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Impact of Complete Pulmonary Metastasectomy on the Prognosis of Children with Metastatic Hepatoblastoma: A Single Center Experience

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ABSTRACT

Background

The survival rate of patients with hepatoblastoma (HB) with distant metastases is unsatisfactory. Although dose-dense chemotherapy with a high incidence of ototoxicity improves the prognosis of these patients, surgical metastasectomy may provide an alternative treatment option avoiding drug side effects. The aim of this study was to examine the efficacy of “complete” pulmonary metastasectomy for the treatment of children with metastatic HB.

Methods

This retrospective study retrieved data from 2004 to 2015 on 22 children with metastatic HB. Separated into two groups; children who underwent only hepatectomy (group H, 14 cases), and children who underwent primary or rescue liver transplantation (group T, eight cases). Each patient was administered initial chemotherapy according to JPLT-2, SIOPEL3 or PLADO protocols. Over the course of this study, we performed metastasectomies for all detectable pulmonary metastases. Indocyanine green fluorescent navigation was used for 15 patients to detect tiny metastases. The follow-up period for survivors after the last metastasectomy ranged from 36 to 186 months.

Results

The cumulative disease-free 5-year survival rate was 84% in group H and 33% in group T. The median number of resected pulmonary metastatic lesions was 10.5 (range: 1-42) in group H and 3.5 (range: 1–97) in group T. None of the survivors developed hearing or respiratory impairment.

Conclusions

Complete pulmonary metastasectomy improves the prognosis of patients with metastatic HB with conventional chemotherapy, especially in the patients with primary HB lesions removed without liver transplantation.

Keywords: hepatoblastoma, pulmonary metastasis, lung metastasis, metastasectomy, ICG

INTRODUCTION

Hepatoblastoma (HB) is the most common liver malignancy in young children, accounting for approximately 1% of childhood malignant tumors (1). The prognosis of patients with HB has significantly improved over the last 20 years, due to the combination of chemotherapy and surgical resection. The 3-year overall survival rate of patients without distant metastases now exceeds 80%, while the 3-year survival rate of patients with distant metastases is lower, at approximately 60% (2,3). HB frequently metastasizes to the lungs. Thus, control of pulmonary metastases appears to be the key to improving prognosis. Recently, the Society of Pediatric Oncology Liver Tumor Study Group (SIOPEL), reported that high intensified (dose-dense) chemotherapy improved the survival rate of HB patients with distant metastases (4), but this has severe adverse effects such as permanent hearing loss. Other reports have emphasized that aggressive pulmonary metastasectomy may improve the prognosis of HB patients (5-12). However, only a few reports have analyzed the effects of complete pulmonary metastasectomy and the number of resected metastatic tumors on the prognoses of patients. The purpose of this article is to report our findings regarding the efficacy of complete pulmonary metastasectomy in these patients.

METHODS

Study Eligibility

In 2004 the Department of Surgery at Kanagawa Children's Medical Center implemented a program to treat metastatic HB patients using chemotherapy as well as complete resection of all detectable metastatic pulmonary tumors. We did not limit the number of metastatic tumors to be resected nor the number/frequency of pulmonary metastasectomies to be performed. All HB patients were eligible for the study regardless of the number, size, or laterality of the metastatic pulmonary lesions, efficacy of chemotherapy on metastases, pre-treatment extent of tumor (PRETEXT), serum alpha fetoprotein (AFP) levels, onset timings of pulmonary metastases, or frequency of recurrences in the lung. In 2012, we started using indocyanine green (ICG) fluorescence to accurately find and extirpate even very tiny metastatic lesions (13). Our study was approved by the ethics committee of our institution (approval no.:1308-02), and it was concluded in 2015. This study was performed in accordance with the Ethical Guidelines for Clinical Research, published by the Ministry of Health, Labor and Welfare of Japan, and complied with the 1975 Declaration of Helsinki.

Patients

After our study was approved, we enrolled 22 HB patients with radiographical evidence of pulmonary metastases which were resistant to conventional chemotherapy. At onset, 13 patients had pulmonary metastases in addition to liver tumors, while another one case was discovered during neo-adjuvant chemotherapy, with the remaining 8 case found during adjuvant chemotherapy.

At the end of neo-adjuvant chemotherapy or during adjuvant chemotherapy, we defined remained metastases as chemotherapy-resistant lesions.

