 5 years of 38.5%. Six patients died of transplant-related toxicity (23%). The use of cyclophosphamide as high-dose consolidation chemotherapy was significantly better than other multidrug regimens used in terms of overall survival (p<0.0001) and progression-free survival (p=0.0004). The presence of liver involvement prior to BMT was a significant adverse prognostic factor by multivariate analysis. Of the 20 patients surviving the transplant, 10 (50%) underwent a local radiotherapy boost. The patterns of failure were as follows: 3 out of 10 “boost”
patients failed overall, none in previous (old) sites of disease only, 1 in new sites only, and 2 in old and new sites; 6 out of 10 “no boost” patients failed overall, 4 in old sites only, none in new sites only, and 2 in old and new sites. There was a trend toward improved 5-year progression-free survival in patients surviving the transplant that received a boost (68% vs. 33%, p = 0.24). A failure analysis was also performed for each of the 59 initially involved sites, of which the majority (64%) were amenable to a radiotherapy boost. Overall, there is a trend toward less failure in sites amenable to a radiotherapy boost that were irradiated (1 out of 10) vs. those not irradiated (6 out of 28). Failure in the liver occurred in three out of four of the patients with liver involvement that did not receive boost radiotherapy, whereas all seven patients with distant nodal involvement were controlled without a boost. Long-term sequelae include learning difficulties (2), cataract formation (1), and hearing loss (2). Sequelae attributable to a radiotherapy boost occurred in only one patient who received whole brain radiotherapy and developed a cataract and learning difficulties. CONCLUSION: We have found an actuarial 5-year survival rate of 40.4% for patients with advanced neuroblastoma treated with BMT, which compares favorably with results of other published series. Disease recurrence following BMT was most common in previous sites of disease. The majority (64%) of these sites were amenable to a radiotherapy boost. An analysis of failure suggests that a low-dose radiotherapy boost improves control of these sites.

Treatment of advanced neuroblastoma with supralethal chemotherapy, radiation, and allogeneic or autologous marrow reconstitution.
August CS, Serota FT, Koch PA et al.

Ten children with recurrent metastatic (stage IV) neuroblastoma received local radiation therapy, supralethal chemotherapy, and total-body irradiation. Rescue with infusions of either allogeneic (four patients) or autologous (six patients) bone marrow followed. The drugs given to the first two patients were individualized combinations based on previous tumor responses. Both patients died with recurrent tumor three and nine months posttransplant. The eight remaining patients were treated more uniformly with local irradiation, VM-26, doxorubicin, melphalan (L-phenylalanine mustard), and 1,000-rad total-body irradiation in three fractions. Two of these patients had cardiac dysfunction and received no doxorubicin. Three children died in the immediate posttransplant period with disseminated fungal infections. A fourth relapsed and died nine months posttransplant. As of December 1, 1983, two children who received allogeneic marrow grafts have survived in complete remission for 54 and 36 months, and two children who received autologous marrow grafts have survived in complete remission for 35 and 22 months. These results suggest that relapsed metastatic neuroblastoma can be controlled by supralethal combinations of chemotherapy and irradiation coupled with bone-marrow rescue.

Neuroblastoma - Chemotherapy

Low Risk

Infants with neuroblastoma and regional lymph node metastases have a favorable outlook after limited postoperative chemotherapy: a Pediatric Oncology Group study.
RP Castleberry, JJ Shuster, G Altshuler et al.
Journal of Clinical Oncology, Vol. 10, 1299-1304

PURPOSE: Infants less than or equal to 1 year of age with neuroblastoma (NB) have a favorable outlook with minimal to moderate therapy. Patients with complete or partial removal of the primary tumor but positive intracavitary lymph nodes (Pediatric Oncology Group [POG] stage C) have a higher risk for recurrent disease. To determine the importance of distinguishing infants with POG stage C NB from those with POG stage B disease and to assess the efficacy and toxicity of treating POG stage C infants with limited, postoperative chemotherapy, a study was conducted by the POG. PATIENTS AND METHODS: Forty-four eligible POG stage C infants received cyclophosphamide 150 mg/m² orally on days 1 to 7 and Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH) 35 mg/m² intravenously (IV) on day 8 (CYC/ADR), every 3 weeks for five courses followed by second-look surgery. No continuation therapy was given if surgical and pathologic complete response (CR) was achieved. Secondary therapy with five courses of cisplatin 90 mg/m² on day 1 followed by teniposide (VM-26) 100 mg/m² on day 3 (CDP/VM) was given to infants with gross residual tumor after CYC/ADR and second-look surgery. RESULTS: Thirty-four infants achieved CR after CYC/ADR alone, three after CYC/ADR and second-look surgery, two after CYC/ADR, surgery, and maintenance therapy, and two after alternative treatment with CDP/VM (total CR rate, 42 of 44). The 3-year survival and disease-free survival are both 93%. Toxicity was nominal. CONCLUSIONS: Infants with POG stage C NB have a favorable outlook, which is similar to infants with POG stage B NB; the surgical staging procedure for distinguishing these infant subsets may not be necessary. Future studies should focus on the reduction of treatment toxicity and efficacy maintenance, and address methods to identify infants at risk for failure.

