Hepatocellular carcinoma is one of the most common malignant tumors in the world. The peak age of onset of hepatocellular carcinoma varies according to geographic barriers. Different hepatocarcinogenesis were found among population of young and elder age and, therefore, the prognosis might be different among them. The aim of this study is to evaluate the therapeutic efficacy of transcatheter arterial chemoembolization in young patients with unresectable hepatocellular carcinoma.

From 1983 to 1998, 42 patients younger than 40 years old with unresectable hepatocellular carcinoma underwent transcatheter arterial chemoembolization. Three patient had oligonodular type hepatocellular carcinoma, 8 had multiple nodular, 21 had massive solitary (14 of them had multiple daughter nodules) and 10 had infiltrative hepatocellular carcinoma. Transcatheter arterial chemoembolization was performed by transcatheter hepatic arterial infusion of adriamycin-lipiodol emulsion followed by delivery of gelatin sponge particles. We retrospectively review the clinical manifestations, tumor features and therapeutic efficacy of transcatheter arterial chemoembolization in young patients. In addition, 113 patients with hepatocellular carcinoma with their age ranged from 61 to 69 years old, and underwent transcatheter arterial chemoembolization during the same period were also reviewed for comparison.

The overall survival rates at 6, 12, 24 and 36 months periods were 70.01, 47.27, 23.76 and 7.92% for patients younger than 40 years old (median survival was 15months) vs 77.88, 65.89, 49.27 and 29.04% for patients aged 61 to 69 years old (median survival was 25 months). Transcatheter arterial chemoembolization does not show as good survival benefit in young patient group as elderly patient group.

**Key words:** Liver neoplasm; Liver neoplasm, therapy; Arteries, therapeutic blockade

Hepatocellular carcinoma is one of the most common malignant tumors of the liver in the world. In all populations, the incidence of hepatocellular carcinoma increases with age. However, people in high risk countries are more frequently exposed to the environmental factors associated with hepatocellular carcinoma and their peak age is one to two decades earlier than people in low risk countries. In Taiwan, hepatocellular carcinoma is the most common cause of cancer death in males and is the third most common cause of cancer death in females [1]. The disease commonly develops as a complication of
longstanding chronic infection of hepatitis B virus. Such chronic infection may lead to cirrhosis of liver and finally hepatocellular carcinoma. Hepatitis B virus is acquired either at adulthood from transfused blood and injections or at birth via perinatal transmission. Therefore, the disease is commonly seen in older patients with peak incidence in the 6 and 7 decades of life. Patients younger than 40 years old are rather uncommon in Taiwan. The peak age of onset of hepatocellular carcinoma varies according to geographic barriers. Different hepatocarcinogenesis were found among young and elderly patients [2] and, therefore, the prognosis might be different among them. In this article, we retrospectively compared the effectiveness of transcatheter arterial chemoembolization on survival between the young and the elderly patients and analyzed the clinical characteristics of the young patients treated with transcatheter arterial chemoembolization.

MATERIALS AND METHODS

From June 1983 to December 1998, 1058 consecutive patients with primary hepatocellular carcinoma underwent transcatheter arterial chemoembolization therapy at Taipei Veterans General Hospital. Among these patients, 53 were younger than 40 years old. Seven of them underwent transcatheter arterial chemoembolization due to tumor recurrence after resection of the of hepatocellular carcinoma. One patient’s tumor was removed 2 weeks after arterial chemoembolization. Three patients lost follow up after discharge. These 11 patients were excluded from this study. Of the remaining 42 patients, 39 were male and 3 were female, aged 12 to 40 years (mean age 32.47 years old). During the same period, 113 elderly patients with hepatocellular carcinoma, aged 61 to 69 years old, underwent transcatheter arterial chemoembolization were compared. Diagnosis of hepatocellular carcinoma was made by histological examination of liver biopsy specimen or hepatitis B virus carrier, high serum alpha-fetoprotein titer (AFP>200ng/ml; ALT and AST <200mg/ml) and typical ultrasound, computed tomography or hepatic angiography as well as clinical course of the disease. Serum AFP values were determined by means of radioimmunoassay and a passive hemaglutination method. A second generation enzyme-linked immunosorbent assay test was used to detect antibodies of hepatitis C virus.

