Impact of Preoperative Fine-needle Aspiration Cytologic Examination on Clinical Outcome in Patients With Hepatocellular Carcinoma in a Tertiary Referral Center

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Hypothesis: Preoperative fine-needle aspiration cytologic examination (FNAC) exerts a statistically significant adverse effect on long-term clinical outcome in patients with hepatocellular carcinoma (HCC).

Design: Retrospective study.

Setting: Tertiary referral center.

Patients: A total of 828 patients with clinical suggestion of HCC received surgical treatment. Ninety-one patients underwent preoperative FNAC, suggesting HCC, and 737 patients did not.

Main Outcome Measures: The resectability and histologic diagnoses of liver masses were evaluated in patients with and without preoperative FNAC. Clinico-pathologic data and operative and survival outcomes of patients who underwent curative hepatic resection for HCC were compared between the FNAC and non-FNAC groups.

Results: The resectability rates of the FNAC (81.3%) and non-FNAC (81.8%) groups did not differ (P = .91). Histologic examination of tumor confirmed HCC in 766 patients. The positive predictive value of preoperative FNAC was 96%, whereas that of preoperative imaging studies was 92% (P = .23). Among patients with nondiagnostic serum α-fetoprotein concentrations (≤400 ng/mL), 3% in the FNAC group (n=66) had benign liver diseases vs 9.5% in the non-FNAC group (n=432) (P = .09). Among patients with curative hepatic resection (70 in the FNAC group and 545 in the non-FNAC group), hospital mortality was 4% and 6% in the FNAC and non-FNAC groups, respectively. In the FNAC group, needle tract tumor seeding was not encountered. Excluding patients with preexisting and iatrogenic tumor rupture, intraperitoneal extrahepatic metastasis occurred in 1 patient (2%) in the FNAC group and in 30 (6%) in the non-FNAC group (P = .34). The cumulative 1-, 3-, and 5-year overall survival rates were 79%, 61%, and 48%, respectively, for the FNAC group and 75%, 55%, and 43% for the non-FNAC group (P = .77). The disease-free survival results of the groups were similar (P = .51).

Conclusions: Preoperative FNAC has no statistically significant adverse effect on the operability, the possibility of extrahepatic tumor spread, or the long-term survival of patients with HCC. Preoperative FNAC may play a diagnostic role in selected patients with liver nodules on imaging studies when the serum α-fetoprotein concentration is not diagnostic.

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Hepatocellular carcinoma (HCC) is a common malignancy in Africa and Asia, where chronic hepatitis B and C infections are prevalent. Its incidence is also rising in Western countries. According to long-term cohort studies, early diagnosis of tumor by widely practiced screening programs has resulted in improved survival of patients with HCC. In current practice, prompt diagnosis of HCC relies on accurate imaging studies (including abdominal ultrasonography, helical computed tomography [CT], magnetic resonance imaging, hepatic angiography, and post-Lipiodol [Guerbet, Aulnay-sous-Bois, France] CT) and on raised serum α-fetoprotein (AFP) concentrations (>400 ng/mL). However, surveillance in high-risk patients has resulted in identification of suspicious liver masses that may lack diagnostic features in imaging studies and serum AFP measurement. Subsequent management may be delayed in the absence of definite diagnosis, thus defeating the screening purpose.

Fine-needle aspiration cytologic examination (FNAC) has evolved to become a mini-
nally invasive diagnostic procedure for suspected liver masses in most clinical situations. A fine needle, by definition, is a needle with a core diameter of less than 1 mm (19 gauge or thinner). In FNAC, cytologic smears are examined using a needle aspiration technique. This examination can be performed percutaneously under imaging guidance (ultrasound or CT) on an outpatient basis. Because of its high accuracy and low complication rate, FNAC has been considered to be the initial evaluation method of choice for most liver masses in the clinical setting.6,8 Nevertheless, its associated risk should not be underestimated, particularly needle tract tumor seeding, which could substantially worsen the patient’s prognosis. Although needle tract tumor implantation after FNAC has been reported,9,12 the risk of its subsequent intraperitoneal tumor spread and hence the survival outcome of patients has not been studied in detail, to our knowledge. As a tertiary referral center, the University of Hong Kong Medical Centre has a policy of avoiding FNAC, but we cared for patients with HCC in whom preoperative FNAC was performed as part of the diagnostic procedures before referral. This study evaluates the impact of preoperative FNAC on long-term clinical outcomes after curative surgery in patients with HCC.

