POST-TEXT III and IV Hepatoblastoma: Extensive Resections or Liver Transplantation?

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Abstract

Introduction: Hepatoblastoma (HB) is a rare condition, and its treatment is based on surgical resection and chemotherapy. Patients with central PRETEXT and POST-TEXT III and IV HB have been submitted to primary liver transplantation. However, in some cases extended liver resection has been performed with good results.

Objective: To analyze one institution’s experience with patients with central PRETEXT and POST-TEXT III and IV HB undergoing extended liver resection or primary liver transplantation.

Method: Thirteen patients were retrospectively evaluated from a single institution from 2009 to 2020. Central POST-TEXT III and IV who have undergone extended liver resection or primary liver transplantation.

Results: Thirteen patients were included, mean age 3 years and 9 months, pre-chemotherapy alpha-fetoprotein range 643-256530mg/l, undergoing neoadjuvant chemotherapy. Central PRETEXT III and IV, 5 and 8 patients respectively. Central POST-TEXT III and IV, 9 and 4 respectively. Ten patients underwent extended liver resection, 5 right trisegmentectomies, 3 left trisegmentectomies, one with pulmonary metastasectomy, and 2 unresected extended resections. There were 3 primary liver transplants and 2 salvage liver transplants. In the extended liver resection group, the follow-up ranged from 3 months to 10 years, and in the primary liver transplantation group, it ranged from 4 to 10 years. The overall survival was 89% for the extended resection group and 100% for the liver transplantation.

Conclusion: Extended liver resection presents good results in selected patients.
Keywords: Hepatectomy; Hepatoblastoma; Liver neoplasm; Liver transplantation

Introduction

Hepatoblastoma is the most common liver tumor in childhood, in approximately 1% of cases. Its incidence has increased with time and with increased survival of premature patients [1,2,3]. It may be associated with genetic syndromes, but most are sporadic [1,4,5]. The diagnosis is usually made by 3 years of age and asymptomatic abdominal mass is the most common finding [4,6,7]. Biologically they are embryonic tumors and may present variations in cell type and differentiation, which might influence patient survival [8,9,5]. Surgical treatment is the mainstay for successful treatment. The introduction of platinum-based chemotherapy increased survival from 30% to 80% [10-16]. Staging and treatment are based on PRETEXT (Pre-treatment extent of disease) before neoadjuvant chemotherapy, and POST-TEXT (Post-treatment extent of disease) after neoadjuvant chemotherapy. [2,8,12,14,17-21]. Primary liver transplantation for patients with POST-TEXT III and IV HB has been recommended [8,22-27]. However, chemotherapy can promote downstaging and increase the possibility of surgical resection [2,14,18,20,21]. The need for disease-free surgical margins has been questioned, and results have been similar in patients with free margins and microscopically compromised, allowing extensive resections in POST-TEXT III and IV patients with hepatoblastoma [2,4,18,27-31]. Considering these aspects, we aimed to compare patients with POST-TEXT III and IV HB from a single institution who underwent extended liver resections and/or primary liver transplantation.

Methods

This study was approved by the Ethics and Research Committee of the Universidade Federal de São Paulo under number 1024/2018, decision 2906389. The study was carried out in a single pediatric oncology referral center. Twenty-seven patients with hepatoblastoma were analyzed, 18 with PRETEXT III or IV and 13 with POST-TEXT III or IV from 2009 to 2020. Patients with PRETEXT I and II, POST-TEXT I and II were excluded, as well as those who were not followed up or deceased before surgical treatment (Figure 1).

Figure 1: show patients’ characteristics and treatment results.

