Received: 19 April 2016 | Revised: 10 August 2016 | Accepted: 20 August 2016 | Published on: 26 October 2016

DOI: 10.1002/pbc.26272

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

Characteristics and outcomes in children with undifferentiated embryonal sarcoma of the liver: A report from the National Cancer Database

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Grant sponsor: Texas Children's Department of Surgery SEED Grant (SAV) Grant sponsor: Baylor College of Medicine Michael E. DeBakey Department of Surgery Faculty Award (SAV) American College of Surgeons and the American Cancer Society are the sponsors of the database which was used. They did not directly fund this study.

Abstract

Objective: To examine patient characteristics and outcomes in children with undifferentiated embryonal sarcoma of the liver (UESL) using a multi-institutional database.

Summary Background Data: UESL is a rare disease (incidence is one per million). Therefore, the current literature is mostly limited to small case series.

Methods: The National Cancer Database was queried for primary UESL diagnosed between 1998 and 2012.

Results: A total of 103 patients (<18 years) were identified. The 5-year overall survival of the entire group was 86%. The best outcomes were seen in children who had tumors smaller than 15 cm and were able to undergo surgical resection with or without chemotherapy. Margin status did not appear to significantly affect survival. The most common type of resection was hemihepatectomy (37%), followed by sectionectomy (10%) and trisectionectomy (10%). Orthotopic liver transplant was performed in 10 children, all of whom survived to 5 years.

Conclusion: Surgical resection with or without chemotherapy should be the mainstay of treatment in children with UESL, and is associated with very favorable outcomes. Negative surgical margins were not associated with improved survival. Orthotopic liver transplantation may be a viable method of attaining local control in tumors, which would otherwise be unresectable.

Abbreviations: CoC, Commission on Cancer; COG, Children's Oncology Group; IQR, interquartile range; NCDB, National Cancer Database; OLT, Orthotopic liver transplant; OS, overall survival; PRETEXT, Pretreatment Extent of Disease; PUF, Participant User File; UESL, undifferentiated embryonal sarcoma of the liver

KEYWORDS
embryonal sarcoma, hepatic sarcoma, liver cancer, liver sarcoma, National Cancer Database, undifferentiated embryonal sarcoma

1 | INTRODUCTION

Undifferentiated embryonal sarcoma of the liver (UESL) is a rare neoplasm that accounts for 9–15% of pediatric liver malignancies[1] and is the third most common malignant liver tumor in children, following hepatoblastoma and hepatocellular carcinoma.[2] The peak incidence of UESL is between 6 and 10 years of age.[1,3] Some series report a female predominance,[4] while others report an even-gender distribution.[1,5,6] Tumor sizes are between 10 and 30 cm.[7] UESL arises more commonly from the right lobe of the liver and presents clinically with nonspecific symptoms of abdominal pain, fever, nausea, and anorexia.[1,3–5,7] Imaging demonstrates cystic and solid components,[8–10] and serum α-fetoprotein is usually normal. Historically, treatment was limited to radical surgical resection, with chemotherapy and radiation used infrequently, leading to a dismal prognosis with a median overall survival (OS) of less than 1 year.[1] Mortality was primarily from recurrent and metastatic disease.[1,11,12] More recently, aggressive treatment regimens that combine chemotherapy and surgical resection have improved survival substantially.[5,13,14]

Due to its low incidence, much of the literature regarding UESL is from small case series or case reports. The largest series from 1978 had 31 patients, and no adult series has more than two cases.[5,15] Therefore, few data exist to help guide therapy and counsel patients and their families. Previously reported factors associated with worse OS are local recurrence, tumor rupture, and metastatic disease.[4,16] Outside of meta-analyses, there are no large retrospective single-source analyses of UESL characteristics and prognostic factors. The National Cancer Database (NCDB) is a U.S.-based, nationwide multi-institutional database that is jointly managed by the American College of Surgeon's Commission on Cancer (CoC) and the American Cancer Society. It captures approximately 70% of all newly diagnosed cases of cancer in the United States from over 1,500 participating CoC programs.[17] Because of its large scale, the NCDB provides a unique opportunity to examine rare pathologies such as this one, where the previous literature is limited. This study aims to outline the patient and disease characteristics, as well as identify factors that correlate with OS in children with UESL using the largest dataset to date from the NCDB.

