# Surgical Treatment of Neuroblastoma

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**ABSTRACT:** **Background:** Neuroblastoma is the most common non-central nervous system (CNS) solid malignant tumor in children. The surgical treatment of high-risk neuroblastoma presents a challenge, and the benefits of aggressive surgical resection have been called into question.

**Objectives:** To examine our experience with surgical resection of neuroblastoma.

**Methods:** We report on a retrospective chart review of our preliminary surgical experience in 25 patients with neuroblastoma who underwent surgery performed by a single surgeon at two institutions over a 3 year period. Demographic data, including stage of tumor and risk stratification, were recorded. Primary outcome was total gross resection. Patients were followed for 3 years after surgery.

**Results:** We found that 80% of the patients, including those with high-risk neuroblastoma tumors, had total gross resection of their tumor with minimal operative morbidity and no mortality; 88% had greater than 90% resection of their tumor. Overall, 3 year survival was 84% (21/25).

**Conclusions:** Resection of neuroblastoma, even large, high-risk, bilateral tumors, was possible when performed by surgical teams with considerable experience.

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**KEY WORDS:** neuroblastoma, total gross resection, *N-myc* proto-oncogene protein (n-MYC), resection

### SURGICAL TREATMENT OF HIGH-RISK NEUROBLASTOMA TUMORS IN ISRAEL

Neuroblastoma is the most common non-central nervous system (CNS) solid tumor in childhood [1]. Despite significant advances in the diagnosis and treatment of neuroblastoma, the overall survival still remains poor. The role of surgery in the treatment of this cancer is evolving. Most children with a stage 1 tumor can be treated with surgery alone. The vast majority of children diagnosed with neuroblastoma are, unfortunately, diagnosed at a later stage, necessitating a multi-modality approach that includes chemotherapy, surgery, and stem cell transplantation. In this study, we examined our early, local experience with the surgical treatment of neuroblastoma.

## PATIENTS AND METHODS

A retrospective chart review was performed on all children with a diagnosis of neuroblastoma who were treated at two major medical centers in Israel: Rambam Medical Center in Haifa and Sheba Medical Center in Tel Hashomer. All children under the age of 18 years of age who underwent surgery with the intent of total gross resection (TGR) by the treating physician and surgeon were eligible for the study. Data were collected retrospectively at Rambam Medical Center from August 2010 until April 2012 and from Sheba Medical Center from May 2012 until December 2013. Demographic data on each patient was obtained as well as the tumor stage, *N-myc* proto-oncogene protein (n-MYC) status, side of lesion, exact location, and final pathology. All patients were staged and treated according to the latest International Society of Paediatric Oncology (SIOP) protocols [2]. All surgeries were performed by the senior author (M.S.A.). TGR was defined as resection of all gross tissue with no obvious visible tumor remaining. The patients were followed for a minimum of 3 years after surgery.

## RESULTS

Patient demographics are summarized in Table 1. A total of 25 patients underwent surgery for complete resection during the 40 months of the study. Sixteen patients (64%) presented with stage 4 neuroblastoma, three with stage 3 (12%), and six (24%) with stage 1. Of the 25 patients in this study who underwent surgery with the intent of TGR, 5 had incomplete resection. Therefore, we had an overall total gross resection rate of 80%. Of the five patients for whom we did not obtain TGR, two had between 90%–95% resection; therefore, in total 88% of patients had at least 90% resection. Of the three children with less than 90% resection, the first was a child presented with a stage 3 neuroblastoma and a tumor encompassing the portal hilum that could not be dissected free of the portal structures. This child underwent biopsy only (patient 2). The second was a child with a bilateral abdominal, pelvic, and retroperitoneal tumor that encased the celiac, superior mesenteric artery, both internal and external iliac arteries and veins, and both renal arteries and veins. The tumor extended into the pelvis (patient 4). This child had a 30% resection. In addition, one child with a stage 3 thoracic tumor

