

Original Article

Undifferentiated embryonal sarcoma of liver: a multi-institutional experience with 9 cases

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Abstract: To summarize the clinicopathological features, therapeutic regimens and outcomes for the patients with undifferentiated embryonal sarcoma of the liver (UESL), 9 cases of UESL were retrospectively reviewed. Complete clinical history, lab studies, imaging examinations and pathological findings were collected for analysis. Overall survival and progression free survival were assessed by Kaplan-Meier Survival Analysis. The patients were 6 to 37 years old, and included 6 males and 3 females. The tumor size ranged from 5 to 26 cm. Pathologically, the tumors consisted of proliferations of medium sized spindle, oval or stellate shaped pleomorphic cells loosely or compactly arranged in an edematous or myxoid matrix, with scattered bizarre multinucleated giant cells. All of the 9 cases were treated with radical resections, 6 of 9 cases received chemotherapy for postoperative treatment. All follow-up data were available, 4 of 9 cases had recurrence, and 2 patients were died. Time to recurrence in these cases was 19, 4, 29, 14 months. The mean overall survival (OS) was 58.25 ± 9.1 months and the mean progression-free survival (PFS) was 39.55 ± 11.6 months. UESL is a potential treatable malignance when treated with combined multiagent chemotherapy after resection.

Keywords: Liver, undifferentiated embryonal sarcoma, hepatectomy, prognosis

Introduction

Undifferentiated (embryonal) sarcoma of the liver (UESL), first documented in 1978, is a rare and highly malignant hepatic neoplasm of mesenchymal origin and shows a divergent differentiation. It occurs predominantly in children, with a peak incidence in the age range of 6-10 years [1, 2]. The diagnosis of UESL may be difficult because it may show overlap features with several other tumors. The standard treatment for UESL has not been defined, likely due to the rarity of the disease and a paucity of prospective clinical trials. Moreover, the usual postoperative course of UES is relatively unknown. Therefore, collecting more clinicopathologic and therapeutic data and summarizing the previously reported cases are important.

In this retrospective multi-institutional study, we present our experience in diagnosis, treat-

ment and outcome of 9 cases of UESL and reviewed the literature with the aim of expanding our understanding of this rare and deadly malignancy.

Patients and methods

Patients

From Jan, 2005 to Dec, 2013, 9 cases of UESL were retrieved from the pathology files of The First Affiliated Hospital of Sun Yat-Sen University and Nanfang Hospital of Southern Medical University, Guangzhou, China. Data including clinical and histological features, management methods, and outcomes of the patients were obtained from patient medical records. The patients gave informed consent for the use of their medical records for research, and approval for the retrospective review was obtained from the Ethics Committee of The First Affiliated Hospital of Sun Yat-Sen University and Nanfang Hospital of Southern Medical University.