2 | METHODS

2.1 | Data source and study population

This dataset was obtained from the NCDB Participant User File (PUF) for liver neoplasms. The PUF files are deidentified for patient and facility-specific information in accordance with the requirements of the Health Insurance Portability and Accountability Act. This study was limited to patients <18 years with primary UESL, who were diagnosed between 1998 and 2012. The dataset was queried using tumor histology codes from the International Classification of Disease for Oncology 3rd Edition (ICD-O-3): code 8805 for undifferentiated sarcoma and code 8991 for embryonal sarcoma.

2.2 | Variables

The variables that were chosen to be included in the analysis were limited to those with fewer than 20% incomplete data and can be found in Table 1. Income and education levels were derived from the 2008 U.S. Census data based on the patients' reported zip code of residence. The variable "Treatment Modality" refers to whether patients had no treatment, chemotherapy only, surgical resection only, or combined therapy. Combined therapy refers to the combination of chemotherapy and surgical resection of any kind. Radiation therapy was not included in this variable, as a small minority of patients had radiation therapy as part of their treatment course.

2.3 | Statistical methods

Continuous variables are reported as a mean or median, with the corresponding absolute range or interquartile range (IQR), respectively. Categorical variables are reported as frequencies with the corresponding percentages.

Kaplan–Meier analyses of OS were conducted for each variable; differences were tested with the log-rank test, and 5-year OS was calculated from mortality tables. Univariate analysis was performed using a Cox proportional hazard model. For multivariate analysis, potential confounding covariates with a *P*-value of <0.20 on univariate analysis were entered into a Cox proportional hazard regression model. Since the variable "treatment modality" is inclusive of the "resection" and "chemotherapy" variables, only "treatment modality" was used in the multivariate model. The optimal cutpoint for tumor size was determined using the minimum *P*-value approach. The statistical analysis was performed using STATA 13.0 (StataCorp LP, College Station, TX) and SAS 9.3 (SAS Institute, Inc., Cary, NC).

3 | RESULTS

3.1 | Study population and demographic variables

A total of 103 children (age <18 years) with a primary diagnosis of UESL between 1998 and 2012 were identified in the NCDB registry. Survival data were available for 100 of these children.

3.2 | Demographics, tumor extent, and treatment

The demographic, tumor, and treatment characteristics are summarized in Table 1. Children with UESL had a median age of 9 years

TABLE 1 Demographic, tumor, and treatment characteristics

		N = 103, n (% of N)
Age	Median	9 (0–17)
Gender	Male	52 (50)
	Female	51 (50)
Race	Caucasian	85 (83)
	African American	11 (11)
	Other	5 (5)
	Unknown	2 (2)
Spanish origin	Non-Hispanic	68 (66)
	Hispanic	26 (25)
	Unknown	9 (9)
Insurance status	Public	41 (40)
	Private	55 (53)
	None	3 (3)
	Unknown	4 (4)
Income	<$63,000	75 (73)
	≥$63,000	26 (25)
	Unknown	2 (2)
Tumor size	Median (IQR)	14 cm (11–16 cm)
	<15 cm	57 (55)
	≥15 cm	30 (29)
	Unknown	16 (16)
Metastases[a]	Not present	54 (81)
	Present	10 (15)
	Unknown	3 (4)
Lymph node status		
	Negative	21 (20)
	Positive	1 (1)
	Not sampled	73 (71)
	Unknown	8 (8)
Radiation therapy		
	No	85 (83)
	Yes	15 (15)
	Unknown	3 (3)
Margins of resection		
	Negative	51 (57)
	Positive	20 (22)
	Unknown	19 (21)
Treatment modality	Chemotherapy only	9 (9)
	No treatment	4 (4)
	Surgery only	5 (5)
	Combined therapy	84 (82)
	Unknown	1 (1)
Chemotherapy	No	9 (9)
	Yes	93 (90)
	Unknown	1 (1)
Resection type	No surgery	13 (13)
	Local destruction	0 (0)
	Sectionectomy	29 (28)
	Hemihepatectomy	38 (37)
	Trisectionectomy	10 (10)
	Orthotopic liver transplant	10 (10)
	Surgery, NOS	3 (3)

NOS, not otherwise specified; IQR, interquartile range.
[a]Data missing in 36 of 103 records.

