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Original Research

Comparison of Tumour Characteristics and Outcomes in Paediatric Conventional Versus Fibrolamellar Hepatocellular Carcinoma: Tertiary Centre Experience

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Abstract

Objectives: Hepatocellular carcinoma (HCC) in the paediatric age group is a rare and unique disease, with limited evidence to guide treatment decisions. The two main histological subtypes, conventional HCC (cHCC) and fibrolamellar HCC (FL-HCC), differ in their natural history and clinical characteristics. Whether the absence of underlying cirrhosis in FL-HCC confers a survival advantage remains unclear due to inconclusive evidence.

Methods: A retrospective analysis was conducted at a tertiary centre in the United Kingdom, evaluating paediatric patients with HCC referred between 1994 and 2022. Subgroup analysis compared outcomes between cHCC and FL-HCC. Kaplan–Meier analysis was used to compare survival, and Cox regression analysis was performed to identify factors associated with worse survival.

Results: A total of 27 patients were included (cHCC = 17, FL-HCC = 10). The median age was 11 years (cHCC = 9 years, FL-HCC = 14 years), with a male-to-female ratio of 2.5:1 (M = 20, F = 8). Cirrhosis was present in 8 of 17 evaluable cHCC cases and absent in all FL-HCC cases. Surgical treatment was undertaken in 15 cHCC patients (hepatectomy = 3, transplantation = 12) and 8 FL-HCC patients (hepatectomy = 6, transplantation = 2). Median overall survival was 29 months for cHCC and 42 months for FL-HCC ($P = 0.580$). Median recurrence-free survival was 29 months for cHCC and 31.5 months for FL-HCC ($P = 0.395$). Cox regression identified PRETEXT stage as an independent prognostic factor for poorer survival.

Conclusion: Although FL-HCC occurs in non-cirrhotic livers and presents in older children, no significant survival advantage was observed compared to conventional HCC. Tumour extent, as reflected by PRETEXT stage, remains a key prognostic factor. Further multicentre studies are needed to better define optimal treatment strategies for paediatric HCC.

Keywords: Paediatric Hepatocellular Carcinoma, Conventional Hepatocellular Carcinoma, Fibrolamellar Hepatoclleular Carcinoma, Liver Transplantation

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Primary liver tumours are rare in children, constituting around 1% of all childhood tumours. The majority are hepatoblastomas (80%), while hepatocellular carcinoma represents only <20% of all cases.[1-3] Although the incidence of hepatoblastoma and mesenchymal tumours have increased over the years, the incidence of HCC remained relatively stable.[4-6]

The treatment pathway for HCC patients is evolving with time. Surgery remains the main stay of any curative intent treatment. Despite the low response rates of HCC tumours to chemotherapy, its role in downstaging advanced tumours is evolving.[7,8] Patients are being increasingly considered in trials, and research is ongoing to dissect the genetic and molecular basis of HCC tumours. Recently, novel vaccinations and immunotherapeutic drugs targeted against tumour specific molecules are being developed.[9,10]

Our understanding of the natural course of HCC in childhood is largely based on analysis of retrospective data extending over a long period of time, while there is limited data from trials or prospective research. Acknowledging the rarity of this disease entity, the latter may prove challenging. The largest ongoing trial is the Paediatric Hepatic International Tumour Trial (PHITT). This is a multi-centre international study evaluating treatment strategies for paediatric liver cancers, including hepatocellular carcinoma. It aims to improve outcomes by tailoring therapy based on risk stratification and tumour biology. Patients with resectable HCC are treated with PLADO (cisplatin + doxorubicin) and may be randomised to receive sorafenib, while patients with unresectable or metastatic HCC receive PLADO alternating with or without GEMOX (gemcitabine +oxaliplatin) and sorafenib.[11]

Similar to adults, conventional HCC (cHCC) and fibrolamellar HCC (FL-HCC) have been distinguished on a histological and clinical basis in paediatric patients.[12,13] Paediatric FL-HCC constitute at least 20-30% of all cases compared to <10% in adults.[14-16] The controversy whether FL-HCC has similar to or better prognosis than cHCC also exists in paediatric patients as in adults.[4,13,17-19]

This study highlights the experience of one of three United Kingdom paediatric hepatobiliary and liver transplant centres in the treatment of paediatric HCC. The treatment pathway and outcomes for paediatric HCC were investigated and presented. We aim to add to the pool of data available and expand our understanding of this rare tumour in the paediatric age group.

