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KENJI SANTO, AKIHIRO YONEDA, SHUICHIRO UEHARA et al. Optimal Surgery for Abdominal Intermediate-risk Neuroblastoma: Retrospective Study in a Single Institution. *Osaka City Medical Journal*. 2021, 67, 29-35.

Osaka City Med. J. Vol. 67, 29-35, 2021

Optimal Surgery for Abdominal Intermediate-risk Neuroblastoma: Retrospective Study in a Single Institution

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Abstract

Background

The treatment outcome of intermediate-risk neuroblastoma has improved and it is an important issue to reduce the treatment complication. To identify the optimal surgery, we evaluate the surgical risk factors for abdominal intermediate-risk neuroblastoma treatment.

Methods

Twelve patients with abdominal intermediate-risk neuroblastoma, according to the risk stratification in the Children's Oncology Group, treated at our hospital between 1995 and 2016 were included. The patients were divided into two groups according to the presence (group A, n=5) or absence (group B, n=7) of surgical complications. Clinical features were compared between groups A and B.

Results

The median age at diagnosis was 7 (range 4-8 months) and 7 (0.1-23 months) months in groups A and B. Surgical complications were nephrectomies (n=2), renal atrophy (n=1), bowel obstruction (n=1), and ejaculation disorder (n=1). All tumors in group A and 29% (n=2) of tumors in group B had ≧95% resection. All patients had tumors with image-defined risk factors at diagnosis. Only one of tumors in group B changed to "image-defined risk factors not present" status after chemotherapy. All patients were alive without disease after a median follow-up of 175 months (44-263 months).

Conclusions

Resection of ≧95% could be a surgical risk factor in abdominal intermediate-risk neuroblastoma treatment. Due to the positive outcomes, less aggressive surgery minimizing surgical complications for abdominal intermediate-risk neuroblastoma is recommended even if residual tumors persist.

Key Words: Neuroblastoma; Pediatrics; Complications; Intermediate-risk; Surgery

Received July 2, 2020; accepted November 24, 2020.

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Introduction

Neuroblastoma, the most commonly occurring extracranial malignant solid tumor in children, is a heterogeneous tumor that exhibits various behaviors, including spontaneous regression and metastatic diseases with poor outcome. Neuroblastoma is classified into low-, intermediate-, or high-risk categories based on the clinical and biological features, with the risk category correlating with outcome. Identification of risk groups has allowed tailoring of therapy to improve outcomes and minimize the risk of deleterious consequences of therapy[1].

A recent large, prospective, multicenter trial by the Children's Oncology Group (COG) revealed that the rate of overall survival of patients with intermediate-risk tumors exceeded 90%, with a consequent reduction in the application of treatment[2]. On the other hand a relatively high surgical complication rate of 28% with four deaths was observed in their trial.

Iehara et al[3] retrospectively reviewed 20 patients with intermediate-risk neuroblastoma after 15 years of the median follow-up time. They concluded that the presence of a residual mass at the end of treatment did not influence the patients' prognoses. Although these results suggested that aggressive surgery is not necessary, optimal surgery for intermediate-risk neuroblastoma has not been clearly discussed previously.

A previous study showed the potential prognostic importance of clinical characteristics, including the primary tumor site. Patients with abdominal primaries have a less favorable prognosis than those with cervical, pelvic, and thoracic primaries[4]. Furthermore, Image-Defined Risk Factors (IDRFs) were separately defined according to the anatomical sites[5]. Therefore, to identify the optimal surgery for intermediate-risk neuroblastoma, we conducted a retrospective study to evaluate the surgical risk factors of abdominal intermediate-risk neuroblastoma treatment.

