



Review Article

Role of surgery in localized initially unresectable neuroblastoma

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Summary**Purpose**

Evaluating the role of surgery and the extent of tumor resection on the outcome of patients with localized initially unresectable neuroblastoma (NB).

Patients and methods

This was a retrospective case review study including patients with localized initially unresectable NB. The primary tumor was considered unresectable according to imaging defined risk factors (IDRFs). Surgical resection was attempted after four to six courses of chemotherapy. The extent of resection was classified as follows: $\geq 90\%$ resection, incomplete resection (50–90%) and cases with $< 50\%$ resection or just a biopsy. Survival analysis was performed using an intention-to-treat approach.

Results

A total of 202 patients with NB were included. Surgical resection was done in 106 patients. It was $\geq 90\%$

in 89 patients (83.9%). Surgical resection was not performed in 96 patients (47.5%). Fifty-five (57.2%) were in good response after primary chemotherapy and 41 patients (42.7%) had persisting IDRFs, nine of them had biopsy only, and a follow-up strategy was considered in the other 32 patients. The overall 5-year event-free survival (EFS) and overall survival (OS) were $89.1 \pm 2.4\%$ and $94.9 \pm 1.7\%$, respectively, with significantly better OS and EFS for patients who had resection versus no resection ($p = 0.003$ and 0.04 , respectively). There was no impact of extent of resection on EFS and OS in the whole group ($p = 0.91$, $p = 0.9$) and in subgroup analysis stratified by site, histology, and age of the patients.

Conclusion

In children with localized initially unresectable NB, surgical resection was the only significant risk factor associated with better survival. The extent of tumor resection had no impact on EFS and OS. The concept of accepting incomplete resection to avoid serious complications was successful.

Introduction

Neuroblastoma (NB) is a heterogeneous malignancy with variable prognosis [1]. The outcome is correlated with risk categories (low, intermediate, or high-risk) [2]. Patients with low and intermediate-risk NB have an estimated overall survival (OS) rate over 90% with an ongoing trend toward minimization of therapy [3–7]. The role of gross total surgical resection for children with localized disease, without MYCN amplification, was evaluated in the Localised Neuroblastoma European Group (LNESEG) [5]. Localized but unresectable NB carries a poorer prognosis except in infants [6–8] or in children with favorable biological features [4,9,10]. The impact of extent of surgical resection on the outcome is a matter of debate, and further investigation is needed [11]. Our null hypothesis was: In patients with localized initially unresectable neuroblastoma

there is no difference in survival between $\geq 90\%$ resection and incomplete resection (50–90%). In this study, we analyzed the impact of surgery and the extent of tumor resection on the outcome of these patients.

Patients and methods

The patients of this retrospective case review study were all consecutive patients with non-metastatic initially unresectable NB without MYCN amplification, treated at Children's Cancer Hospital Egypt 57357, between July 2007 and December 2015 in accordance with the International Neuroblastoma Staging System (INSS) risk classification NB [12]. Initially, disease status was assessed by computed tomography or magnetic resonance imaging, meta-iodobenzylguanidine (MIBG) scan, urine catecholamines, bilateral bone marrow (BM)

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biopsies and aspirates, and MYCN status. Molecular biology (11q LOH) was not available for treatment allocation.

Patients received systemic chemotherapy, in the form of etoposide and carboplatin (VP16/CARBO) alternating with cyclophosphamide, doxorubicin, and vincristine (CADO), administered at 3-week intervals, with a total of six or eight cycles guided with attaining objective overall response (CR/VGPR/PR).

VP16/CARBO:

Etoposide: 200 mg/m²/day (6.67 mg/kg/day for patients ≤12 kg) infused IV over 2 h × 3 days.

Carboplatin: 450 mg/m²/day (15 mg/kg/day for patients ≤12 kg) infused IV over 1 h on day 1.

CADO:

Cyclophosphamide: 300 mg/m²/day (10 mg/kg/day for patients ≤12 kg) infused IV over 1 h daily for 5 days.

Doxorubicin: 60 mg/m²/day (2 mg/kg/day for patients ≤12 kg) infused IV over 6 h on day 5.

Vincristine: 1.5 mg/m²/day (0.05 mg/kg/day for patients ≤12 kg) IV bolus days 1 and 5 (maximum dose 2 mg).

