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Retrospective Study

Oncologic outcomes in hepatocellular carcinoma patients after liver transplantation with simultaneous splenectomy

Risk of cancer development status post liver transplantation with simultaneous splenectomy

Hsiu-Lung Fan, Chung-Bao Hsieh, Shih-Ming Kuo, Teng-Wei Chen

Abstract

BACKGROUND

Splenectomy has previously been found to increase the risk of cancer development, including lung, non-melanoma skin cancer, leukemia, lymphoma, Hodgkin's lymphoma, and ovarian cancer. The risk of cancer development in liver transplantation with simultaneous splenectomy remains unclear.

AIM

To compare HCC recurrence and de novo malignancy between hepatocellular carcinoma patients undergoing liver transplantation with and without simultaneous splenectomy.

METHODS

We retrospectively analyzed the outcomes of 120 patients with hepatocellular carcinoma within the University of California San Francisco criteria who received liver transplantation with (n = 35) and without (n = 85) simultaneous splenectomy in the Tri-Service General Hospital. Univariate and multivariate Cox regression analyses for cancer-free survival and mortality were established. The comparison of the group survival status and group cancer-free status was done by generating Kaplan-Meier survival curves and log-rank tests.

RESULTS

The splenectomy group had more hepatitis C virus infection, lower platelet count, higher alpha fetoprotein level, and longer operative time. Splenectomy and age were both positive independent factors for prediction of cancer development. (Hazard ratio: 2.560 and 1.057, respectively, $P < 0.05$). Splenectomy and hypertension were positive independent factors for prediction of mortality. (Hazard ratio: 2.791 and 2.813 respectively, $P< 0.05$). The splenectomy group had a significantly worse cancer-free

survival (CFS) and overall survival (OS) curve compared to the non-splenectomy group (5-year CFS rates: 53.4% vs. 76.5%, *P* = 0.003; 5-year OS rate: 68.1 vs. 89.3, *P* = 0.002).

CONCLUSION

Our study suggests that simultaneous splenectomy should be avoided as much as possible in HCC patients who have undergone liver transplantation.

Key Words: Hepatocellular carcinoma; Liver transplantation; Splenectomy; de novo malignancy; Age; Hypertension

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Core Tip: This retrospective study compared the outcomes of HCC recurrence and de novo malignancy development between HCC patients who underwent liver transplantation (LT) with and without simultaneous splenectomy. Splenectomy leads to a significantly higher risk of cancer development after LT and is a significant risk factor of mortality. Simultaneous splenectomy should be avoided as much as possible.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in men and the ninth most common in women worldwide[1]. Liver transplantation (LT) is one of the potential curative therapies, according to the Barcelona-Clinic Liver Cancer staging classification and treatment schedule[2]. The incidence of recurrent HCC after LT was found to be approximately 7%-25%[3]. Various pre-, intra-, and postoperative factors influence the outcomes and disease-free survival in patients with HCC after LT[4,5].

The indications for splenectomy are generally divided into traumatic and non-traumatic reasons[6]. Two early papers found an increased risk of cancer after splenectomy,

especially in patients with non-traumatic splenectomy[6,7]. The most common post-splenectomy malignancies include lung, non-melanoma skin cancer, leukemia, lymphoma, Hodgkin's lymphoma, and ovarian cancer[6,7]. A nationwide population-based cohort study published in 2015 revealed that patients undergoing splenectomy were 1.94 times more likely to develop cancer than patients not undergoing splenectomy[8].

There are a number of indications for simultaneous splenectomy in LT recipients, including the prevention of small-for-size syndrome, ABO-incompatible LT (ABO-i LT), or the prevention of thrombocytopenia during therapy for HCV after LT[9-12]. The purpose of this study was to compare the outcomes of HCC recurrence and de novo malignancy development between HCC patients who underwent LT with and without simultaneous splenectomy.

MATERIALS AND METHODS

Patients

Between May 2009 and August 2019, 179 patients with HCC underwent LT and received follow-up management. All patients with HCC met the University of California San Francisco (UCSF) criteria for radiological examinations (a single tumor with a size of 6.5 cm; a maximum of three tumors with none of them having a size of >4.5 cm; and a cumulative tumor size of <8 cm). The records of these patients were retrospectively reviewed. Fifty-nine patients who had no residual HCCs or who had HCCs without fitting the UCSF criteria on pathologic examinations were excluded. Thirty-five of the 120 LT recipients (35/120, 29.2%) underwent simultaneous splenectomy and were assigned to the splenectomy group. The remaining LT recipients (85/120, 70.8%) did not undergo simultaneous splenectomy and were, thus, assigned to the non-splenectomy group. The indications for simultaneous splenectomy in our institution include modulation of portal inflow, thrombocytopenia in recipients with HCV, or ABO-incompatible LT recipients. The reasons for simultaneous splenectomy in the 53 recipients were modulation (22/53, 41.5%), thrombocytopenia in recipients with