**Table 1.** Patient demographics

| Patient | Age (month) | Location | Stage at presentation | Side | Complete resection | Admittted to ICU | NPO (days) | Complications | n-MYC | Risk | Status |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 40 | a,p | 4 | right | yes | yes | 2 | | non-amp | High | S |
| 2 | 35 | abd | 3 | bilateral | no | yes | 2 | | non-amp | Intermediate | S |
| 3 | 0.01 | a | 1 | left | yes | yes | 35 | massive hemorrhage, DIC | non-amp | Low | S |
| 4 | 38 | p/abd | 4 | bilateral | no | yes | 3 | | non-amp | High | DOD |
| 5 | 72 | a | 4 | right | yes | yes | 2 | pneumonia preop and postop | non-amp | High | S |
| 6 | 72 | a | 4 | left | yes | yes | 2 | renal artery thrombosis | non-amp | High | S |
| 7 | 71 | a | 4 | bilateral | yes | yes | 3 | | amp | High | S |
| 8 | 84 | p/c | 3 | left | no | yes | 2 | | non-amp | Intermediate | S |
| 9 | 100 | p | 4 | left | yo | no | 3 | | non-amp | High | DOD |
| 10 | 40 | a | 4 | right | No (95%) | no | 2 | | amp | High | S |
| 11 | 24 | p | 4 | bilateral | No (90%) | yes | 2 | iliac artery injury | amp | H | S |
| 12 | 8 | p, abd/c | 1 | right | Yes | Yes | 2 | | non-amp | Low | S |
| 13 | 41 | p | 1 | right | yes | yes | 2 | | non-amp | Low | S |
| 14 | 46 | a | 4 | right | yes | no | 1 | | amp | High | S |
| 15 | 11 | a | 4 | right | yes | no | 2 | | non | Intermediate | S |
| 16 | 189 | a | 1 | right | yes | no | | | non | Low | S |
| 17 | 16 | a | 1 | left | yes | no | 2 | | non | Low | S |
| 18 | 10 | a | 4 | right | yes | no | 2 | | non | Intermediate | S |
| 19 | 14 | a | 4 | right | yes | no | 2 | | non | Intermediate | S |
| 20 | 15 | p/c | 1 | left | yes | yes | 1 | cellulitis of surgical wound | 2 subpopulations: n-myc+/- | Low | S |
| 21 | 135 | a | 4 | left | yes | no | 1 | | non | High | S |
| 22 | 11 | a | 4 | right | yes | yes | 3 | vena cava injury | amp | High | DOD |
| 23 | 41 | a/c | 4 | left | yes | yes | 2 | | non | High | S |
| 24 | 34 | a | 4 | left | yes | no | 1 | | non-amp | High | DOD |
| 25 | 28 | a | 3 | left | yes | yes | 1 | | amp | High | S |

a = adrenal, p = paraspinal, c = chest, abd = abdominal not adrenal, S = 3 year survivor, DOD = died of disease, NPO = nothing by mouth, ICU = intensive care unit, n-MYC = N-myc proto-oncogene protein

who presented with a preoperative Horner's syndrome and signs of spinal cord compression, had a 50% resection of his tumor (patient 8). The tumor completely encased the subclavian artery and vein preoperatively and extended into the thoracic inlet.

One of the patients in our study was a child who had previously undergone surgery. The operation described in this series was a re-operation. This child presented with stage 4 disease and previously underwent surgery to remove a para-spinal tumor. During the first procedure the surgeon chose to perform an incomplete resection rather than risk resection of the kidney. The patient underwent intensive chemotherapy and stem cell transplantation followed by TGR of residual disease without nephrectomy. Fourteen of our patients were considered to have a high-risk neuroblastoma of which 12 (85%) had TGR. Five were considered to have intermediate-risk tumors of which four (80%) had TGR, and all six of our low-risk patients had TGR.

### LOCATION

In our study, 20 of the patients had an isolated abdominal and/or pelvic tumor, two had an isolated thoracic lesion, and three had tumors in both the abdomen and thoracic cavities. One of these patients had a para-spinal tumor that extended from the abdomen into the chest (patient 12), one had a large abdominal tumor that extended into the chest (patient 4), and one patient had an abdominal tumor with thoracic metastases (patient 23). Four of the patients with abdominal tumors had bilateral disease. The rest had tumors localized to one side. The majority (16) of primary abdominal tumors were located in the adrenal, five were para-spinal, and two were combined para-spinal and adrenal.

