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The impact of gross total resection on survival in children with stage III/IV neuroblastoma – study of clinical efficacy in 21 cases

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Abstract. – OBJECTIVES: A retrospective study was conducted in 21 children with stage III/IV retroperitoneal neuroblastoma to evaluate the outcome of gross total tumor resection using vascular skeletonization.

PATIENTS AND METHODS: Between 2003 and 2008, 22 patients with stage III/IV neuroblastoma were included in this study. The treatment was initiated with four to six cycles of induction chemotherapy using the most recent Children's Oncology Group (COG) regimen to reduce the size of the tumors. This was followed by a primary gross total resection by skeletonising the blood vasculature. Gross total resection was accomplished in 21 patients who also received subsequent chemotherapy and bone marrow transplant. Routine follow-ups were performed by phone calls or letters to acquire information about postoperative recovery, distant metastasis or recurrence at the primary site, mortality and cause of death.

RESULTS: Twenty-one patients received gross total resection with complete resection rate of 95.45%. Neither severe postoperative complications nor perioperative death occurred. Three patients were excluded due to a loss in follow-up. Tumor-free survival reached 55.56% (n=10). Three tumor-bearing patients (16.67%) survived. Five patients (27.78%) died after surgery. Overall five-year survival reached 72.22% (13/18).

CONCLUSIONS: Using the skeletonizing major vasculature of retroperitoneum approach to achieve delayed total gross resection for advanced neuroblastoma, significantly improved postoperative survival.

Key words:
Blood vessels, Skeletonized, Surgery, Neuroblastoma.

Introduction

Neuroblastoma is the most common malignant retroperitoneal solid tumor in children. Most patients present with stage III or IV at the initial diagnosis. Despite chemotherapy, surgery, radiotherapy, biological therapy, bone marrow transplants and other comprehensive treatment, the outcome of advanced-stage neuroblastoma is depressing with a three-year survival rate reported to be only 40%[1] and five-year event-free survival at 32%[2]. Neuroblastoma often extensively invades surrounding tissues or encases large retroperitoneal vascular structure, which result in a low complete resection rate of 66.4%-79% for primary surgery[3]. A secondary procedure or even third surgical procedure is required during treatment. Currently, it remains controversial as to whether gross surgical resection can improve survival in patients with advanced-stage disease[2-9]. In this study, 21 children with stage III or IV neuroblastoma underwent gross total resection surgery using the retroperitoneal vascular skeletonization procedure. The tumor resection rate at primary surgery was 95.45% (21/22), and the five-year overall survival rate was 72.22%, which were significantly higher than the results reported in the literature[2].

Patients and methods

Patients

Between March 2003 and May 2008, 22 children (16 males, 6 females) with International Neuroblastoma Staging System (INSS) Stage III/IV retroperitoneal neuroblastomas, admitted in our hospital, were enrolled in this study. The primary sites of the tumor were found at the adrenal gland (n=18) and the retroperitoneal sympathetic nerve chain (n=4). The initial symptoms were presented at the age of two months to six years and one month.

Methods

A diagnosis of neuroblastoma was made based on the clinical manifestations, imaging studies, and laboratory findings which included increased

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level of serum lactate dehydrogenase (LDH), neuron-specific enolase, ferritin concentration, urinary vanillyl mandelic acid (VMA) and catecholamine (CA). The diagnosis was further confirmed by ultrasound-guided needle biopsy. The treatment was initiated with four to six cycles of induction chemotherapy, using the most recent Children's Oncology Group (COG) regimen to decrease the size of the tumors, followed by primary gross total resection with lymph nodes removal by skeletonising blood vasculature[10]. Consolidation with chemotherapy, radiotherapy, bone marrow transplant and biological therapy was performed after primary surgery. Follow-up was conducted by routine inquiries, physical examinations and CT scan of the abdomen, pelvis and chest to uncover disease relapse or distant metastasis. In addition, the whole body bone scan was performed to investigate the occurrence of bone metastases, and bone marrow aspiration and biopsies, were performed to determine metastases. Follow-up phone calls and letters were also conducted for further details.

