The role of pulmonary metastasectomy for hepatoblastoma in children with metastasis at diagnosis: Results from the JPLT-2 study

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Abstract

Background/purpose: The purpose of this study was to clarify the role of pulmonary metastasectomy in hepatoblastomas with lung metastasis at diagnosis. We reviewed cases enrolled in the JPLT-2 study.

Methods: A total of 360 cases with hepatoblastoma were enrolled. The clinical courses and outcome of 60 cases with pulmonary metastasis at diagnosis were reviewed, focusing on metastasectomy.

Results: Induction chemotherapy resulted in eradication of nodules in 26, residual nodules in 33, and early treatment-related death in one. Of the 33 cases with residual nodules, 11 underwent complete resection of the lung lesions, and among these, progression was reported in five. Complete resection of the liver tumor was not achieved in two of these. Three underwent incomplete resection of lung nodules, eventually leading to progression. Twelve cases with incomplete or no liver tumor resection progressed regardless of the status of lung lesions. Contrarily, among patients who underwent complete resection of the liver tumor, half were cured without metastasectomy.

Conclusions: Metastasectomy for residual pulmonary nodules after induction chemotherapy is effective provided that the liver tumor could be completely resected.

Type of study: Prospective Cohort Study.

Level of evidence: Level II.

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Hepatoblastoma (HBL) is the most common malignant hepatic tumor in infants and young children, representing approximately 1% of all pediatric malignancies [1,2]. Roughly one fifth of the patients have pulmonary metastasis at diagnosis [3,4], and recurrence of HBL most frequently occurs in the lung [5–8]. Although treatment outcome of metastatic disease has improved during the last two decades mostly owing to intensified pre- and postoperative chemotherapy including high-dose cisplatin, the presence of distant metastasis at diagnosis is still the most powerful predictor of poor prognosis [9–11]. The role of surgery for lung nodules remains unclear, although many have advocated its effect on prolonged disease-free survival of the patients [8,12–14]. It is widely accepted that lung disease should be treated with chemotherapy first, and those that are residual after chemotherapy would be candidates for pulmonary metastasectomy [10].

JPLT-2 was a multicenter collaborative study conducted by JCCG (Japan Children’s Cancer Group) liver committee (formally called JPLT) [3]. This study aimed to elucidate the role of pulmonary metastasis by clarifying which patient would benefit from pulmonary metastasis using a large cohort of HBL enrolled in the JPLT-2 study.

1. Patients and methods

1.1. Patients and data collection

JPLT conducted a study of children with hepatic tumors that was open for enrollment from 1999 to 2012 (JPLT-2). The main results of the JPLT-2 study have been previously published [3,15]. Eligible patients were children younger than 15 years of age at diagnosis with previously untreated malignant liver tumors. A total of 360 cases with the diagnosis of hepatoblastoma were enrolled in the JPLT-2 study. This analysis was a retrospective review of 60 patients with hepatoblastoma who were identified to have pulmonary metastasis at diagnosis. Information on response of pulmonary nodules after induction chemotherapy, date, type, and radicality of first definitive liver resection, date and details of
pulmonary metastasectomies, and outcome including event-free and overall survival as well as surgical complications was collected from the JPLT-2 database.

1.2. Treatment

Patients who initially had lung metastasis were subjected to preoperative chemotherapy. The design of the JPLT-2 studies has been previously described [3]. All cases with distant metastasis received two courses of cisplatin 80 mg/m² on day 1 followed by pirarubicin 30 mg/m² on days 1 and 2 (CITA regimen). After two courses, responders whose tumor diameter had shrunk more than 30% or whose AFP levels had decreased more than 1 log underwent two more CITA regimens, and nonresponders received two courses of an intensified regimen, named ITEC. The ITEC regimen consisted of a combination of 3 g/m² ifosfamide on days 1 and 2, 400 mg/m² carboplatin on day 3, 30 mg/m² pirarubicin on days 4 and 5, and 100 mg/m² etoposide on days 1 – 5. Patients undergoing definitive liver resection received postoperative chemotherapy, except for some who underwent liver transplantation. The final decision for the indication and timing of pulmonary metastasectomy was left to the local team’s discretion, although the protocol recommended removal of metastatic lesions that cannot be eradicated by chemotherapy. For postoperative follow-up, serum AFP levels and abdominal ultrasound were carried out monthly in all patients. Patients received a thoracoabdominal contrast-enhanced CT scan or MRI once every 2 – 3 months in the first 2 years after surgery, and once every 6 months thereafter. Further investigations were carried out when clinically indicated or when tumor recurrence was suspected. Response to chemotherapy was evaluated immediately before liver resection. For cases that never underwent liver resection, response after 4 courses was evaluated. In this analysis, complete resection was defined as microscopic resection of all tumor sites based on surgical findings and postsurgical images. Incomplete resection was defined as macroscopic residual of any active lesion for both the liver resection and pulmonary metastasis. Overall survival (OS) was defined as the time period from the date of enrollment until death or last contact. Patients who did not experience an event were censored on the date of their last contact. Event-free survival (EFS) was defined as the time period from the date of enrollment until occurrence of an event (recurrence, progressive disease, death, or diagnosis of a second malignant neoplasm) or last contact, whichever occurred first.

