

Post-resection prognosis of patients with hepatic epithelioid hemangioendothelioma

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Purpose: Epithelioid hemangioendothelioma (EHE) is a rare borderline vascular tumor. This retrospective, single-center study evaluated the outcomes of hepatic resection (HR) in patients with hepatic EHE.

Methods: Over the 10-year period from 2009 to 2018, 11 patients with hepatic EHE underwent HR, accounting for 0.1% of the 11,979 adults who underwent HR at our center. Diagnosis of hepatic EHE was confirmed by immunohistochemical staining for CD34, CD31, and factor VIII-related antigen.

Results: The 11 patients included 9 females (81.8%) and 2 males (18.2%) with mean age of 43.5 ± 13.6 years. Preoperative imaging resulted in a preliminary diagnosis of suspected liver metastasis or EHE, with 9 patients (81.8%) undergoing liver biopsy. No patient presented with abnormally elevated concentrations of liver tumor markers. The extents of HR were determined by tumor size and location from trisectionectomy to partial hepatectomy. All patients recovered uneventfully from HR. Five patients showed tumor recurrence, with 4 receiving locoregional treatments for recurrent lesions. The 1-, 3- and 5-year disease-free survival rates were 90.9%, 54.5%, and 54.5%, respectively. Currently, all patients remain alive and are doing well. Univariate analysis on tumor recurrence showed that tumor size ≥ 4 cm was significantly associated with tumor recurrence ($P = 0.032$), but tumor number ≥ 4 was not related to ($P = 0.24$).

Conclusion: Hepatic EHE is a rare form of primary liver tumor often misdiagnosed as a metastatic tumor. Because of its malignant potential, HR is indicated if possible. HR plus, when necessary, treatment of recurrence yields favorable overall survival rates in patients with hepatic EHE.

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Key Words: CD31 antigen, CD34 antigen, Hemangioendothelioma, Hemangioma, Vascular tissue neoplasms

INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor, consisting of cords of epithelioid cells on a background of myxohyaline stroma. The 2002 World Health Organization (WHO) classification described EHEs as lesions with metastatic potential [1,2]. EHEs can be observed in any site in the human body, with the most common sites being the liver (21%), liver and lungs (18%), lungs (12%), and bones (14%) [3]. These rare

borderline vascular tumors have an aggressiveness graded between hemangioma and hepatic hemangiosarcoma [4]. Because many patients with hepatic EHE are asymptomatic, are detected incidentally [5-8]. Due to their rarity and protean behavior, the optimal treatment of hepatic EHEs has not yet been standardized [5]. Partial hepatectomy is used to treat patients with unilobar hepatic EHE, although aggressive tumor recurrence has been reported in the literature [9,10]. To date, only a few patients from Korea have undergone hepatic

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resection (HR) for hepatic EHE [11,12]. The present study investigated the outcomes of HR in patients with hepatic EHE at our center over a 10-year period.

METHODS

Patient selection

The primary liver cancer database at our institution was extensively searched to identify patients diagnosed with hepatic EHE following HR. Of the 11,976 patients who underwent HR for various indications during the 10-year period from January 2009 to December 2018 [13], 11 (0.1%) underwent HR for hepatic EHE. The medical records of these patients were retrospectively reviewed. The study protocol was approved by the Institutional Review Board at Asan Medical Center (No. 2019-1347), which waived the requirement for informed consent due to the retrospective nature of this study. This study was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki 2013. The patients were followed up until July 2020 by medical record review and with the assistance of the National Health Insurance Service.

Preoperative evaluation, surgical procedures, and postoperative follow-up

Routine preoperative evaluation for primary liver tumors has been described [14]. In general, patients who underwent HR for borderline malignancy were followed up every 3–4 months during the first year after surgery and every 4–8 months thereafter. Patients with recurrent liver tumors were treated as described [14-17].

