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Hepatocellular carcinoma surveillance and appropriate treatment options improve survival for patients with liver cirrhosis

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ABSTRACT

Objective/aim: Hepatocellular carcinoma (HCC) surveillance is a common practice for patients with liver cirrhosis. The aims of the study were to assess impacts of surveillance and therapeutic options on survival of patients with HCC.

Methods: A total of 1436 cirrhotic patients with newly diagnosed HCC were enrolled between January 2002 and December 2004. Patients with HCC detected within periodic surveillance were the surveillance group ($n = 318$, 22.1%). The other patients with HCC incidentally detected were the non-surveillance group ($n = 1118$, 77.95%). Initial treatment options were recorded and overall survival was analysed.

Results: Compared with patients in the non-surveillance group, larger proportions of patients in the surveillance group possessed small tumours, at an early stage without vascular invasion or metastases, and afforded more curative treatment options including surgical resection, radiofrequency ablation and percutaneous ethanol injection. The overall survival was better for patients in surveillance (3-year survival rate: 59.1% versus 29.3%, $p < 0.001$), early stages by Barcelona Clinic Liver Cancer (BCLC) staging or curative treatment options. Multivariate analysis demonstrated surveillance, hepatitis aetiology, alpha-fetoprotein, tumour gross type, tumour stage and treatment options were associated factors for patients' survival. Moreover, surveillance patients in curative BCLC stage following the treatment guideline for HCC proposed by the American association for the study of liver disease (AASLD) had a significantly better 3-year survival rate (77.1% versus 55.2%, $p < 0.001$).

Conclusions: HCC surveillance for cirrhotic patients could detect HCC at early and curative stages. However, appropriate treatment options following AASLD guideline further improve the survival for patients in early stage.

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumours in the world,[1] and has been the leading cause of cancer death in Taiwan, claiming an approximate 7800 lives annually.[2] More than 80% of HCCs arise in cirrhotic patients, suggesting that patients with cirrhosis form the main risk group of HCC.[3] The prognoses of patients with HCC are determined by tumour status, liver function reserve, general health status, treatment modalities and therapeutic effect.[4,5] The screening programmes in high-risk populations such as cirrhotic patients have led to an early detection of small tumours eligible for curative therapies, which might bring about a better outcome.[6] Consequently, Western and Eastern guidelines for HCC management recommend offering surveillance to patients with cirrhosis or chronic liver disease.[4,7,8]

Several cohort studies have demonstrated that cirrhotic patients might benefit from HCC surveillance with serum alpha-fetoprotein (AFP) and ultrasonography (US),[9–11] however, there is considerable controversy about the role of surveillance in its management.[12] Small HCC could afford more effective treatment,[13] however, even those patients in early stages had a variant prognosis due to different treatment options available.[14,15] The aims of this study were to determine the impact of surveillance on survival and to assess the effectiveness of treatment options after HCC diagnosis.

2. Materials and methods

2.1. Patients

The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital. We reviewed the clinical records of patients with HCC evaluated and treated at our institute – Chang Gung Memorial Hospital-Kaohsiung Medical Center between January 2002 and December 2004. A total of 1436 HCC patients with liver cirrhosis were enrolled in this study, and their data including age, gender, aetiologies of HCC, Child-Pugh classification, biochemical variables, serum AFP level, performance status, tumour stage and initial treatment options were recorded. The patients were divided into two groups according to the clinical scenario in detection of HCC, i.e. surveillance and non-surveillance groups. In the surveillance group, HCC was detected by a surveillance programme based on AFP determinations and abdominal US repeated within 1 year. Those who were diagnosed HCC as a result of symptoms or due to a diagnostic workup for other diseases were the non-surveillance group.

2.2. HCC diagnosis, staging, and comparative variables

The diagnosis of HCC was based on the American Association for the Study of Liver Disease (AASLD) practice guidelines.[7] The gross type of HCC was classified according to imaging findings of both US- and triphasic-computed tomography (CT) scan. The macroscopic types of HCC were classified as: solitary, paucifocal ($\leqslant$3 nodules), multifocal (>3 nodules), infiltrating and massive.[16] The patients were staged according to the modified 6th version of the tumour nodes metastases (TNM) system[17] and the Barcelona Clinic Liver Cancer (BCLC) system.[18]

2.3. Initial treatment options for HCC

Initial treatment options for HCC were recorded. Individual decisions regarding treatment were determined by clinical physicians and patients' wishes. Patients who received liver transplantation were not analysed due to the small number of patients (six patients). Hepatic resection and local ablation therapy, including percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA), were assessed as curative treatment.[7] Indocyanine green retention rates at 15 min was used by surgeons to confirm the best candidates for HCC resection. Either hepatic lobectomy or segmentectomy was performed for HCC resection. To ablate the tumour, US-guided PEI was performed with multiple sessions of 99.5% ethanol injection. As for percutaneous RFA, it was performed with Cool-tip needle (Radionics, Burlington, MA) for one or two sessions. Non-curative treatment included transcatheter arterial embolisation (TAE), systemic chemotherapy or conformal radiotherapy (RT).[7] TAE was performed using digital subtraction angiography techniques via the femoral artery approach. After identifying the feeding artery, a mixture of 99.5% ethanol and Lipiodol was injected.[19] Then, gelatin sponge was used to embolise the feeding artery. Systemic chemotherapy was performed using various combinations of Cisplatin, Doxorubicin, Fluorouracil, Etoposide and Tamoxifen. Three-dimensional conformal RT was performed using computed tomography-simulation to acquire the images, and three-dimensional computerised treatment planning to design the treatment fields and dose calculation. A 10 MV linear accelerator was used to deliver a total dose of 55–64 Gy in 22–32 fractions.

2.4. Survival analysis

Survival was defined as the interval between the diagnosis and either the death of the patient or the end of 2006. The identification of overall mortality was according to national mortality datasets up to the end of 2006, established by the Statistics Office, Department of Health, Taiwan. The Student *t*-test or the χ^2 test was used to compare continuous variables or discrete variables, respectively. Kendall's τ_c method was used to compute a coefficient representing strength and direction of a trend for equally spaced data. Cumulative survival rates were analysed by the Kaplan–Meier method, and the difference in survival rates was compared between the groups by the log-rank test. The Kaplan–Meier method was used for univariate analysis, while the Cox proportional hazards model was used for multivariate analysis. Statistical analyses were performed with the Statistical Package for the Social Sciences 15.0 (SPSS Inc., Chicago, IL). The statistical significance was defined as $p < 0.05$.

3. Results

3.1. Patients

There were 318 (22.1%) patients in the surveillance group, including 122 patients regularly followed at other hospitals, and 1118 (77.9%) in the non-surveillance group. The mean