METHODS

Between January 1, 1989, and December 31, 2001, 828 patients with clinical suggestion of HCC received surgical treatment in the Department of Surgery, University of Hong Kong Medical Centre. Preoperative investigations revealed discrete liver masses suggestive of HCC on imaging studies (CT, magnetic resonance imaging, hepatic angiography, or post-Lipiodol CT) or raised serum AFP concentrations (>400 ng/mL). Among these patients, 91 underwent preoperative FNAC, suggesting HCC, and the remaining 737 did not. In most cases, FNAC was performed by a radiologist using a 22-gauge needle under ultrasound or CT guidance. The aspirated material was expelled, smeared onto glass slides, and fixed with 95% ethanol. Excess material was fixed in 50% ethanol to make cell blocks for additional cytologic examination.

TREATMENT STRATEGIES

Surgical resection was considered to be the first choice of treatment and was offered to all patients with resectable tumors within 2 to 4 weeks of the date of diagnosis or referral. All patients underwent preoperative chest radiography to rule out lung metastases. Liver functional reserve was assessed by liver biochemical analysis, Child-Pugh grading,13 and measurement of the indocyanine green retention rate at 15 minutes. Absolute contraindications for surgery included extrahepatic metastasis, main portal vein or inferior vena cava tumor thrombus, and poor liver function (Child-Pugh class C). Tumor invasion of the ipsilateral portal vein or hepatic vein branches or adjacent organs was considered resectable provided that en bloc resection of all the tumor tissues could be carried out with adequate tumor-free margins. Multiple tumors in more than 1 lobe were resected en bloc by extended right- or left-sided hepatectomy given a favorable liver functional reserve (Child-Pugh class A). Patients with ruptured HCC were treated conservatively if they were hemodynamically stable or by transarterial embolization if they were unstable. Subsequent liver resection was offered if the tumor was considered resectable. Only patients with Child-Pugh class A were offered major hepatectomy, defined as the resection of 3 or more liver segments according to the classification of Couinaud.14 For selected patients with Child-Pugh class B, tumor was resected by minor hepatectomy, defined as the resection of no more than 2 liver segments.

Since 1994, we have routinely performed laparoscopy and laparoscopic ultrasonography immediately before laparotomy to confirm tumor resectability. Subsequent laparotomy can be avoided if unfavorable tumor (peritoneal metastasis or main portal vein or inferior vena cava tumor thrombus) or poor liver status (small liver remnant or severe liver cirrhosis) is encountered. In addition, intraoperative ultrasonography was routinely performed to detect additional tumors or tumor invasion to major intrahepatic vasculatures and to delineate the transection line for hepatectomy with adequate tumor-free margin (>0.5 cm).15,16 Operative techniques have been described in a previous study by our group.17 Hospital mortality was defined as death after surgery during the same admission. All resected specimens were examined by an experienced pathologist (L.O.-L.N.) for histologic staging. The pTNM staging was evaluated according to the American Joint Committee on Cancer classification revised in 2002.18

FOLLOW-UP OF PATIENTS

All patients were followed up at the University of Hong Kong Medical Centre monthly for the first year after surgery and every 3 months thereafter. Serum AFP concentration was measured, and abdominal ultrasonography or CT was performed every 3 months to detect tumor recurrence that had radiologic features of HCC (contrast enhancement and hypodensity in the arterial and portovenous phases of CT, respectively). Suspected intrahepatic recurrence was confirmed by hepatic angiography and post-Lipiodol CT. Patients with intrahepatic recurrence and satisfactory liver functional reserve were offered another resection of recurrent tumor if feasible. Otherwise, they were treated with transarterial chemoembolization, percutaneous ethanol injection, or radiofrequency ablation.