Methods

Our study cohort was based in a tertiary paediatric hepatobiliary and liver transplant unit. Patients' records were retrieved and all cases with suspected diagnosis of HCC referred to our unit between 1994 and 2022 were included. All patients were discussed in a multi-disciplinary team meeting, and patients who were considered candidates for curative intent treatment were either offered upfront surgery in the form of liver resection or transplantation, or referred to oncology for consideration of neoadjuvant treatment, possibly in the setting of a clinical trial. Patients without underlying liver parenchymal disease and where two or more contiguous liver segments can be preserved were considered for liver resection after the staging scans confirm absence of metastatic disease. On the other hand, underlying liver cirrhosis or non-metastatic locally unresectable disease (PRETEXT IV) were indications for liver transplantation. Multi-visceral transplantation was only considered in selected cases, mainly extensive thrombosis of the porto-mesenteric venous system.

Inclusion criteria included age of 16 years and below, pre-operative radiologic or histologic diagnosis of HCC and patients with incidental diagnosis of HCC on liver explant histology. Patients with non-HCC diagnosis on final histology or with inconclusive diagnosis due to overlapping features of HCC or hepatoblastoma were excluded. Patients with a minimum of 2 years follow up after diagnosis were included in the study. The following variables were collected: patients' demographics, PRETEXT stage, alpha-feto protein (AFP), extent of surgical intervention, background liver histology, chemotherapy details, enrolment in clinical trials and survival data. Mann-Whitney U test was used to compare numerical variables, and Chi Square test was used for categorical variables.

For survival analysis, overall survival (OS) was calculated from the date of radiological diagnosis to the date of death or last follow up. Disease-free survival (DFS) was calculated from the date of surgery to the date of recurrence or last follow up. Kaplan-Meier analysis was used to compare survival and generate survival curves. Cox regression analysis was performed to investigate factors associated with worse outcomes. SPSS version 26.0 software package (SPSS Inc., Chicago, IL, United States) was used to perform statistical analyses.

Results

Demographics and Clinical Characteristics of Tumours and Patients

Demographics of Whole Cohort

A total of 33 patients with possible diagnosis of HCC were referred over the study period. Six patients were excluded as final histology either confirmed a diagnosis other than HCC or was inconclusive. Twenty-seven patients with HCC were identified and included. Median age at diagnosis was 11 years (interquartile range (IQR)= 8-14 years). Male to female ratio was 2.5:1 (20 males and 8 females). 17/27 (63%) patients had cHCC based on pre-operative biopsy or histopathological examination of the resected specimen, while 10/27 (37%) patients were diagnosed with FL-HCC.

Comparison Between Patients with cHCC and FL-HCC (Table 1)

Patients with cHCC had a median age of 9 years and were younger compared to FL-HCC patients who had a median age of 14 years, p=0.031. There was no difference in gender distribution between the two entities. Eight out of seventeen (47%) patients with cHCC had underlying liver cirrhosis secondary to: chronic hepatitis B infection (n=1), tyrosinemia (n=1), congenital hepatic fibrosis (n=1), progressive familial intrahepatic cholestasis (n=1), congenital porto-systemic shunt (n=1), mitochondrial disease (n=1), biliary atresia (n=1) and Alagille's disease (n=1). However, none of the patients with FL-HCC showed macroscopic or microscopic features of cirrhosis. Eleven out of seventeen (65%) patients with cHCC had raised AFP levels compared to 2/10 (20%) patients with FL-HCC. Although more advanced PRETEXT stages were noticed in cHCC patients, this was not statistically significant. More patients underwent liver resection than transplantation in the FL-HCC group (resection= 6, transplantation=2), compared to cHCC patients (resection= 3, transplantation= 12).

Table 1. Demographics, tumour characteristics and spectrum of surgical treatment for the study cohort.