Intermediate Risk

Impact of intensified therapy on clinical outcome in infants and children with neuroblastoma: the St Jude Children’s Research Hospital experience, 1962 to 1988
LC Bowman, ML Hancock, VM Santana et al.
Journal of Clinical Oncology, Vol 9, 1599-1608

To gauge the impact of intensified therapy on the survival of infants (younger than 1 year, n=129) and children (greater than or equal to 1 year of age, n=275) with neuroblastoma, we analyzed the results of eight successive clinical trials comparing various combinations of antineoplastic drugs, surgery, and radiotherapy. Changes in treatment did not affect the survival of children with involved noncontiguous lymph nodes or distant metastatic disease until the combination of cisplatin and teniposide (CDDP/VM26) was added to a basic regimen of cyclophosphamide and doxorubicin (CTX/DOX). The resulting 4-year survival was 28% +/- 5% (SE) compared with 7% +/- 2% for previous treatments (P less than .001 by the log-rank test). The 4-year survival of infants with metastatic disease was improved by administering CTX/DOX to all patients, reserving CDDP/VM26 for those whose disease was resistant to the former combination: 82% +/- 6% versus 45% +/- 8% in earlier studies; P less than .001. In the subset of infants whose tumors had disseminated to bone or bone marrow at diagnosis, this therapeutic approach increased the probability of long-term survival from 48% +/- 10% to 85% +/- 9% (P=.01). The small group of children over 1 year of age with localized unresectable tumors also fared significantly better with the switch to CTX/DOX chemotherapy (4-year survival, 93% +/- 7% v
42% +/- 13%; P=.02). Multivariate analysis indicated that young age, limited-disease stage, nonadrenal primary site, and intensified treatment were independent predictors of a more favorable outcome. We conclude that substantial advances in the treatment of neuroblastoma have occurred over the past 25 years at this institution. The current overall 4-year survival probability of 57% +/- 4% compares favorably with estimates for most other common solid tumors of childhood.

Treatment of stage III neuroblastoma with emphasis on intensive induction chemotherapy: a report from the Neuroblastoma Group of the Spanish Society of Pediatric Oncology.
Castel V, Badal MD, Bezanilla JL et al.

From October 87 to April 92, 172 children were admitted in the N-I-87 protocol of the Spanish Society of Pediatric Oncology for the diagnosis and treatment of neuroblastoma. Forty-eight were considered Evans stage III, 33 of them being older than 1 year. All children were treated with induction chemotherapy (IC) and surgery. IC consisted of three courses of high-dose cisplatin-VM-26 alternating with three further courses of cyclophosphamide-doxorubicin (CAD). Infants less than 1 year received the same drugs at lower doses. After surgery, maintenance chemotherapy was administered to all children during 14 months. It consisted of four pairs of drugs rotated every 4 weeks. Radiotherapy was administered exclusively to patients older than 1 year with residual tumor after IC and surgery. Response was evaluated after IC and surgery. In children older than 1 year, response was obtained in 28/33 (88%). Fifteen of them (47%) achieved complete remission (CR), seven (22%) good partial response (GPR), six (19%) partial response (PR); and in three patients (9%) there was progressive disease (PD). Actuarial survival at 48 months was 0.60 +/- 0.10 and EFS was 0.61 +/- 0.12. Audiologic impairment was considered the worst toxicity. In children less than 1 year the response rate to IC and surgery was 93% (14/15); nine infants obtained complete response and four had GPR. Only one patient experienced PD in the first 6 months of therapy and died. The other 14 are alive and well at a mean follow-up time of 48 months. Chemotherapy toxicity was mild and reversible.

High Risk
N7: a novel multi-modal therapy of high-risk neuroblastoma (NB) in children diagnosed over 1 year of age.
Cheung NK, Kushner BH, LaQuaglia M et al.

