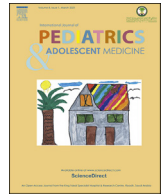


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International Journal of Pediatrics and Adolescent Medicine

journal homepage: <http://www.elsevier.com/locate/ijpam>

Experience of treating pediatric hepatoblastoma at King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia – Timely surgical intervention playing a key role



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ARTICLE INFO

Article history:

Received 8 June 2020

Received in revised form

10 September 2020

Accepted 5 November 2020

Available online 13 November 2020

Keywords:

Hepatoblastoma

Pediatric

Outcome

Surgical intervention

ABSTRACT

Background: Many studies have demonstrated that outcome in patients with hepatoblastoma is determined by tumor resectability and the presence or absence of metastatic disease.

Purpose: To evaluate and disseminate information on diagnosis, treatment, and outcome of hepatoblastoma patients at a tertiary care hospital in Saudi Arabia.

Patients and methods: Twenty-four pediatric patients with hepatoblastoma were treated at our institution between January 2005 and December 2012. The majority of our patients were stage III and above, while one-third of them presented with metastatic disease. Four (16.7%) had vascular invasion. Two-thirds of our patients (n = 16, 66.7%) had alpha-fetoprotein (AFP) level above 100,000 ng/mL. Twenty-one patients underwent surgery; two had upfront surgery before getting any chemotherapy, and 15 had surgery on schedule after pre-operative chemotherapy. Four patients had delayed surgery as the tumor was not resectable and received extra cycles of chemotherapy. Chemotherapy regimens used were based on SIOPEL study protocols until 2011 and Children's Oncology Group (COG) protocol from 2012 onwards. Relapse, progressive disease, or death from any cause were defined as events.

Results: Five-year overall survival (OS) of the cohort over a median follow-up time of 56.1 months was 70.6% ± 9.4% with seven (29.2%) events of mortality. No significant difference was found for age at diagnosis (less than 2 years vs. more), stage of disease, AFP levels (less than 100,000 vs. more), vascular invasion, or presence of metastatic disease at presentation in terms of OS. However, children receiving upfront or scheduled as-per-protocol surgery fared better than those who had delayed surgery (as the tumor was not resectable and they received extra cycles of chemotherapy) or did not undergo any surgery (P-Value .001).

Conclusion: Favorable survival outcome could be achieved with complete tumor excision and adjuvant chemotherapy. Inability to perform surgical excision was the single most important predictor of mortality in our patients.

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1. Introduction

Primary hepatic neoplasms are rare and account for 1–2% of all

childhood cancers, and hepatoblastoma is the most common malignant liver neoplasm in children [1]. Surgical resection is the mainstay of curative therapy for children with hepatoblastoma, and only one-third of newly diagnosed patients with hepatoblastoma can be expected to have resectable disease at presentation [2,3]. The clinical outcome in patients with hepatoblastoma is determined by tumor resectability and the presence or absence of metastatic disease [4]. Patients with hepatoblastoma who undergo primary complete resection generally have an excellent prognosis

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Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

with an event-free survival (EFS) of 90% [4–8]. The use of chemotherapy has improved survival in patients with unresectable hepatoblastoma by increasing the number of patients whose tumors can be resected [9–12]. Cisplatin has been identified as the most active agent for the treatment of hepatoblastoma [13–15], while doxorubicin appears to be the next most active agent in line [16]. The current data on EFS for patients with non-metastatic, unresectable hepatoblastoma at diagnosis (<60%) and for patients with metastatic disease at diagnosis (20–30%) strongly suggest consideration of novel therapeutic strategies [3,17]. However, only approximately two-thirds of patients with unresectable tumors at diagnosis become resectable with chemotherapy leaving too many children with gross residual disease [3]. Orthotopic liver transplant (OLT) is sometimes the only option that may result in complete tumor removal and increased chance for cure [17,18].