Transcatheter arterial chemoembolization was carried out by Seldinger’s technique of hepatic arterial catheterization. A 4.1 F arterial catheter was introduced into the right, left or segmental hepatic artery. 3.0F coaxial microcatheter (Radiofocus’ SP catheter, 130cm length, 300psi, guide wire diameter 0.53mm; Terumo Corporation, Tokyo, Japan) was used if necessary. We performed superselective arterial chemoembolization with a mixture of 30mg of doxorubicin hydrochloride (adriamycin; Pharmacia & Upjohn, Kalamazoo, Mich), 10mg mitomycin C, 3ml 0.5% normal saline and 5-15ml ethodized oil (lipiodol Ultrafluid, Laboratorie Guerbet, Aulnay Sous Bois, France). They were emulsified by a pumping method. Under fluoroscopic control, this emulsion was injected into the left or right hepatic arteries or the first- or second-order branches of these arteries. The volume of lipiodol was estimated by the size and number of tumor vessels. Finally, 1 × 1mm gelatin sponge particles (Gelfoam Film, Ferrosan, Danmark) were then injected until occlusion of blood flow in tumor feeding vessels was achieved. Microcatheter may be required to occlusion of feeding vessels. When necessary, embolization was also performed for the feeding vessels arising from inferior phrenic artery, left gastric artery, intercostal artery or internal mammary artery.

After transcatheter arterial chemoembolization, levels of tumor maker (alpha-fetoprotein), serum albumin, total bilirubin, ALT, AST and white blood cells were measured at the proper intervals. Patient’s vital sign and clinical symptom and signs were recorded. Hepatic ultrasound, computed tomography or magnetic resonance imaging were performed at a regular interval. Diagnostic digital subtraction angiography was performed when necessary. Multiple transcatheter arterial chemoembolizations might be performed to treat primary and recurrent tumors.

Univariate analysis of survival was performed by computing survival curves according to the Kaplan-Meier method. Survival curves were compared statistically using the long-rank test. A p value less than 0.05 was considered significant.

RESULTS
Forty five patients were treated while long-term follow up result was available in only 42 of them. Thirty-seven of the 42 patients had Child-Pugh A, 4 had Child-Pugh B and 1 had Child-Pugh C. Twenty-four patients had moderate advanced cirrhosis of liver. Thirty-six patients called at hospital due to clinical symptoms and signs of hepatic disease, such as right upper quadrant abdominal pain, poor appetite, general malaise, body weight loss and so on. Jaundice due to biliary duct obstruction was found in 4 patients. Five patients had episode of paraneoplastic syndrome. Three of them suffered from massive watery diarrhea. Two had symptoms of hypoglycemia. Two HBV carriers visited hospital regularly and unfortunately hepatic tumors were found eventually. One patient came for health check up because his father was found to have hepatocellular carcinoma several weeks ago.

Hepatitis B surface antigen (HBsAg) was present in 39 (92.86%) patients, while antibody of hepatitis C virus was present in 2 (4.76%). All patients showed elevation of serum alpha-fetoprotein values (>12ng/ml) and the mean alpha-fetoprotein value was 81161.4 ng/ml (Table 1).

