



# Standard resection procedure can increase the complete resection rate in pediatric patients with locally advanced abdominal neuroblastoma

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**Background:** To investigate the clinical effectiveness of standard procedure in treating children's locally advanced abdominal neuroblastoma (NB).

**Methods:** Totally 71 consecutive patients with stage III or IV NB received pre-operative chemotherapy first, followed by standard procedure (including skeletalization of retroperitoneal vessels and grid-shaped excision of tumor) to remove the tumors. The results were analysed and compared with findings in literature.

**Results:** The complete resection (CR) rate was 97.2% (69/72), which was significantly higher than those in previous reports. No severe surgical complication or perioperative mortality was reported.

**Conclusions:** Standard procedure can improve CR and survival rates in pediatric patients with locally advanced abdominal NB.

**Keywords:** Neuroblastoma (NB); standard procedure; children's neoplasm

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## Introduction

Neuroblastoma (NB) is one of the most common malignant solid tumors in children, accounting for about 8–12% of all childhood malignancies. NB mainly arises from retroperitoneal sympathetic nerve tissue. Due to its insidious onset, the local tumor is often in advanced stage when it is detected. While multidisciplinary treatment mode including chemotherapy, surgery, radiotherapy, and bone marrow transplantation has been applied for the treatment of this disease, surgery remains the most important link. Complete resection (CR) of the primary tumor can dramatically increase the patients' 5-year survival rate (1). For locally advanced NB (stage III and IV), however, the resection can be difficult because the tumor often surrounds

the major blood vessels and organs in the retroperitoneal region. In our center the standard procedure including skeletalization of retroperitoneal vessels and grid-shaped excision of tumor (2) has been applied for the treatment of locally advanced NB, with satisfactory effectiveness.

## Methods

### Patients

Totally 71 pediatric patients with stage III or IV NB were treated in our center from March 2003 to December 2013. The general data of these patients are shown in *Table 1*. All the patients received 4–8 cycles of preoperative chemotherapy according to the standard chemotherapy

**Table 1** General information of 71 pediatric patients with locally advanced abdominal neuroblastoma

General data	Number
Age	
>2 years	51
1–2 years	20
INSS stage	
Stage III	42
Stage IV	29
Primary tumor site	
Upper abdomen	60
Lower abdomen	9
Pelvic cavity	2
Biopsy	
Needle biopsy	33
Open biopsy	38
MYCN gene	
With amplification	26
Without amplification	45

INSS, International Neuroblastoma Staging System.

protocol for NB proposed by Children's Oncology Group, USA. The surgery was performed after the tumor shrank.

### *Surgical methods*

The surgical principle was to achieve complete gross resection (CR), whereas near-complete gross resection (NCR) was allowable. Vessels of major organs (e.g., the superior mesenteric vessels and renal vessels) were reconstructed using vascular surgery techniques. Under the premise of ensuring surgical safety and quality of life, some organs such as the body and tail of pancreas and the spleen could be removed.

Under general anesthesia, the patients were placed in a supine position, with their back padded. A transverse abdominal incision closing to the tumor was made; alternately, the biopsy incision was extended. First, the lateral peritoneum of the ascending or descending colon was cut open to turn the colon inwards to expose the anterior side of the tumor. Beginning from the distal side of the tumor, dissection was performed upwards along the

inferior vena cava and abdominal aorta, so as to skeletalize these vessels, which was performed along the extravascular space. The perforator branches of tumors and the involved lumbar branches were transected after ligation. In rare cases, the vessels were seriously infiltrated by tumors and thus could not be divided; then, parts of the affected blood vessel walls could be removed first, then the blood vessels could be reconstructed using vascular surgery techniques. The dissection continued along the inferior vena cava to expose the left and right renal veins and along the abdominal aorta to expose the inferior mesenteric artery, left/right renal arteries, superior mesenteric artery, and celiac trunk. With the major vessels as the “grid lines”, the tumor tissues in each “grid” were resected block after block. Notably, the NB following chemotherapy usually had no clear boundaries; thus, the resection scope must be decided according to baseline computed tomographic (CT) findings, so as to ensure the CR of the tumors.

