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TUMOR HISTOLOGY FOLLOWING INDUCTION CHEMOTHERAPY AND / OR HIGH-DOSE CHEMOTHERAPY AND ITS IMPACT ON THE OUTCOME OF PATIENTS WITH HIGH-RISK NEUROBLASTOMA（ポスター）	**Tomoro Hishiki**, Hiroshi Horie, Yasuyuki Higashimoto, Katsumi Yotsumoto, Shugo Komatsu, Yuri Okimoto, Harumi Kakuda, Yuichi Taneyama, Takeshi Saito, Keita Terui, Tetsuya Mitsunaga, Mitsuyuki Nakata, Hidemasa Ochiai,	46th annual congress of SIOP	2014.10.22-25	国外

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半定量的MIBGスコアによる転移性神経芽腫治療反応性の判定と初期反応不良例の臨床的生物学的特徴（口演）	**Tomoro Hishiki**, Yasuyuki Higashimoto, Katsumi Yotsumoto, Shugo Komatsu, Yuri Okimoto, Harumi Kakuda, Yuichi Taneyama, Kazuki Furudate, Takeshi Saito, Keita Terui, Tetsuya Mitsunaga, Mitsuyuki Nakata, Hidemasa Ochiai, Moeko Koshino, Kumiko Ando, Hideo Yoshida, and Jun Iwai.	第52回日本小児血液・がん学会学術集会	2014.11.28-30	国内

粒子線治療の小児がんへの適応	**櫻井英幸，福島敬**，水本斉志，大城佳子，沼尻晴子，大西かよ子，福光延吉，石川仁，奥村敏之，坪井康次，栄武二，須磨崎亮，増本幸二，金子道夫	岡山・岡山コンベンションセンター（第56回日本小児血液・がん学会学術集会）	2014.11.28	国内
Re-irradiation by proton beam therapy with chemotherapy for a patient with recurrent germ cell tumor	Shoko Okawada Hiromi Kato, Hiroshi Fuji, Yoko Nakasu, **Yuji Ishida**	INTERNATIONAL SYMPOSIUM ON PEDIATRIC NEURO-ONCOLOGY (ISPNO) 2014 in Singapore	2014.6.30	国外

2．学会誌・雑誌等における論文掲載

掲載した論文(発表題目)	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Application of nuclear medicine to achieve less invasive surgery for malignant solid tumors in children	Hotta R, Fujimura T, Shimojima N, Nakahara T, Fuchimoto Y, Hoshino K, Morikawa Y, Matsufuji H, **Kuroda T**	Pediatr Int.56(6):896-901	2014.11	国外
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Ⅳ.　学会等発表実績の刊行物・別冊

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Original Article

Application of nuclear medicine to achieve less invasive surgery for malignant solid tumors in children

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Abstract ***Background***: The use of nuclear medicine for the management of malignant tumor, such as radioguided surgery and sentinel lymph node biopsy (SLNB), has been widely accepted in the adult practice. However, there are very few studies to apply those techniques for pediatric diseases. The aim of this study was to investigate the feasibility of application of nuclear medicine in surgery for neuroblastoma (NB) or rhabdomyosarcoma (RMS) in children.

Methods: Radioguided surgery using ^{123}I-metaiodobenzylguanidine was performed on six children with NB. SLNB using technetium-labeled tin or sulfur colloid was performed on two children with perineal RMS. Histological evaluation of resected specimens was performed to determine the accuracy of intraoperative detection and SLNB. All patients were evaluated for overall survival and complications.

Results: Intraoperative tumor localization using hand-held gamma probe was helpful in 85.7% of NB patients. Sensitivity and specificity of this technique were 81.8% and 93.3%, respectively. There were no postoperative complications, and four out of five patients with high-risk NB experienced disease-free survival (median follow up, 57 months). Sentinel lymph nodes were easily detected in patients with perineal RMS, and histological assessment revealed complete consistency with regional lymph node status.

Conclusions: Nuclear medicine may have a potential application in the use of less invasive surgery for advanced NB or perineal RMS, the two most challenging pediatric malignancies.

Key words children, neuroblastoma, rhabdomyosarcoma, radioguided surgery, sentinel lymph node biopsy.

Nuclear medicine has been widely accepted as a powerful tool for diagnosing malignant tumors in children and a useful modality for assessing treatment outcomes. The accumulation of radioactive material in viable cells makes possible radioguided surgery and sentinel lymph node biopsy (SLNB).

Radioguided surgery was first used for intraoperative detection of parathyroid adenoma in the late 1990s.[1] Preoperative localization of diseased parathyroid glands following injection of radiotracer, combined with intraoperative detection using a hand-held gamma probe, has rapidly gained popularity because of excellent outcomes that can be achieved in a minimally invasive manner.[2] Radioguided localization of occult lesions can also be facilitated by the hand-held gamma probe; a recent meta-analysis has demonstrated easier and more accurate localization of non-palpable breast cancer in comparison with conventional techniques.[3] To date, a few reports describe the use of radioguided surgery in the management of neuroblastoma (NB),[4–7] including recurrent disease.[8] However, no available evidence supports the use of this technique based on long-term outcomes.