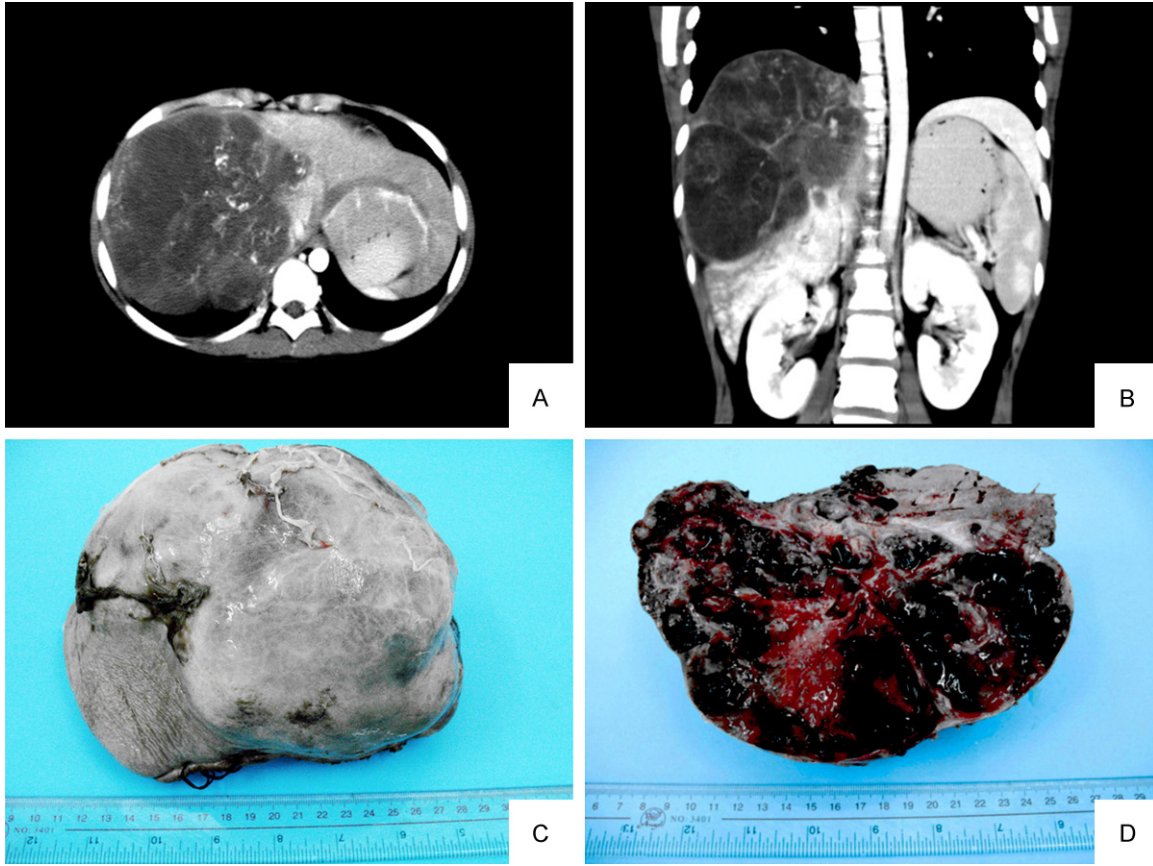


Figure 1. A, B. CT scan showed a hypodense mass with a multicystic appearance in the right lobe liver. Peripheral rim of the mass was enhanced but not the hypodense area in enhanced scan (Case No. 8). C. The tumor was globular and well demarcated with complete encapsulation (Case No. 9). D. The cut-surface is grey-white, with prominent haemorrhagic and necrotic areas.

Clinical and pathological evaluation

The information of clinical presentation, imaging studies and lab examination were collected from the medical records. Haematoxylin and eosin (HE) slides and all special stains were reviewed and all pathologic diagnoses were made according to the WHO classification of tumors of the digestive system (2010) [3]. Immunohistochemistry was performed on representative blocks using a panel of antibodies and the EnVision + system. Appropriate positive and negative controls were used throughout the experiment. Staining was considered positive when > 5% of cells showed staining with the appropriate pattern.

Outcome evaluation

The overall survival (OS) duration was calculated from the time of diagnosis to the time of death or the last follow-up. Progression-free

survival (PFS) was measured from the time of diagnosis to the time of treatment failure, recurrence, or death from UESL.

Statistical analysis

Survival analysis was performed with the Kaplan-Meier method. Statistical analyses were performed using the SPSS Statistics 19.0 software package (SPSS Inc., Chicago, IL, USA).

Results

Clinical findings

The patients, including 6 males and 3 females, aged from 6-37 years (mean age is 15.3 years). They all were primary lesions. Lesions involved the right lobe in 4 cases, right and caudal lobe in 1 case and the left lobe in 4 cases. The main presenting complains were abdominal pain and mass. Fever and anorexia also presented in Case No. 9.