Methods

Of the 148 patients with neuroblastoma treated at our hospital between January 1995 and December 2016, 17 were classified as intermediate-risk neuroblastoma cases following the COG risk classification. Intermediate-risk neuroblastoma was defined as International Neuroblastoma Staging System (INSS)[6] stage 3 or 4 disease without *MYCN* amplification in an infant (<1 years), stage 3 disease with favorable histopathological features in a child (≧1 years), and stage 4S disease with a diploid tumor-cell DNA index, unfavorable histopathological features, or both[2]. We did not recruit in accordance with the current International Neuroblastoma Risk Group (INRG) risk classification[7] because no information of 11q LOH was available in patients treated prior to the publication of the INRG risk classification. Of these patients, 12 with abdominal neuroblastoma were selected. We divided the patients into two groups according to the presence (group A, n=5) or absence (group B, n =7) of surgical complications. We retrospectively evaluated the risk factors in the surgical treatment of abdominal intermediate-risk neuroblastoma. The study design was approved by the ethics review board of our institution (No. 1804002).

IDRFs were determined according to the Guidelines for imaging and staging of neuroblastic tumors[5]. Therefore, isolated contact with renal vessels was considered an IDRF-positive condition in this study. Surgical complications were defined as major complications of surgery that occurred during the intraoperative or postoperative period. With respect to nephrectomy, expanded resection was also allowed at that time, and it was not considered a complication. However, we classified planed nephrectomy as complications according to the current neuroblastoma treatment policy. The

Table 1. Patients' characteristics

	group A (N=5)	group B (N=7)
Sex, n (%)		
Male	4 (80)	4 (57)
INSS, n (%)		
3	4 (80)	6 (86)
4	1 (20)	1 (14)
4S	0 (0)	0 (0)
Intraspinal extension, n (%)	1 (20)	1 (14)
Primary therapy, n (%)		
Chemotherapy	4 (80)	6 (86)
Surgical resection	1 (20)	1 (14)
INPC, n (%)		
FH, NB	5 (100)	7 (100)
DNA ploidy, n (%)		
Hyperdiploidy	3 (60)	6 (86)
Diploidy	0 (0)	1 (14)
Unknown	2 (40)	0 (0)

INSS, International Neuroblastoma Staging System; INPC, International Neuroblastoma Pathology Classification; FH, Favorable histology; and NB, Neuroblastoma.

extent of resection was classified into the following three categories: resection of ≧95%, 50%-95%, and <50% of the tumor volume[8]. Two surgeons decided the extent of resection according to the preoperative and postoperative images and surgical records.

Age of onset, INSS stage, initial treatment, pathological findings [International Neuroblastoma Pathology Classification (INPC)], tumor biology (*MYCN* amplification, DNA diploidy), primary tumor location, tumor size, IDRFs, association with renal pedicles, extent of resection, and prognoses were compared retrospectively between the two groups.

Data were expressed as medians and ranges. To obtain pairwise comparisons of the data, the Fisher exact test and Student's t-tests was applied. A p value of 0.05 indicated statistical significance. All analyses were performed using R version 3.4.0 (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/)[9].

Results

The patients' characteristics are shown in Table 1. Four patients (80%) in group A and six patients (86%) in group B had stage 3 tumors. Intraspinal extensions were present in one patient in both groups. Of the patients in groups A and B, 80% (n=4) and 86% (n=6) received chemotherapy as an initial treatment, respectively. None of the patients had *MYCN* amplified or an INPC unfavorable tumor in both groups.

The median age at diagnosis was 7 months (range: 4-8 months) in group A and 7 months (0.1-23 months) in group B (Table 2 and Table 3). The treatment protocols were not uniform. The drugs of chemotherapy were used in this study, cyclophosphamide (CPM), vincristine (VCR), pirarubicin (THP), cisplatin (CDDP), carboplatin (CBDCA), dacarbazine (DTIC) and etoposide (VP). The surgical

Table 2. Clinical features in group A

Case	Age at diagnosis (month)	Preoperative chemotherapy (cycle)	Chemotherapy after surgery (cycle)	Complications	Median follow-up period (month)
1	4	VCR+CPM (7)	NA	Nephrectomy	167
2	5	VCR+CPM+THP (2) VCR+CPM+THP+CDDP (2)	VCR+CPM+THP+CDDP (1)	Nephrectomy	177
3	8	NA	VCR+CPM+THP (5)	Bowel obstruction	172
4	7	VCR+CPM+THP (2)	VCR+CPM+THP (5)	Renal atrophy	205
5	7	VCR*CPM+THP (3) VCR+CPM+THP+CDDP (3)	VCR+CPM (5)	Retrograde ejaculation	263

VCR, vincristine; CPM, cyclophosphamide; THP, pirarubicin; CDDP, cisplatin; and NA, not applicable.