The median age of the patients was 26 months (range: 4–118 months), and the male to female ratio was 15:7. About 17 (77%) of the patients were referred to our institution after having undergone neoadjuvant chemotherapy, hepatectomy, or adjuvant chemotherapy at their previous institutions. Induction chemotherapy, composed of cisplatin and other drugs, was administered according to with the Japanese pediatric liver tumor study (JPLT)-2 study (14) to 18 patients, according to the SIOPEL-3 study (3) to two patients, and according to the PLADO protocol (15) to two patients.

After neoadjuvant chemotherapy, the primary liver lesions were resected through a hepatectomy in 18 patients, and through primary liver transplantation in 4 patients. After hepatectomy, 4 of the 18 patients developed tumor recurrence in the liver and underwent rescue liver transplantation (Fig. 1). Because the pulmonary metastases of patients in this

study were resistant to the initial chemotherapy mentioned above, sorafenib was administered to six patients (16), irinotecan to 12 patients, and other agents to 4 patients after the primary liver lesions were removed through hepatectomy or liver transplantation.

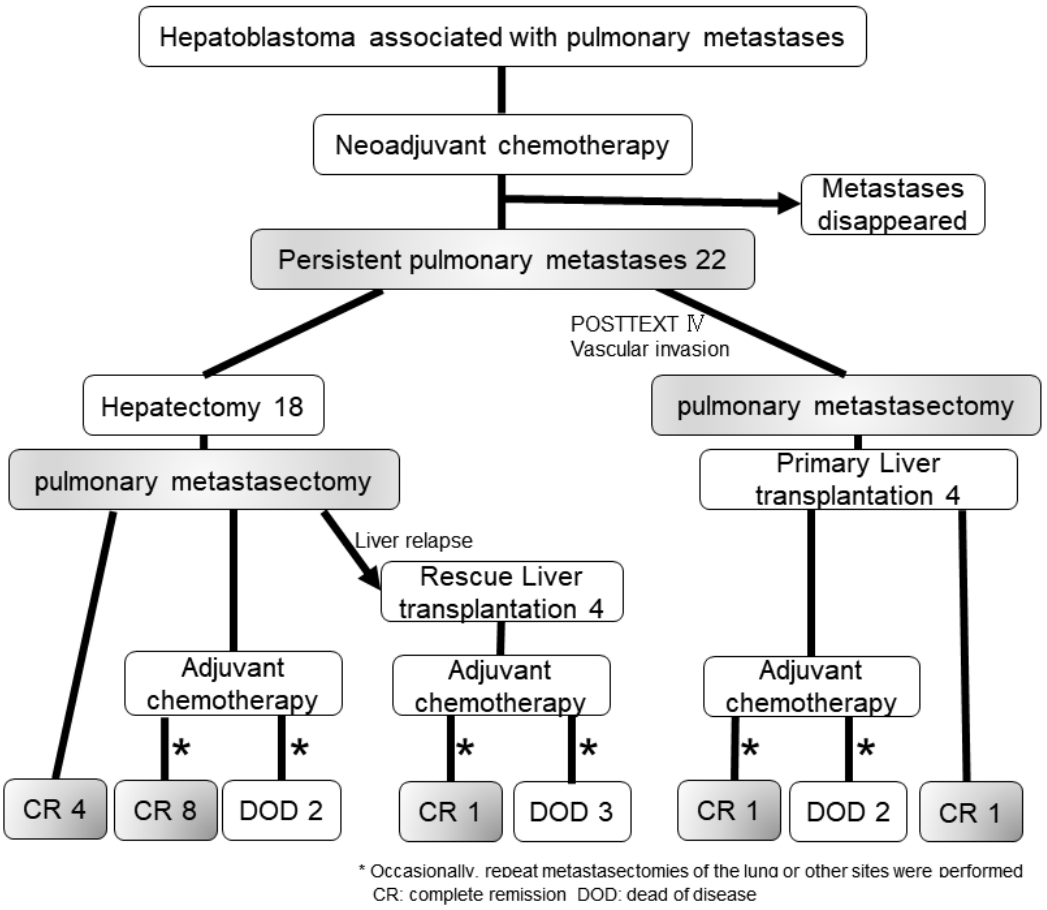

Figure 1. Flow chart of study participants and results. Twenty-two patients in whom pulmonary metastases persisted even after neoadjuvant chemotherapy at their previous hospitals, were referred to our facility.