DATA ANALYSIS

All epidemiologic and clinicopathologic data were prospectively collected in a computerized database by a research assistant. Continuous data were compared using the unpaired t test, and they are expressed as mean±SD. Categorical data were compared using the χ2 test with Yates correction or the Fisher exact test where appropriate. The overall and disease-free survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Hospital deaths were included in the overall survival analysis but were excluded from the disease-free survival analysis. Thirteen clinicopathologic variables of potential prognostic value were analyzed for their effects on overall and disease-free survival. These variables were categorized as binary and included 7 clinical factors (age [<60 years vs ≥60 years], sex, hepatitis B surface antigen status, indocyanine green retention at 15 minutes [≥14% vs >14%], serum AFP concentration [≥1000 or >1000 ng/mL], preexisting or iatrogenic tumor rupture, and postoperative adjuvant chemotherapy), 3 surgical factors (major or minor resection, intraoperative blood loss [≥2 L vs >2 L], and any perioperative blood transfusion), and 3 pathologic factors (histologic margin involvement, tumor size [≥5 cm vs >5 cm], and cancer stage [I/II vs III]). Multivariate analysis was performed using the Cox proportional hazards regression model to identify independent prognostic factors. The overall and disease-free survival rates of patients in the FNAC and non-FNAC groups were then compared using the log-rank test after adjustment for the identified independent prognostic factors using the Cox hazard ratio. All statistical analyses were performed using statistical software (SPSS version 11.0; SPSS Inc, Chicago, Ill.). P<.05 was considered statistically significant.

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RESULTS

IMPACT OF FNAC ON OPERABILITY OF PATIENTS

All patients (n=828) in whom no contraindication to surgery was observed during the preoperative assessment underwent laparoscopy, exploratory laparotomy, or both. Curative hepatic resection was performed in 74 (63 men and 11 women) and 603 (482 men and 121 women) patients in the FNAC (n=91) and non-FNAC (n=737) groups, respectively. There was no significant difference in the resectability rate between the FNAC group (81.8%) and the non-FNAC group (81.3%) (P=.91). The extent of the hepatic resections performed is summarized in Table 1. Reasons for inoperable liver tumors in the remaining 151 patients (17 in the FNAC group and 134 in the non-FNAC group) included multifocal tumor involving both lobes of the liver (n=62), tumor invasion into the main portal vein or inferior vena cava (n=46), peritoneal metastases (n=18), small liver remnants (n=10), severe liver cirrhosis (n=12), and uncontrolled bleeding during attempted liver transection (n=2). In 1 patient, no liver tumor could be identified during exploratory laparotomy with intraoperative ultrasonography. However, this patient developed HCC 6 months after surgery. He required transarterial chemoembolization treatment owing to poor liver reserve. At the time of surgery, there was no significant difference in the incidence of bilobar liver tumor (n=9 in the FNAC group and n=53 in the non-FNAC group; P=.29), tumor invasion to the main portal vein or inferior vena cava (n=3 in the FNAC group and n=43 in the non-FNAC group; P=.22), or peritoneal metastases (n=2 in the FNAC group and n=16 in the non-FNAC group; P=.98) in patients with or without preoperative FNAC. After curative hepatic resection, adjuvant chemotherapy was given to 61 patients who were either recruited in a randomized trial of adjuvant transarterial and systemic chemotherapy or given transarterial chemotherapy because of a positive microscopic margin. Follow-up of this study ended on December 31, 2002. Hence, all patients were followed up for at least 1 year after surgery. Median follow-up was 45.5 months (range, 12-165 months).

FNAC AND HISTOLOGIC DIAGNOSIS OF LIVER TUMORS

Histologic examination of tumors confirmed HCC in 766 patients (87 in the FNAC group and 679 in the non-FNAC group), 17 (1 in the FNAC group and 16 in the non-FNAC group) of whom were diagnosed as having mixed hepatocellobiliary carcinoma. The positive predictive value of preoperative FNAC in this study was 96% (87 of 91 patients), whereas that of preoperative imaging studies was 92% (679 of 737 patients) (P=.23). Other pathologic diagnoses in the remaining 62 patients (4 in the FNAC group and 58 in the non-FNAC group) are listed in Table 2. Among these patients, 43 had benign liver diseases and 19 had liver malignancies other than HCC. For patients with nondiagnostic serum AFP concentrations (>400 ng/mL), 3% (n=2) in the FNAC group had benign liver diseases compared with 9.5% (n=41) in the non-FNAC group (P=.09). No patients with diagnostically serum AFP concentrations (>400 ng/mL) had benign liver disease in the present study.