SLNB was introduced in adult patients with malignant melanoma[9] as a less invasive alternative to formal regional lymph node dissection. Detection and evaluation of the sentinel lymph node, the first node draining the primary tumor along its lymphatic pathway, allows accurate staging without formal lymph node dissection. This technique has recently been accepted as standard practice for staging newly diagnosed and clinically non-metastatic malignant melanoma and breast cancers, as postoperative complications are significantly less likely to occur compared with extensive lymphadenectomy.[10,11] However, only a few papers have described SLNB for malignant tumors in children.[12,13]

In this study, we aimed to investigate the feasibility of intraoperative application of nuclear medicine for the management of advanced NB and perineal rhabdomyosarcoma (RMS) in children. The accuracy of intraoperative detection of metastatic tumors or sentinel lymph nodes (SN) was evaluated. Medical records were reviewed retrospectively to determine overall survival and morbidity of those procedures.

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Methods

Eight patients were enrolled in this study. Six children underwent radioguided navigation surgery for resection of NB, and two children with perianal RMS had lymphatic mapping with SLNB followed by resection of primary tumor with regional lymph node dissection. The medical records of these patients were reviewed retrospectively and data were obtained regarding patient demographics; type of malignancy; surgical interventions; adjuvant therapy; pre- and postoperative radiological findings; intraoperative findings; histology results; and clinical course, including status at last contact.

Written informed consent was obtained from the parents of all patients. The following protocol was applied during radioguided navigation surgery using ^{123}I-metaiodobenzylguanidine (MIBG): A tracer dose of ^{123}I-MIBG (111MBq) was injected intravenously 12–24 h prior to surgery. Lugol's iodine (1%) solution was administered for 3 days prior to operation (0.5 mL/day). A gamma probe (Navigator System; US Surgical, a division of Tyco Healthcare Group LP, Norwalk, CT, USA) with a sterile cover was placed directly on suspected tissues (Fig. 1). The points of highest count were explored and a tumor-to-background ratio of 5 or more was considered significant. To determine the specificity of this procedure, some clinically negative (probe-negative) specimens were sampled following fully informed consent. At the end of the operation, the absence of residual activity was confirmed by scanning the tumor bed.

The protocol for SLNB for RMS was as follows: The tumors were injected with technetium-labeled tin or sulfur colloid 24 h prior to operation. Lymphoscintigraphy was performed (Fig. 2) and the patient was transferred to the operation room. Lymphazurin blue was injected peritumorally just before starting the operation. The draining basin was examined using a gamma probe in a sterile cover and a mark made to designate the area of high count. A small incision was then made overlying the area of high count and the underlying tissue examined for the presence of the blue dye. Dissection was then undertaken, carefully isolating the blue-dyed area and ligating the blue lymphatic channels that were traversed, thus decreasing the chance of chyloma. The gamma probe was again used to assist in localization of the sentinel nodes. A few blue nodes with high counts were sent to pathology labeled as SN. The absence of residual activity was confirmed and resection of primary tumors with formal lymph node dissection was performed.

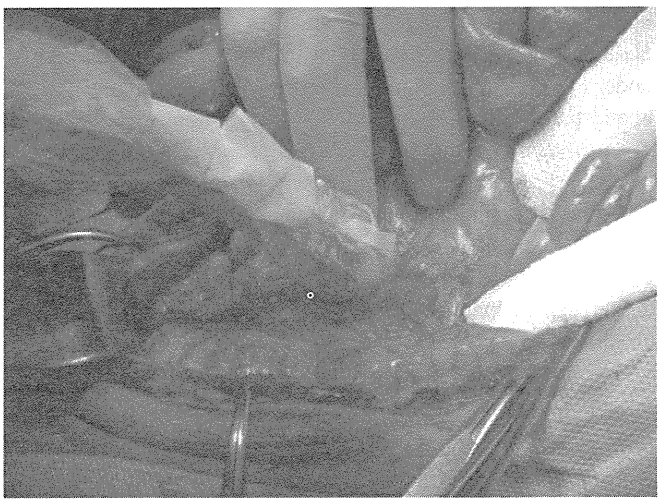

Fig. 1 Use of the gamma probe for intraoperative tumor localization.

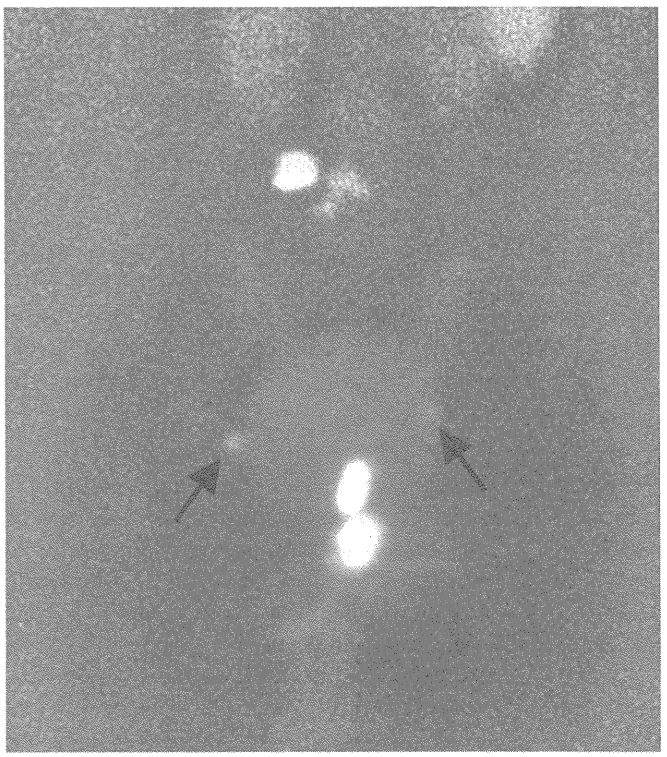

Fig. 2 Lymphoscintigraphy taken prior to the operation (case 7). Peritumoral injection of technetium-labeled tin or sulfur colloid followed by lymphoscintigraphy shows accumulation of radiotracer to external iliac lymph nodes (arrows), regional lymph nodes of perineal rhabdomyosarcoma (RMS).

