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RESEARCH ARTICLE

Multidisciplinary Management of Hepatoblastoma: Three Years of Experience at a Single Centre

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ABSTRACT

Objective: The aim of this study was to report the short-term outcomes of paediatric hepatoblastoma managed by hepatobiliary surgery and paediatric oncology from a single centre.

Methods: Children with hepatoblastoma diagnosed between May 2020 and February 2023 and treated comprehensively in a single centre, were retrospectively reviewed. Management was multidisciplinary and followed the SIOPEL protocols (SIOPEL III-IV).

Results: Eight paediatric patients with a median (range) age at diagnosis of 24 (5-68) months were included. The most common complaint was abdominal distension. There were no patients with PRETEXT stage I. Patients were graded as stage II (n=4), stage III (n=2), and stage IV (n=2). Half of the patients were classified in the standard risk group and the other half in the high-risk group. Chemotherapy was initiated in seven patients, and one was transferred directly to surgery for overt rupture. After neoadjuvant chemotherapy, complete response (CR) was not achieved in any patient, partial response (PR) was achieved in half (n=4), progressive disease and stable disease were present in one patient each, and one patient died. Four patients underwent radical hepatectomy with negative surgical margins after chemotherapy. The median (range) follow-up period was 18 (2-47) months. No recurrence was observed in any patient during follow-up, and the overall and event-free survival rates were 88% and 75%, respectively.

Conclusions: The collective work of surgery and paediatric oncology in management is essential to achieve optimal results.

Keywords: Hepatoblastoma, children, hepatectomy, chemotherapy

INTRODUCTION

Hepatoblastoma is the most common primary malignant liver tumour and accounts for approximately two-thirds of all malignant liver tumours seen in childhood (1-3). They are usually observed in the infantile period and are very rarely encountered after the age of 5 years, but there are case reports of patients older than 10 years (4,5). Although the aetiology of this embryonal tumour, which is known to originate from hepatocyte precursors, is unknown, its association with premature birth, low birth weight (<1500 g), and some familial syndromes, such as Beckwith-Wiedermann syndrome, familial adenomatous polyposis, and trisomy 18, has been well recognised (6-8).

After the diagnosis is made, the stage and risk group of the disease are determined according to both the pretreatment extent of disease (PRETEXT) staging system, defined by The International Childhood Liver Tumour Strategy Group (SIOPEL) based on the involving hepatic sections, evidence of abdominal extrahepatic disease, presence of metastasis, and serum alpha fetoprotein (AFP) levels (9).

The cornerstone of treatment is complete resection, including total hepatectomy and transplantation in selected cases. With the discovery of the sensitivity of this tumour to chemotherapy, cisplatin- and doxorubicin-based chemotherapy regimens that have been added to the treatment protocol have increased the chance of complete resection. Indeed, with the addition of chemotherapy to treatment in the 1980s, survival rates gradually improved, and the 5-year overall survival rates have reached around 80% today (10-12). Moreover, the contribution of improved surgical techniques and most recently developed

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supportive therapies to the improvement in survival cannot be denied. Thus, a multidisciplinary approach is essential in the management of this patient group in which treatment is highly complicated.

In this study, we retrospectively evaluated the clinical characteristics, treatments, and outcomes of paediatric patients diagnosed with hepatoblastoma in a newly established comprehensive treatment (chemotherapy, hepatectomy, liver transplantation, transarterial chemoembolization and radioembolization available) centre in Turkey.

MATERIALS AND METHODS

The charts of children diagnosed with hepatoblastoma between May 2020 and February 2023 and treated comprehensively at our institution were retrospectively evaluated. Patients' demographics, tumour characteristics (histology, location, spread at the diagnosis, relationship with vessels, pre- and post-treatment volumes,) AFP levels (at the diagnosis and during follow-up), complete blood count, liver function tests, surgical procedures, chemotherapy protocols, treatment-related complications, and survival data were analysed.

All patients were discussed in a multidisciplinary council involving paediatric oncology, hepatobiliary surgery, paediatric gastroenterology, radiology, and pathology specialists. The diagnosis was made by biochemical tests, imaging and tumour biopsy. Abdominal ultrasound, computed tomography (CT), and/or magnetic resonance imaging (MRI) were used as imaging modalities.

