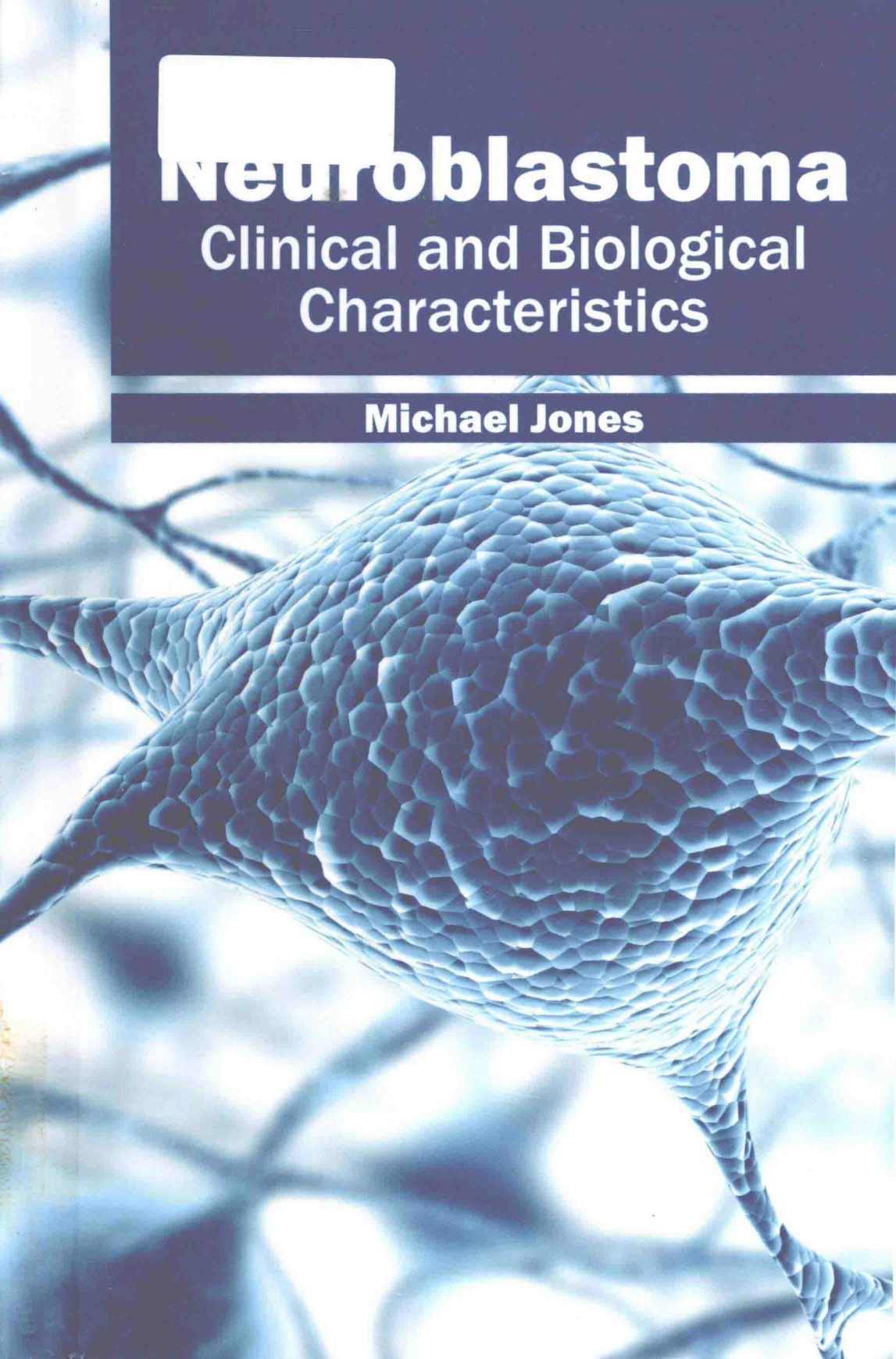
Neuroblastoma

Clinical and Biological Characteristics

Michael Jones



Neuroblastoma: Clinical and Biological Characteristics

Edited by **Michael Jones**

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Preface

Over the recent decade, advancements and applications have progressed exponentially. This has led to the increased interest in this field and projects are being conducted to enhance knowledge. The main objective of this book is to present some of the critical challenges and provide insights into possible solutions. This book will answer the varied questions that arise in the field and also provide an increased scope for furthering studies.

