Factors affecting the prognosis of small hepatocellular carcinoma in Taiwanese patients following hepatic resection

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BACKGROUND: Small hepatocellular carcinoma (HCC) affects millions of individuals worldwide. Surveillance of high-risk patients increases the early detection of small HCC.

OBJECTIVE: To identify prognostic factors affecting the overall survival (OS) and recurrence-free survival (RFS) of patients with small HCC.

METHODS: The present prospective study enrolled 140 Taiwanese patients with stage I or stage II small HCC. Clinical parameters of interest included operation type, tumour size, tumour histology, Child-Pugh class, presence of hepatitis B surface antigen and liver cirrhosis, hepatitis C status, alpha-fetoprotein, total bilirubin and serum albumin levels, and administration of antiviral and salvage therapies.

RESULTS: Tumour size correlated significantly with poorer OS in patients with stage I small HCC (P=0.014); however, patients with stage II small HCC experienced a significantly poorer RFS (P=0.033). OS rates did not differ significantly between patients with stage I and stage II small HCC. Tumour margins, tumour histology and cirrhosis did not significantly affect OS or RFS (P>0.05).

DISCUSSION: Increasing tumour size has generally been associated with poorer prognoses in cases of HCC. The present study verified the relationship between small HCC tumour size and OS; however, a reduction in OS with increasing tumour size was demonstrated for stage II small HCC. Tumour margins, tumour histology and cirrhosis did not significantly affect OS or RFS (P>0.05).

CONCLUSION: Patients with stage II small HCC may benefit from aggressive surveillance for tumour recurrence and appropriate salvage treatment. Further studies are needed for additional stratification of stage I patients to identify those at increased risk of death.

Key Words: Prognosis; Small hepatocellular carcinoma; Tumour size

Hepatocellular carcinoma (HCC) represents the fifth most common cancer worldwide, and is the most common cancer diagnosed in Taiwan (1,2). According to the International Journal of Cancer, liver cancer accounted for nearly 700,000 deaths worldwide in 2008 (3). Liver cirrhosis, particularly as a consequence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, is recognized as the most common risk factor for the development of HCC (4). Other factors associated with HCC include alcoholic liver disease, nonalcoholic steatohepatitis, obesity and diabetes (5).

Routine screening of high-risk patients (those with cirrhosis and those with HBV and/or HCV) have been shown to increase survival rates. Chen et al (6) demonstrated a 24% reduction in HCC mortality for high-risk patients using blood tests (including those for HBV surface antigen [HBsAg], HCV antibody [anti-HCV], alanine aminotransferase and alpha-fetoprotein [AFP]) and ultrasonography. In another randomized controlled trial (7), AFP measurements and ultrasonography revealed a 37% reduction in HCC mortality.

Early detection of HCC remains critical for long-term survival, and potentially offers more treatment options for patients (8). Currently, surgical resection offers the best chance for cure; however, impaired liver function can present a contraindication to partial hepatectomy (9,10). The known risk factors for HCC enable the identification and screening of at-risk patients; however, less is known about the factors associated with prognosis, which would enable stratification of HCC patients into treatment groups following surgical resection (11). In the present study, the prognostic factors associated with overall survival (OS) and recurrence-free survival (RFS) were analyzed in 140 Taiwanese patients with stage I or stage II small HCC.
Patient selection

Data were collected from the Changhua Christian Hospital (Taiwan) for all cases of newly diagnosed small HCC surgically treated between January 2001 and December 2007. In the present study, small HCC was defined as tumour(s) ≤ 5 cm in size. Operations involving the removal of three or more segments of liver were regarded as major hepatectomies; otherwise, these operations were considered to be minor surgeries. A total of 140 consecutive patients with small HCC were enrolled. Following partial hepatectomy, each small HCC case was classified as either stage I or stage II based on the American Joint Committee on Cancer criteria, 6th edition (12). Stage I HCC is defined as a solitary tumour (regardless of size) without vascular invasion. Stage II HCC is defined as either a solitary tumour (regardless of size) with evidence of vascular invasion or multiple tumours, each < 5 cm in size.

Follow-up

After partial hepatectomy, patients were followed for a mean of 43.4 months (range 2.6 months to 119.1 months). OS was defined as the time from the date of surgery to the date of death or last follow-up.

