Research Article

JOURNAL OF HEPATOLOGY

Perioperative blood transfusion does not influence recurrence-free and overall survivals after curative resection for hepatocellular carcinoma
A Propensity Score Matching Analysis

Tian Yang[1,2], Jun-Hua Lu[1], Wan Yee Lau[1,3], Tian-Yi Zhang[4], Han Zhang[1], Yi-Nan Shen[1], Kutaiba Alshebeeb[2], Meng-Chao Wu[1], Myron Schwartz[2,*], Feng Shen[1,*]

[1]*Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China;* [2]*Liver Cancer Program, Recanati/Miller Transplantation Institute, Icahn School of Medicine at Mount Sinai, New York 10029, NY, USA;* [3]*Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong Special Administrative Region;* [4]*Department of Health Statistics, Second Military Medical University, Shanghai, China*

Background & Aims: Whether perioperative blood transfusions (PBTs) negatively impact oncologic outcomes after curative resection for HCC remains controversial.

We aimed to identify the independent predictive factors of PBT for curative resection of hepatocellular carcinoma (HCC), and to investigate the impact of PBT on long-term recurrence and survivals after resection.

Methods: Of 1103 patients who underwent curative liver resection for HCC between 1999 and 2010, 285 (25.8%) patients received PBT. Univariable and multivariable regression analyses were used to identify independent predictive factors of PBT. Propensity scores and Cox regression analyses were used to compare the overall survival (OS) and recurrence-free survival (RFS) between patients who did and did not receive PBT.

Results: Multivariable regression analysis revealed that performance status, preoperative hemoglobin, cirrhosis, portal hypertension, tumor rupture, tumor size, macroscopic vascular invasion, and intraoperative blood loss were independent predictive factors of PBT for HCC resection. Propensity score matching analysis created 234 pairs of patients. Before propensity matching, PBT was significantly associated with increased risks of OS (HR: 2.455, 95% CI: 2.077–2.901, p <0.001) and RFS (HR: 2.018, 95% CI: 1.718–2.370, p <0.001) in the entire cohort. After propensity matching, PBT was not significantly associated with increased risks of OS (HR: 1.229, 95% CI: 0.988–1.527, p = 0.063) and RFS (HR: 1.188, 95% CI: 0.960–1.469, p = 0.113). After adjustment for other prognostic variables in the propensity matched cohort, PBT was still found not to be associated with OS and RFS after HCC resection.

Conclusions: The present study identified that PBT did not influence RFS and OS after curative resection of HCC.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor and the second leading cause of cancer-related death worldwide [1]. It is particularly prevalent in Southeast Asia and Africa. The incidence and mortality of HCC is also on the rise in the United States [2]. With appropriate patient selection, surgical resection is currently the primary treatment of choice for HCC [3,4]. During the past few decades, hepatic surgeons have focused on improving surgical techniques and perioperative management for patients undergoing liver resection for HCC, resulting in greatly improved perioperative outcomes. Operative mortality rates are now less than 5%, and they can even be 0% in some experienced centers [5–7]. Unfortunately, long-term prognosis, especially tumor recurrence after curative resection of HCC, remains unsatisfactory [3,4].

Previous studies have shown clinicopathologic factors which are associated with long-term recurrence or survival after curative resection of HCC and include: performance status as defined by the Eastern Cooperative Oncology Group (ECOG), hepatitis virus infection status, Child-Pugh score, underlying liver disease,

Keywords: Hepatocellular carcinoma; Hepatectomy; Perioperative blood transfusion; Overall survival; Recurrence-free survival.

Received 24 December 2014; received in revised form 12 October 2015; accepted 13 October 2015; available online 24 October 2015

* Corresponding authors. Addresses: Liver Cancer Program, Recanati/Miller Transplantation Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1104, New York 10029, NY, USA (M. Schwartz) or Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai 20438, China (F. Shen).

E-mail addresses: myron.schwartz@mountsinai.org (M. Schwartz), shenfengdfgd@163.com (F. Shen).

Abbreviations: PBT, Perioperative blood transfusion; HCC, Hepatocellular carcinoma; OS, Overall survival; DFS, Disease-free survival; HR, Hazard ratio; 95% CI, 95 percent confidence interval; ECOG, Eastern Cooperative Oncology Group; AFP, Alpha-fetoprotein; US, Ultrasonography; CT, Computed tomography; MRI, Magnetic resonance imaging; TACE, Transcatheter arterial chemoembolization; ASA, American Society of Anesthesiologists; AST, Aspartate aminotransferase; HBsAg, Hepatitis B surface antigen; HCV, Hepatitis C virus.

Cancer

portal hypertension, tumor size, tumor number, macroscopic and microscopic vascular invasion, preoperative alpha-fetoprotein (AFP) level, and resection margin [5,8–12]. Many studies have reported on the negative effects of perioperative blood transfusion (PBT) on oncologic outcomes after curative resection of HCC [10–19]. One recent meta-analysis which enrolled 5635 patients from 22 studies demonstrated that PBT was associated with adverse clinical outcomes after resection for HCC patients, which included increased death, tumor recurrence and complication rates. The authors, therefore, concluded that PBT should not be used if technically possible [20].

Admittedly, it is the primary duty of hepatic surgeons to minimize intraoperative blood loss during liver resection for HCC. However, PBT may become necessary for patients with anemia, complicated surgical procedures, or for postoperative hemorrhage. Thus, we hypothesize that worse oncologic outcomes for HCC patients receiving PBT are not necessarily due to PBT itself, but rather due to other liver- or tumor-related poor prognostic factors associated with PBT. In other words, whether the association between PBT and worse oncologic outcomes after HCC resection is causal or coincidental is of key importance.

