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Recurrence Rate of Hepatoblastoma in Children Following Preoperative Chemotherapy and Surgical Resection

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Abstract

Background: Liver tumors account for 1-2% of childhood cancers, with hepatoblastoma (HB) representing two-thirds of these cases. HB primarily affects children under two years old, often presenting as an asymptomatic abdominal mass. Treatment is challenging, with surgical resection being crucial. The PRETEXT staging system and neoadjuvant chemotherapy are vital in guiding treatment. While advancements have improved the 5-year survival rate for metastatic HB to 79%, about 20% of cases recur, significantly increasing fatality rates. Recurrence remains a significant challenge, highlighting the need for ongoing research to improve long-term outcomes for affected children.

Aim of the study: This study aims to explore the recurrence rate of hepatoblastoma in children following preoperative chemotherapy and surgical resection.

Methods: This prospective observational study at BSMMU, Dhaka, Bangladesh, spanned August 2021 to August 2023, involving 12 children with hepatoblastoma, excluding those with lung metastasis. After neoadjuvant chemotherapy following the SIOPEL protocol, patients underwent hepatic resection. Comprehensive clinical and radiological evaluations confirmed diagnoses, including PRETEXT staging and image-guided biopsies. Post-operative care included adjuvant chemotherapy and structured follow-ups. Data on demographics, staging, surgical outcomes, and complications were analyzed using SPSS. The study adhered to ethical standards, ensuring thorough patient counselling, informed consent, and standardized management protocols to optimize treatment outcomes.

Result: This study examined 12 participants with a median age of 22.5 months. The majority were between 13 and 24 months old, with more males than females. PRETEXT stage IIC was the most common. The study noted significant changes in serum bilirubin and S. Transaminase levels post-operation, with fluctuations in AFP levels. Recurrence rates varied by PRETEXT stage and annotation factors: Stage II had a low recurrence rate (12.5%), while stage III had a higher rate (50%). Annotation factor C was associated with a 20% recurrence rate, while factor F had a 50% recurrence rate. The presence of multiple annotation Factors (CF) experienced a 100% recurrence rate.

Conclusion: This study reveals that recurrence in paediatric hepatoblastoma post-chemotherapy and resection is linked to higher PRETEXT stages and specific annotation factors. Elevated serum AFP levels correlate with recurrence, suggesting AFP as a potential biomarker. It highlights the need for careful postoperative monitoring and calls for further research to enhance management strategies.

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Keywords: Recurrence Rate; Hepatoblastoma; Children; Chemotherapy; Surgical resection

Introduction

Liver tumors account for about 1-2% of all cancers found in children under the age of 18 [1]. Hepatoblastoma (HB) represents about two-thirds of liver tumors [2] and roughly 1% of all cancers in children [3]. HB originates from immature hepatic stem cells, which develop into the liver's epithelial structures [4]. HB most often occurs within the first two years of life. Most cases of hepatoblastoma present with an asymptomatic abdominal (right upper quadrant or epigastric) mass palpated by parents or physicians [5]. Sometimes, patients may have fever, anorexia, weight loss, and fatigue. Rarely, it may present with pain and haemorrhage [4,6]. Treatment of these tumors remains a significant clinical challange. Surgical resection remains the cornerstone of treatment for hepatoblastoma [7]. The PRE-treatment Extension of disease (PRETEXT) staging system designed by the International Childhood Liver Tumor Strategy Group (SIOPEL), combined with detailed annotation factors, can guide the indications for surgical resection and has become an internationally recognized standard [8]. Using neoadjuvant chemotherapy, studies have reported that extensive liver resection for POST-TEXT hepatoblastoma appears to have a comparable overall survival (OS) rate compared with liver transplantation when combined with chemotherapy [9,10]. HB is life-threatening for some patients due to the recurrence or progression of the disease. Prognosis is based on numerous factors including the age of diagnosis, PRETEXT group, metastasis, alfa fetoprotein (AFP) levels, histologic subtype, tumor response to chemotherapy, completeness of resection, and clinical stage of the disease [11]. Advancements in treatment protocols have led to a significant improvement in outcomes for hepatoblastoma, surpassing the progress seen with many other solid tumors. The 5-year survival rate for children with metastatic hepatoblastoma increased markedly from 27% in the 1990s to 79% by 2013 [12,13]. Despite many children reaching complete or partial remission through a combination of surgery and chemotherapy, about 20% of those with hepatoblastoma still experience a recurrence of the disease [14]. When recurrence happens, the fatality rate rises sharply. Studies have shown that the 3-year event-free survival (EFS) rate and overall survival (OS) rate for children with recurrent hepatoblastoma is just 34% and 43%, respectively [15]. Nonetheless, the recurrence of hepatoblastoma remains a formidable challenge, underscoring the need for ongoing research and the development of more effective treatment modalities. Understanding the recurrence patterns and their implications is essential for improving long-term outcomes and ensuring the best possible care for children with hepatoblastoma. This study aims to explore the recurrence rate of hepatoblastoma in children following preoperative chemotherapy and surgical resection.