BACKGROUND: The N7 protocol for poor-risk neuroblastoma uses dose-intensive chemotherapy (as in N6 protocol [Kushner et al.: J Clin Oncol 12:2607-2613, 1994] but with lower dosing of vincristine) for induction, surgical resection and 2100 cGy hyperfractionated radiotherapy for local control, and for consolidation, targeted radioimmunotherapy with 131I-labeled anti-GD2 3F8 monoclonal antibody and immunotherapy with unlabeled/unmodified 3F8 (400 mg/m2). PROCEDURE: The chemotherapy consists of: cyclophosphamide 70 mg/kg/d x 2 and a 72-hr infusion of doxorubicin 75 mg/m2 plus vincristine 2 mg/m2, for courses 1, 2, 4, and 6; and cisplatin 50 mg/m2/d x 4 and etoposide 200 mg/m2/d x 3, for courses 3, 5, and 7. 131I-3F8 is dosed at 20 mCi/kg, which is myeloablative and therefore necessitates stem-cell support. RESULTS: Of the first 24 consecutive previously untreated patients more than 1 year old at diagnosis, 22 were stage 4 and two were
unresectable stage 3 with MYCN amplification. Chemotherapy achieved CR/VGPR in 21 of 24 patients. Twenty patients to date have completed treatment with 131I-3F8, and 15 patients have completed all treatment. With a median follow-up of 19 months, 18 of 24 patients remain progression-free. CONCLUSIONS : Major toxicities were grade 4 myelosuppression and mucositis during chemotherapy, and self-limited pain and urticaria during antibody treatment. Late effects include hearing deficits and hypothyroidism.

Treatment of High-Risk Neuroblastoma with Intensive Chemotherapy, Radiotherapy, Autologous Bone Marrow Transplantation, and 13-cis-Retinoic Acid
Katherine K. Matthay, Judith G. Villablanca, Robert C. Seeger et al.
NEJM, Volume 341:1165-1173 October 14, 1999 Number 16.

Background : Children with high-risk neuroblastoma have a poor outcome. In this study, we assessed whether myeloablative therapy in conjunction with transplantation of autologous bone marrow improved event-free survival as compared with chemotherapy alone, and whether subsequent treatment with 13-cis-retinoic acid (isotretinoin) further improves event-free survival. Methods : All patients were treated with the same initial regimen of chemotherapy, and those without disease progression were then randomly assigned to receive continued treatment with myeloablative chemotherapy, total-body irradiation, and transplantation of autologous bone marrow purged of neuroblastoma cells or to receive three cycles of intensive chemotherapy alone. All patients who completed cytotoxic therapy without disease progression were then randomly assigned to receive no further therapy or treatment with 13-cis-retinoic acid for six months. Results : The mean (±SE) event-free survival rate three years after the first randomization was significantly better among the 189 patients who were assigned to undergo transplantation than among the 190 patients assigned to receive continuation chemotherapy (34±4 percent vs. 22±4 percent, P=0.034). The event-free survival rate three years after the second randomization was significantly better among the 130 patients who were assigned to receive 13-cis-retinoic acid than among the 128 patients assigned to receive no further therapy (46±6 percent vs. 29±5 percent, P=0.027). Conclusion : Treatment with myeloablative therapy and autologous bone marrow transplantation improved event-free survival among children with high-risk neuroblastoma. In addition, treatment with 13-cis-retinoic acid was beneficial for patients without progressive disease when it was administered after chemotherapy or transplantation.

NB87 induction protocol for stage 4 neuroblastoma in children over 1 year of age: a report from the French Society of Pediatric Oncology
C Coze, O Hartmann, J Michon et al.

PURPOSE : NB87 was designed to test the efficacy of a short, non cross- resistant, induction protocol for unselected patients over 1 year of age with stage 4 neuroblastoma. A secondary objective was to compare in a randomized study the toxicity of two modalities of cisplatin administration. PATIENTS AND METHODS : A total of 183 patients received two cycles of alternating sequences: cyclophosphamide 300 mg/m2/d on days 1 to 5, vincristine 1.5 mg/m2/d on days 1 and 5, and doxorubicin 60 mg/m2/d on day 5 (CADO); and cisplatin 40 mg/m2/d and etoposide 100 mg/m2/d on days 1 to 5 (CVP), followed by surgery of the primary tumor (126
patients). Ninety-one were randomized to receive cisplatin either as bolus (BO; n=48) or continuous infusion (CI; n=43). International Neuroblastoma Staging System (INSS) and Response Criteria (INRC) were used with emphasis on skeletal evaluation by meta-iodobenzylguanidine (MIBG). RESULTS: Hematotoxicity was predominant, with a higher incidence of neutropenia (P=.01) for CADO and of thrombocytopenia for CVP (P<.001). Severe infections, as well as nonhematologic toxicities, occurred more often after the first sequence. Gastrointestinal complications were predominant during both courses of CVP. The toxic death rate, including surgery, was 3%. Complete remissions (CRs) were less frequent on MIBG (45%) compared with marrow (66%) or other metastases (61%). Combining all metastatic sites resulted in a 39% CR rate. After surgery, the final CR rate was 42%. Nephrotoxicity was minimal in both arms (92% normal clearance for CI v 82% for BO). Hearing loss greater than 40 dB at 6,000 to 8,000 Hz was reported equally in both arms (n=6 for CI v n=5 for BO). CONCLUSION: Intensified chemotherapy using CADO/CVP increases CR rates despite a shorter induction duration. However, the rate of MIBG normalization remains unsatisfactory and could be raised through the dose-intensive use of agents such as cyclophosphamide.

