Long-Term Outcome of Splenectomy in Advanced Cirrhotic Patients with Hepatocellular Carcinoma and Thrombocytopenia

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Summary: Splenectomy may be a treatment option in hepatocellular carcinoma (HCC) and cirrhosis when there is no potential donor for liver transplantation. We retrospectively investigated the long-term outcome of splenectomy on survival in advanced cirrhotic patients with HCC and thrombocytopenia. Between 1999 and 2009, 46 cirrhotic patients with thrombocytopenia (Child-Pugh class B or C) who underwent splenectomy for the simultaneous or secondary treatment of HCC at our institute were evaluated. The 1-, 3-, and 5-year survival rates were 93.5, 76.0, and 37.9%, respectively. Splenectomy resulted in a significant reduction in mean portal venous pressure from 21.2 to 16.8 mmHg and improvements in liver function tests such as total bilirubin, prothrombin time, platelet count, Child-Pugh score for 3 years, and albumin for 2 years. The mean frequency of treatment for HCC recurrence after surgery was 3.0 times (range 1-11). Seven patients out of 16 scheduled for Interferon (IFN) therapy after surgery achieved a sustained virological response (SVR). Multivariate analysis identified SVR after IFN therapy as an independent significant prognostic factor (Hazard ratio 0.18, 95%CI 0.03-0.65, P=0.006). Postoperative complications including liver failure (n=1), portal thrombosis (n=7), ascites (n=5), and bacterial infections (n=4) were observed in 14 patients (30%). Splenectomy can be a feasible supportive therapy for the continuation of anticancer therapy and completion of IFN therapy based on improvements in liver function and thrombocytopenia with minimum complications in patients with HCC and advanced cirrhosis with no potential donor.

Key words splenectomy, survival, hepatocellular carcinoma, advanced liver cirrhosis, Interferon, no potential donor

INTRODUCTION

The role of the spleen in cirrhosis remains unclear. The development of liver fibrosis leads to portal hypertension accompanied by splenomegaly and hypersplenism [1]. Hypersplenic thrombocytopenia interferes with treatments such as hepatectomy, radiofrequency ablation (RFA), and transcatheter hepatic arterial chemoembolization (TACE) in patients with liver cirrhosis and hepatocellular carcinoma (HCC) [2-4]. In such cirrhotic patients with hypersplenism thrombocytopenia, splenectomy has recently been shown to improve the outcome of hepatectomy for HCC [5], allow the induction of interferon (IFN) therapy for hepatitis C viral (HCV) infection [6], and modulate portal venous pressure in...
living-donor liver transplantation [7]. In 1999, splenectomy was performed in one of our cirrhotic patients with HCC and hypersplenemic thrombocytopenia [8]. This single treatment modality resulted in an improvement in liver function and thrombocytopenia, and thence allowed us to administer a full course of hepatic arterial infusion chemotherapy (HAIC), which resulted in the disappearance of the liver tumor. Backed by this outcome, we have subsequently performed splenectomy as a supportive therapy for anticancer therapies including hepatectomy, RFA, TACE, and HAIC in such patients.

Liver transplantation is the only ultimate cure for advanced cirrhotic patients with HCC, and it can achieve acceptable outcomes [9]. Recently, the indication of living-donor liver transplantation has been greatly expanded for HCC beyond the Milan criteria [10]. Salvage living-donor liver transplantation has also been performed in patients with untreatable HCC by conventional treatments or in cirrhotic patients with Child-Pugh class B or C [11]. The demand for liver transplantation by HCC patients has increased worldwide [12]. However, in the face of an organ shortage, the use of liver transplantation is limited [10]. Increasing drop-out rates have also been reported for deceased-donor liver transplantation candidates with HCC when waiting times exceeded 12 months [13]. Such patients with no potential donor require another option besides liver transplantation. Splenectomy may be applied as a supportive therapy in patients with HCC and advanced cirrhosis [14]. However, it is not clear whether splenectomy can improve the overall outcome and survival of such patients. Furthermore, major life-threatening complications in such patients include overwhelming post-splenectomy infection associated with a high mortality rate and a high incidence of portal thrombosis [15,16]. Hence, the debate continues as to whether splenectomy worsens or improves patient outcomes.