	Conventional HCC (n=17)	Fibrolamellar HCC (n=10)	p
Median age at diagnosis (IQR)	9 years (6-14)	14 years (11-15)	0.031
Gender			0.370
Male	13	6	
Female	4	4	
Background liver histology			0.002
Normal	9	10	
Cirrhotic	8	0	
AFP levels			0.013
<=20	4	7	
>20	11	2	
Missing	2	1	
Pre-operative biopsy	12	8	0.562
PRETEXT stage			0.178
Stage I	4	0	
Stage II	3	4	
Stage III	1	3	
Stage IV	8	1	
Missing	1	2	
Neoadjuvant chemotherapy	5	3	0.974
Resected disease	15	8	0.566
Hepatectomy			
Right	-	2	
Extended right	2	-	
Extended left	-	4	
Extended left + ablation	1	-	
Transplant			
Split/reduced OLT	7	1	
Whole graft OLT	5	-	
Multi-visceral transplant	-	1	
Complete resection			0.940
R0	13	6	
R1	2	2	
Missing	2	2	

OLT: Orthotopic Liver Transplant.

Treatment Pathway

Upfront surgery was performed in 17/27 (63%) patients, while 2/27 (7%) patients neither received neoadjuvant treatment nor underwent surgical resection. Of the 8/27 (30%) patients who received neoadjuvant treatment (NAT), curative surgery was performed in 6 patients.

Surgically Treated Patients

A total of 23/27 (85%) patients had curative intent surgery (cHCC= 15/17 patients, FL-HCC= 8/10 patients). Thirteen patients underwent liver transplantation, 9 patients had liver resection, either in the form of a hemihepatectomy or an extended hemihepatectomy, and one patient underwent multi-visceral transplantation due to extensive portal and mesenteric venous thrombosis.

Neoadjuvant Treatment Followed by Surgery

Five patients with cHCC had neoadjuvant treatment, however only four patients underwent surgery; two out of the four patients received peri-operative chemotherapy (neoadjuvant and adjuvant) according to Group D of the PHITT trial (Cisplatin intensive regimen followed by consolidation Carboplatin/Doxorubicin); one of the two patients had lung metastasis that completely responded to treatment and the other patient had partial response. One of the four patients with cHCC had chemotherapy according to Group F (Arm 2) of the trial and received alternating cycles of PLADO/Sorafenib with cycles of Gemcitabine/Oxaliplatin (GEMOX) and sorafenib. One patient had treatment abroad in the form of Cisplatin, 5-FU, Vincristine and Doxorubicin. Both of the latter two patients had stable disease and proceeded to surgical resection.

Three patients with FL-HCC received NAT, but only two patients proceeded to surgery. One patient was enrolled in Group F (Arm 1) and received Cisplatin/Doxorubicin (PLADO) and sorafenib, and one patient had Lenvatinib as a single agent treatment. Both patients had stable disease post chemotherapy and underwent surgery subsequently.

Surgery Followed by Adjuvant Chemotherapy

Of the 17 patient who underwent upfront surgery, 5 patients received adjuvant treatment. Only one patient with cHCC received chemotherapy with doxorubicin and sorafenib, while four patients with FL-HCC received adjuvant treatment; two patients were enrolled in Group F (Arm 1) of the PHITT trial, one patient had cisplatin and doxorubicin based regimen, while data about type of adjuvant chemotherapy was missing for the last patient.

Unresected Patients

Four patients did not undergo curative resection. Two patients with cHCC and two patients with FL-HCC. Among the two patients in the cHCC group, one patient had chronic hepatitis B cirrhosis and the other had mitochondrial disease. One of them was not fit for neoadjuvant chemotherapy, and the other patient had four cycles of neoadjuvant cisplatin and doxorubicin and showed stable disease. However, both of these patients had extensive disease not allowing for liver resection and significantly high levels of AFP outside the criteria for organ transplantation.

Of the two unresected patients in the FL-HCC group, one patient received alternating cycles of Cisplatin and Carboplatin/doxorubicin (Group D) but showed progressive disease. While the other patient had advanced disease along with extensive portal vein thrombosis that the possibility of disease downstaging to allow resection or transplantation was low, therefore chemotherapy was not offered in favour of better quality of life.

Survival Analysis of Conventional vs Fibrolamellar HCC

Median overall survival (OS) for the whole cohort of patients was 36 months (IQR= 18-86), and the recurrence-free survival (RFS) was 31 months (IQR= 9-57). Median OS for cHCC patients was 29 months (IQR= 15.5-78) and shorter than median OS of FL-HCC patients of 42 months (IQR= 21.3-53.3) though not statistically significant, p= 0.580 (Fig. 1; A). Median RFS was shorter for cHCC compared to FL-HCC patients (29 months (IQR=5-71 months) compared to 31.5 months (IQR= 10-49 months), respectively); however, this also did not differ significantly, p=0.395 (Fig. 1; A).

