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REVIEW ARTICLE

Role of surgery in neuroblastoma

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Abstract
Neuroblastoma is the most common malignant solid tumor handled by pediatric surgeons. It is well-known that neuroblastoma shows variable biological and clinical behaviors. In this review article, surgical strategy in neuroblastoma was described by risk stratification. Also, strategy of biopsy and clinical conditions that require special considerations such as neuroblastoma detected by mass screening, relapsed neuroblastoma, patients with stage MS and dumbbell type tumors was mentioned. As multimodal systemic treatments have been expanding, the role of surgery in neuroblastoma has become relatively less significant but requisite. We surgeons should decide therapeutic strategy based on the correct understanding of biology of neuroblastoma thinking of the better future of children.

Keywords Neuroblastoma · Surgery · Risk stratification · Multimodal treatment

Introduction

Neuroblastoma is the most common malignant solid tumor handled by pediatric surgeons. It is well-known that neuroblastoma shows variable biological and clinical behaviors. For example, favorable neuroblastoma sometimes regresses or spontaneously differentiates without any treatment (Fig. 1) [1–4]. On the other hand, nearly half of high-risk patients still cannot be rescued by a multidisciplinary approach consisting of chemotherapy (including high-dose chemotherapy) with stem cell transplantation, surgery, radiotherapy (including ^{131}I-metaiodobenzylguanidine [MIBG] therapy) [5], immunotherapy, and differentiation-inducing therapy [6]. Although novel treatments, such as anti-GD2 immunotherapy [7] and tandem autologous stem cell transplantation [8] have led to an improved survival, there are still patients who cannot be rescued.

As multimodal systemic treatments have been expanding, the role of surgery in neuroblastoma has become relatively less significant. With this background, this review article will present the author's opinion and discuss the real sense of the term "role of surgery in neuroblastoma".

Surgical strategy

Low-risk/intermediate-risk neuroblastoma

Most low-risk/intermediate-risk neuroblastomas are localized disease. Surgeons play more important role in localized disease than metastatic disease. According to the international neuroblastoma risk groups' risk classification [9], only metastatic neuroblastomas with favorable biology occurring in patients of less than 18 months of age are classified as low risk, while only metastatic diploid tumors with other favorable biology occurring in patients of less than 12 months of age are classified as intermediate risk. Other metastatic neuroblastomas are assigned to the high-risk category. Survival is usually favorable in patients with low-risk or intermediate-risk neuroblastoma. Tumors sometimes remain stable or regress without any treatment [2–4]. Previous evidence showed that complete resection is not always necessary. In 1989 Matthay et al. from the Childrens Cancer Study Group (CCSG) reported that there was no difference in the outcomes of patients who achieved complete resection, those who were left with a microscopic residual tumor, and those who were left with gross residual disease.

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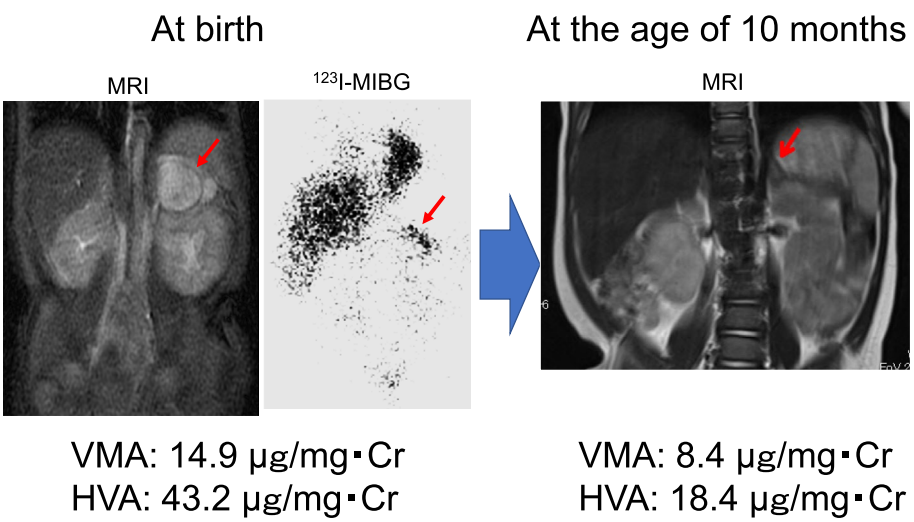