The aim of the present study was to investigate the long-term outcome of splenectomy on survival in patients with HCC and advanced stage liver cirrhosis. We retrospectively analyzed the clinical results of 46 cirrhotic patients with Child-Pugh class B or C who had difficulties with therapies for HCC due to thrombocytopenia.

SUBJECTS AND METHODS

Subjects

Subjects included 46 patients diagnosed with advanced liver cirrhosis and HCC who underwent splenectomy as a supportive therapy for the treatment of HCC or IFN therapy after anticancer therapy at Kurume University between January 1999 and December 2009. Patients with Child-Pugh class A were excluded from this study. The background characteristics of patients and tumor-related factors are shown in Table 1 (males/females: 31/15, mean age: 62 years, HCV/HBV/both/unknown: 36/7/1/2, Child-Pugh class B/C: 44/2, Child-Pugh score 7-11). HCC tumor stage (I/II/III/IV) evaluated preoperatively according to the American Joint Committee on Cancer (AJCC) classification was 11/20/8/7, respectively [17]. The indications for splenectomy were: difficulties with therapies for HCC due to thrombocytopenia (n=30), difficulties with thera-

| TABLE 1. Background characteristics and tumor-related factors in the patients of this study. |
|-------------------------------------------------|-------------------------------------------------|
| Background characteristics | Age (years) | 62±7 |
| Gender (male/female) | Gender (male/female) | 31/15 |
| Etiology of cirrhosis (HCV/HBV/both/unknown) | 36/7/1/2 |
| Child-Pugh class (B/C) | 44/2 |
| Albumin (g/dL) | 2.9±0.4 |
| Total bilirubin (mg/dL) | 1.7±0.6 |
| Prothrombin time (%) | 66±9 |
| Platelet count (×10³/μL) | 38±14 |
| MELD score | |
| <10 | 3 |
| ≥10 to <20 | 42 |
| ≥20 | 1 |
| Esophagogastric varices (yes/no) | 40/6 |
| Spleen weight (g) | 714±336 |
| Tumor-related factors | |
| Maximum tumor size (mm) | 23±8 |
| Number of tumors (single/multiple) | 30/16 |
| Macroscopic vascular invasion (yes/no) | 4/42 |
| Tumor stage (I/II/III/IV) | 11/20/8/7 |
| Milan criteria (yes/no) | 36/10 |
| Previous treatment for HCC (yes/no) | 34/12 |

Data are mean±Standard Deviation or the number of patients.

HBV, hepatitis B surface antigen positive; HCV, hepatitis C virus antibody positive; HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease.
pies for HCC and the subsequent induction of IFN therapy due to thrombocytopenia (n=16). IFN therapy was scheduled in patients with controllable HCC. There were no significant differences in background characteristics or tumor-related factors between patients with IFN therapy and those without (data not shown). The median follow-up period after splenectomy was 4.3 years (range: 0.03-8.0 years).

In addition to cirrhosis and HCC, all patients were diagnosed with hypersplenism, which was defined by splenomegaly with thrombocytopenia (platelet count <80×10^3/μL) and/or leukopenia (leukocyte count <3.5×10^3/μL). The diagnosis of HCC was based on dynamic enhanced computed tomography (CT) or magnetic resonance imaging (MRI) using gadoxetic acid disodium. Liver cirrhosis was diagnosed histopathologically by examination of intraoperative liver biopsy or resected liver tissue, in addition to various clinical findings, such as esophagogastric varices and ultrasonographic findings. Gastroduodenal endoscopy was conducted routinely before surgery. Esophagogastric varices were identified in 40 patients (87%), and the red-colored sign was positive in 9 patients (20%). Endoscopic sclerotherapy or ligation was carried out before surgery in patients with esophageal varices risk factors such as the presence of the red-colored sign. All patients with advanced liver cirrhosis who had difficulties with the HCC treatment were candidates for liver transplantation. Thirty-six patients met the Milan criteria in this study; however, the chance for such transplantation was minimal because of the lack of potential donors. This study was performed following the guidelines of our Institutional Review Board, and all patients provided written informed consent.