HCV (25/53, 47.2%), and ABO-incompatibility LT (6/53, 11.3%). We recorded the recipient characteristics, including age, sex, underlying liver disease, signs of portal hypertension (ascites, hepatic encephalopathy, bleeding varices), preoperative serum biochemistry results (levels of total bilirubin, creatinine, ammonia, albumin, and glucose), international normalized ratio, blood platelet count, Model for End-stage Liver Disease score (MELD score), alpha fetoprotein (AFP), operative factors (surgery types in deceased donor LT including split liver, living donor LT, graft weight, graft *vs* recipient weight ratio (GRWR), blood loss, and operative time), and pathological results (tumor size, tumor number, tumor necrosis, and lympho-vascular invasion). Neutrophil-Lymphocyte ratio (NLR) was calculated by dividing neutrophil count by lymphocyte count. Platelet-lymphocyte ratio (PLR) was calculated by dividing platelet count by lymphocyte count.

Post-LT follow-up

Post-surgical follow-up evaluations included monitoring of AFP levels and performing abdominal sonography, CT, or magnetic resonance imaging every 3 mo and chest radiography yearly. Brain CT was performed in patients with worsening headaches or neurologic symptoms, and whole-body bone scans were performed in patients with severe bone pain. Positron emission tomography was performed if the AFP levels were elevated, even if the other above-mentioned examinations showed normal findings. Annual chest radiography and stool examination for occult blood were performed to screen for de novo lung cancer and gastrointestinal tract malignancy, respectively. Chest CT or lung biopsy was performed if lung nodules were found by chest radiography. Esophagogastroduodenoscopy and colonoscopy were performed if occult blood was detected in the stool. In female participants, annual breast sonography was performed to monitor for de novo breast cancer. The time and site of tumor recurrence and patient death were established through follow-up studies. The present study was approved by the institutional review board of Tri-Service General Hospital (IRB No. 2-108-05-127), and informed consent was not required according to the guidance of the institutional review board because this was a retrospective study.

Statistical analysis

Continuous variables were represented as a median with the corresponding range and comparisons between subgroups were performed using the Mann-Whitney U test. Categorical variables were expressed as the number (percent) and assessed by Fisher's exact test following Bonferroni correction for comparisons between subgroups. To determine the variables associated with recurrence or death, univariate and multivariate Cox proportional hazard models were established. All factors with a P-value < 0.1 in the univariate analysis were entered into a reverse multivariate hazard model. The duration of cancer-free survival (CFS) was calculated from the date of surgery to the date of HCC recurrence, HCC distant metastases, secondary malignancy, or the date of death for patients who died before the end of follow-up. The overall survival (OS) duration was defined as the period between the date of surgery and the date of death. Kaplan-Meier survival curves were generated, and a log-rank test was performed to compare the group survival status. All 2-sided statistical analyses were performed using SPSS 15.0 statistical software, version 15.0 (SPSS Inc, Chicago, IL). Significance was defined as $P<0.05$.

RESULTS

Patients' characteristics

A total of 120 HCC patients (89 men and 31 women) with a median age of 57 (37-69) years were included in the analyses. Eighty-five patients did not undergo simultaneous splenectomy, whereas 35 (29.2%) patients did. The average follow-up duration was 55 mo (range 0–128 mo). Patients' characteristics are summarized in Table 1. Age, gender, BMI, signs of portal hypertension (ascites, hepatic encephalopathy, and varices bleeding), comorbidities (hypertension and diabetes mellitus), pre-operative serum tests (white blood count, total bilirubin, creatinine, ammonia, albumin, glucose, INR, and MELD scores), surgical factors (surgical type, graft type, GRWR, and bleeding), and pathology (tumor size, tumor number, tumor necrosis, and lympho-vascular invasion)

were not significantly different between these two groups (all P>0.05), indicating that the groups has a similar baseline. Nevertheless, patients who underwent simultaneous splenectomy had a lower HBV infection rate (40% *vs* 77.6%, P<0.001), higher HCV infection rate (65.7% *vs* 25.9%, P<0.001), lower platelet count (P<0.003), higher AFP level (P = 0.012), and longer operative time (P = 0.001) than patients who did not undergo simultaneous splenectomy.

Outcomes

Upon completion of the analysis, the splenectomy group was found to have a higher proportion of HCC recurrence (42.9% *vs* 18.8%, P = 0.011) and mortality (31.4% *vs* 10.6%, P = 0.013) compared with that in the non-splenectomy group (Table 1). Five of the 85 patients (6.4%) in non-splenectomy group had de novo cancer development. Of 5 patients with de novo cancer development, 1 had lung cancer, 1 had urothelial carcinoma, 1 had squamous cell carcinoma of the tongue, 1 had breast cancer, and 1 had adenocarcinoma of the esophagus. In the splenectomy group, no de novo cancer development was found. However, the length of hospital stay was not significantly between these two groups (P>0.05, Table 1).