Pathological evaluation

Formalin-fixed paraffin-embedded tissue samples were immunohistochemically stained with antibodies to CD34 (1:500, QBEND10, Immunotec Inc., Monrovia, CA, USA), CD31 (1:800, JC70, Cell Marque, Rocklin, CA, USA), and coagulator factor VIII-related antigen (FVIII:Ag) (1:2,000, DAKO, Glostrup, Denmark) using a Benchmark autostainer (Ventana Medical System, Tuscon, AZ, USA). Histological features and immunohistochemical profiles for diagnosis of hepatic EHE were based on the 2010 WHO classification of liver tumors [18].

Statistical analysis

Numerical data are presented as means and standard deviations. Continuous variables were compared by 1-way analysis of variance. Survival was estimated using the Kaplan-Meier method. A P-value < 0.05 was regarded as statistically significant. All statistical analyses were performed using IBM SPSS Statistics ver. 22 (IBM Corp., Armonk, NY, USA).

Table 1. Clinical profiles of patients who underwent hepatectomy for hepatic EHE

Patient No.	Age (yr)	Sex	Clinical presentation	HBV infection	Preoperative diagnosis	Preoperative imaging	Preoperative biopsy	Operation	Tumor recurrence	DFS (mo)	Recurrence treatment	Survival status	Follow-up (mo)
1	59	F	Follow-up after gastric cancer operation	No	R/O liver metastasis	metastasis	EHE-confirmed	RAS	No	127	No	Alive	127
2	22	M	RHS	No	EHE or metastasis	metastasis	ND	PH	No	126	No	Alive	126
3	62	F	RHS	No	ICC, HCC or EHE	EHE-confirmed	EHE-confirmed	RL	No	111	No	Alive	111
4	42	F	RHS	Yes	EHE or metastasis	metastasis	EHE-confirmed	RPS	No	106	No	Alive	106
5	58	F	RHS	No	R/O liver metastasis	metastasis	EHE-confirmed	RL	Yes	24	RFA, PH	Alive	93
6	53	F	RHS	No	R/O liver metastasis	metastasis	ND	RL	No	84	No	Alive	84
7	39	M	RHS	No	EHE or metastasis	metastasis	EHE-confirmed	CBS + PH	Yes	18	TACE	Alive	82
8	26	F	RHS	No	EHE or metastasis	metastasis	EHE-confirmed	RTS + PH	Yes	6	RFA, lung Mx, PH	Alive	58
9	34	F	RHS	Yes	EHE or metastasis	metastasis	EHE-confirmed	RL + Nx	No	56	No	Alive	56
10	48	F	RHS	No	R/O liver metastasis	metastasis	EHE-confirmed	RL	Yes	18	Observation	Alive	50
11	35	F	Flank pain	No	EHE or metastasis	metastasis	EHE-confirmed	RL + PH	Yes	30	RFA	Alive	32

EHE, epithelioid hemangioendothelioma; DFS, disease-free survival; F, female; M, male; R/O, rule out; RAS, right anterior sectionectomy; RHS, routine health screening; ND, not done; PH, partial hepatectomy; ICC, intrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; RL, right hepatectomy; RPS, right posterior sectionectomy; RFA, radiofrequency ablation; CBS, central bisectionectomy; TACE, transarterial chemoembolization; RTS, right trisectionectomy; Nx, nephrectomy; Mx, metastasectomy.

RESULTS

Patient demographics and preoperative diagnosis

The clinicopathological features of the 11 patients with hepatic EHE are described in Table 1. The 11 patients included 9 females (81.8%) and 2 males (18.2%) with mean age of 43.5 ± 13.6 years. Two patients (18.2%) were positive for hepatitis B virus infection, but none was positive for hepatitis C virus infection or alcoholic liver disease. Only 1 patient reported vague right flank pain, whereas the other 10 patients were asymptomatic at the time of diagnosis. Liver lesions were detected incidentally during routine health screening in 9 patients, during postoperative cancer screening in 1, and during general examination for abdominal pain in 1.

