Advances in the Surgical Treatment of Neuroblastoma

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Abstract

Objective: This study was to review the efficacy of surgical resections in different clinical situations for a better understanding of the meaning of surgery in the treatment of neuroblastoma (NB).
Data Sources: The online database ScienceDirect (2016–2018) was utilized. The search was conducted using the keywords "neuroblastoma," "neuroblastoma resection," "neuroblastoma surgery," and "high-risk neuroblastoma."
Study Selection: We retrospectively analyzed of patients who underwent surgical resections in different clinical situations. The article included findings from selected relevant randomized controlled trials, systematic reviews, and meta-analyses or good-quality observational studies. Abstracts only, letters, and editorial notes were excluded. Full-text articles and abstracts were extracted and reviewed to identify key articles discussing surgery management of NB, which were then selected for critical analysis.
Results: A total of 7800 English language articles were found containing references to NB (2016–2018). The 163 articles were searched which were related to the surgical treatment of NB (2016–2018). Through the analysis of these important articles, we found that the treatments of NB at low- and intermediate-risk groups were basically the same. High-risk patients remained controversial.
Conclusions: NB prognosis varies tremendously based on the stage and biologic features of the tumor. After reviewing the relevant literature, patients with low-risk disease are often managed with surgical resection or observation alone with tumors likely to spontaneously regress that are not causing symptoms. Intermediate patients are treated with chemotherapy with the number of cycles depending on their response as well as surgical resection of the primary tumor. High-risk patients remain controversial. Multidisciplinary intensive treatment is essential, especially for patients who received subtotal tumor resection. Minimally invasive surgery for the treatment of NBs without image-defined risk factors in low- to high-risk patients is safe and feasible and does not compromise the treatment outcome. We conclude that ≥90% resection of the primary tumor is both feasible and safe in most patients with high-risk NB. New targeted therapies are crucial to improve survival.

Key words: Advance; High Risk; Neuroblastoma Surgical Resection; Survival

INTRODUCTION

Neuroblastoma (NB) is the most common extracranial solid tumor in children, arising from neural crest cells that differentiate to the sympathetic ganglia and adrenal medulla.[1,2] The occurrence of NB is unusual in adolescents and adults.[3] Metastatic NB in children older than one year is still associated with a poor prognosis, as the majority of these patients, after an initial response to chemotherapy, suffer relapse of drug-resistant disease. Staging is performed using bone marrow and mIBG scan. Age, stage, histopathological grading, *MYCN* amplification, and 11q aberration are important prognostic factors utilized in risk stratification.[4,5] Timing and choice of treatment modalities varies according to the stage, location of tumor, associated risk factors, and patient's age. A surgical resection is the mainstay of treatment for a localized tumor. Patients with low- and intermediate-risk NB have an estimated overall survival (OS) rate over 90% with an ongoing trend toward minimization of therapy.[6] However, high-risk disease has a suboptimal outcome, though the survival is improving with multimodality therapy including autologous stem-cell transplant and immunotherapy. Relapse after multimodality

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therapy is difficult to salvage. High-risk NB is considered challenging and has one of the least favorable outcomes among pediatric cancers. A systematic review and meta-analysis are reported to address robust evidence for curative "gross total resection" (GTR) in Stage 3 and Stage 4 NB.[7] We reviewed the efficacy of surgical resections in different clinical situations for a better understanding of the meaning of surgery in the treatment of NB. We also reviewed the current management options available to pediatric surgeons.

CLINICAL FEATURES

Clinical presentation of NB varies widely by age and stage. Survival remains poor with greater than 50% of children having widespread metastatic disease at initial clinical presentation. The location of the primary tumor and any metastatic sites dictates the symptomatology.[8] It is a highly malignant tumor comprising undifferentiated and differentiating cells originating from neural crest-derived sympathoadrenal precursors. NB can originate from anywhere along the sympathetic chain, presenting as a mass arising in the neck, mediastinum, abdomen, or pelvis.[4] Cases have been detected antenatally, during ultrasound examination, and some of these patients, together with those diagnosed in the 1st day of life, have been observed to undergo spontaneous regression. Hypertension is common and managed with oral antihypertensives, typically resolving with surgical resection/ chemoreduction of the tumor. Although not specific markers for neuroblastoma - high levels at diagnosis of serum markers ferritin (more than 142 ng/ml), neuron specific enolase (NSE, more than 100 ng/ml), and lactate dehydrogenase (LDH, more than 1500 IU/L) have been shown to be predictive of poorer outcome. High-performance liquid chromatography has a sensitivity/specificity as close to 100%.[9] Random/ spot urine samples are as effective as 24-h collections and more practical.