### SURGICAL TECHNIQUE

All abdominal procedures were performed through an abdominal incision. None of the children had a thoraco-abdominal incision and none of the abdominal incisions had to be converted to a thoraco-abdominal incision. One patient, the child who had a 30% resection, had a midline incision. The rest of the abdominal tumors were resected through a subcostal incision. A thoracotomy was performed for patients with thoracic lesions, and in the child with an abdominal primary thoracoscopy was performed to remove small thoracic nodules. The

extent of gross resection was determined by intraoperative assessment. In addition, postoperative imaging was compared with preoperative imaging to determine the extent of resection.

#### SURGICAL COMPLICATIONS

There was no operative mortality. One patient with a tumor that completely surrounded the renal artery had a partial thrombosis of the artery after a complete resection. The patient was treated with angiographic stent placement and never lost renal function or required further intervention. There were four minor vascular injuries to the vena cava or aorta. All were repaired primarily with no further intervention. None of the patients with complete encasement of the renal artery and/or vein required nephrectomy to achieve TGR. In fact, no nephrectomies were performed in our series.

One patient (patient 3) was a baby who presented on the first day of life with a large adrenal tumor that bled spontaneously. She underwent an emergency resection of the tumor and suffered the effects of prolonged hypotension resulting in ischemic injury to the liver, kidneys and brain. The patient had a prolonged stay in the intensive care unit (ICU) (50 days) and eventually had complete recovery of her kidneys and liver. She still has somewhat decreased hearing but has reached her developmental milestones so far. She was discharged 2 months after her operation and has since developed metastases in the liver, necessitating a diagnosis of stage 4S disease.

Sixteen of the patients in the study required postoperative care in the ICU. Aside from the newborn with stage 4S disease, the average postoperative ICU stay was 2.2 days. The average length of time with nothing by mouth (NPO) after surgery was 2 days [Table 1].

#### OUTCOMES BY STAGE

*Stage 1 and stage 2 disease:* Six patients in our cohort presented with stage 1 disease. We had no patients with stage 2 disease. All had 100% resection of their tumor and required no further treatment. All were alive at follow-up. One example is a child who presented at age 16 months with a large abdominal mass (patient 17) [Figure 1]. The magnetic resonance imaging showed that the tumor did not encase any vessels or surrounding organs. The tumor was completely resected through a subcostal approach and the child remains disease free more than 3 years postoperatively.

*Stage 3:* Three patients presented with stage 3 disease. Two of the three did not have a total gross resection of their tumor. The first was a patient with a thoracic tumor that completely encased the subclavian artery and vein and presented with a Horner's syndrome and spinal cord compression (patient 8). This child is alive and well more than 2 years postoperatively. The second is the child with the tumor that encased the porta hepatis (patient 2).

*Stage 4:* There were 16 patients that presented at stage 4. Three of these patients did not have total gross resection of their tumor. In one patient with bilateral diseases extending into the pelvis encasing both renal and iliac arteries and veins, we could not achieve greater than 90% resection (patient 4). This patient subsequently died of the disease. In the other two patients (patients 10 and 11) 90%–95% resection was obtained. Both of these patients had n-MYC amplified tumors and both survived. All of the other patients had total gross resection for an overall TGR rate of 81% in these patients. All tumors, even large tumors encompassing the renal vessels, were resected through a subcostal incision. One example (patient 22) is an 11 month old child who presented with a large abdominal mass that crossed midline and encased the right renal vessels as well as aorta and vena cava. The tumor was initially felt to be unresecteable and the child was treated with chemotherapy and stem cell transplantation according to the SIOP protocol. After her treatment, the tumor shrunk considerably [Figure 2] but she had residual, albeit slight, disease in her bone marrow. The patient was hypertensive and required seven medications to keep her blood pressure under control. After performing a computed tomography angiogram the team decided that the hypertension was a result of pressure on her renal vessels and operative