Histologic subtypes, especially macrotrabecular and small-cell undifferentiated, PRETEXT group, surgical margin, surgical complications, diffuse multifocal tumors, and AFP<100 ng/mL have been reported to have potential prognostic value in hepatoblastoma and need to be further investigated in a prospective, multi-group setting [6,19–28]. The barrier of unresectability can be redefined with the concept of total liver resection and salvage OLT [29]. For patients with stage IV disease, liver transplant is offered once all metastatic extra-hepatic disease has been radiographically documented to either have disappeared as a result of neoadjuvant chemotherapy or has been surgically removed [30].

Children's Hepatic Tumors International Collaboration (CHIC) recommends functionally dividing patients into very low, low, intermediate, and high-risk groups in order to try to diminish toxicity in low-risk patients, increase survival in intermediate-risk patients, and identify new agent(s) that may be used in high-risk and relapsed patients [31].

We conducted a retrospective chart review of pediatric patients treated with hepatoblastoma at our institution to assess the outcome of our treatment efforts.

2. Material and methods

The medical record numbers of all pediatric hepatoblastoma patients (age <14 years at diagnosis) registered at the Department of Pediatric Hematology/Oncology were identified from the computerized patient information management system based on clinical databases maintained prospectively. For this retrospective, non-interventional, observational study, the medical charts were reviewed. The data pertaining to the patients (age at diagnosis and gender), disease (stage, histology, and classification), treatment details (surgery, and chemotherapy administered) and response to treatment, and survival outcome were collected on a case report form. Relapse, progressive disease, or death from any cause were defined as events. The final dataset was prepared in IBM-SPSS for Windows® Version 20.0 after data cleaning and quality checks and was analyzed accordingly.

2.1. Ethical considerations

This clinical research study was approved by the Institutional Review Board (IRB) of our hospital to be conducted under the international guidelines for enrollment of human subjects. The data from patients' medical records were collected and maintained at the Department of Pediatric Hematology/Oncology in accordance with institutional policy on data confidentiality, security, and safety. As the study was designed as a retrospective review, no consent/assent was taken from patients/parents. A waiver of informed consent/assent was sought from the IRB and was duly granted.

2.2. Statistical considerations

After performing quality checks on the dataset, descriptive statistics were calculated. EFS and overall survival (OS) were calculated using Kaplan-Meier survival analysis and compared using log-rank or Tarone-Ware test as appropriate.

3. Results

3.1. Patients

Twenty-four pediatric patients with hepatoblastoma were treated at our institution between January 2005 and December 2012. Diagnosis was confirmed by histology in all cases. Median age at diagnosis was 1.2 years (Range: 0.04–13.2 years) with 16 (66.7%) patients below the age of 2 years, while male to female ratio in this cohort was 2:1. Histopathology of the tumor was fetal epithelial in 10 (41.7%), embryonal epithelial in 1 (4.2%), epithelial mixed (fetal and embryonal) in 7 (29.2%), and a mix of epithelial and mesenchymal in 6 (25%). The diagnosis was established by Tru-Cut biopsy in 19 (79.2%), excision biopsy in 4 (16.7%), and open biopsy in 1 (4.2%).

Two-thirds of the patients (n = 16, 66.7%) had stage III disease, followed by stage IV in six (25%) and stage I and II in one each (4.2%). Eight (33.3%) cases presented with metastatic disease - five had pulmonary, one had pulmonary and pelvic, one had omentum and kidney, and one had metastasis to the anterior abdominal wall from omentum. Four (16.7%) had vascular invasion. One patient had Beckwith-Wiedemann syndrome. Two of six patients tested had positive Hepatitis A serology. Of 15 tested, none was found to have a positive Hepatitis B or C serology. Two-thirds of our patients (n = 16, 66.7%) had alpha-fetoprotein (AFP) level above 100,000 ng/mL. AFP was markedly elevated (above 100,000 ng/mL) for age in 11 (68.8%) patients under two years of age at diagnosis.

3.2. Chemotherapy

Chemotherapy regimens administered to our patients were based on Société Internationale d'Oncologie Pédiatrique – Epithelial Liver (SIOPEL) study protocols until 2011 and Children's Oncology Group (COG) protocol from 2012 onwards. The chemotherapeutic agents used were cisplatin, vincristine, 5-fluorouracil, doxorubicin, carboplatin, etoposide, and ifosfamide. More than half of the cohort received a total of 6 cycles of chemotherapy (n = 15, 62.5%). From the remaining nine, two patients each received 3, 7, and 8 cycles, while one each received 1, 9, and 14 cycles of chemotherapy.