The book sets out to present the facts and contradictions of neuroblastoma. Tumors of neuroblastoma group are heterogeneous and their genomic/molecular properties are intimately associated with the prognosis of patients; certain children enjoy a distinguished clinical course post the surgery/biopsy alone, and others face a catastrophic result even after a thorough treatment. Latest advancement has also began unveiling crucial importance of cross-talking between neuroblastoma cells and their microenvironment in predicting clinical behaviors of individual cases. The biological and clinical characteristics of this disease are presented in this book by renowned investigators.

I hope that this book, with its visionary approach, will be a valuable addition and will promote interest among readers. Each of the authors has provided their extraordinary competence in their specific fields by providing different perspectives as they come from diverse nations and regions. I thank them for their contributions.

Editor

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Neuroblastoma, Clinical

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Clinical Presentation of Neuroblastoma

Josef Malis

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1. Introduction

Neuroblastoma is a cancer of the peripheral sympathetic nervous system, derived from embryonic neural crest cells (a neuroendocrine tumor) and is one of the few cancers known to undergo spontaneous regression from an undifferentiated state to a benign tumor.

Neuroblastoma is the most common extracranial solid tumor in children, accounting for 7% to 8% of all childhood cancers. The prevalence is about 1 case per 7,000 live births. This incidence is fairly uniform throughout the world, at least for industrialized nations. Neuroblastoma is slightly more common in boys than in girls, with a male-to-female sex ratio of 1.1 to 1 in most large studies [1]. While it accounts for 7% of all childhood malignancies, neuroblastoma accounts for 10% of childhood cancer mortality. Neuroblastoma is a pediatric neoplasm that is the most common cancer diagnosed during infancy. POG and CCG institutions from 1986 to 2001 showed a median age at diagnosis of about 19 months. In this cohort, 36% were infants, 89% were younger than 5 years, and 98% were diagnosed by 10 years of age. The distribution of cases by age shows that this is a disease of infancy and early childhood, with the highest number of cases diagnosed in the first month of life [2].

2. Current outcome

Patients with low- and intermediate-risk NBL have an overall survival rate exceeding 90% with a trend toward minimization of therapy [3,4,5]. Standard therapy for patients with high-risk NBL involves multi-agent chemotherapy induction, surgery and external beam radiotherapy, myeloablative consolidation with autologous hematopoietic stem cell recue and biologic agents, including the recent demonstration that GD2- directed immunotherapy combined with cytokines significantly improves survival. Despite these achievements, 50% of

patients with newly diagnosed high-risk disease, and less than 10% of patients whose disease recurs, will survive [6].

3. General remarks

Neuroblastoma is very often called "enigmatic tumor" for its broad spectrum of clinical presentation, biological features and prognosis varying from clinically incidence benign to unresectable or metastic disease with very poor outcomes. Neuroblastomas can arise anywhere throughout the sympathetic nervous system, most common primary site is adrenal gland, followed by abdominal (extraadrenal), thoracic, cervical, and pelvic sympathetic ganglia. Neuroblastoma metastasizes to lymph nodes, bone marrow, bones (long bones, flat bone soft the scull, orbits), liver, and skin, rarely to lungs or brain. Widespread bone and bone marrow disease causes bone pain, which can lead to limping, or irritability in a younger child. There may be bone marrow replacement and symptoms such as anemia, bleeding, or infection. Skin involvement is seen almost exclusively in infants with INSS stage Ms (4S) tumors and is characterized by a variable number of nontender, bluish subcutaneous nodules.

Constitutional symptoms associated with disseminated disease may include failure to thrive and fever, the latter observed most often in the presence of extensive bone metastases [7]

Regional lymph node metastases are noted in up to 35% of patients with apparently localized tumors and 30% of patients with stage M (4) and Ms (4S) disease also have regional lymph node involvement. Spread of tumor to lymph nodes outside the cavity of origin is considered to be INSS stage 4 disease, but these patients may have a better outlook if there is no bone marrow, cortical bone, or other parenchymal organ involvement. [8,9]

Most primary tumors occur within the abdomen (65%), although the frequency of adrenal tumors is slightly higher in children (40%) compared with infants (25%). Infants also have more thoracic and cervical primary tumors. A primary tumor cannot be found in about 1% of patients.