Results

Of the 22 neuroblastoma patients, 21 received primary gross total resection of the tumors and eradication of the involved lymph nodes. No macroscopic residual tumors were detected, and the peripheral vital organs were perfectly preserved. The complete resection rate of 95.45% (21/22) was achieved. One patient who received subtotal resection had residual tumor, which was likely due to incomplete separation of the tumor from the involved celiac arteries. No perioperative complications or death were observed in these patients. Three patients were excluded due to loss of follow-up. Tumor-free survival reached 55.56% (n=10). The pathological study showed ganglioneuroblastomas in six of these 10 patients. Three tumor-bearing patients (16.67%) survived, one of which had ganglioneurobalstoma. Five patients (27.78%) died after surgery, one of which was also confirmed to be ganglioneuroblastoma. The death was due to the progression of the tumors after bone marrow transplant, metastases to the liver and multiple bones and respiratory failure resulting from mediastinal metastasis. Overall five-year survival reached 72.22%. Postoperative tumor recurrence at primary site was detected in four patients with a recurrence rate of 22.22% (4/18). There were two tumor-bearing patients who survived while two patients died. Delayed complications were present in two patients (11.11%, 2/18). One patient suffered from a chronic postoperative diarrhea during the eight month follow-up. In addition, one patient died from extensive tumor invasion of the renal vasculature. Left renal atrophy was observed at six months postoperative follow-up even though complete separation of the left renal vessels from the tumor was achieved during surgery.

Discussion

Kiely et al[11] discovered that frequently, neuroblastoma only invades tunica adventitia but spares the tunica media in the major blood vessels. On this basis, they proposed a surgical technique for radical resection of the neuroblastoma by dissecting and separating the involved blood vessels and excising the tumors together with the vascular adventitia in the involved blood vessels. Four to six cycles of preoperative induction therapy resulted in significantly smaller and harder tumors. As well, areas of necrosis, resulting from damaged and defective microvascular network, were observed inside the tumor[12,13]. Despite the obvious invasion of the major blood vessels observed in the imaging study, relatively clear boundaries were found between the vascular sheath and the adventitia, particularly in the inferior vena cava and the abdominal aorta. The adventitia was spared from the tumor invasion. Blood vessels can be separated from the tumor by dissection in the subadventitial plane along the vessel. Involved blood vessels in the retroperitoneum were successfully skeletonized in all of the 21 patients undergoing gross total resection, and a vascular graft replacement was not required. Cavitron Ultrasonic Surgical Aspirator (CUSA)[14] was used during the surgery of a patient whose celiac arteries were extensively invaded by the tumor. The CUSA combines continuous fragmentation, irrigation, and aspiration. During the CUSA procedure, the tumor tissues, high in water content, are selectively fragmented and aspirated, while the vascular tissues, which are also high in collagen, are selectively spared. The CUSA procedure is effective in separating the major blood vessels from the tumor tissues.

Theoretically, a complete surgical resection would eliminate local invasion by the tumor cells, thereby avoiding further lymphatic or blood metastasis. Subsequent treatment includes

chemotherapy, local radiotherapy, autologous bone marrow transplantation, biological therapy and immunotherapy. Complete tumor resection can reduce the burden of the above mentioned therapy. However, chemotherapy, as a pretreatment strategy, has a major risk of toxic death (rate up to 15%) predominantly during the periods of bone marrow depression and the development of secondary leukemias (up to 7% cumulative risk after four years). Accordingly, some researchers believe that the use of cytotoxic drugs can be completely omitted in a substantial proportion of low risk patients with only localized neuroblastomas but without distant metastasis. On the other hand, for high risk patients with the disease, flexible chemotherapy protocol is required and tailored to achieve different goals including curbing rapid tumor progression, relieving symptoms, and inducing and maintaining remission. Protocol varies in the duration of treatment ranging from one week to nine months and in the chemotherapy dosage. Increased efficacy of chemotherapy in neuroblastoma stage IV (five-year survival increased from eight to 33%) was achieved[15]. In the present study, overall five-year survival reached 72.22% which was higher than that of recent 20 years reported in the literature[15].

Some authors[16] studied the effect of a complete tumor resection on the prognosis of neuroblastoma and suggested that the biological markers of the tumor rather than surgical resection, influence the prognosis of the disease. In addition, complete tumor resection procedure carries a higher possibility of complications. A complete tumor resection was proposed in intermediate-risk patients to improve survival. However, sacrificing the vital organs to achieve complete tumor resection for high-risk patients is not justified, because the surgery will not improve prolonged survival and bears the high risk of serious complications. In this study, despite the fact that complete tumor resection was accomplished in all 21 patients, survivals differ significantly in patients due to the different histopathological natures of each tumor. Of the five patients who died after surgery, two had postoperative recurrence of the tumor at primary site, and one had a relapse after the second surgery. Both patients had tumors of histological type with poor prognosis. In this group, only one patient (20%, 1/5) had ganglioneuroblastoma and finally died of skeletal metastasis. Three tumor-bearing patients survived after surgery, and two of them had recurrence at the primary site. Both tumors were of the histological type with poor prognosis; the other one was ganglioneuroblastoma (33%, 1/3) and had no recurrence. This patient had preoperative metastases to the control on both sides; skull and bone marrow and the bone marrow metastatic lesion disappeared after surgery. In 10 postoperative tumor-free surviving patients, six patients presented with ganglioneuroblastoma (60%, 6/10). Five of them had preoperative skeletal or bone marrow metastatic disease which disappeared after further postoperative treatment and so far, no recurrence at the primary site was detected. Taken together, for those patients who received complete tumor resection at the primary site and whose metastatic diseases responded well to postoperative treatment (metastatic lesions disappeared after treatment), complete tumor resection plays a pivotal role in preventing the incidence of metastasis through local invasion, blood circulation and lymphatics. Residual tumors can be radically eliminated by postoperative therapeutic strategies including chemotherapy, bone marrow transplantation, biological therapy and other comprehensive treatments, allowing for favorable long-term outcome. On the other hand, for tumors with poor prognosis, complete surgical resection is important but not sufficient for achieving clinical treatment. The unfavorable biological behavior of the tumors leads to metastatic tumor growth in bones, contributing to the incurable nature of and resulting in the recurrence at the primary site. Accordingly, localized radiotherapy is required and is a more effective tumor killing strategy. Surgical resection needs to be further studied.