### *Literature search and statistical analysis*

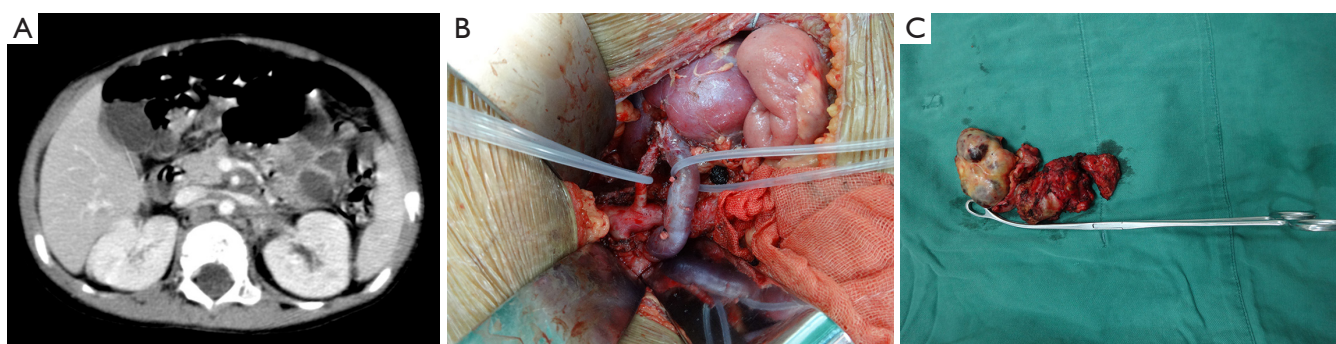
Literature search was performed in PubMed using the search conditions being: command: “neuroblastoma” AND “surgery” AND (“stage 3” OR “stage 4” OR “stage III” OR “stage IV”); fields: “title/abstract”; language: English; and publication date: after the year of 2000.

Statistical analysis was performed using SPSS 16.0 software. Comparison of count data was performed using chi square test, with a P value of less than 0.05 being considered statistically significant.

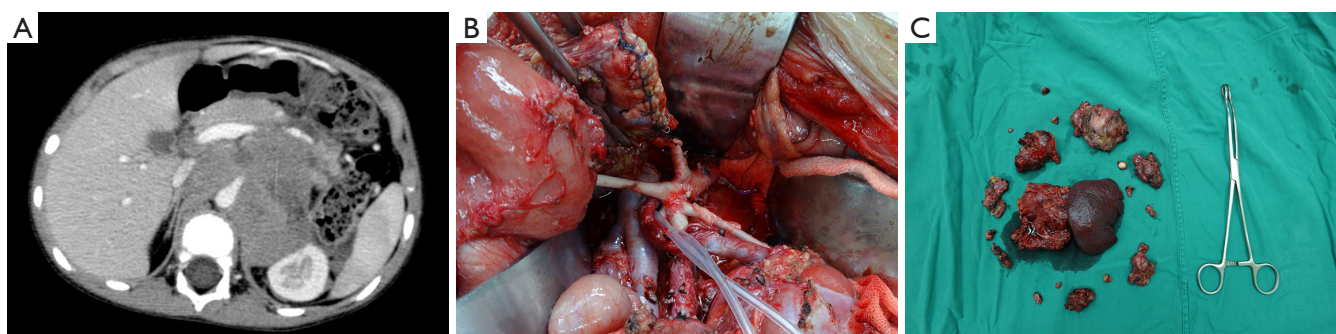
## **Results**

### *Clinical outcome*

CR or NCR was achieved in 69 of 71 cases (97.2%). Two patients only underwent partial resection. In one of these two patients, the tumor had invaded the head of the pancreas, and the patient's family refused to undergo pancreaticoduodenectomy. In the other patient, the pelvic tumor had invaded the presacral ureter and the affected ureter and parts of the bladder and thus the radical surgery was abandoned. Unilateral nephrectomy was performed in 10 patients because the renal pedicle could not be isolated due to tumor infiltration. Renal vascular reconstruction was performed in 3 cases after parts of renal vein was resected due to tumor infiltration. Superior mesenteric artery was reconstructed after partial resection in