(IQR: 5–12 years) and no gender predilection. The median size was 14 cm (IQR: 11–16 cm). Lymph nodes were sampled in only 22 of 89 (25%) patients who underwent a surgical operation. Of these, lymph node involvement was seen in 1 of 22 (4.5%) nodes sampled. Combined therapy was utilized in a great majority of cases (82%). Eighty-nine (86%) patients underwent resection, while 13 (13%) did not. Among the patients who had surgery, hemihepatectomy (37%) and sectionectomy (28%) were the most commonly utilized methods of resection. Almost all patients were treated with chemotherapy (90%), while only 15 (15%) had radiation therapy. All patients who had radiation also underwent combined chemotherapy and surgical resection. Metastases were present in 15% of patients. Among patients who did not have surgery, metastatic disease was present in three (38%) patients compared to seven (13%) patients who did have surgery. Ten orthotopic liver transplants (OLT) were also performed, and all these patients survived to 5 years. A margin-free resection was achieved in 51 of 89 (57%) children who underwent resection, and all children with positive margins received chemotherapy.

3.3 | Survival analysis

3.3.1 | Univariate analysis

Table 2 shows the results of the univariate survival analysis. The 5-year OS for the entire patient population was 86%. In children who underwent combined therapy, the 5-year OS was 92%. Factors associated with better OS were combined therapy ($P < 0.01$), sectionectomy ($P = 0.03$), and hemihepatectomy ($P = 0.001$). Unknown tumor size is likely only significant as it comprises a larger proportion of patients who did not have surgery. Socioeconomic factors such as gender, race, ethnicity, insurance type, and income did not have an impact on survival. Chemotherapy alone, radiation, and surgical margins were not significant prognostic factors. All the patients who had radiation treatment also had combined therapy. There was no significant difference in survival within the combined therapy group with the addition of radiation treatment ($P = 0.26$). Radiation was also not used exclusively for patients with positive margins. Radiation was given to six patients with negative margins and seven patients with positive margins, two patients had margins that were unknown. The OS of the five patients who had surgical resection alone was 100%. There was one sectionectomy, two hemihepatectomies, one trisectionectomy, and one OLT. All these patients had negative margins.

TABLE 2 Univariate survival analysis and 5-year overall survival (OS) of demographic, tumor, and treatment characteristics

		N = 100			
		HR	95% CI	*P*-value	5-year OS (%)
Gender	Male	REF			80
	Female	0.43	0.13–1.4	0.16	92
Race	Caucasian	REF			87
	African American	0.60	0.08–4.7	0.63	89
	Other	1.83	0.24–14	0.56	67
	Unknown	-	-	-	-
Spanish origin	Non-Hispanic	REF			82
	Hispanic	0.47	0.10–2.1	0.32	92
	Unknown	-	-	-	-
Insurance status	Public	REF			87
	Private	0.83	0.25–2.7	0.76	88
	None	7.5	0.87–66	0.07	50
	Unknown	0.28	0.12–4.6	0.37	75
Income	<$63,000	REF			82
	≥$63,000	0.22	0.03–1.7	0.15	96
	Unknown	-	-	-	-
Tumor size	<15 cm	REF			92
	≥15 cm	1.9	0.49–7.8	0.35	85
	Unknown	**5.1**	**1.4–19**	**0.02**	**69**
Radiation therapy	No	REF			86
	Yes	1.1	0.24–4.9	0.91	84
	Unknown	-	-	-	-
Margins	Negative	REF			95
	Positive	4.4	0.73–26	0.11	83
	Unknown	1.3	0.11–14	0.85	
Treatment modality	Chemotherapy only	REF			44
	No treatment	1.27	0.25–6.6	0.775	50
	Surgery only	-	-	-	-
	Combined therapy	**0.10**	**0.03–0.33**	**<0.01**	**92**
	Unknown	-	-	-	-
Chemotherapy	No				
	REF			78	
	Yes	0.44	0.10–2.0	0.29	87
	Unknown	-	-	-	-
Resection type	No surgery	REF			46
	Local destruction	-	-	-	-
	Sectionectomy	**0.09**	**0.02–0.45**	**0.003**	**93**
	Hemihepatectomy	**0.10**	**0.03–0.39**	**0.001**	**90**
	Trisectionectomy	0.14	0.02–1.1	0.07	86
	Orthotopic liver transplant	-	-	-	-
	Surgery, NOS	-	-	-	-