Surgical Procedures

Each patient underwent complete pulmonary metastasectomy at our institution between 2004 and 2015. Before the surgery, each pulmonary lesion was confirmed and precisely located using computed tomography. Pulmonary metastasectomies were performed on a case-by-case basis about 2 weeks after hepatectomy or about 4 weeks before liver transplantation. Repeat metastasectomies were performed when recurrent pulmonary lesions were detected.

Pulmonary metastasectomy was performed as follows: the patient was placed under general anesthesia with one-lung ventilation, an open thoracotomy was performed, and all metastatic lesions were detected and resected. Before 2011, metastatic lesions were detected by visual inspection and palpation alone, but after 2012, we used ICG fluorescence imaging which was introduced as an additional tumor detection method (13). All metastatic tumors were removed by wedge shaped resection of the lung followed by suturing of the lung tissue by hand instead of mechanical stapling. Recurrent pulmonary metastases were also extirpated by repeat thoracotomy as tolerated by the patients, and based on their respiratory function.

To enable ICG fluorescence imaging, ICG (Diagnogreen, Daiichi-Sankyou, Tokyo, Japan) was administered intravenously a day before the surgery. Metastatic lesions were

visualized by PDEneo (Hamamatsu photonics. Hamamatsu, Japan), which emits infrared radiations and detects evoked fluorescence by CCD-camera (Fig.2). Postoperatively, recurrence was evaluated by computed tomography and serum AFP levels. In this study, the follow-up period after the final metastasectomy ranged from 33 to 183 months (median: 72 months).

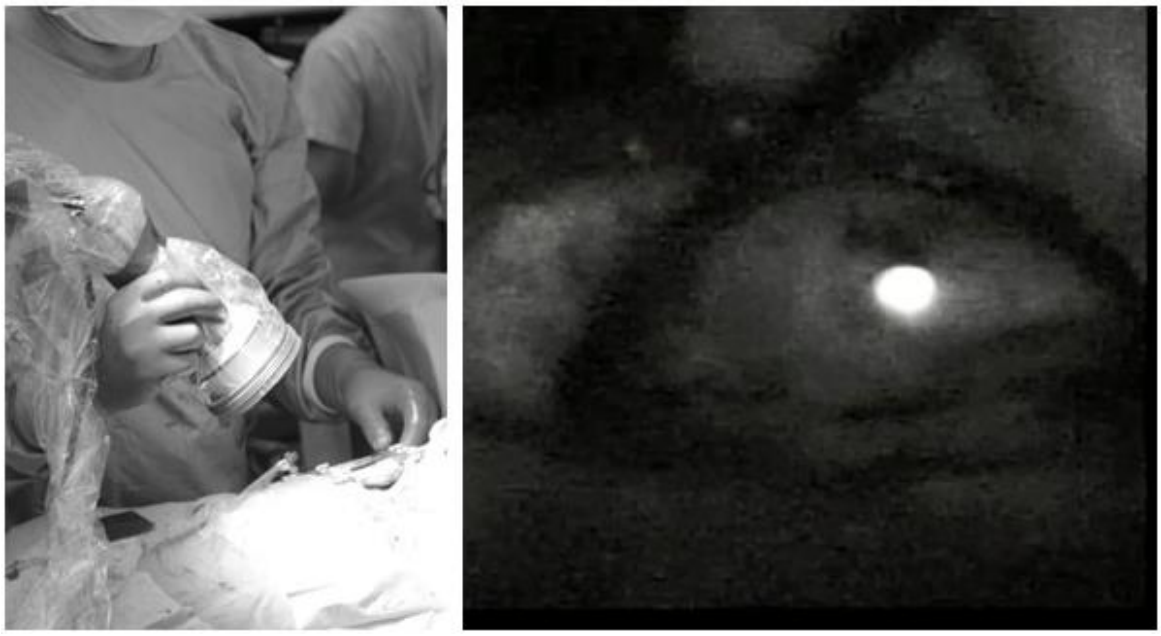

Figure 2. Indocyanine green fluorescent navigation. Left: intraoperative usage of a device consisting of an infrared light radiator and an evoked fluorescence detector (PDE-neo). Right: Evoked fluorescence from a pulmonary metastasis of hepatoblastoma of 5 mm in diameter.