**Figure 1** Preoperative CT (A) of a 2-year-old male patient reveals that the tumor surrounds bilateral renal blood vessels; (B) intraoperative findings after resection of the tumor; (C) the resected tumor blocks.



**Figure 2** Preoperative CT of a 3-year-old male patient reveals that the tumor surrounds the vessels of all the major organs in the upper abdomen and invades the pancreas (A); (B) findings after tumor resection, in which the abdominal aorta, inferior vena cava, celiac trunk, superior mesenteric artery, and bilateral renal arteries have been skeletalized; (C) the resected tumor blocks.

1 case. The body and tail of pancreas and the spleen were removed in 2 cases. Resection of the descending colon was performed in 1 case.

The operative time was 5 h 20 min (2 h 30 min to 8 h 30 min). The intra-operative blood loss was 100–1,200 mL (mean: 550 mL). After the surgery, 7 children suffered from chylous leakage, in whom the drainage tube was withdrawn within 1 month after surgery after adequate drainage, restricted diets, and management for preventing infections; 35 patients developed watery diarrhea, which was improved within 5 postoperative days after symptomatic treatment including fluid replacement and antidiarrheal therapy; 2 patients suffered from incomplete intestinal obstruction during chemotherapy beginning on the 14th postoperative day, and the condition was improved after fasting and fluid replacement. No peri-operative death was noted. No other severe complication such as postoperative bleeding, wound infection, or renal atrophy was detected. Two typical cases are shown in *Figures 1,2*.

### *Comparison with literature*

Of 95 articles searched from PubMed, 8 randomized controlled trials (RCT) were enrolled for analysis (*Table 2*). Since watery diarrhea is an inevitable outcome shortly after the CR of retroperitoneal NB, it was not listed as a surgical complication for analysis. The rate of CR/NCR following the standard procedure was higher in our series than those in previous literature ( $P>0.05$ ), whereas the incidences of complications did not increase ( $P>0.05$ ).

### **Discussion**

NB seen in patients of different ages has dramatically different response to certain treatment. Infants with NB accompanied by *MYCN* gene amplification often respond poorly to multidisciplinary treatment including surgery. Castel *et al.* (10) reported 35 cases of such patients (staged II, III, or IV) and found that the 2-year survival

**Table 2** Comparison with literature

Authors	Total cases	Number of cases reaching CR/NCR (%)	Number of patients with post-operative complications (%)	Whether the survival was approved when compared with partial resection
Castel <i>et al.</i> (3)	71	39 (54.9)*	7 (9.9) <sup>#</sup>	Yes
von Schweinitz <i>et al.</i> (4)	791	467 (59.0)*	152 (19.2) <sup>#</sup>	Yes/unsure <sup>+</sup>
La Quaglia <i>et al.</i> (1)	141	103 (73.0)*	11 (10.6) <sup>#</sup>	Yes
Adkins <i>et al.</i> (5)	468	211 (45.1)*	61 (13.0) <sup>#</sup>	Yes
Koh <i>et al.</i> (6)	26	10 (38.5)*	-	Yes
Escobar <i>et al.</i> (7)	104	52 (50.0)*	23 (22.1) <sup>#</sup>	Yes
Bowne <i>et al.</i> (8)	30	19 (63.3)*	-	Yes
Sultan <i>et al.</i> (9)	291	169 (58.1)*	-	Yes
Our series	71	69 (97.2)	9 (12.7)	Yes