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Table 1. Clinical features of 9 cases

Case	Gender/Age	Chief Complain	Location	BUS	CT/MRI	Imaging diagnosis
1	Male/37	Upper abdominal Pain	Left	Hyper-echoic	Hypodense	Hepatocellular carcinoma?
2	Male/13	Right upper abdominal pain suddenly	Right	Hetero-echoic	Hypodense	Mesenchymal Tumor
3	Male/7	Upper abdominal mass	Left	Hetero-echoic	N/A	Teratoma or Echinococcosis
4	Female/24	Upper abdominal Pain	Right	Hetero-echoic	N/A	Angiosarcoma?
5	Male/14	Upper abdominal Pain	Left	N/A	Hypodense	Hepatocellular carcinoma?
6	Female/14	Right upper abdominal pain	Right	Hetero-echoic	Hypodense	Malignant fibrous histiocytoma
7	Male/6	Upper abdominal mass	Right and caudal lobe	Hetero-echoic	Hypodense	Malignant mesenchymal tumor
8	Female/9	Upper abdominal mass	Left	Hetero-echoic	Hypodense	Malignant mesenchymal tumor
9	Male/14	Right upper abdominal pain, fever, anorexia	Right	Hetero-echoic	Hypodense	Angiosarcoma

BUS, B Ultrasonography Scan; CT, Computerized tomography; MRI, Magnetic resonance imaging; N/A, Not Available.

