Journal of Pediatric Surgery 51 (2016) 525–529

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Original Articles

Relapsed hepatoblastoma confined to the lung is effectively treated with pulmonary metastasectomy

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ARTICLE INFO

Article history:
Received 5 May 2015
Received in revised form 15 September 2015
Accepted 13 October 2015

Key words:
Pulmonary relapse
Lung metastasis
Hepatoblastoma
Recurrence
Metastasectomy
Surgical resection

ABSTRACT

Background: In children diagnosed with hepatoblastoma (HB), the lungs are the most common site of metastasis at both initial presentation and relapse. Previous studies have encouraged pulmonary metastasectomy to achieve a disease-free state after resection of the primary hepatic lesion. However, there is no consensus about how to manage recurrent pulmonary metastasis.
Procedure: A retrospective, multi-institutional review was performed from 2005 to 2014 to identify HB patients ≤18 years of age who had disease recurrence associated with pulmonary metastases alone.
Results: Ten patients between the ages of 8 and 33 months were identified. Pulmonary metastatic recurrence was detected by measuring alpha-fetoprotein (AFP) levels and/or with CT scans of the chest. All patients subsequently underwent pulmonary metastasectomy without post-operative complications. At last follow-up, 8 patients were alive and had normal AFP levels. The 8 survivors had a median follow-up from therapy completion of 18.5 months. Two patients who presented with extrapulmonary recurrence subsequently died of treatment refractory disease.
Conclusions: This review supports surgical resection as a safe and, in the context of multimodal therapy, efficacious approach to manage HB patients who present with isolated pulmonary relapse.

Hepatoblastoma (HB) is the most common malignant liver tumor in children, accounting for 1% of childhood malignancies [1]. It is an embryonal tumor with diverse histologic subgroups which include fetal, embryonal, small cell undifferentiated, macrotrabecular, and rarer variants [2,3]. Multiple studies have established surgical resection and adjuvant chemotherapy as the standard of care [4–6]. The overall survival of HB patients with resectable tumors now exceeds 80% at 5 years; conversely, the survival of patients with metastatic or chemotherapy-resistant hepatoblastoma is poor [7–9]. A prospective trial by the International Society of Pediatric Oncology Liver Tumor Study Group (SIOPEL) noted visible metastases in almost 20% of patients presenting with hepatoblastoma [10]. This is considered an indicator of poor event-free survival [11].

Hepatoblastoma most commonly metastasizes to the lung [12,13]. Historically, management of pulmonary metastases has been approached in a variety of fashions integrating chemotherapy and surgical resection. Results from recent clinical trials have established the strategy of neo-adjuvant chemotherapy first, followed by surgical resection for persistent pulmonary lesions [7]. Current literature about how to treat metachronous pulmonary metastasis after a period of remission is limited and lacks consistency [10,13–16]. In this case series, 10 patients are described who were free of disease for at least 1 month and

Abbreviations: HB, hepatoblastoma; SIOPEL, International Society of Pediatric Oncology Liver Tumor Study Group; COG, Children's Oncology Group; AFP, alpha-fetoprotein; C5V, cisplatin, 5-flurouricil, vincristine; C5VD, cisplatin, 5-flurouricil, vincristine, doxorubicin.

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http://dx.doi.org/10.1016/j.jpedsurg.2015.10.053
0022-3468/

recurred with lesions in the lung, 8 of which had a favorable outcome after metastasectomy.

1. Patients and methods

After obtaining institutional IRB approval at the individual sites (two large tertiary pediatric referral centers), a retrospective chart review of all patients treated for HB from January 2005 through March 2015 was performed. The inclusion criteria for this case series were patients with recurrent pulmonary metastasis who had primary treatment with complete surgical resection (including orthotopic liver transplant) of the primary liver tumor and adjuvant chemotherapy, achieved complete remission confirmed by imaging and normalized alpha fetoprotein (AFP) levels for ≥ 4 weeks, and subsequently developed pulmonary metastasis which was treated, in part, with metastasectomy. Evidence of pulmonary disease was defined by the presence of suspicious nodules detected with computed tomography (CT) scan of the chest in conjunction with persistently elevated serum AFP levels, or biopsy-proven HB. Clearance of pulmonary metastases was defined by radiographic clearance of suspicious pulmonary nodules with a corresponding normalization of serum AFP (≤10 ng/ml). Subsequent recurrence was defined by the reappearance of suspicious radiographic findings on CT scans and an associated elevation of serum AFP levels. Charts were analyzed for patient demographics, Children's Oncology Group (COG) stage, histology, imaging findings, AFP levels, surgical details, systemic treatment, and outcomes. To specifically examine the clinical history of each pulmonary nodule, all patient CT scans were reviewed by an experienced pediatric radiologist within each institution. Special attention was devoted to distinguish novel pulmonary recurrences, from the recurrence of previously treated nodules.