Results

The study included four boys and four girls (mean age, 7 ± 5 years) and their demographic findings are shown in Tables 1 and 2.

All patients with NB had received intensive chemotherapy prior to surgical resection (Tables 1,3).[14,15] ^{123}I-MIBG scintigraphy was routinely performed prior to the operation (Fig. 3). Seven navigation surgeries performed for six patients with NB were included in this study. Intraoperative detection of MIBG was considered helpful in six out of seven operations (85.7%). A hand-held gamma probe was used to determine the locations of primary tumors and metastatic lymph nodes. The probe detected invisible or tiny, non-palpable lymph nodes with high MIBG counts in which viable neuroblastoma cells were confirmed by postoperative histological examination. Correlation between probe findings and pathologic analysis was evaluated in 26 resected specimens (primary site; two cervical sympathetic

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Table 1 Patient characteristics (NB)

Patient no.	Age (years)	Sex	Location	Stage	Histology	Preoperative treatment	Histology of resected specimen	Complication	Outcome	Follow up
1	2	M	Neck	2A	Favorable	A_1	GNB	None	DFS	10 years
2	5	M	Adrenal grand	4	Unfavorable	A_3	Metastatic NB	None	Death	7 months
3	3	F	Adrenal grand	4	Unfavorable	A_3 and new A_1 with PBSCT → Resection → Rec	Metastatic NB	None	DFS	9 years
4	6	M	Adrenal grand	4	Unfavorable	CDDP+VP-16, CPT-11, high-dose VP-16 with PBSCT → Resection → Rec	Metastatic NB	None	DFS	5 years
5	4	M	Adrenal grand	4	Unfavorable	$A_1 \rightarrow A_3 \rightarrow$ Resection → Residual disease	Maturation	None	DFS	2 years
6	13	F	Adrenal grand	4	Unfavorable	$A_1 \rightarrow A_3 \rightarrow A_3$	Metastatic NB	None	DFS	2 years

A_1, regimen A_1; A_3, regimen A_3; CDDP, cisplatin; CPT-11, irinotecan; DFS, disease-free survival; GNB, ganglioneuroblastoma; MIBG, metaiodobenzylguanidine; NB, neuroblastoma; new A_1, regimen new A_1; PBSCT, peripheral blood stem cell transplantation; Rec, recurrence; VP-16, etoposide.

ganglia and one adrenal gland, 10 metastatic lymph nodes, 12 lymph nodes with no metastasis, and one bone tissue) (Table 4). The sensitivity of this technique was 81.8% and specificity was 93.3% (accuracy 88.5%).

Patients were evaluated within the first postoperative month by MIBG scintigraphy. In 85.7% of procedures (six out of seven; three complete resection and three partial resection/biopsy), the surgical findings were consistent with postoperative radiological evaluation (Table 5). One child with recurrent retroperitoneal NB, whose surgical findings were complete resection, revealed residual tumor by postoperative MIBG scintigraphy, for which a second laparotomy was performed (Table 5).

The median follow-up of surviving patients in the group of children with NB was 57 months. Four out of five patients with stage 4 NB of unfavorable histology had disease-free survival (Table 1).

For two patients with perineal RMS, SLNB followed by resection of primary tumor and regional lymph node dissection was performed. In both cases, SN were detected as blue-stained lymph nodes with the highest counts by hand-held gamma probe. Histological evaluation showed complete consistency between sentinel and regional lymph node status (Table 2). However, long-term surveillance showed that one adolescent with perineal RMS survived disease-free for 8 years following operation despite positive regional lymph node metastasis whereas the other perineal RMS patient without lymph node metastasis died 14 months after surgery.

Discussion

This pilot study shows the feasibility of applying nuclear medicine to the surgical management of NB and perineal RMS in children. This is the first study to determine long-term outcomes of radioguided surgery for advanced NB, which may confer a survival benefit. Moreover, preliminary data from patients with perineal RMS demonstrated lymphatic spread of RMS via SN, suggesting a feasible strategy of SLNB in the management of this rare and challenging malignant soft tissue tumor in children.

The usefulness of radiolabeled MIBG in the diagnosis and treatment of NB has been well established. Some authors have described the application of radiolabeled MIBG for tumor detection intraoperatively using a hand-held gamma probe and have reported improved definition of tumor limits and extension to locoregional nodes.[5–7] Martelli *et al.* evaluated the correlation between probe and histology and reported sensitivity and specificity of this technique to be 91% and 55%, respectively. In the current study, intraoperative gamma probe was helpful in detecting residual or recurrent tumors or metastatic lymph nodes in 85.7% of procedures. The sensitivity and specificity of this technique were 81.8% and 93.3%, respectively. Relatively high false-negative results in our study contributed to the lower sensitivity compared with previous reports. A possible explanation for the number of false negatives is the complete necrosis or fibrosis of tumor due to intensive chemotherapy as reported previously,[16,17] in which residual tumor cells that were either small in number or only partially matured did not provide sufficient signal to be

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Table 2 Patient characteristics (RMS)

Patient no.	Age (years)	Sex	Location	Stage/ Group	Histology	Radiotracer	Sentinel node positive/total	LN dissection	Node status	Outcomes	Follow up
7	14	F	Perineal	3A/III	Alveolar	99mTc-phytate	1/2	Yes	1/3	DFS	8 years
8	11	F	Perineal	4/IV	Alveolar	99mTc tin colloid	0/2	Yes	0/16	Death	2 years

DFS, disease-free survival; LN, lymph nodes; RMS, rhabdomyosarcoma.

picked up by the probe intraoperatively but were found by pathologists postoperatively.