To eliminate cirrhosis as a cofounding factor in survival analysis, we excluded cHCC patients with underlying cirrhosis. There was no significant difference in the median OS between non-cirrhotic cHCC (18 months) and FL-HCC groups (42 months), p=0.851. However, median RFS for non-cirrhotic cHCC was found to be only 12 months and approached but did not reach statistical significance compared to FL-HCC patients (median RFS= 31.5), p=0.092. (Fig. 1;B).

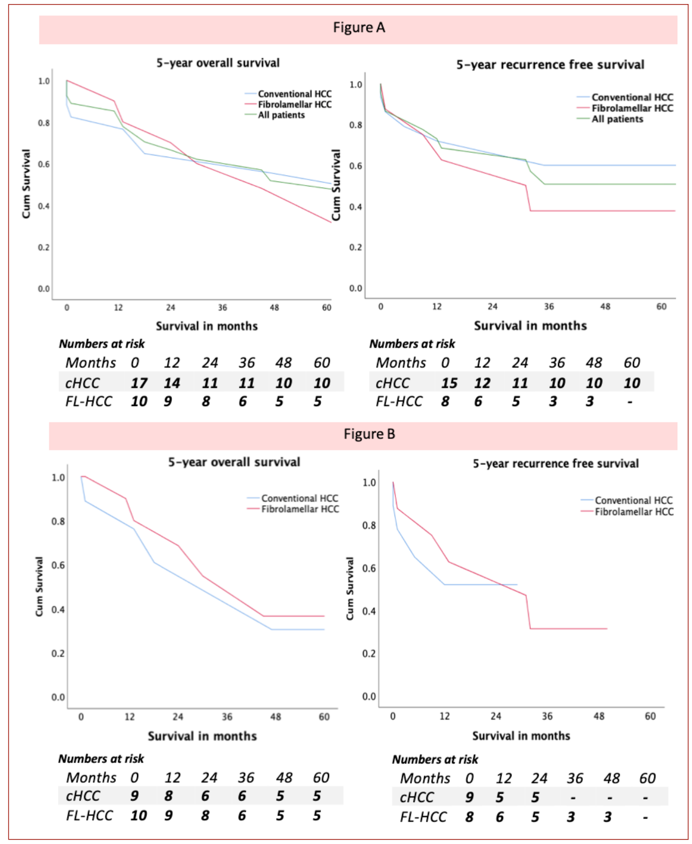

Figure 1. Kaplan-Meier survival curves. **(a)** Comparison of OS and RFS of cHCC and FL-HCC patients who underwent surgery. **(b)** Comparison of OS and RFS of cHCC and FL-HCC patients without cirrhosis.

Recurrence Pattern

A total of ten patients had recurrence following resection (five patients in each group). In the cHCC group, three had recurrence limited to the liver (2 post hepatectomy, 1 post liver transplant) and two patients developed recurrence in the lungs only (both post liver transplant).

Three patients with FL-HCC had isolated lymph node (LN) recurrence (2 in regional LNs, 1 in mediastinal LNs), one patient had recurrence in regional LN and lungs and one patient had liver and lung recurrence.

Factors Predicting Survival

Age, gender, AFP (normal vs high), PRETEXT stage, type of HCC, background liver histology, surgical resection, resection margin status and neoadjuvant treatment (NAT) were entered into a univariate cox regression hazard model. This identified higher PRETEXT stage, absence of surgery and lack of NAT to be associated with worse survival, increasing the risk of mortality by 2.5, 5 and 4.4 times, respectively. These factors were further entered into a multivariate model and this identified higher PRETEXT stage to be independent predictor of poor survival Table 2.

Table 2. Cox regression analysis for overall survival

	Univariable analysis		Multivariable analysis	
Variable	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**
Age	0.787	0.982 (0.86-1.12)	-	-
Gender	0.394	1.77 (0.48-6.57)	-	-
AFP	0.394	1.65 (0.52-5.23)	-	-
PRETEXT stage	0.021	2.54 (1.16-5.61)	0.033	2.44 (1.07-5.55)
Type of HCC	0.816	1.15 (0.36-3.64)	-	-
Cirrhosis	0.545	1.50 (0.40-5.64)	-	-
No surgery	0.013	5.05 (1.41-18.09)	0.107	3.36 (0.77-14.70)
R status	0.640	1.65 (0.20-13.48)	-	-
No NAT	0.038	4.46 (1.09-18.30)	0.326	0.40 (0.07-2.47)

