**Results of Retroperitoneal Lymphadenectomy in the Treatment of Abdominal Neuroblastoma**

Kazuaki Tokiwa, MD, PhD; Shigehisa Fumino, MD; Shigeru Ono, MD, PhD; Naomi Iwai, MD, PhD

**Hypothesis:** Adequate locoregional surgical treatment prevents local relapse of abdominal neuroblastoma.

**Design:** A retrospective review of a consecutive series of patients who underwent surgical excision for abdominal neuroblastoma.

**Setting:** University hospital.

**Patients:** Forty-seven patients with abdominal neuroblastomas whose primary tumor site was restricted to the adrenal gland or the adjoining sympathetic ganglia.

**Intervention:** Complete excision of the primary tumor and retroperitoneal lymphadenectomy.

**Main Outcome Measures:** Surgical intervention, postoperative complications, survival, and local recurrence.

**Results:** The average duration of surgery was 5 hours 28 minutes; the mean intraoperative blood loss was 27.7 g/kg of body weight. We had no intraoperative major complications leading to visceral insufficiency or perioperative deaths. The following 15 postoperative complications were observed in 12 patients; these complications included diarrhea (8 patients), renal atrophy (3 patients), intestinal obstruction (2 patients), chylous ascites (1 patient), and wound infection (1 patient). The mean follow-up period for the entire patient population was 8.5 years. All 30 patients with Evans stage I, II, III, or IV-S and 8 of the 17 patients with Evans stage IV were alive without evidence of disease. Eight patients died of progressive disease; 1 died of cytomegalovirus infection. No local recurrence was detected within the lymphadenectomy field in any of the patients.

**Conclusion:** Complete excision of the primary tumor and retroperitoneal lymphadenectomy can be done safely and provides excellent locoregional control for patients with abdominal neuroblastoma.

Arch Surg. 2003;138:711-715

**NEUROBLASTOMA (NB) is one of the most common childhood cancers. Patients with advanced stages of this tumor have a low cure rate despite aggressive treatment including intensive chemotherapy followed by bone marrow transplantation. In addition to various prognostic factors identified in the past, recent molecular biology-based studies have demonstrated that the poor prognosis is correlated with N-myc amplification, euploid tumor DNA, deletion of chromosome 1p, and absence of TrkA expression. These biological analyses, which are ongoing, suggest that (1) NB is a heterogeneous disease and (2) therapeutic strategies should be altered to fit individual cases. However, the actual management of patients who have NB remains a therapeutic challenge. An NB is usually treated with a combination of surgery, chemotherapy, and/or radiotherapy.**

The contribution of surgical treatment is clear in patients with localized disease, and complete excision provides a significant survival advantage for patients with localized NB. Although total tumor removal in cancer surgery includes organ-specific regional nodal dissection, rationalization of lymph node dissection for regionality has not been established as the standard surgical treatment of abdominal NB. The reasons are that the lymphatics of the retroperitoneum are complex and the anatomical localization of nodal involvement has not been well understood.

We studied the lymphatic drainage of adrenal NBs using intraoperative vital staining and histologically confirmed that this tumor involves retroperitoneal lymph nodes bilaterally. Accordingly, we per-
involve across the midline), 17 had stage IV (ie, distant metastasis, including the skeleton, soft tissue, and/or distant lymph nodes), and 4 had stage IV-S (ie, primary stage I/II lesion, with remote disease confined to the liver, skin, subcutaneous tissue, or bone marrow). Primary resection was performed in 26 patients; delayed primary or second-look resection was performed in 21 patients. Nodal involvement was confirmed histologically in 28 patients including all 6 patients who had Evans stage II NB, 4 who had stage III, 16 who had stage IV, and 2 who had stage IV-S. A combination of vincristine sulfate, doxorubicin hydrochloride, cyclophosphamide, and cisplatin was most commonly used in those patients who received preoperative chemotherapy. Similar postoperative chemotherapy was also administered to patients with advanced cases of NB. However, no patient received either preoperative or postoperative radiotherapy to the primary tumor site. In patients who had Evans stage IV disease, the delayed primary or second-look operation was planned after iodine-123 metaiodobenzylguanidine scintigraphy was performed to determine that distant metastasis was negative and major vessel involvement was considered negative or minimal.

SURGICAL PROCEDURES

Our previous study revealed the topography of lymphatic drainage from adrenal NB to be as follows: primary lymphatic drainage is to the nodes at the origin of the renal artery, those around the hemiazygos vein for a left adrenal NB, and those around the azygos vein for a right adrenal NB. The secondary regional nodes are the interaortocaval nodes, the para-aortic nodes for a left adrenal NB, and the paracaval nodes for a right adrenal NB. In patients who had a right-sided retroperitoneal NB (Figure 1A). In patients with a left-sided retroperitoneal NB, lymph nodes at the origin of the left renal artery, those around the hemiazygos vein, the interaortocaval nodes, and the para-aortic nodes were dissected (Figure 1B).