FNAC AND CURATIVE HEPATIC RESECTION FOR HCC

The clinical details of 615 patients (70 in the FNAC group and 545 in the non-FNAC group) who underwent curative hepatic resection for HCC were further analyzed. Hospital mortality was 4% (n=3) in the FNAC group and 6% (n=31) in the non-FNAC group. The underlying causes of death included liver failure (n=17), intra-abdominal sepsis (n=10), intra-abdominal bleeding (n=5), acute myocardial infarction (n=1), and hemorrhagic stroke (n=1). The clinicopathologic data for patients with and

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Table 1. Types of Curative Hepatic Resection in Patients With Liver Masses Suggestive of Hepatocellular Carcinoma With or Without Preoperative Fine-needle Aspiration Cytologic Examination (FNAC)*

<table>
<thead>
<tr>
<th>Procedure</th>
<th>FNAC Group (n = 74)</th>
<th>Non-FNAC Group (n = 603)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hepatectomy</td>
<td>28 (38)</td>
<td>197 (33)</td>
</tr>
<tr>
<td>Extended right hepatectomy</td>
<td>16 (22)</td>
<td>129 (21)</td>
</tr>
<tr>
<td>Left hepatectomy</td>
<td>2 (3)</td>
<td>29 (5)</td>
</tr>
<tr>
<td>Extended left hepatectomy</td>
<td>6 (8)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Segmentectomy (IV, V, VI)</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Minor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>12 (16)</td>
<td>123 (20)</td>
</tr>
<tr>
<td>Subsegmentectomy</td>
<td>10 (14)</td>
<td>96 (16)</td>
</tr>
</tbody>
</table>

*Because of rounding, percentages do not total 100.

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Table 2. Histologic Diagnosis Other Than Hepatocellular Carcinoma in Patients With or Without Preoperative Fine-needle Aspiration Cytologic Examination (FNAC)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>FNAC Group (n = 4)</th>
<th>Non-FNAC Group (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign liver diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal nodular hyperplasia</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Regeneration of liver nodule</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Hemangiomia</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Liver cell adenoma</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Malignant liver diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Carcinoid tumor</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dendritic cell tumor</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
without preoperative FNAC are given in Table 3. Tumor size and serum AFP concentration of patients in the FNAC group were statistically significantly lower than those in the non-FNAC group. Otherwise, there were no statistically significant differences between the 2 groups with respect to epidemiologic characteristics, liver status, tumor status, or operative details. The incidences of stages I, IIIB, and IIIC disease were higher in the FNAC group than in the non-FNAC group, but the differences were not statistically significant. There was no statistically significant difference in the incidence of preexisting tumor rupture in both groups. Most patients (70% in the FNAC group and 65% in the non-FNAC group) underwent major hepatic resection, and the extent of surgery was similar in both groups in terms of the need for adjacent organ resection in continuity with liver tumor, operative time, intraoperative blood loss, and requirement for postoperative blood transfusion.

For patients in the FNAC group, needle tract tumor seeding was not encountered at the time of surgery or during follow-up, as revealed by clinical examination and imaging studies. Excluding patients with preexisting (n=6 in the FNAC group and n=49 in the non-FNAC group) and iatrogenic (n=13 in the non-FNAC group) tumor rupture, intraperitoneal extrahepatic metastasis occurred in 1 patient (2%) in the FNAC group and in 30 (6%) in the non-FNAC group (P=.34). Other sites of distant metastases included lung (n=122), bone (n=24), brain (n=15), and abdominal wall (n=5) (Table 4). Intrahepatic tumor recurrence occurred in 38 patients (54%) in the FNAC group, which was not statistically different from that in the non-FNAC group (n=282; 52%) (P=.68).