After four to six cycles of chemotherapy, assessment for the feasibility of tumor resection was done with the aim of ≥90% resection. After institutional review board (IRB) approval, data on extent and complications of resection were collected retrospectively using operative notes, post-operative pathology, and imaging reports. The extent of resection was classified as follows: <50% or just a biopsy; incomplete resection (50–90% of tumor volume present at the time of surgery); and ≥90% resection. Patients were divided into two groups: Resection Group (RG) with ≥50% resection and No Resection Group (NRG) including cases with no surgery, <50% resection or just a biopsy. The extent of resection in the RG was divided into two subgroups (≥90% and 50–90% resection). The patients' response to chemotherapy was assessed according to international NB response criteria [12].

Statistical analysis

Patients' characteristics were described in the overall cohort using count and percentage. Similar descriptions were made of the (RG) and (NRG), which were compared using Pearson's × 2 test. Event-free survival (EFS) and overall survival (OS) were estimated. The time to an event was calculated from the diagnosis to the first occurrence of relapse, progression, death from any cause, or secondary cancer, or the time to the last contact if no event was observed using Kaplan–Meier analysis.

The log-rank test was used to determine the prognostic significance of selected variables. A *p*-value ≤0.05 was considered significant. Subgroup analysis on the impact of the extent of resection on outcome was performed. Events were defined as relapse, progressive disease (PD), secondary malignancy or death, and in case of no event, the last date of contact was used as time to the event. In case of OS, time to event was defined as time to death from any cause or till the date of the last contact in case of no event. Survival outcome was reported as 5 year-

survival ± standard error. The analysis was performed using the statistical package, SPSS version 20.

Results

A total of 202 patients with localized initially unresectable NB were included. The median age at diagnosis was 12 months (range 4 days–16 years), and the median follow-up time was 41 months (range 2–103 months). Patients' demographic and clinical characteristics varied between RG and NRG as shown in Table 1. Most primary tumors were extra-adrenal, 144 patients (71.2%). Imaging defined risk factors (IDRFs) were present at diagnosis in all patients and consequently were deemed unresectable. After chemotherapy, the RG included 106 patients (52.5%). Eighty-nine patients (83.9%) underwent ≥90% resection of the primary tumor while incomplete resection 50–90% was done in 17 patients (16.1%). The NRG included 96 patients (47.5%). Fifty-five (57.3%) were in complete response (CR *n* = 13) or very good partial response (VGPR *n* = 42, and of these 42 patients, 35 had negative MIBG). Out of 96 patients in the NRG, 41 patients (42.7%) had persisting IDRFs, of whom nine patients were re-explored with <50% resection or had a biopsy only. Follow-up was considered in the other 32 patients. There was no operation-related mortality; the overall complication rate was 6.6%, with a total of seven patients developing postoperative complications (post-operative intestinal obstruction (*n* = 3), lung collapse (*n* = 2), Horner's syndrome (*n* = 1), and chylous effusion (*n* = 1)). Nephrectomy was performed during tumor resection in two patients in which the tumor was infiltrating the kidney and it was non-functioning in the preoperative renal scan.

Out of 20 events, 13 patients experienced either disease progression (*n* = 10, local) or relapse (*n* = 3, 1 metastatic and 2 local) at a median time of 10 months (range 2 months–2.5 years), three of whom died despite salvage therapies. Another seven patients died without any relapse or disease progression; two because of infection, another two died after finishing treatment outwith the hospital (from unknown causes), and three died during the treatment because of high tumor burden. The 5-year EFS and OS rates of all 202 patients were 89.1 ± 2.4% and 94.9 ± 1.7%, respectively. In the present study surgical resection was the only factor associated with significantly better OS (*p* = 0.003) and EFS (*P* = 0.04) (Figs. 1 and 2). When the NRG included only patients who were irresectable because of persistent IDRFs, surgical resection was confirmed as the most important prognostic factor for OS (*p* ≤ 0.001) and EFS (*p* ≤ 0.001).

The OS and EFS of the patients who had CR or VGPR by chemotherapy + surgery or chemotherapy only were 98.2 ± 1.3% and 93.5 ± 2.2%, respectively. The OS and EFS of the patients who had no response to chemotherapy and no surgery because of persistent IDRFs after chemotherapy were 72 ± 8.5% and 69.6 ± 7.1%, respectively, with significantly intergroup difference (*p* < 0.0001) (Figs. 3 and 4). Other factors (age, histology, site, and extent of resection) had no impact on OS or EFS (Table 2).

Of the 41 children with a persisting unresectable primary who did not undergo a secondary surgery, seven patients

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