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Adult Hepatoblastoma: Systemic Review of the English Literature

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Key Words
Hepatoblastoma · Adult · Systemic review

Abstract
Aims: To review all the case reports or case series of patients with adult hepatoblastoma. ***Methods:*** A search of all case reports on adult hepatoblastoma in the English literature was performed using the PubMed database. Demographic information, clinical findings, treatment modalities and outcomes were extracted and analyzed. ***Results:*** A total of 36 English articles and 40 patients with adult hepatoblastoma were collected. All these cases were confirmed by pathological diagnosis. The median age of the 40 patients was 41.5 years, including 21 males and 19 females. Hepatitis B virus tests were positive in 6 patients, and 15 patients were positive for α-fetoprotein (AFP). Liver cirrhosis was only confirmed in 7 cases. Hepatoblastoma commonly forms a single giant mass within the liver. Twenty-three cases underwent radical liver resection, including 9 cases of comprehensive treatment. The median survival time for 27 patients with available follow-ups was 4 months; 1-year survival was 29.6%. In Cox multivariate analysis, curative liver resection was an independent prognostic factor for prolonged survival ($p = 0.003$). ***Conclusions:*** Curative liver resection can prolong survival. Improvements in outcome will require the development of more effective systemic therapies.

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Introduction

Hepatoblastoma is composed of various differentiated epithelial elements resembling fetal hepatocyte with or without mesenchymal elements. Hepatoblastoma is the most common hepatic malignancy in children [1]. In recent decades, diagnosis and treatment have been significantly improved in pediatric hepatoblastoma, and many patients may expect a long survival [1–3]. In contrast, adult hepatoblastoma is a very rare and aggressive neoplasm with a dismal prognosis. To date, only a few cases have been adequately reported in the medical literature, and no effective diagnostic and therapeutic strategy has been established. The aim of this study was to review all the case reports on adult hepatoblastoma, to explore the clinical features and outcomes, and to provide clinical clues for further study.

Methods

A PubMed search of English language reports from 1958 to 2011 was performed using the key words: 'hepatoblastoma' and 'adult'. Articles were further considered after reviewing the titles and abstracts when available. Only those reports were included in which the diagnosis of hepatoblastoma was confirmed histologically by an autopsy, a biopsy or the resection specimen. Demographic infor-

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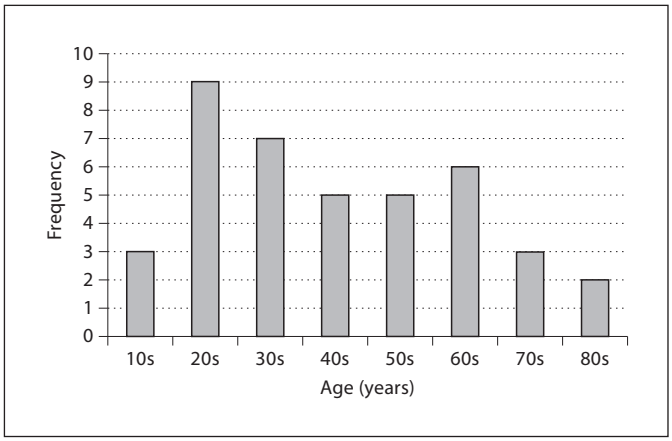

Fig. 1. Age distribution of adult hepatoblastoma in the English literature.

mation, clinical symptoms and signs, laboratory test and medical imaging, treatment and clinical outcomes were extracted and analyzed. Finally, in order to better characterize the outcome of adult hepatoblastoma, survival was assessed by the Kaplan-Meier method and group comparisons were performed using the log-rank test. A p value <0.05 indicated statistical significance. Analyses were conducted using SPSS 15.0 (SPSS, Chicago, Ill., USA).