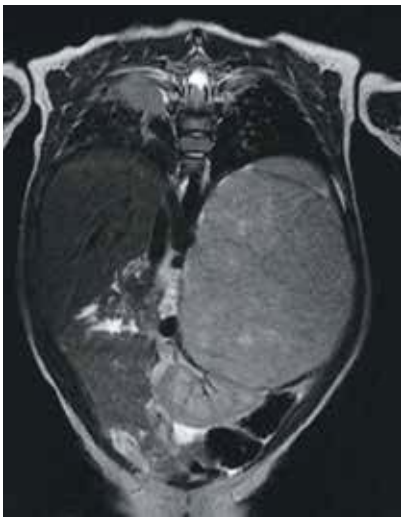

**Figure 1.** Large, stage 1, low-risk neuroblastoma in the left flank (patient 17)

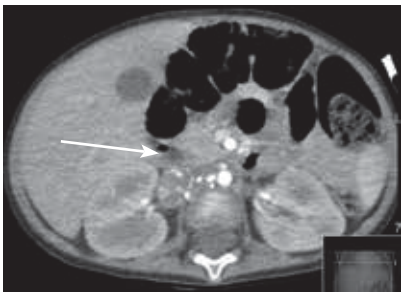

**Figure 2.** After chemotherapy and transplantation, tumor still surrounds right renal vessels (arrow) (patient 22)

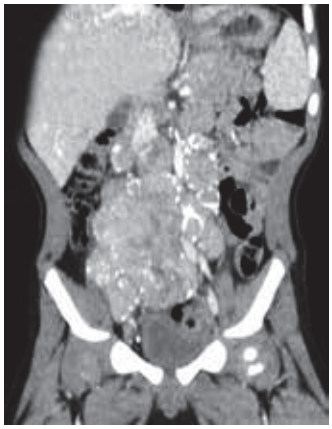

**Figure 3.** Large bilateral abdomen tumor in patient with stage 4, high-risk neuroblastoma. Tumor was 90% resected (patient 11)

exploration was performed. The tumor was completely resected through a subcostal incision, the kidney was spared, and the child was weaned off all blood pressure medications within 2 weeks postoperatively. Unfortunately the child died 6 months postoperatively from metastatic disease.

Another example is a child with a large tumor that encased vessels on both sides of the abdomen (patient 10) [Figure 3]. This child was treated with chemotherapy and had resection of 90% of his tumor prior to stem cell transplantation. He is alive and doing well.

### HIGH-RISK NEUROBLASTOMA

We had 14 high-risk patients, of whom 11 had total gross resection (78%). Two of the patients who did not have total gross resection still did have 90%–95% resection. Therefore, 93% of the high-risk patients had greater than 90% resection.

### SURVIVAL

The overall 3 year survival in our study was 84% (21/25 patients). All non-survivors had been diagnosed with stage 4 neuroblastoma. The survival rate in our study for stage 4 tumors was 75%. One patient had an n-MYC amplified tumor and the other non-survivors all had non n-MYC amplification. [Table 1].

Looking at the data based on risk stratification, our study included 14 patients with high-risk neuroblastoma tumors of whom 12 are still alive, for a survival rate of 85%. We operated on five intermediate-risk patients with a 100% survival and all six of our low-risk patients are alive [Table 1].

## DISCUSSION

Neuroblastoma remains the most common non CNS solid tumor of childhood [1]. Traditional treatment consists of upfront surgical resection for early stage tumors. Often this procedure is the only treatment necessary [3]. For more advanced tumors, treatment consists of a combination of chemotherapy, stem cell transplantation, and surgery. The role of surgery in advanced stage tumors, while well described, is controversial and its role in the treatment of neuroblastoma has been debated [4]. Moreover, measuring resection as total gross resection is objective.

Recently the role of aggressive surgical therapy in the treatment of neuroblastoma has been called into question [4]. At Memorial Sloan Kettering Cancer Center (New York, NY), aggressive surgical therapy using a thoracoabdominal incision has been advocated as the best approach for all patients with neuroblastoma [5]. However, their results have not been duplicated elsewhere. In this study we showed that neuroblastoma is amenable to surgical resection. However, whether the resection affects outcome is still unclear. Recently Simon et al. [4] showed that surgical resection in advanced stage neuroblastoma has no impact on local control or long-term outcome. However, a recent study has shown that while TGR is not associated with improved overall survival when compared to less than TGR, resection of greater than 90% does [6]. In our study TGR was accomplished in 80% of the patients, and 88% had more than 90% resection.

According to the latest SIOP protocol, only non-mutilative surgery should be performed prior to transplant and if a tumor encompasses a great vessel or there is a risk for nephrectomy, chemotherapy treatment is started before attempting surgery [2].