Based on imaging modalities, these patients were preoperatively diagnosed with suspected liver metastasis or EHE (Fig. 1). Nine (81.8%) underwent preoperative liver biopsy, with all 9 diagnosed with hepatic EHE (Fig. 2). One patient was followed up for 5 years after initial liver biopsy and finally

underwent HR due to slowly progressive tumor growth.

The mean preoperative serum concentrations of α -FP (2.8 ± 1.6 ng/mL; reference, 7.5 ng/mL), des- γ -carboxy prothrombin (19.8 ± 11.0 mAU/mL; reference, 40 mAU/mL), and for CA 19-9 (11.4 ± 7.1 ng/mL; reference, 37 ng/mL) were within normal ranges. None of these patients presented with abnormal elevation of these tumor markers.

Outcomes after hepatic resection

Preoperative indocyanine green retention tests at 15 minutes yielded a mean of $10.6\% \pm 2.5\%$ in the 11 patients. One patient underwent preoperative portal vein embolization for right hepatectomy.

The extent of HR was based on the tumor location and size. Six patients underwent right hepatectomy, with 1 each undergoing right anterior sectionectomy, right posterior sectionectomy, central bisectionectomy plus partial hepatectomy, right trisectionectomy plus partial hepatectomy, and partial hepatectomy (Fig. 1). One of the patients who

