Review of 336 patients with hepatocellular carcinoma at Songklanagarind Hospital

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Abstract

AIM To determine the clinical presentations, survival and prognostic factors of hepatocellular carcinoma (HCC) in Southern Thailand.

METHODS Retrospective analysis was performed on the 336 hepatocellular carcinoma patients treated at Songklanagarind hospital between 1 January 1991 and January 1999.

RESULTS Of these 336 patients, 276 were males and 60 were females. The mean age was 54.4 years. The common symptoms and signs were abdominal pain and hepatomegaly. The most common presentation of tumor was a dominant mass with daughter nodules. Portal vein involvement was found in 50% of total. Extra hepatic metastasis was found in 13%, and the lung was the most common site. There were 65.4% with evidence of cirrhosis and half of them were in Child's class B. HBsAg was positive in 72.6%. Regarding Okuda's tumor staging, 15%, 61% and 24% were stage I, II and III, respectively. Overall median survival was 2.1 months (11.5, 2.6 and 0.7 months for stage I, II and III respectively). Treatments of HCC improved patient survival (5.5 months vs 1.6 months for untreated patients). Most common causes of death were hepatic failure. Using multivariate analysis, the prognostic factors identified were tumor staging, alpha-fetoprotein level above 10 000 μg·L⁻¹, extrahepatic metastasis, portal vein thrombosis and treatment.

CONCLUSION HCC in Thailand is a fatal disease with poor outcome due to late presentation and high prevalence of liver cirrhosis. Early detection and proper management may improve outcome.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and is the leading cause of cancer death especially among males in South-East Asia including Thailand[1,2]. This may be related to high prevalence of chronic hepatitis B infection (8%-15% in Asia and Africa, and 8%-12% in Thailand)[3-7]. Though many types of treatment have been tried, HCC is still a fatal disease possibly associated with the advanced stage at which the disease is usually diagnosed [2,8-11]. Thus, it remains a serious medical problem in this part of the world. There were many reports of the natural history of HCC in Japan, Mainland China, Southern Africa, Alaskan Eskimos, Taiwan, Italy, Spain and North America, but little information has been published from South-East Asia[22-24]. Therefore, we reviewed 336 HCC patients at Songklanagarind Hospital to describe the clinical presentations and history of known risk factors and determine the survival rate, prognostic factors and the benefit of treatments.

MATERIALS AND METHODS

Patients

The medical records of 336 HCC patients admitted at Songklanagarind hospital between January 1, 1991 and January 31, 1999 were reviewed retrospectively. The diagnosis of HCC was made by liver biopsy or elevated serum alpha-fetoprotein level above 500 μg·L⁻¹ with radiologic findings suggestive of HCC in patients whose liver biopsy was not available[25]. Data from medical records, including patient demographic, known risk factors, clinical manifestation, abnormal physical findings, laboratory data (complete blood count, coagulogram, renal function test, liver function
tests, viral hepatitis serology, serum alpha-fetoprotein level, chest X-ray, ultrasonography, CT scan, liver biopsy and other tissue biopsy if suggested metastasis), survival and treatments modality, were used for analysis. The known risk factors include d alcohol drinking, history of blood transfusion and history of jaundice or viral hepatitis infection or known cases of cirrhosis. Patients were classified into 6 groups based on their clinical presentation: group 1, mass-related symptoms (abdominal pain or fullness, dyspepsia, palpable mass); group 2, cirrhosis-related symptoms (jaundice, GI bleeding, edema, abdominal enlargement, hepatic encephalopathy); group 3, liver abscess-like symptoms (high fever with abdominal pain and tender rness); group 4, non-specific symptoms (anorexia, nausea, vomiting, malaise, weight loss and anemia); group 5, metastasis symptoms (dyspnea, cough, bone pain and palpable lymph node); and group 6, asymptomatic cases (accidental finding by routine check-up or complain of other unrelated disease). The abnormal physical findings included anemia, jaundice, fever, hepatomegaly, splenomegaly, ascites and sign of chronic liver stigmata such as palmar erythema, spider nevi, gynecomastia and superficial dilated vein. A test of viral marker for hepatitis B (HBsAg) was done in most of patients but that for hepatitis C (anti-HCV) was not available until 1996. Tumor volume was calculated from ultrasonography or CT scan of the liver by a radiologist. Tumor volume or sum of tumors in instances multiple nodules were expressed as fraction of total liver and subsequent classified into two groups (tumor size ≤50%, >50% of the whole liver). Staging of HCC was made according to Okuda’s[10]. Cirrhosis was confirmed by liver biopsy or ultrasonography or CT scan and classified by Child-Pugh’s (Class A, B or C)10. The extrahepatic metastasis was confirmed by histology (incisional biopsy, excisional biopsy, necropsy or autopsy).