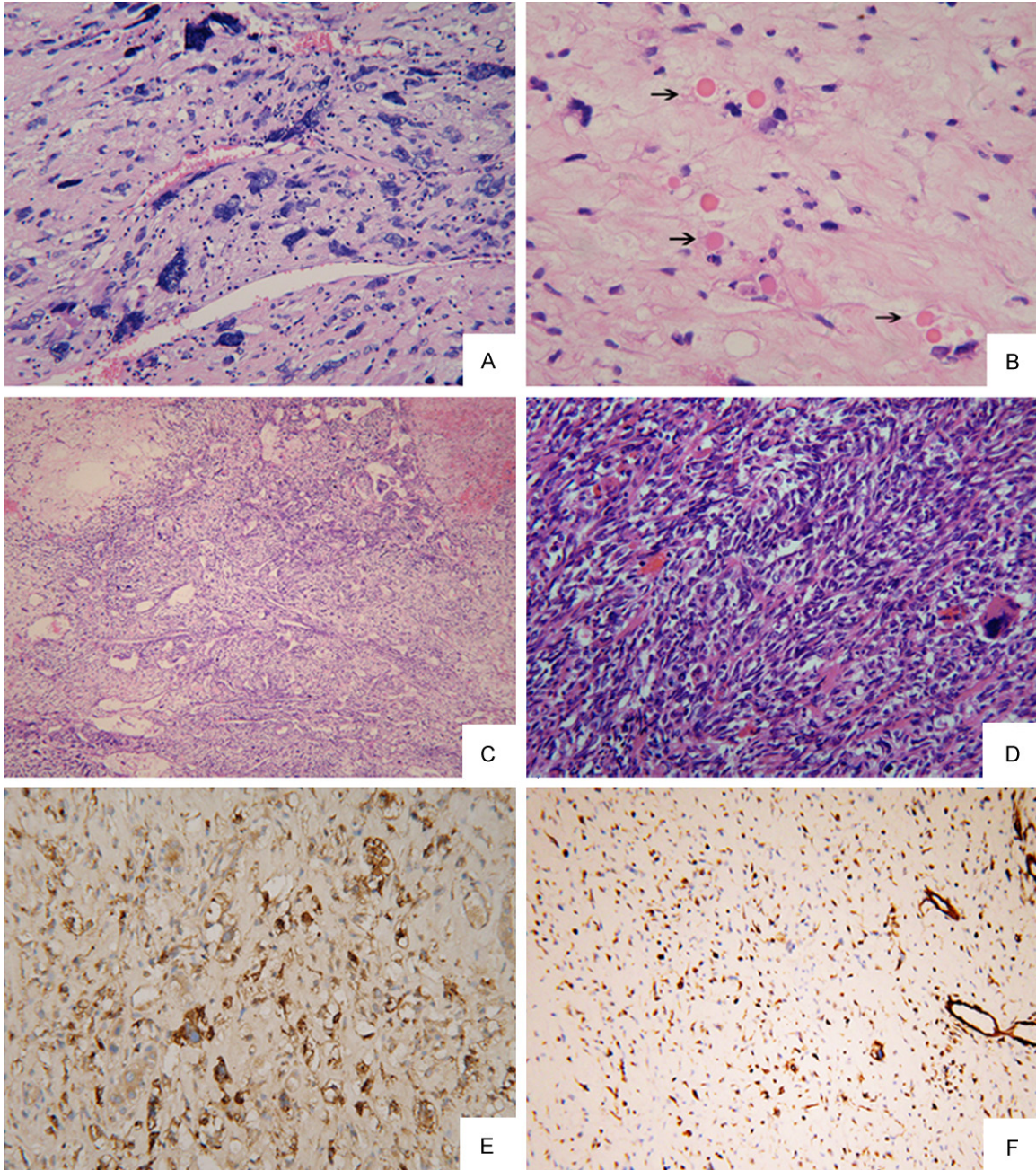


Figure 2. (A) There were foci of uniform small round cells admixed with a small number of pleomorphic cells in an edematous background (HE \times 200) (Case No. 4); (B) Variable sized eosinophilic globules were present in the cytoplasm of large tumor cells or in extracellular matrix (arrow) (HE \times 200); (C) Haemangiocytopoma-like compact areas with collagenization (HE \times 100) (Case No. 2); (D) Fibroblast-like fascicles and bundles were seen in compact areas (HE \times 200) (Case No. 8); (E, F) Tumor cells were strongly positive for AAT (E) and Vimentin (F) (Case No. 4) (Envision Immunohistochemistry, \times 100).

Imaging studies

Ultrasonography scan showed either hetero-echoic mass containing some echoless areas (in Case No. 2, 3, 4, 6, 7, 8, 9) or hyper-echoic (in Case No. 1). Computerized tomography (CT)

or Magnetic resonance imaging (MRI) showed a hypodense mass with a multicystic appearance with an enhanced peripheral rim. The hypodense area of the mass did not enhance in the enhanced scan. (**Figure 1A, 1B**) Most of the cases were misdiagnosed as malignant mesen-

