- 1．小児がん専門医が複数名診療に従事している。2．各都道府県に一カ所の設置地理的に一カ所とは限らないでよいと思う。静岡県、北海道のように広いところは複数の設置が必要と思われる。臨床心理士などがいて精神的ケアが可能であること。患児に対する病名告知や両親などに対する精神的ケアに関われる医師以外にスタッフがいること。

- オンラインネットワーク化。

- センター病院については意見なし。サテライト病院の要件を明確にして病院連携を活性化しセンター病院の負担を減らし、一方では患者の利益になるシステムを構築すべき。

- “放射線診断、治療部門、病理部門に小児がん担当者がいる”が要件になっている理由をお教えください。放射線診断にしても当院には小児がん専属の担当者はいないが、日常がん治療で全く支障は感じていない。診断は本来小児科医がするものでは？病理部門にも小児がん専属の担当者はいないが生育の病理にメール等で相談しており日常のがん診療での支障はない。放射線治療を要する患者は多く、院内の放射線治療がむずかしい場合は近くの大学病院等に照射をお願いしたりするがいずれも小児がん専門ではない。

- 「有能な小児科医」の集約化が最重点と思います。病院の診療体制の完備は当然として、年間の取り扱い症例数が一定以上の施設に集約すべきと思います。米国 COG などは、スタディの参加に設基準があり年に一定数の症例がないと参加できないようになっています。症例が少なすぎると一定の治療レベルを維持できないからと考えます。

- 院内学級 etc は年長児例であり、小児固形腫瘍の殆どは小学校入学以前である。従って固形腫瘍のみを扱う我々には院内学級 etc は不要と考える。2.化学療法を行う専門家という意味で小児白血病リンパ腫専門の医師が close up されてきているが、小児の腫瘍専門医が常勤でなければ化学療法は安全に行えないという訳でもないので、小児がんの中でも特に固形腫瘍専門あるいは血液腫瘍専門という様に分化して良いと考える。3.長期 follow を行っていると Mental care の重要性を痛感する。従って小児病院よりは精神科の充実している一般総合病院の方がメリットのある事もある。いずれにせよ専門化が責任を持ってチームでみていくことが大切だと痛感している。

- 国、県レベルでの財政的補助。特に長期フォローにおける検査費用等。

- スタッフ数の充実。CLS、看護士、保母スタッフ、を含めたパラメディカルスタッフの充実。診療レベルの維持および安定化を目的とした小児がん診療の全国レベルの情報共有システムの構築と臨床研究に向けたシステム作り。日本全国をブロック化し、その中で診断治療を行う中心的病院を作り、初期診断と治療を行う。しばらくしてから（2～3 ヶ月）より居住地に近い準中心病院へ移り、その後の治療とフォローを継続するなどの層状の集約化がより現実的ではないでしょうか。そのためには研修の体制（施設・身分保障・症例数の確保、等々）の整備が必要でしょうか。

- 患者数は施設ごとに違うと思いますが、血液・腫瘍に関与する（専門とする）常勤医は 2 名以上要ると思います。

- 〈中学生～高校生について〉前述された要件をすべて満たせる施設は大学病院や小児病院になると思いますが、小児病院では年長児～20 歳未満（10 代）の患者がフォローしきれなくなることがあります。大学病院では小児科と内科の境界を何才にしているかが各病院で一致していないところがあるように思います。がんセンターといわれるような病院に思春期患者を集約するとよいと思います。成人になってからの再発などに対応がスムーズにできると考えます。その年齢は対応が難しいこともあり、集約化により、よりよい対応が可能となり、また臨床研究もよいものができると考えます。

- 〈すべての年齢に対して〉サイコオンコロジーや緩和ケアは必須になってくるのではないでしょうか。

- 小児がん専門医の存在。小児血液腫瘍医だけでなく小児外科医も常勤。小児がん登録に参加。臨床試験に参加。腫瘍別グループに参加。

- 小児がん専門医（化学療法）、小児外科医をはじめとした連携が必要。また院内で満たされない際は、近隣の病院との連携による病院間でのグループ診療体制も方法と思われる。

- 別記された施設要件は一部の小児病院以外ほとんど満たすことはできていない＝我国の要件としてはオーバースペックです。特に放射線・病理に小児担当がいる施設はほとんどないでしょう。それから小児がん専門医の研修体制が整っている所はないのではないか。小児がん専門医というのも今は制度がない。「長期フォロー体制」というのも定義がよくわからない。

- 私どもは小児外科はありませんが、外科処置（手術）のみ近所の大学病院にお願いすることもよくあります。一定の入院期間後当院に再び転院し化学療法をおこなうこともしばしなあります。必ずしも小児外科が院内になくても協力体制さえしっかりしていれば小児固形がんの治療は可能と考えます。

- NST。医療社会事業部（ソーシャルワーカー）。小児心理士。

- （後期）研修医なども含めてよいと思うが医師数が多いこと。仕事に余裕があること。

- 集約化するには、小児腫瘍科と外科だけあればいい訳ではなくて小児科の他分野の専門家がいない病院はがん診療をすべきではない。もっとがん診療を評ぼう標榜するための条件を厳しくすべき。

- グループスタディへの理解と参加。1.小児がん登録による全数把握。2.医師以外で運営される第三社的なデータセンターと検索バンク。3.上記を運営する参加医師による委員会。4.症例登録数、治療成績らの公表。5.経済的基盤としての公的研究費の支出状況の公表。6.上記研究費の持ち寄りによる無駄のない透明な運営管理。が必要と思われます。

- 臨床試験実施には特に十分な人的支援が必要。

- 単に医療成績の向上のみではなく、子どもの生活、子どもの立場、子どもの発達という目線からの整備も必要と考えます。

- 1.外科・放射線科・小児内科・病理が少なくとも小児がんの専門医が複数人確保できる病院。2.病棟が小児がんおよび免疫抑制患者のみで構成できること。3.ソーシャルワーカー、教育士、学童など（院内学級）がある施設。

8　　参考資料

「Guidelines for Pediatric Cancer Centers」

AMERICAN ACADEMY OF PEDIATRICS　　Section on Hematology/Oncology

POLICY STATEMENT

Pediatrics 2004; 113; 1833-1835

「小児がんセンターのためのガイドライン」

米国小児科学会　血液/腫瘍部門

人的条件

- 在宅ケアーを進めるに当たり不可欠となる一般小児科医との連携
- 小児がん・血液認定専門医
- 化学療法、小児がんプロトコールに精通し治療合併症の看護の経験のある小児がん専門看護師
- 乳児、小児、青年期患者の画像診断に特に精通した放射線専門医
- 小児外科専門医
- 小児に精通した脳外科医、泌尿器科医、整形外科医、眼科医、耳鼻科医、口腔外科医、婦人科医
- 乳児、小児、青年期患者の治療の研修と治療の経験のある放射線治療専門医
- 小児、青年期の固形腫瘍・血液悪性疾患の診断の研修と経験のある病理専門医
- 各領域の小児科専門医·麻酔、集中治療、感染症、循環器、神経、内分泌代謝、遺伝、消化器、 児童心理、腎臓、呼吸器
- 小児の身体的、心理的リハビリテーションを行う理学療法士、臨床心理士
- 小児ソシアルワーカー、小児臨床心理士、チャイルドライフスペシャリストそして在宅医療支援グループ
- 完全静脈栄養を含む小児栄養管理に精通した管理栄養士