We skeletonized some parts of the abdominal aorta and vena cava. However, bilateral kidney and mesenteric vessels were preserved in all operations; testicular or ovarian vessels and hypogastric plexus were also preserved as much as possible. In this series of surgical procedures, we performed the same pattern of lymphadenectomy in those patients who had a tumor originating from a sympathetic ganglion adjoining the adrenal gland, in addition to nodes around the azygos vein, the interaortocaval nodes, and the paracaval nodes in patients who had a right-sided retroperitoneal NB (Figure 1A). In patients with a left-sided retroperitoneal NB, lymph nodes at the origin of the left renal artery, those around the hemiazygos vein, the interaortocaval nodes, and the para-aortic nodes were dissected (Figure 1B).

We skeletonized some parts of the abdominal aorta and vena cava. However, bilateral kidney and mesenteric vessels were preserved in all operations; testicular or ovarian vessels and hypogastric plexus were also preserved as much as possible. In this series of surgical procedures, we performed the same pattern of lymphadenectomy in those patients who had a tumor originating from a sympathetic ganglion adjoining the adrenal gland, in addition to nodes around the azygos vein, the interaortocaval nodes, and the paracaval nodes in patients who had a right-sided retroperitoneal NB (Figure 1A). In patients with a left-sided retroperitoneal NB, lymph nodes at the origin of the left renal artery, those around the hemiazygos vein, the interaortocaval nodes, and the para-aortic nodes were dissected (Figure 1B).

The medical records of all patients, including operative and the postmortem examination reports, were reviewed, and clinically relevant data on surgical intervention, postoperative complications, survival, and local recurrence were analyzed. Local recurrence was defined as recurrence after complete tumor control in the primary site and was determined by periodic imaging studies using computed tomography, nuclear magnetic resonance imaging, and/or scintigraphy using...
SURGICAL INTERVENTION

The average duration of surgery was 5 hours 28 minutes (range, 2 hours 30 minutes to 13 hours 30 minutes) (Table 1). The mean intraoperative blood loss was 27.7 (34.5) g/kg of body weight (range, 1.9-155.9 g/kg of body weight), and intraoperative blood loss was significantly less in patients who had early stages of NB than those with advanced stages of NB (P < .01). The mean transfusion requirement in the 28 patients who received an intraoperative blood transfusion was 15.4 (24.0) mL/kg of body weight (range, 3-129 mL/kg of body weight). There was no necessity for blood transfusion in 19 patients, including 11 of the 14 patients who had Evans stage I disease and 3 of the 6 patients who had Evans stage II disease. In addition, there were no intraoperative major complications leading to visceral insufficiency or perioperative death. Postoperative chemotherapy was administered within 2 weeks after surgery in advanced cases of NB. The preoperative therapeutic schema was not changed by the results of surgery in any of the patients.

POSTOPERATIVE COMPLICATIONS

Postoperative complications were observed in 12 patients (Table 2). Diarrhea was the most common problem and was noted in 8 patients. This postoperative diarrhea resolved within a few weeks in most patients, with the exception of 1 patient who had prolonged diarrhea lasting 6 months after surgery. Chylous ascites was found in 1 patient who was treated with conservative therapy and was cured within 2 weeks. Intestinal obstruction was noted in 2 patients, who underwent laparotomy for postoperative intussusception and adhesion. Renal atrophy was observed in 3 patients who had Evans stages II, III, and IV disease. The atrophic kidney was on the same side as the tumor in all cases. Postoperative ejaculatory function could not be assessed in all patients because most patients had not reached the reproductive age.

SURVIVAL AND LOCAL RECURRENT

The mean follow-up period for the entire patient population was 8.5 years (range, 0.7-15.8 years), and for survivors it was 10.1 years (range, 3.5-15.8 years). All 30 patients with Evans stage I, II, III, or IV-S disease; 8 of the 17 patients with stage IV disease were alive without evidence of disease (Figure 2). Survival rate of patients with stage IV disease was 47.1%; there were statistically significant differences in the survival rates between patients with Evans stage I, II, III, or IV-S disease and those with stage IV disease (P = .001). Eight patients, including 6 of the 7 patients with N-myc amplification, who all had Evans stage IV disease, died of progressive disease. The remaining 1 patient died of cytomegalovirus infection. There was no local recurrence detected within the lymphadenectomy field in any subjects, including those who died.