Four female and 9 male patients with a mean age of 3 years and 9 months, one patient had microdeletion of chromosome 15q11.2, and the highest incidence in our clinical findings was 10 patients with asymptomatic abdominal mass. Mean alpha-fetoprotein
on admission was 583.055mg/l and post neoadjuvant chemotherapy 31.764mg/l. The highest histological incidence type was mixed. Five PRETEXT III and 4 PRETEXT IV patients were eligible and received neoadjuvant chemotherapy according to the SIOP (International Childhood Liver Tumor Strategy Group) protocol. Nine patients were classified with POST-TEXT III and IV HBL, one patient maintained pulmonary metastasis and another vascular compromise to the right atrium in POST-TEXT classification. Three patients were submitted to primary liver transplantation, one from live donor, which evolved to graft thrombosis requiring new transplantation, and two with deceased donors, one presented bile duct stenosis treated with interventional radiology. Ten patients underwent extended liver resections, 5 right trisegmentectomies, 3 left trisegmentectomies, one with pulmonary metastasectomy, one with resection of thorbus with cardiopulmonary bypass, and 2 nonanatomical extended resections. One patient had postoperative bowel obstruction which was surgically treated. Surgical margins were free of disease (R0) in 5 patients, with microscopic compromise (R1) in 4, and with macroscopic compromise (R2) in one. This patient was indicated for primary liver transplantation, but this was not possible due to cerebral palsy, so the patient underwent liver resection intending to improve survival. Recurrence occurred in 3 patients, 2 (R0) and one (R1). Two of these patients were salvage transplanted and the other was waiting for a graft in the analyzed period. Of these patients, one was the patient with vascular extension up to the atrium that progressed to death and the other is off treatment. Patient (R2) had disease progression and 5 years survival. The overall survival at 12, 36, and 60 months in the group undergoing primary liver transplantation was 100%, and, in the group, undergoing extended resection it was 89% (Table 1).

| PRETEXT | BIOPSY | PATHOLOGY | INITIAL SURGERY | AFP-AF- | POST-TEXT | EXTRAHE- | RESSECTION | SUR- | INTRAOP COMPLI- | POST-OP COMPLI- | RESCUE- | PATHOL- | NECRO- | MARGIN | ADJU- | RE- | LOCAL |
|---------|--------|-----------|----------------|---------|-----------|----------|------------|------|----------------|-----------------|----------|---------|--------|--------|--------|------|-------|
| V2+Atrium | Yes | Mixed | No | Yes | 321604 | 3 | No | Right trisegmentectomy | R0 | No | No | No | Mixed | No | Yes | No | No |
| 3 V2+Atrium | Yes | Mixed | No | Yes | 38163 | 3 | No | Right trisegmentectomy | R1 | No | No | No | Mixed | No | No | Yes | No |
| 3 | Yes | Epithelial | No | Yes | 4949 | 3 | No | Right trisegmentectomy | R1 | No | Bowel obstruction | Waiting | Epithelial | Yes | Yes | Yes | Yes | Hepatic bed |
| 4 | Yes | Epithelial | No | Yes | 13225 | 3 V2+Atrium | abdomen + atrium | Left trisegmentectomy | R1 | No | No | Yes | Epithelial | Yes | Yes | Yes | Yes | Right segment |
| 4 | Yes | Epithelial | No | Yes | 11283 | 4 | No | Right trisegmentectomy | R0 | No | No | No | Epithelial | Yes | Yes | Yes | No | No |
| 3 | Yes | Epithelial | No | Yes | 1134 | 4 | No | Transplant | R0 | No | Graft thrombosis | Yes | Mixed | Yes | Yes | No | No | No |
| 4 | Yes | Mixed | No | Yes | 3745 | 3 | No | Nonanatomical heptatectomy | R0 | No | No | No | Mixed | No | Yes | Yes | Yes | Right segment |
| 3 | Yes | Mixed | No | Yes | 8435 | 3 | No | Left trisegmentectomy | R0 | No | No | Yes | Mixed | No | Yes | Yes | Yes | Right segment |
| 4P+M | Yes | Mixed | No | Yes | 28 | 4P | No | Left trisegmentectomy + pulmonary metastasectomy | R2 | No | No | No | Mixed | Yes | No | Yes | Yes | Hepatic bed |
| 4P2 | Yes | Mixed | No | Yes | 9.6 | 3P2 | No | Left trisegmentectomy + pulmonary metastasectomy | R0 | No | Estenose de via biliar | No | Epithelial | Yes | Yes | No | No | No |
| 4M | Yes | Mixed | No | Yes | 162 | 3 | Lung | Nonanatomical heptatectomy | R1 | No | No | No | Mixed | No | No | Yes | No | No |
| 3P+V | Yes | Mixed | No | Yes | 323 | 3 | No | Right trisegmentectomy | R1 | No | No | No | Mixed | No | No | Yes | No | No |
| 4P2 | Yes | Mixed | No | Yes | 9872 | 4p2 | No | Transplant | R0 | No | No | No | Mixed | Yes | Yes | No | No | No |
Discussion

