Hepatoblastoma—Evolution of Management and Outcome and Significance of Histology of the Resected Tumor. A 31-Year Experience With 40 Cases

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Background/Purpose: The aim of this study was to retrospectively evaluate and compare the clinical features, treatment strategy, pathology, and outcome of all patients with hepatoblastoma treated at an African hospital over a 31-year period (1970 to 2001).

Methods: Forty patients with hepatoblastoma were divided into 3 groups according to the treatment given. Group I (1970 to 1983, 14 patients) had no protocol therapy; group II (1984 to 1988, 6 patients) received protocol treatment according to Children's Study Group (CCSG) guidelines; group III (1989 to 2001, 20 patients) received SIOPEL protocol therapy. All available clinical, surgical, radiologic, and pathologic data were reviewed and analyzed.

Results: Overall patient survival was as follows: group I, 14%; group II, 50%, and group III, 80%. Deaths in group II were caused by chemotherapy-induced immunosuppression only. Prognostic data for group III showed that all tumor-related deaths could be predicted by identifying multifocal disseminated growth patterns ($P = .001$) or vascular invasion ($P = .001$) in resected tumors. Of the 40 diagnostic tumor biopsies performed, 2 significant complications (1 death, 1 intraperitoneal tumor seeding) occurred. Histologic criteria evaluating these biopsies were not predictive of overall survival.

Conclusions: The introduction of protocol therapy has resulted in a marked improvement in survival. Immunosuppression-related sepsis in our setting resulted in unacceptable mortality in patients treated according to CCSG guidelines. A diagnostic biopsy in hepatoblastoma is of value but not without complications. Preoperative chemotherapy followed by complete surgical excision according to International Society of Paediatric Oncology guidelines yields excellent results with a current survival rate of 80%.

INDEX WORDS: Hepatoblastoma, prognosis, pathology.

THE PROGNOSIS of hepatoblastoma has changed dramatically since the advent of effective chemotherapy in the 1980s. Improved surgical technique, better understanding of the hepatic segmental anatomy, safer anesthesia, improved postoperative care, and liver transplantation have all contributed to this better outcome.[1,2]

Before the introduction of effective chemotherapy, successful cure was sporadic and confined to only those tumors that could be completely resected. At this time, it was also apparent that only patients with tumors with a predominantly fetal epithelial component on histologic examination were likely to be cured.[3,4] Tumors of the macrotrabecular or anaplastic (small cell undifferentiated) types were invariably associated with a very poor prognosis.[5,6]

The introduction of preoperative cytotoxic agents was described in 1970.[7] Because more than 50% of children present with unresectable tumors or metastatic disease,[8] effective preoperative chemotherapy has allowed for considerable tumor shrinkage, easier surgical resection, and a greatly improved prognosis. Many treatment strategies for hepatoblastoma currently are under investigation in large multicenter cooperative study groups and are either primarily doxorubicin based or cisplatin based, with most units using a combination of cisplatin and doxorubicin in pre- and postoperative schedules. Other agents such as 5-fluorouracil, vincristine, carboplatin, etoposide, and ifosfamide have also been used.[9-14]

With current treatment most centers now achieve 3-year survival rates approaching 80%.[12,13] The overall prognosis in hepatoblastoma depends on numerous factors, some clinical and others histologic. The most important factors appear to be gross resectability of the tumor[15] and the presence of distant metastases to the lung.[16] Microscopic residual disease, ie, microscopic evidence of tumor at the resection margin, although associated with a slightly poorer outcome, appears not to be an independent prognostic factor.[12,17] Other indicators of poor prognosis include lymph node metastases, a multifocal disseminated growth pattern in the liver, the presence of vascular invasion, alpha-fetoprotein (AFP)

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0022-3468/04/3909-0004$30.00/0
doi:10.1016/j.jpedsurg.2004.05.020

levels less than 100 or greater than 1,000,000 ng/mL, involvement of both liver lobes, and an unfavorable epithelial grade.[17] The presence of differentiating mesenchymal elements, therapy-related necrosis involving more than 75% of the resected tumor, and the quantity of viable mesenchyme (bone, muscle, cartilage) are factors considered to indicate an improved outlook in hepatoblastoma.[18] In this paper, we review our experience in children with hepatoblastoma.

MATERIALS AND METHODS

Forty cases of hepatoblastoma were treated at Red Cross Children's Hospital, Cape Town over a period of 31 years (1970 to 2001).