**OPEC/OJEC for stage 4 Neuroblastoma in children over 1 year of age.**
Tweddle DA, Pinkerton CR, Lewis IJ et al.

BACKGROUND: This paper reports the toxicity of OPEC/OJEC chemotherapy in stage 4 neuroblastoma patients over 1 year of age. PROCEDURE: Ninety-five patients with stage 4 neuroblastoma received alternating courses of OPEC/OJEC – vincristine 1.5 mg/m2 (O), cisplatin 80 mg/m2 (P), etoposide 200 mg/m2 (E), cyclophosphamide 600 mg/m2 (C), and carboplatin 500 mg/m2 (J), every 21 days if there was haematological recovery. RESULTS: Seventy out of ninety-five (74%) patients completed seven or more courses and were evaluable for toxicity. Of these 70 patients, 33% had more than three episodes of fever and sepsis, 35% required more than five blood or platelet transfusions, 36% had grade 2 or more gastrointestinal toxicity and 9% had neurotoxicity. There was a median reduction in GFR of 32 ml/min/1.73 m2 (-46 to 134) and there was one toxic death. CONCLUSIONS:

**OPEC/OJEC is a well-tolerated therapy for stage 4 neuroblastoma over 1 year of age. stage 4 neuroblastoma with MYCN amplification.**
Kaneko M, Tsuchida Y, Mugishima H et al.

PURPOSE: Patients with high-risk neuroblastoma who have multiple copies of MYCN fare much worse than do those without MYCN amplification; however, it has not been clarified whether intensified chemotherapy with or without blood stem cell transplantation can alter the extremely poor prognosis of patients with amplified MYCN. METHODS AND RESULTS: Between 1985 and 1999, 301 patients older than age 12 months with stage 4 neuroblastoma were treated. From January 1985 to February 1991, 80 patients with stage 4 neuroblastoma with and without MYCN amplification uniformly received induction chemotherapy with regimen A(1) (cyclophosphamide 1,200 mg/m2 and vincristine 1.5 mg/m2 on day 1, tetrahydropyranyl [THP]-Adriamycin 40 mg/m2 on day 3, and cisplatin 90 mg/m2 on day 5). Among 22 patients with MYCN amplification, nine (40.9%) achieved a complete remission and seven (31.8%) underwent stem cell transplantation. Of 58 patients without MYCN amplification, 43 (74.1%) achieved a complete remission and
14 (24.1%) underwent stem cell transplantation. The 5-year relapse-free survival rates were 23.2% for stage 4 patients with MYCN amplification and 33.3% for those without MYCN amplification (P=0.029); the 5-year overall survival rates were 32.8% for stage 4 patients with MYCN amplification and 42.8% for those without MYCN amplification (P>0.05). From March 1991 to June 1998, patients with stage 4 neuroblastoma who had 10 or more copies of MYCN were treated with regimen A(3) (cyclophosphamide 1,200 mg/m(2) per day on days 1 and 2, THP-Adriamycin 40 mg/m(2) on day 3, etoposide 100 mg/m(2) per day on days 1 to 5, and cisplatin 25 mg/m(2) per day on days 1 to 5); those with fewer than 10 copies of MYCN received regimen new A (cyclophosphamide 1,200 mg/m on day 1, THP-Adriamycin 40 mg/m on day 3, etoposide 100 mg/m per day on days 1 to 5, and cisplatin 90 mg/m on day 5), which is similar in intensity to regimen A. Among 88 patients with MYCN amplification, 63 (71.6%) achieved a complete remission and 63 (71.6%) underwent stem cell transplantation. Of 133 patients without MYCN amplification, 93 (69.9%) achieved a complete remission and 71 (53.4%) underwent stem cell transplantation. The 5-year relapse-free survival rates were 36.0% for stage 4 patients with MYCN amplification and 32.2% for those without MYCN amplification (P>0.05), the 5-year overall survival rates were 34.0% for stage 4 patients with MYCN amplification and 38.9% for those without MYCN amplification (P>0.05). The difference in relapse-free survival rates was significantly different (P=0.003) between patients with MYCN-amplified tumor treated before [regimen A(1)] versus after 1991 [regimen A(3)].

