

Hepatoblastoma in Children

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Abstract. Hepatoblastoma is the most common primary liver tumour in children. Complete surgical removal is the treatment of choice for cure ; however, in most cases the tumour is unresectable because of its extensive hepatic involvement.

Nineteen pediatric cases (11 boys, 8 girls) with ages ranging from three months to 17 years were referred for management to our clinic from 1982 until 2000. All but three suffered from abdominal distention. The other frequent complaints were abdominal mass, anorexia, fatigue, abdominal pain and fever. Physical examination revealed enlarged liver in all patients. In addition to laboratory studies, they were pre-operatively examined by ultrasonography and, in recent cases, computed tomography was also used. Serum alpha-fetoprotein levels were found to be elevated in all patients. In thirteen cases, hepatic resections (10 lobectomies, 2 trisegmentectomies, 1 segmentectomy) were performed. In six children only liver biopsies could be done because of the huge tumour size. However, in three of them the tumours were excised at the second laparotomy, but only one patient survived. All of the patients – except two who were lost in the early post-operative period – received chemotherapy whether the tumour was excised or biopsied. In this series the mortality rate was found to be very high (91%) in the 1980s, and more reasonable (50%) in the 1990s, with an overall mortality rate of 73 per cent.

This result might be explained with late referral and advanced stage at diagnosis. In addition, we speculate that a combination of improved chemotherapy and technical advances in anesthesia and hepatic resection caused the obvious differences in the survival rates between the two periods.

Introduction

Hepatoblastoma is the most common malignant primary liver tumour in infants and children (1). It is embryonal in origin and frequently occurs in the first three years of life. Complete surgical removal is mandatory for cure ; however, it often has extensive hepatic involvement making the tumour unresectable ; thus, prognosis of patients with the disease has been unfavourable (2). Starting from 1970s, a number of chemotherapy protocols have been used to increase the resectability and improve long-term survival (3-6).

The purpose of this report is to review our experience with 19 children diagnosed with hepatoblastoma and to expose the causes of high mortality in the series.

Materials and methods

Between 1982 and 2000, 19 children with hepatoblastoma (HB) were seen in the Department of Pediatric Surgery, Istanbul Medical School. The diagnosis was made from history and from clinical and radiological findings associated with high serum α -fetoprotein (AFP) levels. In all cases, abdominal ultrasonography was used

to diagnose and assess the extent of tumour. After the technique became available in 1987, computed tomography (CT) was also used for the same purposes. Radiography and CT scan of the chest were also used to detect the presence of lung metastases.

After physical examination and completion of the laboratory and radiological studies, all cases were discussed at the Pediatric Surgical Oncology Joint Meeting of the Hospital, for resectability and tumour histology. Laparotomy was planned for all patients. The patients were given vitamin K and prophylactic antibiotics and preoperatively transfused as necessary with fresh frozen plasma and blood. Arterial and central venous lines were placed. The peritoneal cavity was entered through an upper abdominal transverse or subcostal incision and, after surgical evaluation of tumour involvement, hepatic resections were performed with standard techniques or, if the tumour was unresectable, only biopsies were done. Following biopsy and subsequent chemotherapy treatment, a second look laparotomy was planned for the assessment of tumour shrinkage and resectability.

After initial surgery, protocols of Children's Cancer Group (CCG) were used for staging the disease and the

Table 1

Localization, Initial Surgical Procedure, Metastatic Disease, Stage and Outcome of Tumour in Children with Hepatoblastoma

No.	Tumour Site	Surgical Procedure	Metastasis	Stage	Outcome
1	Right and left	Biopsy	None	III	Dead
2	Right	Right hepatectomy	None	III	Dead
3	Right	Right hepatectomy	None	III	Dead
4	Left	Segmentectomy	None	III	Dead
5	Right and left	Biopsy	None	III	Dead
6	Right	Right hepatectomy	None	I	Dead
7	Right	Right hepatectomy	None	I	Dead
8	Right and left	Biopsy	None	III	Dead
9	Right and left	Right hepatectomy	None	III	Dead
10	Right	Right hepatectomy	None	III	Dead
11	Right	Right hepatectomy	None	I	Alive
12	Right and left	Biopsy	Lung	IV	Dead
13	Right	Right hepatectomy	None	II	Dead
14	Right and medial left	Trisegmentectomy	None	II	Alive
15	Right	Right hepatectomy	None	I	Dead
16	Right and left	Biopsy	Lymph node	IV	Dead
17	Right and left	Biopsy	Lymph node	IV	Alive
18	Right and medial left	Trisegmentectomy	None	I	Alive
19	Right	Right hepatectomy	None	I	Alive

institution of chemotherapy (5). According to these protocols, in the 1980s Vincristine (VCR), Adriamycin (ADR), 5-fluorouracil (5FU), and Cyclophosphamide (CTX) were used; where, in the 1990s, Cisplatin (CDDP) and ADR regimens were used (3, 5, 6). In two patients ifosfamide was also used, in addition to CDDP and ADR, according to the German Co-operative Liver Tumour Study (7).

