



Evaluation of surgical strategies and long-term outcomes in pediatric hepatocellular carcinoma

Merve Karayazili¹ · Ulgen Celtik¹ · Eda Ataseven² · Deniz Nart³ · Orkan Ergun¹

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Abstract

Purpose Hepatocellular carcinoma (HCC), the second most common pediatric malignant liver tumor after hepatoblastoma, represents 1% of all pediatric tumors.

Methods A retrospective study was conducted on children with HCC treated at our center from March 2002 to October 2022, excluding those with inadequate follow-up or records. Demographic data, initial complaints, alpha-fetoprotein (AFP) values, underlying disease, size and histopathological features of the masses, chemotherapy, and long-term outcomes were analyzed.

Results Fifteen patients (8 boys, 7 girls) with a mean age of 11.4 ± 4.1 years (0.8–16.4 years) were analyzed. The majority presented with abdominal pain, with a median AFP of 3.9 ng/mL. Hepatitis B cirrhosis in one patient (6.6%) and metabolic disease (tyrosinemia type 1) in two patients (13.3%) were the underlying diseases. Histopathological diagnoses were fibrolamellar HCC (n:8; 53.3%), HCC (n:6; 40%). Four of the 15 patients underwent liver transplantation, and 9 underwent surgical resection. Due to late diagnosis, two patients were considered inoperable (13.3%). The survival rate for the four patients who underwent liver transplantation was found to be 75%.

Conclusion Surgical treatment of various variants of HCC can be safely performed in experienced centers with a multidisciplinary approach, and outcomes are better than in adults.

Keywords Pediatric liver tumor · Pediatric hepatocellular carcinoma (HCC) · Fibrolamellar HCC · Liver resection · Liver transplantation · Child

Ulgen Celtik, Eda Ataseven, and Deniz Nart contributed equally.

✉ Orkan Ergun
orkanergun@gmail.com
Merve Karayazili
merve.karayazili@gmail.com
Ulgen Celtik
ulgenceltik1988@gmail.com
Eda Ataseven
edataseven@yahoo.com
Deniz Nart
deniznart@gmail.com

¹ Department of Pediatric Surgery, Faculty of Medicine, Ege University, Izmir, Turkey

² Department of Pediatric Oncology, Faculty of Medicine, Ege University, Izmir, Turkey

³ Department of Pathology, Faculty of Medicine, Ege University, Izmir, Turkey

Introduction

Primary tumors of the liver are rarely seen in the pediatric age group and constitute about 1% of all pediatric malignancies [1, 2]. Hepatoblastoma is the most common malignant liver tumor (48%) in children, followed by hepatocellular carcinoma [1, 3, 4]. HCC accounts for 27% of all liver tumors and 4% of all pediatric liver transplantations [5]. HCC is generally associated with poor survival and is mainly seen in adults, more often in males, whereas in the pediatric age group, it is usually seen in older children/adolescents [2, 6].

Surgical resection is the mainstay treatment for HCC. For children diagnosed with non-metastatic HCC, numerous pediatric studies emphasize the significance of complete tumor excision, ensuring clear surgical margins during liver resection, or opting for liver transplantation as the most definitive treatments [7–10]. In this study, we aimed to evaluate the findings obtained through a detailed evaluation of the demographics, tumor characteristics, and surgical

treatment options to provide insights about the outcomes of pediatric HCC patients.

Methods

Study design

Following the approval of the institutional review board, a retrospective analysis was conducted on 15 pediatric patients diagnosed with hepatocellular carcinoma treated at our institution from March 2002 to October 2022. We conducted an analysis of demographic data, lesion size, underlying disease, radiological features, bridging therapy, and the post-operative outcomes.

A total of 15 patients (8 boys and 7 girls) were included in the study. All patients had a histopathologically confirmed diagnosis, either through a tru-cut or a surgical biopsy. Pre-operative AFP values, abdominal ultrasonography (USG), computerized tomography (CT), and/or magnetic resonance imaging (MRI) were evaluated for all patients. The PRE-Treatment Extent of Tumor (PRETEXT) [11] system designed by International Society of Paediatric Oncology (SIOPEL), was used for tumor staging. Analysis of radiologic images (CT scans and MRI) obtained at the time of diagnosis was performed to determine both the size and number of liver lesions, and to assign an appropriate PRETEXT score following the adaptations by the Children's Oncology Group (COG) to the original 2005 PRETEXT guidelines. The patient cohort ($n = 15$) was then assigned into groups based on their treatment pathways: "Mass/Liver Resection Group" ($n = 9$), "Liver Transplantation Group" ($n = 4$), and "Inoperable Group" ($n = 2$). Their respective PRETEXT stages were recorded with a breakdown as follows: in the mass/liver resection group, two patients were PRETEXT 1, six patients PRETEXT 2, and one patient PRETEXT 3. Conversely, all patients in the transplant group were PRETEXT 3 and inoperable group was PRETEXT 4, respectively.

