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• LIVER CANCER •

Transcatheter arterial embolization treatment in patients with hepatocellular carcinoma and risk of pulmonary metastasis

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Abstract

AIM: To investigate the relationship between transcatheter arterial embolization (TAE) and pulmonary metastasis in subjects with hepatocellular carcinoma (HCC).

METHODS: A total of 287 patients with HCC followed up for more than 1 week were included. 102 patients underwent transcatheter arterial embolization (TAE group) and 185 received conservative treatment (control group). The patients' chest x-rays and chest CT scans were examined for pulmonary metastasis.

RESULTS: Patients with TAE had a median survival of 19.3 months while that of the control group was only 10.0 months ($P<0.05$). Pulmonary metastasis occurred in 14 (13.7 %) patients in the TAE group and 14 (7.6 %) patients in the control group, there was no significant difference ($P>0.05$). The 1-year, 2-year and 5-year cumulative incidence of pulmonary metastasis was 11.8 %, 17.6 % and 24.0 % in the TAE group and 7.0 %, 13.0 % and 21.7 % in the control group, respectively ($P>0.05$). On the univariate analysis, tumor size, abnormal serum alanine aminotransferase levels and heterogeneity on sonography were significantly associated with pulmonary metastasis. However, on the multivariate analysis, only tumor size was significantly predictive of pulmonary metastasis.

CONCLUSION: TAE is effective on prolonging survival of patients with HCC. It does not significantly increase the risk of pulmonary metastasis. Tumor size is the only significant predictive factor associated with lung metastasis.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common cancer in Taiwan and certain other parts of the world where hepatitis B virus infection is hyperendemic[1]. HCC has a dismal overall prognosis, with 94 % of affected individuals dying of the disease[2]. Treatment leading to long-term survival generally includes resection or ablative therapy for small or localized hepatic tumors[3-6]. Unfortunately, patients with HCC are usually diagnosed at a late stage when few can be treated with surgical resection. Factors indicating unresectability are (1) large or multicentric liver tumors, (2) the presence of metastatic disease, and (3) insufficient functional hepatic reserve[3]. Therapies other than surgical resection include systemic or infusional chemotherapy, hepatic artery ligation or embolization, and radiolabeled antibodies[7]. Transcatheter arterial embolization (TAE) has been performed for the treatment of unresectable HCC[8,9] and has been shown to be able to prolong survival[7, 10-11]. One study found survival of post-TAE to be comparable to that of post-hepatectomy[12].

However, it has been suggested that TAE-induced necrosis might result in hematogenous dissemination from the primary tumor[13]. The lung is the most common site of extrahepatic metastasis in HCC[14]. A higher incidence of pulmonary metastasis following TAE in patients with HCC has been reported. However, the subjects who developed lung metastasis in that series were followed for a longer period than those without metastasis[15]. We designed this case control study to evaluate the risk of pulmonary metastasis in patients with HCC following TAE, taking into account duration of follow up.

MATERIALS AND METHODS

Patients

Patients with HCC diagnosed from January 1996 to December 1999 at our hospital were included in this study. Diagnosis of HCC was based on high serum alpha-fetoprotein (AFP) values, ultrasonography, computed tomography (CT), and angiographic findings with or without needle biopsy or aspiration cytological examination. Patients who had pulmonary metastasis before or within 1 week after admission or who died within 1 week after admission were excluded, as were those eligible for surgical resection or percutaneous ethanol injection. There were 102 patients receiving TAE treatment during the study period. We selected another 185 patients with HCC who had refused either TAE or chemotherapy as a control group.

Methods

TAE was performed with lipiodol mixed with gelatin particles at an interval of 12 to 16 weeks. All patients were followed until death or December 31, 2000. Chest x-rays were taken at each admission or every 3 months in the outpatient clinic. Multiple nodules in the lung fields on chest x-ray and chest CT scans were diagnosed as pulmonary metastasis. Liver ultrasonography was performed every 3 months. Tumor size and sonographic patterns were recorded. Tumors with both hyper-echoic and hypo-echoic patterns were classified as heterogeneous. The presence of portal vein thrombosis was evaluated with a combination of ultrasonography, angiography and CT. Tumor stage was assessed according to the staging system described by Okuda *et al*[8].