Tumors often infiltrate local structures and surround nerves or vital vessels such as the celiac artery axis. Tumors typically metastasize to regional lymph nodes and bone marrow.

MYCN ONCOGENE

MYCN is correlated with advanced stage, unfavorable tumor biology and poor outcome even in infants and lower stages. Cancer cells reprogram their metabolism to survive, grow, and proliferate. *MYCN* is the underlying cause of metabolic changes in cancer cells.[10] In NB, a *MYCN* amplification (more than 10 copies per cell) is strongly associated with rapid disease progression and poor outcome in patients at all ages, infants included, and at all tumor stages. However, almost 80% of NBs harbor nonamplified *MYCN*. Several other somatically acquired chromosomal aberrations associated with DNA copy number alterations, together with tumor cell DNA content, have been shown to predict NB outcome. Aggressive tumor behaviors with poorer outcomes are associated with deletions at the chromosomal region 1p36.3 or 11q23. MYC oncoproteins are transcription factors which may cause deregulated tumor growth on overexpression. Therefore, many efforts have been made in developing suitable *MYCN* drug that could impair its functions, and the same attempts are still ongoing. This is because of difficulties in developing an optimal therapy against *MYCN* due to a lack of appropriate surfaces on its DNA-binding domain to which drugs can bind. This problem persists not only for *MYCN* but also for other Myc family members.[11] Therefore, at present, a more widely accepted approach for *MYCN* regulation involves its indirect targeting.[12]

DIAGNOSIS

Biopsy

Biopsy of the tumor confirms the diagnosis and provides important information on prognosis. Open surgical biopsy has been traditionally deployed in many centers worldwide, but minimally invasive image-guided biopsy is also highly efficient at tumor diagnosis and has decreased complication rates. Multiple bone marrow biopsies and aspirates are also taken at diagnosis to stage metastases. An unequivocal pathological diagnosis from tumor tissue is made by light microscopy, with or without immunohistochemistry (IHC) or raised urine/serum homovanillic acid (HVA) or vanillylmandelic acid (VMA). IHC aids in distinguishing NBL from other small round blue cell tumors.[13] The VMA/HVA ratio has also been shown to provide additional information. A study reported that percutaneous core needle biopsy is adequate for complete tissue diagnosis of NB and can be safely performed.[14] This can be considered as an alternative to open surgical biopsy.

Radiological staging

Radiological staging of the primary tumor is commonly performed with a contrast-enhanced computed tomography scan.[9] Magnetic resonance imaging is preferred in paraspinal lesions. Metastatic evaluation classically includes bilateral bone marrow aspirate and trephine and a mIBG scan. mIBG is the most sensitive metastatic investigation for skeletal/soft tissue. Re-evaluation following chemotherapy is recommended with mIBG or fluorodeoxyglucose-positron emission tomography (FDG-PET).[13] A bone scan is not reliable for re-evaluation.[15] In a recent study, FDG-PET was superior to mIBG for detection of lymph nodal and bone/bone marrow lesions.[16]

RISK STRATIFICATION

The traditional International Neuroblastoma Staging System (INSS) categorizes the tumors into four stages, based on the extent of surgical resection. The associated risk stratification schema classifies tumors into low, intermediate, and high risk, depending on the stage of the tumor, as well as whether the tumor exhibits amplification of the *MYCN* gene and has favorable histologic features. The International Neuroblastoma Risk Group (INRG) system stratifies risk