Subsequently, the Cox regression model was used to investigate cancer development and mortality, as shown in Table 2 and Table 3. In the univariate Cox regression analysis, splenectomy, age, and HBV were significantly associated with cancer development (all P<0.05, Table 2), while splenectomy, HBV, HCV, and hypertension were associated with mortality (all P <0.05, Table 3). In the multivariate Cox regression analysis, splenectomy (hazard ratio [HR]= 2.560; 95% confidence interval [CI]: (1.198-5.471), and age (HR=1.057, 95%CI: 1.001-1.117, P = 0.015) were positive independent factors for prediction of cancer development (Table 2), while splenectomy (HR=2.791, 95%CI: 1.081-7.206, P = 0.034), hypertension (HR=2.813, 95%CI: 1.111-7.123, P = 0.029), and HBV (HR=4.077, 95%CI: 1.001-16.615, P = 0.050) were positive independent factors for prediction of mortality (Table 3). In addition, Kaplan-Meier curve analyses revealed that splenectomy could identify subjects at higher risk for cancer development or mortality (all P<0.05, Figure 1 and Figure 2). The cumulative cancer-free survival (5-

year CFS rates: 76.5% in non-splenectomy group; 53.4% in splenectomy group) and cumulative OS rates (5-year OS rate: 89.3% in the non-splenectomy group; 68.1% in the splenectomy group) differed significantly between the two groups.

DISCUSSION

The present study analyzed the outcomes of patients with HCC within the UCSF criteria who underwent LT with and without simultaneous splenectomy. In the past, simultaneous splenectomy was performed in cases of ABO-incompatible living donor liver transplantation (ABO-i LDLT) because of immunological concerns, or in patients with HCV for prevention of thrombocytopenia. In recent years, simultaneous splenectomy is performed less due to the advancement of the desensitization protocol in ABO-i LT and the development of direct-acting antiviral agents as anti-HCV therapy. However, inflow modulation was still necessary in many living-donor liver transplantation (LDLT) patients. The topic of simultaneous splenectomy still deserves attention. In our cohort, simultaneous splenectomy was independently correlated with cancer development and overall survival, suggesting that simultaneous splenectomy should be a factor for concern in patients with HCC who undergo LT.

The increased cancer risk associated with splenectomy was reported in previous clinical studies and in a nationwide Taiwanese population-based cohort study[6-8]. In the Taiwanese study, the hazard ratio was 2.06 in the splenectomy cohort[8]. Cancer risk was higher in cases of non-traumatic splenectomy than in traumatic splenectomy, especially in splenectomy cases caused by hematologic conditions[6,8]. Splenectomy significantly increases the risk of all malignant neoplasms, especially those of the lung, non-melanoma skin cancer, leukemia, lymphoma, and Hodgkin's lymphoma[6]. A study published by Linet *et al* revealed a higher incidence of lung and ovarian cancers in patients who underwent splenectomy[7]. Buccal, esophagus, liver, colon, pancreas, lung, prostate, and multiple hematologic malignancies were observed in a cohort of cancer-free American veterans after splenectomy[13]. The previously mentioned Taiwanese study found that the most common cancers after a splenectomy were those of the

gastrointestinal tract, head and neck and liver, as well as hematological malignancies[8]. The relationship between splenectomy and cancer has also been proven in animal experiments[14-17]. An early experiment inferred that the ability of the spleen to protect a rat from cancer is due to the preservation of immunologic surveillance and not due to the DNA repair mechanism[14]. Splenectomy enhances metastatic ability through the immunological tolerance of regulatory T-cells[15]. Splenectomy was also found to enhance tumor growth and peritoneal seeding in an orthotopic syngeneic murine pancreatic cancer mouse model, which is explained by its immunological effects[16,17].

To the best of our knowledge, there are no studies discussing the oncological effects of simultaneous splenectomy in LT. Therefore, we reviewed the oncological effects of simultaneous splenectomy and hepatectomy in patients with HCC to gain a greater understanding of this relationship. Some studies have found that the results of hepatectomy with simultaneous splenectomy in HCC patients with hypersplenism were positive. Chen *et al* showed that the 5-year disease-free survival (DFS) rate was significantly higher in patients with HCC who underwent hepatectomy and splenectomy than in those who underwent hepatectomy alone (37% *vs* 27.3%; P = 0.003)[18]. Zhang *et al* also found that HCC patients with hypersplenism who underwent hepatectomy and simultaneous splenectomy exhibited significantly better DFS and OS rates than those who underwent hepatectomy alone[19-21]. It seems, therefore, that splenectomy benefits surgical management in selected cases of HCC. The role of splenectomy in improving oncologic outcomes has also been reported in animal studies[22,23]. Spleen cells release tumor-enhancing factors that promote tumor growth activity in vivo[22], and the spleen may also evoke a complex vascular response[23], which suggests that splenectomy could inhibit tumor growth. Besides inhibiting tumor growth, simultaneous splenectomy has been reported to decrease tumor metastasis[24]. However, some papers have put forth opposing views, suggesting that simultaneous splenectomy and hepatectomy did not benefit OS and DFS rates, in comparison to hepatectomy alone[25,26]. The oncological benefits of simultaneous splenectomy in patients with liver cirrhosis are, therefore, still controversial.