Treatment and timing of HCC

The treatment and timing of HCC was determined according to liver function and tumor-related factors such as tumor size and number. Simultaneous treatment for HCC was provided for patients who expected to undergo hepatectomy or RFA with splenectomy at the same time. On the other hand, secondary treatment for HCC was provided for patients with insufficient hepatic function reserve who were unable to undergo simultaneous treatment for HCC. RFA was performed in patients with a single tumor or a few tumors measuring less than 20 mm in diameter. A combination of TACE and RFA was used in patients in whom the main HCC tumor measured more than 20, but less than 30 mm in diameter, and TACE or HAIC was performed in patients with multiple HCCs. We used TACE as treatment for the main tumor prior to splenectomy to prevent the growth of the main tumor in patients with a vascular tumor stain of more than 30 mm.

Measurement of portal vein pressure

A catheter was inserted in 25 of the 37 patients who underwent open splenectomy through the ileocolic vein to the portal vein and portal vein pressure (PVP) was measured at the main portal trunk before and after splenectomy.

Liver function tests

Liver function tests such as total bilirubin, albumin, and platelet count were examined before splenectomy and 1, 6, 12, 24, and 36 months after splenectomy. Prothrombin time and the Child-Pugh score were assessed at 12, 24, and 36 months in patients who were not given warfarin potassium to prevent postoperative portal thrombosis.

Complications after splenectomy

Postoperative complications were investigated. To prevent portal thrombosis after splenectomy, prophylactic anticoagulation therapy using warfarin potassium was started from January 2003, although such prophylactic treatment was not used between 1999 and 2002. The protocol for prophylactic anticoagulation therapy was modified after October 2005, and danaparoid sodium (a specific anticoagulant for factor X) was used at 2500 units/day for 7 days from the first few days after surgery, followed by warfarin potassium until 3-6 months after surgery.

Statistical analysis

Data were expressed as mean±Standard Deviation. Differences between the mean portal vein pressure at laparotomy and after splenectomy were tested by the paired t test. The paired t test was used to compare the mean of each liver function test at each post examination time point and before splenectomy. Survival rates were estimated by the Kaplan-Meier method. Survival rates for IFN- sustained viral response (SVR), IFN- no responder (NR), and non-IFN were compared by the multivariate adjusted Cox proportional hazards model using landmark analysis. An 18-month landmark was chosen at which point the response had been determined for most patients, such as SVR or NR after IFN therapy. Candidates for confounding factors were considered as follows: age (<60, ≥60 years), gender (male/female), platelet count (≥40×10^3, <40×10^3/μL), Child-Pugh score (<9, ≥9), MELD (≤13, ≥13 mm), number of tumors (single/multiple), maximum tumor size (<20, ≥20 mm), macrovascular invasion (absent/
RESULTS

Effect of splenectomy on survival rate

Overall survival rates 1, 3 and 5 years after splenectomy were 93.5%, 76.0%, and 37.9%, respectively (Fig. 1). Survival rates in patients without IFN therapy were 90.0, 63.3, 18.9% at 1, 3 and 5 years, respectively. Twenty-one patients died of cancer progression, 6 of liver failure, and 1 of biliary bleeding after RFA. Two patients with Child-Pugh class C continued anticancer therapy for more than two years for HCC recurrence after surgery. However, they died within 3 years.

