

# Molecular Genetics of Neuroblastoma and the Implications for Clinical Management: A Review of the MSKCC Experience

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## ABSTRACT

Neuroblastoma (NB) is a biological, genetic, and morphological heterogeneous neoplasm and demonstrates diverse clinical behavior. There exist at least three clinical patterns of NB: A) spontaneously regressing widespread disease; B) not metastatic local-regional disease, and C) metastatic disease (stage 4), frequently with lethal consequences. Patients with non-stage 4 NB are expected to survive even without medical treatment whereas stage 4 patients have an overall survival rate of 20% despite multimodality therapy protocols. The clinical management of patients with NB is therefore challenged by the objective identification of

cases in which noncytotoxic approaches can be safely taken. Experience in the last decade at Memorial Sloan-Kettering Cancer Center supports the hypothesis that the natural history of disease defines relevant clinical groups of NB and has distinct molecular genetic profiles allowing therapeutic approaches tailored for each group. Here we review the natural history and clinicobiological features of 113 NB cases managed uniformly in our institution in an attempt to characterize useful genetic markers to support the decision making of noncytotoxic versus cytotoxic approaches for each category of NB. *The Oncologist* 2001;6:263-268

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## INTRODUCTION

Neuroblastoma (NB) is one of the most common neoplasms in childhood, accounting for approximately 40% of solid tumors presenting in the first 4 years of life [1]. They are regarded as embryonal tumors, developing during fetal or early postnatal life, from neural crest-derived cells that are still immature or dedifferentiated. These tumors are heterogeneous in their biological, genetic, and morphological characteristics and demonstrate diverse clinical behavior.

There are at least three clinical patterns of NB: A) widespread disease that can spontaneously regress without medical intervention (International Neuroblastoma Staging System [INSS] stage 4S); B) local-regional (LR) tumor that may recur but does not metastasize to bone or bone marrow (INSS stages 1, 2, 3), and C) metastatic disease that responds to cytotoxic therapy but frequently recurs with lethal consequences (INSS stage 4). More than half of the patients present with stage 4 NB, and when more than 1 year of age at diagnosis,

their overall survival (OS) rate is generally low (~20%) [2-6]. In marked contrast, most patients with non-stage 4 NB are expected to survive even without medical treatment. More importantly, for these patients, cytotoxic therapy may not alter the natural history of NB, and locally recurrent or residual tumor post-surgery does not generally evolve into the lethal metastatic form of NB [7].

The study of the molecular genetics of NB in the last two decades has elucidated several nonrandom genetic events: allelic losses on chromosomes 1p, 11q, 14q, 7q, 2q, 3p, and 19q implicating putative tumor-suppressor genes [8-13]; allelic gains on chromosomes 17q, 18q, 1q, 7q, and 5q probably affecting growth control genes [14-17]; amplification of the oncogene *MYCN* [18], and changes in the normal diploid chromosomal content [19]. However, except for *MYCN* status, the relationship of each of these individual genetic events to the clinical course of NB has not been firmly established. Furthermore, although some are strongly

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associated with survival or progression-free survival for NB as a whole, their significance for individual categories of NB remains unclear. Thus, their utility remains questionable in the management of individual patients.

Currently, the clinical management of patients with NB is based on prognostic categories derived from studies correlating outcome and clinicobiological variables. For instance, Children's Oncology Group (COG) defines three risk categories: low-risk disease including stages 1 and 2A and infants with stages 2B, 3, and 4S disease. Patients in this category managed with surgery alone have a disease-free survival (DFS) rate greater than 90% [1]. High-risk disease includes stage 4 in children older than 1 year of age. The outcome of this group is poor despite multimodality protocols with 15% DFS in their experience [1]. An intermediate-risk category includes children with stages 2B and 3 and infants with stage 4. A 70% DFS is achieved in this group using moderately aggressive chemotherapy [1].