Statistical Analysis

The patients were divided into two groups; namely, patients who underwent hepatectomy only (group H: n = 14), and patients who underwent liver transplantation (group T: n = 8). The patients in each group were analyzed individually. Each patient's profile is shown in Table 1. Survival curves were drawn using the Kaplan-Meier method and compared between groups by the log-rank test. Statistical significance was defined as $p < 0.05$. All statistical analyses were done using SPSS version 22 computer software (SPSS, Chicago, IL, USA).

Table 1

Table 1. Patients, treatment and prognosis.

	Sex	Onset	Neoadjuvant chemotherapy	Hepatectomy	Liver transplantation	Lung metastases			Lung operation		Chemotherapy after metastasectomy	Extrapulmonary metastases /recurrence	Observation period (months)	Prognosis	
						Onset* (months)	Laterality	Number	Number	Navigation					
1	M	1y1m	JPLT2	L3		5	L	1	1		IRN		186	CR	
2	F	7y0m	JPLT2	R3		0	B	42	8		IRN		69	CR	
3	M	9y10m	JPLT2	R2		9	B	26	5		CYtopo+IRN	bone, liver	18	DOD	
4	M	7m	SIOPEL3	C2		0	B	7	1		IRN		98	CR	
5	M	2y0m	JPLT2	R2		0	B	9	2		IRN		100	CR	
6	M	1y9m	JPLT2	R3		0	B	28	11	yes	none		73	CR	
7	M	1y7m	SIOPEL3	R3		7	R	1	1		IRN	brain	74	CR	
8	F	4y0m	JPLT2	L3		0	B	5	2	yes	NA		81	CR	
9	F	9m	JPLT2	R2		0	B	12	5	yes	none		89	CR	
10	M	2y2m	JPLT2	R3		7	B	15	8	yes	IRN+Sor	liver	72	CR	
11	M	1y5m	PLADO	R3		0	B	1	1	yes	none	heart	71	CR	
12	M	5y5m	PLADO	R2		19	B	7	3	yes	IRN+Sor	LN, liver	12	DOD	
13	M	9y10m	JPLT2	R2		8	B	13	10	yes	IRN+Sor	LN	36	CR	
14	M	2y11m	JPLT2	R3		0	L	2	1	yes	none		49	CR	
15	M	3y3m	JPLT2	-	Yes	0	B	5	1		CYtopo+IRN		17	DOD	
16	M	8y11m	JPLT2	-	Yes	0	B	97	5	yes	CDDP, TOTEM		7	DOD	
17	M	5y7m	JPLT2	L3	Yes	0	B	34	11	yes	IRN+Sor	liver, kidney	3	DOD	
18	F	4m	JPLT2	-	Yes	5	L	1	1	yes	IRN		44	CR	
19	F	2y2m	JPLT2	R2	Yes	0	B	5	2	yes	none	liver	86	CR	
20	F	10m	JPLT2	R2	Yes	5	B	2	2	yes	IRN+Sor+BZV	LN	20	DOD	
21	M	3y6m	JPLT2	-	Yes	0	B	1	1	yes	none		32	CR	
22	F	6y1m	JPLT2	R2	Yes	30	R	1	1	yes	IRN+Sor		19	DOD	

*Onset after the first diagnosis of hepatoblastoma

L(R)2: left(right) lobectomy, C2: central bisegmentectomy, L(R)3: left(right) trisegmentectomy B: bilateral, CR: complete remission, DOD: dead of disease,
JPLT2: Protocol of Japanese study group for pediatric liver tumor, SIOPEL: Protocol of International Childhood Liver Tumours Strategy Group, PLADO: cisplatin+doxorubicin,
IRN: irinotecan, Sor: sorafenib, BEV: bevacizumab, CDDP: cisplatin, CYtopo: cyclophosphamide+topotecan, TOTEM: topotecan+temozolomide, NA: not available

RESULTS

The median number of extirpated pulmonary metastatic lesions was 10.5 (range: 1-42) in group H and 3.5 (range: 1-97) in group T. The specimens from those extirpated lesions were histopathologically confirmed as viable metastatic lesions. The median number of surgeries was 2.5 (range: 1-11) in group H, and 1.5 (range: 1-11) in group T. There were no major complications from the surgeries, e.g. surgical site infection, deep venous thrombosis, or pneumonia. The follow-up period after each patient's final metastasectomy

ranged from 36 to 186 months. The cumulative 5-year survival rate was 84% in group H and 33% in group T (Fig. 3).