Treatment modality for HCC with splenectomy

The surgical procedure used for splenectomy was conventional open splenectomy in 36 patients, hand-assisted laparoscopic splenectomy in 9 patients, and Hassab’s operation in 1 patient with refractory gastric varices. All patients received simultaneous or secondary treatment for HCC. Simultaneous treatment for HCC with splenectomy was provided in 20 patients, including partial hepatectomy in 1 patient and RFA in 19 patients. Secondary treatment for HCC was provided in 26 patients; TACE was performed in 6 patients before splenectomy, RFA in 15 patients, TACE in 1 patient, and HAIC in 4 patients after splenectomy. HCC recurrence after treatment occurred in 42 patients (91.3%). Forty patients were treated by RFA (n=23), HAIC (n=6), TACE (n=10), and partial lung resection for metastatic lung tumor (n=1), which was followed by improvements in liver function tests and significant increases in platelet counts, although two other patients with an aggravation in the hepatic function reserve or cerebral hemorrhage were not treated. HCC recurrence occurred repeatedly after that and was treated in a similar manner. The mean frequency of treatment for HCC recurrence was 3.0 times (range: 1-11). Three of the patients with uncontrolled HCC recurrence underwent living-donor liver transplantation. Treatment progress of 3 patients who received living-donor liver transplantation was shown in Table 2.

IFN therapy after HCC treatment and splenectomy

Among the 16 patients scheduled for IFN therapy after surgery, treatment was completed in 13 patients

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TABLE 2.

<table>
<thead>
<tr>
<th>Age</th>
<th>HCC stage</th>
<th>Child-pugh class at the time of splenectomy</th>
<th>Treatment modality for HCC recurrence</th>
<th>HCC tumor status at the time of transplantation</th>
<th>period from splenectomy to LDLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>65y</td>
<td>stage II</td>
<td>B (8)</td>
<td>RFA, RFA</td>
<td>S2/3: 28mm, S6: 9mm</td>
<td>31 months</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td>C (10)</td>
<td></td>
</tr>
<tr>
<td>59y</td>
<td>stage II</td>
<td>B (8)</td>
<td>TACE, TACE</td>
<td>S4: 20mm, S8: 15mm, S8: 10mm</td>
<td>36 months</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td>C (11)</td>
<td></td>
</tr>
<tr>
<td>67y</td>
<td>stage II</td>
<td>B (7)</td>
<td>RFA, RFA</td>
<td>S7: 17mm, S7: 10mm, S7: 13mm, S4: 15mm</td>
<td>14 months</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td>B (7)</td>
<td></td>
</tr>
</tbody>
</table>

LDLT, living donor liver transplantation, HCC, hepatocellular carcinoma, RFA, radiofrequency ablation, TACE, transcatheter hepatic arterial chemoembolization.
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(81.3%), while it was interrupted in 3 patients due to HCC recurrence or discomfort. Of the 13 patients receiving the full course of IFN therapy, including 7 patients treated with peginterferon plus ribavirin therapy, 7 patients achieved SVR after IFN therapy, while 6 were considered to be NR. HCC recurrence occurred in 5 out of 7 patients with SVR, and 5 out of the 6 NR. There was no significant difference in rate of HCC recurrence between patients with SVR and NR.

**Multivariate analysis for survival after splenectomy**

By the univariate Cox proportional hazards model for each candidate of confounding factors, the number of tumors (single/multiple) and Child-Pugh score (≤9, >9) were selected as confounding factors (p<0.20) (data not shown). The multivariate adjusted Cox proportional hazards model using landmark analysis showed SVR after IFN therapy as an independent prognostic factor after splenectomy (Hazard ratio 0.18, 95%CI 0.03-0.65, P=0.006). Survival in patients with SVR was significantly better than that in patients without IFN (Fig. 2).

**Splenectomy reduces PVP**

PVP before splenectomy was 21.2±4.3 mmHg and fell to 16.8±3.8 mmHg immediately after splenectomy. This difference was significant (p<0.01) (Fig. 3).

**Splenectomy improved the platelet count and liver function tests**

Serial measurements showed significant increases in the platelet count 1 month after splenectomy, and these were maintained over the 3-year postoperative period (Fig. 4). Furthermore, splenectomy was followed by significant improvements in total bilirubin at 1 month, which was also maintained for the next 3 years. Serum albumin increased significantly from 1 month to 2 years after surgery. This was also true for prothrombin time from 1 year to 3 years after surgery. The Child-Pugh score was significantly lower 1 year after surgery, and showed similar significant improvements for 3 years.