Discussion

This study introduces the experience of a regional paediatric hepatobiliary and transplant centre in the treatment of HCC over a 28-year period. Despite this, only twenty-seven patients were identified after thoroughly scanning data bases and MDT outcomes. This shows the rarity of this tumour and therefore limits our understanding of the disease. Key areas of debate in paediatric HCC include optimal chemotherapy regimen, the role of neoadjuvant treatment, use of adult guidelines, criteria for resectability and indications for liver transplantation. The purpose of this study is to track the treatment pathway of HCC patients including neoadjuvant treatment regimens and extent of surgical treatment provided, and compare outcomes for the two main histologic subtypes of HCC in the paediatric age group, namely conventional and fibrolamellar HCC.

The age distribution and slightly higher incidence in male patients noticed in our cohort correlates with what is reported in literature.[6,20] Patients with paediatric cHCC were younger than FL-HCC, the later being a disease of teens or adolescents. The proportion of FL-HCC in the current study corresponds to the published data.[2] Categorising HCC patients into subgroups is mandated as both diseases have different clinical and histopathological characteristics.[21,22] cHCC in paediatric patients can occur on a background of liver pathology or, more commonly than in adults, de novo. 20-30% of paediatric patients will have underlying liver disease compared to 85% in adults.[2] However, this was noticed to be higher in our cohort (8/17 patients). This may reflect referral bias to a tertiary centre, where children with more complex or pre-existing liver conditions are more likely to be managed, or it could suggest geographical variation in underlying liver disease prevalence. On the other hand, none of the patients with FL-HCC had underlying liver pathology, consistent with its known occurrence in non-cirrhotic livers.

Almost two thirds of cHCC patients in our study had elevated AFP levels, while only two patients with FL-HCC had elevated values. This is likely because AFP is an oncofoetal glycoprotein that is elevated not only in tumour cases, but also a marker of acute and chronic liver disease and cirrhosis.[23] The L3 fraction of AFP has shown greater specificity, especially in early disease, than AFP alone.[24,25] In addition, when combined with another tumour marker, Des-gamma-carboxyprothrombin (DCP), also known as PIVKA-II (Protein Induced by vitamin K absence or antagonist-II), the sensitivity and specificity approach 90%.[23,26] Recently, a novel tumour marker derived from dysregulated RNA processing in HCC tumours; extracellular vesicle-derived long noncoding RNA (lncRNA), has shown promising results in identifying early HCC but is still under investigation.[27]

Less than half of our patients received peri-operative chemotherapy. Hepatocellular carcinomas in general are well known for their chemo-resistance.[7,28,29] However, it is reported that paediatric HCC have higher response rates to chemotherapy.[30] The reported response rate for chemotherapy in paediatric HCC can be up to 50% compared to around 20-25% in adults.[31] This remains unsatisfactory and account for the relatively low rates of chemotherapy administration reported in this group of patients. It also contributes to the fact that the majority of patients with less advanced disease will be offered upfront surgery. Seven out of thirteen patients with PRETEXT stage 3- and 4-disease in our cohort received neoadjuvant chemotherapy, while none of the patients with PRETEXT stages 1 and 2 received neoadjuvant treatment. In addition to low response rates, differences in local practices and expertise have also led to variations in chemotherapy protocols administered. In the majority of patients, this is usually based on cisplatin and doxorubicin. The addition of immunotherapeutic and molecular targeted agents has made it difficult to standardize regimens and identify associated outcomes.[31,32] The implementation of systematic chemotherapy protocols, within clinical trials, might enable us to explore response rates to different protocols and identify disease patterns for which treatment can be tailored.

Survival In patients with cHCC and FL-HCC was comparable. Survival was initially better for FL-HCC patients in the first two years after diagnosis until survival curves crossed and cHCC patients had survival advantage, though this was not statistically significant. Results from the current literature comparing survival between the two disease entities are mixed.[17-20] Better prognosis in patients with FL-HCC reported by some researchers is thought to be due to the absence of underlying liver parenchymal disease.[12,33] This might explain the better short-term survival noticed in FL-HCC compared to cHCC patients, despite the fact that our subgroup analysis comparing FL-HCC with non-cirrhotic cHCC still showed a survival advantage for the earlier group, though this was not statistically significant. Also, these patients would expectedly tolerate and benefit from more extensive resections and peri-operative chemotherapy.[34,35] On the other hand, research showing similar outcomes for the two categories report that any survival advantage is offset by the higher tendency for lymphatic spread in FL-HCC patients and its role in early disease recurrence,[17,36,37] which may explain why the 5-year survival in FL-HCC patients was lower in the study.