**Therapy**

The treatment of HCC ranged from no treatment, transhepatic artery oily chemoembolization (TOCE), percutaneous ethanol intralesional injection (PEI), hepatectomy, systemic chemotherapy and multimodality combination chemotherapy.

For systemic chemotherapy before 1995, we used intravenous adriamycin and/or 5-FU injection. Later this was changed to PIAF regimen (cisplatin 80 mg·m–2 body surface area (BSA) and adriamycin 40 mg·m–2 BSA at d1, followed by 5-FU 500 mg·m–2 infusion over 24 h for the following 3 d, with alpha-Interferon 5 mU·m–2, iv, 3 h after cisplatin and 5-FU every day).

TOCE was performed monthly by super-selective insertion of catheter to the right or left hepatic artery branch feeding the tumor then injection adriamycin 50 mg, lipiodol 8 mL and gelfoam. PEI was performed by using 10 mL of absolute ethanol injected percutaneously under CT-scan guide.

Multimodality combination therapy comprised a combination of several treatments depending on the tumor staging and complication, such as the patients who presented with advanced HCC and had portal vein involvement with lung metastasis, the treatment was started with systemic chemotherapy (PIAF regimen) until no evidence of extrahepatic metastasis remained and was then followed by TOCE and/or intralesional ethanol injection (PEI). Because of the limitation of retrospective study, we were unable to determine the exact outcome or improvement of general condition after treatments, so we determined the outcome by survival analysis.

In patients who were lost to follow-up, we determined the date and cause of death from the population register and personal contact with the family. Patient status was unable to determine in 20% of the patients. For statistical analysis these patients were considered as censored at the date of last contact.

Survival profiles were constructed using the Kaplan-Meier method. Prognostic factors were identified using Cox proportional hazards regression. P value <0.05 was considered statistically significant.

**RESULTS**

Of the 336 patients, 276 (82%) were male with a male to female ratio of 4.6:1. The mean age was 54.4 (a range of 20–89) years (54.3 years in male and 55 years in female) (Table 1). Diagnosis was confirmed histologically in 273 (72.3%) cases and 63 (18.7%) cases were diagnosed by a combination of elevated serum alpha-fetoprotein level above 500 µg·L–1 and imaging such as ultrasound or CT scan showing a lesion compatible with HCC.

The most common symptom was mass-related such as abdominal pain, abdominal discomfort, dyspepsia and palpable mass (Table 2). Mean duration of symptoms was 49 d (range <1 day -1 year). Among the abnormal physical findings hepatomegaly was the most common, followed by fever and jaundice (Table 2).

Elevation of alkaline phosphatase and serum aspartate aminotransferase (AST) was the most common abnormal finding in the liver function test. Serum bilirubin above 51.3 µmol·L–1 was found in 30%. The most common radiologic finding was a solitary mass with or without daughter nodules (73%, Table 1). The tumor was located most frequently in the right lobe (53%) followed by both
The most common risk factor was chronic hepatitis B infection (72.6%), and 65.2% showed evidences of liver cirrhosis (Table 1). Patients with cirrhosis were classified into Child A, B and C in 20%, 55.3% and 24.7% respectively. Cirrhosis was found in 76.2% of alcoholic patients, 66.4% of HBV infected patients and 76.2% of alcoholic patients, 66.4% of HBV infected patients. Okuda’s staging distribution was 51%, 24% and 24% for stage I, II and III respectively (Table 1). Spontaneous rupture of HCC was found in 11% (4%, 9.3% and 20% in stage I, II and III). At the time of diagnosis, extrahepatic metastasis occurred in 43 cases (13.1%), 13.7%, 10.7% and 18.8% of stage I, II and III respectively. The metastatic sites were lung (76%), lymph node (16%) and bone (7%).

Overall median survival was 2.1 months (Stage I, 11.5 months; Stage II, 2.6 months; and Stage III, 0.7 months) (Table 3, Figure 1). The 1 and 2-year survival rates were 15% and 8% respectively. Treatment of HCC was associated with improvement of patient survival (5.5 vs 1.6 months in non-treated group; $P = 0.011$) (Table 3, Figure 2). In the non-treated group ($n = 245$) median survival was 1.6 months (7.7, 1.8 and 0.6 months for stages I, II and III respectively, Table 3, Figure 3). Regarding treatment, patients treated with TOCE, intravenous chemotherapy, multimodality combination therapy and Tamoxifen administration had median survival times of 6.3, 5.33, 17.1 and 3 months, respectively (Table 3). Compared to the non-treated group, patients treated with TOCE, intravenous chemotherapy or combination therapy had significantly better survival ($P = 0.0005, 0.011$ and $0.007$ respectively) whereas survival of the patients treated with Tamoxifen was not significantly different from non-treated ($P = 0.86$) patients.