3.3. Surgery

Twenty-one patients underwent surgery; two had upfront surgery before getting any chemotherapy; and 15 had surgery on schedule after getting pre-operative chemotherapy. Four of our patients had delayed surgery as the tumor was not resectable and received extra cycles of chemotherapy. Among those three patients who did not undergo surgery, two died before their scheduled surgery - one with septic shock, and the other with tumor hemorrhage and multi-organ failure - while for the remaining one, surgery was not possible due to progressive disease. Alpha-fetoprotein values at various time points during the treatment and at relapse were recorded for the cohort and are depicted in Fig. 1 (median, minimum-maximum).

Five-year OS of the cohort over a median follow-up time of 56.1 months was 70.6% ± 9.4% with seven (29.2%) events of mortality. No significant difference was found for age at diagnosis (less than 2

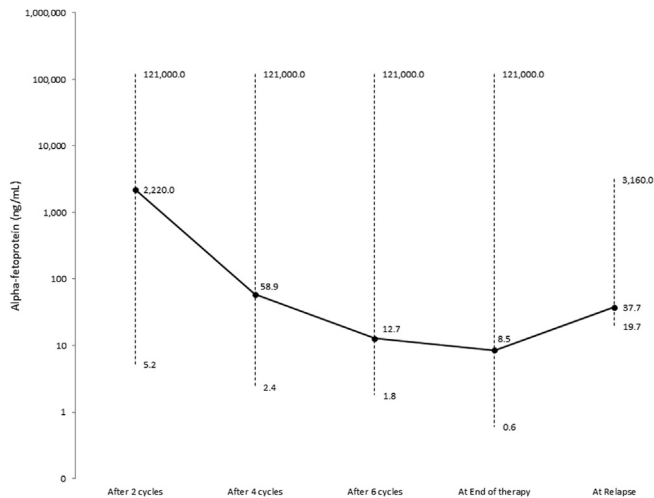


Fig. 1. AFP values at various time points during the course of disease.

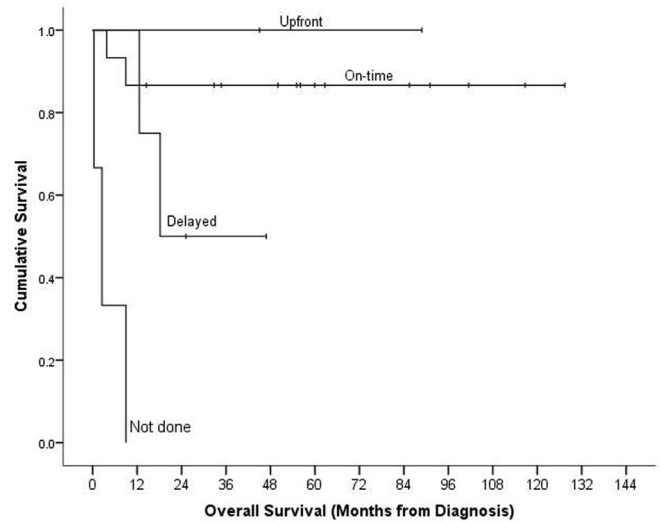


Fig. 2. Overall survival with respect to timing of surgery.

years vs. more), stage of disease, AFP levels (less than 100,000 vs. more), vascular invasion, or presence of metastatic disease at presentation in terms of OS. However, children who received upfront or scheduled as-per-protocol surgery fared better than those who had delayed (as the tumor was not resectable and they received extra cycles of chemotherapy) or did not undergo any surgery (*P*-Value .001, Table 1, Fig. 2).