Fig. 1 Spontaneous regression

Thus, they concluded that the excellent outcomes of stage II neuroblastoma are independent of residual disease after surgery [10]. Hero et al. conducted "wait and see" observation for localized infantile neuroblastoma. Of 93 patients with unresected tumors, 44 tumors regressed spontaneously. Complete regression was observed in 17 of 44 patients at 4–20 months after the diagnosis [11]. Iehara et al. reported that the presence of a residual mass at the end of treatment did not influence the prognosis of intermediate-risk patients. Twelve patients had a residual tumor mass at the completion of therapy, including seven International Neuroblastoma Staging System (INSS) stage 3 patients, and five INSS stage 4 patients. Five of twelve patients showed the uptake of MIBG at the end of treatment, but the uptake disappeared during the follow-up period. The follow-up period ranged from 1.3 to 20.4 years. They reported that invasive radical surgical resection and additional treatment may not be necessary [12]. Taken together, aggressive surgical resection, involving the sacrifice of vital organs, may not be necessary for non-high-risk neuroblastoma.

In 2009, the International Neuroblastoma Risk Group (INRG) published a new preoperative staging system[13]. In comparison to the previous staging system, the INSS, which is a postoperative staging system, the INRG stage can be determined at the diagnosis. In this staging system, according to diagnostic imaging, locoregional tumors are staged as L1 or L2 based on the absence or presence of one or more image-defined risk factors (IDRFs), respectively [13]. IDRFs were initially propounded as surgical risk factors in 2005 by Localized Neuroblastoma European Study Group 1 (LNESG1)[14].

Japan Children's Cancer Group (JCCG), Neuroblastoma Committee (JNBSG) has conducted prospective clinical studies for low-risk/intermediate-risk neuroblastoma using IDRFs. Since 2010, JNBSG has employed a protocol using IDRFs for localized neuroblastoma to minimize surgical complications. In this protocol, when IDRF is absent, initial tumor extirpation is recommended, and when IDRF is present, biopsy followed by chemotherapy should be performed. Finally, second look surgery is performed. JN-L-10 is a prospective clinical trial using IDRFs to inform surgical decisions for children with low-risk neuroblastoma [15]. In JN-L-10, the presence of IDRFs was a key factor in determining whether a patient should undergo surgery or chemotherapy at the time of evaluations. Evaluations were performed at diagnosis, and after every three courses of chemotherapy. According to the IDRFs, tumor markers, and the uptake of MIBG, we determine whether to proceed to the next treatment or to end treatment. The 3-year overall survival rate was 100% and the 3-year progression-free survival rate was 82.8%. Regarding major surgical complications, vascular injury was the most frequent complication and was observed in three of five patients with major complications. For intermediate-risk patients, JNBSG conducted JN-I-10, a phase II efficacy study of IDRF-based surgical decisions and stepwise treatment intensification for patients with intermediate-risk neuroblastoma. A protocol paper was published in 2020 [16]. The JN-I-10 study is not complete; it is currently in the follow-up period. The role of IDRF in intermediate-risk neuroblastoma will be evaluated in JN-I-10.