Methodology and Materials

This Prospective observational study was conducted at the Department of Paediatric Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, over two years from August 2021 to August 2023. Twelve children with upper abdominal masses, confirmed as hepatoblastoma, were included after receiving neoadjuvant chemotherapy according to the SIOPEL protocol. Patients with lung metastasis were excluded. Comprehensive histories were taken, and clinical examinations were documented using a structured data sheet. The diagnosis was confirmed through a complete blood count, liver function tests, serum alfa-fetoprotein levels, radiological evaluations (ultrasound, CT scan), and image-guided core biopsies. The study received ethical approval from the Institutional Review Board (IRB) of BSMMU.

PRETEXT staging was determined through radiological evaluation. The patient was then referred to the Department of Paediatric Hemato-oncology and received 4-6 cycles of neoadjuvant chemotherapy following the SIOPEL protocol. For patients without lung metastasis, those eligible were admitted to the Department of Paediatric Surgery after thorough parental counselling and obtaining consent. Hepatic resection was performed after ensuring fitness for general anesthesia from the Department of Anesthesia, analgesia and intensive care medicine.

After post-operative recovery, patients were referred back to the Department of Paediatric Hematooncology for adjuvant chemotherapy, with follow-ups at 14 days, three months, and six months. Operative findings, complications, and the standardization of techniques for different hepatic resections were thoroughly documented. Post-operative management was carefully standardized, with adjustments made for patient benefit. Standard discharge criteria and management protocols were adhered to, and patients and their parents received detailed counselling regarding the diagnosis, treatment options, procedure performed, potential complications, and expected outcomes. Consent for surgery was obtained after thorough counselling, and routine investigations were completed to ensure fitness for anesthesia and surgery.

Data collection and analysis:

Data was collected using a pretested sheet that captured demographic details, relevant history, PRETEXT staging, examination findings, and investigation reports for all study subjects. Complications during follow-up were also recorded. The data was compiled, sorted, and analyzed using standard statistical methods, including percentage, proportion, ratio, mean±SD, median, and a P value of <0.05 for significance. Statistical analysis was conducted using computer-based

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software, specifically the Statistical Package for Social Sciences (SPSS), and other standard statistical tools.

Result

This study included a sample of 12 participants. The median age of the study group was 22.5 months, with an age range of 10 to 75 months. The majority of the children (58.33%) were aged between 13 and 24 months. The sex distribution indicated a greater prevalence of males (66.67%) than females (33.33%) (Table 1). Figure 1 shows that the most frequent PRETEXT stage among the participants was IIC, comprising 33.3% of the cases. Other stages, including II, IIF, and III, were less common, each occurring in 16.7% of the subjects. The least frequent stages were IIIC and IIICF, each seen in 8.3% of the participants. Additionally, 66.7% of the participants tested positive for annotation factors. The mean serum bilirubin level rose significantly from 100.0±0.0 preoperatively to 441.25±524.45 at 14 days post-operation (P = 0.041) but declined non-significantly at three months (P = 0.074) and fluctuated by six months (P = 0.132). There was a significant rise of S. Transaminase at 14 days post-operation (P = 0.034), followed by a non-significant reduction at three months (P = 0.143) and near normalization by six months (P = 0.501). A significant drop in AFP level was observed at 14 days (P = 0.003) and three months (P = 0.015). However, a non-significant increase was found at six months (P = 0.105) (Table 2). Sonographic estimation showed focal lesions found at 6 months post-operative period in 25% of patients (Figure 2). In the recurrence group, median AFP levels were extremely high at diagnosis, reaching 400,000, and fell to 8,249 before surgery. Postoperatively, AFP levels decreased to 2,000 at 14 days and 1,000 at three months but then surged to 300,000 by six months. In contrast, for the non-recurrence group, median AFP levels were significantly lower, starting at 2,000 at diagnosis and steadily declining to 93.5 before surgery, 8.5 at 14 days, 2.3 at three months, and 1.3 at six months post-operation (Table 3). Patients with PRETEXT stage II had a low recurrence rate, with only 1 out of 8 (12.5%) experiencing recurrence, while 87.5% did not. Conversely, PRETEXT stage III had a higher recurrence rate, with 50% of patients (2 out of 4) showing recurrence (Figure 3,4). Among the annotation factors, factor C was found in 5 patients, resulting in a 20% recurrence rate, whereas factor F, present in 1 out of 2 patients, was associated with a 50% recurrence rate. The presence of multiple annotation factors (C&F) was found with a 100% recurrence rate (Table 4).