Genetic features have been used to classify NB into three risk groups by *Brodeur et al.* [1]. The three resulting groups do not coincide with the risk categories used in COG trials and they do not match the natural history of disease either since metastatic (stage 4) and nonmetastatic tumors (stage 3) are grouped. Experience in the last decade in our institution supports the hypothesis that the natural history of disease defines relevant clinical groups of NB and has distinct molecular genetic profiles for each pattern of disease. Therapeutic approaches have been tailored for each group. Recently, biological studies have shown that genetic markers can help distinguish each category of NB further supporting our hypothesis [20-23].

In this review we evaluate the natural history and clinicobiological features of 113 NB cases in an attempt to characterize useful genetic markers to support the decision-making of noncytotoxic versus cytotoxic approaches for each category of NB.

Table 1 summarizes the clinical characteristics for the three groups of patients analyzed.

### NONMETASTATIC OR LR NB; INSS STAGES 1, 2, AND 3

One-third of NB cases present without distant metastasis, and clinical experience has shown that cytotoxic therapy does not alter the natural history [7]. These tumors usually have a good prognosis without cytotoxic therapy, however, some will recur locally, and a few will progress to stage 4 disease. The risk factors that predict disease progression in this particular group of NB are not well-established. Clinical and biological variables including age, stage, extent of surgical resection, *MYCN* amplification, 1p36 loss of heterozygosity (LOH), histology, and ploidy have shown to have limited predictive value in previous studies [20]. The importance of

individual biological markers in predicting specifically the clinical behavior of LR NB is often confounded by various methods of stratification and therapy [24-29]. Consistent genetic alterations unique for LR NB have not been identified.

### Clinical Characteristics

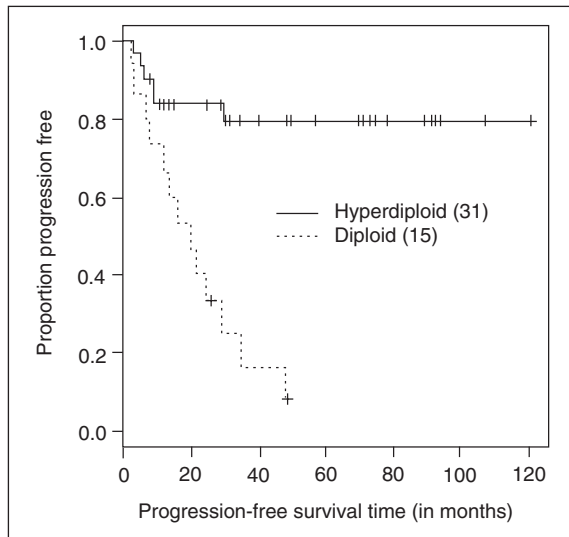
During the last 12 years at Memorial Sloan-Kettering Cancer Center (MSKCC), 57 patients diagnosed with LR NB were managed conservatively and initially treated only with surgery. Forty-six patients diagnosed with LR NB including 10 stage 1, 18 stage 2, and 18 stage 3 had frozen tumor samples available and were further analyzed. Thirty-seven were initially diagnosed at MSKCC and nine referred at relapse. Eight referred patients had prior chemotherapy for their LR NB. Seventeen patients (37%) were younger than 1 year of age at diagnosis.

Fifteen of the 37 patients (40%) managed from diagnosis at MSKCC had disease progression. Seven had local relapse including three stage 2 and four stage 3. Five tumors (two stage 1, two stage 2, and one stage 3) progressed to stage 4 at the time of first relapse (at 7, 11, 3.5, 2.8, and 13 months from diagnosis, respectively) and one tumor progressed to stage 4 after many LR recurrences 64 months after diagnosis. Two tumors (stage 3 initially) progressed to stage 4N (lymph node metastasis but not bone or bone marrow metastasis) at 1 month and 1 year, respectively, from diagnosis.

Nine patients are dead, five of progressing disease, three as stage 4, and two as LR stage 3. Overall, 37 patients (84%) are alive and well, progression-free (median follow-up of 50 months).