For staging, the PRETEXT system adopted by the SIOPEL protocol was initially used. Patients were stratified as standard or high-risk based on the SIOPEL guidelines, and chemotherapy protocols were administered according to the risk groups. Patients with tumours limited to no more than three sections (PRETEXT 1, 2, or 3) without any additional risk factors were included in the standard-risk (SR) group, and these patients received cisplatin (80 mg/m^2/day). Patients who met at least one of the following criteria were included in the HR group: tumour involving all four hepatic sections (PRETEXT IV); abdominal extrahepatic disease (any of V+, P+ or E+); presence of metastases (M+); very low serum AFP (<100 ng/mL) levels; and tumour rupture at diagnosis irrespective of PRETEXT (H+). (V+: extension into the vena cava and/or all three hepatic veins (V3), P+: extension into the main and/or both left and right branches of portal vein (P2) , E+ extrahepatic disease except for P+ and V+ that must be biopsy proven (including enlarged lymph nodes on radiological investigation) and these patients received chemotherapy blocks including cisplatin (70- 80 mg/m^2/d), doxorubicin (20-30 mg/m^2/d), and carboplatin (AUC 10.6 mg/mL/min) according to the SIOPEL IV HR protocol.

In principle, resectable or ruptured tumours were surgically removed upfront, whereas patients with unresectable tumours received neoadjuvant chemotherapy. Evaluation of response to neoadjuvant chemotherapy was performed using serial imaging techniques and measurement of AFP levels after each chemotherapy block. Administration of chemotherapy blocks was continued until the appropriate time for surgery, and postoperative TEXT staging was performed before surgery. Response to neoadjuvant chemotherapy was evaluated after all cycles of treatment were delivered before surgery as follows: complete response (CR) defined as no evidence of disease and AFP level in the normal range for age; partial response (PR) defined as reduction in tumour size and decrease in AFP levels by more than 1 log relative to baseline; stable disease (SD) defined as no change in tumour volume or decrease in AFP levels by less than 1 log; and progressive disease (PD) defined as increase in tumour size at any measurement and/or increase in AFP levels detected in three consecutive measurements or weeks. In patients with inadequate chemotherapy response, chemotherapy protocols were escalated to include doxorubicin and carboplatin.

Complete surgical resection was defined as macroscopic total removal of all tumour lesions. The timing of surgery and decision to perform liver resection or liver transplantation were made according to the hepatobiliary multidisciplinary treatment council. Adjuvant chemotherapy was administered in consecutive blocks, considering the agents given in neoadjuvant chemotherapy. After termination of treatment, the patients were followed up with serial abdominal ultrasounds, and serum AFP levels were measured at intervals of 1-3 months.

The study was approved by the hospital ethics committee (approval number: KAEK/2022.03.82), and informed consent was obtained from the parents of the patients.

Statistical analysis

The data were analysed using IBM Statistical Package for the Social Sciences, version 23.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics are presented as mean ± standard deviation and median (minimum-maximum) values. Kaplan–Meier survival analysis was used to analyse overall survival. A $p<0.05$ was considered statistically significant.

RESULTS

During the study period, 10 patients with hepatoblastoma were followed in the paediatric haematology-oncology clinic. Two patients who received some parts of their treatment at other centres as well as patients who were referred for surgery (hepatectomy or liver transplantation) after chemotherapy at other centres, were excluded from this report. Thus, eight patients treated comprehensively at our centre were included with a median (range) age at diagnosis of 24 (5-68) months, and half of the patients were male (4/8) (Table 1). The most common complaint was abdominal distension. In addition, one infant was restless and had crying fits, and another had recurrent febrile and daily episodes of vomiting in the week before diagnosis. A third patient had jaundice and respiratory distress. Except for two patients, borderline prematurity (37 weeks) in one and prematurity (29+5 weeks) in the other, gestational age and birth weights were within normal limits. The premature patient was a twin and was diagnosed with cerebral palsy (CP) and congenital cardiac pathology, defined

