Prognosis of Aggressive Treatment of Primary Hepatic Angiosarcoma: A Single-Center Experience

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Abstract:

Background and Aims: Of all primary liver tumors, primary hepatic angiosarcoma (PHA) is a rare and aggressive malignant vascular tumor. The standard therapeutic care for hepatic angiosarcoma remains unclear.

This study compared the survival outcomes of aggressive treatment (resection and liver transplant) and nonaggressive treatment (chemotherapy, transarterial chemoembolization [TACE], and conservative treatments) for patients with PHA and analyzed the prognostic factors influencing survival.

Materials and Methods: Data of patients diagnosed as having PHA at our facility were retrospectively reviewed. The primary outcome was survival time. The secondary outcome was calculated baseline characteristics.

Results: We included a total of 19 patients, who were divided into 2 treatment groups: aggressive (8 patients had undergone resection or transplants) and nonaggressive (11 patients had undergone TACE, chemotherapy, or conservative treatment). The mean survival time was 233.1 ± 189.7 days in the aggressive treatment group and 146.5 ± 115.8 days in the nonaggressive treatment group. A Kaplan-Meier plot revealed no significant difference in survival time between the 2 treatment groups ($P = .3256$).

Conclusions: The survival time of patients receiving aggressive treatment was

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longer than that of those receiving nonaggressive treatment. The long term survival time in some selective cases of aggressive treatment will be achieved. Thought a difference was not significant between the groups. Because the number of patients was limited, more cases are required to confirm these findings.

Key words: aggressive treatment; Liver transplant; nonaggressive treatment; Primary Hepatic Angiosarcoma; tumor resection

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Introduction

Primary hepatic angiosarcoma (PHA) is a rare and aggressive malignant vascular tumor that accounts for only 0.6% to 2% of primary liver tumors[1]. Identifying the right remedy against PHA is difficult, particularly if the patient has no proof of exposure to arsenicals or the carcinogens thorotrast and vinyl chloride monomer[1]. PHA originates from endothelial cells and usually presents as an abdominal mass with unspecific signs and symptoms, making it difficult to diagnose at an early stage. The tumor's rapid progress, high recurrence rate, and resistance to chemotherapy mean that the PHA survival rate is extremely low[2-4]. Even liver transplants have been eliminated as a treatment option because of the tumor's high recurrence rate and patients' poor survival rate after a transplant. Therefore, the standard therapeutic care for liver angiosarcoma has remained unclear[2-4]. Partial hepatectomy, chemotherapy, and transhepatic arterial chemoembolization (TACE) have been used in the treatment of PHA. Our study evaluated the prognosis of PHA after aggressive treatment with tumor resection or liver transplant versus nonaggressive treatment with TACE, systemic chemotherapy, or conservative treatment. We included patients with histologic proof of PHA in this study.

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Methods

The study was approved by the Ethics Committee of China Medical University Hospital, Taichung, Taiwan (approval no: CMUH110-REC3-098). We selected 6328 patients diagnosed as having primary malignant hepatic tumors (*International Classification of Diseases* code 155.0) from January 2011 to December 2018 from our database. We collected data on 19 patients who were diagnosed as having PHA with histologic proof in central Taiwan. The 19 patients were divided into 2 treatment groups: an aggressive treatment group, comprising 8 patients (4 received resection and 4 received transplants); and a nonaggressive treatment group, comprising 11 patients (3 received TACE, 3 received chemotherapy, and 6 had conservative treatment).

Patient information obtained from medical records comprised age; gender; signs and symptoms; PHA characteristics (size; location; number; and presence of ascites, rupture or metastasis); and laboratory profiles including carcinoembryonic antigen (CEA) levels, alpha-fetoprotein (AFP) levels, liver function, and routine blood panel data. The patients were followed up until death. Survival time was defined as the period from the first day of treatment to death.

