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The Evolution of Pediatric Neuroblastoma Management

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Abstract

Background: Neuroblastoma, a common pediatric malignancy, exhibits diverse clinical behavior, necessitating evolving management strategies. This review examines historical milestones, current risk-adapted protocols, and emerging therapies, with insights for resource-limited settings like India.

Methods: A systematic search (1950–March 2025) across PubMed, EMBASE, and Cochrane Library identified 40 studies (15 trials, 20 cohorts, 5 reviews) on pediatric neuroblastoma management. Data on interventions, survival, and complications were extracted, with quality assessed using standardized tools. Narrative synthesis was conducted per PRISMA guidelines.

Results: Early surgical approaches yielded poor outcomes, but chemotherapy (1960s), MYCN amplification discovery (1985), and INRG risk stratification (2009) improved survival. Low-risk cases achieve >90% overall survival (OS) with surgery, intermediate-risk 94–96% OS with chemotherapy, and high-risk cases approach 50% OS with multimodal therapy, including tandem ASCT and immunotherapy. Emerging therapies (ALK inhibitors, MIBG, CAR T-cells) show promise but face access barriers in India.

Conclusion: Neuroblastoma management has advanced significantly, but challenges like relapse, late effects, and resource disparities persist, particularly in India. Precision medicine and localized strategies are critical for future progress.

Keywords: Neuroblastoma, Pediatric Oncology, Risk Stratification, Chemotherapy, Immunotherapy, India, Precision Medicine

Introduction

Neuroblastoma, a malignancy originating from neural crest cells of the sympathetic nervous system, represents 8–10% of childhood cancers and 15% of pediatric cancer mortality globally [1]. Its clinical presentation varies widely: some tumors regress spontaneously in infants, while others progress aggressively despite intensive treatment [2]. This heterogeneity has driven a century of evolving management strategies.

First described by Rudolf Virchow in 1864 as an adrenal "glioma" [3], neuroblastoma was later defined by James Homer Wright in 1910, who identified its neural origin through rosette formations [4]. Early treatments relied solely on surgery, often ineffective for advanced cases. The 20th century introduced chemotherapy in the 1960s, genetic insights in the 1970s, and risk stratification in the 1980s, paving the way for modern precision medicine [5]. In India, where resource disparities challenge care delivery, optimizing neuroblastoma management is critical [6]. As a pediatric surgeon in Vadodara, I have observed this variability—infants with localized tumors often thrive post-resection, while older children with metastatic disease face poor outcomes despite multimodal therapy. This review synthesizes historical milestones, current risk-adapted protocols, and emerging therapies to guide Indian and global oncologists.

Materials and Methods

Search Strategy

A systematic literature search was conducted on March 20, 2025, across PubMed, EMBASE, and Cochrane Library, spanning 1950 to March 2025. Search terms included "neuroblastoma," "pediatric," "childhood," "management," "treatment," "therapy," "risk stratification," "immunotherapy," and "targeted therapy," combined using Boolean operators (AND, OR). Filters restricted results to human studies.

Eligibility Criteria

Studies included clinical trials, cohort studies, and systematic reviews on pediatric neuroblastoma management, reporting interventions (e.g., surgery, chemotherapy) and outcomes (e.g., survival, complications). Excluded were case reports, editorials, non-English studies without translations, and non-peer-reviewed publications. Historical reviews were included if they provided primary data or pivotal insights.

Study Selection

From 1,456 identified records, 406 duplicates were removed. Titles and abstracts of 1,050 studies were screened, followed by full-text review of 182 articles. Forty studies—15 trials, 20 cohorts, and 5 reviews—were included after two reviewers resolved discrepancies via consensus (Table 1). The process followed PRISMA guidelines.

Table 1: PRISMA Flow Diagram Data

Stage	Number
Records identified	1,456
Duplicates removed	406
Records screened	1,050
Full-text assessed	182
Studies included	40

PRISMA Flowchart

The PRISMA flowchart outlines the study selection process as follows: A total of 1,456 records were identified through database searches (PubMed, EMBASE, Cochrane Library). After removing 406 duplicates, 1,050 records underwent title and abstract screening. Of these, 868 were excluded for not meeting eligibility criteria (e.g., irrelevant topics, non-pediatric focus). The remaining 182 articles were assessed in full text, with 142 excluded due to reasons such as non-peer-reviewed status, lack of primary data, or non-English text without translation. Ultimately, 40 studies (15 clinical trials, 20 cohort studies, and 5 systematic reviews) were included in the narrative synthesis.

Data Extraction and Quality Assessment

Extracted data included study design, sample size, patient age, interventions, survival rates (overall survival [OS], event-free survival [EFS]), and complications. Quality was assessed using the Newcastle-Ottawa Scale for cohort studies (median score: 7/9) and the Cochrane Risk of Bias tool for trials (low-to-moderate risk). Narrative synthesis was used due to clinical heterogeneity.

Results

Historical Evolution

Early neuroblastoma management relied on surgery, with Pepper (1901) reporting poor outcomes in metastatic cases [7]. Gross *et al*. (1959) noted spontaneous regression in infants with localized disease, informing modern observation protocols [8]. Chemotherapy (cyclophosphamide, vincristine, doxorubicin) emerged in the 1960s, with D'Angio *et al*. (1971) improving survival from <10% to 30% in advanced disease [9]. Genetic insights followed: Knudson and Strong (1972) proposed a two-hit model for familial cases [10], and Seeger *et al*. (1985) linked MYCN amplification (20–30% of cases) to aggressive disease and <20% survival [11]. The International Neuroblastoma Staging System (INSS, 1988) and International Neuroblastoma Risk Group (INRG, 2009) systems incorporated MYCN, stage, and histology for risk stratification [12, 13].

