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Prognostic value of pretreatment levels of tumor markers for hepatocellular carcinoma on survival after curative treatment of patients with HCC☆

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***Background/Aims*: We evaluated the prognostic value of the pretreatment elevation of tumor markers for hepatocellular carcinoma (HCC) in patients who underwent curative treatment.**

***Methods*: We studied 801 patients who had been diagnosed as initial HCC and fulfilled the following criteria: maximum tumor size, $\leqslant$3 cm; number of tumors, $\leqslant$3; remnant liver function, Child-Pugh class A or B; treated by hepatectomy or locoregional thermal ablation (LTA); and alpha-fetoprotein (AFP), *Lens culinaris* agglutinin A-reactive fraction of AFP (AFP-L3), and des-gamma carboxy prothrombin (DCP) were measured at diagnosis. We analyzed the effects of elevated tumor markers on patient survival in these 2 distinct groups with different types of treatment, i.e. hepatectomy and LTA.**

***Results*: By multivariate analysis in 345 patients who underwent hepatectomy, no tumor marker significantly affected decreased survival rate. In the 456 patients who underwent LTA, the elevation of AFP-L3 ($p = 0.0171$) and DCP ($p = 0.0004$) significantly affected decreased survival rate; DCP elevation had the strongest effect on patient survival.**

***Conclusions*: The prognostic value of pretreatment tumor marker elevation was different in patients who underwent the curative treatment according to the type of treatment. Pretreatment elevation of AFP-L3 and DCP had prognostic values only in patients treated with LTA.**

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Abbreviations: AFP, alpha-fetoprotein; AFP-L3, Lens-culinaris agglutinin A-reactive fraction of AFP; CT, computed tomography; DCP, des-gamma-carboxy prothrombin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LTA, locoregional thermal ablation; PIVKA-II, protein induced by vitamin K absence-II; PMCT, percutaneous microwave thermocoagulation; RFA, radiofrequency ablation.

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1. Introduction

Hepatocellular carcinoma (HCC) is a common malignancy, especially in southern and eastern Asia. The incidence of HCC is also increasing in the United States [1,2]. The development of various scanning techniques and the identification of sensitive and specific tumor markers for HCC have contributed not only to the detection of HCC, but also to the evaluation of its progression and the determination of patient prognosis.

Three tumor markers specific for HCC are currently used in Japanese clinics: alpha-fetoprotein (AFP), *Lens culinaris* agglutinin A-reactive fraction of AFP (AFP-L3), and des-gamma carboxy prothrombin (DCP), which is also referred to as protein induced by vitamin K absence-II (PIVKA-II). Previous reports have detailed the usefulness of each of these tumor markers in the detection and diagnosis of HCC, the evaluation of tumor progression, and the determination of patient prognosis [3–7]. The elevation of each tumor marker has been reported to indicate poor prognosis and decreased survival rates [8]. However, the prognostic value of these tumor markers in distinct patient subpopulations who underwent potential curative treatments for HCC has not been well studied.

In the present study, we attempted to evaluate the effect of the pretreatment elevation of these tumor markers for HCC (AFP, AFP-L3, and DCP) on the outcome of patients who underwent curative treatments: hepatectomy and locoregional thermal ablation that includes percutaneous microwave thermocoagulation (PMCT) and radiofrequency ablation (RFA).

2. Patients and methods

2.1. Patients

A total of 3725 patients were initially diagnosed with HCC at one of the five institutions that participated in the study between July 1994 and December 2004. Three tumor markers for HCC (AFP, AFP-L3, and DCP) were measured at the time of diagnosis, and drugs that would influence the serum DCP levels, such as warfarin or vitamin K, were not being taken by 2600 of the 3725 patients [8]. Of these 2600 patients, 736 received hepatectomy and 945 received locoregional ablative therapies as an initial treatment for HCC. Of the patients who underwent hepatectomy, 345 were enrolled in this study, while 391 were excluded as their maximum tumor size was greater than 3 cm or their number of tumors was greater than 3 (Fig. 1A). With regard to the patients who underwent locoregional ablative therapies, we first excluded 344 patients who received percutaneous ethanol injections because percutaneous ethanol injection is reported to be less effective as a therapy for HCC compared to other locoregional ablative therapies [9]. As a result, the patients in the study were primarily those who underwent PMCT ($n = 123$) or RFA ($n = 478$). We defined these patients as patients who underwent locoregional thermal ablation (LTA). We further excluded 139 patients in whom the maximum tumor size was greater than 3 cm or the number of tumors was greater than 3. Finally, we excluded 6 patients in whom the pretreatment remnant liver function was estimated as class C according to the Child-Pugh classification [10]. A total of 456 patients were therefore enrolled in this study (Fig. 1B). These patients were treated by hepatectomy and LAT solely, and no patients received an addition of other kinds of therapy for HCC as multimodality treatment until the recurrent HCC developed. The study protocol was approved by the Institutional Ethics Review Board at each of the participating institutions and was in compliance with the Declaration of Helsinki. Written informed consent for the use of information on the pretreatment tumor marker values for future study on patient outcome was obtained from each patient prior to treatment.

2.2. Diagnosis of HCC, treatment, and follow-up

Patients were diagnosed with HCC based on histologic examination of tumor tissue taken from resected specimens in 345 patients who underwent hepatectomy. In patients treated by LTA, the diagnosis of HCC had been made based on fine-needle biopsy of specimens from 198 of the 456 patients (43.4%). In the remaining 258 patients, the diagnosis was made based on clinical criteria [11,12]: a pertinent clinical background (association with liver cirrhosis or viral hepatitis) and typical imaging findings. Typical imaging features of HCC include a mosaic pattern with a halo by B-mode ultrasonography; hypervascularity on angiographic images; and a high-density mass on arterial phase dynamic computed tomography (CT) images and a low-density mass on portal phase dynamic CT images obtained with a helical or multidetector row CT scanner. When findings typical of HCC were not obtained by means of dynamic CT or angiography, CT during hepatic arteriography and CT during arterial portography or T1- and T2-weighted imaging associated with superparamagnetic iron oxide-enhanced magnetic resonance imaging were performed.

All patients underwent the treatment for HCC within 2 weeks after the diagnosis of HCC. In patients who underwent LTA, dynamic CT was performed 1 to 3 days after the last session of ablation to evaluate the efficacy of treatment. Complete ablation was defined by CT findings as non-enhancement in the entire lesion with a safety margin in the surrounding liver parenchyma. Patients received additional sessions of ablation until complete ablation was confirmed in each nodule.

Patients were prospectively followed up from 0.8 months to 175.1 months (median follow-up period, 26.6 months). All 801 patients were followed up at one of the five participating institutions.

2.3. Measurement of tumor markers and cut-off levels

AFP, AFP-L3, and DCP were measured in serum samples obtained from each patient at the time of HCC diagnosis. The serum AFP levels were determined by enzyme-linked immunosorbent assay with a commercially available kit (ELISA-AFP, International Reagents, Kobe, Japan). Serum AFP-L3 levels were measured by lectin-affinity electrophoresis coupled with antibody-affinity blotting (AFP Differentiation Kit L, Wako Pure Chemical Industries, Ltd., Osaka, Japan) and are expressed as a percentage (AFP-L3 level/total AFP level X 100) [13,14]. The serum DCP levels were determined by sensitive enzyme immunoassay (Eitest PIVKA-II kit, Eisai Laboratory, Tokyo, Japan) according to the manufacturer's instructions [15–17]. We designated

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