Table 1: Distribution of the study subjects by demographic profile (n=12).

Demographic profile	Frequency (n)	Percentage (%)
Age (in months)		
≤12	1	8.33
13-24	7	58.33
25-36	1	8.33
37-48	0	0
49-60	1	8.33
>60	2	16.67
Sex		
Male	8	66.67
Female	4	33.33

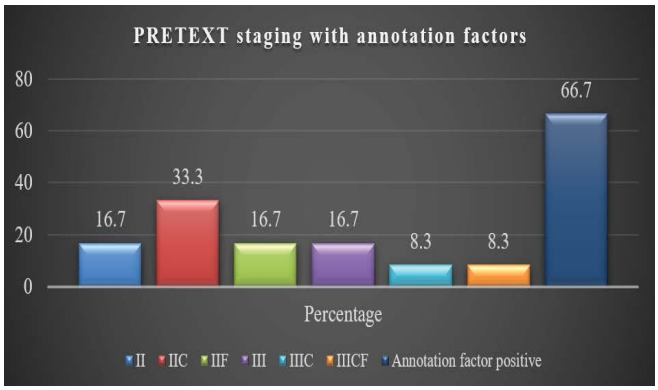

Figure 1: Distribution of the study subjects by PRETEXT staging with annotation factors (n=12).

Table 2: Serum profile of the study populations (n=12).

Variable	Preoperative	Post-operative					
		14 days	P value	3 months	P value	6 months	P value
S. Bilirubin							
Mean±SD	100.0±0.0	441.25±524.45	0.041s	142.78±69.85	0.074ns	595.83±1061.38	0.132ns
S. Transaminase							
Mean±SD	100.0±0.0	195.15±135.76	0.034s	168.96±151.41	0.143ns	106.48±32.21	0.501ns
S. Alfa fetoprotein (AFP)							
Mean±SD	2544.7±4448.7	690.4±10709	0.003s	624.1±1547.8	0.015s	66668.01±137068.2	0.105ns

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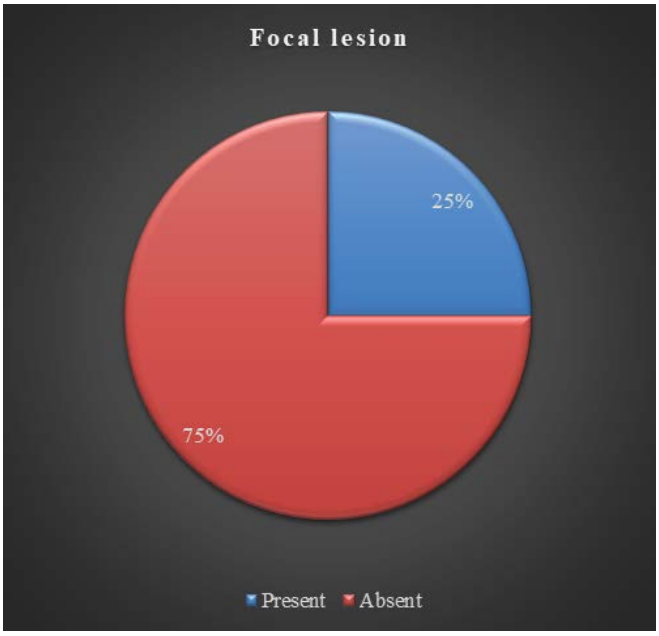

Figure 2: Distribution of the study subjects by sonographic estimation of focal lesion after 6 months post operative period (n=12).