Table 1: Baseline features and laboratory data of the patients

Age, months	
Median	24
Range	5-68
Male: female ratio	1/1
Total leukocyte count, 10^9/L	
Mean	12,8
SD	4,8
Hemoglobin, g/dl	
Median	8.2
Range	4,9-10
Thrombocyte count, 10^9/L	
Median	629
Range	198-1212
AST, U/L	
Median	63
Range	28-132
ALT, U/L	
Median	46
Range	5-51
GGT, mg/dl	
Median	128
Range	34-881
Bilirubin, mg/dl	
Median	0.57
Range	0.28-12.5
LDH, mg/dl	
Median	369
Range	290-646
AFP, ng/dl	
Median	237341
Range	4583-1256800
PRETEXT stage, no. of patients, (%)	
I	0
II	4 (50)
III	2 (25)
IV	4 (25)
Risk Groups, no. of patients, (%)	
High Risk	4 (50)
Standard Risk	4 (50)

Abbreviations: AST: aspartate transaminase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, LDH: lactate dehydrogenase, AFP: alpha fetoprotein

as pulmonary stenosis, secundum atrial septal defect, and dilatation of the right ventricular cavity.

Histopathological diagnoses were epithelial (foetal-embryonal) hepatoblastoma in seven patients and epithelial- mesenchymal hepatoblastoma in one patient. There were no patients with PRETEXT stage I. Half of the patients (n=4) were categorised as PRETEXT stage II, and on risk assessment, half of the patients (n=4) were in the HR group. Serum AFP levels were above 100 ng/dL at the time of diagnosis. Thrombocytosis (platelet count >600000/mm^3) was detected in 5/8 patients and >1000000/mm^3 in 2/8 patients. One patient had cholestasis at admission. The baseline features and laboratory data of the patients are shown in Table 1.

Chemotherapy was initiated in seven patients, one of whom died during chemotherapy. One patient was transferred directly to surgery because of overt tumour rupture and bleeding. Patients in the SR group received single cisplatin treatment at the beginning of therapy, and one patient in the HR group received a first cycle with cisplatin, considering her general condition. In patients in the HR and SR groups with insufficient response to chemotherapy, patients were given additional chemotherapy, including cisplatin and doxorubicin or carboplatin and doxorubicin, according to the SIOPEL IV HR protocol. Neoadjuvant chemotherapy response was evaluated in the six surviving patients, CR was not achieved in any patient: PR in four patients, PD in one patient, and SD in one patient. When PRETEXT and POSTTEXT staging were compared, disease regression was noted in 2/6 patients. Two patients had an AFP level >1000000 ng/dL at the time of diagnosis. With neoadjuvant chemotherapy, AFP decreased by more than 1 log in all patients. (Table 2)

Surgical resection could not be performed in three patients. One of them had progressive disease in interim evaluations performed during neoadjuvant chemotherapy sessions, and he was admitted to an external centre and lost to follow-up. The second patient (with CP) responded very well to chemotherapy. Because of her unsuitable general health status for surgery, she was scheduled for transarterial radioembolization, but she was lost to follow-up. When she was re-attended in the 23rd month of the follow-up, her AFP level was found to be 8.9 ng/dl (the level was 414182 ng/dl at the time of diagnosis), and the mass appeared calcified and there was no difference in size. The third patient died preoperatively during neoadjuvant chemotherapy. This patient had severe abdominal distension, cholestasis, and respiratory distress at initial presentation, received three cycles of chemotherapy, and died on the eighth day after the last chemotherapy cycle when she was transferred to the intensive care unit because of decreased urine output and deterioration of renal function. Figure 1 shows the CT images of this patient's tumour involving all segments of the liver at the time of diagnosis.

