Postoperative Transhepatic Arterial Chemoembolization and Portal Vein Chemotherapy for Patients with Hepatocellular Carcinoma: A Randomized Study with 131 Cases

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Transarterial chemoembolization • Portal vein chemotherapy • Hepatocellular carcinoma

Abstract
Objective: To explore the value of postoperative transarterial chemoembolization (TACE) and portal vein chemotherapy (PVC) in patients with hepatocellular carcinoma (HCC) in the prevention of recurrence, and to evaluate prognostic factors in a randomized study.

Method: 131 patients with HCC were randomly divided into 3 groups: operation only (group A, n = 45); operation plus TACE (group B, n = 39), and operation plus TACE and PVC (group C, n = 47). Disease-free survival rates as well as prognostic factors were analyzed.

Results: Most of the side effects and complications related to the operation, catheters and local chemotherapy were liver decompensation (16.1%), catheter obstruction (12.9%), and nausea and loss of appetite (25.8%), respectively. The disease-free survival curves were significantly different between the 3 groups as estimated by the Kaplan-Meier method (p < 0.05). Group C had a significantly higher disease-free survival rate compared to group A (p < 0.05). But no statistical differences were found between groups A and B and groups B and C (both p > 0.05). Tumor number and treatment modalities were independent prognostic factors for HCC patients (p < 0.05).

Conclusion: Postoperative TACE combined with PVC may benefit the survival of patients with HCC. In specialized medical centers, aggressive methods such as TACE and PVC should be attempted on HCC patients without contraindications.

Introduction
Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and is particularly prevalent in China [1–3]. The incidence of HCC will likely increase dramatically over the next few decades due to the high infection rate with hepatitis B and C, which are known to be intimately associated with HCC [4, 5]. Despite the marked progress in diagnostic techniques and therapeutic procedures, the prognosis for patients with HCC remains discouraging. Surgical resection or liver transplantation for these individuals is frequently not
feasible due to poor hepatic reserve function, advanced HCC stage, and/or lack of suitable donor livers [6, 7]. Even after curative resection, the prognosis for these patients is still very poor due to the high recurrence rate caused by microscopic tumor thrombosis. Tsai et al. [8] reported that this can be observed in 59.0% patients with HCC. Therefore the prevention of recurrence constitutes one of the most important challenges to improving surgical efficacy. Systemic chemotherapy has also been attempted in cases of this type, but without any appreciable survival benefit [9]. Recent advances with implantable drug delivery systems have made it possible to administer repeated arterial infusions of chemotherapeutic agents [10, 11]. Transarterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy have the advantages of increased local drug concentrations and a reduction in systemic side effects. Several authors in this field have reported their efficacy [12, 13]. In the mean time, it has been shown that blood with micro-tumor foci (especially with nodamic cancer cells) mainly comes from the portal vein [8]. Thus, portal vein chemotherapy (PVC) may further improve the patient’s prognosis. In 2002, after a 1.5-year follow-up, we reported that the survival and recurrence curves for HCC patients receiving postoperative TACE and PVC combined with macroscopic tumor thrombosis were significantly better than those of patients receiving only TACE [14]. At that time, we also studied the efficacy of the procedures in patients without macroscopic tumor thrombosis. The aim of this paper is to explore the value of TACE and PVC in preventing recurrence in patients with a few years follow-up, and analyze the prognostic factors.

Patients and Methods

From January 1998 to January 2001, 637 HCC patients were admitted to the Cancer Hospital of Tianjin Medical University, China. Among these patients, initially 180 cases were selected and met the inclusion criteria (no previous management; solitary or multiple tumors mainly located in one lobe of the liver; no distant metastases; good or moderate hepatic function (Child-Pugh stage A or B evaluated by the score of hepatic encephalopathy, ascites, bilirubin, albumin and prothrombin time) and no contraindication for laparotomy). The nature of the study was explained fully to the patients, and informed consent was obtained from all. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Tianjin Anti-Cancer Association. Forty-nine patients were excluded because of serious complications (21 patients) and non-HCC (28 patients) proven by pathology. In total 131 patients entered the study.