According to histological, ultrasound, computed tomographic or angiographic findings, 24 (57.1%) patients had moderate advanced cirrhotic change in liver parenchyma. Twenty-one patients had massive solitary hepatocellular carcinoma. Fourteen of them had daughter nodules in one or both lobes of liver. Eight patients had multiple nodular lesions and 10 had diffuse infiltrative lesions. Only 3 patients had oligonodular hepatocellular carcinoma. Portal vein thrombosis was found in 16 patients. The tumor had already ruptured at presentation in six patients. One patient was sent to the emergent room due to massive hemorrhage from hepatocellular carcinoma. Emergency transcatheter arterial chemoembolization with gelfoam cubes was performed. Successful hemostasis was achieved. Sixteen patients’ main or left or right portal veins were invaded by the tumors. One of these patients was sent to emergent room due to massive hematoemesis. Hepatic angiography showed an infiltrative hypervascular tumor in right lobe of liver. Severe arteriportal shunting with hepatofugal portal blood flow was found. Serum bilirubin value more than 3.0 mg/dl was found in four patients. Computed tomogram of the liver revealed tumor invasion or compression of the left or right lobe bile ducts in two of the patients.

Transcatheter arterial chemoembolization related complications, e.g. abdominal pain, nausea, vomiting, fever and transient elevation of transaminase levels, were found in most patients. Liver function deterioration was noted in 3 patients. Tumor rupture with intraperitoneal bleeding occurred in 2 patients. The tumors were big and the portal veins were obstructed. However, the bleeding was self-limited and was controlled by conservative treatment in these patients. Blood culture revealed septicemia in one patient. The sepsis was controlled with intravenous administration of antibiotics.

Thirty-two patients were died at the follow up period. Twenty-eight of them died of cancer or cancer-related complications, three patients died of hepatic failure and one died of massive gastrointestinal bleeding. Seven patients lost follow up at 8, 8, 10, 15, 17, 24, 26 months after treatment. Three patients are alive at 45, 55 and 56 months.

The survival curve after treatment in all patients studied is shown in Figure 1.

<table>
<thead>
<tr>
<th>Alpha-fetoprotein (ng/ml)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200</td>
<td>4</td>
</tr>
<tr>
<td>201 - 400</td>
<td>2</td>
</tr>
<tr>
<td>401 - 1,000</td>
<td>1</td>
</tr>
<tr>
<td>1,001 - 10,000</td>
<td>12</td>
</tr>
<tr>
<td>10,001 - 100,000</td>
<td>10</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>13</td>
</tr>
</tbody>
</table>

Figure 1. Survival rates of the young and elder patient groups
cumulative survival rates at 6-, 12-, 24- and 36-month were 71.01, 47.27, 23.76 and 7.92% for the young group (median survival was 15 months), 77.88, 65.89, 49.27 and 29.04% for the elderly group (median survival was 25 months). There were significant difference in 3-year survival between the young and elderly groups (p=0.0094). The survival rates in the elderly group were significantly higher than young group.

**DISCUSSION**

The clinical course of hepatocellular carcinoma progresses rapidly. Doubling time of asymptomatic hepatocellular carcinoma is 117 days [3]. According to Okuda et al. the natural history of each stage without treatment is stage I: 8 months, stage II: 2 months and stage III: less than 1 month [4]. Most untreated patients die within 4 to 6 months after diagnosis. The reported median survival period was 1.6 months in patients who did not undergo treatment [4]. The 5-year survival rate is low. When hepatocellular carcinoma is presented at an early stage, surgical resection can offer a chance for cure. However, there is only a few patients have chance to resection the tumor.

Transcatheter arterial chemoembolization has been widely performed in treating unresectable hepatocellular carcinoma. The prognosis of patients treated with transcatheter arterial chemoembolization is more favorable, as compared with prognosis of patients with untreated hepatocellular carcinoma [5-9]. Analysis of the prognostic factors of hepatocellular carcinoma revealed that Okuda’s stage III (compromised hepatic functional reserve, biliary obstruction, alpha-fetoprotein greater than 400 ng/ml, presence of symptoms, moderate to severe ascites, tumor involving both lobes of liver, multinodular or massive type, portal vein thrombosis) were predicted as high risk of death [10, 11].