Results

Case Report Overview

An extensive English literature search revealed only 36 reports including 40 patients with adult hepatoblastoma dating back to 1958 [4–40]. Before Carter [9] initially reported a patient with adult hepatoblastoma in the English literature, hepatic embryonic mixed tumor, mixed tumor and embryonic tumor had been reported as hepatoblastoma [5–8, 10]. Eleven cases were reported before the 1980s, 20 cases were reported in the 1980s and the remaining 9 cases were reported in the present century. Of these, 16 cases were reported by authors from Asia (Japan, Korea, China, and India) and 12 cases by European authors (Italy, Germany, UK, France, Sweden, and the Slovak Republic); 9 cases were reported by US authors, and the other 3 cases were reported by authors from Australia, Mexico and South Africa, respectively.

Baseline Characteristics

The male:female ratio was 1.1 (21:19). The mean age at diagnosis was 41.5 years, and the age span was 19–84 years (fig. 1). Most cases were in their 20s. Clinical symptoms were confirmed in 31/40 cases, 3/40 cases were incidental cases, and in 6/40 cases there were no available data in the literature. Pain was the most common symptom (23/31, 74.2%), including epigastric pain in 14 cases, right upper abdomen pain in 8 cases, abdominal pain in 3 cases, and lumbago in 1 case. Other clinical symptoms included fever, gastrointestinal symptoms, such as anorexia, nausea and vomiting, and rare findings, such as leg swelling, upper gastrointestinal bleeding and dyspnea. Twenty-five cases had positive findings on physical examination. The most common signs were as follows: abdominal mass (9/25, 36.0%), hepatomegaly (10/25, 40.0%) and weight loss (8/25, 32.0%). Other rare signs were leg edema, jaundice and anemia. Adult hepatoblastoma often presents with a giant mass, and almost all patients had a main tumor of more than 5 cm in diameter with a median size of 15 cm in diameter. Adult hepatoblastoma affects the right or left liver lobes, and the tumors are very often single (29/40, 72.5%). Patient characteristics were shown in table 1.

Diagnostic Modalities

In the literature, laboratory studies revealed nonspecific results. A slight increase in the serum hepatic zymogram was observed in a few cases. Of all 40 patients, only 6 cases tested positive for hepatitis B virus; the remaining 34 cases were negative hepatitis B virus, and in some cases, no descriptions of hepatitis status were found on careful reading. Fifteen of the patients were positive for α-fetoprotein (AFP), and the serum AFP level ranged widely from 35,819 to 1,548,000 ng/ml. In addition, serum vitamin K antagonist-II was elevated in 3 cases (case 32: 579,000 mAU/ml; case 3: 6,880 mAU/ml, and case 38: 38,496 mAU/ml).

The radiological investigations commonly used consisted of abdominal X-ray plain film, ultrasound, computed tomography, magnetic resonance imaging and selective celiac angiography. In earlier studies, X-ray film was the main imaging method; it showed elevation of the diaphragm, an enlarged liver and intratumoral calcification. After that, ultrasound, computed tomography, magnetic resonance imaging gradually became the most common imaging methods, and revealed clear liver lesions. Selective celiac angiography was performed in 18 cases and almost all patients (14/18, 77.8%) were characterized by high vascularization. Only 1 case (1/7, 14.3%) of those who underwent needle biopsy had a positive diagnosis of hepatoblastoma. Histopathologic examination was the final diagnostic method. Necrosis and hemor-

Table 1. Summary of the 40 cases of adult hepatoblastoma in the English literature