METHODS

Patient groups

Table 1 summarizes the demographic data for patients with stage I small HCC (n=99) and stage II small HCC (n=41). The clinical parameters measured included operation type (major or minor hepatectomy), tumour size, tumour histology, Child-Pugh class, HCV status, AFP, total bilirubin and serum albumin levels, the presence of HBsAg and/or liver cirrhosis, and the administration of antiviral and/or salvage therapy. Child-Pugh class (A, B or C), which is determined by the summation of points assigned to laboratory values (total serum bilirubin and serum albumin levels, and international normalized ratio) and clinical signs (ascites and encephalopathy) in patients with liver disease, can help to predict OS (13).

Follow-up

After partial hepatectomy, patients were followed for a mean of 43.4 months (range 2.6 months to 119.1 months). OS was defined as the time from the date of surgery to the date of death or last follow-up.
TABLE 2
Univariate and multivariate Cox proportional hazard models for death (for all patients and according to cancer stage)

| Characteristic                  | All patients (n=140) | Stage I (n=99) | Stage II (n=41) |
|--------------------------------|----------------------|----------------|-----------------|
|                                | Univariate           | Multivariate   | Univariate      | Multivariate   |
|                                | HR (95% CI)          | P              | HR (95% CI)     | P              |
| Age                            | 1.02 (0.99–1.05)     | 0.22           | 1.02 (0.98–1.06)| 0.36           |
| Tumour size                    | 1.28 (0.95–1.73)     | 0.14*          | 1.61 (1.10–2.34)| 0.54*          |
|AFP ≤400 ng/mL vs <400 ng/mL    | 0.87 (0.34–2.27)     | 0.66           | 0.96 (0.22–4.14)| 0.56           |
|Total bilirubin                 | 1.91 (0.76–4.81)     | 0.38           | 1.73 (0.44–6.80)| 0.45*          |
|Albumin                         | 0.57 (0.29–1.77)     | 0.086          | 0.51 (0.23–1.10)| 0.521          |
|Sex (male vs female)            | 2.15 (0.89–5.22)     | 0.375          | 1.58 (0.57–4.38)| 0.25*          |
|Margin (≥1 cm vs <1 cm)         | 0.61 (0.30–1.23)     | 0.468          | 0.73 (0.30–1.78)| 0.12*          |
|Histology (moderate to poor vs well) | 0.62 (0.22–1.77)     | 0.409          | 0.59 (0.17–2.04)| 0.15*          |
|Operation type (major vs minor) | 0.80 (0.28–2.27)     | 0.670          | 1.09 (0.25–4.73)| 0.39           |
|Child-Pugh class (B vs A)       | 2.05 (0.49–8.61)     | 0.327          | 2.53 (0.56–11.00)| NA             |
|HBsAg (negative vs positive)    | 1.59 (0.80–3.18)     | 0.414          | 1.23 (0.51–2.98)| 0.61*          |
|HCV (positive vs negative)      | 1.25 (0.63–2.49)     | 0.525          | 1.18 (0.48–2.87)| 0.50           |
|Cirrhosis (present vs absent)   | 1.06 (0.47–2.36)     | 0.891          | 1.11 (0.40–3.08)| 0.746          |
|Microvascular invasion          | 1.27 (0.53–3.00)     | 0.590          | NA              | 0.58           |
|Multifocality                   | 2.00 (0.69–5.80)     | 0.201          | NA              | 1.60           |
|Antiviral therapy               | 0.71 (0.29–1.77)     | 0.465          | 0.79 (0.26–2.44)| 0.53           |
|Salvage therapy                 | 0.71 (0.28–1.77)     | 0.464          | 0.66 (0.19–2.31)| 0.72           |
|Stage II vs stage I             | 1.85 (0.92–3.73)     | 0.085          | NA              | 0.629          |

Variables with P<0.1 in the corresponding univariate Cox proportional hazard models were selected for the multivariate model by the forward conditional method. *P<0.05 indicated that the 95% CI of HR did not include 1. AFP, alpha-fetoprotein; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; NA, not available due to zero patients who were classified as Child-Pugh B in the stage II group, and zero patients with microvascular invasion and multifocality in the stage I group; vs, versus.

RESULTS

Demographic and clinical findings for all patients and for those with stage I and stage II HCC are presented in Table 1. Of the 140 patients, 41 (29.3%) were female and 99 (70.7%) were male, with a median age of 59 years. Patients with stage II small HCC were more likely to present with an AFP level of ≥400 ng/mL (P<0.012) and to have tumours demonstrating poorly to moderately differentiated histological grades than were patients with stage I small HCC (P=0.008). However, no significant associations were observed with respect to age, sex, tumour margins, operation type, Child-Pugh class, presence of HBsAg, HCV status, presence of liver cirrhosis, tumour size, total serum bilirubin and serum albumin levels, antiviral therapy or salvage therapies (all P>0.05).