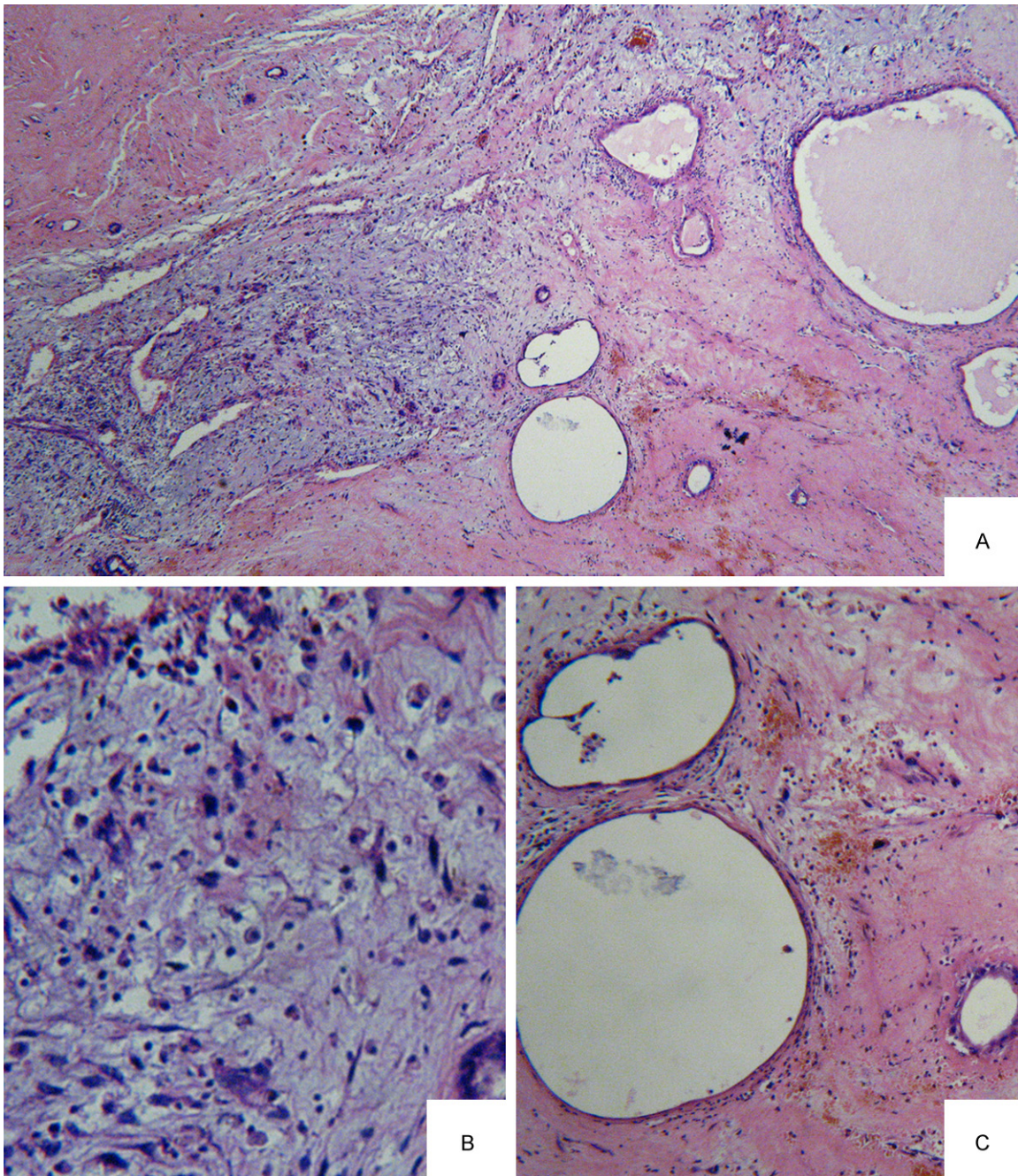


Figure 3. A. Transitional zones containing a histological mixture of the UESL and MHL (HE × 100) (Case No. 4); B. UESL areas showed pleomorphic malignant stromal spindle to stellate-shaped elements with numerous mitoses (HE × 200); C. MHL-like areas consisted of a loose myxoid stroma without cytonuclear atypia or mitoses and dilated bile duct (HE × 200).

chymal tumor or angiosarcoma, malignant fibrous histiocytoma (MFH) in imaging study (in Case No. 2, 4, 6, 7, 8, 9). Two cases were misdiagnosed as hepatocellular carcinoma (HCC), and one case was considered as teratoma or echinococcosis. The clinical data are summarized in **Table 1**.

Laboratory examination

The 9 cases had no relation to hepatitis B and C virus infection. The serum alkaline phosphatase (ALP) activity and lactate dehydrogenase (LDH) were increased in most of the cases, the mean level was 180.6 IU/L and 336.3 IU/L (nor-

Table 2. Treatment and prognosis data of 9 cases

Case	Treatment	Chemotherapy regimens	Follow-up
1	Lobectomies	No	DOD, 34 mo. intrahepatic recurrence in the 19 mo, treated with TACE. Tumor metastasis in the 24 mo.
2	Lobectomies + Chemotherapy	MAID	FOD, 76 mo No recurrence
3	Lobectomies + Chemotherapy	MAID	FOD, 18 mo No recurrence
4	Lobectomies + Chemotherapy	MAID	FOD, 24 mo (recurrence in the 4mo)
5	Lobectomies + Chemotherapy	MAID	FOD, 50 mo. (intrahepatic recurrence in the 29 mo. Treated with segmentectomy
6	Lobectomies + Chemotherapy	MAID	DOD, 47 mo. Intrahepatic recurrence in the 14 mo
7	Chemotherapy + TACE + Lobectomies	THP-ADM + CDDP	FOD, 29 mo. No recurrence
8	Lobectomies + Chemotherapy	MAID	FOD, 5 mo
9	Lobectomies + Chemotherapy	MAID	FOD, 5 mo