into four groups – very low, low, intermediate, and high depending on *MYCN* amplification (high risk), stage, and biological features. The INRG staging system evolved based on presurgical radiology and metastatic status.[17,18] In this system, nonmetastatic tumors are assessed for surgical risk factors that predict unresectability using radiographic imaging, known as image-defined risk factors (IDRFs). Variables utilized for risk stratification include age, stage, histopathological grading, serum LDH, serum ferritin, DNA ploidy, *MYCN* gene amplification status, and segmental chromosomal aberrations.[9,13,18] The original Shimada pathological classification has been replaced by the more comprehensive International Neuroblastoma Pathological Classification (INPC) system. The new INPC system is based on age at diagnosis, mitosis-karyorrhexis index (MKI), neuroblastic differentiation, and stromal content. INPC has a proven role in predicting outcome. The system classifies tumors as favorable/unfavorable based on age, differentiation, maturation, Schwannian stroma, and MKI. The International Society of Pediatric Oncology (SIOP) guideline encourages INPC whenever expertise is available. Patients with Stage 4 disease in the age group of 12–18 months are considered high risk, if the tumor is classified unfavorable by INPC and/or diploidy/hypodiploidy (even if *MYCN* nonamplified). In a study, the polymorphism rs1800795 is associated with serum interleukin-6 level and level of NB risk. Genotype might indicate that the tumor is highly malignant (prone to metastasis) and associated with poor prognosis.[19] These risk stratifications help in understanding the amount that each risk factor contributes to survival in a way that separate survival curves cannot.

TREATMENT

Treatment strategies are guided by the Children's Oncology Group (COG) risk stratification as low-, intermediate- and high-risk groups. The various modalities deployed in the treatment of NB include surgery, chemotherapy, radiotherapy, differentiation therapy, immunotherapy, and in selected cases careful observation only. Surgical resection alone has proven to be curative for most patients with low-risk NB with 5-year OS of 97%. Because antibody therapy seems most effective against bone marrow and not soft-tissue masses, its use might unmask a positive effect of resection on outcome. Antibody therapy has been shown to improve event-free survival (EFS) and OS in high-risk NB.[20] Alternatively, improved survival might obscure any clinically apparent effect of resection.

Low-risk neuroblastoma

Low-risk disease including Stage 1 and asymptomatic Stage 2 disease has an excellent prognosis with nonmutilating surgery alone. The 3-year OS in this group approaches 97%.[13] The goal has been to decrease therapy for low-risk patients to avoid long-term complications while augmenting and targeting therapies for high-risk patients to improve OS.[21] Perinatal adrenal NB maybe managed with close observation alone, unless there are life- or organ-threatening

symptoms at diagnosis. Treatment for asymptomatic low-risk patients with an estimated survival of >98% is often observation or surgical resection alone.

Intermediate-risk neuroblastoma

Patients with "intermediate-risk" group tumors which are not amenable for primary resection receive chemotherapy to halt rapid tumor progression, treat life-threatening symptoms, or improve tumor resectability. Chemotherapy (4–8 cycles) for debulking and metastatic remission, followed by surgery aiming at maximum safe resection (residual tumor need not cause concern), is the recommended approach. If metastases are in remission and primary tumor has responded by >50%, a judicial resection can be done, with no further chemotherapy.[13] If such a response has not been achieved, resection is attempted following administration of additional four cycles of chemotherapy. Patients with intermediate-risk NB with or without postchemotherapy residual tumor resection had an excellent long-term outcome. However, patients with intermediate-risk NB with or without postchemotherapy residual tumor resection had an excellent long-term outcome.[22] The extent of resection does not affect the survival and complications can occur even when the resection is incomplete.[23] Therefore, aggressive attempts at complete resection are unnecessary, as the biology here favors differentiation rather than progression and can lead to life-threatening complications. There was no difference in OS or EFS among the patients with complete resection, minimal residual disease, or biopsy only.[24] Very high proportions of survival are currently achievable in patients with intermediate-risk NB.

High-risk neuroblastoma

Treatment strategies of high-risk neuroblastoma are guided by the Children's Oncology Group (COG) based on age, International Neuroblastoma Staging System (INSS) stage, and tumor biology notably International Neuroblastoma Pathology Classification system (INPC), amplication of N-myc proto-oncogene and DNA ploidy. Literature available at the present time were all nonrandomized observational studies with much study heterogeneity owing to variable treatment protocols and chemotherapy regimens in different institutions.[7] High-risk NB patients who receive four cycles of chemotherapy before surgical resection have a superior OS than patients who receive 2.[25] However, the 5-year OS rate of high-risk patients remains around 40–50%.[18] Patients diagnosed with high-risk factors often have poor prognoses.