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Statistical Analysis

We evaluated the effect of treatment (aggressive vs nonaggressive) on patient survival rates. Baseline characteristics were compared between patients with PHA who received aggressive treatment and those who received nonaggressive treatment. Categorical variables are presented as proportions, and continuous variables are presented as mean ± standard deviation. The significance of between-group differences was examined using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. The person-days of follow-up for each patient were calculated as the duration of treatment from diagnosis until death. Mortality was calculated by dividing the number of deaths by the follow-up person-days. The statistical analyses were 2-sided, and $P < .05$ was considered significant. All statistical analyses were performed using SAS software (version 9.4; SAS institute, Cary, NC, USA).

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Results

Characteristics of Study Population

This study included a total of 19 patients, 8 of whom underwent aggressive treatment and 11 underwent nonaggressive treatment. The baseline characteristics and signs and symptoms of all patients are listed in Table 1. In the aggressive treatment group, all 8 patients were men; their average age was 63.6 ± 12.9 years. Of the patients in this group, 4 (50%) reported abdominal pain and 4 (50%) reported general malaise. In the nonaggressive treatment group, 7 of the patients were men and 4 were women; their average age was 66.2 ± 7.1 years. Of the patients in this group, 7 (63.6%) reported abdominal pain and 4 (36.4%) reported general malaise. We observed no statistically significant differences between the 2 treatment groups in terms of age or signs and symptoms. However, these groups differed significantly in terms of sex

Tumor Behavior

Tables 2 and 3 present the tumor behaviors of patients in the aggressive and nonaggressive treatment groups, respectively. In the aggressive treatment group, 4 patients had tumors in the bilateral hepatic lobes, whereas the other 4 had tumors in the unilateral hepatic lobe. Regarding the total number of tumors in each patient, 4 patients had 1 tumor, 1 patient had 2 tumors, and 3 patients had multiple (>3) tumors. The average size of the tumors was 8.38 ± 4.66 cm. Five patients showed abnormal liver

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function, and 3 exhibited hemoglobin levels of <10 g/dL. No patient had chronic viral hepatitis markers. Two patients experienced PHA rupture. In the nonaggressive treatment group, 9 patients had tumors in the bilateral hepatic lobes, and 2 had tumors in the unilateral hepatic lobe. Regarding the total number of tumors in each patient, 4 patients had 1 tumor, 1 patient had 3 tumors, and 6 patients had multiple (>3) tumors. The average size of the tumors was 9.75 ± 4.13 cm. Seven patients showed abnormal liver function, and 3 exhibited hemoglobin levels of <10 g/dL. No patient had chronic hepatitis viral markers. Six patients experienced PHA rupture. In the aggressive treatment group, 2 of the 8 patients had lung metastasis, 2 had bone metastasis, 1 had colon metastasis, and 1 had small intestine metastasis. In the nonaggressive treatment group, 2 of the 11 patients had bone metastasis, 1 had spleen metastasis, 1 had peritoneum metastasis, and 1 had kidney metastasis. We observed no statistically significant differences between the 2 treatment groups in terms of tumor location, number, size, markers, rupture, or metastases. Moreover, we observed no statistically significant between-group differences in chronic viral hepatitis markers, liver function, platelet count, or hemoglobin levels (Tables 2 and 3).

Computed Tomography Findings

Table 4 presents abdominal computed tomography (CT) findings before histologic proof of PHA. In the aggressive treatment group, only 1 patient was diagnosed as

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having PHA through abdominal CT before treatment commenced; the patient's family insisted on a liver transplant. In other patients, CT findings before histologic proof included 1 metastasis, 5 hepatocellular carcinomas, and 1 cholangiocarcinoma. In the nonaggressive treatment group, CT diagnoses made before histologic proof included 4 angiosarcomas, 4 metastases, 2 hepatocellular carcinomas, and 1 hemangioma. We observed no significant difference between the 2 treatment groups in terms of abdominal CT finding before histologic proof of PHA.