Four patients relapsed, while the same number of children exhibited disease progression. Of those who relapsed locally (16.7%), three of them received salvage chemotherapy and one patient underwent liver transplant. All of them were alive at the last follow-up with a median follow-up of 40.6 months (Range: 14.5–116.7), while all those who had disease progression had expired. Five-year EFS for our cohort of patients was observed to be 52.5% ± 10.6%. No significant difference was found for age at diagnosis (less than 2 years vs. more), stage of disease, AFP levels (less than 100,000 vs. more), vascular invasion, or metastatic disease at presentation in terms of EFS (Table 1, Fig. 3).

Table 1
Five-year overall survival (OS) and event free survival (EFS).

| | n (%) | Alive (%) | OS | PValue | EFS | P value |
|--------------------------|-----------|-----------|-------------|--------|--------------|---------|
| Age at diagnosis | | | | .633 | | .996 |
| <2 years | 16 (66.7) | 11 (64.7) | 68.2 ± 11.8 | | 53.6 ± 13.3 | |
| ≥2 years | 8 (33.3) | 6 (35.3) | 75.0 ± 15.3 | | 50.0 ± 17.7 | |
| AFP at diagnosis (ng/mL) | | | | .221 | | .145 |
| <100K | 8 (33.3) | 7 (41.2) | 87.5 ± 11.7 | | 75.0 ± 15.3 | |
| ≥100K | 16 (66.7) | 10 (58.8) | 61.9 ± 12.3 | | 40.0 ± 13.4 | |
| Pretext stage | | | | .137 | | .381 |
| I | 1 (4.2) | 1 (5.9) | 100.0 ± 0.0 | | 100.0 ± 0.0 | |
| II | 1 (4.2) | 1 (5.9) | 100.0 ± 0.0 | | 100.0 ± 0.0 | |
| III | 16 (66.7) | 13 (76.5) | 81.3 ± 9.8 | | 53.6 ± 13.3 | |
| IV | 6 (25.0) | 2 (11.8) | 33.3 ± 19.2 | | 0.333 ± 19.2 | |
| Vascular Invasion | | | | .476 | | .495 |
| Negative | 20 (83.3) | 15 (88.2) | 75.0 ± 9.7 | | 60.0 ± 11.0 | |
| Positive | 4 (16.7) | 2 (11.8) | 50.0 ± 25.0 | | 25.0 ± 21.7 | |
| Metastatic disease | | | | .138 | | .101 |
| Negative | 16 (66.7) | 13 (76.5) | 81.3 ± 9.8 | | 68.8 ± 11.6 | |
| Positive | 8 (33.3) | 4 (23.5) | 50.0 ± 17.7 | | 25.0 ± 15.3 | |
| Surgery timings | | | | <.001 | | <.001 |
| Upfront | 2 (8.3) | 2 (11.8) | 100.0 ± 0.0 | | 100.0 ± 0.0 | |
| Scheduled | 15 (62.5) | 13 (76.5) | 86.7 ± 8.8 | | 65.2 ± 12.7 | |
| Delayed | 4 (16.7) | 2 (11.8) | 50.0 ± 25.0 | | 25.0 ± 21.7 | |
| Not Done | 3 (12.5) | None | 0.0 ± 0.0 | | 0.0 ± 0.0 | |

OS, 5-year overall survival (70.6% ± 9.4%); EFS, 5-year event-free survival (52.5% ± 10.6%); AFP, Alpha-fetoprotein; Values are presented as n (%) and cumulative proportion of subjects surviving at the specified time with ±standard error.

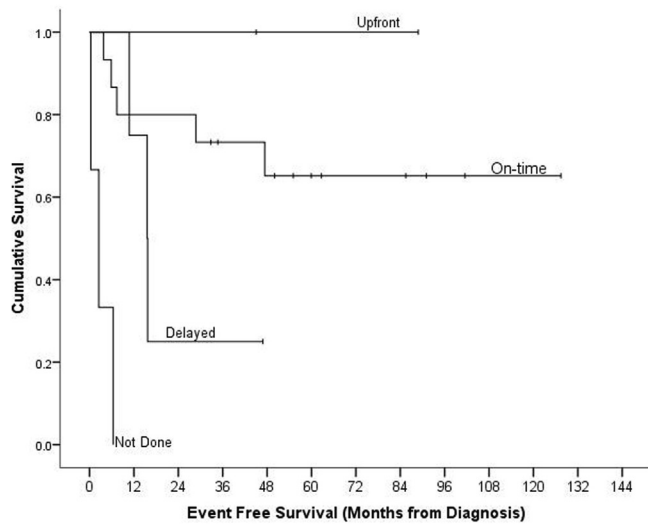


Fig. 3. Event-free survival with respect to timing of surgery.