**Table 1.** Clinical characteristics of the three groups of patients analyzed

	LR <i>n</i>	Stage 4 <i>n</i>	Stage 4S <i>n</i>
Total (113)	46	59	8
at Dx	37	59	8
at rel	9	–	
Age			
<1 y	17	12	8
>1 y	29	47	
INSS stages			
1	10		
2	18		
3	18		
Progression			
locally	7/37		5
stage 4	6/37		
stage 4N	2/37		
Outcome			
A	37/46	40/59	8/8
D	9/46	19/59	
Median F/u (months)	50	31	120



**Figure 1.** Kaplan-Meier curves for progression-free survival for LR cases showing a significant difference between diploid and hyperdiploid LR tumors.

### Molecular Genetics

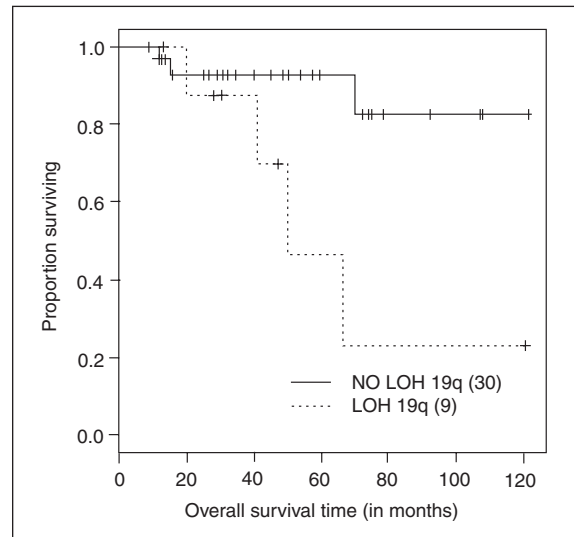
Eighteen of 40 cases (45%) for which Shimada classification was applicable had unfavorable histology. DNA index was in the diploid-tetraploid range in 15 patients (32%) and hyperdiploid (near-triploid) in 31 (67%). *MYCN* copy number was amplified in six (13%) cases. Seventeen of the 43 (39%) cases had 1p36 LOH and 11 (25%) cases had 1p22 LOH. All *MYCN*-amplified tumors exhibited 1p deletions. Eleven (25%) showed 11q LOH; 14 (32%) had 14q LOH; 5 of 39 cases (12%) had 9p LOH; 9 of 40 cases (21%) presented with 19q LOH.

### Prognostic Features

Among all the biologic and clinical features analyzed including age, stage, histology, ploidy, *MYCN*, and 1p36, 1p22, 11q, 14q, 9p, and 19q LOH in multivariate analysis, diploidy was the most significant factor associated with progression-free survival and stage 4 progression (Fig. 1). Patients with diploid DNA index had a 6.38 and 8.3 times chance of relapse and progression to stage 4, respectively, compared with patients with near-triploid DNA index. Ploidy was associated with OS as well as 19q LOH (Fig. 2). Patients with diploid DNA index had a 9.39 times chance of dying compared with patients with aneuploid DNA index. Patients with 19qLOH had a 2.19 times chance of dying compared with patients without 19q LOH.

### Clinical Strategy

A successful clinical strategy avoiding cytotoxic therapy for LR NB can be applied for all LR NB tumors with a

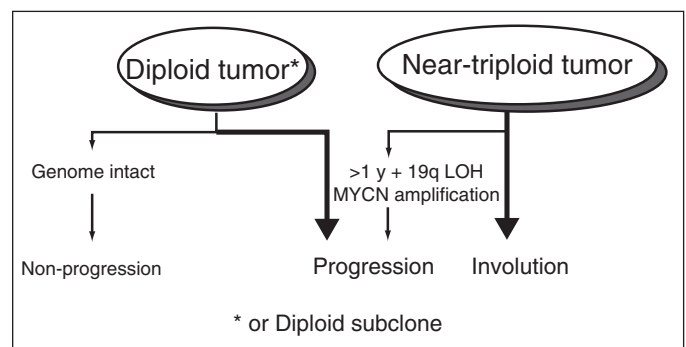


**Figure 2.** Kaplan-Meier curves for OS for LR patients. Patients with 19q LOH tumors had a significantly poorer survival compared to patients with 19q intact tumors.