The role of surgical resection of the primary tumor in high-risk NB is controversial with conflicting studies in the literature regarding the benefit of aggressive surgery.[26] Study results indicate that local treatment with gross total resection" (GTR)/subtotal resection (STR) with local irradiation may be safe and sufficient for preventing local recurrence in INSS 4 NB patients who received "delayed local treatment." Rich BS reported that a gross total resection is possible in high-risk patients with IDRFs without increasing morbidity.[27] In addition, we reviewed other literature. We

conclude that ≥90% resection is both feasible and safe in most patients with high-risk NB.[28] Hence, the treatment strategy may have advantages in terms of surgical invasiveness and the rates of postoperative complications and recurrence.[29] Nevertheless, other study showed no substantial survival benefit in patients with high-risk NB undergoing gross total tumor resection.[30] Multidisciplinary intensive treatment was essential, especially for patients who received STR. Long-term follow-up is needed to survey complications in surviving patients who received intensive chemotherapy and radiotherapy. The outcome for patients with NB has improved; however, the field continues to expand efforts in more targeted therapies for high-risk patients.

SURGERY

Extent of resection

Surgery has an important role both at the time of diagnosis and during treatment. NB has an elevated tropism for lymphatic vessels and lymph node infiltration; surgical tumor resection should include exploration of locoregional lymph nodes, especially in abdominal and pelvic locations. Surgical resection aims to achieve macroscopic tumor resection with minimal residual disease. In other cases, when the features of the tumor (site, size, and relationship with surrounding structures) indicate that surgical resection is not feasible without risk, surgery is limited to providing enough tumor tissue to make the histological diagnosis and to carry out biologic studies. If one or more of these features have been documented, presurgical chemotherapy should be administered to shrink the tumor and enable safe tumor resection.[2,31,32] Such as paravertebral locations with spinal canal invasion through intervertebral foramina, laminectomy is indicated only in the presence of rapidly progressive neurological symptoms, as chemotherapy can rapidly reduce the volume of the tumor and relieve compression.[33] Complete resection can be difficult to attain in this disease because of primary tumor encasement of nerves and blood vessels and frequent regional lymph node involvement. In addition, metastases to bone, bone marrow, distant lymph nodes, and other sites are unaffected by primary tumor resection. Maximum tumor resection with as much preservation of organ/neurologic function as possible is attempted postinduction chemotherapy.[34] Although the greatest impact of resection should be on local control, some researchers argue in favor of GTR.[26] A meta-analysis showed a survival benefit for GTR in Stage 3, while GTR did not significantly improve OS in Stage 4 disease.[7] For patients, high-risk NB remains controversial.[35] Recent prospective data from both COG and International Society of Pediatric Oncology Europe-Neuroblastoma (SIOPEN) support more complete resection in high-risk patients. However, given the high incidence of local relapses, the current indication in the majority of treatment protocols is resection of the primary tumor after debulking at metastatic sites. In contrast with its pivotal role in local disease, surgery has a somewhat controversial role in metastatic disease.[35] von Allmen et al.[28]

found poor concordance between the assessment of resection extent by the operating surgeons and assessment through central imaging review. Despite discordance between clinical assessment of resection extent and assessment through central imaging review, a surgeon-assessed resection extent ≥90% was associated with significantly better EFS. Improving OS, however, remains a challenge in this disease.

Minimally invasive surgery (MIS) has gained popularity in pediatric oncology, and recent results have suggested the safety and effectiveness of this approach when IDRFs are absent.[36] A study showed that laparoscopic adrenalectomy was safe, and among patients who met selection criteria for this procedure, there was no difference in mortality or recurrence rates between high-risk and low/intermediate-risk patients.[37] These results suggest that MIS is indicated for the resection of selected NBs without IDRFs, while open surgery should be preferred if vascular control is considered difficult or complete tumor resection uncertain or risky.[38] In addition, MIS for the treatment of NBs without IDRFs in low- to high-risk patients is safe and feasible and does not compromise the treatment outcome.