Survival Times

Figure 1 illustrates patient survival times in the aggressive and nonaggressive treatment groups. In the aggressive treatment group, 4 patients received transplants and the other 4 received tumor resection. In the nonaggressive treatment group, 3 patients received TACE, 2 received chemotherapy, and 6 received conservative treatment. The mean survival time was 233.1 ± 189.7 days in the aggressive treatment group and 146.5 ± 115.8 days in the nonaggressive treatment group. The median survival time was 233.1 days in the aggressive treatment group and 146.5 days in the nonaggressive treatment group. All patients died during follow-up. A Kaplan-Meier plot revealed no significant difference in survival time between the 2 treatment groups (P = .3265).

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Discussion

PHA is an aggressive malignant tumor that originates in the endothelium of liver blood vessels. It is a rare condition and accounts for only 0.6% to 2.0% of all primary liver tumors and less than 5% of all angiosarcomas[1]. Although PHA is an uncommon clinical entity, it constitutes the most common malignant mesenchymal tumor of the liver. The tumor is highly invasive; in most cases, diagnosis is made in the advanced stage, and patients usually die within a year of diagnosis[2-4]. In our study, we retrospectively reviewed 19 patients with PHA, 8 of whom underwent aggressive treatment (4 patients received tumor resection and 4 received liver transplants) and 11 underwent nonaggressive treatment (3 patients received chemotherapy, 3 received TACE, and 5 received no treatment). All patients had died within 538 days of diagnosis. In Western countries, PHA occurs most frequently in the sixth and seventh decades of age and more frequently in men (male-to-female ratio: between 3:1 and 4:1)[5, 6]. In Taiwan, Huang et al analyzed data from the National Cancer Registry Program from 1981 to 1999 and found the male-to-female ratio for PHA to be 1.9:1[7]. In our study, the male-to-female ratio for PHA was 3.75:1, and the corresponding mean age was 65.1 years. This male-to-female ratio is the same as that in Western countries and not the same as that previously reported in Taiwan. We observed that the male predominance was significantly higher in the aggressive treatment group than in the nonaggressive

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treatment group ($P = 0.0399$).

Clinical manifestations of PHA include abdominal symptoms, anorexia, fatigue, weight loss, fever, and low back pain[5]. Most patients in our study presented with abdominal pain (58.9%) and general malaise (41.1%). We observed no significant difference between the 2 groups in terms of clinical presentation.

The laboratory data in our study were nonspecific. We noted that 31.6% of the patients presented with hemoglobin levels of <10g/dL and that 21.1% of the patients presented with a platelet count of <80 000/μL. This anemia may have been due to PHA being a hypervascular tumor of the liver; moreover, the tumor bleeding may have been due to the consumption of platelets. A review by Zeng et al revealed that AFP and CEA levels were not elevated in 90.2% of patients with PHA, unlike in patients with other hepatic cell carcinoma or metastatic liver tumors[8]. In our study, 15.8% of the patients had elevated AFP and CEA levels. Our 2 treatment groups showed no significant difference in laboratory data or tumor markers.

In a previous study, more than 70% of patients with PHA had multifocal or bilobed lesions of the liver, and most of them had metastatic lesions at the time of presentation or during follow-up, such as lung or splenic metastasis[9]. In our study, 42.1% of patients had unifocal lesions, and 68.4% had unilobed lesions. The number of patients with lung, bone, spleen, peritoneum, kidney, colon, and small intestine

metastases were 6 (31.6%), 4 (21.1%), 1 (5.3%), 1 (5.3%), 1 (5.3%), 1 (5.3%), and 1 (5.3%), respectively. PHA usually presents with a large tumor size. In our study, the average tumor sizes in the aggressive and nonaggressive treatment groups were 8.38 and 9.75 cm, respectively. The 2 treatment groups showed no significant difference in tumor number, size, or metastasis. Spontaneous hepatic tumor rupture is not uncommon and is associated with high mortality and morbidity rates[5]. Li et al performed a pooled analysis of previous PHA data and revealed a trend toward shorter overall survival (OS) for those with rupture compared with those without (median OS 9 vs 17 mo) [10]. Our study indicated 2 patients (25%) with PHA rupture in the aggressive treatment group and 6 patients (54.6%) with rupture in the nonaggressive treatment group. Although we noted a trend toward poorer prognosis in the nonaggressive treatment group, we observed no significant difference between the 2 treatment groups.