near-triploid DNA index regardless of any other clinical or biological feature (Fig. 3). The risk for such tumors to progress to stage 4 disease is extremely low in our experience [20, 30]. On the other hand, diploid LR NB have a significantly higher risk of progressing to stage 4 disease or multiple relapse as malignant LR disease. The presence of 19q13 LOH in an LR NB patient more than 1 year old is also associated with local aggressiveness and decreased overall survival [21]. Such cases require more intensive vigilance or aggressive multimodality therapy upfront.

### METASTATIC NB (INSS STAGE 4)

The majority of clinically detectable NB do not undergo spontaneous regression or maturation, but present as advanced stage tumors (INSS stage 4) that initially respond to radio- and chemotherapy, but frequently recur



**Figure 3.** Proposed genetic model to explain clinical progression and non-progression among LR NB patients according to our experience.

and become progressively resistant to medical treatment. A genetic profile for stage 4 tumors includes: diploid/tetraploid DNA index and a variable combination of 1p36 LOH and 1p22 LOH [22], 11q LOH [9], 17q gain [16], 14q LOH [10], *MYCN* amplification [8, 18], and 1q21 gain [17]. Except for *MYCN* status, no other variables have been able to stratify among stage 4 patients, mainly due to the poor overall outcome of the whole group with standard therapeutic approaches [8, 31].

### Clinical Characteristics

Fifty-nine newly diagnosed stage 4 patients, 28 females and 31 males, treated with two consecutive very similar protocols at our institution were analyzed. Seventeen patients were treated with the N6 protocol and 41 with the N7 protocol. One patient with near-triploid DNA index and 13 months of age, although stage 4 according to the INSS staging system, was treated like a stage 4S with no cytotoxic therapy. Median age at diagnosis was 3.1 years. Twelve patients (20%) were younger than 1 year of age at diagnosis. Nineteen patients (32%) have died of disease progression. Forty patients (68%) are alive with a median follow-up of 31 months.

### Molecular Genetics

Unfavorable histology was found in 39 of 47 patients (82%). Twenty of 54 cases studied (37%) had *MYCN* amplification. Diploid/tetraploid DNA index was found in 34 (91%) of 37 cases studied. Twenty-six cases (44%) had

1p36 LOH, 28 (47%) 1p22 LOH, 27 (45%) 11q LOH, 19 (32%) 14q LOH, 7 (11%) 9p LOH, and 5 (8%) 19q LOH.

### Prognostic Features

Among all the biologic and clinical features analyzed including age, stage, histology, ploidy, *MYCN*, and 1p36, 1p22, 11q, 9p, 14q, and 19q LOH in multivariate analysis, only *MYCN* amplification showed statistically significant *p* values when predicting for survival (Fig. 4).

### Clinical Strategy

Current management for stage 4 NB consists of multimodality regimens including high-dose chemotherapy, radiation therapy, immunotherapy, and surgery. Only *MYCN* status allows for prognostic stratification of this group of patients. No other clinical or biological marker we evaluated is of clinical significance when age-based intensive regimens are used in the management of this most common group of NB.

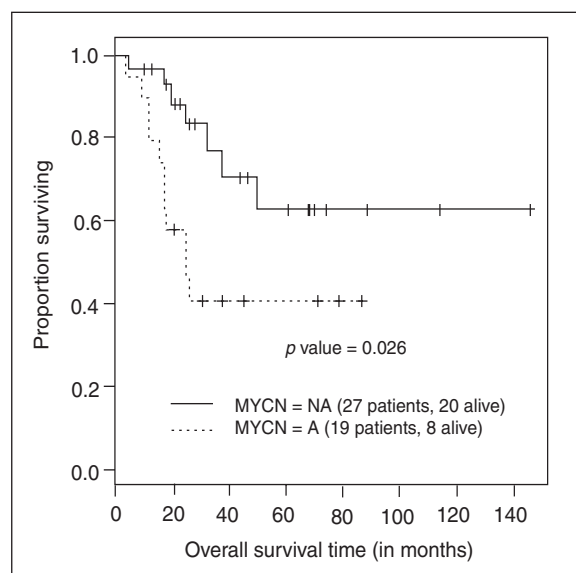
### WIDESPREAD BUT SPONTANEOUSLY REGRESSING NB (STAGE 4S)