In the present study, complete tumor resection was accomplished in 21 patients with neither perioperative complications nor death. Delayed complications presented in two patients (11.11%) which were lower than the complication incidence of 15-30% reported in the literature[3,5,9,17,18]. Chronic postoperative diarrhea occurred in one tumor-free patient who survived without any treatment. During a follow-up of eight months post-op, this patient had three to five loose stools per day. One patient died of postoperative skeletal metastasis. Extensive tumor invasion was found in the blood vessels of the left kidney. Even though complete separation of the renal blood vessels from the tumor was achieved during surgery, the patient eventually developed a left renal atrophy. Postoperative diarrhea probably resulted from the disruption of the autonomic nerve supply to the gut during clearance of the

tumor from the major vessels of the retroperitoneum, which is common after resection of advanced abdominal neuroblastoma with an occurrence of 30%[17]. The treatment using loperamide can decrease intestinal peristalsis and reduce the symptoms in 65% of patients. However, long-term treatment is required. A portion of patients will present with persistent multiple loose stools and a few patient may have progressive neuroblastoma. It has been reported that surgical resection of the retroperitoneal neuroblastoma resulted in a 15% occurrence of renal impairment including nephrectomy[18]. It is suggested that preoperative chemotherapy may decrease the number of nephrectomies[19]. Intraoperative procedures which include monitoring of central venous pressure (CVP) and urine output, diuresis, i.v. administration of electrolyte solutions, mannitol, and furosemide as well as local application of lidocaine to the renal vessels, can effectively prevent renal damage due to renal vascular spasm. Color Doppler ultrasound (CDUS) of the renal vasculature should be performed on the seventh postoperative day. Simultaneous increases of temperature (> 38.5°C) and LDH (> 1.500 IU/l) and/or reduction of urinary flow (< 1.5 ml/kg/h) were indicative of renal damage: in these cases dopamine can be administered and CDUS performed. Dopamine should be continuously administered for another two days, if the renal blood flow was normal on the CDUS. If a vascular thrombosis is detected, fibrinolytic agents (urokinase 4,000 IU/kg bolus and then 4,000 IU/kg/h for 24 h) can be utilized. These intra- and postoperative measures can effectively avoid renal impairment in neuroblastoma patients. During the first five postoperative (p.o.) days, CVP, diuresis, body temperature (T), and lactate dehydrogenase (LDH) levels were monitored; color Doppler ultrasound (CDUS) was also performed on the seventh p.o. day. Simultaneous increases of T (> 38.5° C) and LDH (> 1,500 IU/l) and/or a reduction of urinary flow (< 1.5 ml/kg/h) were indicative of renal damage. In these cases, dopamine was administered and CDUS performed. These preliminary results show that these intra- and postoperative measures reliably avoid renal impairment. Four patients (19%) undergoing initial resection received nephrectomy due to renal vascular involvement, whereas no significant tumor invasion of renal vasculature was observed in most patients undergoing delayed resection and the renal vessels were successfully separated from the tumors. Reported postoperative complications including abdominal pain, abdominal distension and chylous ascites, did not occur in these patients. We believe that preoperative chemotherapy will lead to fibrosis of the tumor bed in retroperitoneum and occlusion of lymphatics, which can reduce the incidence of postoperative chylous ascites. On the contrary, patients undergoing initial resection without preoperative chemotherapy present more incidences of chylous ascites, such as in patients with Wilms' tumor and benign ganglioneuroma.

Conclusions

Complete tumor resection by skeletonising the involved blood vessels, improves the respectability of stage III/IV neuroblastoma at initial surgery. This reduces the burden of subsequent treatment, alleviating anxiety and fear in patients, enhancing confidence, reducing social and economic burden, improving patients' survival and resulting in low incidence of postoperative complications.