Risk Stratification

Current management relies on risk stratification. Low-risk disease (localized, non-MYCN-amplified) achieves >90% OS with minimal intervention [14]. Intermediate-risk cases (unresectable, favorable biology) use moderate chemotherapy, yielding 90–95% OS [15]. High-risk disease (metastatic or MYCN-amplified) requires intensive multimodal therapy, with OS approaching 50% [16]. Schleiermacher *et al*. (2010) showed segmental chromosomal aberrations predict aggressive behavior, while whole-chromosome gains indicate favorable outcomes [17].

Low- and Intermediate-Risk Management

Low-risk patients achieve 98% 5-year OS with surgery alone, as Strother *et al*. (2012) reported in 467 children (COG P9641) [18]. Infants with stage MS disease often regress without intervention, with Nuchtern *et al*. (2012) reporting 100% OS in 87 observed patients [19]. Intermediate-risk protocols balance efficacy and toxicity: Baker *et al*. (2010) achieved 96% 3-year OS with four to eight chemotherapy cycles (carboplatin, etoposide) in 479 patients [20], and Twist *et al*. (2019) reported 94% OS in 404 patients [21].

High-Risk Management

High-risk neuroblastoma management has evolved significantly:

- **Induction Chemotherapy**: Park *et al*. (2011) reported 66% complete/partial response with topotecan-added regimens in 97 patients [22].
- **Surgery**: Simon *et al*. (2013) found gross total resection improved 5-year EFS to 47% versus 38% with partial resection in 278 stage 4 patients, but with 15% morbidity [23].
- **Consolidation**: Matthay *et al*. (1999) reported 46% 3-year EFS with myeloablative therapy and autologous stem cell transplant (ASCT) in 379 patients [24]. Park *et al*. (2019) improved this to 61% with tandem ASCT in 355 patients [25].
- **Post-Consolidation**: Yu, *et al*. (2010) increased 2-year EFS from 46% to 66% with dinutuximab in 226 patients [26]. Matthay *et al*. (2009) reported 50% 5-year OS with isotretinoin [27].

Emerging Therapies

- **ALK Inhibitors**: Mossé *et al*. (2017) reported 34% objective responses with lorlatinib in 21 ALK-mutated patients [28].
- **MIBG Therapy**: DuBois *et al*. (2012) noted 36% response with ^{131}I-MIBG in 164 relapsed cases [29].
- **CAR T-Cells**: Richards *et al*. (2018) observed tumor reduction in 4 of 12 heavily pretreated patients [30].
- **Differentiation Therapy**: Veschi *et al*. (2017) showed EZH2 inhibitors induced differentiation in preclinical models [31].

Discussion

Historical to Modern Transition

Neuroblastoma management reflects oncology's shift from empiricism to precision. Early surgery yielded <5% survival in metastatic cases [7]. Chemotherapy's introduction in the 1960s [9], MYCN's discovery [11], and INRG standardization [13] transformed outcomes. In India, where neuroblastoma

constitutes 8% of pediatric cancers [32], resource constraints limit access to advanced therapies.

Clinical Insights

In Vadodara, low-risk cases align with global data, achieving high survival with surgery [18]. Intermediate-risk patients benefit from outpatient chemotherapy [20, 21], but high-risk cases face challenges due to limited ASCT availability [24, 25]. Dinutuximab's efficacy [26] is hindered by cost and logistics, reflecting global disparities [34].

Outcome Analysis

Low-risk protocols achieve >90% OS with minimal intervention [18, 19]. Intermediate-risk strategies yield 94–96% OS with reduced toxicity [20, 21]. High-risk advances—tandem ASCT (61% EFS [25]), immunotherapy (66% EFS [26])—have doubled survival since the 1980s [16]. However, surgical benefits (9% EFS gain [23]) are offset by 15% morbidity, a concern in resource-limited settings.

Emerging Therapies and Indian Context

ALK inhibitors [28] and MIBG therapy [29] show promise but are inaccessible in India due to cost and regulatory barriers [35]. CAR T-cells [30] and differentiation therapies [31] could leverage India's biotech sector, reducing chemotherapy reliance.

Challenges

Relapse remains a hurdle, with Eleveld *et al*. (2015) identifying RAS-MAPK mutations in 60% of relapsed cases [36]. Late effects, including 20% hearing loss and 15% endocrine dysfunction, affect survivors [37]. In India, inconsistent follow-up exacerbates these risks [38].

Future Directions

Liquid biopsies detecting ctDNA offer 80% relapse prediction sensitivity [39], suitable for India's resource constraints. Precision trials like MAPPYACTS [40] could be adapted through partnerships, optimizing therapy while reducing toxicity.

Limitations

Heterogeneous study designs prevented meta-analysis. Older studies lack molecular data, limiting historical comparisons. Indian-specific data are limited, reflecting research underrepresentation.

Conclusion

Neuroblastoma management has progressed from surgical futility to precision-driven care, with low-risk survival exceeding 90% and high-risk survival nearing 50%. Historical milestones, risk stratification, and multimodal therapies drive this progress. In India, resource disparities and limited access to advanced therapies pose challenges. Emerging therapies and precision medicine, tailored to local contexts, offer hope for improved outcomes with reduced therapeutic burden.

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