Evaluation of the Clinical Data and Pathologic Investigation

Clinical information, radiologic data, operative reports, laboratory results, and follow-up were obtained in all cases. Archival histologic slides were reviewed, and paraffin blocks were available for study by routine or special stains as required. All cases were reclassified according to a modified system of Ishak and Gluntz.[19,20] The epithelial differentiation of the tumors was graded as 1, purely fetal; 2, predominantly fetal; or 3, predominantly embryonal, as previously described.[4,17] An additional grade (grade 4) was used to indicate tumors showing small cell undifferentiated (anaplastic), macrotrabecular, or rhabdoid features. The pretreatment extent of disease (PRETEXT) staging system[21] was used to record the extent of the primary liver tumor and the presence of distant metastases, venous invasion, or extrahepatic tumour at presentation. Postsurgical staging according to the TNM system for liver carcinoma[22] was utilized. In addition, resection margins were evaluated as follows: R0 to indicate macroscopic removal of the entire tumor (confirmed by microscopy), R1 to indicate microscopic involvement of the resection margin by tumor, and R2 to indicate macroscopic residual tumor.[17,22]

Prognostic Indicators

The following prognostic factors were evaluated: the extent of the primary tumor according to the PRETEXT system, the presence of distant metastases at presentation, the adequacy of surgical resection according to the postsurgical stage (R status), the growth pattern of tumor nodules in the liver (single, well-defined nodules or multiple, ill-defined tumor nodules), the presence of vascular invasion, and regional lymph node involvement. In addition, the grade and mitotic rates in both the preoperative biopsy and resection specimen were evaluated as possible prognostic factors.

Data Analysis

A database was generated using the program Epi-Info-6. Only those patients treated according to International Society of Paediatric Oncology (SIOPEL) guidelines[12] were compared to generate prognostic information. A follow-up period of more than 24 months was required. Univariate analysis for each prognostic criterion versus patient survival was performed (dead of disease *v.* alive and well) using the Fisher's Exact test. Significance was assumed when P was $\leq .05$. Multivariate analyses were performed using the Cox proportion hazards model.

RESULTS

Race, Age, and Sex

Age of the patients at diagnosis ranged from 1 day to 53 months. The mean age was 15.9 months with a median age of 12.8 months. Three patients had tumors that could be classified as "congenital," all presenting by the age of 3 months. One of these patients was a premature baby of 36 weeks' gestation who presented with a ruptured tumor at birth. The male to female ratio was 1.5:1. Twenty-four of the patients were of mixed racial grouping (60%), 8 were black (20%) and 8 were white (20%), which reflected local and regional racial demographics.

Presenting Symptoms

The most common complaint was that of abdominal swelling, present in 36 of the 40 cases (90%). Twelve patients had lost weight, and, in 5 patients, the parents noticed a fever. One of these patients presented with pneumonia and an incidental abdominal mass. Gastrointestinal symptoms were relatively uncommon with abdominal pain in 4, vomiting in 5, and anorexia in 9.

Physical Signs

All patients had a palpable abdominal mass. Only 1 patient with terminal disease (in the early 1970s) had jaundice at presentation and was not actively treated. Three patients presented with signs and symptoms of an acute abdominal crisis with sudden onset of abdominal pain, peritonism, and abdominal distension as a result of tumor rupture. A single male patient presented with virilizing features in addition to an abdominal mass. Three patients (8% of cases) had splenomegaly, but only 1 patient had esophageal varices, which were confirmed by gastroscopy. No patients had hemihypertrophy or other recognizable syndromes.

Laboratory Data

A complete set of laboratory results at the time of presentation was not available in all patients. In 35 patients, the average hemoglobin level on admission was 8.9×10^9/L (range, 5.3 to 12.9). Sixteen patients had an average mean cell volume of 67.6, indicating that microcytic anemia was the usual cause of the low hemoglobin. No patient presented with a coagulopathy in this series. Results of liver enzyme assays were available in 30 patients. The alanine transaminase (ALT) level ranged from 9 to 59 U (mean, 22.8 U) indicating that significant hepatitis was not present. Alkaline phosphatase (ALP) levels ranged from 44 to 889 U with an average of 233 U. Of the 30 patients, 6 (20%) had an abnormal level suggesting a degree of biliary obstruction, probably caused by local compression by the mass. The mean alpha-fetoprotein (AFP) level in 27 cases at presentation over the last 20 years was 1.1×10^6 ng/mL with a median level of 170,000 ng/mL. Levels ranged from 150 ng/mL to 12 million ng/mL.