### Table 1 HCC patient characteristics

| Patient characters | $n$ | % | Mean | Range |
|--------------------|-----|---|------|-------|
| Age(years)         | All | 54.4 | 20-89 |
|                    | Male | 54.3 | 20-89 |
|                    | Female | 55.0 | 20-81 |
| Sex                | Male | 276 | 82.0 |
|                    | Female | 60 | 18.0 |
| Risk factors       | Alcohol drinking | 126 | 38.0 |
|                    | HBsAg positive (299 sample) | 217 | 72.6 |
|                    | anti-HCV positive (135 sample) | 10 | 7.4 |
|                    | Cirrhosis | 219 | 65.2 |
| Liver function test | Total bilirubin (µmol L$^{-1}$) | 63.8 | 3.4-752.4 |
|                    | Direct bilirubin (µmol L$^{-1}$) | 38.8 | 0.5-581.4 |
|                    | Aspartate aminotransferase (U·L$^{-1}$) | 225 | 17-3980 |
|                    | Alanine aminotransferase (U·L$^{-1}$) | 97 | 4-3370 |
|                    | Alkaline phosphatase (U·L$^{-1}$) | 304 | 8-2080 |
|                    | Albumin (g·L$^{-1}$) | 35.6 | 20-52 |
|                    | Globulin (g·L$^{-1}$) | 38.2 | 18-78 |
| Radiologic finding | Solitary type (total) | 240 | 73.0 |
| (n = 329)          | with daughter nodules | 144 | 43.8 |
|                    | without daughter nodules | 96 | 29.2 |
|                    | Multinodular type | 47 | 14.3 |
|                    | Diffuse or infiltrative type | 42 | 12.7 |
| Alpha fetoprotein  | (µg L$^{-1}$) (n = 295) | 145110 | 27900 |
| <10                | 38 | 13.0 |
| 10-99              | 36 | 12.0 |
| 100-499            | 33 | 11.0 |
| ≥500               | 188 | 64.0 |
| Okuda’s staging    | Stage I | 51 | 15.0 |
|                    | Stage II | 205 | 63.0 |
|                    | Stage III | 80 | 24.0 |

### Table 2 Presenting symptoms and abnormal physical findings of patients

| Presenting symptoms | $n$ | % |
|---------------------|-----|---|
| Mass-related symptoms | 188 | 56 |
| (Abdominal pain or fullness, dyspepsia, palpable mass) | |
| Cirrhosis-related symptoms | 59 | 17.6 |
| (Jaundice, GI bleeding, edema, abdominal enlargement, encephalopathy) | |
| Liver abscess-like symptoms | 45 | 13.4 |
| (High fever with acute abdominal pain and tenderness) | |
| Non-specific symptoms | 26 | 7.7 |
| (Anorexia, nausea, vomiting, malaise, weight loss, chronic anemia) | |
| Metastasis symptoms | 11 | 3.2 |
| (Dyspnea, cough, bone pain, palpable lymph node) | |
| Asymptomatic | 7 | 2.1 |
| (Routine checked up or other unrelated disease) | |
| Abnormal physical findings | |
| Hepatomegaly | 282 | 83.9 |
| Fever | 185 | 50.5 |
| Jaundice | 143 | 42.6 |
| Anemia | 138 | 41.1 |
| Ascites | 123 | 36.6 |
| Cachexia | 86 | 25.6 |
| Chronic liver stigmata | 86 | 25.6 |
| Edema | 59 | 17.6 |
| Splenomegaly | 42 | 12.5 |

### Table 3 Median survival

| Group of patients | $n$ | Median survival (months) |
|-------------------|-----|--------------------------|
| All | 336 | 2.1 |
| Stage I | 51 | 11.5 |
| Stage II | 205 | 2.6 |
| Stage III | 80 | 0.73 |
| Untreated | 245 | 1.6 |
| Stage I | 26 | 7.7 |
| Stage II | 146 | 1.8 |
| Stage III | 73 | 0.63 |
| Treated | 91 | 5.5 |
| Stage I | 25 | 13.7 |
| Stage II | 59 | 4.2 |
| Stage III | 7 | 1.7 |
| TOCE | 44 | 6.3 |
| Stage I | 11 | 24.3 |
| Stage II | 29 | 5.5 |
| Stage OOO | 4 | 1.4 |
| Chemotherapy (adriamycin and/or 5-FU) | 16 | 5.2 |
| Multimodality therapy | 12 | 17.1 |
| (PIAF, chemotherapy±TOCE±PEI) | |
| Tamoxifen | 9 | 3.0 |
| PIAF regimen chemotherapy | 5 | - |
| Hepatocetomy | 4 | 5 |
| PEI | 1 | 8 |