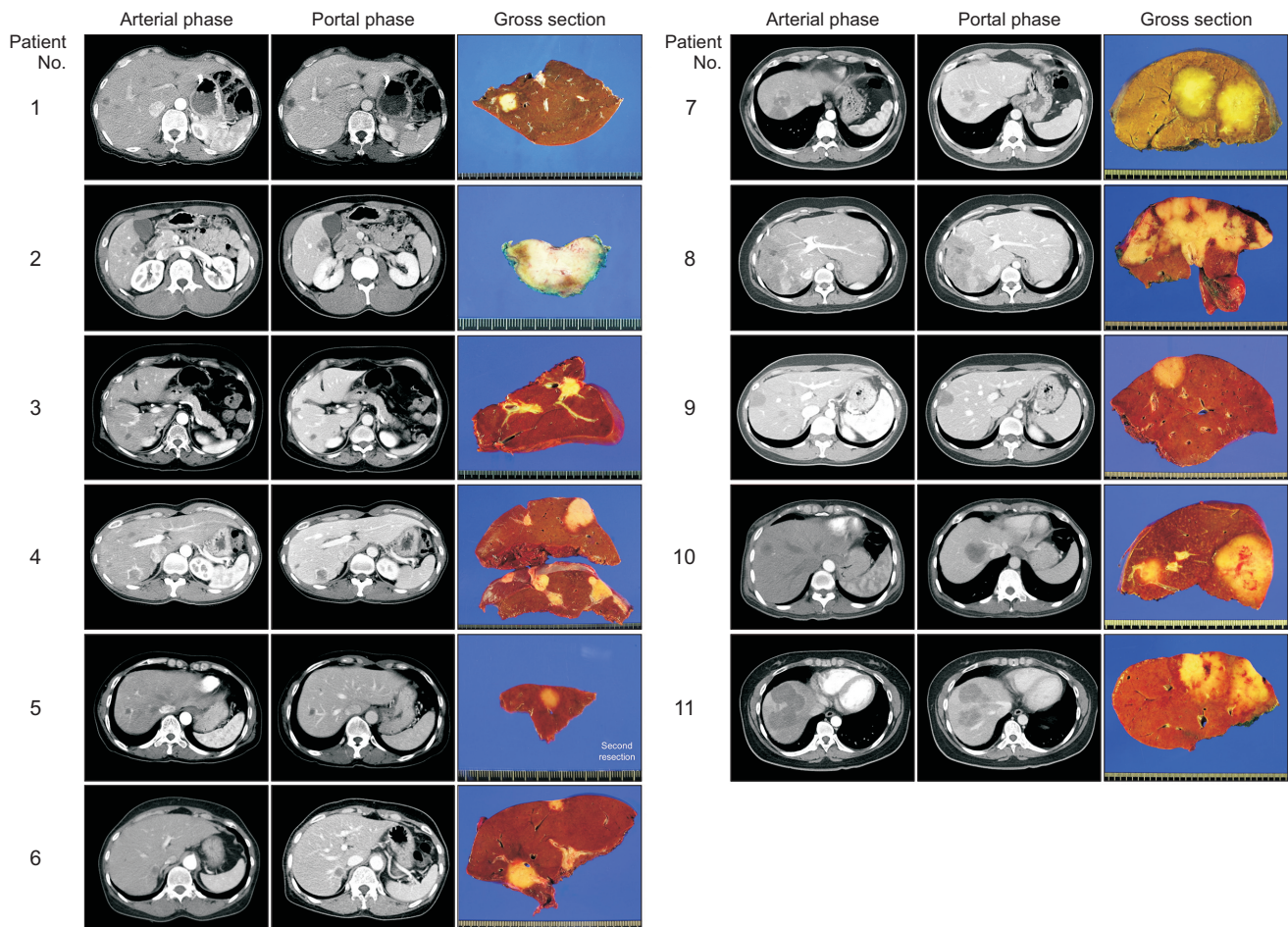


Fig. 1. Preoperative computed tomography findings and gross photographs of the surgical specimens obtained after initial hepatectomy. Numbers denote the patient number. The specimen from patient 5 was obtained during the second hepatectomy for recurrent tumor.

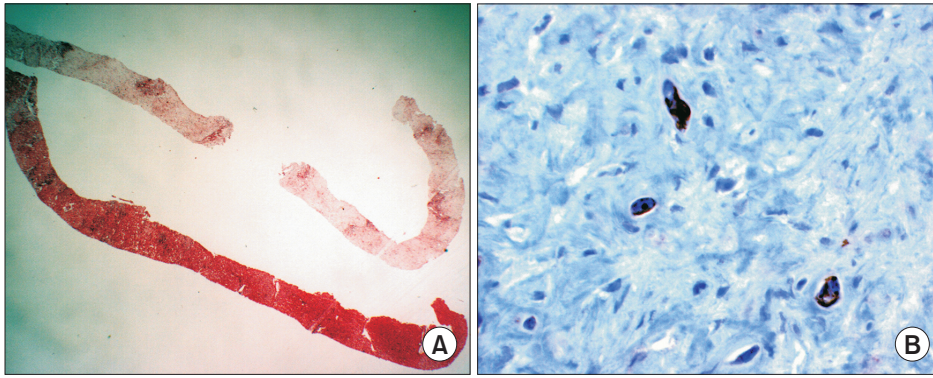


Fig. 2. Microscopic findings of percutaneous needle liver biopsy taken from patient 4. (A) Needle liver biopsy specimen is visible (no stain, $\times 10$). (B) Tumor cells show immunopositivity for CD34 ($\times 400$).