REF, reference variable; NOS, not otherwise specified; HR, hazard ratio; CI, confidence interval; '-', insufficient cases for analysis. *P* values <0.05 are shown in bold.

TABLE 3 Multivariate Cox proportional hazards regression

		N = 100		
		HR	**95% CI**	***P*-value**
Gender	Male	REF		
	Female	0.49	0.13–1.9	0.30
Insurance status	Public	REF		
	Private	1.4	0.38–5.1	0.61
	None	3.8	0.23–62	0.36
	Unknown	4.3	0.31–61	0.28
Income	<$63,000	REF		
	≥$63,000	0.47	0.06–4.0	0.50
	Unknown	–	–	–
Tumor size	<15 cm	REF		
	≥15 cm	**8.1**	**1.3–48**	**0.02**
	Unknown	4.7	1.0–22	0.05
Treatment modality	Chemotherapy only	REF		
	No treatment	2.2	0.25–19	0.49
	Surgery only	–	–	–
	Combined therapy	**0.03**	**0.004–0.27**	**<0.01**
	Unknown	–	–	–
Margins of resection	Negative	REF		
	Positive	5.7	0.96–37	0.07
	Not applicable	–	–	–
	Unknown	1.3	0.10–17	0.86

REF, reference variable; HR, hazard ratio; CI, confidence interval; "–", insufficient cases for analysis. *P* values <0.05 are shown in bold.

OS was 91% in patients who did not have metastatic disease ($N = 51$) and 70% in patients who did ($N = 10$). The OS for patients who had metastatic disease and underwent combined therapy was 86% ($N = 7$). It is important to note that the presence of metastatic disease was only recorded in 64 of 103 records.

The OS of the pediatric transplant patients was 100% ($N = 10$). Nine of 10 children had chemotherapy with OLT. The mean tumor size of transplant patients was 13.7 cm (1.4–24 cm).

3.3.2 | Multivariate analysis

Table 3 shows the results of the Cox model multivariate analysis for OS. The covariates used in the model were gender, insurance, income, tumor size, tumor margins, and treatment modality. The ending sample size in this model was 100.

Tumor size ≥15 cm (hazard ratio [HR] = 8.1, 95% CI = 1.3–48; $P = 0.02$) and combined therapy (HR = 0.03, 95% CI = 0.004 – 0.27; $P < 0.01$) were the only two independent prognostic factors.

4 | DISCUSSION

The purpose of this study was to broadly characterize patient and disease characteristics and identify factors associated with prognosis in UESL using the largest dataset of patients to date from the NCDB. There is currently a paucity of data related to demographics, tumor characteristics, prognostic indicators, and optimal treatment in patients with UESL. This analysis demonstrates that surgical resection alone, and combined therapy were associated with the best prognosis.