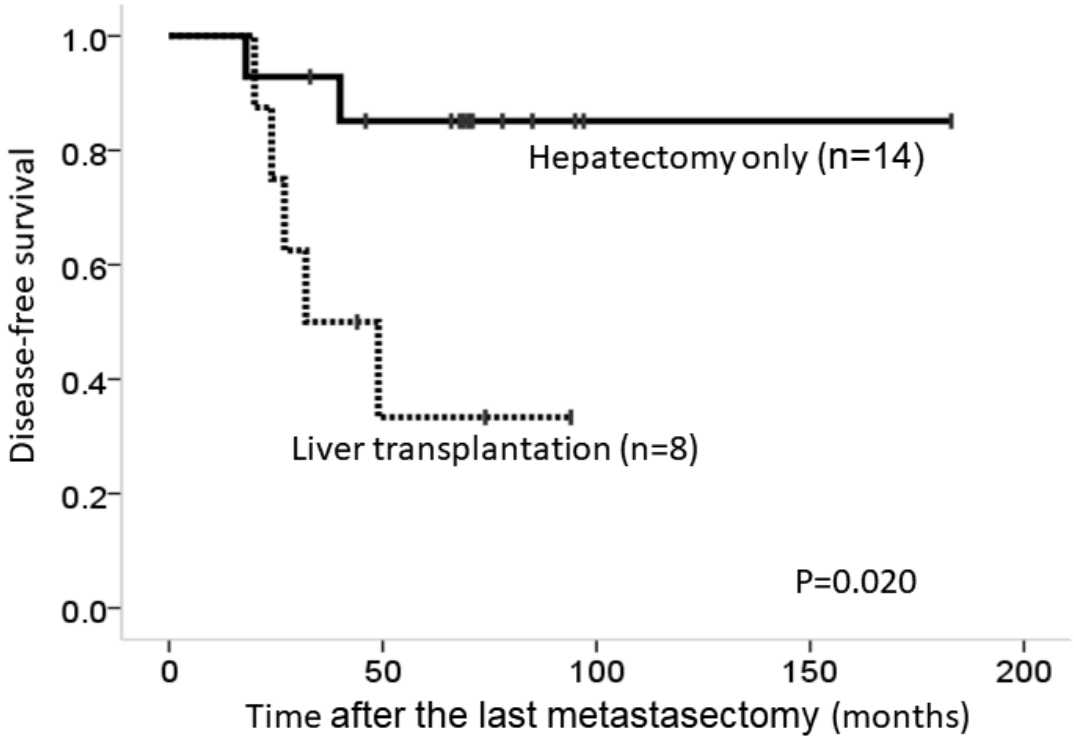

Figure 3. Overall/disease-free survival after the last metastasectomy. 5-year overall survival was 85% in the hepatectomy group and 33% in the liver transplantation group.

After the first metastasectomy, 43% of patients in group H and 38% of patients in group T, developed metastases in other sites apart from the lungs. Notably, the tumor metastasized to the brain of one patient, the lymph nodes of another and to a cardiac valve in a third patient; these lesions were subsequently resected. These 3 patients survived without recurrence for 6,

5 and 3 years respectively. Other patients with bone marrow metastases were treated successfully with chemotherapy; however, another patient with bone metastases died. Among the survivors, the maximum total number of metastatic lesions resected in a single patient was 42. They were resected in nine surgeries. There was no relapse in this patient for 5 years (Fig.4).