In 2011, Dr. Brisse and the INRG committee published new guidelines for imaging and staging of neuroblastic tumors [17]. In these guidelines, several precise definitions of IDRFs are mentioned. For example, encasement of an artery means that more than 50% of the vessel's circumference is in contact with the tumor, which should be considered as IDRF-present. This consensus report was written to optimize imaging and staging and to reduce interobserver variability. More importantly, in these new guidelines, a special IDRF definition was mentioned. Even if the tumor is in contact with the renal vessels alone, this situation, which used to be diagnosed as IDRF-absent, should be

considered as IDRF-present. The new guideline ("contact with renal vessels" as IDRF) raises the IDRF-positive rate in abdominal neuroblastomas. "Contact with renal vessels" might be a potential surgical risk factor for abdominal neuroblastoma. It was retrospectively evaluated how this new guideline would change the IDRF results in localized neuroblastoma. This new guideline increased the percentage of IDRF-present patients from 31 to 71%. Although this new guideline improved the sensitivity of the IDRF for predicting surgical complications (from 47 to 100%), it reduced the specificity (from 75 to 32%) and the accuracy (from 71 to 46%) [18]. Furthermore, only 27% of the tumors with IDRFs became negative for IDRFs after neoadjuvant chemotherapy. For negative IDRFs, tumors should shrink to < 20% of the volume at the time of the diagnosis [19]. Surgical decision-making based on the new guideline may reduce the risk of renal complications; however, the number of patients receiving additional chemotherapy for residual tumors would probably increase.

Taken together, the role of surgery in low-risk/intermediate-risk neuroblastoma seems to be limited. Tumors with no IDRF at the diagnosis according to the new guideline could be safely resected. Tumors with IDRF at the diagnosis would be initially treated by chemotherapy. After neoadjuvant chemotherapy, surgeons should carefully evaluate surgical risks by imaging studies. There are only a few patients whose tumors became IDRF-negative or for whom the number of IDRFs was reduced, even after neoadjuvant chemotherapy. Again, tumors with IDRFs at the diagnosis do have surgical risk factors, even after neoadjuvant chemotherapy. Thus, in such cases, complete resection is not necessary. The author strongly recommends conservative surgery for non-high-risk neuroblastomas. Please maximize your efforts to avoid surgical complications to preserve major organs like the kidneys, to support a better future for pediatric patients.

On the other hand, although the number of such cases is relatively small, some low-risk/intermediate-risk neuroblastomas should be resected, regardless of the risk. For example, symptomatic tumors involving opsoclonus-myoclonus syndrome, oncologic emergency (e.g., respiratory symptoms), functional tumors (e.g., adrenergic, dopaminergic neuroblastoma), vasoactive intestinal polypeptide secreting tumors (VIPoma), and other such cases.

High-risk neuroblastoma

The optimal extent of surgery in high-risk neuroblastoma is still a matter of debate. Table 1 shows recent major reports about the extent of resection in high-risk neuroblastoma. The top four reports supported the advantage of complete resection or gross total resection in terms of survival, whereas the two bottom reports did not.

Simon from the GPOH study analyzed the impact of the extent of tumor resection on the outcome of patients with stage 4 disease who were 18 months of age or older (classified as high-risk neuroblastoma). Two hundred seventy-eight