Case	Reference (first author)	Country	Year	Sex	Age years	Size	Number	Pathology	AFP ng/ml	Treatment	Follow-up months	Status
1	Barnett [5]	US	1958	male	35	42 cm	single	mixed		gastrojejunostomy	1	death
2	Alexander [6]	UK	1961	female	68	15 cm	single	mixed		no		death
3	Ojima [7]	Japan	1964	male	48	3,800 g	single	mixed		no		death
4	Kerr [10]	Australia	1966	male	56			mixed		no		death
5	Blanding [8]	US	1968	male	84	8 cm	multiple	mixed		laparotomy biopsy	0	death
6	Carter [9]	US	1969	male	78	19 cm	multiple	mixed		laparotomy biopsy	1	death
7	Goldman [11]	US	1969	female	65	35 cm	single	mixed		peritoneoscopy		death
8	Meyer [12]	US	1974	female	19	19 cm	single	mixed		liver resection		
9	Ludwig [13]	US	1975	female	53	2,515 g	multiple	mixed		peritoneoscopy	0	death
10	Ludwig [13]	US	1975	male	40	4,500 g	single	mixed		no		death
11	Jameson [14]	South Africa	1978	female	51	12 cm	single	mixed	–	no		death
12	Honan [15]	UK	1980	female	27	25 cm	single	mixed		laparotomy biopsy	0	death
13	Kishimoto [16]	Japan	1984	male	60	2,350 g	multiple	mixed	256	chemotherapy	56 days	death
14	Kawarada [17]	Japan	1985	male	43	4,000 g	single	mixed	–	liver resection	32	DFS
15	Kawarada [17]	Japan	1985	male	49	3,000 g	multiple	mixed	–	laparotomy biopsy	2	death
16	Sugino [18]	Japan	1989	male	22	6.5 cm	single	embryonal	3,021	comprehensive	9	death
17	Seabrook [32]	US	1989	male	24	2,650 g	single	mixed		liver resection		
18	Oda [33]	Japan	1990	male	82	7 cm	single	mixed	–	TACE (mitomycin C)	4	death
19	Slugen [40]	Slovak Republic	1990	male	66	12 cm	multiple	mixed		no		death
20	Altmann [19]	FRG	1992	male	73	18 cm	single	mixed		liver resection		
21	Altmann [19]	FRG	1992	female	35		single	fetal		liver resection		
22	Anderson [20]	US	1992	female	39	25 cm	single	mixed		en bloc resection	18	DFS
23	Harada [21]	Japan	1995	female	24	11 cm	single	mixed	120,000	comprehensive	16	death
24	Inoue [22]	Japan	1995	female	22	14 cm	single	fetal		en bloc resection	38	DFS
25	Kacker [23]	India	1995	female	28	diffuse	multiple	mixed	9,000	laparotomy biopsy	1	survival
26	Bortolasi [24]	Italy	1996	female	21	15 cm	single	embryonal	80	liver resection	151	survival
27	Bortolasi [24]	Italy	1996	male	39	8 cm	single	mixed		en bloc resection	15	death
28	Hiroki [34]	Japan	1996	female	61	8 cm	single	mixed	5,779.3	comprehensive		
29	Ahn [25]	Korea	1997	female	51	11 cm	single	mixed	43,850	liver resection	2	death
30	Parada [26]	Sweden	1997	male	67	8 cm	single	mixed	–	en bloc resection	2 weeks	death
31	Dumortier [36]	France	1999	male	47	diffuse	multiple	mixed	30,000	no		death
32	Inagaki [27]	Japan	2001	male	19	10 cm	single	mixed	1,548,000	comprehensive	12	DFS
33	Yamazaki [4]	Japan	2004	female	20	18 cm	multiple	embryonal	162,000	comprehensive	3	death
34	Ke [28]	Taiwan	2005	female	52	22 cm	multiple	mixed		liver resection + RFA	6	survival
35	Kasper [29]	Germany	2005	female	78	23 cm	single	mixed	121,000	liver resection	69 days	death
36	Remes-Troche [30]	Mexico	2006	female	19	14 cm	single	mixed	–	comprehensive	6	death
37	Zhang [35]	China	2007	male	34	17 cm	single	mixed	565,000	liver resection	3	death
38	Nakamura [31]	Japan	2010	female	25	25 cm	single	epithelial	1,340,000	comprehensive	48	survival
39	Fiaschetti [39]	Italy	2010	male	30	23 cm	single	mixed	45	comprehensive	6	DFS
40	Di Benedetto [37]	Italy	2011	male	33	19 cm	single	mixed	35.819	comprehensive	12	death

US = United States; UK = United Kingdom; FRG = Federal Republic of Germany; TACE = transcatheter arterial chemoembolization; RFA = radiofrequency ablation; DFS = disease-free survival.