COMPLICATIONS

Surgeons should always consider the efficacy of a tumor resection, while also considering the occurrence of possible surgical complications. The basic principles of surgical resection include the accurate and safe display of vital vascular anatomy with the optimal exposure of the tumor to achieve gross resection. Indeed, the effect of primary tumor resection has not been included as a specific aim in any reported cooperative group studies until a recent analysis by the SIOPEN. The international has recently identified several imaging features (IDRFs) potentially associated with surgery-related complications. IDRFs include tumor extension into a second body compartment, encasement of any large blood vessels, tracheal or large bronchial compression, involvement of major nerve roots (such as the brachial plexus), invasion of the spinal canal, or infiltration of the nearby kidneys, mesentery, pericardium, liver, diaphragm, or pancreas. These are predictive of worse event-free and OS. The preservation of vital organs or vessels should be more important in high-risk patients in the era of intense chemotherapy and radiotherapy.[39] The attempt at tumor resection in the presence of IDRFs lowers the chance of complete resection rate and implies greater risk of surgery-related complications.[40] No significant difference in the proportion of patients with a complication was detected between the <90% and ≥90% resection.[28] Hence, the complication rate was not increased in patients who underwent more extensive surgery. However, the complications induced by intense chemotherapy and radiotherapy have not been clearly elucidated. Future long-term follow-up studies of chemotherapy- or radiotherapy-related complications such as growth retardation, hearing impairment, infertility, endocrine dysfunction, and most importantly second

cancer will reclarify the role of surgery in the treatment of NB.[39]

Outlook

Over the years, the outcome of patients with NBL has improved more slowly than that of patients with other childhood tumors. In the last decade, however, fruitful preclinical research has yielded many insights into the biology of NBL. The recent technological developments discussed above will certainly contribute to increase further our knowledge of these tumors and may enable us to identify the molecular aberrations and the cellular networks leading to tumor initiation and progression in each individual patient. Furthermore, access to an increasing number of actionable drugs now offers the possibility to develop new clinical trials. Together with this change in the approach for forthcoming clinical trials, a strengthening of international expert collaboration will enforce the development of clinical and biological studies and will speed the application of precision medicine for children diagnosed with NBL. In this way, precision medicine could finally be directed toward increasing survival rates and improving the quality of life of patients with NBL.

Conclusion

NB is a challenging disease for pediatric cancer specialists and surgeons. Surgery plays a role in the diagnosis and management of all stages of NB. NB being a highly infiltrative tumor presents many challenges for the surgeon as it is not usually possible to get microscopically negative resection margins where gross resection (GTR) is desirable. The role for surgery in localized, low-risk NB remains clearly defined, as gross total resection can be curative in these patients. However, the role of surgery greatly varies according to the clinical situation. The extent of resection, in high-risk NB, continues to evolve. Much of these data, however, come from retrospective studies, and prospective surgical studies are needed to further define the importance of surgical resection in intermediate- and high-risk patients.

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Conflicts of interest
There are no conflicts of interest.

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神经母细胞瘤外科治疗进展

摘要

背景： 在过去的几年中，神经母细胞瘤（NBL）手术治疗已经取得了一些进展，并对局部神经母细胞瘤手术治疗的作用进行了一些研究，但手术时机和原发肿瘤切除范围对高危患者预后的影响仍存在争议。本文回顾了手术切除在不同临床情况下的疗效，以便更好地理解手术治疗在神经母细胞瘤治疗中的意义。

数据资料： 在ScienceDirect 数据库中我们通过使用关键词"神经母细胞瘤"、"神经母细胞瘤切除术"、"神经母细胞瘤手术"和"高危组神经母细胞瘤"检索从2016到2018有关神经母细胞的文章。

研究选择： 我们回顾性分析了在不同临床情况下接受手术切除的患者。这些文章包括相关的随机对照试验，综述和meta分析和高质量的报告研究。只有摘要和编辑注释的文献被排除在外，我们回顾性分析与NBL外科治疗有关的含全文文章和摘要的文献。

结果： 共检索到7800篇有关神经母细胞瘤的文献（2016～2018年）。检索到163篇与神经母细胞瘤外科治疗相关的文献（2016～2018）。通过分析这些重要文献，我们发现低中危神经母细胞瘤的治疗基本相同。但是高危患者仍存在争议。

结论： 神经母细胞瘤的预后根据肿瘤的分期和生物学特征而有很大差异。在回顾相关文献后，低危患者通常通过手术切除或仅仅随访观察，肿瘤可能自发地消退而不会引起症状。中危患者接受化疗的周期取决于原发肿瘤的手术切除的效果。高危患者治疗仍存在争议。多学科强化治疗是必不可少的，尤其是对于接受次全切除术的患者。如果IDRFs评估没有风险因素，对于低中危患儿，微创手术是安全可行的。我们认为，在大多数高危神经母细胞瘤患者中，90%以上切除是可行的和安全的。新的治疗目标是提高患者生存率。