Table 1 Previous reports of extent of surgery in high-risk neuroblastoma

Author (Study)	Year	Patients	Number of the patients	5YEFS(%) *5YOS(%)	*P* value	Complication (%)	Nephrectomy (%)	Radiation (Gy)
Englum (Duke Univ.) Post hoc. analysis	2015	High risk	**87** > 90% 56 < 90% 31	> 90% around 55?* < 90% around 22?*	0.08	–	GTR 18 < GTR 11 (NS)	20? (92% of Pts.)
von Allmen (COG A3973)	2017	High risk	**220** > = 90% 154 < 90% 66	> = 90% 45.9 < 90% 37.9	0.04	NS	> = 90% 5 < 90% 15 (organs)	21.6 (All Pts)
Fischer (Germany NB97)	2017	Localized high risk > 18 M	**179** CR(> 95%) 123 GTR(90–95%) 30	CR 82.8 > 90% 59.8 50–90% 58.0	0.001	CR 22.4 GTR 13.3 (ns)	–	40 (3.9%of Pts.w. unresectable residuals)
Holmes (SIOPEN HR-NBL 1)	2020	Stage 4 High risk	**1531** CME 1172 IME 359	CME 40 IME 33	< .001	CME 7.9 IME 15.8 (P < 0.001)	CME 7.9 IME 11.9 (P = 0.028)	21 (All Pts)
Simon (Germany NB97)	2013	Stage 4 > = 18 M	**278** CR(> 95%) 152 GTR(90–95%) 68	CR 33.9 > 90% 27.9 50–90% 35.3 B/no 34.9	0.877	23	7	40 (10.1% of Pts. W unresectable residuals)
Englum (Duke Univ.)	2015	High risk	**87** GTR 33 < GTR(any tumor remaining) 54	GTR 53* < GTR 42*	0.49	–	GTR 18 < GTR 11 (NS)	20? (92% of Pts.)

patients were treated homogenously in NB97. The extent of the best operation had no impact on event-free survival, local progression-free survival, or overall survival. Thus, they concluded that surgical treatment of the primary tumor site had no impact on the local control rate or outcome [20]. However, after this article, the same group reported that the extent of surgical treatment at the primary tumor site improved the local control rate and survival in high-risk patients with localized neuroblastoma [21].

The recent results of the COG A3973 study of high-risk neuroblastoma revealed that ≥ 90% resection had better EFS and a lower cumulative incidence of local progression. However, no differences were found in OS or in the complication rate. In this report, it is quite interesting that concordance between surgeons' assessments of the extent of resection and central image–guided review was low, with 63% agreement [22].

The largest report of stage 4 high-risk neuroblastoma from SIOPEN published in 2020 by Holms et al. also supported that, in patients with stage 4 high-risk neuroblastoma who responded to induction therapy, complete macroscopic excision of the primary tumor is associated with improved survival and local control after HDT, local radiotherapy (21 Gy), and immunotherapy [23]. In this report, surgical resection was attempted after high-dose therapy in 215 of 1,531 (14%) patients who underwent surgical resection. There was no significant difference in the complete macroscopic excision rate according to the time point of operation.

The world largest study groups, COG and SIOPEN, reached the conclusion that ≥ 90% resection or complete macroscopic excision of the primary tumor was related to local control and partly related to survival. However, according to the author, these results do not strongly support aggressive surgery for high-risk neuroblastoma. It is possible that the more the tumor responds to neoadjuvant chemotherapy, the easier it is to resect more than 90% of the tumor. Thus, there is always a selection bias in this type of clinical study. Another concern is the method used to evaluate the extent of resection. In COG A3973, the concordance between surgeons' assessments of the extent of resection and the central image-guided review was low, with only 63% agreement. Although evaluation by imaging seems to be objective, it is associated with some difficulties. In the early postoperative period, it is difficult to find out whether a space occupied lesion is a real residual tumor or whether it is just postoperative edematous normal tissue. There is no consensus on the timing for postoperative imaging evaluations. JNBSG recommended maximum removal of the viable tumor tissue with minimum complications while making an effort to preserve the kidneys for future treatment and to minimize the chemotherapy interval.