To address this issue, we conducted a retrospective cohort study to elucidate the relationship between PBT and long-term recurrence and survivals after curative resection of HCC using propensity score matching and multivariable Cox regression analyses.

Patients and methods

Patient selection

1109 consecutive patients underwent curative liver resection for HCC in the 5th Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital of Shanghai, China from January 1999 to December 2010. The diagnoses of HCC were confirmed by postoperative histopathology. Curative liver resection was defined as complete resection of all macroscopic tumors with microscopically clear resection margins in the resected specimen. As this study focused on long-term oncologic outcomes after liver resection, we excluded six patients who died in hospital. Finally, 1103 patients were enrolled into the present study. This study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of the Eastern Hepatobiliary Surgery Hospital of Shanghai, China.

Preoperative evaluation

Preoperative investigations including ultrasonography (US), computed tomography (CT), and/or magnetic resonance imaging (MRI), liver function test, hepatitis B and C serology, AFP and Child-Pugh classification are conducted to evaluate the readiness of patients for surgery. Patients older than 60 years and those with significant co-morbid illnesses routinely underwent full cardiopulmonary assessments. Child-Pugh C grade was considered as an absolute contraindication for resectional surgery. The selection criteria for liver resection for HCC were constant over the study period, and included the location and number of tumors, presence or absence of tumor thrombus and metastatic disease, liver functional reserve and volume of the future liver remnant as reported in our previous studies [21,22]. Portal hypertension was defined by the presence of either esophagogastric varices, or splenomegaly with a platelet count of less than 100×10^9/L, or a hepatic venous pressure gradient of >10 mmHg during the operation.

Surgical procedures

All operations were performed by experienced liver surgeons. The Pringle's maneuver was routinely used, with cycles of clamp/unclamp times of 15/5 min. Transection of hepatic parenchyma was performed using the clamp-crushing technique, and hemostasis was secured on the raw liver surface using sutures and an argon beam coagulator. Major hepatectomy was defined as resection of three or more Couinaud liver segments, and minor hepatectomy as resection of fewer than three segments. Anatomical resections as defined by the Brisbane 2000 nomenclature of liver anatomy and resections [23,24] were preferred for patients with normal liver or mild cirrhosis, but non-anatomical resections (including wedge resection or limited resection) were used for tumors situated at the junction of several liver segments, or in patients with severe cirrhosis.

Postoperative management

Patients were monitored in the intensive care unit on the first postoperative day before transfer to the general ward, the timing of which was dependent on the patient's condition. Broad-spectrum antibiotics were administered intravenously for 3 to 5 days in all patients. Fresh frozen plasma or albumin was given when the patient's plasma albumin level was lower than 30 g/L. Blood tests and serologic liver function tests were performed 1, 3, 5, and 7 days after the operation. All patients received US during the first week of surgery. Parenteral nutrition was started immediately after the operation.

Perioperative blood transfusion

PBT was defined as transfusion of allogeneic whole blood and/or packed erythrocytes either during operation or within 1 week after operation. Blood transfusion during operation was decided according to the amount of intraoperative blood loss, hemodynamical stability, and patient's hemoglobin level during the operation, while blood transfusion within 1 week after the operation was administered to patients whose hemoglobin level was below 7 mg/dl or if the patient was hemodynamically unstable due to postoperative acute intra-abdominal hemorrhage.

Follow-up

All patients were investigated using serum AFP, US or CT, and chest X-ray at 1 month after surgery. The patients were then followed-up at a 2-monthly intervals for the first 6 months and at a 3-monthly intervals thereafter. CT, MRI, angiography, bone scan or positron emission tomography were performed when recurrence or distant metastasis was suspected. Tumor recurrence was defined as new appearance of intra- or extrahepatic tumor nodule, with or without a rise in serum AFP. Patients with tumor recurrence were actively treated with re-resection, transcatheter arterial chemoembolization (TACE), percutaneous ablative therapy, radiotherapy, oral sorafenib (since 2007), or conservative treatment, either alone or in combination. Further treatment decision was based on the pattern of recurrent tumor, residual hepatic functional reserve, and general condition of patient.

Variables and outcomes

The data were prospectively collected and retrospectively reviewed. The database included patient characteristics, operative variables and follow-up information. All data were updated before the patients were discharged from hospital and after each follow-up visit in our outpatient clinic. Patients who failed to attend their follow-up visits were contacted by our research nurse by phone, e-mail and letter. Before December 2006, all the data were entered using "Excel". After January 2007, the data were entered using "Epidata". In this study, tumor satellites were defined as those tumors presenting within 2 cm of a main tumor and their sizes were less than 2 cm in diameter. Meanwhile, multiple tumors were defined as two or more tumor nodules of any size but over 2 cm from each other in distance. If any one of two or more tumor nodules was present within 2 cm from each other in distance and their diameters were more than 2 cm, they were also defined as multiple tumors.

The main outcomes of this study were overall survival (OS) and recurrence-free survival (RFS). The OS was calculated from the date of the resection to either the date of death or the date of the last follow-up visit. The RFS was calculated from the date of the resection to the date of first recurrence, or the date of death or the last follow-up visit. For patients who underwent a repeat resection for tumor recurrence, the patient's RFS were calculated based on the date of the initial resection was carried out.

Propensity score matching

Patients in the PBT and non-PBT groups were matched using the propensity score method as described by Rubin and Rosenbaum [25,26], which was carried out using R software version 2.10.0. The propensity score for an individual was