1.3. Statistical analysis

Overall and event-free survival curves were obtained using the Kaplan–Meier method. The log-rank test was used for comparison of the survival probability between subgroups. Statistical significance was defined as $P < 0.05$.

2. Results

2.1. Patient characteristics

Of the 60 patients with pulmonary metastasis at diagnosis, three were PRETEXT I, nine PRETEXT II, 21 PRETEXT III, and 27 PRETEXT IV tumors. Seventeen had nodules in either of the lungs, 37 had nodules in bilateral lungs, and laterality of lung lesions was not specified in six. All cases received neoadjuvant chemotherapy. Early death from treatment-related toxicity was documented in one case. The remaining 59 cases underwent at least four courses of preoperative chemotherapy and were subjected to response evaluation.

2.2. Surgical resection in cases with metastasis at diagnosis and survival

Among the 59 cases that completed induction chemotherapy, complete response (CR; clearance of all pulmonary lesions) was achieved in the lung at the time of evaluation in 26 cases. Out of the remaining 33 cases with residual nodules, 14 underwent at least one procedure of metastasectomy. These resulted in complete removal of all visible nodules in 11 cases, while a part of the visible nodules was not resected in three. Metastasectomy was performed before liver surgery in two cases and after liver resection in 11, and one after liver surgery and high-dose chemotherapy. There were no attempts to perform metastasectomy in the remaining 19 cases. No information was available for the reason why these nodules were not removed.

Recurrence or progression was observed in a total of 22 out of the 59 cases that completed induction chemotherapy (summarized in Fig. 1).
The recurrence/progression rate of patients who achieved CR in the lung by chemotherapy solely was lower than those whose metastasis remained visible (27% vs 67%). All cases (12 out of 12) that did not successfully undergo macroscopic complete resection of the liver tumor had a recurrence or progression, regardless of the status of the lung disease. There were only two cases that underwent orthotropic liver transplantation (OLT), both resulting in complete resection. In one of these, lung metastasis was cleared by induction chemotherapy and the patient subsequently underwent living-donor OLT. In the other case, the nodules remained, and the patient further received off-protocol chemotherapy that eventually eradicated the lung lesions. This patient also underwent living-donor OLT thereafter. There were no patients that underwent metastasectomy for lung disease and subsequent OLT.

Among the 33 cases in which nodules were persistent after induction chemotherapy, patients who received complete resection of both the liver tumor and lung nodules had the lowest recurrence/progression rate. However, it is worth noting that among patients who underwent complete resection of the liver tumor, half achieved event-free survival without metastasectomy, indicating that, provided that the liver tumor is well controlled, some pulmonary nodules may have a chance to be eradicated with further use of chemotherapy.

For survival analysis, we first compared the EFS and OS rate between patients who underwent complete liver resection and cases who did not; and cases with CR by chemotherapy only versus cases whose nodules were persistent, using the 59 cases that completed induction as a cohort. Cases that underwent complete liver resection had a significantly higher EFS (p < 0.0001) and OS (p < 0.0001) compared to those that did not (Figs. 2A and 3A). Similarly, the EFS (p < 0.0071) and OS (p < 0.004) of cases with lung CR after induction chemotherapy were significantly higher than those that had residual nodules (Figs. 2B and 3B).