施設条件

- 緊急時にも利用できそしてスタッフのそろったPICUを施設内にそなえている
- 最新の画像診断設備−レントゲン、CT、MRI、超音波、シンチグラフィー、血管造影、PETその他新規の装置
- 小児患者治療のための最新の放射線治療装置
- フローサイトメトリー、免疫組織化学、遺伝子診断、染色体分析により細胞の表現型の分析が可能でコロニーアッセイやPCRを行える血液・病理検査室
- 血液透析や血液濾過が行えるそして造血幹細胞の採取や保存が出来る臨床部門

保証すべき医療水準

- 抗生物質や抗がん剤の血中濃度の測定が可能な生化学検査室
- 照射された、サイトメガロウイルス陰性の、白血球除去血液製剤を含むすべての血液製剤が供給可能の輸血部門
- 正確でよく管理された抗がん剤や治験薬の調製が可能な薬剤部門
- HEPAろ過やラミナエアフローそして陰圧・陽圧室により空気中の病原体より患児を十分に隔離できること
- 造血幹細胞移植ができること
- プライマリーケア医を含む医療職者への教育およびトレーニングのプログラムがある
- 在宅ケアー、疼痛コントロール、緩和医療、終末期医療のチームがあること
- 定期的な多角的小児がん検討会が開催されている
- 小児がん経験者に対して長期の多角的、計画的なフォローアップのプログラムをもっていること　これは自院でも晩期障害に精通したチームに依頼してもかまわない
- COGの正会員か協力会員で通常の臨床試験に参加できるそして患児の経過を把握して臨床データを維持管理できる支援部門がある
- 両親、保護者そして患者自身に教育の機会を提供できる
- 正確な翻訳と効果的なコミュニケーションを医療従事者と両親及び患者に保証する翻訳サービスをいつでも利用できる
- 常に安全で質の高い医療を提供し続けているかの評価プログラムが機能している
- 家族のための公式のがん教育事業および自己評価の指示

Ⅱ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表レイアウト

書籍　　＊：別刷り添付なし

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Ⅲ．研究成果の刊行物・別刷

CHAPTER 16

Yoshiaki Tsuchida
Hitoshi Ikeda
Shin Itsu Hatakeyama

Neuroblastoma

In remembrance

Prof. Yoshiaki Tsuchida (25-10-36 to 28-06-05) was a renowned pediatric surgeon, who devoted most of his life to basic and clinical research. He has contributed to the International Society of Pediatric Oncologists with various academic achievements in the field of pediatric oncology. This is probably the last chapter by him on his favourite subject.

Neuroblastoma is the second most common solid tumor in infancy and childhood after brain tumors. It accounts for 7 to 10 percent of cancers of childhood, and the annual incidence is 1 per 100,000 children under the age of 15 years in the United States[1] and 1 per 76,000 in Japan where mass screening is carried out.[2]

The history of neuroblastoma dates to 1864 when Virchow first described its typical histological features.[3] In 1901, Pepper reported autopsy findings of 6 infants with suprarenal and liver tumors, which were probably the first patients with the disease type now called stage IV-S neuroblastoma.[4] In 1907, Huntington recorded older patients with "sarcoma" of the adrenal gland and metastases to the skull.[5] In 1910, Wright first used the term neuroblastoma by likening the rosettes and neural fibrils of such tumors to the developing adrenals,[6] and since then the term neuroblastoma has been widely used.

The biology of neuroblastoma is enigmatic and it is important to understand it to the extent possible in order to improve its treatment and clinical results further. It is widely accepted that neuroblastoma is a tumor of the sympathetic nervous system. While neuroblastoma may produce catecholamines, this is not always true in advanced neuroblastoma. Le Douarin and her associates have shown that the fate of neural crest-derived cells is highly dependent upon environmental causes.[7] That is, neural crest cells that are supposed to produce catecholamines may begin to synthesize acetylcholine under specific conditions[8] and vice versa.[9] Cloned adrenergic neuroblastoma cells may even become cholinergic after serial transplantation.[10] In addition, we have confirmed that only 75 percent of clinically detected neuroblastomas have the key enzyme, i.e. tyrosine hydroxylase, required to produce catecholamines.[11]

Cytogenetically, chromosome 1p deletions, extrachromosomal double minutes, and homogeneously staining regions (HSRs) are commonly observed in neuroblastoma cell lines and advanced-stage neuroblastoma tumors. It was also recently found that

an HSR represents genomic amplification of *MYCN*, which plays a key role in determining the aggressiveness of neuroblastoma.[12,13] However, stage IV neuroblastomas or cell lines that lack *MYCN* amplification are also progressive, and some of them show evidence of *MYCN* expression in terms of mRNA and/or *MYCN* oncoprotein.[14,15] It was also recently shown that a small proximal locus mapped between 1p35-36.1 and 1p36.23 may function as a suppressor gene of *MYCN* amplification.[16] However, the relation is not simple,[17] because it has been reported that chromosome 17q gain may also be associated with *MYCN* amplification.[18] In addition, loss of heterozygosity on chromosomes 2q, 9p, 11q, 14q, and 18q has been reported in some patients with advanced neuroblastoma.[19,20]

Cellular DNA content or ploidy is relevant to clinical outcome.[21] Hyperploidy is closely associated with a favorable patient outcome, while diploidy usually predicts poor patient prognosis. Ploidy analysis using *in situ* hybridization showed that numeric chromosome aberrations are found in neuroblastic/ganglionic cells, but not in the Schwann cells which have long been thought to be neoplastic in origin.[22] This led to the hypothesis that Schwann cells in neuroblastoma are infiltrating normal cells that are responsible for the differentiation of neuroblastoma cells.[22]

In sympathoadrenal lineage cells in the later stages of neural crest development, the *Trk-A* tyrosine kinase receptor for which nerve growth factor (NGF) is a ligand is expressed.[23] While NGF binding to the receptor transmits a signal that leads immature sympathetic neurons to differentiate into mature ganglion cells, deprivation of NGF results in apoptosis, or programmed cell death, of the neurons. In neuroblastoma, *Trk-A* is expressed in tumors with a favorable prognosis, and tumor cells expressing high levels of *Trk-A* differentiate in response to NGF.[23,24] The NGF that is produced by schwannian stromal cells may regulate the differentiation and survival of neuroblastoma cells.[25] *MYCN* amplification downregulates *Trk-A* expression and low or absent expression of *Trk-A* is associated with an unfavorable prognosis.[23,24] *Trk-B*, a high-affinity receptor for brain-derived neurotrophic factor (BDNF), also is expressed in aggressive neuroblastoma.[26]