It is well-known that most relapses in high-risk neuroblastoma are observed at distant sites. The Japanese data revealed that only 10 high-risk neuroblastoma patients (16.4%) experienced local recurrence alone, whereas 27 had distant site recurrence and 24 had multiple site (both local and distant sites) recurrence [24]. According to a very recent report from the INRG about the pattern of sites of relapse, only 8% of the patients with INSS stage 4 had isolated local relapse. Whereas 76% had distant only relapse, 16% had combined local and distant relapse [6]. Hashii et al. hypothesized that systemic disease control (named time-intensified strategy) is important for reducing the rate of recurrence in high-risk patients. They conducted a novel treatment strategy consisting of postponed primary surgery until the end of systemic chemotherapy, including HDC without interruption by local therapy. As 7 of 11 patients remained in complete remission for 21–171 months, they concluded that this treatment strategy seems feasible [25]. The possible advantages of the time-intensified strategy are the avoidance of interruption of systemic chemotherapy by surgery, which may promote the acquisition of drug resistance, clonal evolution, and host immune suppression. Therefore, time-intensified chemotherapy with delayed local treatment enables more effective control of systemic disease. Uehara et al. reported the role of surgery in delayed local treatment for INSS 4 neuroblastoma from the some institution as Hashii [26]. They retrospectively analyzed patients with INSS 4 neuroblastoma who received delayed local treatment and concluded that gross total resection or subtotal resection with local irradiation may be a safe and effective delayed local treatment for patients with INSS 4 neuroblastoma.

Based on these observations, JNBSG conducted the JN-H-11 and JN-H-15 clinical trials for high-risk neuroblastoma to focus attention on the timing of surgery (called delayed local treatment). These clinical trials have finished, and the results will soon be published.

Biopsy

Detailed information of tumor cell biology is necessary for planning neuroblastoma treatment. More than two decades ago, pathology and biology guidelines were published [27]. In these guidelines, it was recommended that at least two tumor samples (at least 1 cm × 1 cm × 1 cm) be taken from morphologically different-appearing areas (if present) at the time of biopsy. In 2009, the INRG Biology Committee reported the international consensus for neuroblastoma molecular diagnostics [28]. With progress in technology, a molecular diagnosis can be performed with a smaller amount of tissue. Recently, needle core biopsy is becoming popular. Hassan et al. reported that needle core biopsy is comparable in efficacy to open biopsy in the diagnosis of intermediate- and high-risk neuroblastoma, with significantly lower rates of major postoperative complications [29]. In addition, a team at Kyoto Prefectural University invented

a new technique for predicting MYCN amplification using serum DNA. Using this technique, we can detect the MYCN status in a tumor without surgical biopsy [30]. With the current rapid expansion of genomic medicine, the role of biopsy is becoming important. For the management of pediatric patients, we must make efforts to obtain tumor samples with less invasive methods.

Clinical conditions that require special considerations

Neuroblastoma detected by mass screening

We Japanese have learned a great deal about localized neuroblastoma from the lessons of nationwide urinary mass screening. Mass screening for neuroblastoma at 6 months of age was initiated by Prof. Sawada in Kyoto, Japan in 1973 [31]. In 1985, nationwide mass screening was started. In the era of HPLC mass screening between 1988 and 2003, more than 200 patients were registered annually (Fig. 2). However, the Japanese mass screening program tended to over-diagnose localized tumors with a favorable prognosis, including occult tumors that spontaneously regressed or matured [2–4]. Therefore, the Japanese government decided to stop mass screening in 2004 [32].

After the cessation of mass screening, only around 100 patients were registered annually.

Relapsed neuroblastoma

There is no recommendation about surgery for relapsed neuroblastoma. It is well-known that relapse in high-risk patients is associated with a poor prognosis [6, 24]. However, as mentioned in the report from the INRG, patients with INSS stage 1 or 2 disease with any distant failure showed inferior outcomes to those with isolated local failure, though all groups had 5-year OS rates of > 50%, suggesting that these patients are salvageable with additional therapy. Therefore, patients with isolated local failure of stage 1 or 2 disease should be the target of surgical treatment if the location of the recurrent disease is not at risk from surgery. Among patients with relapsed high-risk disease, surgery has a less significant role. According to the INRG report [6], although isolated local failure was no longer associated with more favorable outcomes, it had superior outcomes to cases with local and distant failure. Therefore, it is assumed that surgery will still have a role in the treatment of patients with only local failure. As it is mentioned in relation to high-risk neuroblastoma, the kidneys should be preserved as much as possible. As most patients with relapsed disease require high-intensity treatment, the renal function should be preserved.