\*,  $P < 0.05$ , compared with our series; <sup>#</sup>,  $P > 0.05$ , compared with our series; <sup>+</sup>, it was believed that the CR surgery could improve the survival in pediatric patients with MYCN gene amplification but had uncertain effectiveness in patients without MYCN gene amplification.

rate was only 30% and the average survival time was only 12 months. In contrast, NB infants without *MYCN* gene amplification often have much better outcomes. Of 125 pediatric patients reported by De Bernardi *et al.* (11), the 2-year survival rate was 97.6%, which was not significantly correlated with surgery; thus, they proposed that treatment might not be required for asymptomatic children and a watchful observation might be more feasible. Therefore, infants were not included in our series.

For older (>1 year old) pediatric NB patients, surgical resection still plays an important role, even for advanced NB (stages III and IV). In a retrospective analysis of 69 patients, Bai *et al.* (12) found that radical resection was the only treatment for patients with non-*MYCN*-amplified stage III tumours, among whom the 10-year survival reached 84.6%; in patients with *MYCN*-amplified stage III NB, radical resection plus other multidisciplinary therapies could achieve a 10-year survival of up to 90%. For stage IV NB, Koh *et al.* (6) believed that radical resection for local tumors were essential and the metastatic lesions could be controlled by chemotherapy; the mean survival of pediatric patients who had achieved local CR was 52.8 months, which was far longer than that (12.2 months) in patients who had only achieved subtotal resection. Bastian *et al.* (13) also argued that the survival of pediatric patients with stage IV NB was determined by the radical resection of primary tumor and the control of metastatic

lesions; a CR surgery not only could increase the local control rate of tumors and decrease complications in the primary sites but also improve the long-term survival. von Schweinitz *et al.* (4) argued that the radical surgery had no definite role for pediatric NB patient without *MYCN* gene amplification but did improve the prognosis of those with *MYCN* gene amplification. However, the locally advanced NB may surround the major organ vessels and thus makes the resection extremely difficult. In *Table 2*, the highest CR rate was 73% and lowest one was only 38.5%. In our series, preoperative chemotherapy was applied to shrink tumors and reduce intraoperative bleeding, followed by standard surgical operation; as a result, the CR rate reached up to 97.2%. According to our experiences, skeletonization of the major vessels in the retroperitoneal region along the extravascular space, followed by grip-shaped resection of tumors, is the key step in ensuring the safe and CR of the tumors. In rare cases, the vessels were seriously infiltrated by tumors and thus could not be divided; then, the involved organs often need to be resected. In our series, unilateral nephrectomy was performed in 10 patients, resection of the body and tail of pancreas and the spleen in 2 cases, and resection of the descending colon in 1 case, accounting for 18.3% of all cases. Similarly, Adkins *et al.* (5) reported that the organ resection rate was also 19% in the CR group. In recent years, we have introduced the vascular surgery techniques in the surgical treatment for NB. In our current series, renal vein was reconstructed in 3 cases and superior

mesenteric artery was reconstructed in 1 case by vascular grafting; the postoperative organ functions were normal, and no complication was noted. Aminzadeh *et al.* (14) reported 5 cases who had undergone reconstruction for injured abdominal aorta during surgical resection for stage IV NB and the surgical outcomes were good; they believed that CR surgery could improve the long-term prognosis of patients and thus high-risk vascular surgery might be performed for this purpose. In our series, arteries surrounded by tumor tissues were easier to be isolated than veins, along with smaller risk of injuring the abdominal aorta. However, the risk of vascular injury may remarkably increase during a second surgery for recurrence following total or subtotal resection. Thus, adequate preparation for blood transfusion is required before such a surgery; meanwhile, prosthetic vessel should be prepared for dangerous abdominal aorta injury.