The presence of cells with characteristic features of apoptosis (e.g. condensed nuclear fragments and eosinophilic cytoplasm) and the demonstration of a ladder of DNA fragments indicate that apoptosis is involved in the process of neuroblastoma cell death.[27] A number of studies showed that neuroblastoma expresses Bcl-2 which inhibits apoptosis, but there is no definitive evidence regarding the relationship between Bcl-2 and other prognostic factors.[28] Expression of proteases involved in the process of apoptosis, caspase-1 and caspase-3, is high in the nuclei of neuroblastoma with favorable prognostic characteristics.[29,30]

Telomerases are DNA-protein structures at the ends of eukaryotic chromosomes and are thought to be important in the positioning, protection, and replication of chromosomes.[31] Telomerase, an RNA-dependent DNA polymerase, stabilizes telomeres and the telomere maintenance is essential for attainment of immortality in tumor cells. Several studies have shown that telomerase activity is detectable in neuroblastomas, except for stage IV-S tumors.[31-33] High telomerase activity is associated with advanced stage or *MYCN* amplification, while neuroblastomas with low or undetectable telomerase activity are usually tumors that are diagnosed in infants and have favorable prognostic characteristics.[31]

Ha-*ras* p21, a product of the Ha-*ras* gene, is expressed in normal neuronal cells and participates in the signal transduction pathway relating to NGF.[34] Expression of Ha-*ras* p21 is significantly associated with patient prognosis and higher expression predicts a favorable patient outcome.[35] Prognostic discrimination based on Ha-*ras* and *Trk-A* gene expression in patients with stage III and IV diseases therefore appears useful, and the survival rate of patients with neuroblastoma highly expressing both genes is significantly better than that of patients with tumors with low expression of the genes.[36]

P-glycoprotein, a plasma membrane efflux pump, plays a role in drug resistance and is responsible for multidrug resistance against the vinca alkaloids, anthracyclines, and epipodophyllotoxins. However, the role of P-glycoprotein in predicting prognosis in neuroblastoma is controversial.[37,38] Expression of the *MDR1* gene that encodes P-glycoprotein is correlated with *MYCN* gene expression in neuroblastoma without *MYCN* amplification, and high expression of *MDR1* is significantly associated with poor outcome.[39] High expression of the *MRP* gene that encodes multidrug resistance-associated protein (MRP) is also associated with poor survival in patients with neuroblastoma and in subgroups of patients without *MYCN* gene amplification and those with localized disease.[40]

The genetic and molecular analyses described above not only have revealed biological differences between neuroblastomas with favorable prognosis and those with aggressive biological behaviors, but also have provided insight into both tumorigenesis and spontaneous

regression of neuroblastoma. It is generally accepted that there are at least two types of neuroblastoma: one seen mainly in infancy and associated with particularly good prognosis; and the other usually encountered in older children with an extremely poor prognosis, often associated with *MYCN* amplification. Brodeur and others place an intermediate group[41] between these two groups, but identification of the intermediate group is equivocal because the prognosis of patients with neuroblastoma is not determined by *MYCN* amplification alone. Furthermore, the prognosis of stage IV neuroblastoma patients older than 12 months of age does not differ greatly whether *MYCN* is amplified or not.[42]

CLINICAL SYMPTOMS

Neuroblastoma may diagnosed prenatally. Seventeen patients with prenatally diagnosed neuroblastoma were identified in a cohort of 591 patients in the Italian Neuroblastoma Registry.[43] It was reported that the tumor was solid in 13 patients (76.5%) and cystic in 4 (23.5%). The tumor occurred in the adrenal gland in 16 and in the retroperitoneal sympathetic ganglion in one. Fifteen patients were in stage I or II, and the remaining 2 patients had stage IV-S disease.[43] The treatment strategy is controversial, but it is generally considered that it should not differ much from that in infantile neuroblasoma identified by mass screening.[43]

Clinical symptoms of postnatally diagnosed neuroblastoma differ based on the mode of diagnosis and the stage/age of the disease. Infants with neuroblastoma identified by mass screening usually present with a small tumor mass in the adrenal glands or paravertebral sympathetic ganglia, or less frequently with multiple hepatic metastases together with a small primary tumor mass. The distribution of tumor masses diagnosed in mass screening is thus similar to that of neuroblastomas identified by antenatal diagnosis. The primary tumors in the adrenal glands or paravertebral sympathetic ganglia are usually not palpable in patients diagnosed by mass screening. On the other hand, multiple hepatic metastases cause significant liver enlargement. Infantile neuroblastoma may also metastasize to the skin and bone marrow.

Some tumors can develop intra- and extraspinally, and can be of the dumbbell or hourglass shape. The site of origin of neuroblastoma varies with age, since adrenal tumors are more common in children than in infants.[44] In children, a fixed, hard, irregular mass is frequently palpable. Tumors originating in the pelvis may cause mechanical obstruction and result in difficulties in defecation or urination. A dumbbell-type tumor can cause paraplegia or fecal/urinary incontinence. Larger thoracic tumors may cause dyspnea or dysphagia, and may also cause superior vena cava syndrome.[44] Upper thoracic and cervical neuroblastomas are sometimes associated with Horner's syndrome. It has been presumed that neuroblastoma of adrenal origin may leads to renovascular hypertension, but the serum renin level is usually normal, and if elevated serum active or inactive renin levels are associated with neuroblastoma, anomalies of the vascular system such as middle aortic syndrome should be considered, as observed in one of the authors' patients or reported by others.[45]

Neuroblastomas in children older than 12 months of age often metastasize to the lymph nodes, bone, and bone marrow. Neuroblastomas have a predilection for the bones of the skull, orbit, jaw, and long bones, and metastases to the orbit produce the characteristic unilateral or bilateral periorbital ecchymosis and exophthalmos. Metastases to the bone marrow are so common that routine examination of bone marrow is essential. Lung and brain metastases are rare at diagnosis.