2. Results

Of 138 total patients with HB, ten patients had a pulmonary recurrence and all of these patients underwent pulmonary metastasectomy as part of their treatment. There were 4 females and 6 males. Among these patients there were 18 total instances of pulmonary recurrence (Table 1). Age at initial disease presentation ranged from 8 to 33 months; the mean age was 23 months. Seven patients were COG stage IV at diagnosis and had initial pulmonary metastases, 2 patients were COG stage III, and the remaining patient stage I. The histology of the primary tumors was evenly divided between mixed epithelial (6/10) and mixed epithelial/mesenchymal (4/10). Of the mixed epithelial tumors, 5 were composed of fetal and embryonal elements and the remaining tumor consisted of fetal and macrotrabecular components. Small cell components were seen in one tumor. The AFP level at the initial time of diagnosis ranged from 455 to >530,000 ng/ml.

Induction chemotherapy consisted of cisplatin, 5-flurouricil, and vincristine (C5V) or cisplatin, 5-flurouricil, vincristine, and doxorubicin (C5VD), according to AHEP0731, POG9645, or SIOPEL-3HR protocols. Two patients had additional rounds of neoadjuvant chemotherapy prior to surgical resection of their primary lesion. The pulmonary nodules in all patients with stage IV disease at presentation, with the exception of one, had good response to neoadjuvant chemotherapy and achieved clearance of pulmonary disease. The remaining patient (Patient #8) had persistent pulmonary metastases after initial chemotherapy and required pulmonary metastasectomy to achieve initial complete tumor clearance.

The median disease-free interval after induction chemotherapy and surgery was 5 months, with a range of 2–15 months. In 7 patients, management of recurrent pulmonary disease consisted of pulmonary metastasectomy without neoadjuvant chemotherapy. Two patients received neoadjuvant chemotherapy before metastasectomy (Patients #4 & #5). The remaining patient (Patient #9) received neoadjuvant chemotherapy and then metastasectomy for 2 instances of recurrence, and initial metastasectomy followed by adjuvant chemotherapy in the remaining 2 instances (Table 2). Five open thoracotomies with either lobectomy or wedge resection, and eight thoracoscopic wedge resections were performed. All patients tolerated their procedures well without post-operative complications and had a mean length of stay of 3.6 days. Eight of 10 patients were survivors; their median follow-up time from therapy completion was 18.5 months (range of 1 to 37 months).

Two patients presented with extrapulmonary recurrence. One recurrence occurred in the brain and the other in the mediastinum. The patient with metastatic disease in the brain died as a result of her intracranial disease. The patient with mediastinal metastasis at diagnosis was treated with a metastasectomy followed by a right lower lobectomy. The patient recurred after 4 months with a mediastinal mass adherent to the pericardium, which was resected. Three months later, the patient recurred again with a right lung nodule which was treated with wedge resection. This patient died after the appearance of a fourth recurrence with extensive hilar lymphadenopathy that was unresectable.

Table 3 details the clinical history of all recurrent nodules for each patient. There were 16 first time recurrences in which initial staging imaging was available for comparison. Of these, 11/16 (69%) nodules were also present at diagnosis and only 5/16 (31%) were previously undetected lesions. There were a total of 34 instances of recurrent thoracic lesions, one of which was extrapulmonary. Resection was performed for 23 instances, and 11 instances received chemotherapy

Table 1
Patient, disease characteristics, and initial therapy.

	Age at Diagnosis, months	COG Stage	Pulmonary Disease at Diagnosis	Gestational Age at Birth, weeks	Histology	AFP at Diagnosis, ng/ml	Primary Therapy (cycles)
Pt #1	24	3	No	32	Epithelial (fetal, embryonal)	Unknown	C5V (4) → SX → C5V (2)
Pt #2	23	4	Yes	32	Mixed epithelial and mesenchymal	Unknown	IRN → C5V (4) → DDP/DOX (1) → OLT → IRN (1) → VCR/IRN (1)
Pt #3	10	1	No	FT	Mixed epithelial and mesenchymal	Unknown	C5V (4) → SX
Pt #4	27	4	Yes	28	Mixed epithelial and mesenchymal	284,896	C5V (4) → SX → C5V (2)
Pt #5	33	4	Yes	FT	Epithelial (fetal, macrotrabecular)	455	C5V (4) → SX → DOX/DDP (3) → IFO/DOX (3)
Pt #6	32	4	Yes	FT	Epithelial (fetal, embryonal)	37,300	C5VD (2) → SX → C5VD (4)
Pt #7	9	4	Yes	FT	Epithelial (fetal, embryonal)	>530,000	C5V (4) → OLT
Pt #8	24	4	Yes	FT	Mixed epithelial and mesenchymal	>36,300	C5V (4) → PM → CBDCA/DOX (2) → OLT → CBDCA/DOX (1) → DOX (1)
Pt #9	27	4	Yes	Unknown	Epithelial (fetal, embryonal)	371,000	C5VD (2) → SX → PM → CBDCA/DOX (2) → DDP (1)
Pt #10	15	3	No	FT	Epithelial (fetal, embryonal)	>52,000	C5VD (3) → OLT

Abbreviations: PM, pulmonary metastasectomy; OLT, orthotopic liver transplantation; SX, surgical resection of primary tumor; IFO, ifosfamide; DOX, doxorubicin; VCR, vincristine; IRN, Irinotecan; CBDCA, carboplatin; DDP, cisplatin; AFP, alpha fetoprotein; FT, full term; COG, Children's Oncology Group.