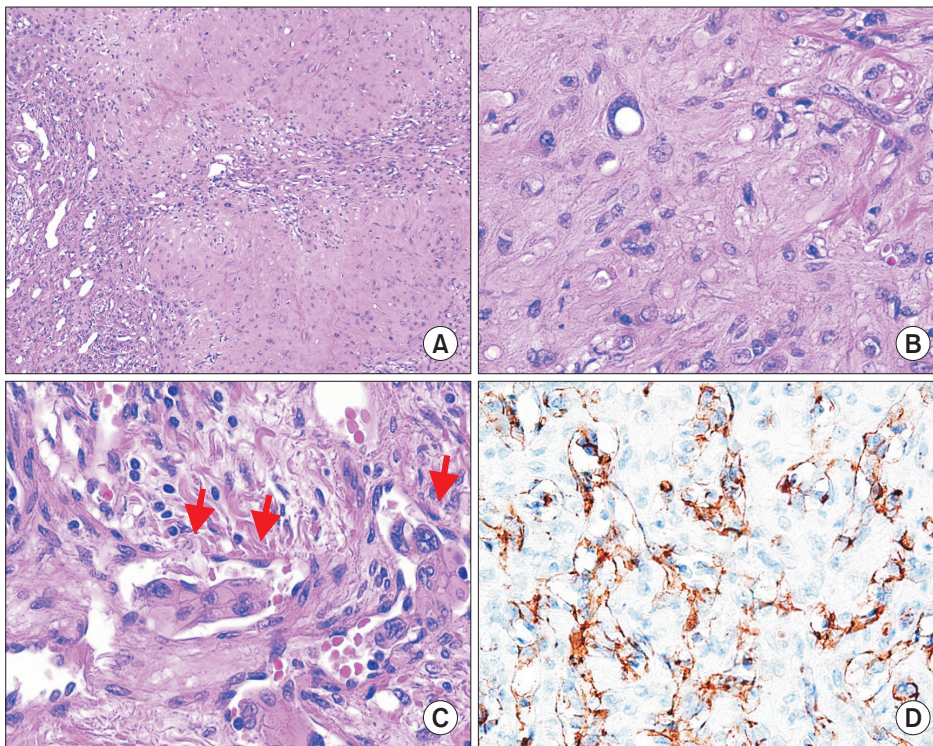


Fig. 3. Microscopic findings of hepatic epithelioid heman-gioendothelioma obtained from patient 5, showing (A) few cellular epithelioid or spindle tumor cells on a background of fibromyxoid stroma (H&E staining, $\times 100$), (B) epithelioid tumor cells containing vacuolated cytoplasm (H&E staining, $\times 400$), (C) thin-walled vessels containing clusters of epithelioid tumor cells (arrows; H&E staining, $\times 400$), and (D) tumor cells diffusely positive for CD31 ($\times 400$).

underwent right hepatectomy also underwent concurrent right nephrectomy due to renal cell cancer.

The tumors showed an infiltrating growth pattern into the surrounding liver parenchyma. Low-power magnification showed small numbers of cellular epithelioid or spindle tumor cells within the fibromyxoid stroma. The epithelioid tumor cells contained vacuolated cytoplasm, mimicking signet ring cells. Thin-walled venules contained tufted or micropapillary clusters of epithelioid tumor cells in peritumoral areas. Immunostaining showed that the tumor cells were diffusely positive for CD31, CD34, and FVIII:Ag (Fig. 3, Table 2), resulting in a final diagnosis of hepatic EHE.

All patients recovered uneventfully from HR without any major complications. During a mean follow-up period of 84.1

± 32.0 months, 5 patients showed tumor recurrence. The 1-, 3-, 5-, and 10-year disease-free survival rates were 90.9%, 54.5%, 54.5%, and 54.5%, respectively (Fig. 4). The 4 patients with tumor recurrence underwent various treatments, including radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and surgical resection of the liver and lung lesions. One patient with tumor recurrence showed no progression of the tumor and has therefore been closely followed up for 2 years. Currently, all 11 patients are alive and doing well.

Univariate analysis assessing factors associated with tumor recurrence showed that tumor size ≥ 4 cm was significantly associated with tumor recurrence ($P = 0.032$), but tumor number ≥ 4 was not related to tumor recurrence ($P = 0.24$) (Fig. 5).