Hypertension, diarrhea, and opsoclonus-myoclonus syndrome are important paraneoplastic syndromes of neuroblastoma. Excretion of catecholamines and stretching (constriction) of the renal arteries are possible causes of hypertension in neuroblastoma, but the latter is less plausible because serum total rennin is usually within the normal ranges. Neuroblastomas are known to produce vasoactive intestinal peptide (VIP), which causes intractable diarrhea. Interestingly, the VIP-producing tumors are mature ganglioneuroblastomas or ganglioneuromas.[46] Opsoclonus-myoclonus syndrome has been observed in up to 4 percent of neuroblastoma patients.[47] This syndrome is neither due to direct involvement of the brain by tumor, nor to the production of catecholamines. While the mechanism is unclear, this syndrome may respond to high doses of corticosteroids.[44,47]

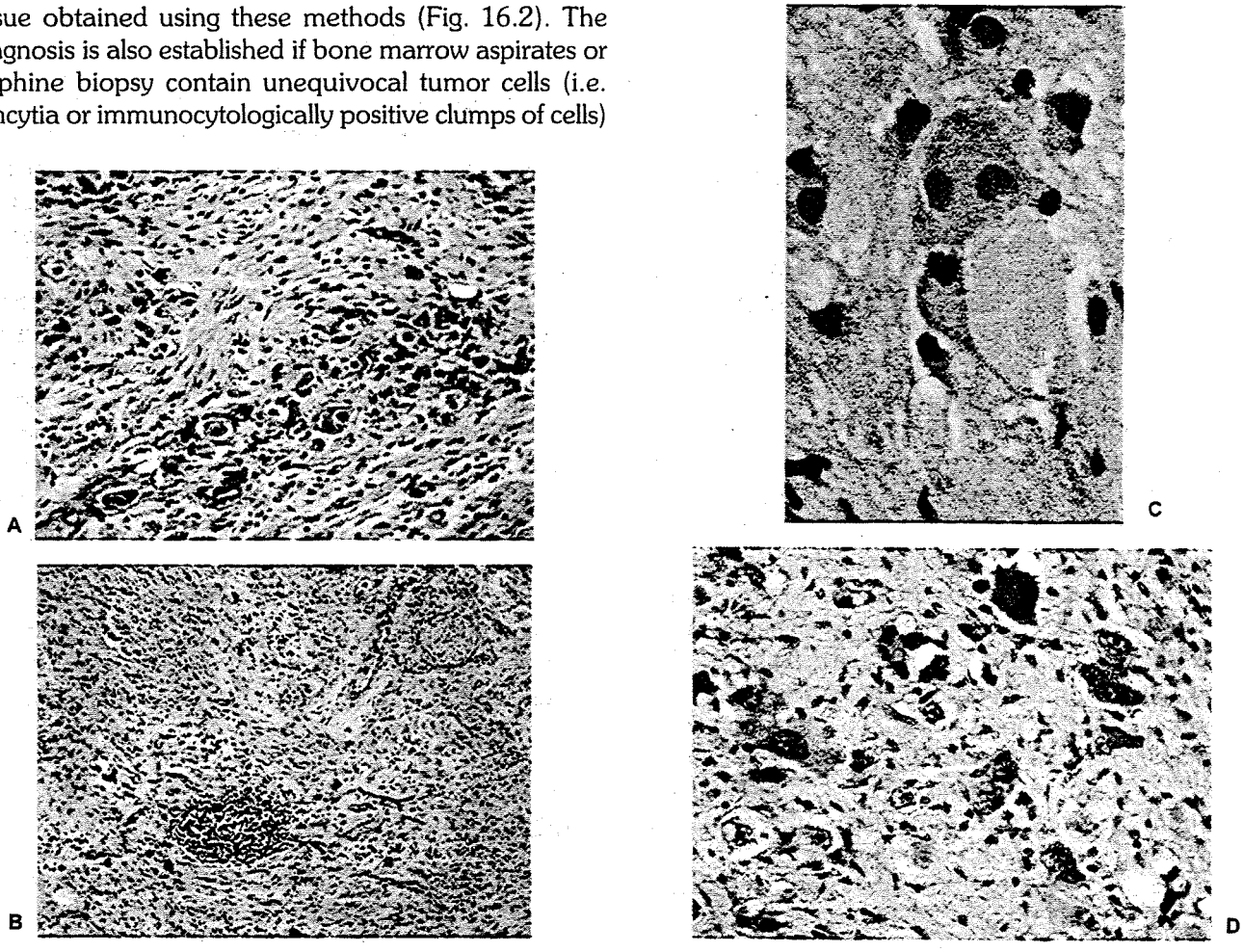
ASSOCIATED ANOMALIES AND FAMILIAL OCCURRENCE

In contrast to Wilms' tumor and acute leukemia in childhood, neuroblastomas are associated less frequently with combined congenital abnormalities. Nishi and coworkers found no Down's syndrome and no undescended testicle but 5 cases of mental retardation in 288 patients with neuroblastoma.[48] Familial occurrence of neuroblastoma is rare.[49]

DIAGNOSIS, STAGING, AND HISTOLOGICAL CLASSIFICATION

The diagnosis of neuroblastoma should be established histologically.[50,51] Characteristic histological features of neuroblastoma are described below. In most cases, a tissue diagnosis of neuroblastoma based upon hematoxylin and eosin staining is not difficult, especially if features suggestive of neuronal differentiation are present (Figs 16.1A to D). However, in some cases neuroblastomas are characterized by densely packed, small blue cells with little differentiation. Electron microscopy and implementation of immunohistochemical methods are recommended to confirm the diagnosis.[50] Core-needle biopsy or fine-needle aspiration is recommended to make the diagnosis by some but discouraged by others because of the small amounts of tissue obtained using these methods (Fig. 16.2). The diagnosis is also established if bone marrow aspirates or trephine biopsy contain unequivocal tumor cells (i.e. syncytia or immunocytologically positive clumps of cells) and increased urine or serum levels of catecholamines or metabolites >3.0 SD above the mean are seen.[50] Serum neuron-specific enolase (NSE) is not decisive of diagnosis, but is of value in monitoring the clinical course.[52]

Evans' staging system[53] has long been used for neuroblastoma. However, the International Neuroblastoma Staging System (INSS) was first proposed in 1988, and after revisions in 1993[50] is currently used worldwide (Table 16.1). Before the INNS, the staging system of the Children's Cancer Group of the United States, its modification by the Japanese Society of Pediatric Surgeons, and that of the Pediatric Oncology Group of the United States were used. Each system had its strengths, but the differences made it difficult to compare the results of clinical trials and biologic studies



Figures 16.1A to D: Histopathological features of neuroblastoma are shown: **(A)** Small uniform cells with dense darkly staining nuclei and scant cytoplasm. **(B)** Rosette formation is seen. **(C)** Photomicrograph depicting a histopathological diagnosis of ganglioneuroma. **(D)** Photomicrograph depicting a histopathological diagnosis of ganglioneuroblastoma with islands of neuroblastoma cells and fibrous stroma