Milan Criteria [10] was considered when deciding for liver transplantation. For patients with a single hepatocellular carcinoma to be eligible for liver transplantation, the tumor should not exceed 5 cm in diameter. In patients with multiple tumors, there could be no more than three tumors, none exceeding 3 cm in diameter. Patients with evident or suspected tumor invasion of blood vessels or lymph nodes were excluded from the study.

Underlying etiological factors were considered for liver transplantation. Two patients were identified as having metabolic liver diseases as the underlying cause for liver transplantation, while one patient was diagnosed with Hepatitis B (HBV) cirrhosis. In these three patients, HCC was not a preoperative diagnosis but discovered at liver explant pathology.

Statistical analysis

The statistical analysis was performed using SPSS for Mac (IBM SPSS Statistics 26) and Excel 2023 (Microsoft Excel for Mac).

All statistical evaluations were carried out on a cohort of 15 pediatric patients diagnosed with HCC. Demographic and clinical variables were analyzed using descriptive statistics. Continuous data, such as age and alpha-fetoprotein (AFP) levels, were presented as means and ranges, while categorical data, such as gender and tumor type, were summarized as frequencies and percentages.

Kaplan–Meier method was used to calculate 1-, 3-, and 5-year overall survival (OS) and disease-free survival (DFS) rates. The survival analyses were further stratified by surgical approach (mass/liver resection vs. liver transplantation), as well as by preoperative and postoperative use of chemotherapy. The log-rank test was applied to identify any significant differences in survival outcomes across these subgroups. The effect of various prognostic factors, including histopathological subtypes, neoadjuvant and adjuvant chemotherapy, and surgical margin status, on 5-year OS was evaluated using the log-rank test. Additionally, we used the log-rank test to assess the impact of metastatic spread, specifically to the lung and bone, on patient survival.

Statistical significance was set at a p -value of less than 0.05. All analyses were conducted using R version 3.6.3, and p -values were two-sided.

Results

Patient characteristics

There were eight boys (53.3%) and seven girls (46.6%) in the series. Mean age was 11.4 ± 4.1 years with a range of 0.8–16.4 years. Demographic variables are summarized in Table 1, and patient details are given in Table 2. Histopathological evaluations of the tumor characteristics revealed that three patients (20%) had well-differentiated HCC (WD-HCC), two patients (13.3%) had conventional HCC (C-HCC), eight patients (53.3%) had fibrolamellar HCC (FL-HCC), and one patient (6.6%) had undifferentiated HCC (U-HCC). One patient was identified with HCC based on HBV cirrhosis.

Clinical presentations

Nine (60%) of the patients underwent mass/liver resection, and four patients (26.6%) underwent liver transplantation. Two patients (13.3%) were not suitable for surgical treatment