Table 3. Clinical features in group B

Case	Age at diagnosis (month)	Preoperative chemotherapy (cycle)	Chemotherapy after surgery (cycle)	Median follow-up period (month)
6	2	VCR+CPM (3)	NA	52
7	7	CBDCA+VP (1) CBDCA+CPM+THP (1)	VP+CPM (2) VP+CBDCA+THP (2) VP+CBDCA (1) CPM+THP (1)	44
8	7	VCR+CPM+THP (4)	VCR+CPM+THP (2)	104
9	23	VCR+CPM+THP+CDDP (5)	VCR+CPM+THP+CDDP (3) CPM+DTIC (1) CPM+THP+CDDP (1)	118
10	0.1	NA	VCR+CPM (18.5)	190
11	7	VCR+CPM+THP (2) VCR+CPM+THP+CDDP (9)	NA	215
12	7	VCR+CPM (3) VCR+CPM+THP (4)	VCR+CPM+THP (3)	208

VCR, vincristine; CPM, cyclophosphamide; CBDCA, carboplatin; VP, etoposide; THP, pirarubicin; CDDP, cisplatin; DTIC, dacarbazine; and NA, not applicable.

complications in group A were planed nephrectomies (n=2), renal atrophy (n=1), bowel obstruction (n =1), and ejaculation disorder (n=1). All the patients were alive without disease after a median follow-up of 175 months (44-263 months). Tumors' characteristics showed in Table 4. Group A had three adrenal tumors (60%), and group B had two (29%). Two retroperitoneal tumors were found in group A (40%); and five, in group B (71%). All the patients had tumors with IDRFs at diagnosis in both groups. Only one of tumors in group B changed from "IDRFs present" to "IDRFs not present" status after preoperative chemotherapy. Three tumors encased renal vessels and two tumors contacted with them in group A. Three tumors encased, three contacted, and one separated in group B. Only one tumor in group B changed from "contact" to "separate" status after preoperative chemotherapy.

The size of the primary tumor was 80 mm (45-110 mm) in group A and 55 mm (32-86 mm) in group B. The preoperative tumor size was 58.5 mm (30-103 mm) in group A and 40 mm (36-80 mm)

Table 4. Tumors' characteristics

	group A (N=5)	group B (N=7)	p-value
Primary tumor location, n (%)			0.56
Adrenal	3 (60)	2 (29)	
Retroperitoneal	2 (40)	5 (71)	
IDRFs at diagnosis, n (%)	5 (100)	7 (100)	1
Preoperative IDRFs, n (%)	5 (100)	6 (86)	1
Primary relationship with RP, n (%)			NA
Separate	0 (0)	1 (14)	
Contact	2 (40)	3 (43)	
Encase	3 (60)	3 (43)	
Preoperative relationship with RP, n (%)			NA
Separate	0 (0)	2 (29)	
Contact	2 (40)	2 (29)	
Encase	3 (60)	3 (43)	
Primary tumor size, mm (range)	80 (45-110)	55 (32-86)	0.13
Preoperative tumor size, mm (range)	58.5 (30-103)	40 (36-80)	0.43
Resection of ≧95%, n (%)	5 (100)	2 (29)	**0.028**

IDRFs, Image-Defined Risk Factors; RP, renal pedicles; and NA, not applicable.

in group B. No tumors were increased in size in group A, while three tumors were increased in size in group B during preoperative chemotherapy.

All the tumors were resected by at least 95% of the tumor volume in group A, including five complete resections, whereas two complete resections, five 50%-95% resections, and one nonsurgical treatment were performed in group B. Thus, all the tumors were resected ≧95% in group A, whereas 29% (n=2) of the tumors were resected ≧95% in group B. Significantly more tumors in group A than in group B were resected ≧95% (p=0.028).