Median overall survival was 54.3 months (95% confidence interval [CI], 35.6-72.6 months) in the FNAC group and 43.5 months (95% CI, 34.6-52.3 months) in the non-FNAC group. The cumulative 1-, 3-, and 5-year overall survival rates were 79%, 61%, and 48%, respectively, for the FNAC group, and 75%, 55%, and 43%, re-

### Table 3. Comparison of Patients Who Underwent Curative Hepatic Resection for Hepatocellular Carcinoma With or Without Preoperative Fine-needle Aspiration Cytologic Examination (FNAC)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FNAC Group (n = 70)</th>
<th>Non-FNAC Group (n = 545)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>54.5 ± 13.2</td>
<td>53.3 ± 12.6</td>
<td>.73</td>
</tr>
<tr>
<td>Sex, M:F, No.</td>
<td>61.9</td>
<td>446.99</td>
<td>.27</td>
</tr>
<tr>
<td>Hepatitis B carrier, No. (%)</td>
<td>54 (77)</td>
<td>464 (85)</td>
<td>.18</td>
</tr>
<tr>
<td>Child-Pugh classification, No. (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class A</td>
<td>68 (97)</td>
<td>524 (96)</td>
<td></td>
</tr>
<tr>
<td>Class B</td>
<td>2 (3)</td>
<td>21 (4)</td>
<td>.67</td>
</tr>
<tr>
<td>ICG-R15, mean ± SD, %</td>
<td>13.2 ± 9.7</td>
<td>12.7 ± 8.8</td>
<td>.92</td>
</tr>
<tr>
<td>α-Fetoprotein, mean ± SD, ng/mL</td>
<td>11 644 ± 63 396</td>
<td>26 541 ± 110 220</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Tumor size, mean ± SD, cm</td>
<td>5.9 ± 4.8</td>
<td>7.5 ± 4.6</td>
<td>.003*</td>
</tr>
<tr>
<td>UICC cancer staging (2002), No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>32 (46)</td>
<td>210 (38)</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>16 (23)</td>
<td>148 (27)</td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>9 (13)</td>
<td>99 (18)</td>
<td></td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>11 (16)</td>
<td>80 (15)</td>
<td></td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>2 (3)</td>
<td>8 (1)</td>
<td>.5</td>
</tr>
<tr>
<td>Preexisting tumor rupture, No. (%)</td>
<td>6 (9)</td>
<td>49 (9)</td>
<td>.9</td>
</tr>
<tr>
<td>Major hepatic resection, No. (%)</td>
<td>49 (70)</td>
<td>355 (65)</td>
<td>.42</td>
</tr>
<tr>
<td>Adjacent organ resection in continuity with tumor, No. (%)</td>
<td>7 (10)</td>
<td>80 (15)</td>
<td>.29</td>
</tr>
<tr>
<td>Operative time, mean ± SD, min</td>
<td>372 ± 137</td>
<td>377 ± 140</td>
<td>.83</td>
</tr>
<tr>
<td>Blood loss, mean ± SD, L</td>
<td>1.8 ± 1.5</td>
<td>2.0 ± 2.5</td>
<td>.63</td>
</tr>
<tr>
<td>Blood transfusion required, No. (%)</td>
<td>32 (46)</td>
<td>223 (41)</td>
<td>.46</td>
</tr>
<tr>
<td>Hospital mortality, No. (%)</td>
<td>3 (4)</td>
<td>31 (6)</td>
<td>.62</td>
</tr>
<tr>
<td>Postoperative chemotherapy, No. (%)</td>
<td>7 (10)</td>
<td>54 (10)</td>
<td>.98</td>
</tr>
</tbody>
</table>

Abbreviations: ICG-R15, indocyanine green retention rate at 15 minutes; UICC, Union Internationale Contre le Cancer.

<sup>a</sup>Statistically significant.