Five patients underwent hepatectomy. In the patient who underwent emergency right hepatectomy for tumour rupture, multiple small implants on the serosa and distal ileum and the peripyloric stomach and duodenum were left in place. Additional interventions that, on the one hand, would increase the risk of morbidity and mortality in the emergency situation, and on the other hand, would be philosophically non-therapeutic due to rupture, were avoided, and R2 resection was a conscious choice. The remaining four patients underwent hepatectomy, and none had postoperative residual tumours. For one patient who responded well to chemotherapy according to AFP levels (from 121 000 to 136 ng/mL) but did not exhibit any regression due to extensive calcification (present before chemotherapy), a living donor was prepared as a backup option. The tumour could be safely removed with an extended right trisectionectomy with negative margins, and transplantation was not necessary. The median (range) duration of postoperative hospitalisation was 16 (7-22) days. Adjuvant

Table 2: Patient's clinical characteristics, tumor characteristics, chemotherapy, surgery procedures, and outcomes

Patient no:	Age (m)	Sex	Characteristics and spread of the tumor at diagnosis	Pre-text (SİOPEL)	Risk Groups (SIOPEL)	Neoadjuvant chemotherapy cycles	Tumor Size 1	Tumor Size 2	AFP -1	AFP-2	Post-text	Surgery	Adjuvant Chemotherapy cycles	Current status	Follow up (months)
1	**28**	**M**	**Segment II III IV** V (1) P (1)	II	SR	CIS (4) Block A1, A2	786	42	1089000	104	II	Left extended lateral sectionectomy	Block A3	remission	12
2	27	F	Segment V VI P (1)	II	SR	(CIS) (1) Block A1, A2	208	22	414182	16.1	I	-	-	stable disease	23.2
3	5	M	Segment V VI VII VIII+I V (1) P (1) C (1)	II	SR	(CIS) (1) Block A1	491	99	>60500	2891	II	Right hepatectomy	Block A2-A3 Block B	remission	24.8
4	68	F	All segments C (1) F (1) E (1) V (3) P (2)	IV	HR	(CIS) (1) Block A1, A2	1844	-	>60500	-	-	-	None	exitus	2.2
5	21	F	Segment V VI VII VIII F (1) H (1) P (1)	II	HR	-	462+40+ 8+24	-	434506	-		Right hepatectomy + omentectomy	CIS (2) Block (A1) (A2)	remission	9
6	8	M	Segment IV VIII VII V+I V (3) P (1) M (+)	III	HR	Block A1, A2, A3	445	909	4583	130	III	-	-	unfollowed	2.1
7	30	M	Segment II III IV VII I+V VI+VIII C (1) F (1) V (3) P (2) M (+)	IV	HR	Block A1, A2, A3 Block B	877+11+4+2	46	>60500	672	III	Left Hepatectomy+ Left caudate lobectomy	Block C	remission	47
8	8	F	Segment I IV V VII VIII C (1) V (2) P (1)	III	SR	CIS (3) Block A1, A2	550	Similar tumor size increased calcification	12456800	60	III	Right extended trisectionectomy	-	remission	34.3

Abbreviations, and chemotherapy schemes:
Tumor size 1: tumor size at time of diagnosis (cm^3); Tumor size 2: tumor size immediately before surgery after neoadjuvant chemotherapy (cm^3)
Abbreviations:
AFP 1, serum alpha fetoprotein level at the time of diagnosis (ng/dL); AFP2, serum alpha fetoprotein level immediately before pre surgery after neoadjuvant chemotherapy (ng/dL); C (1), caudate lobe involvement; E (1), extrahepatic direct invasion; E2, extrahepatic peritoneal implant; F (1), multifocal tumor; H (1), tumor rupture; V (1), involvement of one hepatic vein; V(2), involvement of two hepatic veins; V(3), involvement of three hepatic veins or inferior vena cava; P (1), involvement of the right or left portal vein; P(2), involvement of main portal vein; M (1), metastases
CIS, cisplatin 80 mg /m^2/day intravenous infusion for 24 hours.
Block A1, Cisplatin 80 mg/m^2/day (D1), cisplatin 70 mg/m^2/day (D8, D15)
Doxorubicin 30 mg/m^2/day (D8, D9)
Block A2, Cisplatin 70 mg/m^2/day (D29, D36, D43)
Doxorubicin 30 mg/m^2/day (D36, D37)
Block A3: Cisplatin 70 mg/m^2/day (D57, D64)
Doxorubicin 30 mg/m^2/day (D57, D58)
Block B: Carboplatin AUC 10.6 mg/mL/min (D1,D22)
Doxorubicin 30 mg/m^2/day (D1,D2,D3,D22,D23,D24)
Block C: Carboplatin AUC 6.6 mg/mL/min (D1, D22,D43)
Doxorubicin 20 mg/m^2/day (D1,D2,D22,D23,D43,D44)
Daily dose equivalents for infants weighing 5-10 kg were as follows: Cisplatin 70 mg/m^2/ day given at 2.3 mg/kg/d; Cisplatin 80 mg/m^2/ day given at 2.7 mg/kg/d; Doxorubicin 20 mg/m^2/day given at 0.67 mg/kg/d; Doxorubicin 30 mg/m^2/day given at 1 mg/kg/d