Table 1. Histologic Classification of Hepatoblastoma at Red Cross Children's Hospital

Tumor Type	No. of Patients	
	Needle Biopsy	Resection
Epithelial		
Fetal	7	3
Embryonal/fetal	17	7
Macrotrabecular	1*	
Small cell undifferentiated	1	
Mixed		
Without teratoid features	10	15*
With teratoid features	0	8*
Total	36	33

*Small cell undifferentiated cytology also present (1 case per category).

Extent of Disease

Of the 40 cases, 7 patients (18%) had pulmonary metastases at presentation. In 5 cases, the metastases were within the lung and, in 2, in a subpleural location. Confirmation by histology was only possible in 2 cases (1 at postmortem). In 1 case in which the initial computed tomography (CT) scan of the chest was clear, pulmonary metastases developed while the patient was on chemotherapy.

Pathology

A total of 36 biopsy specimens and 33 resections were available for review (Table 1). Six patients in group I and 1 patient in group II died before surgery, so there was no resection in these cases to examine. A noticeable feature was the large proportion of cases of mixed epithelial-mesenchymal tumors with teratoid features (8 of 33 cases).

Treatment and Subsequent Course

The patients were divided into 3 groups according to the year in which the diagnosis was made and the therapy given. Survival times were calculated in months from the time of diagnosis to the time of the study or the time of death.

Group I (1970 to 1983, n = 14) did not have a specific surgical or chemotherapy protocol. Four had primary surgery without preoperative chemotherapy, 3 a biopsy only, 5 chemotherapy (various agents) after a diagnostic biopsy, and only 2 had a definitive resection after chemotherapy.

Group II (1984 to 1988, n = 6) received the protocol regimen[13] described by the Children's Cancer Study Group (CCSG). Four cycles of preoperative and 2 cycles of postoperative chemotherapy were given after a diagnostic open or closed trucut needle biopsy. Each cycle of chemotherapy consisted of intravenous (IV) cisplatinum (90 mg/m^2 for patients >1 year of age and 3 mg/kg for patients <1 year of age) administered over 6 hours followed by IV hydration and continuous infusion of Adriamycin (20 mg/m^2/d). This was given for 96 consecutive hours and was initiated during hydration 4 hours after completion of cisplatinum. Each cycle was given greater than 3 weeks apart depending on recovery of peripheral neutrophil and platelet counts to greater than 1.0×10^9/L and 100×10^9/L, respectively.

Group III (1989 to 2001, n = 20) was treated according to SIOPEL guidelines.[12] In this regimen, preoperative chemotherapy (PLADO chemotherapy) consisted of IV cisplatinum (80 mg/m^2 for patients >1 year of age and 3 mg/kg for patients <1 year of age) administered over 24 hours followed by IV hydration and continuous infusion of Adriamycin (20 mg/m^2/d) given for 48 consecutive hours. After a diagnostic biopsy, cycles of chemotherapy were administered as described above for group II. In 1 patient, no prechemotherapy biopsy was performed because the diagnosis was confidently made on clinical, radiologic, and biochemical grounds.

Patient Outcome

Group I. In this group there were only 2 survivors who are still alive 20 and 27 years respectively, after diagnosis. Both had unifocal tumors, involving only the right lobe of the liver, that were resected fully at the time of initial surgery. They were both classified as mixed epithelial-mesenchymal hepatoblastomas. There was no vascular invasion. The first patient (follow-up of 20 years) had a congenital hepatoblastoma with a predominantly fetal epithelial component (grade 2) and received no chemotherapy after surgery. The second patient (follow-up of 27 years) presented with an abdominal crisis caused by a ruptured tumor. This hepatoblastoma was a predominantly embryonal tumor (grade 3). The patient received postoperative methotrexate and Adriamycin. Of the nonsurvivors, 1 patient died of pneumonia soon after diagnosis; 1 died during emergency surgery while attempting to resect a ruptured, large, left-sided tumor, and 1 died of hemorrhage after an open tumor biopsy. The rest of the patients died as a direct consequence of their disease or during the treatment.