**Complications after splenectomy**

Postoperative complications including liver failure (n=1), portal thrombosis (n=7), ascites (n=5), and bacterial infections (n=4) (pneumonia: 2 patients, MRSA colitis: 1 patient, urinary tract infection: 1 patient) were observed in 14 patients (30%). Portal thrombosis was treated with anticoagulants according to our protocol. The prevalence of portal thrombosis in patients with no prophylactic anticoagulation, with prophylactic anticoagulation using warfarin potassium, and prophylactic anticoagulation using danaparoid sodium and warfarin potassium were 33.3% (2/6 patients), 16.7% (4/24 patients), and 6.3% (1/16 patients), respectively. Bacterial infections and ascites were successfully controlled.
treated with antibiotics and diuretics, respectively. One patient died of liver failure associated with postoperative bleeding. The patient was scheduled to undergo simultaneous partial resection of the caudate lobe and splenectomy, but treatment for HCC was intraoperatively switched to RFA due to prolonged surgery caused by intra-abdominal adhesions associated with repeated open surgery for recurrent HCC. Accordingly, the mortality rate was 2.2%.

**DISCUSSION**

Liver transplantation is the ultimate treatment for patients with HCC and advanced cirrhosis. However, the chance to undergo liver transplantation is minimal in countries where cadaveric or living donations are limited. Splenectomy may be an alternative option to liver transplantation for these patients. The present study showed that the 1-, 3-, and 5-year overall survival rates after splenectomy in patients with HCC and advanced cirrhosis were 93.5, 76.0, and 37.9%, respectively, while those after living donor liver transplantation for HCC in Japan were 82.6, 72.6, and 68.9%, respectively [9]. These findings are comparable to those of the 3-year survival rate in our study. Thus, splenectomy in these patients achieved an acceptable outcome as assessed by the 3-year survival outcome. The results indicated that splenectomy could be applied as an alternative option in patients with HCC and advanced cirrhosis who have no potential donor.

The survival rates after splenectomy without IFN therapy also achieved a close outcome to that after liver transplantation as assessed by the 3-year survival; however, splenectomy without IFN therapy could not produce long-term survival benefits. Increased drop-out rates have reported for waiting times exceeding 12 months among deceased-donor liver transplantation candidates with HCC [13], and approximately 12

![Fig. 4 Serial changes in liver function tests after splenectomy.](image-url)
months has also been reported as the time for living donor liver transplantation candidates with HCC to decide whether or not to undergo transplantation [18]. A limited time exists because of liver damage or tumor progression. Therefore, splenectomy may be beneficial in extending the waiting time of these candidates, and may also be viewed as a supportive bridging therapy to liver transplantation.

HCC recurrence occurred in 42 patients (91.3%) after surgery in the present study. In comparison, the cumulative recurrence rate after living donor liver transplantation for HCC in Japan was 21.6% at 5 years [9]. Liver transplantation can achieve a better outcome because of the total removal of cancerous lesions and underlying liver disease. This study showed that 40 patients with recurrence after surgery could be treated for HCC with improvements in liver function tests and a significant increase in platelet counts. Splenectomy enabled the continuation of HCC treatment for repeated recurrence even in patients with advanced cirrhosis and thrombocytosis. Further research about the immunological aspects of spleen is required in the cirrhotic patients, because the immunological change against cancer after splenectomy may be unclear.

Peginterferon plus ribavirin therapy is the most effective therapy for the eradication of HCV [19]. However, in cirrhotic patients with low baseline platelet counts, a full course of pegylated IFN plus ribavirin therapy is often not possible due to the development of severe IFN-induced thrombocytopenia. In the present study, a full-course of IFN therapy was administered to 13 patients, including 7 patients on peginterferon plus ribavirin therapy, with 7 patients achieving SVR among the 16 patients scheduled for IFN therapy. Our study showed that splenectomy allowed cirrhotic patients with HCC and thrombocytopenia to receive full-dose IFN therapy after anticancer therapy. SVR in IFN therapy has been reported to suppress recurrence after local curative treatment for HCC [20]. However, no significant difference in HCC recurrence between patients with SVR and those with NR was observed in this study. Most of HCC recurrence occurred within two years after IFN therapy. HCC recurrence in the long term might be suppressed. Multivariate analysis for survival after splenectomy identified SVR after IFN therapy as an independent prognostic factor. The 5-year survival of patients with SVR was comparable with that of patients undergoing living donor liver transplantation. Patients who did not achieve SVR or those in whom IFN therapy could not be started after surgery require liver transplantation for their long-term survival.