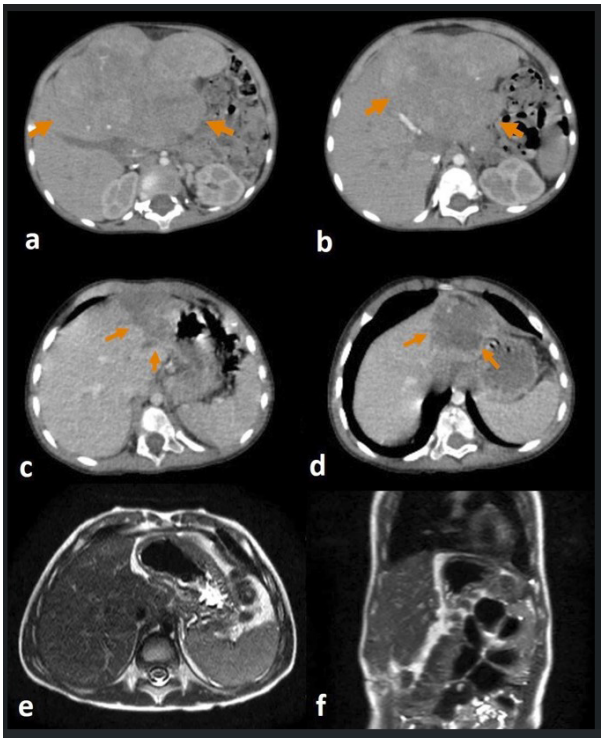

Figure 2: In a 28 month-old boy (case 1); Axial contrast-enhanced CT (a,b) reveals a lobulated, heterogeneously enhancing solid mass lesion in the liver segments II, III, and IV. Follow-up axial contrast-enhanced CT after chemotherapy (c, d) demonstrates a regressing hypodense mass lesion on the portal venous phase in the liver segments II and III. The lesion was located superiorly adjacent to the middle hepatic vein (not shown). An extended left hepatectomy was successfully performed on the patient (e, f).

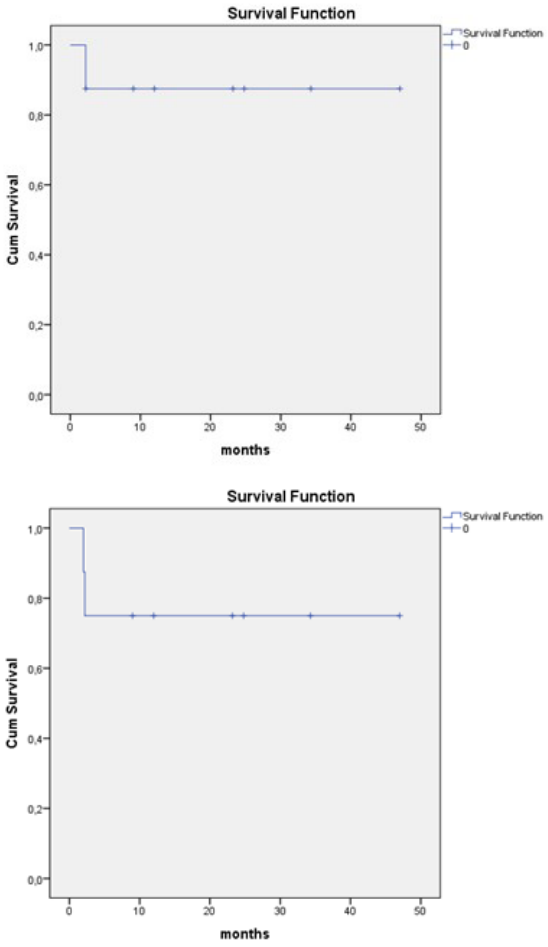

Figure 3: Kaplan-Meier curves of overall survival (OS) and event free survival (EFS) for all patients (n=8).