The Cox proportional hazard models for OS for all patients in the present study are summarized in Table 2. No significant factors associated with OS were identified in this group of 140 patients (P>0.05). After model selection using the forward conditional method, albumin level and sex were selected for the multivariate Cox proportional hazard model. For each unit (10 g/L) increase in the albumin level, the HR decreased by a factor of 0.40 (95% CI 0.19 to 0.85; P=0.018).
TABLE 3
Univariate and multivariate Cox proportional hazard models for recurrence (for all patients and according to cancer stage)

| Characteristic | Total (n=140) | Stage I (n=99) | Stage II (n=41) |
|----------------|--------------|----------------|----------------|
|                | Univariate   | Multivariate   | Univariate     | Multivariate   |
|                | HR (95% CI)  | P              | HR (95% CI)    | P              |
| Age            | 1.03 (1.00–1.05) | 0.023*         | 1.03 (1.01–1.05) | 0.016*         |
| Tumour size    | 1.19 (0.95–1.50) | 0.287          | 1.07 (0.96–1.20) | 0.287          |
| AFP level (>400 ng/L vs ≤400 ng/L) | 0.96 (0.99–1.91) | 0.901          | 1.00 (0.86–1.15) | 0.279          |
| Total bilirubin| 1.02 (0.98–1.25) | 0.968          | 0.90 (0.81–1.00) | 0.607          |
| Albumin level  | 0.77 (0.45–1.30) | 0.325          | 0.81 (0.58–1.16) | 0.266          |
| Sex (male vs female) | 1.63 (0.92–2.97) | 0.108          | 1.38 (0.68–2.82) | 0.385          |
| Tumour margin (≥1 cm vs <1 cm) | 0.69 (0.84–1.55) | 0.513          | 0.75 (0.47–1.21) | 0.263          |
| Multifocality  | 0.64 (0.32–1.19) | 0.143          | 0.80 (0.34–1.87) | 0.609          |
| Operation (major vs minor) | 0.58 (0.27–1.21) | 0.145          | 0.54 (0.23–1.29) | 0.175          |
| Histology (moderate-poor vs well) | 0.58 (0.27–1.21) | 0.145          | 0.54 (0.23–1.29) | 0.175          |
| Child-Pugh class (B vs A) | 1.31 (0.52–3.27) | 0.565          | 1.06 (0.38–2.99) | 0.931          |
| HCV (positive vs negative) | 1.19 (0.72–1.97) | 0.492          | 1.21 (0.64–2.29) | 0.551          |
| Cirrhosis (present vs absent) | 1.32 (0.73–2.37) | 0.259          | 1.30 (0.63–2.69) | 0.479          |
| Microvascular invasion | 1.53 (0.88–2.65) | 0.132          | 0.58 (0.27–1.21) | 0.565          |
| HBsAg (negative vs positive) | 1.50 (0.72–3.47) | 0.259          | 0.58 (0.27–1.21) | 0.565          |
| HBsAg positive | Yes | 55 (72.4) | 41 (64.1) | 0.361 | 36 (70.6) | 30 (62.5) | 0.261 | 19 (76.0) | 11 (68.8) | 0.436 |
| No | 21 (27.6) | 23 (35.9) | NA | 15 (29.4) | 18 (37.5) | 0.609 | 6 (24.0) | 5 (31.3) | NA | 11.3 (45.2–78.8) | 0.789 |
| Antiviral therapy | Yes | 41 (53.9) | 1 (1.6) | <0.001* | 26 (51.0) | 1 (2.1) | <0.001* | 15 (60.0) | 0 (0.0) | <0.001* |
| No | 35 (46.1) | 63 (98.4) | 25 (49.0) | 47 (97.9) | 10 (40.0) | 16 (100.0) | 0.0001 | 16.0 (95.2–100.0) | 0.0001 |

Variables with P<0.1 in the corresponding univariate Cox proportional hazard models were selected for the multivariate model by the forward conditional method.

Male patients had a significantly higher risk of death than female patients (HR 3.00 [95% CI 1.16 to 7.75]; P=0.023).