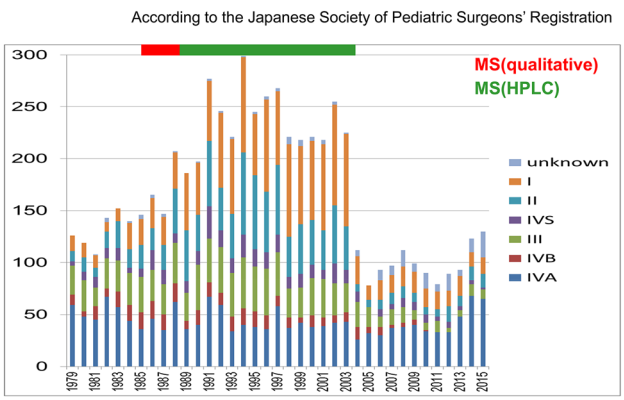

Fig. 2 Number of newly diagnosed neuroblastoma patients in Japan

Stage MS

Prof. Evans first pointed out a special category in metastatic neuroblastoma. In Evans' staging system, stage IV-S was defined as follows: patients who would otherwise be Stage I or II, but who had remote disease confined to only one or more of the following sites: liver, skin, or bone marrow (without radiographic evidence of bone metastasis on a complete skeletal survey). Evans et al. mentioned that patients with Stage IV-S appeared to have a better prognosis than those with Stage IV disease. Twelve of sixteen (75%) children with Stage IV-S disease survived, whereas only four of fifty-six (7%) patients with Stage IV disease survived [1]. In the next international staging system, named the International Neuroblastoma Staging System (INSS), stage 4S took over from stage IV-S. Stage 4S was defined as localized primary tumor (as defined for stage 1, 2A or 2B), with dissemination limited to skin, liver, and/or bone marrow (limited to infants of < 1 year of age) [33]. The latest international staging system, the INRG staging system (INRGSS) defined stage MS as metastatic disease in children younger than 18 months of age with metastasis confined to the skin, liver, and/or bone marrow [13]. Unlike INSS stage 4S, stage MS includes patients with primary tumors infiltrating the midline (INSS stage 3). In the SIOPEN 99.2 trial, all 30 infants with INSS stage 4 disease with primary tumors corresponding to INSS stage 3 disease because of midline infiltration, and with a stage 4S metastatic pattern, survived. Eight patients received no chemotherapy, and the remainder received only one course or a few courses of chemotherapy to control symptoms. Only five of the patients had their primary tumor excised. The remaining three patients survived with primary tumors. Metastatic tumors could not be resected totally, as most cases involve multiple tumors.

Dumbbell type

De Bernardi et al. reported that 76 of 1462 children with neuroblastoma in the registry of the Italian Cooperative Group for Neuroblastoma (ICGNB) presented with spinal cord compression [34]. Although laminectomy used to be a primary treatment for neuroblastoma with spinal cord compression, recent research revealed that chemotherapy, which causes rapid regression of tumors with intraspinal extension, could be a good alternative to laminectomy and radiotherapy (RT) for neurological recovery [35]. Kraal et al. performed a systematic review and found that the burden of long-term health problems is high; a median of 50% of patients suffered from neurological motor deficit, 34% suffered from sphincter dysfunction, and 30% suffered from spinal deformity [36]. Currently chemotherapy should be the first choice and the role of surgery in intraspinal compression is becoming less important.

Conclusion

As multimodal systemic treatments have been expanding, the role of surgery in neuroblastoma has become relatively less significant but requisite. We surgeons should decide therapeutic strategy based on the correct understanding of biology of neuroblastoma thinking for the better future of children.

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Author contributions A.Y wrote the main manuscript text and prepared figures and tables.

Data availability Due to the nature of the paper, no original data are presented.

Declarations

Competing interests The authors declare no competing interests.

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