The efficacy of surgery and transarterial chemoembolization for hepatocellular carcinoma patients with portal vein tumor thrombus

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Received November 11, 2015; Accepted January 23, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: Background: According to Barcelona Clinic Liver Cancer (BCLC) Group, hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (PVTT) are defined as BCLC stage C who are recommend with sorafenib. Several studies have found survival benefits followed by hepatectomy and transarterial chemoembolization (TACE) other than recommend therapies. In order to discuss this controversy, we aim to find out which therapy is better for these patients. Methods: From 2010 to 2011, 170 HCC patients were enrolled in this study (surgery group, n=85; TACE group, n=85). Databases were searched to conduct meta-analysis to evaluate the efficacy of surgery and TACE in patients with PVTT. Results: In our study, patients underwent hepatectomy had significantly better survival than patients underwent TACE [mean survival (MS): 17.28 months vs. 10.28 months, P=0.001]. Patients with PVTT type I (MS: 18.97 months) had significantly longer survival than patients with PVTT type II (MS: 11.71 months, P=0.010) and type III (MS: 6.98 months, P<0.001). The difference between patients with PVTT type II or III was also significant (P<0.001). Meta-analysis results also showed that patients in surgery group had better 1-year survival [risk ratio (RR)=1.23, 95% confidence interval (CI) 1.09 to 1.39], 2-year survival (RR=1.86, 95% CI 1.54 to 2.24) and 3-year survival (RR=2.09, 95% CI 1.62 to 2.71) than patients in TACE group. Conclusion: The study demonstrated that hepatectomy has potential to improve survival and is safe for HCC patients with PVTT. However, further well-designed controlled trials needs to confirm this effect.

Keywords: Surgery, hepatocellular carcinoma, meta-analysis, portal vein thrombus, transarterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common type of cancer worldwide [1]. Approximately 10% to 40% of HCC patients have concurrent portal vein tumor thrombus (PVTT) [2]. PVTT is the independent poor prognostic factors for survival in HCC patients [3, 4].

Surgery still remains the curative therapy, but only available for early stage HCC patients which may provide 5-year survival rate up to 75% [5, 6]. According to Barcelona Clinic Liver Cancer (BCLC) Group, hepatectomy is only suitable for BCLC stage A patients [7, 8]. Patients with PVTT are defined as BCLC stage C for whom sorafenib is recognized as the standard therapy [9, 10]. Although surgery is a not curative therapy for patients with PVTT. However, surgery concludes hepatectomy and thrombectomy were reported to prolong survival [11]. Transarterial chemoembolization (TACE) has been characterized as effective and safe methods for the treatment of HCC patients with PVTT [12, 13]. Also, TACE procedure have been reported to prolong survival periods compared to conservative treatments [14]. Compared with TACE, surgery seems to be more effective and would prolong survival in HCC patients [15]. Nevertheless, rare studies had specifically investigated the survival benefit between surgery and TACE in HCC patients with PVTT.

Therefore, we performed this study to comprehensively compare the safety and efficacy of surgery and TACE for HCC patients with PVTT.
Surgery vs. TACE for patients with PVTT

Table 1. Baseline characteristics of HCC patients in each treatment group

<table>
<thead>
<tr>
<th></th>
<th>Surgery group (n=85)</th>
<th>TACE group (n=85)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD</td>
<td>50 ± 12</td>
<td>49 ± 16</td>
<td>0.974</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>77 (91%)</td>
<td>75 (88%)</td>
<td>0.618</td>
</tr>
<tr>
<td>Positive for HBsAg</td>
<td>67 (79%)</td>
<td>68 (80%)</td>
<td>0.850</td>
</tr>
<tr>
<td>PLT, 10^9/L</td>
<td>255± 113</td>
<td>267 ± 108</td>
<td>0.814</td>
</tr>
<tr>
<td>TBil, μmol/L</td>
<td>19 (11-35)</td>
<td>18 (10-32)</td>
<td>0.926</td>
</tr>
<tr>
<td>ALB, g/L</td>
<td>38 ± 7</td>
<td>36 ± 6</td>
<td>0.973</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>42 (22-76)</td>
<td>46 (21-89)</td>
<td>0.249</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>45 (27-89)</td>
<td>43 (20-76)</td>
<td>0.841</td>
</tr>
<tr>
<td>PT, s</td>
<td>13 ± 1</td>
<td>14 ± 2</td>
<td>0.837</td>
</tr>
<tr>
<td>AFP, mg/L</td>
<td>978 (164-1210)</td>
<td>876 (267-1210)</td>
<td>0.230</td>
</tr>
<tr>
<td>Child-Pugh A/B</td>
<td>72/13</td>
<td>70/15</td>
<td>0.679</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>10 ± 5</td>
<td>12 ± 6</td>
<td>0.467</td>
</tr>
<tr>
<td>Tumor number (≥3), n</td>
<td>31 (36%)</td>
<td>37 (44%)</td>
<td>0.348</td>
</tr>
<tr>
<td>PVTT type, I/II/III</td>
<td>35/25/25</td>
<td>36/27/22</td>
<td>0.868</td>
</tr>
</tbody>
</table>