DOD, dead of disease; FOD, free of disease; TACE, transcatheter arterial chemoembolization (lipiodol, epirubicin, and hydroxy camptothecin); MAID, mesna + adriamycin + iphosphamide + dacarbazine; THP-ADM, pirarubicin-adriamycin; CDDP, cis-diaminedi-chloroplatinum.

mal level: ALP < 110, LDH (114-240)). Serum α -fetoprotein (AFP), cancer antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA) levels were within the normal range. Cancer antigen 125 (CA125) was increased in Case No. 5, 8. In addition, γ -glutamyltransferase (GGT), leucine aminopeptidase (LAP) was slightly increased in some cases.

Gross features

The largest dimensions of the tumors in the cases were ranged from 5 to 26 cm. Most of cases showed a large, solitary mass. The cut surfaces were variegated, mainly solid and grey-white, with some cystic gelatinous areas. Haemorrhagic and necrotic areas were common (**Figure 1C, 1D**).

Microscopically and immunohistochemistry

The tumors were separated from the adjacent compacted hepatic parenchyma by a fibrous pseudocapsule. The tumors consisted of proliferations of medium sized spindle, oval or stellate shaped pleomorphic cells loosely or compactly arranged in an edematous or myxoid matrix, with scattered bizarre multinucleated giant cells (**Figure 2A**). Variable sized eosinophilic globules were present in the cytoplasm of large tumor cells or in extracellular matrix (**Figure 2B**). Haemorrhage and necrosis were frequently seen. In all cases, satellite lesions and tumor embolus were not found in sections. Foci of haemangiocyoma-like compact areas

with collagenization were present in case No. 2 (**Figure 2C**). Fibroblast-like fascicles and bundles were seen in compact areas in Case No. 8 (**Figure 2D**). With regard to immunohistochemistry, eosinophilic globules were typical positive for PAS and diastase resistant. Most tumor cells consistently were positive for markers α 1-antitrypsin (α 1-AT) and vimentin (**Figure 2E, 2F**). While makers CK, CK19, actin, desmin, CD56 showed positive staining occasionally in some cases. Makers MyoD1, HHH35, S-100, CD31, CD34, Hepatocyte and AFP were all immunonegative in our cases.

In addition to those features, interestingly, some zones containing UESL and mesenchymal hamartomas of the liver (MHL) could be found in Case No. 3, 4 (**Figure 3A**). Part of areas corresponded to a typical UESL composed of pleomorphic malignant stromal spindle to stellate-shaped elements with numerous mitoses (**Figure 3B**). Close to UESL area, there were some peripheric MHL-like areas consisted of a loose myxoid stroma populated by spindle or stellateshaped cells without cytonuclear atypia or mitoses, and dilated bile duct (**Figure 3C**).

Treatment

Radical resections (lobectomies) were performed in all cases. In Case No. 1, the patient received transcatheter arterial chemoembolization (TACE: lipiodol, epirubicin, and hydroxy camptothecin) until intrahepatic recurrence in the 19 month. No preoperative treatments but