To date, long-term outcomes of this procedure have not been reported. In the current study, the overall survival of children with NB who underwent radioguided surgery was 83.3% in reasonably long-term follow up (median follow up, 57 months). The role of intensive surgery for advanced NB has remained controversial and it is less likely that the type of surgery contributes to improving patient survival;[18,19] however, it should be noted that there were no significant postoperative complications in our patients. Some previous reports, including ours, described that over 30% of children with high-risk NB were experiencing at least one complication postoperatively, such as renovascular problems, resection of normal organs, and postoperative hemorrhage.[20,21] Moreover, a number of recent studies have shown that neither the extent of tumor resection nor formal lymph node dissection influences the overall prognosis of intermediate- or high-risk NB,[20,22,23] suggesting that less aggressive surgical resection should be considered for tumors of which attempted surgical resection may pose life-threatening or organ-threatening risks.[18] The use of intraoperative gamma probe to reduce complications by accurately determining tumor limits and locoregional metastatic nodes appears to be a feasible, reasonable, less invasive surgical approach.

Neville *et al.*[24] reported for the first time the use of lymphatic mapping with SLNB in pediatric malignancies, including RMS. They found one patient with SN metastasis among three children with RMS following lymphoscintigraphy/SLNB; however, formal lymph node dissection was not performed on this patient. Therefore, the correlation between the results of SLNB and the status of regional lymph nodes was not evaluated. Several papers have been published to demonstrate SLNB on a variety of childhood malignancies, such as melanomas,[12,13,25] RMS,[12,13,25–27] non-RMS soft tissue sarcomas[13,27,28] and breast cancers.[25] Parida *et al.*[13] reported that they achieved a feasibly high success rate

Table 3 Chemotherapy regimens[14,15]

Regimen A_1
Cyclophosphamide 1200 mg/m^2 on day 1
Vincristine 1.5 mg/m^2 on day 1
THP-adriamycin 40 mg/m^2 on day 3
Cisplatin 90 mg/m^2 on day 5
Regimen A_3
Cyclophosphamide 1200 mg/m^2 per day on day 1 and 2
THP-adriamycin 40 mg/m^2 on day 3
Etoposide 100 mg/m^2 per day on days 1 to 5
Cisplatin 25 mg/m^2 on days 1 to 5 (Continuous)
Regimen new A_1
Cyclophosphamide 1200 mg/m^2 per day on day 1 and 2
THP-adriamycin 40 mg/m^2 on day 3
Etoposide 100 mg/m^2 per day on days 1 to 5
Cisplatin 90 mg/m^2 on day 5

THP, thermal enhancement of pirarubicin.

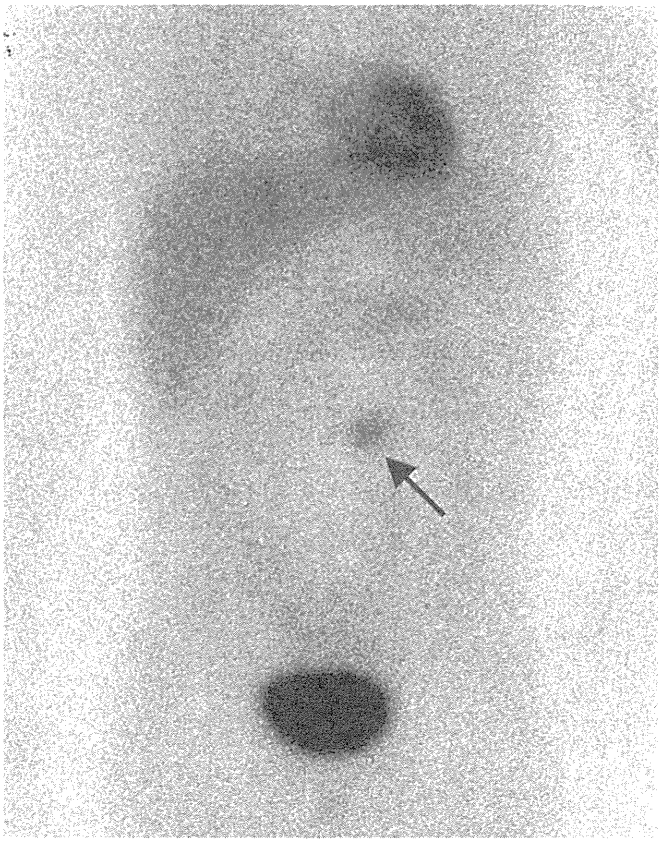

Fig. 3 ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy performed prior to the operation (case 4). Routine MIBG scintigraphy was taken for every neuroblastoma (NB) patient. Abnormal accumulation of MIBG was seen in left upper abdomen (arrow), suggesting recurrent site of tumor.