Table 2. Serological and pathological profiles of patients who underwent hepatectomy for hepatic epithelioid hemangioendothelioma

Patient No.	ICG-R15 (%)	α-FP (ng/mL)	DCP (mAU/mL)	CA 19-9 (ng/mL)	Tumor size (cm)	No. of tumor	LN metastasis	Macrovascular invasion	Tumor location	CD31 stain	CD34 stain	Factor VIII-related antigen stain
1	14.4	2	1.8	9.2	1.5	1	No	No	S7	Positive	Positive	ND
2	9.8	2.3	ND	10.2	3.4	1	No	No	S5	Positive	Positive	ND
3	7.9	7.2	ND	8.7	2.7	5	No	No	S6, 8, 4	Positive	Positive	Positive
4	13.8	2.5	ND	19.3	4	3	No	No	S5-8	Positive	Positive	ND
5	9.8	2.7	ND	25.4	2	2	No	No	S7, 8	Positive	ND	Positive
6	11.4	2.1	ND	14.4	2	3	No	No	S6, 7	Positive	ND	ND
7	9.5	1.7	20.0	5.9	4	4	No	No	S4-8	Positive	Positive	ND
8	13.1	3.1	36.0	4.9	11.5	6	No	No	S5-8, S2	Positive	Positive	ND
9	6.1	1.3	19.0	9.2	2.9	4	No	No	S5-8	ND	Positive	ND
10	10.1	2	24.0	17.5	4.4	4	No	No	S8, 7	Positive	Positive	ND
11	10.5	3.3	18.0	0.7	9	3	No	No	S5, 8, 2	Positive	Positive	ND

ICG-R15, indocyanine green retention test at 15 minutes; DCP, des-γ-carboxy prothrombin; LN, lymph node; ND, not done.

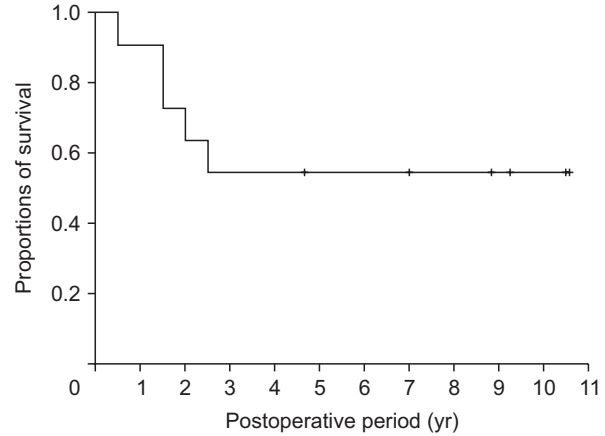


Fig. 4. Kaplan-Meier analysis of disease-free patient survival.

DISCUSSION

Hepatic EHE is a rare borderline vascular tumor, with an aggressiveness graded between that of hemangioma and hepatic hemangiosarcoma [3]. Many hepatic EHEs are detected incidentally because of absence of specific symptoms. Imaging findings of hypovascularity and multiplicity suggest the need for liver biopsy because hepatic EHEs are often confused with liver metastases. Therefore, most of the patients in the present study underwent percutaneous liver biopsy and were diagnosed with hepatic EHE based on histological characteristics and immunohistochemical profiles [18].

Treatments for hepatic EHE can include HR, liver transplantation (LT), chemotherapy, radiotherapy, hormone therapy, RFA, and surveillance alone. Five-year patient survival rates have been reported to be 75% in 22 patients who underwent HR, 20% in 60 patients treated with chemotherapy/radiotherapy, and 4.5% in 70 patients who underwent surveillance alone [6]. A study of 11 patients who underwent HR and 11 LT recipients reported 5-year patient survival rates of 86% and 73%, respectively [19], whereas a study with 17 patients who underwent HR and 12 patients who underwent TACE reported 3-year patient survival rates of 74.1% and 81.6%, respectively [7]. Two patients with diffuse lesions who received LT and 1 who underwent RFA were alive without recurrence, whereas all 3 patients who underwent HR showed recurrence [20]. In addition, 6 patients opted for observation without treatment.

Although these studies showing similar outcomes following HR, LT, and nonsurgical locoregional treatments, the indications for each treatment modality differed. HR is indicated for resectable intrahepatic lesions, whereas LT and TACE can be considered if the lesions are unresectable. Extrahepatic involvement, such as lymph node metastasis and metastases to other organs, is a contraindication for surgical treatment.

