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Validity of image-defined risk factors in localized neuroblastoma: A report from two centers in Western Japan

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ABSTRACT

Background: Japanese Neuroblastoma Study Group (JNBSG) has been employing image-defined risk factors (IDRFs) since 2010. However, the report from INRG in 2011 supplemented description stating that isolated contact is considered to be IDRF-positive only in renal vessels. The aim of this study was to evaluate the validity of IDRFs by comparing the previous (PG) and new guidelines (NG).

Methods: IDRFs of patients with localized neuroblastoma treated at two centers in Western Japan from 2002 to 2013 were retrospectively reviewed by radiologists.

Results: 47 neuroblastomas (abdomen 38, pelvis 2, mediastinum 7) were evaluated. For abdominal neuroblastomas, IDRFs were present in 15/38 (39.5%) using PG and in 31/38 (81.6%) using NG. Moreover, the IDRF-positive rate increased from 26.7% (4/15) to 80.0% (12/15) in 15 cases diagnosed during mass screening. Of the IDRF-positive cases, complete primary resection was achieved in 2/15 (13.3%) using PG and 17/31 patients (54.8%) using NG. There were two major surgical renal complications in the IDRF-positive cases based on the use of either guidelines, and the specificity decreased from 64% to 19%.

Conclusions: According to NG, the IDRF-positive rate increased, and the resection rate decreased. NG may overestimate surgical risks, leading to unnecessary chemotherapy and a prolonged hospital stay.

Neuroblastic tumors are the most common extracranial solid cancers in childhood, representing approximately 8–10% of all childhood cancers [1]. The clinical staging of neuroblastoma is currently the most significant and clinically relevant prognostic factor and can be used to predict whether children have favorable or unfavorable disease at diagnosis. Therefore, accurate staging is most important for risk assessment and selecting the optimal treatment.

In 2009, the International Neuroblastoma Risk Group (INRG) Project proposed a new staging system for tumor staging prior to treatment, including surgery [2]. Compared with the focus of the conventional International Neuroblastoma Staging System (INSS) [3], which is applied postsurgically and is currently the most widely used classification, the focus has now shifted from surgicopathological findings to imaging findings. The new INRG Staging System includes two stages of localized disease that are dependent on whether image-defined risk factors (IDRFs) are present or absent. IDRFs are features detected using imaging at the time of diagnosis. The present consensus report was written by the INRG Imaging Committee to optimize imaging and staging and reduce interobserver variability. The rationale for using imaging methods (ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT), scintigraphy), as well as technical guidelines, are described, and the definitions of the terms recommended for assessing IDRFs are provided with examples. The Japanese Neuroblastoma Study Group (JNBSG) has been employing IDRFs since 2010 [4]. However, the latest guidelines from the INRG issued in 2011 provide a supplemented description stating that even isolated contact is considered to be IDRF-positive only in renal vessels [5].

The aim of this study was to evaluate the validity of IDRFs in assessing surgical resectability and complication by comparing the previous guideline (PG) issued in 2009 and the new guideline (NG) proposed in 2011 for localized tumors treated at two tertiary-care hospitals located in different regions of Western Japan.

1. Materials and methods

The INRG new staging system published in 2009 was designed for tumor staging prior to surgery or other treatments [2]. Localized tumors are classified as stage L1 or L2 disease based on the presence of one or more 20 IDRFs. IDRFs are surgical risk factors detected on images that

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make total tumor excision risky or difficult at the time of diagnosis. In summary, IDRF exists when the tumor encases or invades the vital structures, most commonly major blood vessels. For arteries, "Contact", which means that less than 50% of the vessel's circumference is in contact with the tumor, is defined as being IDRF-negative. For veins, "Flattened", in which the vessels have a reduced diameter with a partially visible lumen, is considered to be equivalent to "Contact." This new staging system is not intended to be a substitute for the INSS, and it is recommended that both systems be used in parallel. Stage L1 tumors are localized tumors that do not involve vital structures, as defined according to the list of IDRFs. In the presence of IDRFs, patients are classified into the stage L2 group and the initial surgery is limited to a biopsy.

In 2011, new guideline was published by the INRG for imaging and staging, and a consensus report was subsequently written to optimize imaging and staging and reduce interobserver variability [5]. However, that report provided a supplemented description stating that even isolated contact is considered to be IDRF-positive only in renal vessels (Fig. 1) because the manipulation of renal pedicles during surgery might cause renal complications such as vessel injury, renal atrophy and unexpected nephrectomy.

This is a retrospective review of children with localized tumors treated at two centers in Western Japan by pediatric oncologists and pediatric surgical oncologists certificated by the Japanese Society of Pediatric Hematology/Oncology. Patients with localized neuroblastoma treated in the period from 2002 to 2013 at each center were enrolled in this study. This series included cases diagnosed on mass screening (MS), which began in 1985 for 6-month-old infants throughout Japan and was discontinued in 2004 [6].