Table 4 Histological evaluation of resected specimens from neuroblastoma patients

Histological findings	Probe findings		Total
	+	−	
Malignancy	9	2	11
No malignancy	1	14	15
Subtotal	10	16	26

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Table 5 Radiological evaluation of neuroblastoma patients

Surgical resection	Radiologic residual disease	Number of procedures (%)
Complete resection	(−)	3 (42.9)
	(+)	1 (14.3)
Partial resection/biopsy	(−)	0
	(+)	3 (42.9)

(95%) to identify SN in patients with melanoma or sarcoma using combination of preoperative lymphoscintigraphy and intraoperative mapping (blue dye/gamma probe), which we performed in our current study. They also found the SN metastasis in one RMS patient out of six cases (16.7%) who underwent lymphoscintigraphy/SLNB whereas no SN metastasis was observed in patients with non-RMS sarcomas (0/17).[13] Those findings were consistent with results from previous reports with 11.1–33.3% SN positivity rate for RMS patients.[12,25,27]

The current study is the first to show lymphatic drainage via the sentinel lymph node from perianal RMS. RMS is the most common soft tissue sarcoma in children, but perineal and perianal RMS are rare, comprising only 2% of all RMS. They are known to have a relatively poor prognosis, which has been described as a 5-year overall survival of 20–49%.[29,30] A report by the Intergroup Rhabdomyosarcoma Studies Group (IRSG) revealed a high incidence of regional lymph node involvement related to a strong negative impact on overall survival in patients with perineal RMS. The IRSG also reported that 50% of patients with perineal or perianal RMS who had positive regional lymph nodes at diagnosis had a 5-year overall survival of only 33%, whereas 5-year survival was 71% when the disease had not metastasized to regional lymph nodes.[29] This prompted recommendations that included a strategy of routine surgical evaluation of ilioinguinal lymph nodes in all cases of perianal or anal RMS. However, there is no sufficiently reliable non-invasive imaging modality for determination of nodal involvement in these patients. Computed tomography (CT) scanning has been shown to underestimate the number of patients with positive lymph nodes determined by pathologic evaluation in patients with paratesticular disease.[31] It has recently been reported that F-18 fluorodeoxyglucose (FDG) positron-emission tomography (PET) combined with CT was useful for assessing lymph node involvement in pediatric RMS.[32] Although it is a less invasive staging modality than lymph node dissection, histologic confirmation of sites demonstrating FDG uptake is still warranted.

The advantage of SLNB is that it provides definitive histologic node status in patients who do not have clinical evidence of lymph node involvement. The current study showed successful identification of SN in patients with perineal RMS. Moreover, the status of SN was consistent with that of regional lymph nodes; hence, the lymphatic pathway of perineal RMS appears to be via the SN. It should be noted that this hypothesis has been rarely proven within a number of previous reports in which children with extremity RMS were enrolled. As discussed above, lymphoscintigraphy/SLNB detected SN metastasis in one out of three to nine RMS patients; however, none of them underwent a subsequent regional lymph-node dissection, but they received additional radiation therapy to the regional lymph-node basin.[12,13,25,27] Therefore, the false positive rate of this procedure has not been evaluated properly. Minimizing the false negative rate is clinically a more important issue if surgeons will omit the formal regional lymph node dissection for cases with SN negative. Further studies will be required to determine the long-term outcomes of patients with localized perineal RMS who have undergone SLNB in order to consider the feasibility of performing SLNB instead of formal regional lymph node dissection.

In summary, we performed radioguided surgery using ^{123}I-MIBG for the management of advanced NB. Intraoperative gamma-probe detection enabled surgeons to identify viable NB cells, even in non-palpable nodules or lymph nodes, with reasonably high accuracy (88.5%) without any complication. We also performed SLNB during primary resection of perineal RMS. SN were easily detected, and histological analysis suggested that lymphatic drainage from perineal RMS spreads via the SN. This may support the hypothesis that regional lymph node dissection can be omitted if SLNB results are negative. These findings demonstrate the feasibility of the application of nuclear medicine to achieve less invasive surgery of malignant solid tumors in children.

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Review Article

Critical hepatic hemangioma in infants: Recent nationwide survey in Japan

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Abstract The International Society for the Study of Vascular Anomalies (ISSVA) classification divides vascular lesions into two major entities: neoplasms originating from the vascular endothelium and vascular malformations. Although this concept has been widely accepted, little has been established regarding vascular lesions in deep organs, such as infantile hepatic hemangioma (IHH). The current nationwide survey identified 19 critical infantile hemangiomas during the most recent 5 years. On histopathology all the lesions examined were neoplastic, but portovenos shunt was found histologically or clinically in some cases. High-output cardiac failure, consumption coagulopathy, and respiratory distress were the major symptoms, and treatment-resistant coagulopathy seemed to be the most reliable predictor of fatal outcome. Although steroid has been the gold standard treatment for these lesions, 25% of the patients were totally insensitive to steroids, whereas propranolol had a prompt effect in one case. For critical IHH with steroid-insensitive thrombocytopenia and prothrombin time prolongation, novel therapeutic options including beta-blocker therapy, surgery, and liver transplantation should be urgently considered as alterative treatment. The present review summarizes the results of the survey.

Key words: coagulopathy, high-output cardiac failure, infantile hepatic hemangioma, ISSVA classification.

Hemangioma is the most common hepatic tumor in children, and was previously considered to be a neoplastic lesion originating from the vascular endothelium.[1,2] Although most hepatic hemangiomas are asymptomatic and are often found incidentally, a certain type of hepatic vascular lesions develop into critical conditions, such as coagulopathy and cardiac failure.[3,4] In particular, some huge or diffuse hepatic hemangiomas seen in neonates and infants are more frequently associated with a critical pathophysiology and are potentially fatal. Recently, Christison-Lagay *et al.* proposed that this rare subtype of infantile hepatic hemangioma (IHH) might be regarded as a distinct clinical entity because of its unique and critical features.[3] Because of its rarity, the precise clinical features, histopathological background, and predictive risk factors of IHH remain mostly unknown; consequently, a treatment strategy for critical IHH has not yet been established. With the progress of modern therapeutic technologies, novel therapeutic means, such as interventional radiology for neonates and liver transplantation, have been raised as treatment options for IHH, although their clinical implications have not been adequately assessed. At the same time, classical treatment options, such as steroid and interferon therapy, are often applied without adequate assessment of efficacy in individual cases. As for chemotherapy, the efficacy of propranolol, a beta-blocker, has been emphasized in recent literature, and is receiving considerable attention.