4. Staging and stratification

The for decades used surgical-pathologic International Neuroblastoma Staging System (INSS) – Table 1 [10] has been recently replaced by the International Neuroblastoma Risk Group Staging System (INRGSS) [11]. The INRGSS uses radiologic features to distinguish locoregional tumors (Table 2) that do not involve local structures (INRGS L1) from locally invasive tumors (INRGS L2), exhibiting image defined risk factors (Table 3) [12]. Stages M and MS refer to tumors that are widely metastatic or have an INSS 4 and 4s pattern of disease, respectively. Neuroblastoma is classified into low-, intermediate-, or high-risk categories based upon clinical and biological features, with risk category correlating with outcome. The recently proposed INRG classification defines similar cohorts that will be used to assess clinical trial

outcome. The International Neuroblastoma Response Criteria (INRC) provide a common basis for disease response comparisons across clinical trials [13]. Importantly, the INRC has limitations with respect to definitions of metastatic site response not measurable using anatomical imaging (bone and bone marrow). A National Cancer Institute-sponsored international meeting was held in 2012 to develop updated consensus response guidelines. Response components of a revised INRC will includeprimary tumor dimensions using anatomic imaging, and metastatic disease assessment using 123I-MIBG imaging and quantification of bone marrow disease.

Stage 1:	Localized tumor with complete gross excis ion, with or without microscopic residual disease; representative ipsilateral lymph nodes negati ve for tumor microscopically (nodes attached and removed with the primary tumor may be positive)
Stage 2A:	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically
Stage 2B:	Localized tumor withor without komplete gross excision, with ipsilateral nonadherentlymph nodes positive for tumor. Enlarged contralateral lymph nodes must benegative microscopically
Stage 3:	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumorwith contralateral regional lymphnode involvement; or midline tumor with bilateral extensit by infiltration (unresectable) or by lymph node involvement
Stage 4:	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S)
Stage 4S:	Localized primary tumor (as defined for stage 1, 2A, or2B), with dissemin ation limited to skin, liver and/or bone marrow (limited to infants <1 year of age)

Table 1. International Neuroblastoma Staging System

Ipsilateral tumor extension within two body compartments

Neck-chest, chest-abdomen, abdomen-pelvis

Neck

Tumor encasing carotid and/or vertebral artery and/or internal jugular vein

Tumor extending to base of skull

Tumor compressing the trachea

Cervico-thoracic junction

Tumor encasing brachial plexus roots

Tumor encasing subclavian vessels and/or vertebral and/or carotid artery

Tumor compressing the trachea

Thorax

Tumor encasing the aorta and/or major branches

Tumor compressing the trachea and/or principal bronchi

Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12

Thoraco-abdominal

Tumor encasing the aorta and/or vena cava

Abdomen/pelvis

Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament

Tumor encasing branches of the superior mesenteric artery at the mesenteric root

Tumor encasing the origin of the coeliac axis, and/or of the superior

mesenteric artery

Tumor invading one or both renal pedicles

Tumor encasing the aorta and/or vena cava

Tumor encasing the iliac vessels

Pelvic tumor crossing the sciatic notch

Intraspinal tumor extension whatever the location provided that:

More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal

Infiltration of adjacent organs/structures

Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery

Conditions to be recorded, but not considered IDRFs

Multifocal primary tumors

Pleural effusion, with or without malignant cells

Ascites, with or without malignant cells

Table 2. Image-defined risk factors (IDRFs)

L1:	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2:	Locoregional tumor with presence of one or more image-defined risk factors
M:	Distant metastatic disease (expect stage MS)
MS:	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

Table 3. International Neuroblastoma Risk Group Staging System

5. Sporadic and familiar neuroblastoma

Most neuroblastomas occur sporadically; around 1-2% are familial and associated with multiple primary tumours, usually occurring at <18 months of age. Familial disease has the same diverse clinical behaviour as somatic neuroblastoma, ranging from aggressive progression to spontaneous regression.11 Within the last 10 years significant advances have been in the understanding of hereditary neuroblastoma, with germline mutations in two genes ALK and paired homeobox 2b gene PHOX2B accounting for the majority of cases, which may present in the neonatal period. ALK mutations are now known to be the most now known common cause of hereditary neuroblastoma, and in familial neuroblastoma [14,15,16]