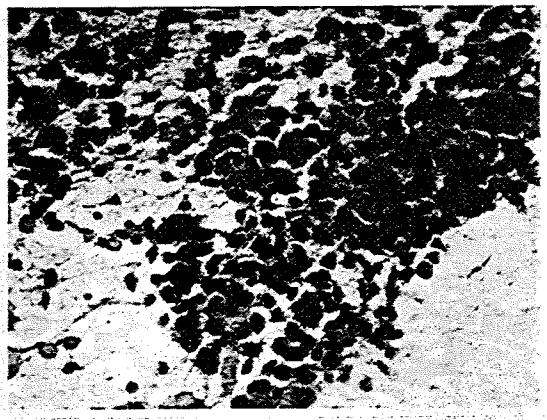


Figure 16.2: Photomicrograph showing the round cell appearance on fine-needle aspiration cytology in a case of neuroblastoma

performed by different groups and in different countries. The tests recommended for the assessment of extent of disease are well outlined in the report by Brodeur and his associates.[50]

It is tempting to consider that the histopathology of neuroblastomas, ganglioneuroblastomas, and ganglioneuromas parallels the pattern of differentiation expressed by the developing sympathetic nervous system.[54] Typical neuroblasts are small uniform cells with dense, hyperchromatic nuclei and a paucity of cytoplasm. The neuritic process or neuropil is noted, and pseudorosettes consisting of neuroblasts surrounding areas of eosinophilic neuropil are seen in a majority of cases. Tumors such as primitive neuroectodermal tumors, undifferentiated soft tissue sarcoma, Ewing's sarcoma, and non-Hodgkin's lymphoma should be carefully differentiated from neuroblastoma. The International Neuroblastoma Pathology Classification (INPC) was recently established.[51] Originally, Shimada and colleagues[55] established a classification in which the presence of Schwann's cells, degree of cellular differentiation, and mitosis-karyorrhexis index are determined to define favorable or unfavorable histologic types. The original Shimada classification was reviewed by an international panel of six member pathologists, and the INPC was approved.[51] In both the Shimada classification and INPC, the age of the patient at diagnosis is one of the factors predicting favorable or unfavorable prognosis.

IMAGING OF NEUROBLASTOMA

As neuroblastoma originates from the sympathetic ganglia and adrenal medulla, imaging investigation must focus on the pertinent area. However, it should be remembered that it is not uncommon for neuroblastoma to present first with the symptoms produced by metastases or even with peculiar clinical manifestations before the actual tumor is detected (Fig. 16.3). Although the imaging evaluation of a child with a presumed neuroblastoma varies from institution to institution, our routine procedures are as follows: plain radiograph of the chest and abdomen; abdominal sonography (US); magnetic resonance (MR) imaging; and bone scintigraphy with ^{99m}Tc MDP (methylendiphosphonate)

Table 16.1: International Neuroblastoma Staging System[50]

Stage	*Definition*
I.	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)
IIA.	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically
IIB.	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically
III.	Unresectable unilateral tumor infiltrating across the midline, 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
IV.	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage IV-S)
IV-S.	Localized primary tumor (as defined for stage I, IIA or IIB), with dissemination limited to skin, liver, and/or bone marrow (limited to infants < 1 year of age)

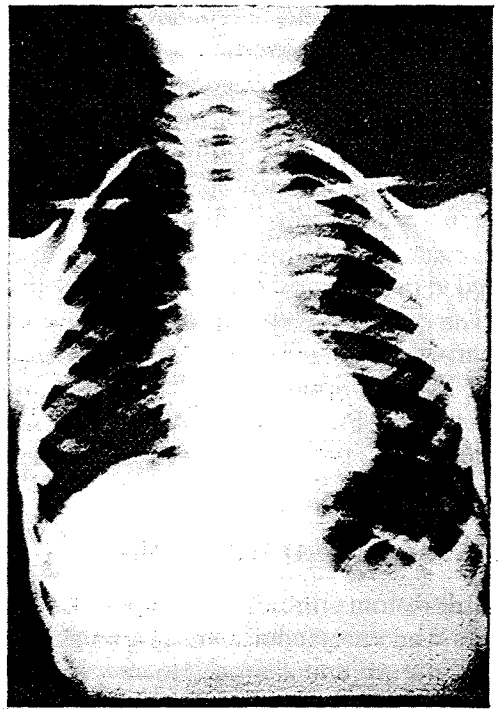


Figure 16.3: Skiagram chest outlining mediastinal deposits in a case of neuroblastoma

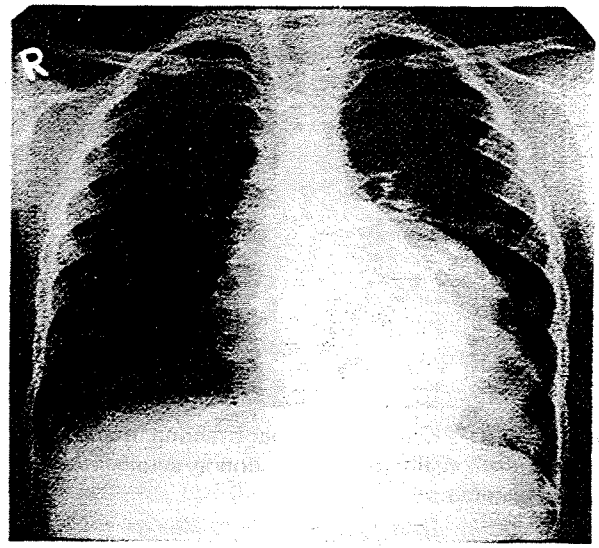


Figure 16.4: Skiagram chest showing a space occupying lesion in the left hemithorax that turned out to be a neuroblastoma of the posterior mediastinum

and metaiodobenzylguanidine (^{123}I MIBG) scintigraphy, if indicated. In Japan, neuroblastoma is not indicated in the application list of ^{123}I MIBG scintigraphy.

In the case of a thoracic neuroblastoma, imaging is 100 percent sensitive in suggesting the diagnosis[56] (Fig. 16.4). The mass is well defined and mediastinal based, associated with widening of the paraspinal line and rib erosion adjacent to the mass. On the other hand, plain abdominal radiography is less sensitive and often superfluous in terms of detection of the mass and intratumoral calcification. Thus the investigation should be followed with US regardless of the findings on abdominal radiograph.

On US, neuroblastoma is heterogeneously echogenic with poorly defined margins, and calcification, which is frequent, is identified as bright echoes with or without acoustic shadowing.[57] Most neuroblastomas demonstrate a "globular" region of increased echogenicity within the mass, which is regarded as an aggregate of uniform neuroblastoma cells marginated by reticulum and collagen.[58] The cystic form of neuroblastoma is rare, and located almost exclusively in the adrenal gland. This could be easily confused with adrenal hemorrhage as both have mainly been identified in neonates. Serial US imaging can resolve this problem as adrenal hemorrhage changes in its echo pattern and size over a period of days. Adrenal hemorrhage is rare *in utero* and any adrenal mass seen *in utero*, whether cystic or solid, is likely to be a neuroblastoma.[59] Careful US examination can demonstrate the origin and extent of the tumor, and the relationship of the tumor to the adjacent organs and major abdominal vessels. However, it is difficult to obtain or propose a convincing anatomic delineation for surgeons in planning surgery and predicting tumor resectability. Intravenous urography may show displayed renal calyces (Fig. 16.5).