We showed surgical success in resecting large, high-risk, even bilateral tumors with minimal morbidity and excellent postoperative recovery. A new staging system for neuroblastoma has recently been proposed [7] that stratifies patients based on image-defined risk factors as well as patient age and stage. We have recently adopted this system in our patients and the patients in the last year of our study were staged based on this system. Prior to that, patients were stratified based on the previous system.

The neuroblastoma group at Sloan Kettering has advocated for a thoracoabdominal incision approach for all abdominal neuroblastomas and cites excellent rates of resection as well as postoperative recovery [5]. Although our study consisted of fewer patients, we showed excellent outcomes using a subcostal incision. In all but one of our patients with an abdominal tumor, no chest tube was placed. The one patient who did have a chest tube had a stage 1 tumor that was located in the right para-spinal region and extended from posterior to the right kidney up into the chest. The tumor was resected through a subcostal incision, but as the diaphragm had to be opened to remove the superior most part of the tumor, a chest tube was place during the operation. The tube was removed on postoperative day 1. We believe that this approach of using a subcostal incision rather than a thoracoabdominal incision has resulted in decreased morbidity, minimal length of stay in the ICU and improved pain management. The average time in the ICU for our patients was 2 days and most of our patients resumed regular feeding protocols within 2 days of surgery.

In patients with early stage tumors, surgery may be the definitive treatment. Decreasing tumor burden in patients with advanced neuroblastoma has been the traditional justification for tumor resection, although this reasoning has been called into question lately [8]. However, there is still no clear consensus on the role of aggressive surgery for advanced neuroblastoma [6]. In patients with advanced stage tumors, surgery remains an integral part of treatment protocols, although the role of "heroic" surgery seems less and less certain. We have demonstrated excellent results for complete resection of advanced stage neuroblastoma as well as early tumors.

**CONCLUSIONS**

Surgical resection of advanced stage, high-risk neuroblastoma is possible. We were able to successfully resect tumors with minimal morbidity and excellent postoperative recovery. Our data suggest that these patients should be referred to regional centers with many cases and operated on by surgeons with particular expertise in this field, as we have done.

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## Capsule

### Blood test for early-stage cancer

Cancer cells release circulating tumor DNA into the bloodstream, which can sometimes be used to measure tumor progression and treatment response. Chan et al. sought to address whether so-called "liquid biopsies" could be used to diagnose cancer before an individual had symptoms. They used nasopharyngeal cancer, which is known to be associated with Epstein-Barr virus (EBV) infection, as a model. By screening EBV DNA in the plasma from more than 20,000 Chinese men, the researchers were able to accurately detect early-stage nasopharyngeal cancer in this high-risk population. In a 3 year study, the blood test increased the patient survival rate to 97%, compared with approximately 70% in a historical cohort.

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## Capsule

### Transcriptome analysis of ankylosing spondylitis patients before and after TNF-α inhibitor therapy reveals the pathways affected

Tumor necrosis factor-α (TNF-α) inhibitors are highly effective in suppressing inflammation in ankylosing spondylitis (AS) patients and operate by suppression of TFN-α and downstream immunological pathways. To determine the mechanisms of action of TNF-α inhibitors in AS patients, Wang et al. used transcriptomic and bioinformatic approaches on peripheral blood mononuclear cells from AS patients pre- and post-treatment. The authors found 656 differentially expressed genes, including the genome-wide significant AS-associated genes, *IL6R*, *NOTCH1*, *IL10*, *CXCR2*, and *TNFRSF1A*. A distinctive gene expression profile was found between male and female patients, mainly because of sex chromosome-linked genes and interleukin 17 receptor C, potentially accounting for the differences in clinical manifestation and treatment response between the genders. In addition to immune and inflammation regulatory pathways, like intestinal immune network for immunoglobulin A production, cytokine–cytokine receptor interaction, Ras signaling pathway, allograft rejection, and hematopoietic cell lineage, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses revealed that infection-associated pathways (influenza A and toxoplasmosis) and metabolism-associated pathways were involved in response to TNF-α inhibitor treatment, providing insight into the mechanism of TNF-α inhibitors.

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