Two major cooperative groups have joined to study pediatric neoplasms, many advances have been achieved with these multi-center studies since pediatric neoplasms are rare pathologies. The COG (Children’s Oncology Group), a North American group, started its work with liver neoplasms in the 1970s comparing chemotherapy regimens. With these studies and the implementation of cisplatin, patients with hepatoblastoma had better survival. [32] Further studies combining platinum with different chemotherapeutic agents have been developed since then, with the aim of decreasing toxicity while maintaining high levels of success. Therefore, it created a risk stratification for treatment guidance. [33] Later, this stratification would join the staging proposal suggested by SIOPEL (International Childhood Liver Tumor Strategy Group). SIOPEL, in contrast to COG, introduced the concept of neoadjuvant chemotherapy for patients with hepatoblastoma, for which it created a risk stratification based on PRETEXT, about two-thirds of patients considered with non-resectable tumor benefited from the reduction of staging and consequent resection of the tumor, other studies have been conducted based on risk stratification, chemotherapy regimens and surgical resection. [12,13,15,16,34-36] Other cooperative groups such as GPOH (Society of Pediatric Oncology and Hematology) and JPLT (Japanese Study Group for Pediatric Liver Tumor) have joined, with the same motivation, to conduct multi-center studies. Some challenges in the treatment of patients with hepatoblastoma still remain, such as high-risk, metastatic, and patients with central POST TEXT III and IV HB. Therefore, the creation of multicenter studies with the collaboration of cooperative groups such as CHIC (Children’s Hepatoblastoma International Collaboration), may develop new therapeutic strategies and obtain better results for the challenges of high-risk diseases.

The present study shows the experience of a single referral center where all patients were treated by the same team. Survival of patients with HB has increased with the use of platinum-based chemotherapy, but surgery with complete resection remains an important step for success. Historically, the surgical treatment for patients with central PRETEXT III and IV HB is primary liver transplantation. [11,37-39] With the implementation of neoadjuvant chemotherapy protocols and the studies of cooperative groups, some authors have demonstrated the possibility of partial liver resection with results similar to those in primarily transplanted patients. [2,27-29,40] In the sample studied, the mean age was 3 years and 9 months, with a range of 3 months to 16 years and 11 months. In other cases, the mean age was lower. [2,28] The mean age in this study was higher due to patients number 7 and number 10, who had late diagnoses. Regarding gender, 4 female and 9 male patients were studied, and we cannot infer a prevalence due to the small number of cases. In other cases, similar distribution between genders occurred [28,40].