Notes: TACE: transarterial chemoembolization; PVTT = portal vein tumor thrombus; SD = standard deviation; HBsAg = hepatitis B surface antigen; PLT = platelet count; TBil = total bilirubin; ALB = albumin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PT = prothrombin time; AFP = alpha-fetoprotein.

Methods

Patients

This retrospective study involved 170 consecutive patients with PVTT admitted to our hospital for treating HCC. According to different therapies, patients were divided into surgery group (n=85), and TACE group (n=85).

Include criteria: (a) 18-75 years old, (b) presence of PVTT type I, II, III (PVTT location not reached the inferior vena cava and mesenteric vein) [16], (c) Child-Pugh liver function stage A or B, (d) patients included in surgery group should have a resectable tumor [15], and (e) diagnosed with HCC based on postoperative pathology. Patients with any previous treatment and patients with other malignant tumors or extra-hepatic metastases were excluded.

Surgical procedure

Patients in surgery group underwent hepatectomy and embolectomy. We recorded the detail data of tumor size, blood loss, operating time, number of tumors, and PVTT location.

During the operation, we used intraoperative ultrasonography to reevaluated PVTT location.

Pringle maneuver was used to occlude the blood inflow of the liver distal to the PVTT. After removing the HCC and PVTT, normal saline was used to flush the portal vein and make sure that no PVTT was remained. Then we closed the opened stump.

TACE procedure

We performed Seldinger technique to conduct TACE. Gelatin sponge was used to perform embolization of the tumor feeding artery. After performing embolization, the drug (a mixture of 100 mg cisplatin or oxaliplatin, 30-50 mg doxorubicin), and 5-10 mL of lipiodol were injected.

Follow-up

Patients were asked to reexamine every one month for every 2 months. Reexamination concludes the same test which had done preoperatively. Patients who cannot be found or connected were defined as dead.

Outcomes

We analyzed the OS in 170 HCC patients in order to find out which therapy is better for HCC patients with PVTT. Moreover, we also performed subgroup analysis depending on PVTT type in each therapy group.

Medline database search and meta-analysis

We conducted a meta-analysis to compare the efficacy of surgery and TACE in HCC patients with PVTT in this study to further proved the efficacy of surgery and TACE in patients with PVTT.

MEDLINE, EMBASE, the Cochrane Library, and the Chinese National Knowledge Infrastructure (CNKI) were systematic searched through August 2015 without language restrictions. Eligible studies were identified using any of the following index words: hepatocellular carcinoma or HCC or liver cancer; transcatheter chemoembolization or transarterial chemoembolization or TACE; surgery or hepatectomy or liver resection; portal vein tumor thrombus or portal vein tumor thrombi or PVTT. Relevant reviews
Surgery vs. TACE for patients with PVTT

Studies would only be included by satisfying following criteria: (1) the trial involving HCC patients with PVTT; (2) the trial conducted the comparison between the treatment of surgery and TACE; (3) the trial reported data on survival outcomes.

Statistical analysis

Original data analyses were performed using SPSS 18.0 (IBM, Chicago, USA). We defined threshold of statistical significance as $P<0.05$. Normally distributed data were expressed as mean ± standard deviation (SD), while asymmetrically distributed data were expressed as median (range). The Kaplan-Meier method was used to calculate OS.

The statistical calculations of meta-analysis used Stata 12.0 (Stata Corp, College Station, TX, USA). Mantel-Haenszel RRs with corresponding 95% CIs were calculated for 1-, 2-, 3-year survival. Heterogeneity was assessed by calculating $I^2$ ($I^2>50\%$, fixed-effects model; $I^2<50\%$, random-effects model).

Results

Characteristics of the study population

From 2010 to 2011, 170 eligible HCC patients with PVTT were admitted to this retrospective study (surgery group, n=85; TACE group, n=85). Patients’ characteristics in both groups were similar (Table 1).