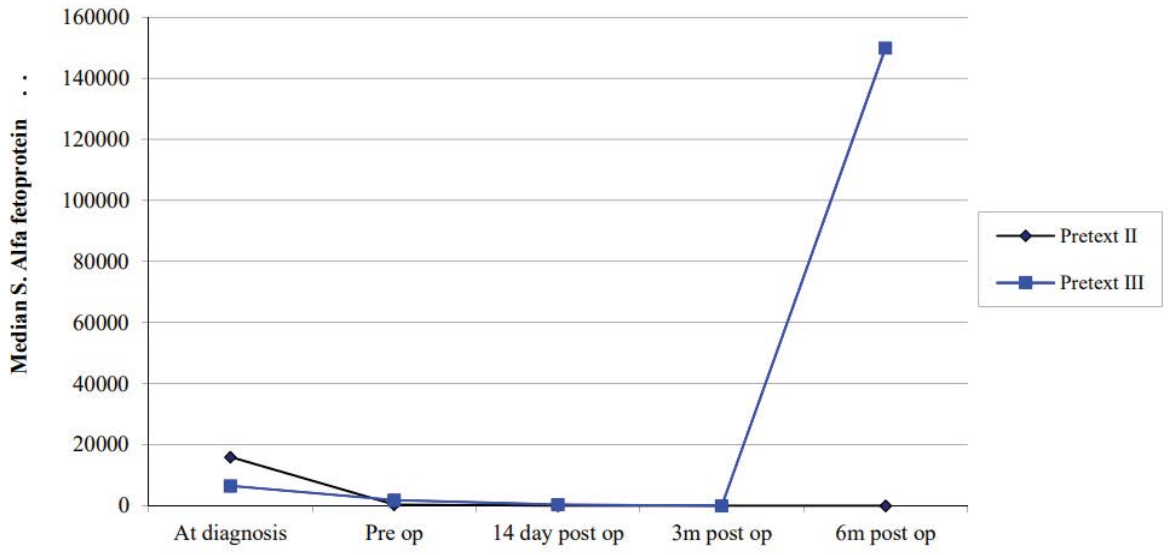

Figure 3: Correlation curve showing median S. alfa fetoprotein level at different time period with PRETEXT staging.

Table 3: S. Alfa fetoprotein (AFP) level at different time period (n=12).

Local recurrence		AFP at diagnosis	Preoperative AFP	AFP at post operative		
				14 days	3 months	6 months
Recurrence (n=3)	Median	400000	8249	2000	1000	300000
	Mean± SD	329266.7±298258.3	7949.7±6804.9	2069.3±1326.4	2134.5±2871.6	266666.7±152752.5
No recurrence (n=9)	Median	2000	93.5	8.5	2.3	1.3
	Mean± SD	30932.8±64539.4	743.1±1014.2	230.7±431.7	120.6±303.2	1.8±0.99

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Table 4: Correlation of PRETEXT staging and annotation factors with local recurrence (n=12).

Stage	Recurrence (n=3)		No recurrence (n=9)		Total		95% CI
	n	%	n	%	n	%	
II	1	12.5	7	87.5	8	66.67	0-31.6
III	2	50	2	50	4	33.33	1-99.0
C	1	20	4	80	5	41.67	0-86.0
F	1	50	1	50	2	16.67	1-99.0
CF	1	100	0	0	1	8.33	100.0-100.0

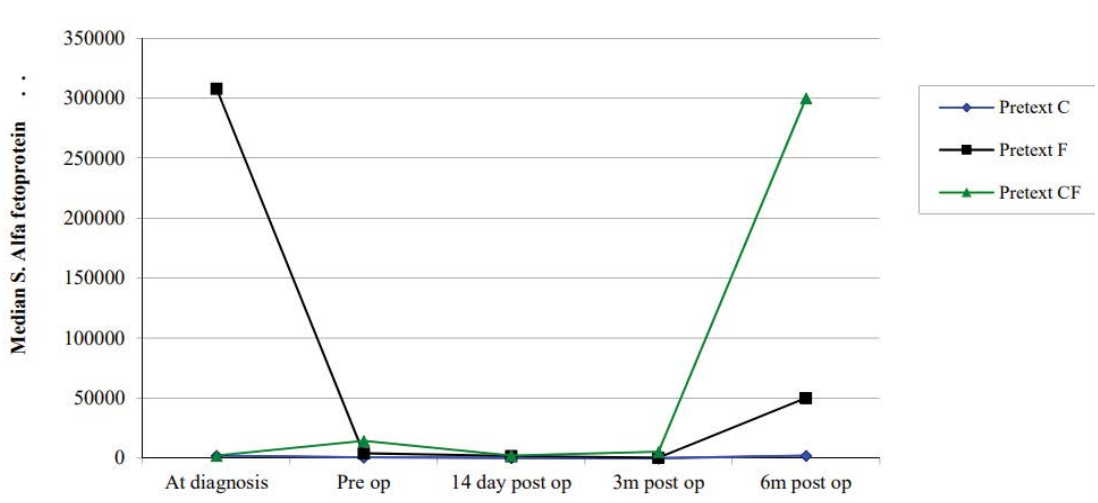

Figure 4: Correlation curve showing median S. alfa fetoprotein level at different time period with annotation factors.