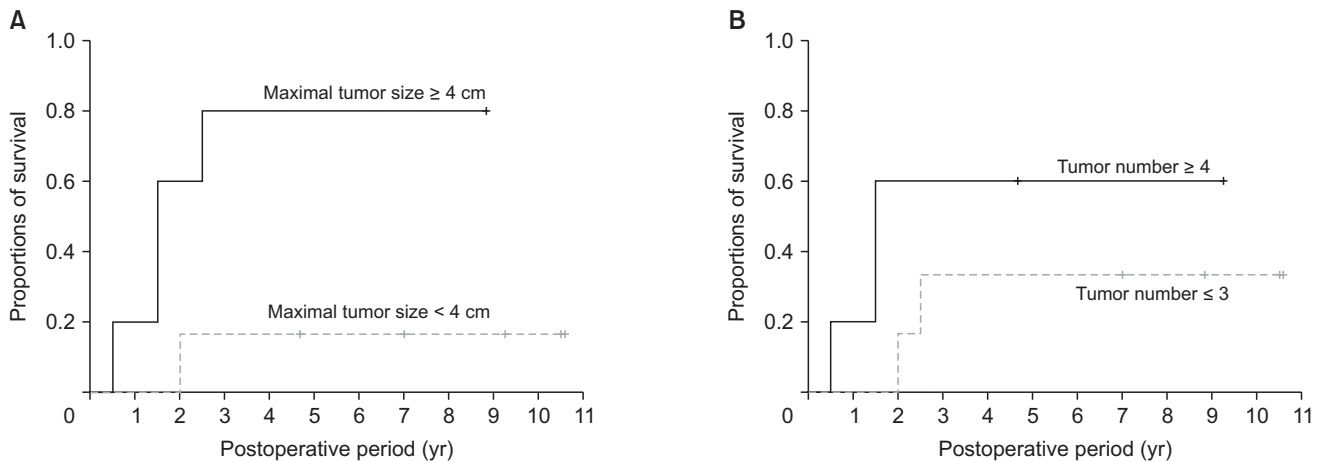


Fig. 5. Kaplan-Meier analysis of tumor recurrence according to the tumor size cutoff of 4 cm (A) and tumor number of 4 (B).

Few studies to date have evaluated outcomes of nonsurgical therapies, including systemic/regional chemotherapy, radiotherapy, hormone therapy, and immunotherapy, in patients with hepatic EHE [21-23].

Factors prognostic of outcomes after hepatic EHE remain generally undetermined to date. Extrahepatic spread of disease beyond the portal lymph node metastasis was reported to be associated with worse outcomes [23]. Patients with multiple nodules have a worse prognosis than those with single nodules. In contrast, prognosis is not mainly affected by the presence of extrahepatic metastases *per se* [19]. Worsened overall survival has been observed in patients with hepatic EHEs of >10 cm in diameter and in older patients. The average 1-year and 5-year overall survival rates following various treatment modalities have been reported to range from 88% to 100% and from 23% to 83%, respectively, depending on the biological behavior of the tumor [24]. Because only a few small case series have evaluated the prognostic factors, extrahepatic metastasis remains the only predictor of patient prognosis. The present study found that tumor size ≥ 4 cm was associated with higher tumor recurrence, but tumor number ≥ 4 was not related to tumor recurrence.

This study had several limitations, including its retrospective design and inclusion of a small number of patients treated at a single center. Multicenter studies are needed to evaluate the characteristics of hepatic EHE and to determine the factors predictive of patient prognosis.

In conclusion, hepatic EHE is a rare form of the primary liver tumor and is often misdiagnosed as a metastatic tumor. Because this disease carries malignant potential, HR is indicated if possible. HR plus, when necessary, treatment of recurrence yields favorable overall survival rates in patients with hepatic EHE.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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