Because of the low incidence and lack of specific clinical manifestations and tumor markers of PHA, most patients with PHA are initially misdiagnosed mainly as having hepatocellular carcinoma, metastatic carcinoma of the liver, hepatic hemangioma, or cholangiocarcinoma[9, 11, 12]. Imaging, including abdominal CT and magnetic resonance imaging, remains essential for an initial diagnosis of PHA. Various appearances of hepatic angiosarcoma on abdominal CT scans have been described in case reports and case series[11, 12]. Few reports on the appearance of hepatic

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angiosarcoma have revealed predominant hypoattenuation compared with the surrounding hepatic parenchyma in unenhanced CT scans; most lesions are hypoattenuated compared with normal liver tissue, but some lesions can be hyperattenuated after images are contrast enhanced[9]. White et al reported progressive centripetal enhancement after contrast enhancement, similar to cavernous hemangioma; recent reports have demonstrated that angiosarcoma does not resemble benign cavernous hemangioma on a dynamic CT scan[13]. All patients in our study had undergone an abdominal CT scan but not magnetic resonance imaging. Even with an abdominal CT scan combined with laboratory data and a review of clinical manifestations and tumor markers, we noted that only 26.3% of the patients in our study had a definite diagnosis of PHA before histologic proof. PHA was initially misdiagnosed as hepatocellular carcinoma, metastatic carcinoma of the liver, hepatic hemangioma, and cholangiocarcinoma in 36.8%, 26.3%, 5.3%, and 5.3% of the patients, respectively. The 2 treatment groups did not differ significantly in terms of misdiagnosis rate.

Due to the rarity and poor prognosis of PHA, few studies have been conducted regarding the best treatment approach for this disease; moreover, no standard treatment exists for this disease. Current treatment approaches are based on case reports, small case series, and pooled analyses[10, 14]. A retrospective study of the Surveillance,

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Epidemiology, and End Results database included 300 patients with PHA and revealed that older age, the male sex, and advanced stage at diagnosis were associated with poor prognosis; resection and chemotherapy significantly prolonged cancer-specific survival[15]. Tripke et al retrospectively reviewed 9 patients who received complete surgical resection and reported that the median overall survival and disease-free survival after resection were 18 and 10 months, respectively; they concluded that complete radical surgical resection seems to be the only curative treatment option for PHA that offers patients a chance of long-term survival[16]. Orlando et al retrospectively examined the European Liver Transplant Registry experience and concluded that a liver transplant was an absolute contraindication for PHA, with a median OS of 6 months[17]. Another pooled analysis conducted by Zeng et al suggested that a liver transplant was less effective than liver resection alone, with the median OS for a liver transplant and liver resection alone being 5.8 and 10 months, respectively[14]. In our aggressive treatment group, 4 patients received liver transplants under 3 misdiagnoses of hepatocellular carcinoma and 1 diagnosis of PHA in which the family insisted on a liver transplant. The other 4 patients received resection under 2 misdiagnoses of hepatocellular carcinoma, 1 misdiagnosis of metastasis, and 1 misdiagnosis of cholangiocarcinoma. The mean survival time in this group was 233.1 ± 189.7 days.