The main clinical finding at diagnosis was abdominal mass, one patient had microdeletion syndrome of chromosome 15q11.2 and right hemihypertrophy, the other patients had no genetic syndromes. The literature associates hepatoblastoma with multiple genetic syndromes such as Beckwith-Wiedemann syndrome, but the sporadic form is more prevalent, [1,5,9] similarly as in the casuistic presented. Some studies show risk factors for tumor recurrence. Among them are high alpha-fetoprotein levels at diagnosis and their poor response to neoadjuvant chemotherapy, radiological staging with PRETEXT, and the type of surgical resection. [2,22,37,41-46] The alpha-fetoprotein levels at diagnosis, pre-chemotherapy, ranged from 643-2565530 mg/l and post neoadjuvant chemotherapy 10-321604 mg/l. In this study, relapse is not associated with higher alpha-fetoprotein levels nor with its lower range post neoadjuvant chemotherapy. Patients who relapsed (Numbers: 3,4,8,9) showed good response in alpha-fetoprotein levels, with reductions greater than 95%. Radiological staging with the PRETEXT classification is important for the initial staging and therapeutic decision. Patients with central PRETEXT III and IV HB are candidates for liver transplantation, however, with neoadjuvant chemotherapy they might suffer a down-staging, making tumor resection possible. In this study, of patients who underwent liver resection (8 patients), 3 of them presented a down-staging after neoadjuvant chemotherapy, POST-TEXT, enabling resection. Other studies also show down-staging on POST-TEXT making liver resection possible. [2,28]

PRETEXT staging may be associated with higher rates of disease recurrence. In this study, the association was not observed, since of the 4 patients who had a recurrence, one had an indication for liver transplantation concerning the tumor, although, due to comorbidities, she underwent liver resection (number: 9); another patient had extrathoracic disease with vascular involvement and thrombus extending to the right atrium (number: 4) and the others (numbers: 3,8) had PRE and POST-TEXT III HB. Regarding staging and tumor recurrence, 3 patients had extrathoracic disease, 2 with pulmonary metastasis, one underwent metastasectomy, and another had resolution of the metastasis with neoadjuvant chemotherapy. The third patient had an abdominal disease and vascular involvement with thrombus up to the right atrium. Of these, only the patient with pulmonary metastasis and resolution with chemotherapy did not present recurrence. Due to the small number of patients, we cannot state an association between relapse and POST-TEXT in this study. As for extended liver resection, only one patient underwent nonanatomical resection, and this patient did not have a recurrence (number: 7). Some studies suggest that nonanatomical resection has a higher chance of recurrence. [27,46] All other patients underwent anatomical resections or primary liver transplantation. No patient undergoing primary liver transplantation relapsed and all have 1-year and 3-year disease-free survival, a finding similar to that described by Uchida et al. in 2018. [2].
Regarding patients who underwent extensive liver resection, there were 2 deaths: Patient number 9, who underwent palliative resection due to the contraindication of liver transplantation because of the patient’s comorbidities, had an overall survival of 5 years. Patient number 4, presented extrahepatic disease with vascular involvement and thrombus up to the right atrium, had an overall survival of 1 year. Two similar cases were described by Fuchs et al. 2017. [28] In the resection group, the overall survival rate at 1 year was 90%, when excluding patient number 9, who had an indication for transplantation. A similar survival rate was found in the literature.[27,28,46,47] No correlation between tumor histology and recurrence was observed, since of the 4 recurrences 2 patients were of the epithelial type and 2 of the mixed type. As in other casuistic [6,11,13,31], microscopically compromised margins are not associated with recurrence in this group of patients. Compromised microscopic margins are not associated with recurrence in this group of patients. Of the patients with recurrence, one had negative surgical margins, one had macroscopic compromising, and two others had compromised margins in microscopy evaluation, but in one of these (number 4), other factors associated with recurrence were present. Some authors question the indications for extended liver resection because survival rates for salvage transplantation are much lower (20%-30%) compared to patients undergoing primary liver transplantation (80%-90%). [4,11,23,25,47]