In our series, CR was not achieved in two patients, among whom the surgery was abandoned in one patient because the family was not willing to take the risk and the other patient had diffuse tumor invasion into pelvic structures. Cruccetti *et al.* (15) reported 17 patients with pelvic NB, among whom only 6 had CR; however, the 5-year survival was up to 82%; permanent postoperative neurological complications occurred in 6 patients (35%). These included sciatic nerve palsy, urinary and fecal incontinence, neuropathic bladder, and leg weakness. They proposed that surgical treatment for CR should not be overaggressive for pelvic NB, otherwise it may cause intractable neurological complications. According to our experiences, due to narrow space and rich nerves, CR is difficult to achieve for pelvic NB. In our series, only 1 of 2 patients with pelvic NB achieved CR.

In conclusion, the standard resection procedure can increase the CR rate in pediatric patients with locally advanced abdominal NB without increasing the surgical risk. It is helpful to improve the long-term survival.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2016.10.53>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee, and written informed consent was obtained from all patients.

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## References

1. La Quaglia MP, Kushner BH, Su W, et al. The impact of gross total resection on local control and survival in high-risk neuroblastoma. *J Pediatr Surg* 2004;39:412-7; discussion 412-7.
2. Bassiri H, Benavides A, Haber M, et al. Translational development of difluoromethylornithine (DFMO) for the treatment of neuroblastoma. *Transl Pediatr* 2015;4:226-38.
3. Castel V, Tovar JA, Costa E, et al. The role of surgery in stage IV neuroblastoma. *J Pediatr Surg* 2002;37:1574-8.
4. von Schweinitz D, Hero B, Berthold F. The impact of surgical radicality on outcome in childhood neuroblastoma. *Eur J Pediatr Surg* 2002;12:402-9.
5. Adkins ES, Sawin R, Gerbing RB, et al. Efficacy of complete resection for high-risk neuroblastoma: a Children's Cancer Group study. *J Pediatr Surg* 2004;39:931-6.
6. Koh CC, Sheu JC, Liang DC, et al. Complete surgical resection plus chemotherapy prolongs survival in children with stage 4 neuroblastoma. *Pediatr Surg Int* 2005;21:69-72.
7. Escobar MA, Grosfeld JL, Powell RL, et al. Long-term outcomes in patients with stage IV neuroblastoma. *J Pediatr Surg* 2006;41:377-81.
8. Browne M, Kletzel M, Cohn SL, et al. Excellent local tumor control regardless of extent of surgical resection after treatment on the Chicago Pilot II protocol for neuroblastoma. *J Pediatr Surg* 2006;41:271-6.

9. Sultan I, Ghandour K, Al-Jumaily U, et al. Local control of the primary tumour in metastatic neuroblastoma. *Eur J Cancer* 2009;45:1728-32.
10. Castel V, Berlanga P. Ototoxicity: a worrying problem for survivors of high-risk neuroblastoma. *Transl Cancer Res* 2014;3:521-4.
11. De Bernardi B, Gerrard M, Boni L, et al. Excellent outcome with reduced treatment for infants with disseminated neuroblastoma without MYCN gene amplification. *J Clin Oncol* 2009;27:1034-40.
12. Bai CQ, Yao YW, Liu CH, et al. Diagnostic and prognostic significance of lysophosphatidic acid in malignant pleural effusions. *J Thorac Dis* 2014;6:483-90.
13. Bastian PJ, Fleischhack G, Zimmermann M, et al. The role of complete surgical resection in stage IV neuroblastoma. *World J Urol* 2004;22:257-60.
14. Aminzadeh S, Vidali S, Sperl W, et al. Energy metabolism in neuroblastoma and Wilms tumor. *Transl Pediatr* 2015;4:20-32.
15. Cruccetti A, Kiely EM, Spitz L, et al. Pelvic neuroblastoma: low mortality and high morbidity. *J Pediatr Surg* 2000;35:724-8.

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