The Cox proportional hazard models for OS for patients with stage I and stage II disease are also presented in Table 2. For the 99 patients with stage I small HCC, only tumour size reached statistical significance (P=0.014). No significant factors were found to be associated with stage II small HCC (HR 1.78 [95% CI 1.06 to 2.99]; P=0.030). Among patients with stage I small HCC, only age reached statistical significance in the corresponding univariate Cox proportional hazard model. For each year increase in age, the risk of recurrence in those with stage I small HCC increased by a factor of 1.03 (95% CI 1.00 to 1.05; P=0.016).

RFS findings for patients with stage I and stage II small HCC are also found in Table 3. A significantly higher risk of recurrence was demonstrated for patients with stage I small HCC (HR 1.78 [95% CI 1.06 to 2.99]; P=0.030). Among patients with stage I small HCC, only age reached statistical significance in the corresponding univariate Cox proportional hazard model. For each year increase in age, the risk of recurrence in those with stage I small HCC increased by a factor of 1.03 (95% CI 1.00 to 1.07; P=0.024). Among patients with stage II small HCC, no factors potentially associated with cancer recurrence reached statistical significance when analyzed in univariate or multivariate Cox proportional hazard models.

Seventy-six patients were HBsAg positive, while 64 were HBsAg negative. The proportion of patients with cirrhosis were 74.2% and 64.1%, respectively, without a significant difference (P=0.361). The proportion of patients who underwent antiviral therapy and were HBsAg positive (53.9%) was significantly greater than those who were HBsAg negative (16.1%) (P=0.021). Similar results were observed after stratification according to HCC stage (Table 4).

Kaplan-Meier OS and RFS curves for all 140 patients with small HCC are shown in Figure 1. The OS at three years was 87.4%, and at five years was 78.6% (left panel). The RFS at three years was 67.3%, and at five years was 50.5% (right panel).

Kaplan-Meier OS and RFS curves for stage I and stage II small HCC are shown in Figure 2. Compared with patients with stage I small HCC,
Patients with stage II small HCC experienced poorer OS (left panel) and RFS (right panel). For stage I small HCC, the OS at three years was 90.7%, and at five years was 81.6%. For stage II small HCC, the OS at three years was 79.3% and at five years was 71.6%. However, the difference in OS at either time between the two groups was not statistically significant (P=0.08). In contrast, the differences in RFS at three and five years between patients with stage I and stage II small HCC were significant (P=0.033). For stage I small HCC, the RFS at three years was 74.4%, and at five years was 60.3%, whereas for stage II small HCC, the RFS was 52.8% at three years and 39.9% at five years.

**Discussion**

In patients with HCC, increasing tumour size has generally been associated with poorer prognoses (10,14-17). The present study verified the relationship between small tumour size in HCC and OS; however, a reduction in OS with increasing tumour size was demonstrated only for stage I small HCC (not for stage II small HCC). By definition, stage I small HCC includes tumours up to 5 cm in size, and an increase in tumour size in small HCC has been shown in several studies to directly correlate with an increased risk of vascular invasion. In patients with stage I small HCC who had larger tumours, the OS and RFS may
be closer to those seen with stage II small HCC. Compared with patients with stage I small HCC, patients with stage II small HCC demonstrated poorer OS and RFS. Although the difference in RFS, but not in OS, was statistically significant, the trend toward improved survival in patients with tumours without evidence of microscopic invasion is clear.

Several clinicopathological risk factors were identified in the current study. For all 140 small HCC patients, older age and male sex were significantly associated with an increased risk of cancer recurrence and death, respectively. The immune system may weaken with advancing age, thereby reducing the quality of surveillance for tumour recurrence. Other comorbidities may also be involved with advancing age. Higher albumin levels, reflective of better overall liver function, were significantly associated with a decreased risk of death. AFP levels ≥400 µg/L were significantly more likely to be associated with stage II small HCC, indicative of more aggressive tumours with vascular invasion. Stage II small HCC histological grades generally indicated more poorly or moderately differentiated tumours compared with stage I small HCC histological grades. Furthermore, in patients with stage II small HCC, the absence – compared with the presence – of HBsAg was associated with a higher risk of death. As shown in Table 2, the HR for patients without HBV infection versus those with HBV infection was 4.06 (P=0.018). Considering that HBV infection is a risk factor for HCC, this surprising finding warrants further study. We further assessed the relationship between HBV infection and cirrhosis status, and confirmed that the majority of the HBsAg-negative patients with stage II small HCC were cirrhotic, while the majority of HBsAg-positive patients with stage II small HCC were noncirrhotic. In the present study, 76 stage I HCC patients were HBsAg positive and 64 were HBsAg negative. The proportions of patients with and without cirrhosis were 72.4% and 64.1%, respectively, without a significant difference (P=0.361). For stage II HCC patients (n=41), 25 patients were HBsAg positive and 16 were HBsAg negative. The proportions of patients with and without cirrhosis were 76.0% and 68.8%, respectively, without a significant difference (P=0.436). In this regard, it was also of interest to determine the percentage of HBsAg-positive patients with stage II small HCC who received antiviral therapy. The proportions of patients who received and did not receive antiviral therapy were 60.0% and 0%, respectively – a statistically significant difference (P<0.001). This finding suggests a reasonable explanation; however, the actual reason needs further evaluation.