### Table 4. Extrahepatic Recurrence After Curative Hepatic Resection for Hepatocellular Carcinoma in Patients Without Preexisting or Iatrogenic Tumor Rupture

<table>
<thead>
<tr>
<th>Location</th>
<th>FNAC Group (n = 64)</th>
<th>Non-FNAC Group (n = 483)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraperitoneal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritoneum</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Colon</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Lymph node</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Stomach</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Kidney</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Adrenal</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Spleen</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lung</td>
<td>9</td>
<td>113</td>
</tr>
<tr>
<td>Bone</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Brain</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Abdominal wall</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviation: FNAC, fine-needle aspiration cytologic examination.
respectively, for the non-FNAC group. There was no statistically significant difference between the 2 groups ($P = .77$) (Figure 1). Excluding hospital deaths, the disease-free survival result of the FNAC group was similar to that of the non-FNAC group ($P = .51$) (Figure 2). Median disease-free survival was 22.7 months (95% CI, 17.5-36.9 months) in the FNAC group and 15.5 months (95% CI, 11.5-19.5 months) in the non-FNAC group. The cumulative 1-, 3-, and 5-year disease-free survival rates were 64%, 37%, and 19%, respectively, for the FNAC group, and 54%, 34%, and 26%, respectively, for the non-FNAC group.

Univariate analyses of prognostic factors for overall survival revealed that 9 of 13 evaluated factors had a statistically significant prognostic effect, including sex, serum AFP concentration, preexisting or iatrogenic tumor rupture, types of hepatic resection, intraoperative blood loss, perioperative blood replacement, microscopic tumor involvement of resection margin, tumor size, and cancer stage (Table 5). On multivariate analyses, only cancer stage (risk ratio [RR], 1.514; 95% CI, 1.371-1.673; $P < .001$), sex (RR, 1.184; 95% CI, 1.014-1.383; $P = .03$), perioperative blood replacement (RR, 1.135; 95% CI, 1.061-1.215; $P < .001$), and tumor size (RR, 1.103; 95% CI, 1.005-1.058; $P = .03$) were independent predictors of overall survival. When the same clinicopathologic factors were analyzed for their effect on disease-free survival, 8 factors (sex, serum AFP concentration, preexisting or iatrogenic tumor rupture, intraoperative blood loss, perioperative blood transfusion, microscopic tumor involvement of resection margin, tumor size, and cancer stage) were statistically significant factors in the univariate analysis (Table 6). Multivariate analyses showed 5 variables to be statistically significant predictive factors for disease-free survival, including cancer stage (RR, 1.108; 95% CI, 1.07-1.145; $P = .009$), serum AFP concentration (RR, 1.138; 95% CI, 1.061-1.215; $P < .001$), preexisting or iatrogenic tumor rupture (RR, 1.080; 95% CI, 1.005-1.058; $P = .04$), and tumor size (RR, 1.096; 95% CI, 1.001-1.061; $P = .05$).

As a minimally invasive technique, the application of FNAC in the diagnostic process of discrete hepatic nod-
Table 6. Significant Prognostic Factors for Disease-Free Survival in Patients Who Underwent Hepatic Resection for Hepatocellular Carcinoma by Univariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival, Median, mo</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F (n = 122)</td>
<td>32.7</td>
<td>.001</td>
</tr>
<tr>
<td>M (n = 459)</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td>Serum α-fetoprotein, ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1000 (n = 388)</td>
<td>21.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;1000 (n = 213)</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>Preexisting or iatrogenic tumor rupture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 504)</td>
<td>17.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes (n = 77)</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Intraoperative blood loss, L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 (n = 399)</td>
<td>19.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;2 (n = 182)</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>Perioperative blood replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 342)</td>
<td>21.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes (n = 239)</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>Microscopic tumor involvement of resection margin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 518)</td>
<td>17.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes (n = 63)</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 (n = 240)</td>
<td>31.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;5 (n = 341)</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>Cancer stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II (n = 383)</td>
<td>29.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>III (n = 198)</td>
<td>5.5</td>
<td></td>
</tr>
</tbody>
</table>

ules remains controversial. This study evaluated its impact on histologic diagnosis, subsequent operability, and long-term survival in patients with HCC.