Overall survival

Patients underwent surgery (mean survival: 17.28 months) had significantly longer survival time than patients underwent TACE procedure (mean survival: 10.78 months) ($P=0.001$). The
Surgery vs. TACE for patients with PVTT

1-, 2-, 3-year survival rates were 47.5%, 26.7%, 7.1% for patients underwent surgery, and 30.0%, 5.0%, 0.0% for patients underwent TACE procedure (Figure 1).

Survival difference among different PVTT types was also analyzed. Patients with PVTT type I (mean survival: 18.97 months) had significantly longer survival than patients with PVTT type II (mean survival: 11.71 months, \( P=0.010 \)) and type III (mean survival: 6.98 months, \( P<0.001 \)). The difference between patients with PVTT type II or III was also significant (\( P<0.001 \)) (Figure 2).

Subgroup analysis

Subgroup analysis depending on PVTT type was conducted in each treatment group. In surgery group, we found patients with PVTT type I (mean survival: 22.23 months) had significantly longer survival than patients with PVTT type II (mean survival: 14.91 months) was significantly longer than patients with PVTT type III (\( P=0.029 \)). Patients with PVTT type I seemed have a longer OS than PVTT type II patients, but the difference was not significant (\( P=0.069 \)). In TACE group, patients with PVTT type I (mean survival: 15.25 months) had significantly longer survival than patients with PVTT type II (mean survival: 11.71 months, \( P=0.003 \)) and type III (mean survival: 6.98 months, \( P<0.001 \)).
Surgery vs. TACE for patients with PVTT

Five studies [17-21] and this study estimated 1-year survival, and found patients in hepatectomy group had significantly longer 1-year survival rates than patients undergoing TACE procedure (RR=1.23, 95% CI 1.09 to 1.39, $I^2=0\%$). Hepatectomy also had significantly better 2-year survival (RR=1.86, 95% CI 1.54 to 2.24, $I^2=81.9\%$) and 3-year survival (RR=2.09, 95% CI 1.62 to 2.71, $I^2=57\%$) than TACE (Figure 4; Table 4).

**Discussion**

Patients with PVTT usually undergo an unsatisfied OS [22]. According to guidelines of EASL, patients with PVTT are only suitable for sorafenib or other palliative therapy [23]. Also, patients with PVTT are often defined as BCLC stage C, and these patients were candidates for sorafenib [24]. However, several studies [25, 26] had figured out patients with PVTT may have survival benefits undergoing hepatectomy or TACE other than sorafenib or other palliative therapy. Since hepatectomy and TACE would bring survival benefit, which treatment is better still remains controversial [4, 27]. Our study aims to find the efficacy and the safety of hepatectomy and TACE in HCC patients with PVTT.

Hepatectomy was once provided for patients with profound liver function, smaller tumor size, and without vessels involvement. In patients with PVTT, they easily occurred portal hypertension and intra-liver metastasis [8]. Advanced tumor stage and symptoms induced by portal hypertension increased the risk and difficulties of hepatectomy. However, the superiority of surgery over other treatments had been demonstrated in many studies [27-29]. Hepatectomy

months) had significantly longer survival than patients with PVTT type II (mean survival: 9.16 months, $P=0.001$) and type III (mean survival: 5.31 months, $P<0.001$). The difference between patients with PVTT type II or III was also significant ($P=0.002$) (Figure 3).

Prognostic factors for overall survival

We conduct univariate logistic regression analysis and found 3 factors associated with worse OS. Then these 3 factors were enrolled in multiple logistic regression analysis and found patients underwent TACE (hazard ratio (HR) =2.498, 95% CI 1.554 to 4.018, $P<0.001$), advanced PVTT type (HR=2.600, 95% CI 1.853 to 3.648, $P<0.001$) were associated with worse OS (Table 2).

**Medline database research and meta-analysis of included studies**

MEDLINE, EMBASE, the Cochrane Library, the Chinese National Knowledge Infrastructure database, and clinical trial registries were searched through Sep. 2015. Totally 214 published studies were initial searched. After manual searching, 201 published trials were removed because they turned out to be systematic reviews, meta-analyses or a conference abstract. Thus, together 5 trials and our study including 1287 patients were enrolled in this analysis. The characteristics of the included studies are shown in Table 3.