Table 2. Diagnostic modalities of the 40 cases of adult hepatoblastoma

Diagnostic clues	Cases
Hepatitis B virus (+)	27, 29, 32, 34, 35, 37
Liver cirrhosis (+)	4, 13, 19, 20, 29, 31, 37
Abdominal X-ray plain film	1, 2, 6, 7, 11, 12, 13, 14, 19
Ultrasound	11, 13, 18, 19, 23, 25, 26, 28, 29, 32, 39
Computed tomography	13, 14, 15, 16, 18, 23, 24, 25, 26, 27, 29, 30, 31, 32, 33, 34, 35, 36, 38, 39
Magnetic resonance imaging	30, 36, 37, 38, 39, 40
Selective celiac arteriography	6, 8, 9, 10, 13, 14, 15, 16, 23, 24, 26, 28, 29, 32, 33, 34, 36, 38
Vascularization	6, 10, 13, 14, 16, 24, 26, 28, 29, 32, 33, 34, 36, 38
Needle biopsy	9 (–), 16 (–), 23 (–), 24 (–), 30 (–), 33 (–), 38 (–), 39 (+)
Necrosis/hemorrhage (+)	1, 2, 4, 5, 6, 7, 8, 11, 13, 14, 18, 19, 20, 24,26, 28, 29, 33, 34, 35, 37
Calcification (+)	6, 9, 10, 13, 20, 28, 31, 32

Table 3. Comprehensive treatment modalities in selected patients

Case	Treatment
16	Preoperative TACE (Adriamycin) + en bloc resection + adjuvant chemotherapy (cisplatin)
23	Preoperative TAE + extended right hemihepatectomy
	Recurrence: liver resection *2
	Recurrence : TACE (mitomycin C), systemic chemotherapy (platinum, Adriamycin)*3, PAI*19
28	Preoperative TACE (epirubicin) + left hemihepatectomy
32	Right hemihepatectomy + adjuvant chemotherapy (cisplatinum, pirarubicin)*6
33	Preoperative HAI (mitoxantrone) + extended left hemihepatectomy
36	Extended right hemihepatectomy + adjuvant chemotherapy (platinum, Adriamycin)
38	Preoperative TACE (cisplatin) and systemic chemotherapy (pirarubicin) *5, TACE (5-fluorouracil, cisplatin) *7
	Lung metastasis: second chemotherapy (ITEC) *1
39	Extended left hemihepatectomy + adjuvant chemotherapy (irinotecan)
40	Extended right hemihepatectomy + adjuvant chemotherapy (platinum, Adriamycin)*4
	Left hepatectomy + subtotal gastrectomy + adjuvant chemotherapy (platinum, Adriamycin) *1
	Recurrence: TACE (farmorubicin)*3

TACE = Transcatheter arterial chemoembolization; TAE = transcatheter arterial embolization; PAI = percutaneous ethanol injection. * = ×.

rhage were confirmed in 21 cases (52.5%) and calcification was found in 8 cases (20%). The diagnostic modalities are summarized in table 2.

Management Modalities and Outcome

Management modalities are shown in table 2. Seven patients did not receive any treatment, and the diagnosis of hepatoblastoma was made post mortem. Exploratory biopsy was performed in 8 cases, including 1 gastrojejunostomy patient, 2 peritoneoscopy patients and 1 case combined with systemic chemotherapy. Two patients received systemic chemotherapy or local transcatheter arterial chemoembolization. Twenty-three cases of adult hepatoblastoma underwent radical surgery, including surgical resection alone in 14 cases and comprehensive treatment in 9 patients. Comprehensive therapy modalities are shown in table 3.