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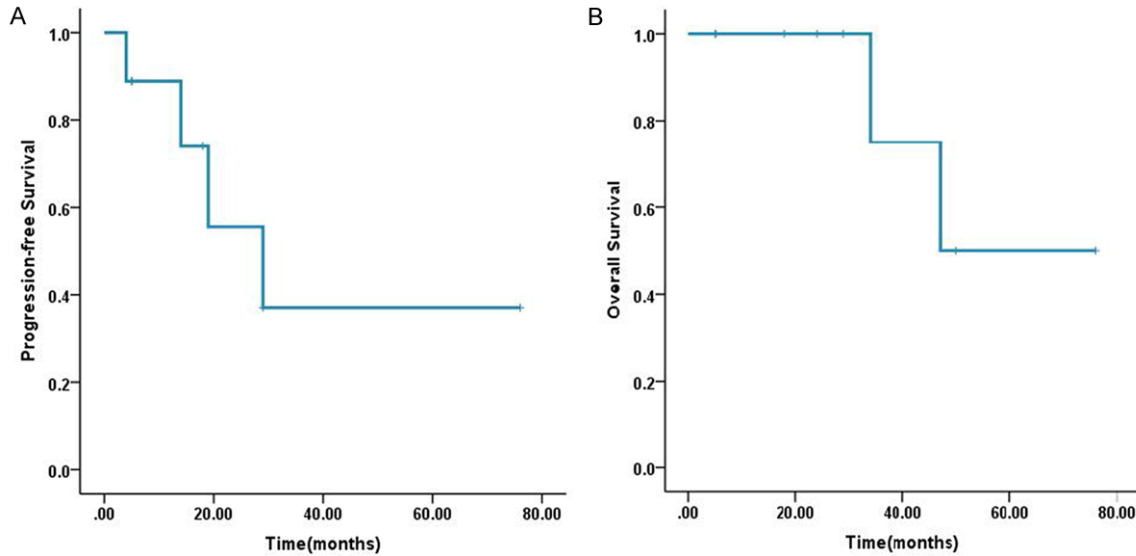


Figure 4. (A, B) Kaplan-Meier Overall survival (A) and Progression-free survival (B) curves.

postoperative chemotherapy were performed in Case No. 2, 3, 4, 5, 6 with a standard regimens for sarcoma (MAID: mesna + adriamycin + iphosphamide + dacarbazine). In Case No. 6, because the tumor invaded diaphragm, partial diaphragm resection and neoplasty were performed simultaneously. In Case No. 7, he received chemotherapy 4 times (pirarubicin-adriamycin + cis-diaminedichloroplatinum) and interventional therapy 2 times but had no significant effect before surgery. Therefore, lobectomy and postoperative chemotherapy was performed.

Outcomes and survival analysis

The follow-up information of all cases was available (**Table 2**). In Case No. 1, TACE was performed when intrahepatic recurrence occurred in the 19 month, unfortunately, distant metastasis emerged in the right lower lung and lymph node of mediastinum in the 24 month. He died of multi-organ tumor metastasis in the 34 month. In Case No. 6, who died in the 47 months while intrahepatic recurrence appeared in the 14 months. The other cases were alive (range from 5 to 76 months). In additional, the time to recurrence was 19, 4, 29, 14 months in Case No. 1, 4, 5, 6. No recurrent lesions were detected in the other cases by routine B-mode ultrasonography examination every 3 months. The OS and PFS analysis was performed using the Kaplan-Meier method. The mean OS was 58.25 ± 9.1 months and the mean PFS was 39.55 ± 11.6 months (**Figure 4A, 4B**).

Discussion

Undifferentiated embryonal sarcoma is the third most common malignant tumor of the liver in children, accounting for 13% of hepatic malignancies in this age group. There were over 150 cases were reported until 2012 [4-6]. In this report, we have presented a descriptive study of 9 cases. The majority of the patients are children, the mean age is 15.3 years. The primary presenting complaints of UESL is always upper abdominal pain or mass that may be correlated with the relatively large size of the tumors. Other complaints, such as nausea, anorexia, fever, or headache, may also be presented [7, 8]. Laboratory studies, such as CA125, CEA, CA199 are nonspecific for this entity, while ALP and LDH elevate generally in most of cases. In imaging study, typical ultrasonography scan (US) showed hepatomegaly and a heterogeneous mass containing some echoless areas, and CT scan showed a lesion occupying a large space with cystic areas, hypodense areas that do not enhance in an enhanced scan, compression or displacement around the tissue [9, 10]. However, it is hard to make an accurate diagnosis through imaging study while it should be considered along with the age of the patient and the size of the tumor.