chemotherapy was administered to 4/5 patients. All patients survived with no evidence of disease at 9, 12, 24, and 47 months after initial diagnosis. Figure 2 shows the preoperative and postoperative CT images of the patient (patient no:1) who underwent a successful extended left hepatectomy.

The median (range) follow-up period was 18 (2-47) months. No recurrence was observed in any patient during follow-up, and the overall survival and event-free survival rates were 88% and 75%. (Figure 3a-b).

Patients received 35 chemotherapy cycles, and 19 neutropenic periods (neutrophil count <500/mm^3) were recorded. Half of the patients (4/8) had >1 and ≤4 episodes of febrile neutropenia and received inpatient intravenous broad-spectrum antibiotics. The patients received treatment with granulocyte colony-stimulating factor (G-CSF) during neutropenic periods. Except for one patient whose general condition had been poor at the time of diagnosis and who also experienced possible chemotherapy toxicity, no chemotherapy-related death or toxicity was reported.

DISCUSSION

According to the Turkish National Paediatric Cancer Registry (2009-2021), primary liver tumours constitute 1.7% (409/24080) of all childhood cancers (13). Surgery is the mainstay of treatment. However, in >60% of patients, resection may not be feasible initially because of locally advanced stage, distant metastatic tumour or large vessel infiltration. At this stage, cisplatin- and doxorubicin-based chemotherapy regimens provide tumour shrinkage in these patients, and the fibrotic and hardened tumour is easily separated from the intact liver tissue. Following neoadjuvant chemotherapy, the surgical resection rate in these patients is approximately 80%. In the remaining 20% of patients, total excision is still not possible, and liver transplantation is considered (14-16). While SIOPEL and the German Society of Paediatric Oncology and Haematology (GPOH) recommend neoadjuvant chemotherapy, surgery, and adjuvant chemotherapy in the management of these patients, some other study groups recommend surgery first and then adjuvant chemotherapy in PRETEXT I-II patients, taking staging and risk groups into consideration (17-21). Dramatic improvement in survival rates with adjuvant chemotherapy has been previously reported (9,22). Guidelines suggest that intrahepatic metastasis and hepatoblastoma recurrence from postoperative residuals are completely or partially reduced with adjuvant chemotherapy (23).

In the present study, neoadjuvant chemotherapy was initiated in all but one patient who underwent hepatectomy due to tumour rupture and bleeding, and the first cycle of

chemotherapy consisted of only cisplatin treatment in 71% of these patients. According to the results of neoadjuvant chemotherapy, the size of the mass decreased in 57% of the patients. The tumour was completely resected without the need for transplantation in 63% of the patients. No patient underwent liver transplantation. At a median follow-up of 18 months, no recurrence was observed in any patient, and OS and EFS rates were 88% and 75%. Shanmugam et al.. reported that all patients with PRETEXT stage I and II hepatoblastoma received neoadjuvant chemotherapy. The authors were able to perform complete surgical resection in 63% of these patients, and 20% of them had undergone liver transplantation. At a median follow-up of 30 months, event-free survival rates were 93% in the SR group and 60% in the HR group (24). Another study compared two patient groups diagnosed with hepatoblastoma who had and had not received neoadjuvant chemotherapy. Overall survival rates were higher in patients who received neoadjuvant chemotherapy, without any significant intergroup difference (88% vs 80%, p=0.95) (23). Küpesiz et al. presented the data of 17 hepatoblastoma patients in their study from Turkey. Surgical resection was performed in 11% of the patients at the time of diagnosis, and neoadjuvant chemotherapy was administered to all remaining patients. Of the patients who received neoadjuvant chemotherapy, 53% underwent complete resection and 40% underwent liver transplantation. The 5-year overall and disease-free survival rates were 88.9% and 80.8%, respectively (16). Another study from Turkey highlighted the better response to chemotherapy in childhood liver tumours in the last two decades and reported 5-year survival rates of patients with hepatoblastoma before and after 1990 as 32.4% and 47%, respectively (25).