Follow-up data were available in 27 patients. Overall outcome of the patient was poor since most of the patients died shortly after diagnosis and treatment. The overall median survival time was 4 months, and the 1-year survival rate was 29.6% (fig. 2). Younger patients showed significantly better prognoses than older patients (fig. 3). The median survival for patients younger than 50 years

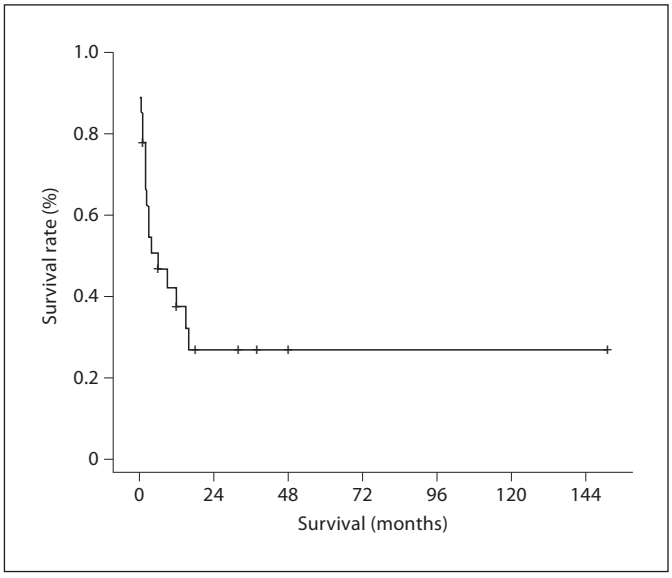

Fig. 2. Overall survival of adult hepatoblastoma (n = 27). Median survival: 4 months (95% confidence interval 0–12.35), 1-year survival: 29.6%.

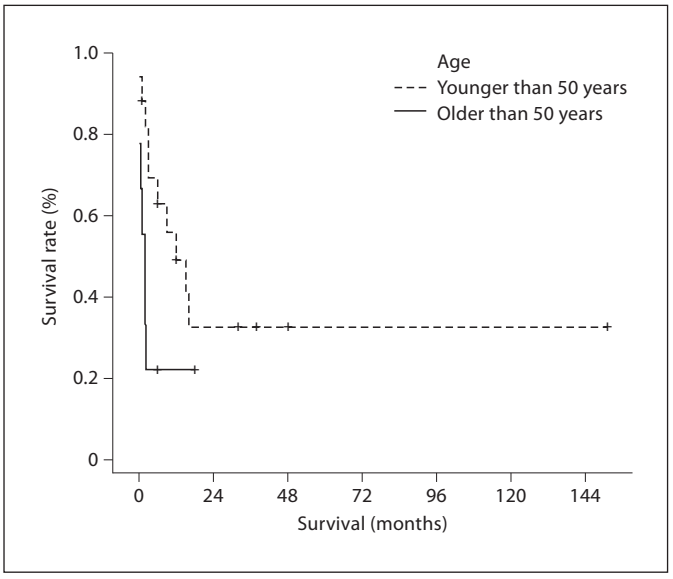

Fig. 3. Overall survival of adult hepatoblastoma patients younger than 50 years (n = 17) and older than 50 years (n = 10). One-year survival for patients younger than 50 year: 41.2%; 1-year survival for patients older than 50 year: 10.0% (log rank test, $\chi^2 = 4.128$, $p = 0.042$).

was 9 months with a 1-year survival rate of 41.2%; however, the median survival for patients older than 50 years was 2 months with a 1-year survival of 10.0% ($\chi^2 = 4.128$, $p = 0.042$). Patients who underwent radical treatment had improved survival compared to those who underwent biopsies and/or nonsurgical treatment (fig. 4). One-year survival for patients who underwent radical resection was 44.4% with a median survival of 10.5 months and 0% in those who did not undergo resection ($\chi^2 = 17.488$, $p = 0.000$). In Cox multivariate analysis, curative liver resection was an independent prognostic factor for improved survival ($p = 0.003$). The median survival for cases reported before 1995 and after 1995 was 2 and 6 months, respectively; however, no significant difference was shown ($\chi^2 = 0.718$, $p = 0.397$). The main tumor size also had no impact on survival ($\chi^2 = 0.643$, $p = 0.422$).