Grouping

Random drawing of lots and a single-blind method were applied in the study: group A (only operation, 45 patients); group B (operation plus TACE, 39 patients), and group C (operation plus TACE and PVC, 47 patients). No statistical differences were found with regard to the patients’ age, gender, α-fetoprotein (AFP) level, positive rates of HBsAg, tumor size, tumor number, tumor capsule, Child-Pugh stage, and resection modalities between the 3 groups (table 1). In total there were 111 men and 20 women with a mean age of 50.5 (range 29–78) years. Serum HBsAg was positive in 109 patients (83.2%). The AFP level was elevated in 100 cases (76.3%). According to the Child-Pugh classification, 73 (55.7%) and 58 (44.3%) patients were in Child-Pugh stages A and B, respectively. The tumor size was 5.13 ± 1.8 (range 2.2–15.7) cm in diameter.

Operation Modalities

According to the tumor location, size and number, different resections were performed on the patients including: 49 cases with one segmentectomy; 54 cases with multiple segmentectomies, and 28 cases with lobectomy. Resection was followed by hepatic artery catheterization in 86 cases. Of these 86 cases, 47 patients also received a portal vein catheter. The catheters were placed into the proper hepatic artery and/or portal vein through the gastroduodenal artery and right gastroepiploic vein, respectively. The ports were completely implanted beneath the abdominal wall. Heparin solution was infused regularly via the injection port to keep the catheter from occluding.

Chemotherapy

In group A the 45 patients were only operated. In group B the 39 cases received operation plus 3 courses of TACE (lipoidal 5–10 ml, adriamycin 30 mg, mitomycin 20 mg, cisplatin 80–100 mg or carboplatinum 400 mg) starting 4 weeks after the operation with intervals of 2 weeks. In group C, apart from TACE, the 47 patients received 3 courses of PVC (5-fluorouracil 750–1,500 mg, through a mechanical infusion pump set at a rate of 50 mg/h) starting 2–4 weeks after the operation with intervals of 2 weeks.

Follow-Up

All patients were followed up at the outpatient clinic every 3 months with measurement of the serum AFP level and hepatic ultrasonography every 2–4 months from the date of initial treatment up to January 2006, or up to the time of death. When recurrence was suspected, further evaluations were made by abdominal CT scan and, if necessary, by ultrasound-guided biopsy to confirm the diagnosis. The defined end point was non-survival. In total 11 (8.4%) patients died of another cause or were lost to follow-up.

Statistical Analysis

The Kaplan-Meier method was used to plot the estimated disease-free survival curves. The results of univariate analysis were compared to those from the log-rank test to identify predictors of survival. The results of the multivariate analysis were then investigated using Cox’s proportional hazards model. A p value of <0.05 was considered to be statistically significant.
Results

Side Effects and Complications

No intraoperative death occurred, but 2.8% (5/180) of the patients died of liver failure within 30 days postoperatively. Other complications included: mild or moderate liver decompensation in 16.1% (29/180); hemorrhage in 12.1% (17/180), and ascites in 5.6% (10/180) of the patients. Transient fever and abdominal discomfort were reported for almost all patients.

Complications associated with catheters included: obstruction in 12.9% (16/124); dislocation of the catheter tip in 5.6% (7/124); infection in 6.5% (8/124); agent leaking in 11.3% (14/124), and hematoma around the injection port in 8.1% (10/124). Remedial measures were performed including infusion of heparin solution, implantation of a new catheter or other medical treatment.

The adverse reactions to TACE and PVC included: nausea and loss of appetite in 25.8% (32/124); deterioration of liver function in 12.1% (15/124) with 6 withdrawals; and leukopenia and thrombocytopenia in 5.6% (7/124) with 3 withdrawals. No pulmonary embolism or renal damage were observed. Seven (5.6%) patients did not complete the three courses of chemotherapy for various reasons and quit the study.