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of Patients (N = 47)</th>
<th>Operation Time</th>
<th>Blood Loss, g/kg†</th>
<th>Blood Transfused, mL/kg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>14</td>
<td>3 h 15 min</td>
<td>8.3 (6.6)a,b</td>
<td>2.4 (5.2)</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>3 h 32 min</td>
<td>8.0 (13.3)a,b</td>
<td>5.7 (6.8)</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>7 h 36 min</td>
<td>33.9 (19.7)</td>
<td>20.8 (25.3)</td>
</tr>
<tr>
<td>IV</td>
<td>17</td>
<td>7 h 42 min</td>
<td>52.6 (45.1)</td>
<td>30.4 (30.9)</td>
</tr>
<tr>
<td>IV-S</td>
<td>4</td>
<td>3 h 25 min</td>
<td>10.1 (2.6)</td>
<td>3.7 (4.4)</td>
</tr>
<tr>
<td>Average</td>
<td>5 h 28 min</td>
<td></td>
<td>27.7 (34.3)</td>
<td>15.4 (24.0)</td>
</tr>
</tbody>
</table>

*Stage I indicates neuroblastoma is limited to the organ of origin; stage II, the homolateral lymph node is involved, the tumor cannot invade across the midline; stage III, the tumor extends across the midline, local lymph nodes can be involved bilaterally; stage IV, distant metastasis, including the skeleton, soft tissue, and/or distant lymph nodes; and stage IV-S, primary stage I/II lesion, with remote disease confined to the liver, skin, subcutaneous tissue, or bone marrow.

†Data are given as mean (SD).

©2003 American Medical Association. All rights reserved.
Surgical management is beneficial in patients with cancer who have localized disease. It is generally accepted that complete tumor resection of an NB has offered the best chance of a cure in patients with Evans stages I and II NBs. Several clinical studies have also demonstrated a better survival rate with complete excision of stage III NB. Additional reports have stated that complete resection along with intensive chemotherapy is associated with improved survival even in patients with Evans stage IV NB. However, the definition of total removal has been obscure in the past literature, suggesting that the true effectiveness of surgery in the treatment of NB remains unknown.

On the other hand, findings from a 1995 and a 1998 study have demonstrated that in many malignancies nodal involvement can only be proved by means of molecular analysis. We similarly believe that micrometastasis of regional lymph nodes is best confirmed by molecular biology analysis in patients with NB, and concur that the histologic validation of resected specimens does not always correlate with complete excision. Therefore, we have delineated a definite area for lymph node dissection in accord with the laterality of the tumor origin and have performed definitive surgery for abdominal NB based on the retroperitoneal lymphatics of NB as determined in a previous study. In the present study, we used the clinical staging system of Evans et al and assessed primarily the efficacy of the surgical contribution among the many factors potentially influencing the clinical outcome in patients with abdominal NB.

The most important focus of this study was local recurrence after surgical resection of the NB. Despite intensive treatment, NB often recurs in the area of the primary tumor. Ikeda et al examined the effect of local treatment in 29 patients with advanced NB who were treated with supralethal chemotherapy and total-body irradiation followed by bone marrow transplantation. They reported that the overall local relapse rate was 17% (5 patients) among the 29 patients, and was 21% (5 patients) in the 24 patients who received local treatment with surgery and radiation. A similar local failure rate was reported by Matthay et al, who observed local recurrence in 22 (26%) of the 84 patients with high-risk NB after aggressive resection and irradiation of residual disease. Compared with these results, our results revealed that sufficient local tumor control of abdominal NB could be achieved by retroperitoneal lymphadenectomy together with primary tumor removal. In the series by La Quaglia et al, 2 (0.05%) of 39 patients who underwent total resection had local recurrence. Thus, we can expect that adequate locoregional treatment with surgery should prevent local relapse of NB.

In addition, although this series did not deal with enough patients to evaluate any difference in survival after this surgery, it is clear that patients with localized abdominal NB had a better prognosis with this surgical procedure. The residual loco-regional disease of some cancers may be more resistant to systemic adjuvant therapy than blood-borne, distant micrometastases. Moreover, local recurrence may lead to reseeding of distant metastatic sites. Therefore, locoregional control with a rational surgical intervention and intensive chemotherapy may contribute to a better outcome in patients with disseminated NB.

Conclusions

We described the significance of the rational approach to surgery for treatment of retroperitoneal NB and subsequently discussed an evaluation of the surgical contribution to retroperitoneal NB. The precise role of surgery in the treatment of advanced NB will be clarified by future randomized trials comparing tumor resection with no resection. The optimal surgery in the current treatment of advanced NB needs to satisfy several conditions: minimal degree of surgical intervention, gross complete excision, and consequently, no delay of postoperative chemotherapy.

Accepted for publication October 19, 2002.

Corresponding author and reprints: Kazuaki Tokiwa, MD, PhD, Division of Surgery, Children’s Research Hospital, Kyoto Prefectural University of Medicine, Kawaramachidori, Kamigyo-ku, Kyoto 602-8566, Japan (e-mail: tokiwa@kato.kpu-m.ac.jp).

REFERENCES


3. Caron H, van Sluis P, de Kraker J, et al. Allelic loss of chromosome 1p as a pre-
Surgical Anatomy

Lymph capillaries are not present in epithelium (e.g., epidermis), cartilage or other tissues devoid of blood vessels; neither are they present in parts possessing sinusoids, nor in the brain or eyeball—though in the brain the perivascular spaces, continuous with the subarachnoid space, substitute for them. Lymph capillaries do not accompany the blood capillaries between the alveoli of the lungs, nor in the glomeruli of the kidneys, since these capillaries are not nutritive in function—but in the lungs lymph vessels do accompany the bronchial vessels.