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No evidence exists regarding the efficacy of chemotherapy for PHA, and no consensus has been reached on a standard chemotherapy regimen for PHA. Several small case series have suggested a survival benefit for patients who receive chemotherapy. Cytotoxic drugs used in such series included 5-fluorouracil, cisplatin, doxorubicin, methotrexate, and adriamycin[18, 19]. Zeng's systematic review of the literature revealed that few patients received chemotherapy alone and that the corresponding prognosis was as long as 12 months. Their review indicated that patients who underwent surgical resection combined with chemotherapy had a longer prognosis than did patients who underwent resection alone, but they observed no significant difference between the 2 groups[14]. Huang et al reported that 2 patients survived for more than 2 years after resection and chemotherapy. Chemotherapy may be considered as a treatment option in cases of unresectable or advanced metastatic disease[7].

Few studies have addressed the effectiveness of TACE in PHA treatment. Although TACE is effective in the management of acute PHA rupture bleeding, it is usually reserved for palliative treatment[20]. In our study, 3 patients received TACE, all of whom had PHA rupture bleeding.

Most patients with poor functional status or advanced-stage PHA undergo conservative treatment alone and face a rapidly fatal outcome[10]. In our study, 3 patients received conservative treatment. One was initially misdiagnosed as having

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benign hepatic hemangioma. The tumor exhibited enlargement during follow-up at 13 months, and a definite diagnosis of PHA was made through histology. She received no treatment due to poor body performance and the prognosis of PHA. The PHA tumor ruptured 5 months later. She lived for 18 months after the detection of the liver tumor and 5 months after the diagnosis of PHA. The entire natural course of PHA from initial diagnosis to rupture was well presented in this case[21].

In our study, the prognosis of patients who underwent aggressive treatment seemed more favorable than that of patients who underwent nonaggressive treatment. However, we observed no significant difference between the 2 treatment groups in terms of survival time, and none of the patients lived longer than 538 days after PHA diagnosis.

This study has several limitations. First, it involved a retrospective design, and selection bias played a role in the treatment approach. For example, patients who could tolerate aggressive treatment such as resection and liver transplants were generally more likely to have a favorable functional status. Second, due to the small number of patients, the statistical power may not be sufficient. More cases are required to confirm our analysis results.

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Conclusions

Our study revealed that the survival time in patients receiving aggressive treatment was longer than that in those receiving nonaggressive treatment, but the difference was not significant. But there may be long term survival time in some selective cases of aggressive treatment. Because the number of patients was limited, more cases are required to validate these results.

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Ethical Approval: The study was approved by the Ethics Committee of China Medical University Hospital, Taichung, Taiwan (approval no: CMUH110-REC3-098). All participants gave written informed consent.

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	Aggressive treatment group (n=8)	**Non-aggressive treatment group (n=11)**	**P-value**
Age	63.6 (36-82)	66.2 (51-75)	$P = 0.521$
Sex (M:F)	8:0	7:4	$P = 0.0399$
Abdominal pain	4 (50%)	7 (63.6%)	$P = 0.5629$
General malaise	4 (50%)	4 (36.4%)	$P = 0.5629$

Table 1. Demographics of basic data and the symptoms and signs of patients

P-values were calculated by chi-square test and Fisher's exact test.

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Table 2. Demographics of tumor behaviors of patients

Tumor behaviors	**Aggressive treatment group (n=8)**	**Non-aggressive treatment group (n=11)**	**P-value**
Bilobe: unilobe	4: 4	9: 2	*P* = 0.5629
Number (1:2:3: multiple)	4: 1: 0: 3	4: 0: 1: 6	*P* = 0.1893
Chronic viral marker	0/8	0/11	*P* = 0.3458
Size (cm)	8.38 (1.2 -15)	9.75 (3.6-17)	*P* = 0.6310
Ascites	6/8	4/11	*P* = 0.1050
CEA >5	1/8	1/11	*P* = 0.8160
AFP	1/8	0/11	*P* = 0.2410
Abnormal liver function	5/8	7/11	*P* = 0.9606
Platelet < 80,000/μL	2/8	2/11	*P* = 0.7261
Hemoglobin< 10 g/dL	3/8	3/11	*P* = 0.6449
Rupture	2/8	6/11	*P* = 0.2100

CEA: Carcinoembryonic antigen, AFP: Alpha-fetoprotein

P-values were calculated by chi-square test and Fisher's exact test.