resection of the primary tumor with microscopically clear margins is an important factor in achieving a successful outcome [4–8]. Still, finding a curative approach for patients with advanced or metastatic Hepatoblastoma is a challenge [14,15].

Our treatment modality was to opt for upfront surgical excision if feasible. For unresectable tumor, 2–4 cycles of neo-adjuvant chemotherapy were given with the intent to shrink the tumor in order to allow optimal resection. With this, in the former subgroup, the five-year EFS and OS were observed to both be 100%, while in the later, five-year EFS and OS were 65.2% and 86.7%, respectively (Table 1).

Comparison of treatment results from the International Society of Pediatric Oncology (SIOP) study (SIOPEL), United States-Inter group, and Japanese studies is difficult because different staging systems were employed in these studies. However, the OS quoted was approximately 75% in these studies [16]. This is slightly superior to our cohort which experienced a five-year OS of 70.6%.

Complete surgical excision and metastatic disease are the most important prognostic factors [8,13]. Factors that were also of prognostic relevance for survival in our study were vascular invasion and AFP levels at diagnosis. Recent reports suggest that AFP < 100 is associated with poor prognosis in hepatoblastoma [19,20]. This was however, not consistent with our results, which could be due to the very small sample size.

Nishimura et al. noted that patients with advanced stage or metastatic disease did well with etoposide-, carboplatin-, and ifosfamide-based chemotherapy [15].

However, liver transplant provides a realistic chance for survival in patients with unresectable or relapsed disease [3]. Early consideration of orthotopic liver transplantation for patients with advanced stage disease has also been found to be beneficial in children with metastatic disease at diagnosis, provided this could be controlled by chemotherapy or by surgery [3,17,18]. One of our patients who underwent liver transplant after relapse was alive at the last follow-up after 25 months.

Favorable survival outcome could be achieved with complete tumor excision and adjuvant chemotherapy. Inability to perform surgical excision was the single most important predictor of mortality. Distant metastatic spread and vascular invasion of tumor on histopathology allude to poor outcome. Based on the results from our study of a small cohort of patients from this part of the world, we highlighted the need to have a unified treatment protocol based

on the recent evidence and to look into newer agents for the treatment of patients with metastatic disease or vascular invasion.

Role of the funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

The authors are not sharing the data used to generate the results of this research due to institutional restrictions. The corresponding author has full access to all the data in the study and has final responsibility for the decision to submit for publication.

Ethical statement

This clinical research study was approved by the Institutional Review Board (IRB) of our hospital to be conducted under the international guidelines for enrollment of human subjects. The data from patients' medical records were collected and maintained at the Department of Pediatric Hematology/Oncology, in accordance with institutional policy on data confidentiality, security, and safety. Since the study was designed as a retrospective review, no consent/assent was taken from patients/parents. A waiver of informed consent/assent was sought from the IRB and was duly granted.

Author statement

Ibrahim Alfawaz: Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing - original draft; Writing - review & editing.

Basheer Ahmed: Conceptualization; Data curation; Investigation; Methodology; Validation; Visualization; Writing - original draft; Writing - review & editing.

Afshan Ali: Writing - original draft; Writing - review & editing.

Mouhab Ayas: Writing - original draft; Writing - review & editing.

Amani AlKofide: Writing - original draft; Writing - review & editing.

Zakaria Habib: Writing - original draft; Writing - review & editing.

Khawar Siddiqui: Data curation; Formal analysis; Methodology; Validation; Visualization; Writing - original draft; Writing - review & editing.

Declaration of competing interest

None of the authors have any conflicts of interest to declare.

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