Group II. Three of the 6 patients treated according to CCSG guidelines are still alive with an average survival time of 16 years. All 3 survivors had unifocal teratoid hepatoblastomas without vascular invasion that were fully resected at surgery. One of the survivors had lung metastases in a subpleural location at presentation. Two of the 3 survivors had tumors that responded well to chemotherapy (>75% of the tumor necrotic or replaced by osteoid and connective tissue) and a low histologic grade (both grade 1). The third survivor, who presented with male precocious puberty, also had a good chemotherapy response (>75% tumor necrosis). However, residual viable foci were high grade microscopically with

Table 2. Tumor-Related Mortality in Hepatoblastoma (Group III) at Red Cross Children's Hospital (1989-2001)

Case	Age (mo)	PRETEXT Stage	AFP (ng/mL) (Presentation)	Distant Metastases	Resected Tumor		Cause of Death	Time to Death (wk)
					Type	Grade/Pattern		
1	21	III	12,000,000	Lung at presentation	Teratoid	4	Local recurrence	44
2	4	III	150	Lung during treatment	Mixed	4	Disseminated disease	20
3	4	III	390,668	Nil	Embryonal/fetal	2	Local recurrence	96

areas resembling a malignant mixed germ cell tumor. One patient died of measles pneumonia 6 weeks after diagnosis following 3 courses of chemotherapy before planned surgical resection of a well-localized tumor. The other 2 deaths also occurred secondary to the complications of chemotherapy-associated immunosuppression 12 and 20 weeks after definitive surgery. One of these patients died of *Klebsiella* pneumonia and the other from *Escherichia coli* septicemia. There was no evidence of disease recurrence clinically at the time of death, and in one case this was confirmed at post mortem.

Group III. Of the 20 patients, 19 received SIOPEL protocol therapy. Of these 20 patients, 16 are alive and well. The average survival time in this group was 7.0 years from the time of diagnosis. One patient, currently alive and free of disease more than 3 years after resection had intraperitoneal seeding after a closed 16-gauge trucut needle biopsy. These tumor deposits were removed macroscopically at the time of surgical resection. There were 4 tumor-related deaths. There was no operative mortality. One patient received treatment used routinely in germ cell tumors (etoposide, 120 mg/m^2/d/72 hr; carboplatinum, 550 mg/m^2/1 hr/d 2; bleomycin, 15 mg/m^2/15 min/d 3) and died 4 months after diagnosis owing to spontaneous tumor rupture; the response to chemotherapy having been poor. This patient was excluded from the study. The other 3 patients had tumor recurrence and death despite optimal therapy (Table 2). In only 1 case was the primary tumor not fully removed macroscopically because of multifocal disseminated tumor within the liver.

Prognostic Factors Evaluated in Group III

The detailed stratification of prognostic variables and results of the univariate analysis can be seen in Table 3. This identified that only vascular invasion ($P = .001$) and a multifocal pattern of tumor growth ($P = .001$) in the resected tumor were significantly associated with tumor-related mortality. In view of the small sample size, multivariate analysis was unsuccessful in identifying any independent variable significantly relating to prognosis. Histologic criteria evaluated in the pretreatment biopsy were not predictive of outcome in this analysis, although it is useful to note that the identification of an obvious small cell undifferentiated pattern in the biopsy always resulted in a tumor-related death (2 cases).

DISCUSSION

This report from a single institution highlights the greatly improved prognosis that has occurred over the last 30 years in children with hepatoblastoma. Survival rates in the 3 groups described in this report improved from 14% to 50% to 80%. This can be attributed to effective chemotherapy, better surgical technique, and

Table 3. Relationship Between Prognostic Factors and Tumor-Related Deaths in Patients With Hepatoblastoma Treated at Red Cross Hospital (Univariate Analysis of 19 Patients)

Prognostic Factor	% Event*	*P* Value†
PRETEXT stage		
Stage I/II	20.0 (0/10)	
Stage III/IV	11.1 (3/9)	.14
Distant metastases at presentation		
Yes	50.0 (2/4)	
No	6.7 (1/15)	.10
Histologic appearance of biopsy		
Grade 1/2	11.1 (1/10)	
Grade 3/4	22.2 (2/9)	.46
Mitotic rate of tumour biopsy		
0-2 mitoses/10 HPF	10.0 (1/10)	
≥3 mitoses/10 HPF)	25.0 (2/9)	.46
At surgery tumor involves		
One liver lobe	14.3 (2/14)	
Both lobes	20.0 (1/5)	.62
1-3 segments	16.7 (2/14)	
≥4 segments	20.0 (1/5)	.62
Growth pattern of tumor		
One or more than one well-defined nodule	0.0 (0/16)	
Multiple ill-defined tumour nodules	100.0 (3/3)	.001
Regional lymph node metastases at surgery		
Yes	100 (1/1)	
No	12.5 (2/18)	.16
Adequacy of resection		
Adequate microscopic and macroscopic removal	11.8 (2/17)	
Removal not achieved	50.0 (1/2)	.3
Histologic appearance of resection		
Grade 1/2	0.0 (1/13)	
Grade 3/4	42.9 (2/6)	.22
Mitotic rate of tumor resection		
0-2 mitoses/10 HPF	0.0 (1/13)	
≥3 mitoses/10 HPF)	42.9 (2/6)	.22
Vascular invasion		
Yes	0.0 (0/16)	
No	100.0 (3/3)	.001

*Tumor-related mortality.