*Data of PIAF regimen chemotherapy is not completely finished. SI were too small number of patients to evaluated.*
The most common causes of hospital death \((n = 54)\) were hepatic failure, GI bleeding and rupture of tumor \((59.2\%, 20.4\% \text{ and } 20.4\% \text{ respectively})\). Among cases with hepatic failure, sepsis was the most common complication leading to death. Cox proportional hazards model reviewed the following, prognostic factors: Okuda’s stage II \((P = 0.014, \text{ hazard ratio } 2.05)\), stage III \((P = 0.001, \text{ hazard ratio } 3.79)\), AFP level above 10 000 µg·L\(^{-1}\) \((P = 0.001, \text{ hazard ratio } 2.03)\), lung metastasis \((P = 0.01, \text{ hazard ratio } 1.93)\), lymph node metastasis \((P = 0.015, \text{ hazard ratio } 3.76)\), portal vein involvement or thrombosis \((P = 0.0005, \text{ hazard ratio } 1.79)\) and treatment \((P = 0.011, \text{ hazard ratio } 0.91)\).

**DISCUSSION**

Similar to other studies, we found that HCC was more common in males \((4.6:1)\) because the risk factors such as cirrhosis, chronic HBV infection and alcoholic are more frequently seen in males than females\([2,8,12-19,27,28]\). In our study, the most common risk factor was chronic HBV infection \((72.6\%)\) as HBV is endemic in South-East Asia\([5]\). The common symptoms were non-specific and included abdominal pain, dyspepsia, jaundice, hepatomegaly, anorexia and weight loss. Clinical jaundice was found in 42.6\% and mainly caused by failure of hepatic function due to cirrhosis. The most common type of tumor in our patients was dominant mass with daughter nodules whereas multiple nodules or diffuse lesion are common in Western patients\([15,17,18]\). The difference in risk factors may explain the variation in tumor characters as chronic HBV infection is the most important risk factors in our region while chronic HCV infection and alcohol drinking are the largest risk factors in Japan and Western countries\([3,8,13-18,27,29]\). Cirrhosis was found in 65\% of our patients and 80\% of them were classified as Child’s B or C. These may be associated with poor prognosis. In our study, heptectomy and TOCE were not suitable in more than half of the patients due to portal vein involvement \((50\%)\) and advanced liver cirrhosis \((24.7\%)\). Extrahepatic metastasis was found in 13\% and most of them were located in the lung, probably because of direct drainage into the right heart via the hepatic vein. Elevated serum alpha-fetoprotein above 500 µg·L\(^{-1}\) was found in only 64\% of patients, so this tumor marker was not very sensitive for diagnosis of HCC in our country. Most our patients had advanced HCC \((61\% \text{ and } 24\% \text{ were stage II and III respectively})\). The overall median survival in our patients was 2.1 months because majority of our patients had advanced disease with significant liver cirrhosis. In treatment of HCC, heptectomy and TOCE could improve survival\([9,13]\), but could not be performed because of liver cirrhosis and portal vein involvement. Systemic chemotherapy, arterial infusion and Tamoxifen administration could not improve survival \([9,20,24,30-32]\), whereas data of PIAF regimen chemotherapy showed complete pathological remission, but survival analyses did not\([33]\). In our study, TOCE and multimodality therapy could improve survival, particularly in patients with stage I and stage II disease as compared with the non-treatment group \((24.3\% \text{ vs } 7.7 \text{ months in stage I and } 5.5 \text{ vs } 1.8 \text{ months in stage II receiving TOCE and 17.1 months vs 0.63 months in patients receiving multimodality therapy})\). However, our study is only a retrospective study that had its limitation in comparing survival rate between different groups. The most of our patients died of hepatic failure \((60\%)\) as a majority of them had
advanced HCC and liver cirrhosis. By multivariate analysis, poor prognosis was associated with advanced stage of the tumor, serum alpha-fetoprotein level >10,000 µg·L⁻¹, extrahepatic metastasis and portal vein involvement.

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