Statistical analysis

Statistical analysis was performed using the χ^2 test to compare

differences between groups. Results were given as the mean ± standard deviation. Comparisons between group means were performed using Student's *t* test. Survival time was calculated from the time of cancer diagnosis until death or December 31, 2000. The time from the date of the diagnosis of cancer to the date of pulmonary metastasis or December 31, 2000 was calculated for analysis of cumulative incidence of pulmonary metastasis. The cumulative probability of survival and the cumulative incidence of pulmonary metastasis were calculated using the Kaplan-Meier method, and the difference between groups was compared using the log-rank test[16]. Univariate and multivariate analyses using Cox proportional hazard models were performed to evaluate clinical parameters associated with pulmonary metastasis and calculate odds ratios (OR). The parameters included in the analysis were age, sex, serum albumin levels, bilirubin levels, AST and ALT values, AFP value, presence of cirrhosis, presence of ascites, presence of encephalopathy, Child scores, tumor size, sonographic pattern, uni- or multifocal tumor, presence of tumor halo, presence of portal vein thrombosis, stage of the disease, and TAE therapy. Significant parameters in the univariate analyses were analyzed with multivariate analysis. The level of significance was set at $P<0.05$.

RESULTS

Demographic and clinical characteristics, liver function tests, and tumor characteristics did not differ significantly between the TAE and control groups (Table 1). Patients who had received TAE had a median survival time of 19.3 months compared with only 10.0 months for controls. The 6 month, one-year and two-year survival rate was 83 %, 59.1 % and 47.5 % respectively, in the TAE group, and 66.8 %, 43.7 % and 25.7 %, respectively, in the control group ($P<0.001$, Figure 1). Pulmonary metastasis developed in 14 (13.7 %) patients in the TAE group and 14 (7.6 %) patients in the control group ($P>0.05$). There was no significant difference in the cumulative incidence of pulmonary metastasis between these two groups. The 1-year, 2-year, 3-year, and 5-year cumulative incidence of pulmonary metastasis was 11.8 %, 17.6 %, 17.6 % and 24 % in the TAE group, 7 %, 13 %, 21.7 % and 21.7 % in the control group, respectively ($P>0.05$, Figure 2).

Table 1 Clinical characteristics of patients with hepatocellular carcinoma

Parameters	TAE group (n=102)	Control group (n=185)	P
Male (%)	75 (74.3%)	148 (80%)	NS
Age (years)*	56.7±10.5	56.8±13.7	NS
Albumin (g/dl)*	3.51±0.57	3.40±0.61	NS
Bilirubin (mg/dl)*	2.02±7.17	1.30±1.25	NS
ALT (IU/ml)*	68.4±63.6	63.0±57.1	NS
Prolonged Prothrombin time*	1.38±1.25	1.48±1.11	NS
Encephalopathy (%)	6 (5.9%)	14 (7.6%)	NS
Cirrhosis (%)	76 (74.5%)	121 (65.4%)	NS
Ascites (%)	14 (13.7%)	32 (17.3%)	NS
Multicentric tumors (%)	19 (18.6%)	39 (21.1%)	NS
Heterogeneous echopattern (%)	34 (33.4%)	72 (39.1%)	NS
Encapsulated tumors (%)	49 (48.0%)	76 41.1%)	NS
PV thrombosis (%)	23 (22.5%)	58 (31.4%)	NS
Large tumor size (%)	56 (54.9%)	103 (55.7%)	NS

Data expressed as means ± standard deviation, comparison with unpaired Student's *t* test. NS=not significant.

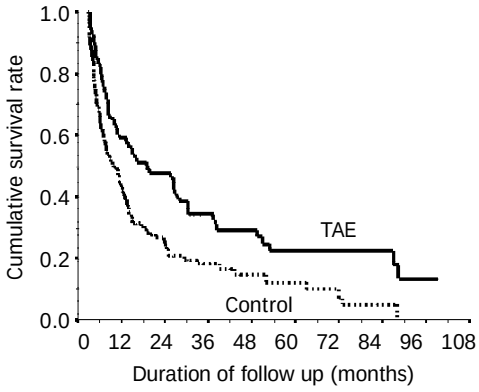

Figure 1 Survival curves of patients with HCC treated with TAE and untreated controls.

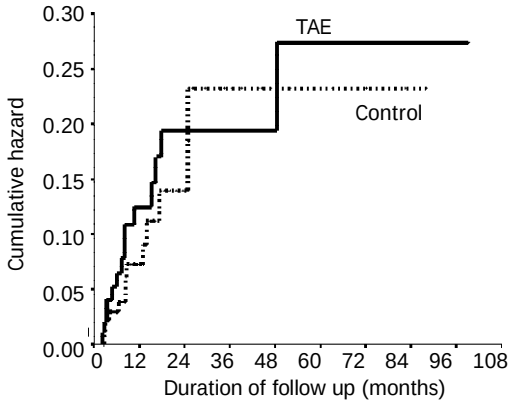

Figure 2 Cumulative incidence of pulmonary metastasis in patients with HCC treated with TAE or untreated controls.