†According to Fisher's Exact test.

improved postoperative care. Increasing expertise in liver surgery, because of the development of a liver transplant program at our hospital, led to improved tumor resection because of increasing familiarity with the techniques of partial and total vascular exclusion. Extended hepatic resections also have been carried out successfully with a donor liver-in-waiting as a safety net. This has resulted in better clearance of disease.[2,23-27] Although our numbers are small, information generated from a single center remains important, particularly when the tumor is rare and requires specialized management, as is the case with hepatoblastoma. In addition, it shows that in a developing country, where patients tend to present late with large tumors and advanced disease, results comparable with many large first-world multiinstitutional studies[12,13] can be achieved. For discussion, our observations highlight a number of important issues.

First, at our hospital, the higher chemotherapeutic dosages given in group II resulted in unacceptable mortality from sequelae of profound immunosuppression. All deaths in this group were patients who should have been long-term survivors.

Second, our results confirm that in chemoresponsive tumors, long-term cure can be achieved if the residual tumor burden after surgical resection of the primary tumor is low. At our hospital, 3 of 5 patients (60%) presenting with lung metastases and treated with cisplatinum-Adriamycin chemotherapy survived (1 in group II, 2 in group III). In addition, 2 of 24 patients (8%) in these treatment groups with microscopic residual disease after surgical resection are also currently alive and well. This is comparable to results of larger studies such as the SIOPEL1 trial, in which 55% of 31 patients presenting with lung metastases achieved a long-term cure.[28] However, it should be noted that at our institution, no "rescue" therapy (different chemotherapy ± thoracotomy) was given, as the routine management of hepatoblastoma with lung metastases remains controversial and is essentially nonstandardized. Lung metastases at presentation resulted in an important negative prognostic factor in SIOPEL1 for the 5-year event-free survival rate,[16] and we hope that future treatment strategies will address this issue.

Third, we suggest that the pathologist should play an important role in predicting which cases are behaving aggressively at the time of definitive surgery. In our experience, a resected tumor with small vessel vascular invasion and a multifocal disseminated pattern of growth was associated with tumor-related mortality. Larger multicenter trials have shown previously that these variables were important in tumor-related death,[17] lending weight to our results. These features are relatively easy to evaluate (Fig 1) and appear to indicate that the treated tumor is actively proliferating, suggesting that it has become resistant to the chemotherapy to which it has been exposed. It is interesting that before the time of effective chemotherapy 2 of our patients (group I) survived. Both patients had unifocal hepatoblastomas, without vascular invasion, which were completely excised at surgery. One of these patients had no chemotherapy at all, suggesting that even in these early cases, the lack of vascular invasion and a unifocal pattern of growth were important but at the time unrecognized biological indicators of a favorable outcome.