The pretreatment imaging studies included CT and MRI. Before 2009, the surgeons determined the indication of surgery and selected the operative procedure including an incisional biopsy and partial or total tumor resection. For this study, the retrospective evaluation of the imaging findings was performed and the presence of IDRF was judged by a single radiologist at each institute (M.N. and A.N.). Since 2009, from when the JNBSG initiated the IDRF concept for low (JN-L-10) and intermediate (JN-I-10) risk protocols, IDRFs were judged prospectively by these radiologists based on CT or MRI findings according to the IDRF criteria [7], and then, a cancer board including pediatric oncologists, the radiologist, and surgeons as a member was held to discuss the validity of interpretation of the imaging. As a result of such discussion, the indication of surgery was determined.

The subjects' medical charts were reviewed for the collection of data on age, sex, presentation at diagnosis, primary tumor site, INSS, presence of IDRFs based on both PG and NG, initial surgical intervention, tumor biology, surgical complications and outcomes.

This study was performed according to the Ethical Guidelines for Clinical Research published by the Ministry of Health, Labour and Welfare of Japan on July 30, 2003 (revised 2008) and complied with the Helsinki Declaration of 1964 (revised 2013).

2. Results

Forty-seven neuroblastomas were enrolled in this study. The background characteristics of the patients are shown in Table 1. The median age was 13 months (range; 0–78 months), and approximately 44.7% of the cases were infantile cases (n = 21). The number of patients diagnosed at MS was 16 (34.0%). The primary tumor location was the adrenal/retroperitoneum in 38 cases, pelvis in two cases and mediastinum in seven cases. The proportion of subjects in INSS stages 1, 2 and 3 was 24 (51.1%), 12 (25.5%) and 11 (23.4%) respectively. The initial surgical interventions were as follows: incisional biopsy in 17 patients (36.2%), partial or subtotal resection in three patients (6.4%) and total resection in 27 patients (57.4%).

Fig. 2 showed an infantile case with right adrenal neuroblastoma, whose IDRF was changed from absence using PG to presence using NG on MRI. He underwent the primary total resection of the tumor without adjuvant chemotherapy. For all neuroblastomas, IDRFs were present in 22/47 cases (46.8%) using PG and 38/47 cases (80.9%) using NG. In particular, among the patients with tumors treated with total resection, the IDRF-positive rate increased from 11.1% to 66.7% (Table 2). Amplification of the *MYCN* gene of more than 10 copies was noted in five patients.

For abdominal neuroblastomas (n = 38), IDRFs were present in 15/38 cases (39.5%) using PG and 31/38 cases (81.6%) using NG (Fig. 3). Moreover, the IDRF-positive rate increased from 26.7% to 80.0% in 15 cases diagnosed at MS (Fig. 3). As for INSS staging, INSS 1 disease (n = 22) was associated with IDRFs in two patients (9.1%) using PG

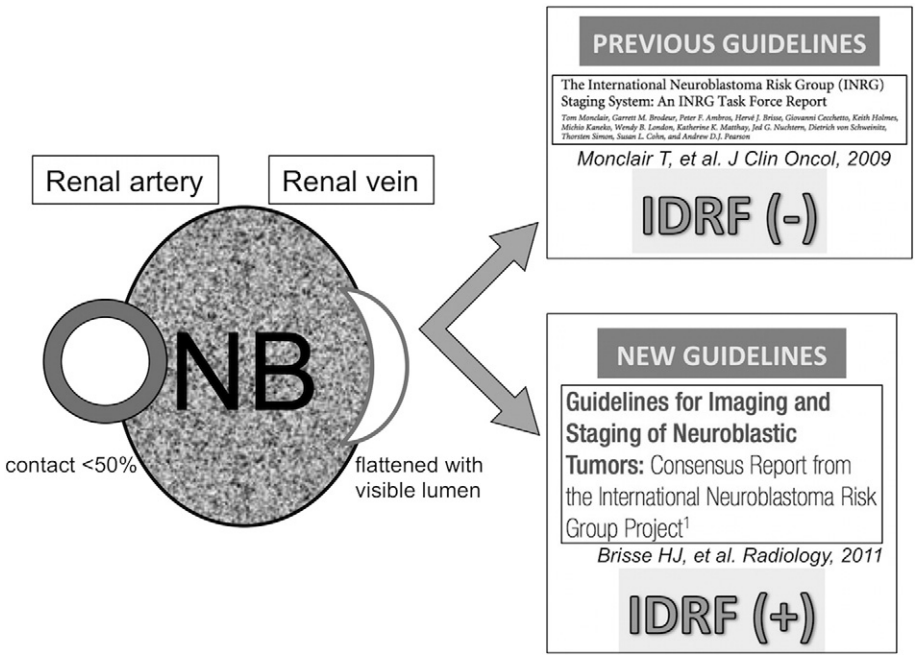

Fig. 1. Schematic figure of the definition of "Contact" and "Flattened" in terms of IDRFs. For arteries, "Contact" means that less than 50% of the vessel's circumference is in contact with the tumor (NB). For veins, "Flattened," in which the vessels have a reduced diameter with a partially visible lumen, is considered to be equivalent to "Contact." These descriptions are considered to be IDRF-negative findings in the previous guidelines and were changed to positive findings in the new guidelines.