Grossly, the tumor is usually a large, solitary mass, predominantly solid but often with variable areas of hemorrhage, necrosis and cystic degeneration. Tumors with and without capsules have been reported. The tumor size often

exceeds 10 cm and can be as large as 30 cm. The right lobe of the liver is more commonly involved [6, 7].

Histologically, the tumor has a variable but distinctive sarcomatous appearance. It is composed of loosely arranged, medium-large spindles, oval and stellate pleomorphic cells with poorly defined cell borders, and giant cells with severe atypia [11-14]. In addition, as in our report, there are prominent eosinophilic, PAS+, and diastase-resistant globules in the tumor cell cytoplasm and extracellular matrix. Although its pathological origin remains unclear, ultrastructural and immunohistochemical studies have shown its fibroblastic, histiocytic, myoblastic, myofibroblastic, rhabdomyoblastic and leiomyoblastic differentiation [15]. Most UESL are diffusely positive for vimentin, a1-AT, and focally positive for cytokeratin, desmin, muscle-specific actin, CD68, myoglobin, non-specific enolase, S100, and CD34, suggesting that embryonal sarcoma is an "undifferentiated" sarcoma, since it may display partial differentiation [16, 17].

The pathogenesis of UESL remains unclear. Some authors assumed that UESL can arise within mesenchymal hamartomas of the liver (MHL), which is the second commonest benign liver tumor in children. Karyotypic analysis of UESL arising in MHL has demonstrated rearrangements of region 19q13.4, including t(11;19)(q11;q13.3-13.4) [18, 19]. In present study, some transitional zones including both histological features supporting the assumptions that MHL and UESL may belong to the same family of mesenchymal hepatic tumors, the latter representing the malignant entity of the spectrum. However, further study about the association between them need to be performed in future.

A standard treatment for UESL has not been defined. Uchiyama et al [20] proposed that surgical resection combined with chemotherapy is the most effective therapy for UESL patients with tumor rupture. Additionally, the authors suggested that chemotherapy containing 3-4 types of drugs, such as adriamycin, cisplatin and others, demonstrated beneficial therapeutic effects and significantly improved survival rates. Yu et al [21] suggested that the best method for improving survival is total resection, regardless of whether the tumor is ruptured. Li

et al [5] demonstrated that a UESL patient who underwent interventional therapy and surgical resection exhibited a prolonged survival compared with patients who underwent surgical resection only. In addition to that traditional therapy, hepatic and stem cells transplantation were performed to this malignance. Kelly et al. [22] have demonstrated that hepatic transplantation is an effective therapeutic method for UESL patients whose tumor is not able to be resected or who have postoperative recurrence of the tumor. And recently, Plant et al. [6] also showed that in cases of unresectable primary tumor or recurrent and refractory disease isolated to the liver, orthotopic liver transplantation (OLT) is a potential therapeutic option. Noguchi K [23] reported a long-term survival case of UESL who was treated with a high dose of etoposide and radiation therapy, then followed with peripheral blood stem cell transplantation.

In previously reported literatures, the prognosis of UESL is poor with historically overall survival of < 37.5% at 5 years and the majority of patients die of tumor recurrence in the upper abdomen or metastasis to lung, pleura, and peritoneum within 2 years of the initial operation. However, more and more literatures reported that the tumor is potentially treatable [6, 24, 25]. In our study, the Case No. 2 is alive and free of disease for more than 6 years without recurrence. And the overall survival (OS) of our case series is close to 5 years (mean OS is 58.25 ± 9.1 months), the progression-free survival (PFS) is also more than 3 years (mean PFS is 39.55 ± 11.6 months). These data also support the idea that UESL is treatable. In light of recent literatures and our retrospective study, we hold the idea that multiagent chemotherapy after resection can significantly improve the survival and some other novel treatments like hepatic or stem cell transplantation provide the potential opportunity to cure this tumor.

Disclosure of conflict of interest

None.

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