Next, to evaluate the effect of pulmonary metastasectomy on prognosis, using the 33 cases that had residual nodules after induction chemotherapy as a cohort, we compared the survival of cases that underwent metastasectomy and those that did not. The metastasectomy group had a higher estimated survival rate both in EFS (45% vs 21.8% at three years) and OS (63.6% vs 41.8% at three years), though the difference was not statistical (Figs. 2C and 3C). When we combined the resectability of the liver tumor and lung nodules, the cases that had both the liver and the lung cleared by surgery had the best chance to survive, with a 3-year EFS of 55.6% compared to 36.9% in patients whose liver was cleared but lung was not, although this was not statistically supported. Those that did not have a complete resection of the liver tumor had an extremely worse outcome regardless of the completeness of lung resection (Figs. 2D and 3D).

3. Discussion

The existence of pulmonary metastasis at diagnosis is one of the most powerful predictors of poor prognosis in HBL. In the past two decades, the outcome of patients with pulmonary metastasis at diagnosis has improved from a 3-year overall survival of 44% in the 1990’s to 79% in the most recent study by the European SIOPEL group [9,16]. Intensification of pre- and postoperative chemotherapy including dose-dense administration of cisplatin has largely contributed to the improvement of outcome, although surgery is still the mainstay of multimodal treatment, and the optimal goal is to achieve complete resection of all tumor burden. It is well accepted that pulmonary metastasectomy is an important tool for lesions that are not cleared by chemotherapy alone [17]. However, it is still unclear which patients truly benefit from the procedure.
In our series with pulmonary metastasis at diagnosis, metastasectomy was restricted to cases that were not eradicated by chemotherapy. Cases in which lung tumors were cleared by chemotherapy only did extremely well, in agreement with other previous reports. CR of lung nodules in the 60 cases with initial lung metastasis was observed in 43% (26 out of 60) in our series. The rate of clearance was slightly lower than the recent studies from SIOPEL. CR of lung metastasis was achieved in 52.2% in SIOPEL-3 [10], and 51% in SIOPEL-4 [9]. The outcome of those that achieve CR by chemotherapy only is generally good. Twenty-five out of 36 in SIOPEL-3 and in 18 out of 20 SIOPEL-4 had no recurrence after achieving CR with chemotherapy. In the present study, 19 out of 26 cases with CR in the lung had no recurrence. The EFS and OS were significantly better than those that did not achieve CR. Thus, intensifying the induction chemotherapy aiming to control the lung disease as in the SIOPEL-4 protocol seems to be a reasonable strategy for improving the survival of patients with lung metastasis.

Not many studies have investigated in detail the relevance of the radicality of liver resection, completeness of pulmonary metastasectomy, and the outcome. The results from the present study showed that, regardless of the status of the lung disease, patients whose primary tumors are completely resected have a better prognosis, with a statistical significance. This agrees with a previous report from JPLT. Matsunaga and colleagues reported that among 20 cases with lung metastases at diagnosis, cases that underwent complete liver resection had a favorable outcome with nine out of 11 patients alive for more than 2 years. Those whose primary tumors were incompletely resected or not resected died of the disease [8]. In the present study, among the patients who had residual lung disease after induction chemotherapy but were able to undergo complete resection of the liver tumor, the EFS and OS were higher in those whose lung nodules were completely resected compared to those whose nodules were not, although the difference lacked statistical significance. This result is suggestive of the positive effect of pulmonary metastasectomy in residual lesions of initially metastatic cases on the condition that the liver tumor could be completely resected. Our findings require verification using a larger cohort.

In the current era, metastasectomy is actively performed for children who require OLT, and the presence of lung metastasis after induction chemotherapy is no longer a contraindication for OLT [14,17–20]. In Japan, OLT for HBLs had not been covered by insurance until 2008, and more than half of the cohort used in the present study did not have access to OLT. In response to the increasing number of OLTs in our country, currently more patients undergo OLT for HBL, including those that have metastasis at diagnosis, or those that achieve lung CR by metastasectomy [18,19]. More patients with pulmonary metastasis may be cured by the extended use of OLT in the current and future trials.

In conclusion, this paper describes a retrospective analysis of HBL with metastasis to the lung at diagnosis, focusing on surgical resection of the metastatic lesions. The best outcome could be expected for those who achieve CR by chemotherapy only, but for cases that have residual disease after chemotherapy, aggressive pulmonary metastasectomy may improve their outcome provided that the liver tumor has been, or is expected to be, completely resected.

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