In the presented casuistic, 2 patients required salvage transplantation, one patient had a 5 years disease-free survival, and the other patient died due to disease progression. The authors who are in favor of extended liver resection are based on survival rates similar to those of primary transplant patients, moreover, other issues are raised such as post-transplant morbidity, mainly due to immunosuppression, [26,28] and complication rates (10%-15%). [48-52] Three patients were submitted to primary transplantation, and 2 presented complications: graft thrombosis requiring new transplantation (number: 6) and bile duct stenosis treated by interventional radiology (number: 10). We must consider that complete resection is the aim in the treatment of hepatoblastoma. Therefore, the surgical indication should be meticulous, and primary liver transplantation should be included in the surgical planning of these patients. Lautz et al.[28] presented a casuistic of 14 patients with central POST-TEXT III or IV HB who underwent liver resection in a period of 11 years, where some patients were referred from other services for evaluation of primary transplantation. Of these patients, 8 have the PRETEXT information, 12 had POST-TEXT III, and 2 POST-TEXT IV, 12 extended resections were performed and one patient required salvage liver transplantation. The overall survival rate at 1, 2, and 5 years was 93%, 91%, and 88%, respectively. Since some patients were referred from other services, there are no staging data before neoadjuvant chemotherapy, which compromises the comparison with our study, since the response to neoadjuvant treatment may be a factor in better prognosis, also do not present data on patients undergoing primary liver transplantation.

Busweiler et al.[40] presented a study of 103 patients over 23 years in the Netherlands, where they stratify only by PRETEXT being 26 patients III and 20 IV. As for the surgeries performed, 18 were primary liver transplants and 76 liver resections with 32 extended resections, the overall survival was 92% at 5 years for the group undergoing liver resection and 77% for the group undergoing primary liver transplantation. In this study, the patients were stratified with PRETEXT, so the comparison with our sample is impaired since no data on the response to chemotherapy are available. In addition, the evaluated survival rate considers 103 patients from PRETEXT I-IV, so we cannot compare with our sample, which evaluates the most advanced stages, despite having similar survival rates. Fonseca et al.[11], in a paper assessing the need for free surgical margins after liver resection, presented 6 patients over 5 years, 3 PRETEXT III and 3 PRETEXT IV patients undergoing extended liver resections. No impact on survival was observed for patients with compromised microscopic margins over the mean observation period of 3.3 years. Although the aim of the paper is different from what we present, we may extract that besides negative surgical margins seeming to have no impact on survival, extended liver resection may be an option for liver transplantation. Fuchs et al.[28] presented 27 patients over 23 years, of which 16 and 11 were PRETEXT III and IV respectively; and POST-TEXT III and IV 21 and 6 respectively. All patients underwent extended liver resections, and the overall survival estimate was 80.7% at 5 years.

In comparison to our work, Fuchs et al.[28] have as exclusion criteria patients undergoing primary liver transplantation. They conclude that in selected cases extended liver resection for patients with POST-TEXT III and IV HB is possible to achieve high survival rates. We present similar results for a similar group of patients, and in addition, we present results from patients undergoing primary liver transplantation. Uchida et al.[2] published a study of 24 patients over 5 years who were referred to their service for evaluation of the need for liver transplantation. They were patients with PRETEXT and POST-TEXT II, III, and IV HB. Twelve patients underwent primary liver transplantation, 8 underwent extensive resection and 4 underwent liver resection. They obtained overall survival of the entire sample of 95.8% at 1, 3, and 5 years in the group of patients who underwent liver resection; of 91.7% and 100% in the group who underwent primary liver transplantation at 5 years. In comparison with our study, the survival rates are similar, but we must take into consideration that only patients with central POST-TEXT III and IV HB were included in the present study, unlike the Uchida et al. [2] study, which included patients with all stages. Due to the small sample size and the limited follow-up time of 1 year in one of the patients, the statistical
analysis was compromised, although it may be considered that concerning patients who underwent extended resection, the overall survival in this sample was about 85%. Excluding patient number 9, who had palliative surgery, the survival rate is 90%. Given these good results, extended liver resection for central POST-TEXT III and IV HB is feasible. We found limitations in the study, the small number of patients, thus making it impossible to perform statistical analyses to substantiate the results, which makes it difficult to establish treatment protocols. In this aspect, multicenter cooperative groups must carry out studies to obtain larger casuistic and more significant results.

Conclusion
Patients with central POST-TEXT III and IV hepatoblastoma undergoing extended liver resection had comparable results to those undergoing primary liver transplantation.

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