Discussion

This perspective type of observational study aimed to assess PRETEXT staging and annotation factors and determine postoperative local recurrence by ultrasonography and serum alfa fetoprotein level. Hepatoblastoma is predominantly a disease of early childhood, with a peak incidence between 12 and 24 months of age. In this present study, it was observed that 58.33% of subjects belonged to ages 13-24 months. The median age was 22.50 months, with ranged from 10 to 75 months. This age distribution aligns with the existing body of knowledge regarding hepatoblastoma, also obtained by Yoon et al. [11], Santini et al. [16], and Koh et al. [17]. Sunil et al. [18] conducted a comprehensive analysis of paediatric hepatoblastoma cases and concluded that almost similar age groups at diagnosis. Age is a crucial factor in the prognosis and management of hepatoblastoma, but its role is intricate and influenced by various clinical variables. One of the key demographic findings in this study was the distribution of male and female subjects, with 66.7% male and 33.3% female. Several studies have reported a higher incidence of hepatoblastoma in males compared to females, as reported by Santini et al. [16], Koh et al. [17], and Aronson et al. [19]. A study conducted by Sunil et al. [18] found that 66.7% of their hepatoblastoma cases were male, which is consistent with the present study findings. This consistent gender bias suggests that there may be underlying genetic or hormonal factors contributing to the development of hepatoblastoma, which warrants further investigation. According to our study, 33.3% of the subjects had PRETEXT IIC, followed by 16.7% with PRETEXT II, PRETEXT IIF and PRETEXT III, and 8.3% with PRETEXT IIIC and IIICF, respectively. Furthermore, two-thirds (66.7%) of the subjects had a positive annotation factor. In the study of Schnater et al. [20], it was noted that a substantial proportion of patients presented with PRETEXT II disease, a finding consistent with our findings. According to Santini et al. [16], among all patients, 6% had a PRETEXT score of I, 16% scored II, 58% scored III, and 19% scored IV. In this study, we have a population of different age groups and liver maturation & function vary in different ages. So, we undertook the preoperative mean value of S. bilirubin, S. transaminase, prothrombin time & INR as a constant 100.0 and values of different time periods were calculated according to the preoperative value of each subject.

Our observation showed that the preoperative mean serum bilirubin level was 100.0±0.0. At 14 days postoperatively, the mean serum bilirubin level significantly rises to 441.25±524. At three months postoperatively, there is a decrease in the mean serum bilirubin level to 142.78±69.85, though it