In prior decades, prognosis for UESL was considered poor; the long-term disease-free survival rate was less than 37%.[1,3,18,19] However, these data were from an era that preceded the widespread use of combined therapy as the preferred treatment. Since then, the long-term survival rate of UESL patients has steadily improved (Table 4) and is currently reported to be >70%.[5,14,20–25] Some of the first cases of long-term survivors treated with combination chemotherapy and surgery were described in the late 1980s.[26] Newman et al. reported long-term survival in two of four patients.[27] Urban et al. then reported a series of four survivors, who were followed for 22–79 months.[28] The only prospective study of UESL treatment outcomes was reported by the Italian and German Soft Tissue Sarcoma Cooperative Group. From 1979 to 1996, 17 patients with UESL were identified and treated with the current regimens for pediatric rhabdomyosarcoma, and/or surgical resection, when appropriate. The authors reported following up on 13 survivors for periods ranging from 14 to 240 months. Three patients died of their disease, two had local recurrence, and one was incompletely resected.[5] The addition of chemotherapy to surgical management is now increasingly being employed and has been credited with increasing the OS for UESL.[5,14,28–30] This analysis supports these prior, smaller case series, which suggested that surgical resection alone, as well as combined therapy, were positive predictors of survival.

TABLE 4 Published reports of UESL (N > 3) from 1987 to 2014. Follow-up and outcome of patients who had surgical resection only, as well as combined therapy, are outlined

				Surgical excision Only			Combined therapy		
Author, publication year	No. of patients	Age range, years	Gender (M/F)	No. of patients	Follow–up, months	Alive	No. of patients	Follow–up, months	Alive
Techavichit et al., 2016[20]	6	5–22	3/3	0	–	–	5	10–133	4/5[a]
Cao et al., 2014[25]	9	6–37	6/3	1	34	0/1	8	5–76	7/8
Walther et al., 2014[21]	6	7–13	4/2	1 (1 OLT)[b]	84	1/1	5 (2 OLT)	12–48	5/5
Plant et al., 2013[35]	5	10–19	4/1	0	–	–	5 (1 OLT)	21–68	5/5
Ismail et al., 2013[23]	10	4 months to 17	8/2	0	–	–	10 (1 OLT)[c]	50–222	9/10
Upadhyaya et al., 2010[24]	11	4 months to 15	–	1	NR	1/1	10	–	7/10
Weitz et al., 2007[13]	5	–	–	–	–	–	–	–	[d]
Bisogno et al., 2002[5]	17	4 months to 16	10/7	1	NR	0/1[e]	15	14–240	12/15[f]
Kim et al., 2002[14]	6	7–13	4/2	0	–	–	6	22–108	5/6
Webber et al., 1999[3]	7	2–12	4/3	0	–	–	7	6–150	4/7
Urban et al., 1993[28]	4	6–13	0/4	0	–	–	4	22–79	4/4
Walker et al., 1992[18]	4	7–29	2/2	2	18–240	2/2	2	13–30	1/2
Lack et al., 1991[19]	16	2–21	10/6	7	4–12	0/7	9	4–60	3/9
Leuschner et al., 1990[26]	9	4–20	5/4	5	3–24	2/4[g]	3	15–59	3/3
Newman et al., 1989[27]	4	5–13	2/2	0	–	–	4	–	2/4
Horowitz et al., 1987[12]	5	4–16	4/1	1	6	0/1	4	12–58	2/4

NR, not reported; OLT, orthotopic liver transplant.

[a]One patient underwent chemotherapy only. The deceased patient from the combined therapy group had an incomplete resection.

[b]This patient underwent OLT without adjuvant chemotherapy due to local recurrence after prior resection with neoadjuvant and adjuvant chemotherapy.

[c]The deceased patient was initially diagnosed with hepatoblastoma and died 4 months posttransplant of postoperative complications.

[d]All patients with embryonal sarcomas of the liver underwent surgical resection with negative margins, however the use of chemotherapy could not be ascertained. The overall survival of UESL patients in this study was 80% (4/5).

[e]Postsurgical death. The patient also had chemotherapy alone and died 1.8 years after diagnosis.

[f]One patient died of unrelated trauma.

[g]One patient had no outcome reported.