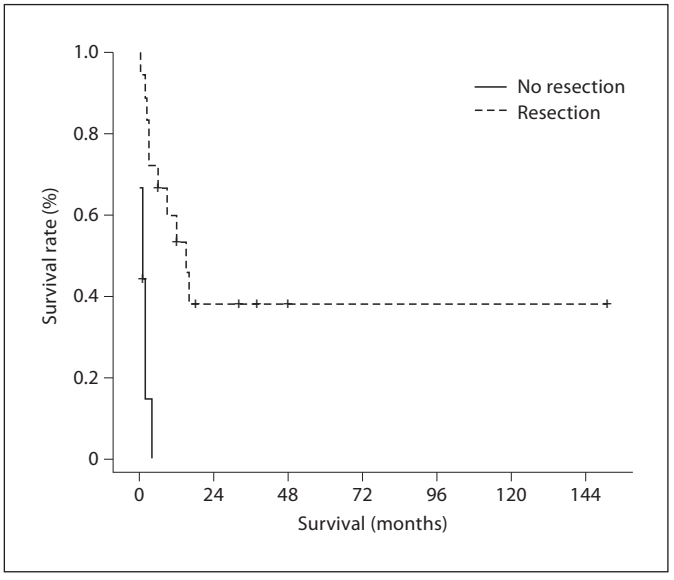

Fig. 4. Overall survival of adult hepatoblastoma patients who underwent resection (n = 18) and those who did not (n = 9). One-year survival for patients who underwent resection: 44.4%; 1-year survival for patients who did not undergo resection: 0% (log rank test, $\chi^2 = 17.488$, $p = 0.000$).

Discussion

Hepatoblastoma may occur in association with genetic disorders. Parada et al. [26] cytogenetically investigated an adult patient with hepatoblastoma and found a genetic variation showing a hypertriploid stemline with multiple numerical and structural chromosomal aberra-

tions. Weber et al. [41] screened 34 hepatoblastoma tumors and 3 hepatoblastoma cell lines for DNA copy number changes. The results identified gains on chromosomes 1q and 2 as the hallmark of DNA copy number changes in hepatoblastoma, 2q24 being a critical chromosomal band; this study also provided evidence that gains on 8q and 20 may play a role as markers of prognostic significance in hepatoblastoma. In addition, the Wnt signaling pathway may play an important role in the development of this malignant neoplasm [42]. Chronic hepatitis B and C virus infection and liver cirrhosis are causally associated with the development of hepatocellular carcinoma [43]. In the present review, there were only 6 patients definitely positive for hepatitis B virus. Liver cirrhosis was found in 7 patients. Interestingly, childhood hepatoblastoma classically arises within a healthy liver, unaffected by underlying disease. Whether there is a link between hepatoblastoma and hepatitis needs further investigation.

The most frequent symptoms of hepatoblastoma are abdominal pain, and the most frequent physical signs were abdominal mass, hepatomegaly and weight loss, but these signs are also found in other types of tumors. No obvious rule can be found regarding age distribution at diagnosis. Nor was there an obvious sexual difference in incidence in adult hepatoblastoma; however, this may be different from childhood hepatoblastoma [44]. Hepatoblastoma commonly forms a single giant mass within the liver. Laboratory data in cases of hepatoblastoma are not specific. Liver function tests were normal or mildly elevated. Serum AFP levels were elevated in 15 cases with a median value of 30,000 ng/ml. In some cases, the serum AFP level even exceeded 1,000,000 ng/ml [27, 31]. These variations may be due to a difference in biological characters as in other tumors [4].