The reported OS rates for patients with small HCC following resection varies widely in the literature, with five-year OS rates ranging from 35% to 70% (18-20). Different staging systems and criteria may account for the disparate outcomes. Data from our study reveal that even patients with early HCC can be stratified into subgroups with distinct long-term prognoses. In the multivariate analysis of the stage I group, only tumour size demonstrated a significant association with OS. Tumour margins, tumour histology, and the presence or absence of cirrhosis did not influence OS for patients with either stage I or stage II small HCC. In the current study, only patients with tumours ≤5 cm in size were included, and the mean tumour sizes for stage I and stage II small HCC were 2.7 cm and 3.0 cm, respectively. The incidence of vascular invasion has been reported to increase with tumour size in several studies (11,14,15). However, even microscopic vascular invasion has been shown to be related to poorer OS in patients with small HCC (11,14). In the present study, 82% of patients with stage II small HCC had tumours with vascular invasion, with the remaining 18% presenting with multifocal lesions. Zhou et al (8) reported a decrease in OS that was significantly associated with tumour size; the five-year OS rates for patients with small HCC tumours ≤2 cm, 2.1 cm to 3.0 cm, and 3.1 cm to 5.0 cm in size were 82.5%, 66.3% and 61.2%, respectively (P<0.05). However, Nanashima et al (21) reported no significant difference in OS between solitary small HCC tumours <2 cm and those 2 cm to 3 cm in size. In another study, the five-year OS for small HCC tumours between 2 cm and 5 cm was found to be 43%

(10). Lu et al (17) observed no significant difference in OS or RFS between tumours measuring 1.1 cm to 2 cm, and 2.1 cm to 3 cm in size. These investigators reported that a tumour size of <3 cm was associated with a better prognosis and suggested that 3 cm represents the optimum size for designation of an HCC tumour as small.

RFS rates of between 35% and 75% have been reported for small HCC (22-25). Wang et al (26) reported that the three- and five-year RFS rates following surgical resection for small HCC tumours <3 cm in size were 49% and 30%, respectively. In our stage I small HCC patients, three- and five-year RFS rates were 71.19% and 50.93%, respectively, and three- and five-year disease-specific survival rates were 92.23% and 82.65%, respectively. In stage II small HCC patients, three- and five-year RFS rates were 49.33% and 35.97%, respectively, and three- and five-year disease-specific survival rates were 79.00% and 79.00%, respectively.

For patients with stage II small HCC (who demonstrated a significantly higher risk of cancer recurrence than those with stage I small HCC), a second surgical resection was performed if the reserve liver function and anatomical pathology permitted. Salvage therapy for recurrent lesions includes transcatheter arterial chemoembolization, radiofrequency ablation, percutaneous ethanol injection and orthotopic liver transplantation (27,28). Three-year and five-year disease-specific survival rates support the effectiveness of salvage therapy; however, further study is needed to confirm survival benefit of this particular therapy.

Limitations inherent to the current study included the relatively small number of patients and a lack of standardization with respect to the follow-up period. Compared with some studies, 140 appears to be a significant sample size; however, additional studies with greater numbers of patients may result in more targeted survival rates. Because some patients were followed for only two to three months, longer follow-up periods might provide further clarification regarding other factors affecting OS and RFS. Additionally, the present study was limited to Taiwanese patients and may not reflect small HCC behaviour in other ethnic groups.

**CONCLUSION**

The present study of patients with small HCC treated with surgical resection revealed that tumour stage II was associated with an increased risk of cancer recurrence, and that tumour size was associated with an increased risk of death in patients with stage I HCC. Additional studies are needed to clarify the relationship between tumour size and overall prognosis. Aggressive salvage therapy may benefit patients in the stage II group such that their overall disease-specific survival is improved.

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