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Table 3. Demographics of metastasis of patients.

metastases	**Aggressive treatment group (n=8)**	**Non-aggressive treatment group (n=11)**	**P-value**
Lung	2	4	$P = 0.6086$
Bone	2	2	$P = 0.7261$
Spleen	0	1	$P = 0.3938$
Peritoneum	0	1	$P = 0.3938$
Kidney	0	1	$P = 0.3938$
Colon	1	0	$P = 0.2410$
Small intestine	1	0	$P = 0.2410$

P-values were calculated by chi-square test and Fisher's exact test.

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Table 4. Demographics of CT finding of patients.

CT findings	Aggressive treatment group (n=8)	Non-aggressive treatment group (n=11)	P-value
Angiosarcoma	1	4	*P* = .2563
metastasis	1	4	*P* = .2563
Hepatocellular carcinoma	5	2	*P* = .0543
Cholangiocarcinoma	1	0	*P* = .2410
Hemangioma	0	1	*P* = .3938

P-values were calculated by independent samples t test, Fisher's exact test, and chi-square test.

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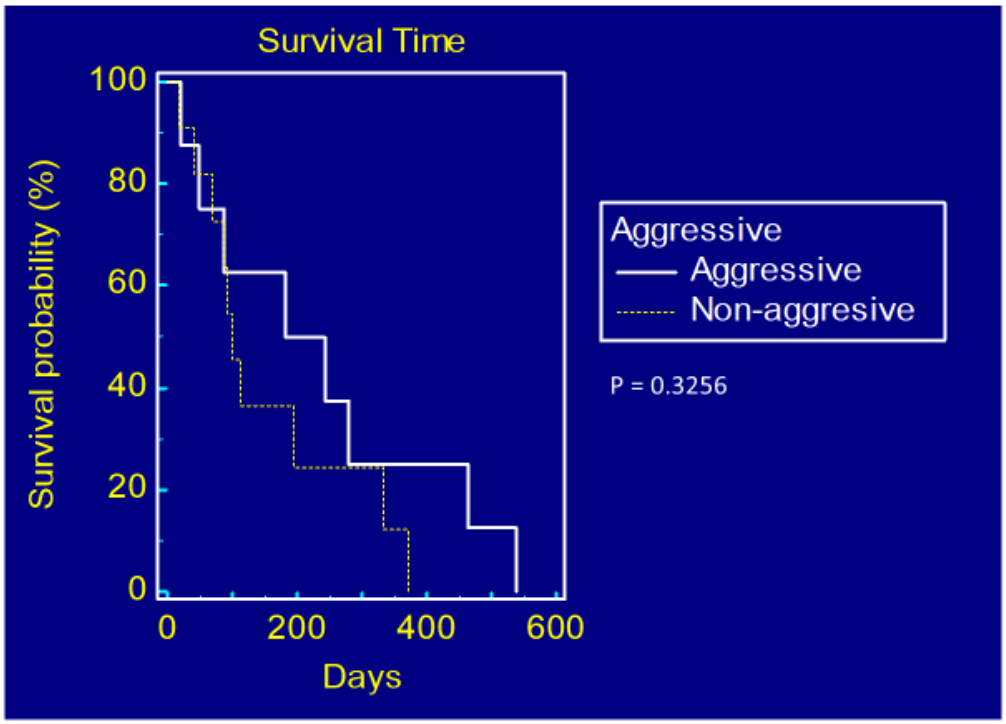

Figure 1. The survival probability of patients in aggressive and non-aggressive therapy (P= 0.3256).