Early detection and diagnosis are believed to improve the prognosis of adult patients with hepatoblastoma. Therefore, it is important to be suspicious of hepatoblastoma when patients present with nonspecific symptoms. It should also be noted that liver function tests, hepatitis status and tumor markers, such as AFP, are not specific as mentioned previously. Hepatoblastoma is difficult to differentiate from other malignant tumors of the liver using imaging techniques. Kishimoto et al. [16] mentioned that intratumoral calcification demonstrated by computed tomography scans was somewhat helpful in the diagnosis of adult hepatoblastoma. The incidence of tumor calcification was significantly higher than in other liver tumors in mixed type [38]. Calcification may be characteristic in all liver tumors with mesenchymal elements [4]. In the present systematic study, we only confirmed 8 cases with calcifications. Morphological characteristics of adult hepatoblastoma are cystic changes and hypervascularity [4]. Cystic changes may be consecutive to intratumoral hemorrhage or necrosis, which is a common pathological finding. Arteriography could detect hypervascular tumors.

Harada et al. [21] insisted on the importance of needle aspiration biopsy to diagnose hepatoblastoma preoperatively. The present review does not consider this procedure to be adequate for a preoperative diagnosis because of its low positivity rate and the risk of bleeding and tumor dissemination. Needle biopsy was successful in only 1 of 7 cases. Postoperative pathological examination has proven to be the best approach for confirming hepatoblastoma. Ishak and Glunz [45] classified hepatoblastoma into two groups: an epithelial type, and a mixed epithelial and mesenchymal type. The epithelial type consists of fetal and embryonic cells. In this study, the mixed type was the most common histological type of adult hepatoblastoma.

From the present review of the literature, it can be seen that there is no standardized management of adult hepatoblastoma. Surgery was the first-line approach, but pre- and postoperative chemotherapy was administered in a few cases. Until now, there has been no established chemotherapy regimen. The chemotherapy protocols used in previous cases were platinum, Adriamycin, irinotecan and pirarubicin. Radical surgical excision appears to be the 'gold standard'. Rougemont et al. [46] suggested treating adult hepatoblastoma in the same way as childhood hepatoblastoma: start treatment with cisplatin-based preoperative chemotherapy, followed by surgery.

Hepatic resection can considerably prolong survival and remains the primary treatment for adult hepatoblastoma. Many adult hepatoblastoma patients are unresectable at diagnosis and often develop intrahepatic recurrence and extrahepatic metastasis after liver resection. For these patients, adjuvant chemotherapy should be a conceivable choice in order to shrink the mass, thus facilitating its complete excision, and prolonging disease-free survival. Nakamura et al. [31] reported a patient with initially unresectable adult hepatoblastoma successfully treated by multimodal treatment, including intensive preoperative chemotherapy, liver resection and postoperative adjuvant chemotherapy who survived over 4 years after diagnosis. Ethanol injection and radiofrequency catheter ablation have been safe and effective in the treatment of primary or metastatic liver cancer. There was an adult hepatoblastoma patient who survived for 151

months after an initial operation with ethanol injection for her repeating recurrences [24]. Ke et al. [28] reported a patient who underwent surgical resection for a larger tumor nodule and radiofrequency catheter ablation for a smaller one. In addition, the role of chemoembolization as a rescue treatment for recurrences of resected hepatoblastoma was evaluated recently in a case report, and the patient survived 11 months after chemoembolization [37]. Multicenter efforts should focus on implementing standardized guidelines [46].

The prognosis of hepatoblastoma is extremely poor. The median survival was only 4 months with a 1-year survival of 29.6%. Younger patients had significantly better prognoses than older patients. Patients who underwent resection displayed improved survival compared to those who underwent biopsies and/or nonsurgical treatment. In Cox multivariate analysis, curative liver resection was an independent prognostic factor for improved survival. These findings are similar to those of a previous review [46]. Although no significant difference was shown, the median survival for cases reported after 1995 was better than that of cases reported before 1995, suggesting an improvement in the management of hepatoblastoma in adults [46]. Improvements in outcome will require the development of more effective systemic therapies.

Disclosure Statement

The authors have no potential conflict of interest to disclose.

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