In contrast, several reports over the last two decades, especially in the fields of dermatology and plastic surgery, have pointed out that the term "hemangioma" actually includes two different types of vascular anomaly: that is, vascular malformation and vascular neoplasm.[5] The terminology is confusing even in the recent literature.[6] A new concept of classification based on this observation has been offered by the International Society for the Study of Vascular Anomalies (ISSVA), and has become widely accepted (Table 1).[7–9] This concept clearly explains why some hemangiomas are sensitive to steroids and others are not. Thus, intrahepatic vascular lesions that were previously called hemangiomas should be identified as either neoplastic or congenital malformations. As for superficial lesions, histopathological assessment of the vascular lesion may be available with fewer risks, but the vascular lesions in the deep organs are difficult to diagnose properly. Radiological assessment may be also required, which yet carries many unsolved problems. Nevertheless, the concept of ISSVA classification has definitely ushered in a new era for the vascular lesion clinic.

In 2009, the Ministry of Health and Labor, Japan, started a new project to highlight rare diseases and to establish standard treatments as part of a reevaluation of the health and welfare service. Supported by the Rare Diseases Study Grant from the Japanese Ministry of Health and Labor, a nationwide survey was performed to describe the occurrence rate, and the precise clinical features in relation to the risk assessment, and to study

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Table 1 ISSVA classification

Vascular tumors	Vascular malformation
Infantile hemangioma	Slow flow
Congenital hemangioma	Capillarly malformation (e.g. port wine navi telangiectasia etc.)
Tufted angioma	
Kaposi-form hemangioendothelioma	Venous malformation
	Lymphatic malformation
Spindle cell hemangioendothelioma	Fast flow
	Arterial malformation
Others, rare hemangioendothelioma	Arteriovenous fistula
	Arteriovenous malformation
Dermatologic acquired vascular tumor	Complex/combined

ISSVA, International Society for the Study of Vascular Anomalies.

the implications of novel treatment options for fatal symptoms. The current survey also accumulated the latest clinical information regarding the histopathological background of these hepatic vascular lesions. The highlights of the survey with regard to IHH are introduced in the present review.

Outline of the survey

The initial survey involved pediatric surgical institutions, given that most IHH patients seemed to have been referred to pediatric surgeons for surgical treatment. A primary survey on IHH was sent to all 117 pediatric surgical institutions nationwide that are registered with the Japanese Association of Pediatric Surgeons, after receiving the permission of the academic board of the association. Based on the results of the primary survey, a more detailed secondary survey was performed. Nineteen IHH infants (8 boys, 11 girls) who required treatment while under the age of 1 year between January 2005 and December 2010 were identified at 11 institutions in this secondary survey. The patients were each treated according to the local protocol of each hospital for IHH. The clinical course, biochemical and hematological data, pathological images, and radiological images were collected to construct a database, and were then statistically analyzed. The current series was not large, despite a nationwide search, but the survey was intended to involve only recent patients, for whom modern therapeutic options were available, so as to assess the clinical implications of modern therapy. The detailed results of the survey have been published in the *Journal of Pediatric Surgery*.[10] Furthermore, a trial to identify more IHH patients in the field of pediatric surgery and also in the field of perinatology in Japan was restarted in 2012.

Survey results

Occurrence rate and demographic data

In the preliminary survey, only 23 institutions (35.4%) out of all the registered pediatric surgical institutions had encountered IHH during the last 5 years. In the secondary survey, 19 patients with IHH were identified and were included in a more precise investigation and analysis. Median age at the time of diagnosis, median birthweight, and median gestational period of these 19 patients were 1 month, 2757 g, and 38 weeks 3 days, respectively. These observations suggested that critical hepatic hemangioma is a very rare clinical entity, with an occurrence rate of approximately 5–10 cases/year throughout Japan, and is mainly seen in young infants. Also in a report from a Boston group, only 54 patients who were treated medically were registered during the recent 15 years in the USA.[11] More patients are now being diagnosed worldwide as having vascular lesions in the liver prenatally, but intrauterine growth retardation and preterm labor are not commonly seen.

Characteristics of the liver tumor

In the current series, 11 patients had a solitary lesion, whereas eight patients had multi-focal lesions (2–10 lesions) in the liver. The tumors were distributed in the four regions of the liver with identical frequencies (Fig. 1). The maximum diameter of the lesions ranged from 25 mm to 100 mm. The median diameter of the solitary lesions measured 60 mm. Christison-Lagay *et al.* highlighted diffuse hepatic hemangioma as belonging to a critical fatal subpopulation and emphasized that focal and diffuse hemangioma represented different clinical entities.[3,11] Of the three patients who died in the current survey in Japan, however, two had huge solitary lesions (maximum diameter >80 mm) and the third had multi-focal lesions. According to the present results, a solitary tumor exceeding a certain size may also be potentially fatal. Judging from the tumor sizes in the current series, patients with a solitary tumor >60 mm should be regarded as being at risk for the development of a fatal pathophysiology. In addition, four out of the 19 patients (21.1%) had extra-hepatic hemangiomas, all of which were skin lesions. Unlike the present results, a group in Cincinnati reported that 73% of hepatic hemangioma patients had skin lesions and emphasized the significance of skin lesions to screen for hepatic hemangioma.[4]