**Table 3. Characteristics of included studies comparing hepatectomy and TACE to treat patients with PVTT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Quality score</th>
<th>Arm</th>
<th>n (male)</th>
<th>Age, yr</th>
<th>Child-Pugh, n (A/B)</th>
<th>HCC etiology, n (HBV/other)</th>
<th>PVTT type, n (I/II/III/IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng et al. 2005</td>
<td>China</td>
<td>Retrospective</td>
<td>7</td>
<td>Surgery</td>
<td>7 (5)</td>
<td>69.3 ± 11.8</td>
<td>NR</td>
<td>6/1</td>
<td>2/1/1/0</td>
</tr>
<tr>
<td>Fan et al. 2005</td>
<td>China</td>
<td>Retrospective</td>
<td>6</td>
<td>Surgery</td>
<td>24 (20)</td>
<td>NR</td>
<td>18/6</td>
<td>NR</td>
<td>16 (I+II/III+IV)</td>
</tr>
<tr>
<td>Liu et al. 2014</td>
<td>China</td>
<td>Prospective with PSA</td>
<td>9</td>
<td>Surgery</td>
<td>108 (84)</td>
<td>62 ± 15</td>
<td>84/16</td>
<td>48/60</td>
<td>NR</td>
</tr>
<tr>
<td>Ye et al. 2014</td>
<td>China</td>
<td>Retrospective</td>
<td>7</td>
<td>Surgery</td>
<td>90 (81)</td>
<td>49.3 ± 10.7</td>
<td>84/6</td>
<td>12/78</td>
<td>66 (I+II/III+IV)</td>
</tr>
<tr>
<td>Our study 2015</td>
<td>China</td>
<td>Retrospective</td>
<td>8</td>
<td>Surgery</td>
<td>85 (77)</td>
<td>50 ± 12</td>
<td>72/13</td>
<td>67/18</td>
<td>35/25/25/0</td>
</tr>
<tr>
<td>TACE</td>
<td>85 (75)</td>
<td>49 ± 16</td>
<td>70/15</td>
<td>68/17</td>
<td>36/27/22/0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HBV, hepatitis B virus infection; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; NR, not reported; PSA, propensity score analysis; PVTT, portal vein tumor thrombus.
Surgery vs. TACE for patients with PVTT

Figure 4. Meta-analysis of data on survival in patients with PVTT following either hepatectomy or TACE.
combined with thrombectomy can reduce portal hypertension and thus prevent the occurrence of intractable ascites and bleeding of esophageal varices [18]. Furthermore, the method also allows the recovery of portal vein blood flow, improves liver function, reduces tumor burden. Moreover it could increase the efficacy of postoperative multimodality treatments. Thus to prolong OS [18, 27, 30].

TACE used to be the contradictions for patient with PVTT according to BCLC group [7]. Invisible intrahepatic metastasis via the portal venous system is the primary mechanism for intrahepatic recurrence [31, 32]. Moreover, TACE also increase the incidence of pulmonary metastasis [33]. However, recently a meta-analysis has proved that patients with PVTT could benefit from TACE other than conservative therapy [14].

In our study, we found that patients underwent hepatectomy had significantly longer OS than patients underwent TACE procedure. Also, patients with less advanced PCTT type were associated with a better survival. Subgroup analysis also convinced this finding. Though a similar OS benefit was found between patient with PVTT type I or II after surgery. This may due to the procedure of embolectomy. We should occlude the end of the first branches when PVTT type was I or II. In our meta-analysis, hepatectomy seemed to have better survival outcome than TACE (1-, 2-, 3-year survival). Compared with TACE, hepatectomy reduced the tumor burden and gained patients more chances to receive further therapy thus to prolong the OS. Nevertheless, risk factor analysis of 5 included trials and our study all claimed that surgery remained the prognostic factors for patients with PVTT.

The treatment for HCC patients was multiple. Patients with single use of any treatment seemed to receive unsatisfied OS. Thus, hepatectomy combined with postoperative TACE may provide a good survival outcome. Postoperative TACE can effectively block the tumor’s nutrient vessels. In this way a large doses of sustainable chemo drugs could kill the residual microscopic HCC cells without damaging normal liver cells [34, 35].

Our study has several limitations. First, study design was retrospective which would have selection bias. However, baseline characteristics were similar between 2 groups. And further meta-analysis convinced our results. Thus the bias would decreas. Second, PVTT in patients under TACE procedure was evaluated by images. This may have the bias.

In spite of differences in study design and population characteristics, our study demonstrated that hepatectomy has potential to improve survival and is safe for HCC patients with PVTT. However, further well-designed controlled trials needs to confirm this effect.

Disclosure of conflict of interest
None.
Authors’ contribution


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References


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