Although metastatic disease may appear to have a devastating prognosis, improved outcomes can also be achieved in these patients treated with chemotherapy. In the study where the results of the SIOPEL-4 treatment regimen in HR patients were reported, good results were noted with dose-dense cisplatin-based chemotherapy and radical surgery, especially in high-risk patients with metastatic disease (63% of the patients in the study had lung metastases). All residual tumours could be completely resected in 69% of metastatic patients, and 74% were in CR at the end of treatment; the 3-year EFS and OS were 76% and 83%, respectively (26). One of the two patients in our cohort with metastatic disease was lost to follow-up, but the disease was still progressing even under chemotherapy, whereas the other patient was in remission in the 39th month following chemotherapy.

The results of hepatectomy and liver transplantation in patients with hepatoblastoma were also compared. Yu et al.. reported that hepatectomy increased 1-year OS from 42.9% to 95.7% and liver transplantation from 42.9% to 90% (p<0.0001) (23). Another study from India reported 1-, 3-, and 5-year survival rates in HR patients who had undergone liver transplantation or surgical resection as 91%, 82%, and 73% vs. 100%, 83%, and 83%, respectively. The authors reported that HR hepatoblastoma patients can be treated with excellent results in resource-challenged countries and that surgical resection is comparable to transplantation, despite being surgically challenging (27). In a study from Turkey including transplantation results of 10 patients diagnosed with hepatoblastoma, a survival rate of 90% was reported at the 21st month of follow-up (28). None of the patients included in the present study required liver transplantation. However, complete resection was possible following neoadjuvant chemotherapy.

Serum AFP is a tumour marker used in the diagnosis of hepatoblastoma, evaluation of response to treatment, and detection of recurrences after termination of treatment. AFP levels measured in response to chemotherapy have been found to be associated with prognosis, and serial monitoring of serum AFP values has been described as a cost-effective and reliable predictor of outcomes (29-30). Although, in general opinion, AFP levels <100 ng/dL or >1,000,000 ng/dL at the time of diagnosis are unfavourable prognostic factors, different results have also been reported (31-32). In our study, serum AFP levels were not below 100 ng/mL in any patient, but two patients had AFP >1,000,000 ng/mL. In terms of outcome, one of the latter two patients was disease-free at the seventh month, while the other was disease-free at the sixteenth month of follow-up. However, the exact levels of AFP were not known in some patients.

Our study had some limitations. First, this was a retrospective, single-centre study. Second, because our study was conducted in a newly established medical centre, relatively small numbers of patients were followed up, and the follow-up period was relatively short.

In conclusion, we report the results of a cohort of paediatric patients with hepatoblastoma treated by a multidisciplinary team at a newly established centre. According to our results, neoadjuvant chemotherapy is critical to shrinking tumours that are not possible for complete resection and appear in the advanced stages; therefore, liver transplantation may not be necessary in every patient. Adjuvant chemotherapy reduces the risks that may occur, especially due to positive surgical margins. Successful results have been achieved with the SIOPEL protocols. Multidisciplinary management is essential for satisfactory outcomes and high survival rates in these patients.

Ethics Committee Approval: This study was approved by the Clinical Research Ethical Committee of Giresun Training and Research Hospital (Number: KAEK-255, Date: 2023-12-04).

Informed Consent: Informed consent was obtained from the parents of the patients.

Author Contributions: Conception/Design of Study- A.B.; Data Acquisition- İ.T., F.A.B.; Data Analysis/Interpretation- A.B., M.B.; Drafting Manuscript- A.B., M.B.; Critical Revision of Manuscript- A.B., M.B.; Final Approval and Accountability- A.B., F.A.B., İ.T., M.B.

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