Splenectomy resulted in improvements in liver function such as decreases in total bilirubin, increases in serum albumin and prothrombin time levels, and increases in platelet counts. While similar findings after splenectomy have been reported [5,21], only a few reports have described changes in liver function tests during long-term follow up after splenectomy in patients with HCC and advanced cirrhosis. The causes of these improvements in liver function following splenectomy may be due to the following: a reduction in bilirubin overload by the removal of a huge spleen with damaged red blood cells [5], the removal of spleen-derived inhibitors of liver regeneration, such as transforming growth factor-β1 [22], and the enhanced production of promoters for liver regeneration, such as platelet-derived serotonin [23]. It is also possible that the beneficial effects observed in the liver because of splenectomy may be due to IFN therapy. We previously reported a significant increase in liver volume following improvements in the Child-Pugh score 1 year after splenectomy in cirrhotic patients without postoperative IFN therapy [8]. These results suggest that splenectomy may accelerate liver regeneration in cirrhotic patients. The MELD score was shown to be significantly improved in patients with HCV and decompensated cirrhosis who achieved SVR after IFN therapy [19]. Therefore, not only splenectomy, but also SVR after IFN therapy has been suggested to contribute to long-term improvements in liver function.

Successful living-donor liver transplantation requires the modulation of PVP, since the maintenance of PVP after reperfusion below 20 mmHg has been reported to ensure liver graft function and improve patient survival [7]. The present study also showed a significant decrease in PVP to less than 20 mmHg after splenectomy, and such a reduction was one of the causes for the improvements observed in liver function after splenectomy. Other studies have demonstrated improved refractory varices and portal hypertensive gastropathy after splenectomy [24,25]. Splenectomy could also control portal hypertension, leading to improvements in refractory esophagogastric varices and severe portal hypertensive gastropathy, which may interfere with the treatment for HCC.

Portal thrombosis and bacterial infection are serious complications of splenectomy. The reported prevalence of portal thrombosis ranges from 2% to 29% in cirrhotic patients [15,26]. In the present study, 7 patients (15.2%) developed portal thrombosis. Our protocol using warfarin potassium and danaparoid sodium reduced the incidence of portal vein thrombosis to 6.3%, and was thus considered to be an effective prophylactic...
tic anticoagulation therapy for the prevention of portal thrombosis after splenectomy. The prevalence of bacterial infection during the natural history of decompensated cirrhosis was reported to be associated with advanced liver fibrosis [27]. It is suggested that splenectomy in a compromised cirrhotic host increases the risk of systemic bacterial infection. None of the patients in the present study developed fulminant infection such as overwhelming postsplenectomy infection. As a strategy for the prevention of bacterial infection, we routinely provided a pneumococcal conjugate vaccination and education about asplenic status before or after splenectomy. One patient with postoperative liver failure was scheduled to undergo simultaneous partial resection of the caudate lobe and splenectomy; however, treatment for HCC was intraoperatively switched to RFA due to prolonged surgery caused by intra-abdominal adhesions associated with repeated open surgery for recurrent HCC. Simultaneous treatment for HCC should be limited to patients who can be treated for HCC within a reasonable time.

In conclusion, splenectomy in patients with HCC and advanced liver cirrhosis can be a feasible and advantageous supportive therapy to allow the continuation of HCC treatments and the completion of IFN therapy after anticancer therapy, based on improvements in liver function and thrombocytopenia with minimum complications. Obtaining SVR after a full course of IFN therapy in patients undergoing splenectomy and anticancer therapy should improve outcomes. Splenectomy is another option for patients with no potential donor, and it may be beneficial in extending their waiting time for transplantation. Future randomized controlled prospective studies are required to confirm these findings.

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