On the univariate analysis using the Cox proportional hazard model, tumor size (OR 2.34), abnormal serum ALT levels (OR 1.94) and heterogeneous sonographic pattern (OR 2.08) were significantly associated with the risk of pulmonary metastasis. However, on multivariate analysis only tumor size was significantly predictive of pulmonary metastasis (OR 2.24, 95 % CI 1.37 to 6.45).

DISCUSSION

It is believed that manipulation of tumor with TAE will increase the risk of hematogenous metastasis due to an increase in activity of serum type IV collagen-degrading enzyme[17], or a decrease in activity of the tumor invasion-inhibiting factor[18]. The disruption of tissue architecture resulting from ischemic necrosis after the TAE treatment may facilitate the dissemination of neoplastic cells[19]. The incidence of extrahepatic recurrence of HCC is increased in patients who receive preoperative TAE treatment compared to those who undergo surgery alone[20]. However, in our study, the incidence of pulmonary metastasis after the TAE therapy was not significantly increased. TAE patients also experienced longer survival and were followed longer than untreated controls (Figure 1). The 1-year, 2-year, 3-year and 5-year cumulative incidence of lung metastasis did not differ between the two groups.

The overall incidence of pulmonary metastasis in our series was 7.2 %, lower than that from an autopsy series of HCC reported in Japan[21]. There may be several reasons for this discrepancy. We excluded patients with obvious pulmonary metastasis within 1 month after the diagnosis of cancer, although we could not exclude the presence of micro-metastasis. Our diagnosis of metastatic disease was based on

multi-nodular lesions on the chest x-ray and confirmed by chest CT. Most of our patients with metastasis had lesions larger than 3 mm on the chest film. Peters reported that pulmonary metastasis larger than 1 cm in size was rare and that, in 55 % of cases, lung metastasis was only recognizable microscopically[22]. We would expect the actual incidence of pulmonary metastasis in our series to be more than 10 %, but this could not be documented, in part because autopsy is not well accepted in Taiwan. However, as both TAE and control groups initially included patients without clinically detectable metastasis, we believe that our results are still valid, as the subjects were similar at baseline.

It has been reported in an autopsy study that the HCC tumor size and invasion of the portal vein were associated with pulmonary metastasis[21]. In another study of patients with long survival, the same association was found, with the coexistence of pulmonary metastasis, a large tumor size and portal vein invasion being the final event leading to death[23]. In our series, on univariate analysis only large tumor size, a heterogeneous echo pattern, or abnormal alanine aminotransferase levels were associated with an increased incidence of pulmonary metastasis.

When HCC is small, the sonographic pattern is homogeneous and hypo-echoic. Most small hepatomas progress from hypoechoic to heterogeneous hyperechoic patterns when they grow larger[24]. In general, small hepatomas without necrosis are hypoechoic; medium-sized tumors have a hypoechoic periphery and a hyperechoic center. The hypoechoic periphery corresponds to viable tumor and the hyperechoic core corresponds to central coagulation necrosis. Large tumors with extensive necrosis have an irregular mixed-echo pattern[25]. A significant correlation between the incidence of metastasis and extent of necrosis in the primary tumor has been reported[26]. The heterogeneous sonographic pattern of the tumor therefore implies later stage disease with more potential of extrahepatic metastasis. The serum alanine aminotransferase level correlates with hepatocellular damage. Tumor necrosis releases alanine aminotransferase enzymes into the blood flow. These observations likely explain our finding of an association on the univariate analysis between these factors and pulmonary metastasis. The fact that tumor size was the only independent predictor of metastasis on the multivariate analysis is thus understandable, as large tumors are almost invariable heterogeneous on sonography and associated with abnormal alanine aminotransferase levels.

Unfortunately, about 80 % of all our patients with HCC were not treated (data not shown). The reasons for lack of specific treatment in the control group varied. Most of them did not have regular serum AFP screening or sonographic examination and some already had late-stage HCC with a poor general condition and were thus too unwell for any specific treatment. Some did not trust Western medicine and tried Chinese herbal medicine instead. Only 20 % of our patients with HCC received treatment, 21 % undergoing surgical resection or percutaneous ethanol injection and 75 % of them being treated with TAE. More frequent sonographic screening of patients at high risk for HCC is important for earlier detection of smaller tumors.

In conclusion, TAE therapy is effective on prolonging survival of some patients with HCC. In our series, TAE did not increase the incidence of pulmonary metastasis. The larger the tumor, the higher the risk for pulmonary metastasis.

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