After completion of treatment all patients were regularly followed-up with abdominal ultrasonography, chest x-ray and serial AFP estimations.

Results

The median age at presentation of the 19 patients (11 boys, 8 girls) was 18 months (range 3 months to 17 years). Abdominal distension, pain or a mass, anorexia, fatigue and fever were the most common clinical features. Enlarged liver or a solid mass was detected on physical examination in 17 patients. Serum AFP levels were elevated markedly in all affected children. After imaging studies all patients underwent laparotomy.

Tumour location, initial surgical intervention, metastatic disease, stage and outcome are shown in Table 1. In six children only biopsies could be done because of the huge tumour size or multinodularity, while 13 underwent hepatic resections. Among these 19 patients, 9 had bilobar involvement, 9 involved the right lobe and one involved the left lobe. The types of resection performed were right hepatectomy (n = 10), trisegmentectomy (n = 2), and segmentectomy (n = 1).

Histological tumour subtypes were fetal (n = 3), fetal plus embryonal (n = 7), mixed (n = 7), small-cell undifferentiated (n = 1), and unclassified (n = 1). Staging

based on the CCG protocols included stage I in 6, stage II in 2, stage III in 8, and stage IV in 3 patients.

Two patients were lost in the early postoperative period due to extensive blood loss during surgery. The remaining 17 received chemotherapy. In three of 6 patients whose tumours were unresectable and initially biopsied, resection was possible at the second look operation, but only one of them survived. Between 1982 and 1991 ten of 11 patients died. As mentioned above two of them died owing to severe haemorrhage during hepatic resection. Three deaths were attributable to sepsis during chemotherapy regimens. The remaining five died of disease progression or metastases. Four of 8 remaining patients who were treated in the 1990s have survived, while the others were lost due to recurrences or metastatic diseases.

The deaths occurred 2 to 42 months after initial surgical intervention except for two who were lost in the early postoperative period. The survival rate of the first 11 patients was 9% compared with 50% in the last 8 patients. The overall survival rate of the series was 27%.

Discussion

Hepatoblastoma is the most common primary liver tumour in children, although it constitutes only 1% of all childhood malignancies (1). Complete surgical removal is the mainstay of treatment and great importance is given to early diagnosis; however, the tumour is often unresectable at the time of diagnosis. Adjuvant chemotherapy should be used to convert an unresectable tumour to a resectable tumour thereby achieving higher survival rates for these children (8). With the use of

chemotherapy Pierro et al (9) were able to successfully resect seven HBs in 11 children with initially unresectable tumours. However, since only one of our six patients whose tumours were unresectable and initially biopsied is alive, it is not possible to stress the superiority of chemotherapy over surgical resectability in our series.

Apart from the imaging techniques, the most noticeable laboratory parameter in HB patients is elevated AFP. In 100% of our patients, the serum level of AFP was found to be elevated. AFP measurements also have great importance during the follow-up period in the diagnosis of a metastatic disease or a recurrence (1, 6). Van Tornout et al (10) suggested that for children with unresectable or metastatic HB, early changes in AFP levels are a reliable predictor of outcome and can be used for identification of poor responders to treatment.

Infants with HB usually present during the first three years of life as in our series. The median age at diagnosis was 18 months. Most of our patients were male (11/19), a finding which is also in accordance with the literature.

Resectability criteria vary between centres, and with modern imaging techniques, the need for surgical exploration is controversial (2, 6). Boechat et al. (11) found 100% accuracy in predicting resectability using MR imaging. However, our policy for resectability was to make definitive decisions surgically. Evaluating different macroscopic features of HBs on their prognostic value, the outcome of the disease is not directly affected by tumour size as long as it is resectable. Large solitary masses can be easily resected technically whereas small central or multinodular tumours are difficult to completely excise (1, 7). In this series, nine of 19 tumours involved both liver lobes and only in one of them could complete surgical removal be done without any evidence of microscopic residual disease.

The prognosis of patients with HB varies with the histology and stage. The favourable outcome associated with pure foetal histology and the poor prognosis of anaplastic (small-cell undifferentiated) HBs has been documented previously but is not universally accepted (12, 13). In the present study, we did not detect any correlation between histologic subtype and prognosis. On the other hand, when the tumour is resected completely (stage I) or when only microscopic residual disease exists (stage II), the long-term survival rate is better (1). In our series, survival rate was 50% in stage I and 50% in stage II, but none of eight stage III patients survived. However the mortality rates in the literature for stage III disease are not more than 30-35%.

The most striking feature of the present series is the very poor survival rate (9%) in the first 11 patients between 1982 and 1991. Between 1991 and 2000, four of the 8 HBs survived (50%), which is quite satisfactory

and can be considered acceptable in comparison with 9 per cent. These obvious differences in the survival rates can be explained by the combination of ameliorated chemotherapy and improved surgical skills due to our experience with hepatobiliary surgery.

Despite the disadvantages of immunosuppression in cases of microscopic diseases or previous lung metastases, liver transplantation may offer an alternative treatment for patients with bilobar disease unresponsive to conventional treatment protocols (14, 15).

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