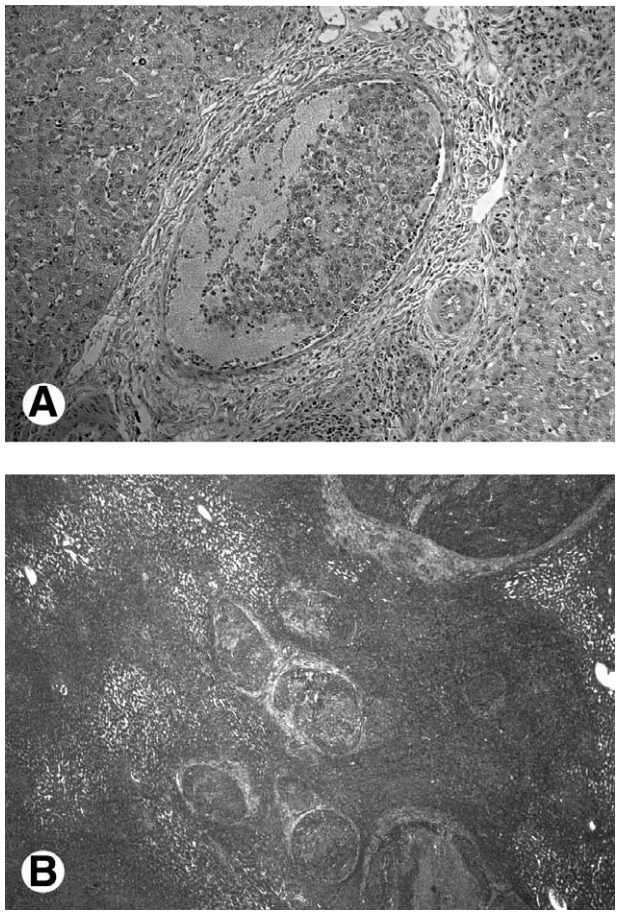

Fig 1. (A) Vascular invasion in hepatoblastoma. Intravascular tumor within a hepatic venule of a portal tract. (H&E, original magnification ×100.) (B) Multifocal disseminated growth pattern in hepatoblastoma. Large tumor nodules can be seen surrounded by nonneoplastic liver in the vicinity of the main tumor mass. (H&E, original magnification ×40.)

Fourth, although we are aware of the benefits of a diagnostic biopsy and its low complication rate,[29] our experience would advise caution in its use. It is a well-recognized complication for a hepatocellular carcinoma to recur at the site of a needle biopsy tract.[30] In developing countries where tumors are very large at presentation and the rate of hepatocellular carcinoma in the population is high, this is a very real consideration. At our institution, a single patient had intraperitoneal me-

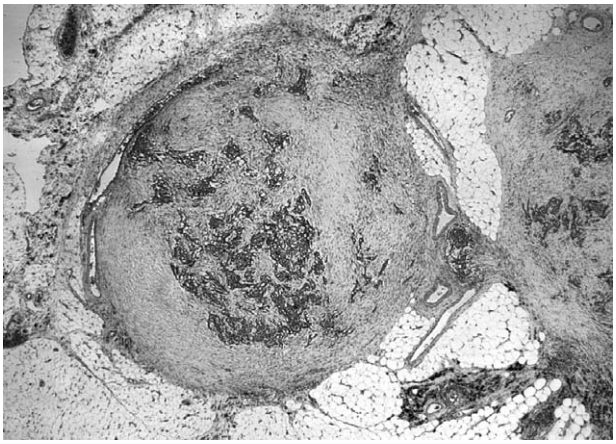

Fig 2. Peritoneal implants after a trucut needle biopsy in hepatoblastoma. (H&E, original magnification ×40.)

tastases after needle sampling (Fig. 2). However, the tumor proved to be chemosensitive, and the patient is alive and well today. An additional patient in the early 1970s died of an unrecognized hemorrhage after an open biopsy. Although one can argue that the outcome would have been different today with more effective patient monitoring after an invasive procedure, it highlights a difficulty in poorer countries where resources are limited.

Finally, we are uncertain if there is any established prognostic value attached to the histologic or cytogenetic evaluation of a small biopsy section taken from an otherwise large and usually heterogeneous tumor. It is important to realize that the distinction between an "aggressive hepatoblastoma" and "hepatocellular carcinoma" may not be possible for the pathologist, particularly when examining a small core of tissue. Protagonists of a diagnostic biopsy will argue that it is at least required if we are to understand more about the molecular biology of the untreated tumor in the future. This is certainly a compelling argument, because there does appear to be growing evidence that the cytogenetic evaluation of untreated resected tumors will, in the future, provide additional valuable prognostic information.[31,32] This will hopefully have implications for establishing additional risk categories for patients with hepatoblastoma, once larger numbers of cases have been evaluated. It also highlights that those tumors that are primarily resected, are, from a scientific point of view, extremely valuable. This is certainly an advantage of the treatment strategy favored for less-extensive tumors in the United States. In addition, our data and those of others[33] would suggest that the identification of a small cell undifferentiated pattern in the preoperative biopsy, as well as the resected tumor, should alert the oncologist of an aggressive tumor. In our experience, this cytologic pattern was predictive of mortality in every case.

Over the last 30 years, a marked improvement in outcome of patients with hepatoblastoma has occurred at our hospital, which is in a developing country. This can be attributed to improvements in surgical technique and the implementation of effective protocol therapy. Clearly, the challenge for the future is to treat and cure all cases of hepatoblastoma. Our current experience would suggest that the pathologist should play a more active role in identifying the high-risk case for treatment stratification. We hope that new data generated by multiinstitutional study groups will suggest effective modifications to current therapy in this group of patients. This will allow the prognosis in hepatoblastoma to be further improved in the future.

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