Disease-Free Survival Rates

The 1-, 3- and 5-year disease-free survival rates in group A were 86.5, 66.0 and 47.8%, respectively, and the rates in group B were 87.2, 76.8, and 60.7%. The rates in group C at the corresponding stages, however, increased to 95.6, 84.5 and 73.2%, respectively. The Kaplan-Meier method was used to estimate the disease-free survival rates in group A (only operation), group B (operation plus TACE) and group C (operation plus TACE and PVC; p = 0.018, by log-rank test). The log-rank test showed significantly higher disease-free survival rates in group C than in group A (p = 0.005), but no statistical differences were found between groups A and B (p = 0.345) and groups B and C (p = 0.077; fig. 1).

Factors Influencing Survival

Among the ten variables, univariate analysis showed that Child-Pugh stage, tumor capsule, tumor size, tumor number, and treatment modalities were significant factors influencing the disease-free survival of HCC patients (p < 0.05; table 2), whereas multivariate analysis only demonstrated that tumor number and treatment modalities were independent prognostic elements (p < 0.05; table 3).
Fig. 1. Kaplan-Meier estimated disease-free survival rates in group A (only operation), group B (operation plus TACE) and group C (operation plus TACE and PVC; \( p = 0.018 \) by log-rank test). Log-rank test showed a significantly higher rate in group C than in group A (\( p = 0.005 \)). No statistical differences were found between groups A and B (\( p = 0.345 \)) and groups B and C (\( p = 0.077 \)).

Table 2. Factors associated with survival rates of patients by univariate analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>( p )</th>
</tr>
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<tbody>
<tr>
<td>Age (( \leq 50 ) vs. &gt;50 years)</td>
<td>0.113</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>0.472</td>
</tr>
<tr>
<td>HbsAg (positive vs. negative)</td>
<td>0.169</td>
</tr>
<tr>
<td>Child-Pugh stage (A vs. B)</td>
<td>0.046</td>
</tr>
<tr>
<td>AFP (( \leq 400 ) vs. &gt;400 ng/ml)</td>
<td>0.392</td>
</tr>
<tr>
<td>Capsule (present vs. absent)</td>
<td>0.044</td>
</tr>
<tr>
<td>Tumor size (( \leq 10 ) vs. &gt;10 cm)</td>
<td>0.033</td>
</tr>
<tr>
<td>Tumor number (uninodular vs. multiple)</td>
<td>0.019</td>
</tr>
<tr>
<td>Resection (segmentectomy vs. segmentectomies and lobectomy)</td>
<td>0.371</td>
</tr>
<tr>
<td>Treatment modalities (groups A/B/C)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Group A = Operation only; group B = operation plus TACE; group C = operation plus TACE and PVC.

Table 3. Factors influencing survival rates of patients by multivariate analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>( \beta )</th>
<th>SE</th>
<th>( p )</th>
<th>( \text{Exp (B)} )</th>
<th>95.0% CI for ( \text{Exp (B)} )</th>
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<tbody>
<tr>
<td></td>
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<td>lower</td>
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<tr>
<td>Child-Pugh stage (A vs. B)</td>
<td>0.325</td>
<td>0.244</td>
<td>0.182</td>
<td>1.384</td>
<td>0.859</td>
</tr>
<tr>
<td>Capsule (present vs. absent)</td>
<td>0.467</td>
<td>0.240</td>
<td>0.052</td>
<td>1.595</td>
<td>0.996</td>
</tr>
<tr>
<td>Tumor size (( \leq 5 ) vs. &gt;5 cm)</td>
<td>0.347</td>
<td>0.235</td>
<td>0.139</td>
<td>1.415</td>
<td>0.894</td>
</tr>
<tr>
<td>Tumor number (uninodular vs. multiple)</td>
<td>0.499</td>
<td>0.236</td>
<td>0.034</td>
<td>1.648</td>
<td>1.037</td>
</tr>
<tr>
<td>Treatment modalities (groups A/B/C)</td>
<td>-0.320</td>
<td>0.144</td>
<td>0.027</td>
<td>0.726</td>
<td>0.547</td>
</tr>
</tbody>
</table>