Computed tomography (CT) is comparable to MR imaging as a cross-sectional imaging modality and both can demonstrate the presence and extent of neuroblastoma (Fig. 16.6). Although unenhanced CT is very sensitive in demonstrating intratumoral calcification and is advised for the evaluation of adjacent bones,[60] the additional information from MR imaging makes findings of less importance than was true previously (Figs 16.7A to C).

Because of its sensitivity to tissue characteristics and multiplanar and angiographic capability, MR has the advantage of distinguishing the tumor from other surrounding soft tissues, defining the tumor extent from the wide view or on any plane, showing its relationship to adjacent vessels without contrast medium, and demonstrating intraspinal spread, as well as accuracy in the recognition of bone marrow involvement (Figs 16.8A to C and 16.9).[61] There is a limitation, however, in

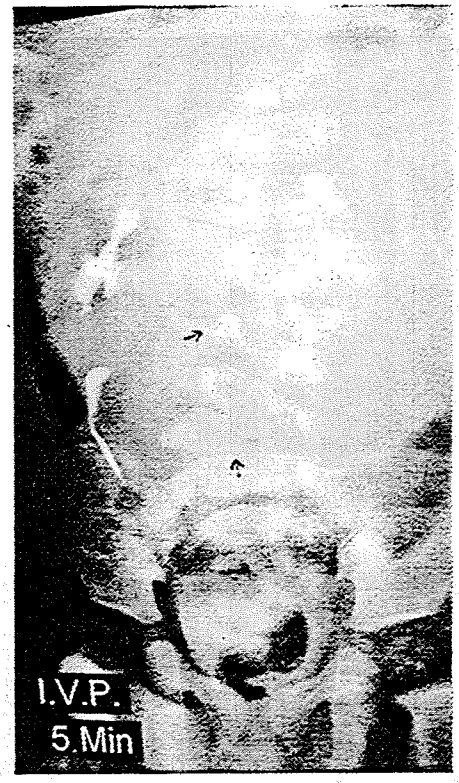


Figure 16.5: Intravenous urogram in a child with a huge neuroblastoma showing displayed renal calyces and vertebral anomalies

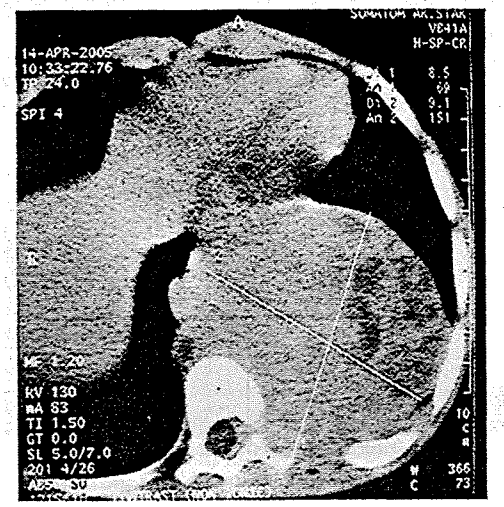


Figure 16.6: CT scan showing a posterior mediastinal neuroblastoma

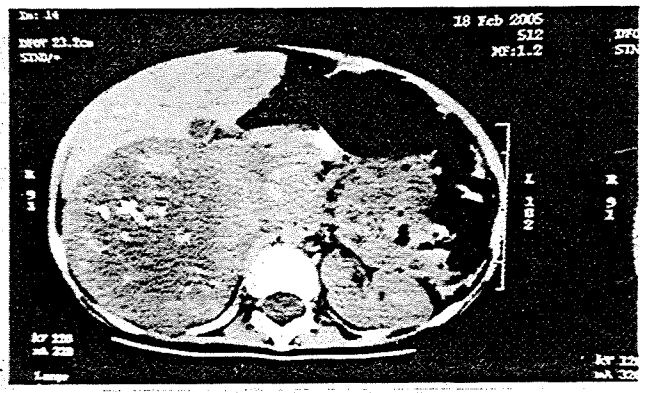


Figure 16.7A: Prechemotherapy CT scan image in axial section showing calcification in a case of neuroblastoma

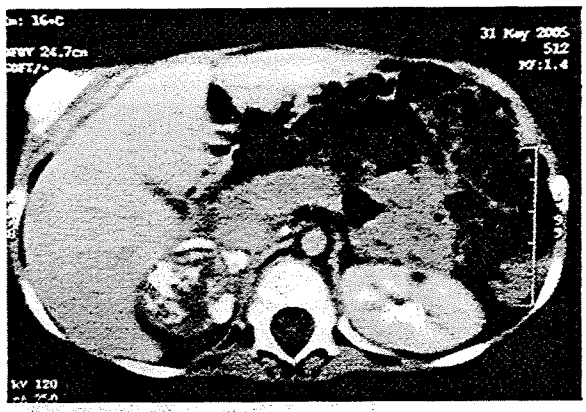


Figure 16.7B: Postchemotherapy CT scan image showing the residual tumor in axial section

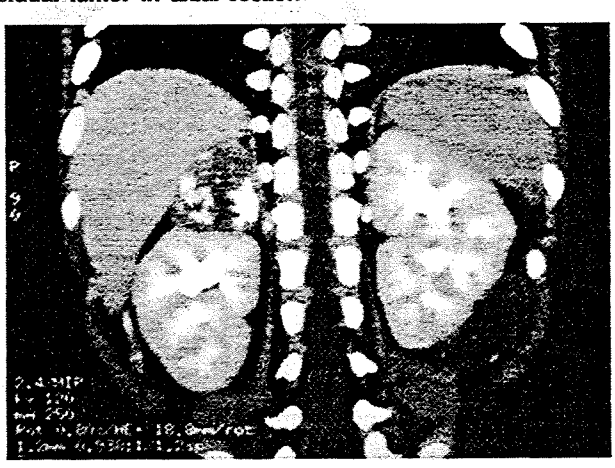
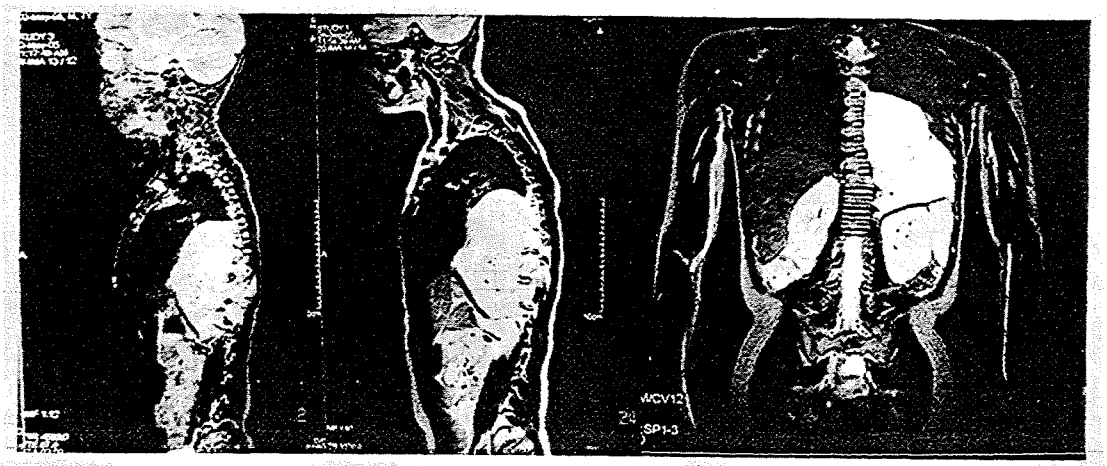