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remains elevated compared to the preoperative baseline. Surprisingly, at six months postoperatively, the mean serum bilirubin level rises significantly to 595.83±1061.38. The statistical significance of these differences is highlighted ($p<0.05$. Needham et al. [21] mentioned in this study that plasma bilirubin levels exhibited a notable peak on the second day following surgery, followed by a gradual decline toward the normal range. However, it is important to note that the true baseline values were not reestablished until a period ranging from 3 to 6 weeks following the resection procedure. Post-hepatectomy S. bilirubin took approximately two weeks to return to normal [22-24]. The results of this study revealed that the mean S. transaminase levels increased sharply (195.15±135.7) at 14 days after surgery, reached a peak, and then gradually decreased at 3 and 6 months postoperative to 168.96±151.41 and 106.48±32.21. The statistically significant difference ($p<0.05$) in S. transaminase levels between the preoperative and postoperative 14-day periods underscores the importance of monitoring liver function after hepatic resection in children with hepatoblastoma. Lin et al. [22] found S. transaminase rose immediately postoperatively and fell rapidly to normal within a week. Needham et al. [21] found that S. transaminase was maximum on the first postoperative day, but values had fallen to normal within the 14th postoperative day. Transaminase values were significantly greater and took longer to normalize among children who had received chemotherapy, which correlates with our study. Our findings reveal that the reduction in S. Alpha-fetoprotein levels is statistically significant at the 14-day and 3-month postoperative periods ($p<0.05$). The reduction at the 6-month postoperative mark was insignificant ($p>0.05$). These results suggest that hepatic resection in children with hepatoblastoma can effectively reduce S. Alpha-fetoprotein levels in the short term (14 days and three months). This reduction may indicate successful tumor removal and a positive early postoperative outcome. However, the lack of significance in the 6-month postoperative period may be due to some extreme values, especially in those three recurrent cases. According to Sunil et al. [18], having an AFP level lower than 100 ng/ml and being diagnosed with small cell undifferentiated histology were statistically significant factors predicting worse outcomes. Towu et al. [25] study observed a wide range of serum alpha-fetoprotein levels, from 49,000 to 3,500,000 ku/L, with a median value of 172,714. The primary finding of this study was that 25.0% of the subjects experienced focal lesions at six months postoperative sonographic estimation following hepatic resection for hepatoblastoma. In a study, Sunil et al. [18] noted that recurrence rates following liver resection spanned from 8.0% to 25.0% across different case series, which supports the present study. The present study highlights a significant correlation between S. Alfa fetoprotein levels and the recurrence of hepatoblastoma. The results indicate that in cases of local recurrence, there is a notable elevation in S. Alfa fetoprotein levels at the time of diagnosis (median: 400,000.0 ng/ml), which decreases postoperatively but remains elevated compared to cases with no recurrence. In contrast, in cases with no recurrence, S. Alfa fetoprotein levels are comparatively lower at diagnosis (median: 2,000.0 ng/ml) and remain low postoperatively. The decrease in S. Alfa fetoprotein levels over time in patients without recurrence is a promising indicator of a successful surgical outcome. Regular monitoring of S. Alfa fetoprotein levels can aid in the early detection and management of recurrence in paediatric hepatoblastoma cases. In this study, we found the correlation of median S.AFP level at different periods with PRETEXT staging shows a better outcome tendency of PRETEXT II over PRETEXT III. Among annotation factors, multifocality (F) and multiple annotation factors (C&F) show worse outcome tendencies.

In this study, it was observed that there were eight cases in PRETEXT II, and 87.5% did not experience local recurrence, while 12.5% developed local recurrence with 95% CI for recurrence in this stage, ranging from 0% to 31.6%. In PRETEXT III, there were 4 cases, and 50.0% had no recurrence, while the other 50.0% did experience recurrence. The confidence interval for recurrence in this stage spans from 1% to 99.0%. Among 5 cases in which the annotation factor C was positive, 80.0% had no local recurrence, and 20.0% did have recurrence. The 95% confidence interval for recurrence in this stage ranges from 0% to 86.0%. There were 2 cases in annotation F positive, and both were divided equally between no recurrence (50.0%) and recurrence (50.0%). The confidence interval for recurrence in this stage spans from 1% to 99.0%. Only 1 case was observed where multiple annotations (CF) were present, and it experienced local recurrence (100.0%). The confidence interval for recurrence in this stage is narrow, indicating a 100% recurrence rate with no variation. The relationship between different PRETEXT stages and the likelihood of local recurrence. PRETEXT II and annotation C have higher percentages of cases with no recurrence (87.5% and 80.0%, respectively). In contrast, PRETEXT III and annotation F have an equal distribution of cases with and without recurrence. Multiple annotation is positive (CF) in only one case and has a 100.0% recurrence rate. Schneller et al. [20] study found that among the cohort of patients examined, ten individuals (8%) experienced a recurrence of their disease. These recurrences were categorized based on the PRETEXT classification system, with three patients having PRETEXT II tumors (3 of 55), five patients having PRETEXT III tumors (5 of 47), and two patients having PRETEXT IV tumors (2 of 6).

Limitations of the Study:

- There were no PRETEXT stages I and IV patients within this study population.

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- The small sample size of only 12 participants limits the generalizability of the findings.
- The follow-up period of six months post-operation might not be sufficient to capture all cases of recurrence, as hepatoblastoma recurrence could occur beyond this timeframe.

Conclusion and Recommendations

This study provides valuable insights into the recurrence patterns of hepatoblastoma in children following preoperative chemotherapy and surgical resection. The findings suggest that PRETEXT staging and the presence of annotation factors are important predictors of recurrence, with higher PRETEXT stages and specific annotation factors (F, CF) associated with increased recurrence rates. The significant correlations observed between serum AFP levels and recurrence highlight the potential utility of AFP as a biomarker for monitoring postoperative outcomes in hepatoblastoma patients. Despite the limitations, the study emphasizes the need for careful postoperative surveillance, particularly in patients with higher PRETEXT stages or positive annotation factors. Future research with larger sample sizes, longer follow-up periods, and a multi-center approach is necessary to confirm these findings and refine the management strategies for pediatric hepatoblastoma.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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