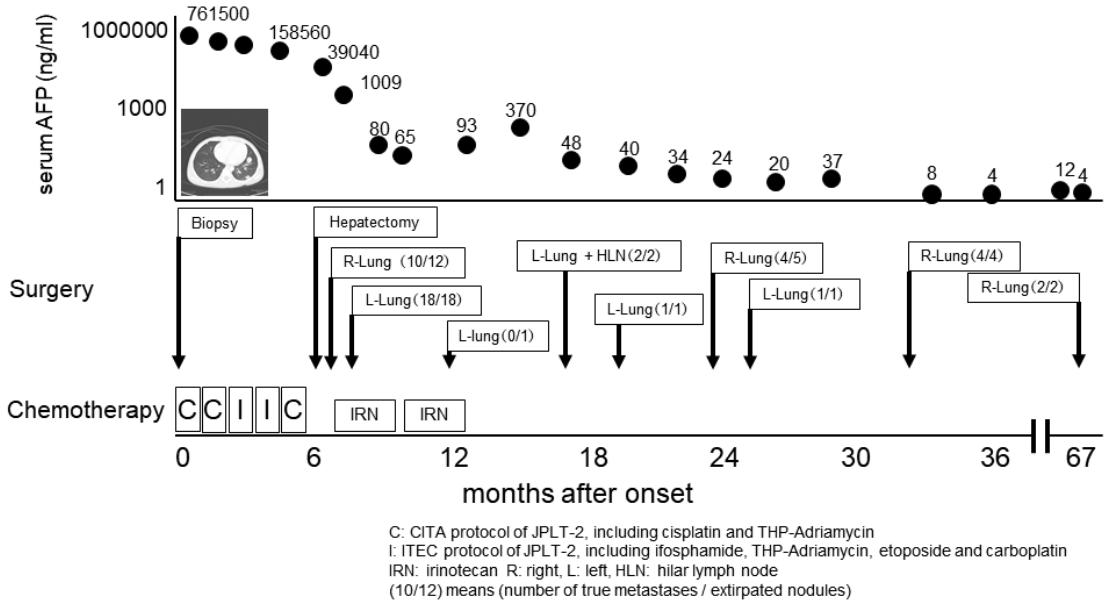

Figure 4. The clinical course of a female patient who underwent nine thoracotomies. She is alive with a forced expiratory volume of 98% of the predicted value in a respiratory function test.

The causes of death were extrapulmonary tumor recurrences in group H, and pulmonary and/or extrapulmonary tumor recurrences in group T. No patient died of metastasectomy-linked surgical complications or respiratory failure.

Survivors who underwent repeated pulmonary metastasectomies did not require oxygen therapy in their day-to-day life. They all attended regular school or kindergarten. Neither scoliosis nor thoracic deformity was observed in any of the surviving patients. At the end of treatment, no survivors developed more than a grade 2 hearing loss, measured using the Brock scale (17). At the end of the follow-up period, no patient required hearing aids in their daily lives. Long-term audiometry follow-up was not performed at our hospital as most of the surviving patients were followed-up in local institutions.

DISCUSSION

The survival rate of patients with HB has significantly improved over the last 20 years, mainly due to advances in chemotherapy and the introduction of liver transplantation. In a JPLT-2 study, patients without metastases had an overall 5-year survival of 87.8% (14). Conversely, the outcome of patients with distant metastases is not as favorable. The 5-year overall survival rate in patients with distant metastases who were treated according

to the JPLT-2 study protocol was 43.9% (14), the 3-year overall survival rate in patients treated according to the Children's Oncology Group protocol (AHEP0731) was 62% (2), and the 3-year overall survival rate in patients treated according to the SIOPEL-3HR study protocol was 69% (3).

Recently, results of the SIOPEL-4 high-risk protocol, including dose-dense chemotherapy (DDC), showed a 3-year overall survival rate of 79% in 39 patients with distant metastases (including seven patients of PRETEXT IV with metastases) (4). Although this result is remarkable, this treatment method also caused moderate to severe hearing disorders in 50% of the patients. This adverse effect reduces the patients' quality of life in countless ways, especially during the periods of language acquisition and speech development. Thiosulfate has been reported to reduce hearing loss caused by conventional doses of cisplatin (18). However, there is no evidence that thiosulfate is effective in patients receiving high doses of cisplatin. We assume that further modifications of DDC or a new strategy combined with DDC and metastasectomy might be considered as the next step to improve therapeutic outcomes of metastatic and chemotherapy-resistant HB.

It has been established that the most important treatment modality for HB is complete resection (19). There have been several reports highlighting the importance of pulmonary

metastasectomy (5-12). However, no report has examined the efficacy of complete pulmonary metastasectomy irrespective of the number and size of resected metastases or the number of operations performed. In this study, by performing complete metastasectomies, we achieved a 5-year survival rate of 84%, surpassing the results of the JPLT, SIOPEL, and COG studies. This indicates that complete metastasectomy may have the therapeutic potential to improve prognosis of patients with metastatic HB resistant to conventional chemotherapy. Notably, most of our patients have already completed conventional chemotherapy and have survived with no additional chemotherapy after pulmonary metastasectomy at the latest follow-up, as there was no drug that effectively inhibited metastases at the time the metastasectomies were performed.