References

1) Haase GM, O'Leary MC, Ramsay NK, Romansky SG, Stram DO, Seeger RC, Hammond GD. Aggressive surgery combined with intensive chemotherapy improves survival in poor risk neuroblastoma. J Pediatr Surg 1991; 26: 1119.
2) Castel V, Tovar JA, Costa E, Cuadros J, Ruiz A, Rollan V, Ruiz-Jimenez JI, Perez-Hernández R, Cañete A. The role of surgery in stage IV neuroblastoma. J Pediatr Surg 2004; 39: 1574-1578.
3) Von Schweinitz D, Hero B, Berthold F. The impact of surgical radicality on outcome in childhood neuroblastoma. Eur J Pediatr Surg 2002; 12: 402-409.
4) La Quaglia MP, Kushner BH, Su W, Heller G, Kramer K, Abramson S, Rosen N, Wolden S, Cheung NK. The impact of gross total resection on local control and survival in high-risk neuroblastoma. J Pediatr Surg 2004; 39: 412-417, discussion 412-417.
5) Von Allmen D, Grupp S, Diller L, Marcus K, Ecklund K, Meyer J, Shamberger RC. Aggressive surgical therapy and radiotherapy for patients with high-risk neuroblastoma treated with rapid sequence tandem transplant. J Pediatr Surg 2005; 40: 936-941, discussion 941.
6) La Quaglia MP, Kushner BH, Heller G, Bonilla MA, Lindsley KL, Cheung NK. Stage 4 neuroblastoma diagnosed at more than 1 year of age: gross total resection and clinical outcome. J Pediatr Surg 1994; 29: 1162-1165, discussion 1165-1166.

7) Kushner BH, Kramer K, LaQuaglia, MP, Cheung NK. Curability of recurrent disseminated disease after surgery alone for local-regional neuroblastoma using intensive chemotherapy and anti-G (D2) immunotherapy. J Pediatr Hematol Oncol 2003; 25: 515-519.

8) Kaneko M, Ohakawa H, Iwakawa M. Is extensive surgery required for treatment of advanced neuroblastoma? J Pediatr Surg 1997; 32: 1616-1619.

9) McGregor LM, Rao BN, Davidoff AM, Billups CA, Hongeng S, Santana VM, Hill DA, Fuller C, Furman WL. The impact of early resection of primary neuroblastoma on the survival of children older than 1 year of age with stage 4 disease: the St. Jude Children's Research Hospital Experience. Cancer 2005; 104: 2837-2846.

10) Liu ZL, Xiao YH, Chen DX. Vascular skeletization--a new concept to improve the gross total resection for childhood high risk neuroblastoma. J Clin Pediatr Surg 2008; 7: 14-17.

11) Li Q, Jin XQ. Advance of treatment of neuroblastoma. Chongqing Med J 2007; 8: 1483-1485.

12) Chen HJ, Li ZL, Wang XN, et al. Current status of surgical treatment for stage III/IV neuroblastoma. Chinese J Clin Oncol 2000; 27: 832-834.

13) Chen JW, Zhou SG. Treatment and prognosis of pediatric neuroblastoma. Shandong Med J 2005; 45: 31-32.

14) Loo R, Applebaum H, Takasugi J, Hurwitz R. Resection of advanced stage neuroblastoma with the cavitron ultrasonic surgical aspirator. J Pediatr Surg 1988; 23: 1135-1138.

15) Berthold F, Hero B. Neuroblastoma: current drug therapy recommendations as part of the total treatment approach. Drugs 2000; 59: 1261-1277.

16) Hsu WM, Jen YM, Lee H, Kuo ML, Tsao PN, Chen CN, Lai DM, Lin MT, Lai HS, Chen WJ, Hsieh FJ. The influence of biologic factors on the surgical decision in advanced neuroblastoma. Ann Surg Oncol 2006; 13: 238-244.

17) Rees H, Markley MA, Kiely EM, Pierro A, Pritchard J. Diarrhea after resection of advanced abdominal neuroblastoma: a common management problem. Surgery 1998; 123: 568-572.

18) Fusaro F, Cecchetto G, Boglino C, Inserra A, Zanon GF, Giusti F, Dall'Igna P. Measures to prevent renal impairment after resection of retroperitoneal neuroblastoma. Pediatr Surg Int 2002; 18: 388-391.

19) Shamberger RC, Smith EI, Joshi VV, Rao PV, Hayes FA, Bowman LC, Shamberger RC, Smith EI, Joshi VV, Rao PV, Hayes FA, Bowman LC, Castleberry RP. The risk of nephrectomy during local control in abdominal neuroblastoma. J Pediatr Surg 1998; 33: 161-164.