General consensus holds that periodic abdominal ultrasound and the measurement of serum AFP concentration can detect HCC in its early stage, which is associated with better prognosis. However, there is still a significant proportion of hepatic nodules detected on ultrasound that are not associated with AFP elevation. Caturelli et al.17 examined focal liver nodules in 287 patients with chronic hepatitis C infection; 68.9% of patients had HCC with normal serum AFP concentrations. A positive FNAC result (Table 2) and all of them had serum AFP concentrations below the diagnostic value (≤400 ng/mL). Despite the high predictive value of FNAC in this study, we could not assess its specificity and sensitivity because the procedure was not practiced routinely at the University of Hong Kong Medical Centre, and all FNACs were performed before referral. On the other hand, the corresponding positive predictive value of the preoperative imaging studies for HCC in our study was 92% (679 of 737 patients), which is similar to that of FNAC. It seems that preoperative FNAC provides no additional diagnostic value for HCC compared with commonly practiced radiologic investigations in our study. Torzilli et al.30 reported high accuracy of various imaging studies for HCC, with sensitivity and specificity of 100% and 98.9%, respectively. Based on these findings, the authors suggested that the use of fine-needle biopsy should be drastically limited in view of its potential risks. However, in patients with serum AFP concentrations of 400 ng/mL or less in our study, we observed that a higher proportion of patients in the non-FNAC group (n = 41; 9.5%) had benign liver pathologies compared with those in the FNAC group (n = 2; 3%), although the difference was not statistically significant. Subsequent major surgery could be avoided in these patients. In other words, preoperative FNAC may help define the pathology of liver nodules in patients with serum AFP concentrations of 400 ng/mL or less so that hepatic resection could be avoided in those with benign liver lesions. Moreover, lymphomatous nodules can also arise in patients with chronic liver disease.7,31,32 Early diagnosis of this disease entity by FNAC may allow prompt medical treatment, thus improving the prognosis of patients.

Although the specificity of FNAC is high, its sensitivity varies widely (range, 76%–93%).21-24 In a recent multicenter study21 of 602 radiologically guided FNACs, 23.5% of benign aspirates were diagnosed as being malignant by follow-up tissue biopsies. In addition, diagnostic difficulty was encountered in differentiating among focal nodular hyperplasia, liver cell adenoma, and well-differentiated HCC in the noncirrhotic liver. This wide variability in the sensitivity of FNAC could be explained by the variability in the performance of biopsy technique and diagnostic criteria used in different medical centers. On-site evaluation of fine-needle aspirates by cytopathologists, collaboration between radiologists and cytopathologists, and the uniform policy in the interpretation of smears with clinical information have helped improve the overall accuracy of FNAC.

The risk of tumor implantation along the fine-needle tract should not be underestimated. In an animal study,31 FNAC of a highly cellular tumor produced a spread of 10^3 to 10^5 tumor cells on the needle tract. Although this complication was not observed in our study, it has been reported worldwide with an incidence of HCC that varies from 0.003% to 2%.25,34 The underlying risk factors include small tumor (<2 cm), well-differentiated tumor, needle diameter greater than 1 mm, multiple needle passes during the procedure, and the lack of nontumoral liver along the needle tract. The tumor implantation necessitates surgical resection and may adversely increase therapeutic morbidity in patients with HCC. Because of this potentially fatal complication, some researchers11,30,35 advocate avoiding FNAC in patients with resectable liver tumor or in candidate patients for liver transplantation. After FNAC, the time lapse to clinically evident tumor seeding can vary widely and can take up to 24 months,36 which might be well beyond the life span.
of most patients with progressive malignant disease. This could explain why this complication was infrequently reported in the literature, as might be the case in our study. Subcutaneous tumor implantation could also occur shortly (within 17 days) after FNAC. This incidence may adversely affect the operability of patients with HCC as tumor spillage from the needle tract could result in peritoneal seeding before any surgical interventions could be performed. Nevertheless, in this study, there was no statistically significant difference in the operability rate between patients with and without preoperative FNAC. For patients with resectable HCC at the time of surgery, it is also possible that preoperative FNAC may lead to an advanced tumor stage as a result of either tumor spread to the surrounding organs through the needle tract or intrahepatic tumor spread through the portal venous system. In this study, although a greater proportion of patients in the FNAC group had stage III cancer compared with those in the non-FNAC group, the difference was not statistically significant.