In our study, transcatheter arterial embolization did not show as good survival benifit in young patients as in the elderly patients. The poor effect of transcatheter arterial embolization in young patients might be due to diagnosis at later stage and worse histological pattern of the hepatic tumors. These patients are usually unaware of the hepatic malignancy until it reaches an advanced stage and thus they commonly call for medical help at the later stages of the disease. Considering patient’s characteristics in this study, most patients had large lesions and a significant high level of serum alpha-fetoprotein (Table 1). It was generally accepted that patients with hepatocellular carcinoma of large tumor volume, daughters or multiple nodules were prone to recur early and had poor prognosis. Presence of high levels alpha-fetoprotein tended to correlate with poorly differentiated or high grade hepatocellular carcinoma [12]. High serum alpha-fetoprotein levels indicated extremely poor prognosis [13]. Jaundice due to biliary duct invasion or compression is found in 4 patients and their liver function were impaired at presentation. Hepatocellular carcinoma with biliary tumor thrombi is usually attributed to the extensive invasion of a spreading type tumor. Sixteen patients had portal vein thrombosis. Partial or complete occlusion of the portal vein in the area involved by tumor is associated with significant decreased survival though it is not an absolute contraindication of transcatheter arterial chemoembolization. In patients with portal vein tumor thrombosis, prognosis is often extremely poor [14, 15]. Spontaneous rupture of hepatocellular carcinoma is a critical and life-threatening condition, which was found at diagnosis in 5 of our patients. Transcatheter arterial embolization can be a life-saving procedure while the prognosis of these patients is still rather poor [16, 17]. Five patients had paraneoplastic syndromes of watery diarrhea or hypoglycemia. Hepatocellular carcinoma with paraneoplastic syndromes had significantly higher serum alpha-fetoprotein level, portal vein thrombosis, larger tumor volume and therefore, had a shorter survival period. They were less likely to be the candidates for effective treatment [18].

Age is not a factor influencing survival in the univariate analysis. However, transcatheter arterial chemoembolization could offer more favorable results in the elder patient group than the young patient group. The different results came from different clinical and tumor status in the different groups. In many elderly cases, transcatheter arterial chemoembolization was performed in patients who were suitable for surgery and therefore had longer survival period. Early detection of hepatocellular carcinoma is the only way to provide chances for effective treatment. However, all except one of our patients of younger age called for medical help when they
suffered from severe symptoms, so the tumors were at advanced stage at the time of presentation. Transcatheter arterial chemoembolization did not show survival benefit in young patients with unresectable hepatocellular carcinoma. We suppose their hepatocellular carcinoma might be treated with tamoxifen alone. Hepatitis B vaccine can prevent infection and its sequelae, and a reduction in hepatocellular carcinoma has been seen in Taiwan with the introduction of universal vaccination of children [19].

REFERENCES

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經導管動脈化學栓塞術治療年輕人無法切除之肝細胞癌療效之評估

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肝細胞癌為世界性最常見的惡性腫瘤中之一種。依照地域的差異，其好發年齡稍有不同，年長者和年輕者其致癌因素也可能稍有不同。本研究之目的在於評估經導管動脈化學栓塞術治療年輕之肝細胞癌病人之療效如何。

自1983年至1998年，有42位40歲以下患肝細胞癌之年輕病人，在本院接受動脈化學栓塞術，其中三人得寡結節型、八人得多結節型、二十一人得單一巨大型、十人得浸潤型肝細胞癌。施行經導管動脈化學栓塞術時，先從肝動脈注射adriamycin和lipiodol混合液，然後再注入gelfoam把動脈堵住。我們對這組年輕病人做回覆式評估其療效，並做檢討。同期間內113位年齡61至69歲老年族接受動脈化學栓塞術之肝細胞癌病人，其存活率亦計算出來，以資比較。

年輕族人組，其6月、12月、24月、36月之存活率分別為71.01%，47.27%，23.76%，7.92%。中位存活時間15個月。年老組為77.88%，65.89%，49.27%，29.04%。中位存活時間25個月。由此可見動脈化學栓塞術對年輕病人療效不如老年組，對其存活助益不大。

關鍵詞：肝臟，腫瘤；肝腫瘤，診療放射學；動脈，治療性栓塞