CONCLUSIONS : With the use of the more intensive induction regimen A plus blood stem cell transplantation for MYCN-amplified patients, survival curves for those with or without MYCN amplification now appear similar. Higher doses of chemotherapy may ameliorate the effect of MYCN amplification in patients with high-risk neuroblastoma.

**Induction chemotherapy in metastatic neuroblastoma—does dose influence response? A critical review of published data standards, options and recommendations (SOR) project of the National Federation of French Cancer Centres (FNCLCC).**


The purpose of this study was to determine, from a review of published data, whether in stage 4 neuroblastoma in children over 1 year of age, the dose or scheduling of induction chemotherapy influenced the response rate in distant metastases. Publications relating to induction chemotherapy since the introduction of cisplatin/epipodophyllotoxin combinations were identified using Medline, Current Contents and personal reference lists. Thirteen publications were identified which described 17 regimens involving 948 children. The doses and the scheduling of the various regimens were compared with a standard regimen OPEC (vincristine, cisplatin, teniposide, cyclophosphamide). These were correlated with the reported response rates in the bone marrow. Due to a lack of standardisation in the nature of restaging investigations, timing of restaging and definitions of response it was difficult to compare all studies. The complete response rate at distant metastases ranged from less than 40% to over 90%. For individual drugs; the comparative doses given in each course ranged up to 4.2 g/m(2) for cyclophosphamide, 280 mg/m(2) for cisplatin, 600 mg/m(2) for etoposide and 4.5 mg/m(2) for vincristine. There was no evidence of any positive correlation between response rate in the marrow and either the dose of any individual drug or the schedule used. In contrast to a previous study which included a number of older studies where disease
assessments was even more variable, this analysis has failed to show any justification for the routine use of very intensive induction regimens in this disease. Such an approach should only be taken in the context of randomised trials in which timing and methods of reassessment can be standardised. Until such studies demonstrate superiority either in terms of response rate or progression-free survival lower morbidity regimens should remain the standard therapy.

**Autologous Bone Marrow Transplant (ABMT)**

*Treatment of High-Risk Neuroblastoma With Triple-Tandem High-Dose Therapy and Stem-Cell Rescue: Results of the Chicago Pilot II Study*

By Morris Kletzel, Howard M. Katzenstein, Paul R. Haut et al.

*Cohn Journal of Clinical Oncology, Vol 20, Issue 9 (May), 2002: 2284-2292*

**PURPOSE:** To investigate whether intensive induction therapy followed by triple-tandem cycles of high-dose therapy with peripheral-blood stem-cell rescue and local irradiation will improve event-free survival for patients with high-risk neuroblastoma.

**PATIENTS AND METHODS:** From August 1995 to January 2000, 25 consecutive newly diagnosed high-risk neuroblastoma patients and one child with recurrent MYCN-amplified disease were enrolled onto the Chicago Pilot II Protocol. After induction therapy and surgery, peripheral-blood stem cells were mobilized with three cycles of high-dose cyclophosphamide and granulocyte colony-stimulating factor. Patients then underwent triple-tandem cycles of high-dose therapy with peripheral-blood stem-cell rescue followed by radiation to the primary site.

**RESULTS:** Twenty-two of the 26 patients successfully completed induction therapy and were eligible for the triple-tandem consolidation high-dose therapy. Sufficient numbers of peripheral-blood stem cells were collected in all but one patient. Seventeen patients were able to complete all three cycles of high-dose therapy and peripheral-blood stem-cell rescue, two patients completed two cycles, and three patients completed one cycle. There was one toxic death, and one patient died from complications of treatment for graft failure. With a median follow-up of 38 months, the 3-year event-free survival and survival rates are 57% ± 11% and 79% ± 10%, respectively.

**CONCLUSION:** The results of this pilot study demonstrate that it is feasible to intensify consolidation with triple-tandem high-dose chemotherapy and peripheral-blood stem-cell rescue and local irradiation, and suggest that this treatment strategy may lead to improved survival for patients with high-risk neuroblastoma.