Chapoutot et al. studied 150 patients with needle tract seeding after FNAC for HCC and found that the prognosis was not affected by FNAC in terms of the possibility of resecting the subcutaneous metastasis or the coexistence of other metastases with progressive disease. However, the long-term clinical outcomes, in particular extrahepatic intraperitoneal tumor spread and survival rates, in patients with preoperative FNAC were not studied in detail. In this study, when patients with preexisting tumor rupture were excluded, no statistically significant difference was observed in the incidence of extrahepatic intraperitoneal metastasis in patients with and without preoperative FNAC. A similar result was obtained for the incidence of intrahepatic tumor recurrence. Long-term overall and disease-free survival did not differ statistically between the 2 groups of patients. By multivariate analysis for survival, 4 independent significant prognostic factors (cancer stage, sex, perioperative blood replacement, and tumor size) and 5 prognostic factors (cancer stage, AFP concentration, sex, perioperative blood replacement, and tumor size) were identified as affecting overall and disease-free survival, respectively, as mentioned in previous studies. After adjustment of overall and disease-free survival for these prognostic factors, no statistically significant difference was observed between the FNAC and non-FNAC groups.

To our knowledge, this is the first study of the impact of preoperative FNAC on long-term clinical outcome in patients with HCC. Although there is no statistically significantly unfavorable outcome in patients with preoperative FNAC in this retrospective study, caution is warranted when interpreting these results since the underlying statistical significance depends largely on the overall number of patients involved. A higher level of evidence by prospective study will be needed before one can confidently apply this phenomenon to clinical practice. Another limitation of this study is related to the fact that preoperative FNAC was performed before the patients were referred to the University of Hong Kong Medical Centre. Therefore, there might not be a strict protocol for the procedure of FNAC for patients in the FNAC group.

In conclusion, FNAC exerts no statistically significant adverse effect on the operability, the possibility of extrahepatic tumor spread, and the long-term survival of patients with HCC. Preoperative FNAC may play a diagnostic role in selected patients with liver nodules on imaging studies when the serum AFP concentration is not diagnostic.

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Anemia and Blood Transfusion in Critically Ill Patients

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Context Anemia is a common problem in critically ill patients admitted to intensive care units (ICUs), but the consequences of anemia on morbidity and mortality in the critically ill is poorly defined.

Objectives To prospectively define the incidence of anemia and use of red blood cell (RBC) transfusions in critically ill patients and to explore the potential benefits and risks associated with transfusion in the ICU.

Design Prospective observational study conducted November 1999, with 2 components: a blood sampling study and an anemia and blood transfusion study.

Setting and Patients The blood sampling study included 1136 patients from 145 western European ICUs, and the anemia and blood transfusion study included 3534 patients from 146 western European ICUs. Patients were followed up for 28 days or until hospital discharge, interinstitutional transfer, or death.

Main Outcome Measures Frequency of blood drawing and associated volume of blood drawn, collected over a 24-hour period; hemoglobin levels, transfusion rate, organ dysfunction (assessed using the Sequential Organ Failure Assessment score), and mortality, collected throughout a 2-week period.

Results The mean (SD) volume per blood draw was 10.3 (6.6) mL with an average total volume of 41.1 (39.7) mL during the 24-hour period. There was a positive correlation between organ dysfunction and the number of blood draws (r = 0.34; P < .001) and total volume drawn (r = 0.28; P < .001). The mean hemoglobin concentration at ICU admission was 11.3 (2.3) g/dL with 29% (963/3295) having a concentration of less than 10 g/dL. The transfusion rate during the ICU period was 37.0% (1307/3534). Older patients and those with a longer ICU length of stay were more commonly transfused. Both ICU and overall mortality rates were significantly higher in patients who had vs had not received a transfusion (ICU rates: 18.5% vs 10.1%, respectively; χ² = 50.1; P < .001; overall rates: 29.0% vs 14.9%, respectively; χ² = 88.1; P < .001). For similar degrees of organ dysfunction, patients who had a transfusion had a higher mortality rate. For matched patients in the propensity analysis, the 28-day mortality was 22.7% among patients with transfusions and 17.1% among those without (P = .02); the Kaplan-Meier log-rank test confirmed this difference.

Conclusions This multicenter observational study reveals the common occurrence of anemia and the large use of blood transfusion in critically ill patients. Additionally, this epidemiologic study provides evidence of an association between transfusions and diminished organ function as well as between transfusions and mortality. (2002;288:1499-1507)

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