Group A = Operation only; group B = operation plus TACE; group C = operation plus TACE and PVC.
Discussion

Surgery remains the most effective treatment for HCC. It is notable that the disease-free survival rate increased greatly for those HCC patients receiving hepatectomy. This is because the operation technique has greatly improved, especially in the control of bleeding which is intimately associated with hepatic function and tumor cell metastasis during the operation. In our center, the mean perioperative blood loss was 330.4 ± 265.5 ml [3]. On the other hand, more and more patients with HCC are being diagnosed earlier because of screening with AFP and medical imaging in high-risk groups, and meanwhile, the healthy consciousness of the Chinese has recently intensified.

However, due to the high postoperative recurrence rate, the prognosis for HCC patients is still very poor compared to other types of tumor. As is well known, HCC has a high predilection for portal vein invasion, which is independently related to the patient’s survival [8, 15, 16]. Although the macroscopic tumor foci have been removed, there might still be microscopic foci that were not detected before surgery, which then would be the source of recurrence. To our knowledge, most of the blood supply to HCC is derived from the hepatic artery, whereas the portal vein supplies the normal liver parenchyma. Therefore it is reasonable to assume that intraarterial administration of cytotoxic agents may facilitate the delivery of a higher therapeutic concentration to the tumor tissue [17]. Using meta-analyses and clinical study, Mathurin et al. [18], Tanaka et al. [19] and Fukuda et al. [20] drew the conclusion that postoperative transarterial chemotherapy or TACE may improve the survival rate and reduce the recurrence rate. In the present study, although the log-rank test did not show a statistical difference between patients treated with operation and those with operation plus TACE, there is a tendency for improved survival of the latter. Therefore TACE may be effective against residual cancer recurrence and improve patients’ survival.

Despite the above-mentioned results, which show the effect of TACE, one must also consider that aside from the hepatic artery, some blood also comes from the portal vein supplying the tumor and the portal vein thrombus. This is especially true for micro-tumor foci that are mainly nourished by the portal vein [8]. Based on this theory, PVC may further improve the survival of patients. PVC has often been used for patients with colorectal carcinoma with liver metastases [21–23]. Fan et al. [24] investigated the use of PVC in HCC patients complicated by PVTT. Hepatic resection combined with thrombectomy was performed in 179 patients with HCC and PVTT. The survival rates at 6 months, 1, 2, and 3 years after surgical resection with postoperative chemotherapy (TACE and/or PVC) were 55.8, 39.3, 30.4, and 15.6%, respectively, and were significantly higher than those of the other group without adjuvant chemotherapy. Multivariate analysis revealed that the strategy of treatment and the number of chemotherapy cycles were independent survival predictors. The results showed the efficacy of postoperative chemotherapy, but did not identify the difference between TACE and PVC or their combination. Combined with our previous report [13], the present study shows that the 1-, 3- and 5-year disease-free survival rates in group C increased to 95.6, 84.5 and 73.2%, respectively, which further demonstrates the efficacy of TACE combined with PVC for patients without macro-tumor thrombus or metastatic foci.

Using univariate analysis of the prognostic factors, Konishi et al. [25] revealed that intrahepatic metastasis, tumor differentiation and operative resectability significantly affected survival. In the present study, univariate analysis showed that Child-Pugh stage, capsule, tumor size, tumor number, and treatment modalities were significant factors, whereas multivariate analysis only demonstrated that tumor number and treatment modalities were independent prognostic elements. Therefore it is essential to perform detailed and strict preoperative examinations to obtain an exact evaluation of the tumor and the patient’s condition. The results also suggest that, in China, the situation of the tumor plays a more important role than that of liver function in the patient’s prognosis. Taking these serious side effects and complications such as infection and agent leaking into consideration, strict operative performance and cautious nursing are also very important.

In conclusion, postoperative adjuvant TACE combined with PVC may be a valuable therapeutic strategy for HCC patients in preventing recurrence. Especially in specialized medical centers, aggressive methods such as TACE and PVC should be attempted on HCC patients without contraindications.
References