Table 1 Characteristics and long-term results of patient

Patient	1 ^a	2 ^a	3 ^a	4	5	6	7	8	9	10	11	12	13	14 ^b	15
Age at diagnosis (years)	11.7	0.8	4.4	9.9	14.5	10.9	15.4	13.5	15.4	14.5	10.5	11.5	11.7	16.4	12
Sex	Male	Male	Female	Female	Female	Female	Male	Female	Female	Male	Male	Male	Male	Female	Male
Underlying disease	HBV cirrhosis	Tyrosinemia type 1	Tyrosinemia type 1	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Fanconi aplastic anemia	Normal	Normal	Normal	Normal
Histology	HBV induced HCC	HCC	WD	FL-HCC	FL-HCC	FL-HCC	FL-HCC	FL-HCC	FL-HCC	FL-HCC	WD	HCC/Hepatoblastoma	FL-HCC	WD	HCC
Extratumor vascular, lymphatic, perineural and capsular invasion		Lympho-vascular perineural				Capsular					Capsular	^d Diaphragm			Lympho-vascular
Disease site(s)	Right lobe	Bilateral	Right lobe	Left lobe	Right lobe	Left lobe	Right lobe	Right lobe	Right lobe	Left lobe + Caudate	Left lobe	Bilateral	Left lobe	Right lobe	Bilateral
Segment	5 + 6	Multifocal	6	4	5	2 + 3	5	5 + 6	5 + 8	1 + 2 + 3 + 4	3	4 + 5 + 6 + 7 + 8	2 + 3	4 + 5 + 6 + 7 + 8	2 + 3 + 4 + 6
Margins(cm)	N/A	N/A	N/A	0,1	Negative	Negative	Negative	Negative	On margin	Negative	0,2	N/A	Negative	N/A	N/A
Maximum diameter of largest foci ^c	6.5	Multifocal	3	6	3,5	4,5	N/A	9	9	3,5	4,2	Multiple	9	12	Multiple
Pretext	3	3	3	2	2	1	2	2	2	3	1	4	2	4	4
Pretext annotation factors (V, P, E, F, R, C, N, M)	P + F + M	F	None	V	None	None	None	None	V + N	P + C	None	P + E + F + M	N + M	V + N + M	P + V + N
Alp at diagnosis (ng/ml)	22,580	N/A	N/A	1.2	3.6	2.13	N/A	3.5	2	2.78	21	60,000	4.25	2.355	303
Chemotherapy															
Neo-adjuvant	N/A	0	0	0	0	0	0	0	1	1	0	1	1	1	1
Adjuvant	N/A	0	0	1	1	1	1	1	1	1	1	0	1	1	N/A
Treatment	LT ^a	LT ^a	LT ^a	Left hepatectomy	Segmentectomy	Lateral segmentectomy	Segmentectomy	Segmentectomy	Right hepatectomy	Left hepatectomy caudectomy	Segmentectomy	Inoperable	Left hepatectomy	LT ^b	Inoperable
Vital status	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Death	Death	Death	Death	Death
Follow-up (months)	254	252	119	178	76	72	68	36	42	67	111		82	46	
Metastasis	Lung	No	No	No	No	No	No	No	Abdominal lymph nodes	No	No	Lung	Lung + bone + Lymph nodes	Bone + Liver	Lung + lymph nodes

Table 1 (continued)

Patient	1 ^a	2 ^a	3 ^a	4	5	6	7	8	9	10	11	12	13	14 ^b	15
Recurrence	No	No	No	No	No	No	No	No	No	Yes	No	N/A	N/A	Yes	
Bridging therapy										Tare					
Re-operation									Lap exci- sion	LT				No	
Cause of death											Rhinocer- ebral mucor- mycosis	Inoperable	Distant metastasis	Recurrence distant metastasis	Inoperable

AFP alpha-fetoprotein, FL-HCC Fibrolamellar variant of HCC, PRETEXT pre- treatment extent of disease system, TARE transarterial radioembolization, LAP lymphadenopathy, V+ involvement of the inferior vena cava and/or hepatic veins, P + portal vein involvement, E + extrahepatic abdominal disease, F + tumor focality, R + tumor rupture, C +, caudate lobe tumors, N + lymph node metastases, M + distant metastases, HCC hepatocellular carcinoma, SIOPEL international childhood liver tumor strategy group

^aPatient diagnosed with HCC postoperatively

^bDuring exploration for planned mass excision, the patient was reclassified as PRETEXT 4 and underwent transplantation

^cMeasured by pathology

^dDiaphragmatic invasion

due to advanced stage-widespread disease. Neo-adjuvant chemotherapy was given to 40% of the patients. Clean tumor-free surgical margin was achieved in all patients who underwent surgical resection. All patients who had total tumor excision with primary liver resection were observed to have low AFP values at the time of admission ($n = 9$, median AFP: 2.78 ng/ml, range: 1.2–21).

Ten patients received postoperative adjuvant chemotherapy, with a 5-year survival rate of 70%. For those patients who received liver transplantation; a 5-year survival rate of 75% was achieved. In inoperable patients, all showed metastatic disease and received neoadjuvant chemotherapy. Chemotherapy treatment was planned individually, with sorafenib treatment prominent in patients with local negative surgical margins, and chemotherapy protocols containing cisplatin and doxorubicin applied in advanced stage patients.

Nasocerebral mucormycosis developed in one of the patients who underwent liver resection resulting in the patient’s demise. The 5-year survival rate among inoperable patients was found to be 0%. For one patient, who was PRETEXT stage 3, mass resection was initially performed to gain time due to the unavailability of a donor. However, during this waiting period, recurrence developed, and the patient later underwent liver transplantation. The same patient also underwent transarterial radioembolization (TARE) until liver transplantation for bridging therapy.