The relationship between cancer risk after splenectomy and LT gained little attention in previous clinical studies. Ito *et al* pointed out that simultaneous splenectomy was associated with re-operation due to postoperative hemorrhage, prolonged operative time, increased intra-operative blood loss, and increased incidence of lethal infectious disease[27]. A meta-analysis found that simultaneous splenectomy during LT was associated with prolonged operative time, increased intra-operative blood loss, increased need for intra-operative blood transfusions, and increased incidence of postoperative hemorrhage, thrombosis, infection, and mortality[28]. Another study revealed that splenectomy significantly increases the rates of postoperative splenic vein thrombosis and cytomegalovirus infection in LDLT[29]. These three studies suggest that splenectomy has a number of short-term risks and should be performed only in carefully selected patients. Our study shed light on the increased long-term cancer risk after LT, which was associated with simultaneous splenectomy. In brief, liver transplantation with simultaneous splenectomy should be avoided as much as possible, whether in the short or long term.

The role of age in the oncological outcomes of HCC after LT is still uncertain. There are reports demonstrating that younger patients tend to have more aggressive tumors and a higher risk of recurrence than older patients[30,31]. In the present study, old age was associated with poor outcomes in patients with HCC after LT. A possible explanation is that older patients have been exposed to HBV and HCV infections for a longer period.

Hypertension is the most common cardiovascular complication to occur after LT, with a prevalence reported to be between 40%[32] and 85%[33]. The mechanisms are multi-factorial, and hypertension is one of the main risk factors leading to post-transplant mortality[34]. An early diagnosis of hypertension, as well as implementation of lifestyle changes and antihypertensive medications is essential for increasing the long-term survival of LT patients[35].

The limitations of this study were the patient selection methods and the relatively small sample size. Because of surgical indications for simultaneous splenectomy, more HCV patients underwent simultaneous splenectomy. There may be biases in terms of patient selection. Nevertheless, this study only analyzed patients with HCCs within the UCSF criteria and that were confirmed by both radiologic and post-operative pathologic examinations. The study did not analyze patients who primarily had HCCs outside the UCSF criteria and had successfully treated HCCs to fit the USCF criteria upon radiologic examination on the day of LT. The reason for this was that the percentage of tumor necrosis would make it difficult for pathologic examination to accurately determine whether patients complied with the UCSF criteria or not. Besides, splenic artery ligation is often considered, instead of splenectomy, for achieving the goal of modulation of portal inflow[36]. The effects of splenic artery ligation, compared to splenectomy, were not discussed in this study.

CONCLUSION

Our study revealed that the patients with HCC who met the UCSF criteria and who underwent LT and simultaneous splenectomy had poorer DFS and OS than patients who did not undergo simultaneous splenectomy. Therefore, simultaneous splenectomy should be avoided in patients with HCC undergoing LT.

ARTICLE HIGHLIGHTS

Research background

Patients undergoing splenectomy were more likely to develop cancer than patients not undergoing splenectomy

There are a number of indications for simultaneous splenectomy in liver transplantation (LT) recipients

Research motivation

The hypothesis is that simultaneous splenectomy has bad outcomes on cancer and mortality in LT recipients.

Research objectives

The purpose of this study was to compare the outcomes of HCC recurrence and de novo malignancy development between HCC patients who underwent LT with and without simultaneous splenectomy.

Research methods

120 patients with hepatocellular carcinoma who received liver transplantation with (n = 35) and without (n = 85) simultaneous splenectomy were analyzed by Cox regression analysis, Kaplan-Meier survival curves and log-rank tests.

Research results

Splenectomy and age were both positive independent factors for prediction of cancer development.

Splenectomy and hypertension were positive independent factors for prediction of mortality.

The splenectomy group had a significantly worse cancer-free survival and overall survival curve compared to the non-splenectomy group

Research conclusions

Simultaneous splenectomy should be avoided in patients with HCC undergoing LT.

Research perspectives

Splenic artery ligation is often considered, instead of splenectomy, for achieving the goal of modulation of portal inflow. The direction of the future research is the comparison on cancer outcome between splenectomy and splenic artery ligation.

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