Clinical symptoms

As thoroughly described in previous reports, abdominal distension, high-output cardiac failure, coagulopathy and respiratory distress are the most common symptoms, seen in >30%–40% of

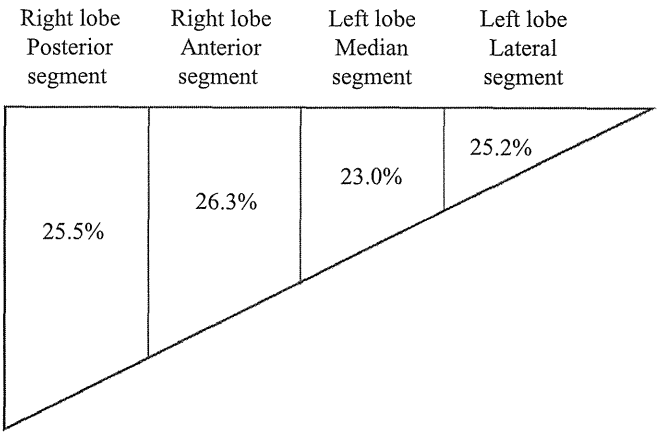

Fig. 1 Tumor locations. Solitary lesion, 18 patients; multiple lesions, eight patients (no. lesions, 2–10); extrahepatic lesions, three patients (all skin lesions).

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all patients. High-output cardiac failure and microangiopathic consumptive coagulopathy are caused by the highly increased vascular bed within the tumor (Table 2). Some other symptoms such as liver dysfunction (15.9%), renal failure (10.6%), hepatosplenomegaly (5.3%), hypertrophic cardiomyopathy (5.3%), hypothyroidism (5.3%), and failure to thrive (5.3%) have also been observed. Interestingly, hypergalactosemia with hyperammonemia was observed in two patients, suggesting that the vascular lesions in these patients had a portovenous shunt flow. Circulatory failure and respiratory distress were not only critical, but were also very common in the patients with large or diffuse hepatic hemangiomas. The cause of death in the three patients who died in the current series was either coagulopathy or cardiac symptoms, indicating that these symptoms are predictors of mortality. Furthermore, pathophysiology such as liver dysfunction and renal failure may potentially coexist in patients with these lesions. Hypothyroidism, which was often described in previous reports, was observed in only one patient in the present series, suggesting that subclinical hypothyroidism associated with IHH might not have been appropriately assessed in the current survey.

Histopathology

In the present series, a histopathological diagnosis was made in only eight patients, because most of the patients underwent neither surgical resection nor biopsy of the hepatic tumor. Histopathology of the specimens of these eight patients was reviewed by one pathologist participating in this study. As described in the previous section in relation to the ISSVA classification, it is clinically very important to determine whether the hepatic lesions are neoplastic hemangioma or vascular malformations. This classification has a significant clinical impact, because the former may be sensitive to steroids through the downregulation of proliferating neoplastic cells of endothelial origin, whereas the latter is unaffected. The histopathological diagnoses of these eight patients included cavernous hemangioma in three patients, and hemangioendothelioma in five patients. The expression of glucose transporter protein 1 (GLUT-1) is a well-known marker for infantile hemangioma and can be used to distinguish neoplastic hemangioma from vascular malformation;[12] Glut-1 expression was seen in two of the six patients examined in the present survey. Hemangioendothelioma is reportedly associated with rapid growth and critical symptoms.[13] Pathologically, two different types of hemangioendothelioma have been identified. Type II hemangioendothelioma is characterized by atypical neoplastic cells and has a faster disease progression compared to type I. Two of the patients who died in the current series were diagnosed as having type I and type II hemangiosarcoma, respectively. In contrast, none of the patients in the survey who were diagnosed as having cavernous hemangioma died. Among the eight patients, some presented with both type I and type II features in a single tumor. Conclusively, neoplastic lesions originating from the vascular endothelium seem to be dominant, and sometimes the histopathology may be heterogeneous in IHH.

Table 2 Clinical symptoms identified in the survey

Symptom	%
Abdominal distension	47.4
High-output cardiac failure	47.4
Coagulopathy	42.1
Respiratory distress	31.6
Liver dysfunction	15.9
Renal failure	10.6
Hypertrophic cardiomyopathy	5.3
Hepatosplenomegaly	5.3
Hypothyroidism	5.3
Failure to thrive	5.3
Hypergalactosemia/hyperammonemia	10.6
CCAM of the lung	5.3
Beckwith–Wiedemann syndrome	5.3

CCAM, congenital cystic adenomatoid malformation.

In contrast, two of the four syndromic patients were considered to have hypergalactosemia arising from a portovenous shunt. In one case, a large portovenous shunt developed after the regression of the hepatic lesions. This patient subsequently required liver transplantation later in infancy because of the progressive deterioration of liver function resulting from the portovenous shunt. This observation suggests an important query: did this lesion originally consist of a vascular malformation contained within a neoplasm, a coexisting vascular malformation and neoplastic hemangioendothelioma, or a vascular malformation that developed secondary to the transformation of a hemangioendothelioma? Whether the portovenous shunt in this case was congenital or acquired has not been clarified. The present study has limitations regarding the pathological assessment, because the study was retrospective.

Histopathological or radiological assessment of vascular lesions in deep organs should be investigated more intensely in the era of the ISSVA classification, because proper assessment provides information regarding the efficacy of treatment. More details regarding the histopathology of hepatic hemangioma are required in future studies.