The most common metastases were seen in the lung and bone, occurring at a rate of 26.6%. Overall, the 5-year survival rate of pediatric HCC patients was determined to be 66.6%. Results of Kaplan–Meier analysis revealed that PRETEXT stage and chemotherapy type were observed to be independent risk factors for 5-year survival (Figs. 1, 2). According to the ROC analysis, it was observed that the average age and AFP values of the patients were independent risk factors for 5-year survival (Fig. 3).

We have 2 cases that have recurrence of the disease (Patient 10, 14), one of them was unable to undergo liver transplantation because lack of donor. He was subsequently put on a bridge treatment while waiting for a donor. However, during this time, a recurrence was observed (Patient 10). The other patient did undergo liver transplantation, but in the second-year post-operation, metastases were detected in the bone and transplanted liver, which were considered as a recurrence (Patient 14).

In our research, one patient (Patient 1) was found to have lung metastasis in the 5th year after liver transplantation, and another patient (Patient 9) was found to have lymph node metastasis in the 2nd year after liver resection. Both patients underwent metastasectomy. While two of our patients were not eligible for surgery due to distant organ metastases (Patients 12 and 15), the other patient was found to have distant organ metastases in the 2nd year after liver resection (Patient 13).

Table 2 Area under the curve

Test result variable(s)	Area	Std. error ^a	P value ^b	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Age	0.777	0.064	0.009	0.452	0.802
Sex	0.544	0.063	0.058	0.320	0.768
AFP	0.617	0.062	0.023	0.495	0.740

The test result variable(s): hb has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased

^aUnder the nonparametric assumption. ^bNull hypothesis: true area = 0.5

In univariate Cox regression analysis, age, neoadjuvant chemotherapy AFP, and PRETEXT staging systems were observed to be associated with 5-year survival. According to the results of multivariate Cox regression analysis, neoadjuvant chemotherapy [HR = 2.840, 95% confidence interval (CI): 0.915–4.671, *P* < 0.001], AFP value [HR = 1.719 95% confidence interval (CI): 1.427–1.915, *P* < 0.001], and PRETEXT staging systems were observed to be independent positive factors for 5-year survival (Table 3).

Fig. 1 Kaplan–Meier curves of chemotherapy types with 5-year survival

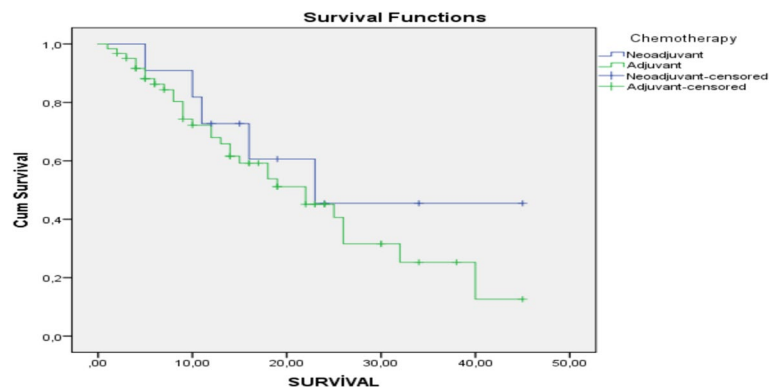
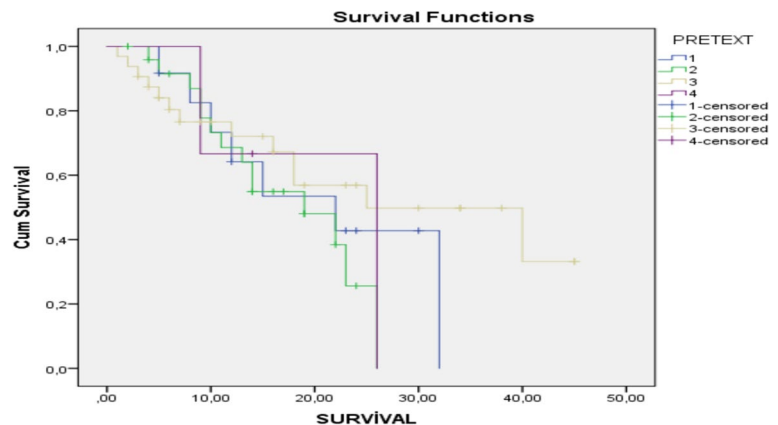