Discussion

In this study, the risk factor in the surgical treatment of patients with abdominal intermediate-risk neuroblastoma could be tumor resection of ≧95%. As all the patients in this study were alive without disease, complete resection could be unnecessary in patients with abdominal intermediate-risk neuroblastoma. This finding is in accordance with some previous reports. Two large studies showed that the extent of resection was not associated with event-free and overall survival in unresectable neuroblastoma without *MYCN* amplification[10,11]. The presence of a residual mass at the end of treatment has been reported to have no influence on patient prognosis after a long-term follow-up in patients with intermediate-risk neuroblastoma[3,12]. These findings supported our opinions that conservative surgery that allows residual tumors to avoid complications was acceptable.

One patient (case 11) who did not undergo surgery for family wishes at the first treatment required additional surgery 8 years after the treatment in this study. Although the pathological finding of the biopsy sample at the time of initial diagnosis was neuroblastoma, it was changed to ganglioneuroma. This result suggests that the residual tumor may have had a differentiation tendency. Marachelian et al showed that the post-chemotherapy histopathology of intermediate-risk neuroblastoma was characterized by regression or maturation[13].

IDRFs have been propounded for predicting the surgical risks of localized neuroblastoma by the INRG task force. The report showed 94% of patients with INSS Stage 3 had IDRFs[14]. In this study, all patients in both groups had tumors with IDRFs at diagnosis. A study from Germany showed that the surgical complication rates were 26.6% and 14.5% (among 366 patients who underwent resection other than biopsy) in patients with localized neuroblastoma tumors identified as IDRF-present and IDRF-absent at diagnosis, respectively[15]. IDRFs at diagnosis were associated with higher rates of operative complications. To avoid surgical complications, a biopsy followed by neoadjuvant chemotherapy is recommended as the initial treatment in patients with IDRF-present tumors, rather than surgical resection. Moreover, due to the positive outcome in this study, conservative surgery to avoid complications is recommended even if residual tumors remain after surgery.

The European Unresectable Neuroblastoma study revealed that the unchanged IDRF pattern was observed in 50% of patients and the appearance of new IDRFs during chemotherapy in approximately 20% of patients[11]. A study from Japan reported that tumors should shrink to <20% of the volume at the time of diagnosis for negative IDRFs and that major surgical complications were observed even in the patients who had disappearance/numerical reduction of IDRFs[16]. In this study, IDRFs disappeared after chemotherapy in only one of patients in group B. Therefore, patients with intermediate-risk neuroblastoma whose tumors had IDRFs at diagnosis may have a potential risk for undergoing surgery even after neoadjuvant chemotherapy.

A previous study showed that the primary tumor size was associated with the risk of nephrectomy[17]. Contrary to expectations, surgical complications were not associated with the primary and preoperative tumor sizes in this study. None of the tumors in group A increased in size, whereas three tumors in group B increased in size.

In Guidelines for imaging and staging of neuroblastic tumors, isolated contact with renal vessels is considered an IDRF-positive condition[5]. On the other hand, only encasement of the renal pedicles is considered an IDRF-positive in Japan Neuroblastoma Study Group (JNBSG)[18]. The previous report showed if isolated contact with renal vessels was considered an IDRF-positive condition, the sensitivity increased but the specificity decreased for the predictor of the complication[18]. In this study, three patients with renal complications in group A had tumors encasing renal pedicles and the tumors were completely resected. In group B, three patients had tumors encasing renal vessels, but no tumors were resected completely. No renal complications were observed on contact in both groups. Therefore, complete resection could be unnecessary in patients with tumors encasing renal pedicles and isolated contact with renal vessels could not be surgical risk.

This study has the following limitations: The number of the patients was limited, and the treatment protocols were not uniform. To better investigate the risk factors in the surgical treatment of patients with intermediate-risk neuroblastoma, larger prospective studies with uniform therapeutic protocols should be designed.

In conclusion, aggressive resection of ≧95% of the tumor could be a surgical risk factor in the treatment of abdominal intermediate-risk neuroblastoma. As all the patients in this study were alive without disease, conservative surgery to avoid complications could be acceptable even if residual tumors persist.

Acknowledgements

All authors have no COI to declare regarding the present study.

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