Recurrence pattern for both HCC types is different.[13] In our study, cHCC patients had recurrence in the liver more commonly than FL-HCC, where recurrence in the latter was mainly in lymph nodes and lungs. Median RFS was relatively similar in both groups although only 3 out of 8 resected patients with FL-HCC remained disease free, compared to 10 out of 15 resected cHCC patients over the study period. Building on the observation that 5-year OS was noted to be worse in FL-HCC due to more frequent lymph node metastases, worse long-term RFS was also seen more commonly in FL-HCC. Lymphatic spread is associated with poor tumour biology and high recurrence rates,[38] and immunohistochemistry showed that FL-HCC is derived from cells that can differentiate into hepatocytes or cholangiocytes, with the latter having more potential to metastasize.[39]

Cirrhosis has been inconsistently reported to be associated with worse outcomes.[18,40-42] Cirrhotic patients have two coexisting morbid conditions that are expected to reflect negatively on survival; the tumour itself and the underlying chronic liver disease. However, the caveat here is that patients with cirrhosis are typically under regular clinical follow up and would have interval surveillance scans or laboratory tests (tumour markers) that might lead to early tumour detection.[43] In our cohort, cirrhosis was not associated with worse prognosis on regression analysis. In addition, when cirrhotic patients were excluded from survival analysis, OS and DFS were not significantly different. Eight out of ten patients with cHCC who had underlying liver cirrhosis had resection and all of them underwent liver transplantation. Removing the diseased liver and achieving clearer margins with total hepatectomy and liver transplantation, might explain why cirrhosis was not identified to be associated with worse survival.

Higher PRETEXT stage was identified in univariate and multivariate analysis to be associated with worse prognosis. The PRETEXT staging system was first described by the International Childhood Liver Tumour Strategy Group (SIOPEL) in 1990 to adopt a uniform method to compare the extent and outcome of the disease.[44] It was revised in 2005 to provide more detailed classification of liver tumours to include the local extent of hepatic and vascular involvement, as well as systemic spread.[45] Higher disease stages are expected to reflect poor tumour biology as the tumour involves more liver parenchyma, whether by direct extension of a single lesion or by multiple intrahepatic metastasis. However, the staging system does not take into account the presence or absence of underlying liver cirrhosis, and the association with worse prognosis with higher stages was not consistently reported in the literature.[13,46]

The overall poor prognosis for HCC patients even after surgery and chemotherapy drives the search for different modalities of treatment. The molecular and genetic basis for HCC is a main focus of ongoing clinical research, as genetic mutations identified in such tumours can be targeted. One trial that started in April 2020 investigates the safety and efficacy of a novel vaccine targeting the pathognomonic fusion kinase protein (DNAJB1-PRKACA) along with immunotherapeutic agents in FL-HCC patients; the trial is still in phase 1 and is expected to conclude in 2027. Another phase 2 trial that also started in 2020, investigates the role of an immunologic drug (pembrolizumab) on the outcomes of patients with HCC (conventional and FL), and aims to explore predictors of response to treatment based on tumour biological factors; completion of the study is expected to be at the outset of 2028.[10]

The limitation of our study resides in its retrospective nature, limited number of patients and the span of the study period over which it was conducted. The variations in chemotherapy treatment and advances in surgical treatment and liver transplantation over time compounded these limitations. Our data showed that there was no significant difference in OS or RFS between cHCC and FL-HCC patients, and that higher PRETEXT stage was independently associated with worse prognosis. Randomised controlled trials would be challenging to perform considering the low incidence of HCC in paediatric age group and its feasibility is uncertain. Combining existing literature with prospective data is the only means to provide strong clinical evidence to help guide treatment pathways.

Disclosures

Ethics Committee Approval: This study received approval from the ethics committee and is registered under CARMS-31035.

Authorship Contributions: Concept – M.A., K.S.; Design – M.A., R.M., K.S.; Supervision – R.M., KS.; Materials – M.A.; Data collection &/or processing – M.A.; Analysis and/or interpretation – M.A., R.M.; Literature search – M.A.; Writing – M.A.; Critical review – D.F.M., D.H., E.O., R.M., K.S.

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