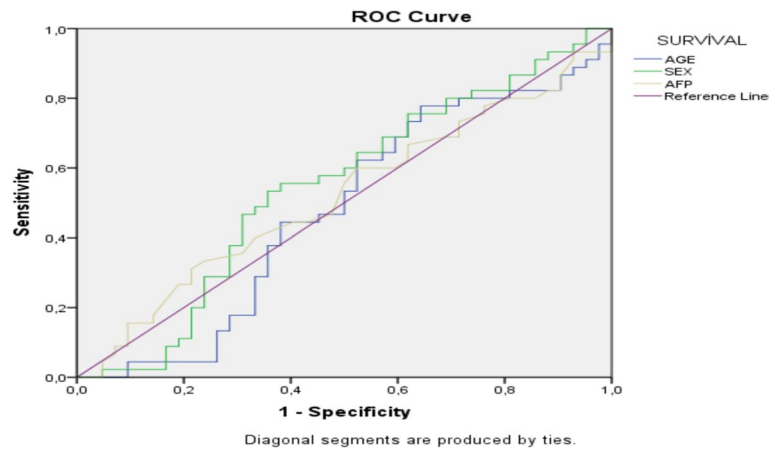
Fig. 2 Kaplan–Meier curves for PRETEXT staging systems versus 5-year survival



Discussion

Hepatocellular carcinoma is a very rare malignancy in the pediatric age group. In adults, HCC predominantly develops on a cirrhotic liver background [5]. However, in the pediatric age group, it can occur on two different bases: the more commonly encountered form (70%) is sporadic/de-novo HCC that develops in normal liver tissue. Histopathologically, sporadic HCC can be classified into “Conventional”, “Undifferentiated” (HCC-NOS- HCC with elements of hepatoblastoma), and “Fibrolamellar” HCC. The fibrolamellar variant of HCC occurs in 24% of cases and generally has a more favorable prognosis [12]. The remaining 30% of HCC mostly arises from chronic liver diseases, cirrhosis, and underlying metabolic, infectious, and vascular liver diseases (hemochromatosis, hereditary tyrosinemias, alpha-1 antitrypsin deficiency, glycogen storage diseases), chronic cholestasis (progressive familial intrahepatic cholestasis), and chronic viral hepatitis, as well as biliary atresia [13]. Tyrosinemia and perinatally acquired hepatitis B infection are major risk factors [4, 13, 14]. Pediatric HCC is more common in males than in females (0.45; 0.37/1 million). Of these, 12.9% are children under 5 years of age, and 34% are adolescents between the ages of 15 and 19 [15]. In our

Fig. 3 ROC curve analysis for independent risk factors for survival



series, only 4 of our 15 patients (28.5%) had underlying liver disease, supporting the fact that most pediatric HCC patients are not related to hepatic cirrhosis but are ‘de-novo’ [16].

Clinical symptoms and signs generally include abdominal pain and a mass in the abdomen, hepatosplenomegaly, gastroesophageal reflux, jaundice, and signs of liver failure [13]. AFP was found to be elevated in over 90% of HCC patients in a relatively large recent series of 65 patients under 20 years of age [17]. AFP correlates with tumor size, thus representing an indirect marker for treatment response [18]. AFP is high in 55–65% of pediatric HCC patients and normal in 25% [19]. The tumor size at diagnosis in pediatric HCC is generally larger compared to adults and falls outside the classic criteria used for surgical resection in adults [20]. On the contrary, in our series, all patients who had total tumor excision with primary liver resection were observed to have normal to low AFP values at the time of admission ($n=9$, AFP: 2.78 ng/ml, range: 1.2–21).

Macroscopic and microscopic features of pediatric and adult HCC are similar [16, 21, 22]. The two most common pathological subtypes are the classical trabecular variant and the fibrolamellar variant, but recently an intermediate form (indistinguishable between hepatoblastoma and hepatocellular carcinoma) has been also defined [23]. In our series, one patient was identified with this indistinguishable type (7.1%).

According to publications from adult series, adult variant of fibrolamellar HCC has a better prognosis than pediatric HCC [24, 25]. However, our experience has not confirmed this; in our study, the 5-year survival of fibrolamellar variant HCC patients was found to be higher than adult series with a rate of 87.5%. This discrepancy between adults and children may be attributed to the distinct biological behavior of the tumor in pediatric cases, which is generally less aggressive.