In 1971 a special subgroup, characterized by a unique pattern of dissemination (restricted to certain organs such as liver, skin, bone marrow, but not bone) and a high incidence of spontaneous regression, was identified among infants with disseminated NB. This subgroup, designated stage 4S, has been recognized as a distinct clinical entity in all subsequent classifications of NB [32], with >90% OS. The requisite clinical features of stage 4S at diagnosis are a small primary tumor (usually resectable and not crossing the midline) in children <1 year of age, with no bony metastasis and minimal (usually <10%) marrow involvement. Accurate staging is essential since the use of aggressive chemotherapy, or just minimal or no therapy approaches, depends on it. Treatment decisions currently rely on available clinical diagnostic tools to assess tumor resectability, bony metastasis or extent of marrow involvement.

Biologically the majority (but not all) of reported stage 4S tumors are aneuploid [33], of favorable histology according to the *Shimada* classification [34], *MYCN* nonamplified [35], and chromosome 1p36-intact [36].

### Clinical Characteristics

Since 1987, a uniform no-cytotoxic therapy approach for stage 4S tumors was adopted at MSKCC. This conservative approach allows for surgical resection or biopsy but no upfront chemotherapy or radiation therapy [7]. Eight stage 4S patients were studied and all underwent spontaneous remission (despite recurrence in 5/8 patients) without cytotoxic therapy. Despite some cases with unusual



**Figure 4.** Kaplan-Meier curves for OS among stage 4 patients. Patients with *MYCN*-amplified tumors had a significantly poorer survival compared to those with *MYCN*-nonamplified tumors.

features such as atypical metastases, progressive disease, persistence of metastatic disease past 365 days of life, all are alive and well, median follow-up of 120 months.

### Molecular Genetics

Seven of the seven evaluable stage 4S tumors were histologically favorable. Seven of the eight stage 4S tumors were near-triploid. None were *MYCN* amplified. Seven of seven stage 4S tumors tested expressed CD44 and *trkA*. None of the stage 4S tumors had 1p36, 1p22, or 14q LOH. Interestingly, five of the eight stage 4S tumors had detectable LOH at 1p31 or 11q, consistent with clonal proliferation.

### Prognostic Features

When compared to 23 clinically matched stage 4 infants, a notable and consistent absence of any 1p36, 1p22, or 14q loss in stage 4S tumors was found [23]. In our experience retention of these markers represented a unique characteristic of spontaneously regressing stage 4S disease.

### Clinical Strategy

No uniform therapeutic strategies have been adopted in the literature for stage 4S disease, and many of the reported cases have received some sort of cytotoxic therapy making correlation with natural history difficult [37-43]. In our experience cases with near-triploid DNA index and absence of 1p36, 1p22, and 14q LOH can be safely managed conservatively with a non-cytotoxic therapy regardless of age,

tumor resectability, and progressive or persistent metastatic disease.

### CONCLUDING REMARKS

The genetic identification of clinically distinct tumors provides useful objective diagnostic and prognostic tools for improved classification and risk stratification of individual NB patients. In summary, according to our experience, a non-cytotoxic approach can be safely taken to all NB tumors presenting as LR disease with near-triploid DNA index and to infants with widespread disease with near-triploid DNA index and absence of 1p36, 1p22, and 14q LOH. On the other hand, diploid LR NB tumors or LR tumors with 19q LOH require a multimodality therapy approach like stage 4 disease. The results of this and other studies show the evolving nature of prognostic single markers with regard to treatment advances. Clinical variables (age) or biological factors (*MYCN* copy number) may no longer have prognostic significance with homozygous clinical groups and advanced therapeutic strategies.

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