As with other hepatic malignancies such as hepatoblastoma and hepatocellular carcinoma,[31,32] complete surgical resection is currently the mainstay of therapy for UESL.[12,15] A distinct survival difference is seen between patients who underwent resection and those who did not. A small subgroup of five patients underwent surgical resection alone. All these patients had negative resection margins. These patients also had a variable extent of hepatic resection that ranged from sectionectomy to trisectionectomy and OLT. This indicated that all these were not small localized tumors. In this small sample, children treated with surgical resection alone with negative margins and no nodal disease had 100% survival. Although no firm conclusions can be drawn from such a small sample size, these data still pose an interesting question that is worth examining should a larger dataset of these patients become available.

In cases in which hepatic lesions are deemed unresectable due to multifocality or proximity to vital structures, OLT is used to achieve local control.[22,33,34] Successful use of OLT in the treatment of UESL has been reported in a few small case reports and series,[21,35–38] and more recently in an analysis of the United Network for Organ Sharing database.[20] Among this dataset of 10 children who underwent OLT, 100% were alive at 5 years. The degree of success seen in this interesting, albeit limited amount of data suggest that OLT could be a valid method for achieving local control for UESL in children, and should be considered when confronted with unresectable lesions. However, this remains a small number of cases and further investigation is warranted.

The objective when treating most liver tumors is to achieve a resection with a negative margin. Surprisingly, positive margins were not found to be significant predictors of outcome in this dataset. Given the reportedly good response to chemotherapy,[28,39] adjuvant chemotherapy may be sufficient to control or eliminate residual disease after resection in UESL. Future examination of resection margin status using a larger patient population may provide a more definitive answer as to its significance.

Metastases have been reported to occur in 5–13% of children.[5,12] Successful treatment using surgical resection with chemotherapy has been reported.[12,21] In this dataset, metastases were present in 15% of patients for whom the records were available, and all these patients received chemotherapy as part of their treatment. These data show that patients who have metastatic disease may have a reasonable chance at long-term survival with combined surgery and chemotherapy. However, this conclusion must be tempered by the few cases available and large proportion of missing data for this field.

Currently, there are no standard chemotherapy regimens designed specifically for UESL. Accordingly, regimens reported in the literature are varied, and protocols originally designed for the treatment of pediatric rhabdomyosarcoma or other soft tissue sarcomas are often

employed.[5,14,21,24] The effectiveness of radiation therapy to prevent recurrence and improve survival in UESL is unknown. In a few cases, radiation therapy has been used in the postoperative setting to prevent recurrence in the tumor bed.[39,40] Also, Plant et al. reported that radiation therapy successfully treated lung and paraspinal metastases in two patients.[35] However, this analysis did not reveal a significant improvement in the OS of patients who received chemotherapy alone or radiation therapy. The lack of survival benefit with chemotherapy and radiation may be attributable to differences in patient populations. Patient receiving chemotherapy or radiation may have more advanced or aggressive disease. Unfortunately, information regarding disease extent is limited to tumor size and lymph node status.

The NCDB is a national database drawing on data centers from the entire United States. Accordingly, findings based on NCDB data may be more generalizable than findings based on data from a single institution. The limitations of this work include the retrospective nature of the data, the relatively limited sample size, and the lack of participation by many large independent children's hospitals in the NCDB. Also, staging of liver tumors according to Children's Oncology Group (COG) or pretreatment extent of disease (PRETEXT) staging was not available. No differentiation between the sequence of chemotherapy and surgical resection could be made, as these data were incomplete in many cases.

The data show that surgical resection is crucial and should be considered an integral part of treatment in children with UESL. Despite the absence of specific tumor staging information, outcomes in children is excellent with surgery or combined therapy. This offers valuable information for physicians in their discussions with patients and their families in regards to the proper treatment and prognosis for children with this rare liver tumor.

ACKNOWLEDGMENTS

The American College of Surgeons and American Cancer Society sponsored the National Cancer Database. The authors thank Ana María Rodríguez, PhD, a member of the Research Core Team at the Michael E. DeBakey Department of Surgery at Baylor, for her editorial assistance during the preparation of this manuscript. The authors also thank Courtney Arredondo, MSPH, a member of the Baylor College of Medicine Michael E. DeBakey Department of Surgery Research Core Team, for her assistance with statistical analysis during the preparation of this manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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