Treatment

For a long time, steroid therapy has been considered the gold standard for controlling the growth and complications of hemangiomas. Other than steroid therapy, α-interferon therapy, chemotherapeutic agents such as vincristine, actinomycin D, cyclophosphamide, and, more recently, propranolol (a beta-blocker) have also been reported as being effective for the medical treatment of hemangiomas, including IHH.[14–19] In the current survey, prednisolone (0.5–10 mg/kg) was given to 13 patients for a period of 3 days to 9 months, but only three of these patients had complete remission of the lesion, and seven had only partial regression. Moreover, three patients were totally insensitive to steroids, and 47.4% required treatment other than steroids. Almost 25% of the patients did not have any response to steroids in the present series. It seems paradoxical that the pathological assessments in the survey suggested that most of the hepatic lesions identified were considered to be neoplastic, yet they were insensitive to steroid treatment. Not only vascular malformation,

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which is totally resistant to chemotherapeutic agents such as steroids, but a considerable proportion of neoplastic hemangioendotheliomas may be insensitive to steroids. α-Interferon, another classically used agent for the treatment of hemangioma, did not seem to control the lesion well. Anti-cancer agents such as vincristine were given to one patient, who had a temporary and limited response. In contrast, propranolol, a beta-blocker, induced a rapid improvement of the hematological data within 1 week in one patient. The anti-tumor effect of propranolol has also been reported in lymphangioma, probably acting through vascular trophic factors such as vascular endothelial growth factor, and seems to be promising. Future assessments of the rapid effect and safety of propranolol in small infants are needed.

Radiation therapy is another classical option for controlling neoplastic hemangioma. In the current series, two patients underwent radiation therapy at the age of 0–1 month, inducing regression of IHH to some extent. As for interventional radiological options, hepatic arterial embolization was performed in one steroid-resistant patient at the age of <1 month, but the procedure failed to improve the hematological disorder significantly and the patient died. Although arterial embolization has also been reported to be effective for the treatment of steroid-resistant IHH,[20] a steroid-resistant patient in the current series did not have improvement in coagulopathy. Surgical ligation of the hepatic artery also did not have a lasting effect in the series. These observations suggest that hepatic arterial intervention may not be capable of adequately controlling critical coagulopathy and tumor growth for longer than a certain period.

Three patients underwent surgical resection of the involved lesions. After surgical resection, the thrombocyte count was sufficiently raised and the prothrombin time (PT) was shortened. A marked improvement in the hematological data seemed to be obtained by the surgical resection of IHH, but the indications for surgery may have been biased. Surgical patients were considered to be in a stable general condition and therefore capable of undergoing a laparotomy.

Liver transplantation is one of the latest therapeutic options for IHH, although some reports emphasized the use of a combination of conventional therapies so as to avoid transplantation.[21] Liver transplantation was performed in one patient who developed progressive liver dysfunction after the regression of IHH as a result of steroid therapy at the age of 1 year 10 months. In the UNOS survey, some patients underwent emergency liver transplantation due to cardiac failure successfully at a younger age.[22] According to this UNOS report, which surveyed patients of all ages, 110 patients with an average age of 36 years underwent 126 liver transplantations for hepatic hemangioendothelioma between 1987 and 2005, and the 5 year survival rate was 64%. Markiewicz-Kijewska *et al.* reported four infantile cases of urgent liver transplantation because of hemodynamic failure.[23] In Japan, emergency transplantation for younger infants seems to be extremely difficult because donor resources are greatly restricted and are mainly used for patients with end-stage liver disease. The problem of donor resources should be further studied in a future discussion. Liver transplantation, however, appears to be an appropriate option for this disease in both the acute and chronic phases.

Of note, the three patients who died were all initially treated with steroids despite an insufficient response; thereafter, they received vincristine or embolization, both of which failed to control their critical conditions. The prompt application of appropriate therapy is necessary to control the life-threatening critical pathophysiologies.

Risk assessment

Given that only a very small proportion of IHH leads to the development of critical pathophysiologies, it is important to identify appropriate risk factors of critical and fatal outcome. In the present analysis, the pathological, cardiac ultrasonographic, biochemical and hematologic parameters were assessed in relation to outcome. Of them, the biochemical parameters of liver function and the cardiac ultrasonographic parameters failed to predict significant risk, whereas thrombocyte count (before treatment: non-survivors, 73 300 ± 52 900/mm^3 vs survivors, 300 000 ± 195 600/mm^3, $P < 0.03$; after treatment: non-survivors, 66 300 ± 20 200/mm^3 vs survivors, 388 700 ± 118 300/mm^3, $P < 0.003$) and post-therapeutic PT (35.0 ± 14.7 vs 12.1 ± 1.4 s, $P < 0.0001$) indicated significant deterioration among the patients who died. An important finding was that these hematological parameters improved after treatment in the survivors, while they deteriorated even after treatment in the patients who died. Treatment-resistant coagulopathy is definitely predictive of fatal outcome, especially if it is symptomatic. Given that all the patients who died did so within 30 days after birth, the rapid improvement of a critical condition in response to treatment is thought to be necessary for survival.

The current Japanese survey clarified that not only patients with diffuse lesions, but also those with huge solitary lesion may be at risk of fatal outcome, unlike previous reports. Furthermore, the current observation also suggested that any subtype of hemangioendothelioma might be potentially associated with a high risk. The previously reported risk factors do not necessarily predict the risk accurately. For those critical IHH patients who have steroid-resistant thrombocytopenia and PT prolongation, novel therapeutic options, including beta-blocker therapy, surgical or radiological intervention, and liver transplantation, should be urgently considered as alterative treatment.

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