Figure 16.7C: Postchemotherapy CT scan image showing the residual tumor in coronal section

differentiating residual tumor from ongoing fibrosis or scar tissue after chemotherapy, and differential criteria remains to be established.

Bone scintigraphy with ^{99m}TC MDP is well established and more sensitive than radiographic bone survey for the diagnosis of skeletal metastases of neuroblastoma (Fig. 16.10). In addition, this radiotracer can accumulate in the tumor itself. MIBG scintigraphy is also able to detect primary tumor and metastases. As a positive finding on MIBG scintigraphy is more specific, it can



Figures 16.8A to C: MRI images in sagittal (**A** and **B**) and coronal sections **(C)** in a case of posterior mediastinal neuroblastoma with intraspinal extension

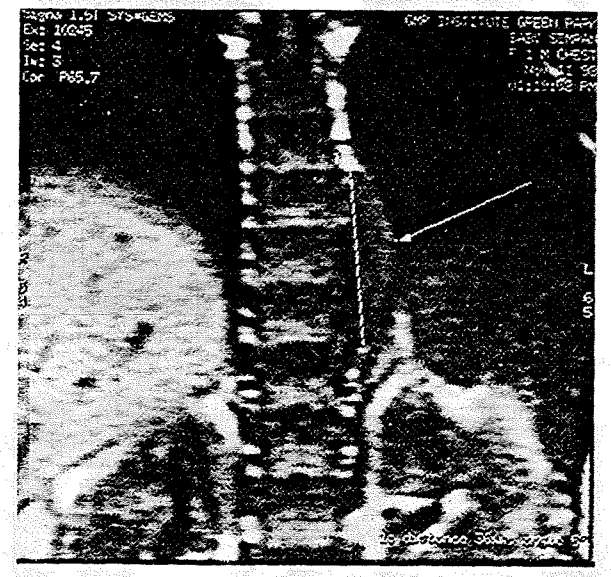


Figure 16.9: MRI image in coronal section showing a small mediastinal neuroblastoma

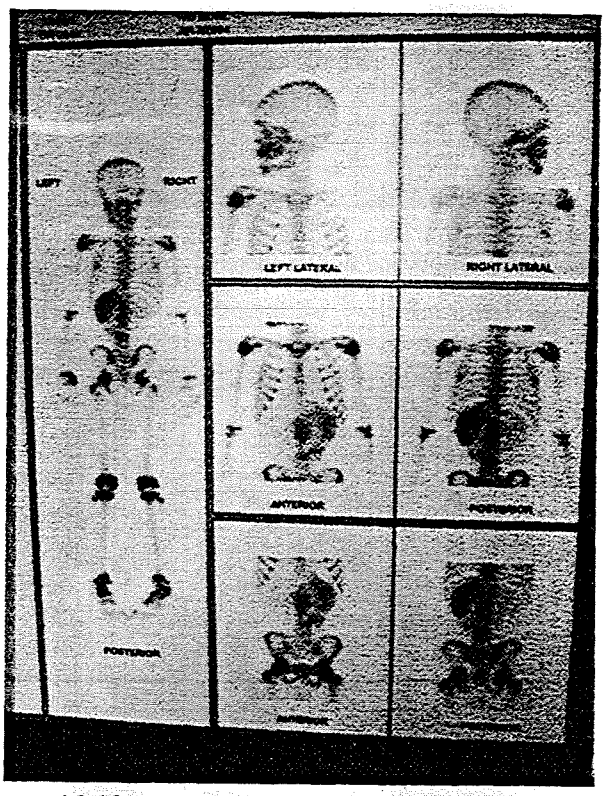


Figure 16.10: Bone scan images in a case of neuroblastoma showing thoracic and abdominal vertebrae involved with metastasis

noninvasively establish the diagnosis of neuroblastoma in a child with a tumor of unknown origin. Cumulative results of MIBG scintigraphy indicate that MIBG scintigraphy should be used initially, followed by bone scintigraphy, if necessary.[62]

TUMOR MARKERS

The implication of determining tumor markers is two-fold. One is to make a definitive diagnosis and monitor patients during the course of treatment, and the other is to predict prognosis. The most definitive diagnostic markers are catecholamines and their metabolites in serum and urine, although the positivity is approximately 75 to 80 percent in clinically diagnosed patients with neuroblastoma. Elevated neuron-specific enolase (NSE) levels are seen not only in the sera of patients with neuroblastoma but also in those with other pediatric tumors. However, serum NSE levels are elevated in all types of neuroblastoma whether or not the metabolic

pathways of catecholamines are present, and NSE serves as a good tumor marker in monitoring the disease course of neuroblastoma.[52,63]

A serum ferritin level > 142 ng/ml is found in many patients with advanced-stage neuroblastoma but rarely in low-stage disease, and it was reported that increased levels of ferritin are associated with a poorer progression-free survival rate.[64] Similarly, serum lactic dehydrogenase (LDH) levels > 1,500 U/ml are associated with a poorer prognosis in neuroblastoma,[65] and a serum NSE level elevated > 100 ng/ml is associated with poor survival in advanced-stage patients with neuroblastoma.[54]