The outcomes of patients in our study who underwent liver transplantation, were unsatisfactory and contrasted with those of patients who underwent only hepatectomy. We performed metastasectomy prior to liver transplantation in eight cases in which there were no distant metastases except in the lung. The use of immunosuppressants after liver transplantation could have suppressed the patients' anti-tumor immunity and might explain the poor prognosis in those patients who had liver transplantation. Therefore, liver transplantation should probably be avoided whenever possible especially in metastatic

HB cases. Fuchs et al. reported the feasibility of aggressive surgical resection without liver transplantation in some patients with POST-TEXT III or IV HB who would usually be considered candidates for liver transplantations (20). On the other hand, SIOPEL-4 HR study included 16 patients who underwent liver transplantation. Although particular results in transplanted patients were not mentioned and pulmonary metastasectomies were performed only in 69% of the patients in the study (4), complete metastasectomy in addition to DDC may help eradicate pulmonary metastatic lesions more effectively and improve the prognosis of the patients who require liver transplantation.

ICG imaging is a useful tool that is used to find tiny metastatic lesions, especially in the lung (Fig. 2). This method relies on the uptake of ICG in hepatocytes (including tumors of hepatocyte origin). While several of its uses have been reported in oncology (21-23), locating pulmonary metastases is one of the best uses of this method, as normal lung tissue rarely takes up ICG. Therefore, ICG serves as an extremely effective contrast agent for HB lesions (13,24,25). ICG imaging undoubtedly facilitates quick and precise identification of small metastatic HB lesions in the lung during surgery and is superior to visual inspection and palpation alone. Using ICG imaging, extremely tiny metastatic lesions as small as 0.062 mm in diameter can be visualized (13). Consequently, very small lesions can be found and extirpated in one operation. This leads to a reduction in the total

number of operations, and increases the interval between surgeries, which may help reduce surgical damage to the lung, enhance recovery of pulmonary function, and secure time for chemotherapy. However, we have not yet performed a study to determine if this imaging method has the potential of improving the prognoses of patients with metastatic HB. It is worth noting that when there is a concern about the potential risk of incomplete resections of primary liver tumors, ICG imaging can be a useful tool to confirm complete resection as it detects tiny residual tumor tissue on the cut surface of the liver when a surgical margin is very thin. We successfully performed hepatectomies in three patients with a primary HB attached to the hepatic veins. Using ICG imaging we confirmed a complete resection with no tumor remaining on the preserved vessel wall.

We are aware of the possibility of a reduction in the quality of life after frequent thoracotomies. Two primary school children included in this study underwent respiratory function tests after their metastasectomy. One female patient who underwent thoracotomies nine times between 9 and 14 years of age (Fig. 4) exhibited a forced expiratory volume of 98% of the predicted value in a respiratory function test. She enjoyed playing tennis and had no thoracic deformity. Although other survivors were too young to perform respiratory function tests, none of them had any respiratory dysfunction that affected their daily life. In young children, favorable postsurgical respiratory

outcomes may be due to the alveoli increase in number until the age of approximately 8 years (26). Denbo, et al. showed that changes in pulmonary function were mild after pulmonary metastasectomy for childhood osteosarcoma (27). Conversely, reduction in respiratory function in adolescents or older patients with other kinds of tumors have been reported.

This study is not without limitations. We assessed a small cohort of children and selection bias could not be eliminated due to the retrospective nature of the study. A larger, prospective study is required to verify the results.

In conclusion, complete pulmonary metastasectomy improves the prognoses of patients with HB which has lost response to conventional chemotherapy. Provided the primary liver lesions are resectable without liver transplantation, complete pulmonary metastasectomies may be an alternative treatment modality for metastatic HB irrespective of the number of metastases, frequency of recurrences, subsequent extrapulmonary metastases, or chemotherapeutic sensitivities. During pulmonary metastasectomy, ICG navigation greatly facilitates tumor detection. Additional innovative strategies including DDC combined with complete metastasectomy may be worth the consideration for patients requiring a liver transplant.

Declarations

Conflict of interest and funding The authors do not have any conflict of interest to disclose and have not received funding.

Data transparency All data generated or analysed during this study are included in this published article

Code availability SPSS version 22, IBM, Chicago, IL, USA. Code: 308013

Author contributions All authors contributed to the study conception and design. The manuscript was written by NK. Supervision was performed by MS. All authors read and approved the manuscript.

Ethical approval Our study was approved by the ethics committee of Kanagawa Children's Medical Center. This study was performed in accordance with the Ethical Guidelines for Clinical Research, published by the Ministry of Health, Labor and Welfare of Japan, and complied with the 1975 Declaration of Helsinki.

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