Surgical treatment, either through liver resection or transplantation, is essential for achieving relapse-free survival in

Table 3 Univariate and multivariate Cox analysis in 15 patients for 5 year overall survival in HCC patients

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Univariate analysis				
Age	1.361 (1.036–1.681)	0.012	–	–
Sex: female vs. male	0.789 (0.562–1.265)	0.478	–	–
Adjuvant chemotherapy	1.221 (0.912–1.668)	0.231	1.067 (0.912–2.388)	0.231
Neo-adjuvant chemotherapy	3.635 (2.321–5.684)	0.033	2.840 (0.915–4.671)	<0.001
AFP	1.856 (1.047–2.190)	0.047	1.719 (1.427–1.915)	<0.001
PRETEXT	1.935 (1.125–2.092)	0.014	1.512 (1.157–1.913)	0.022
1	2.635 (1.712–3.029)	<0.001	2.367 (1.174–2.357)	<0.001
2	1.226 (1.068–1.681)	0.006	1.188 (1.023–1.617)	0.012
3	3.852 (1.836–7.910)	<0.001	3.589(1.940–6.539)	<0.001
4	2.284 (1.24–4.18)	0.008	3.412 (2.111–4.216)	<0.001
Metastasis	2.367 (1.487–3.711)	0.456	2.158 (1.517–2.943)	0.415
Recurrence	1.892 (0.987–2.822)	0.521	1.632(1.365–2.573)	0.352

In univariate Cox regression analysis, age, neoadjuvant chemotherapy AFP, PRETEXT staging systems predicted 5 year survival ($P<0.05$)

hepatocellular carcinoma (HCC) patients [26]. Liver transplantation (LT) is particularly critical for those with chronic liver disease and HCC, offering a dual benefit of removing the tumor and addressing the underlying liver condition [27]. Despite its advantages, the use of LT in pediatric cases is not fully supported by adult-oriented staging systems like the Milan Criteria. Research indicates that LT could be more advantageous for pediatric patients not meeting these criteria, with survival rates ranging from 72 to 83% [28–30]. However, the scarcity of liver grafts and the high HCC recurrence rates limit LT's broader application. Additionally, the long wait times exacerbate tumor progression, leading to high dropout rates from transplant lists. Locoregional therapies, such as radiofrequency ablation (RFA), transarterial radioembolization (TARE), and transarterial chemoembolization (TACE), are used to manage disease progression and bridge the gap to transplantation [31, 32]

One of the most important issues here is the recurrence rate after transplantation. This rate has been reported as 10–30% in studies [33]. Recurrence significantly reduces post-transplant survival, and treatment options are very limited in these patients [34]. The recurrence rate of our existing 4 transplantation patients is 25% and this has also been confirmed in our study. Overall survival is not encouraging in studies, but we found a 5-year survival of 66.6% in our series.

Specialized centers with expertise in hepatobiliary surgery, liver transplantation, and pediatric oncology are needed for pediatric HCC patients, who require both surgical and oncological aggressive treatment.

Limitations

Present study has several limitations. The relatively small sample size of 15 patients may confine the generalization of the findings. Additionally, the study's retrospective design relied on existing medical records, which may introduce recall and selection bias.

The single-center nature of our study means that the results reflect the specific characteristics, the experience, and

the treatment practices of our institution. It would be beneficial to conduct multicenter studies for a broader perspective. Moreover, the follow-up periods for some patients were limited, which might have prevented a comprehensive understanding of long-term survival and recurrence rates.

The cohort's heterogeneity, with patients having varying stages of hepatocellular carcinoma (HCC), different underlying conditions, and diverse treatment pathways presents another challenge for this study.

This diversity mirrors real-world clinical scenarios but complicates direct comparisons and limits the potential for specific subgroup analyses.

Addressing these limitations in future research could provide more definitive insights into the efficacy of the surgical technique.

Conclusion

The effectiveness of surgical treatment in pediatric hepatocellular carcinoma patients and the favorable outcomes of liver resection and liver transplantation have been demonstrated in this study. The use of postoperative adjuvant chemotherapy and individualized chemotherapy protocols has increased survival rates. However, it should be emphasized that the treatment options for inoperable patients are limited and that more studies are needed.

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Author contributions M.K. performed all the data collection, and was involved in the drafting and critical revision of the manuscript for important intellectual content. U.C. contributed to the study design, data analysis, interpretation of results. E.A. contributed to the data collection and was involved in drafting the manuscript. D.N. provided the histopathological data, interpreted the pathology findings. O.E. designed and conceptualized the study, supervised the project, contributed to the data interpretation, and was involved in drafting and critically revising the final version of the manuscript.

Data availability Data supporting the findings of this study are provided within the manuscript.

Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors declare no competing interest.

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