6. Associated conditions

Neuroblastoma can be associated with several inborn conditions, like Hirschsprung disease, congenital central hypoventilation syndrome (CCHS or Ondine's curse), neurofibromatosis type I, or Beckwith-Wiedemann syndrome

7. Clinical presentation

The presenting signs and symptoms of neuroblastoma are highly variable with a broad spectrum. Presenting symptoms of neuroblastoma depend on the location of the primary tumor, presence of metastatic lesions, systemic symptoms from catecholamine secretion. Weight loss and fever are present at advanced stages neuroblastoma.

8. Anatomical site of the primary tumour

8.1. Head and neck

Unilateral palpable mass developing in infants or in preschool age children, rarely are diagnosed in newborn mimicking cervical teratoma. [17]

Horners syndrome (ptosis, miosis, anophthalmos, anhydrosis). This syndrome is unilateral, Tatli reported a 28 old child with bilateral prosis [18]. Primary cervical neuroblastoma are ussually non agressive and thein prognosis is very good. But some are fatal - extremely rare case described Güzelmansur et al. – diagnosed prenatally with progression to brain. [19]

Orbit and eye exophthalmoses, periorbital ecchymoses (raccoon eyes), palpable masses, edema of conjunctiva, papilledema, strabismus, anisocoria. The periorbital ecchymoses can be present in about 20% of disseminated neuroblastoma. This clinical findings is related to obstruction of the palpebral ond orbita vessels by metastatic lesions within orbital bones. Frequently these

children are investigated for an abuse or a trauma (basal skull fractures) [20,21]. Usually further systemic symptoms are present – weight loss, fever.

Opsoclonus also known as dancing-eye syndrome, presents in early childhood with opsoclonus (rapid, multidirectional, conjugate eye movements) usually associated with myoclonus, ataxia, and behavioral changes such as irritability and sleep problems.– opsoclonus-myoclonus syndrome (OMS) [22]

Chest Upper thoracic tumours: Primary thoracic tumors present as symptomatic masses or can be discovered incidentally when chest radiographs are obtained to evaluate patients for other reasons. High thoracic and cervical masses can be associated with Horner syndrome, which consists of unilateral ptosis, myosis, and anhydrosis. Occasionally, large thoracic tumors are associated with mechanical obstruction and resultant superior vena cava syndrome.

Lower thoracic tumours: usually no symptoms, usually accidental discovery on chest X-ray or thoracic CT performed for other reasons.

8.2. Abdominal neuroblastoma

About 60% of primary neuroblastomas arise in the abdomen, two thirds of them are from the adrenal glands (adrenal neuroblastoma), one third are from paravertebral ganglion (extraadrenal neuroblastoma). Only about one tenth of neuroblastoma are detected as an abdominal mass during a routine examination. The mass is ussually fixed,and firm.

Symptoms: abdominal pain or fullness, abdominal mass, or rarely intestinal obstruction, enlarged and/or displaced liver and spleen. Massive involvement of the liver with metastatic disease is particularly frequent in infants with stage Ms (4S) and may result in respiratory compromise (Pepper Syndrome). Occasionally, the size of primary or metastatic abdominal tumors can result in compression of venous and lymphatic drainage from the lower extremities, leading to scrotal and lower extremity edema. Rarely, patients will experience renin-mediated hypertension because of compromise of renal vasculature.

Hypertension, tachycardia, flushing, and sweating are uncommon symptoms because epinephrine is rarely released from most neuroblastomas, since they lack the enzyme necessary for synthesis.

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Spontaneous rupture from hemorrhage into the tumor occurs very rarely and only in rapidly growing tumors.

There is a small subgroup of abdominal neuroblastomas arising near to the aortic bifurcation (commonly called organ of Zuckerkandl, O. Z.) to assess their biologic outcome and problems in diagnosis and therapy. The organ of Zuckerkandl comprises of a small mass of chromaffin cells derived from neural crest located along the aorta, beginning cranial to the superior mesenteric artery or renal arteries and extending to the level of the aortic