The roles of CD44, ganglioside GD2, chromogranin A, neuropeptide Y (NPY), and proliferating cell nuclear antigen (PCNA) have been studied.[54] CD44 is a glycoprotein found in the cell surface of many tumors and is associated with aggressive behavior. Interestingly, expression of CD44 in neuroblastomas correlates with less aggressive behavior and has been highly predictive of favorable outcome.[66] Ganglioside GD2 is the characteristic ganglioside on human neuroblastoma cell membranes and increased plasma levels of GD2 have been found in patients with neuroblastoma. Shed ganglioside may accelerate tumor progression,[67] and human-type anti-GD2 monoclonal antibody combined with interleukin-2 is currently undergoing clinical trials in the United States.[68] Chromogranin A is an acidic protein present in the neurosecretary granules of neuroendocrine tumor cells, and has been identified as a marker possibly indicative of neuronal differentiation.[69] NPY is another neurosecretory protein, and its plasma levels may also indicate the level of neuronal differentiation in neuroblastoma.[70] PCNA correlates with the level of cell proliferation. The PCNA index in neuroblastoma is closely related to *MYCN* amplification and to poor prognosis.[71]

MASS SCREENING

The purpose of screening infants for neuroblastoma is to reduce the number of advanced-stage neuroblastomas in older children by identifying more number of infants with the favorable type of neuroblastoma. The concept of detecting catecholamine metabolites in urine dates back to LaBrosse, who first used spot tests of catecholamine metabolites for infants with neuroblastoma in 1968.[72,73] In 1972 Sawada started to screen infants for neuroblastoma in Kyoto using a quantitative vanillylmandelic (VMA) test (VMA spot test).[74] This test was changed to quantitative measurements of urinary VMA and homovanillic acid (HVA), mass screening of neuroblastoma was introduced in all prefectures in Japan in 1985, and the methods for the measurement of urinary VMA and HVA were refined to sensitive high-performance liquid chromatography (HPLC) in 1988.[75] As a result, the incidence of neuroblastoma changed after the introduction of nationwide mass screening. Between 1980 and 1985, approximately 120 patients with neuroblastoma were registered yearly, while the number of annual neuroblastoma patients increased to about 250 during the period from 1991 to 1995.[2,75] Neuroblastomas identified in infancy through mass screening were exclusively of the favorable types, and roughly 99 percent of such infants have been cured, some of whom were only observed.

It must be remembered that the purpose of mass screening is to decrease the number of older children with advanced neuroblastoma. Some questions have been raised in this respect,[76] and it was shown that the absolute number of stage IV (excluding stage IV-S) neuroblastoma patients older than 12 months of age was not decreasing significantly when the number of live births was taken into account (Table 16.2).[2] Not all neuroblastoma, perhaps only 75 to 80 percent, possess the metabolic pathways of catecholamines.[11] Overdiagnosis of infant neuroblastoma which otherwise might have regressed spontaneously has also been pointed out.[76,77] A consensus conference to discuss the true value of mass screening was held in Lyon, France, in December 1998. Investigators from North America reported that they were negative toward mass screening based upon their own data,[77] and the majority of European researchers agreed with the contention of the North American group,[78] but the German group emphasized that one must consider the results of the German mass screening conducted at the age of 12 months[79] and which may reduce overdiagnosis of infant neuroblastoma.

TREATMENT OF LOW-RISK NEUROBLASTOMA

The treatment of neuroblastoma should be planned individually according to the risk group. There has been argument over whether neuroblastoma consists of two or three types of tumor. Brodeur and Ambros[41] consider that it consists of three types, low risk (type 1), intermediate risk (type 2A), and high risk (type 2B), but the differentiation between their type 2A and type 2B is difficult from a clinical viewpoint, and it should be

Table 16.2: The incidence of stage IV neuroblastoma in Japan, according to Tsuchida et al[2]

Year	Number of neuroblastoma cases*	Number of stage IV neuroblastoma patients older than 12 months of age	Number of live births
1981	107 (1)	55	1,529,455
1982	139 (4)	63	1,515,392
1983	152 (8)	62	1,508,687
1984	136 (12)	46	1,489,780
1985	142 (32)	40	1,431,577
1986	162 (39)	56	1,382,946
1987	143 (49)	30	1,346,658
1988	198 (88)	57	1,314,006
1989	179 (90)	33	1,246,802
1990	190 (108)	40	1,221,585
1991	238 (138)	51	1,223,245
1992	229 (121)	54	1,208,989
1993	207 (135)	32	1,188,282
1994	298 (208)	41	1,238,328
1995	222 (140)	32	1,187,064
1996	238 (162)	28	1,206,555
1997	276 (164)	47	1,191,665
1998	229 (147)	29	1,203,147

*Numbers in parentheses represent cases identified by mass screening and are part of the total. Cases with incomplete data with regard to patient age and disease stage are excluded.[61]

taken into account that prognosis is not determined by *MYCN* amplification alone. Therefore, division into two types, as proposed by Tsuchida and La Quaglia,[80] appears to be more reasonable (Table 16.3).

Low-risk neuroblastomas here denote those occurring in infants younger than 12 months of age in INSS stage I, II, III, and IV-S and without *MYCN* amplification. These tumors should be treated less intensively compared with high-risk tumors.[81] Some neuroblastomas found by mass screening at about 6 or 7 months of age may be treated by observation only if the mass is less than 3 to 4 cm in diameter and does not show any signs of enlargement during the observation period.[82] Nevertheless, in the majority of institutions, the tumor is excised and less aggressive surgery is recommended.[83] Original tumors in stage I, II, and IV-S are excised at the start of treatment, but they should be removed after chemotherapy when they are in stage III.

Chemotherapy for low-risk neuroblastoma should not be aggressive. In Japan, no chemotherapy is administered for stage I and II tumors after complete resection. The recommended preoperative chemotherapy for infant neuroblastoma in stage III consists of alternating weekly administration of vincristine 1.5 mg/m^2 iv and cyclophosphamide 300 mg/m^2 iv, repeated six times. For stage IV without bone cortex metastases, regimen C2 consisting of vincristine 1.5 mg/m^2 on day 1, cyclophosphamide 600 mg/m^2 on day 1 and pirarubicin (THP-adriamycin, Nihon Kayaku, Tokyo) 30 mg/m^2 on day 3 is given nine times at 4-week intervals.[81]

When the tumor is associated with *MYCN* amplification and/or 1p-deletion and/or bone cortex metastases, the infants are treated with a modification of the regimens for advanced neuroblastoma.

TREATMENT OF HIGH-RISK NEUROBLASTOMA

High-risk neuroblastomas here denote those occurring in children older than 12 months of age, in INSS stage III and IV, and with/without *MYCN* amplification. Reports[84,85] show that the results of treatment of stage III and IV disease in older children are still not very good, and are poorer when associated with *MYCN* amplification. Yet it is generally agreed that these two groups, *MYCN* amplified and unamplified, should be given the same consideration as high-risk neuroblastoma. The prognostic significance of *MYCN* amplification is very clear in low-stage patients, but not as clear in stage IV patients.[42,85,86] In the treatment of high-risk neuroblastoma, chemotherapy is vitally important.