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*Article*

# Sequential Regorafenib or Nivolumab Therapy in Recurrent Hepatocellular Carcinoma with Sorafenib Failure in Liver Transplant Patients Does Not Improve Prognosis

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**Abstract:** Background: Systemic treatment options for hepatocellular carcinoma (HCC) after liver transplantation (LT) are limited in patients in whom sorafenib treatment was failed. The purpose of our study was to compare outcomes among sorafenib, regorafenib, and nivolumab treatment groups in patients with recurrent HCC after LT. Methods: This study retrospectively evaluated patients who received sorafenib for recurrent HCC treatment after LT at a single center from March 2007 to December 2018. Some patients received regorafenib or nivolumab after sorafenib treatment failure. Results: Fifty-six patients were treated with sorafenib due to HCC recurrence. Among these, 38 patients (67.9%) continued treatment with sorafenib only; the other 18 patients (32.1%) were converted to regorafenib treatment. Ten patients (17.9%) of these 18 were converted to nivolumab after sorafenib and regorafenib therapy failed. The disease-free survival and overall survival (OS) from LT were not different among the three groups. In addition, OS from HCC recurrence, sorafenib usage, and usage of each systemic therapeutic agent were not different among the three groups. Three cases in the nivolumab group developed acute rejection; one of these led to graft failure and death due to antibody-mediated rejection. Conclusion: Sequential regorafenib or nivolumab treatment in recurrent HCC LT patients does not improve OS compared sorafenib treatment.

**Keywords:** graft rejection; survival; mortality; chemotherapy

## 1. Introduction

Liver transplantation (LT) is an effective treatment for hepatocellular carcinoma (HCC), and the post-transplant survival rate of patients is continuously improving [1]. HCC recurrence after LT remains a major therapeutic challenge and carries a poor prognosis [2]. Despite strict selection criteria, LT recipients are at a high risk of HCC recurrence; the recurrence rate is 15%–20% within 5 years [1]. Although immunosuppression therapy after LT aims to prevent allograft rejection and limit alloimmunity, the immunosuppression often impairs the recipient's ability to protect against recurrent HCC. The prognosis is generally worse for patients with multiple tumors, large tumors, extrahepatic metastases, and poorly differentiated tumors.

Management of HCC after LT is complex and challenging, and previous studies have provided little treatment guidance [2, 3]. The treatment of patients with recurrent HCC after LT depends on several factors, including the size and number of tumors, the location of the tumors, and the extent of the recurrence. The choice of treatment depends on the individual patient's circumstances and the specific characteristics of recurrent HCC. Timely and appropriate treatment is required to improve chances of survival in cases of recurrent HCC.

Over the past 20 years, sorafenib has been the standard of care in unresectable, recurrent HCC [3]. In recent years, regorafenib and other drugs have been approved as second-line systemic treatments in patients with HCC who tolerate sorafenib with disease progression [4, 5]. Immune

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checkpoint inhibitor (ICI) treatment has recently been developed and is promising in various cancer types with remarkable survival benefits. ICI treatment could be a potentially effective option for malignant tumors of LT recipients. LT recipients have a problem in that, while adequate inhibition of autoreactivity is required, immunotherapy strongly activates cellular immunity which may break the host's immunological tolerance to the allograft, possibly leading to T-cell-mediated rejection.

The use of systemic chemotherapy in LT patients with recurrent HCC is a topic of debate because of the lack of available data on the safety and efficacy of immunotherapy in liver transplant recipients. All registry trials that led to the approval of immunotherapeutic agents for HCC excluded liver transplant recipients. Therefore, most of the data on immunotherapy for HCC after LT is drawn from case reports and case series [6, 7]. We aimed to compare outcomes among sorafenib, regorafenib, and nivolumab treatment groups in patients with recurrent HCC after LT.

## 2. Methods

### *2.1. Patients*

This retrospective and observational study was conducted at Samsung Medical Center. Adult LTs were performed between March 2007 and December 2018. HCC recurrence after LT was confirmed by pathological and/or radiological assessment based on Korean HCC guidelines [8]. Exclusion criteria were pediatric liver transplant patients, combined hepatocellular-cholangiocarcinoma, presence of other malignancies at the time of LT, re-transplantation cases, and patients who received systemic chemotherapeutic agents for < 1 month. Eligible patients received sorafenib due to extrahepatic metastasis or unresectable HCC recurrence. Patients were classified into 3 categories: Sorafenib group (ie, sorafenib ≥400 mg daily for at least 20 of the last 28 days as defined in the RESORCE trial) [5]; Regorafenib group, patients who discontinued sorafenib for any reason (e.g., patient's willingness or physician's judgment), and regorafenib was used instead' and Nivolumab group, patients who discontinued sorafenib and regorafenib due to symptomatic progression.

For each patient, the following clinical baseline features were recorded: characteristics of HCC before LT including tumor extension at explant; the time from LT to HCC recurrence or death; the time from LT to sorafenib treatment; and the time from the start of sorafenib, regorafenib, or nivolumab treatment to death. Patients were followed until the date of death from any cause or until the date of the last follow-up.

The study was approved by the Samsung Medical Center Ethic Committee (SMC-2023-08-103) and complied with the Declaration of Helsinki. The Institutional Review Board waived the need for patient consent because of the retrospective nature of this observational study and its use of data from patient medical records.

### *2.2. Immunosuppressive Medications*

Regimens included everolimus and tacrolimus. The plasma level targets were, for everolimus 3-8 ng/mL, and for tacrolimus 3-5 ng/mL. Mycophenolate mofetil was not prescribed.

### *2.3. Statistical Analysis*

Data were collected by experienced medical personnel involved in the study using a common electronic database. The primary outcomes were analyzed by the intention-to-treat principle. Continuous variables are expressed as median and range, and categorical variables are presented as frequency and percentages. Significant continuous variables are classified into two groups according to the ROC curve. Survival was analyzed by the Kaplan-Meier estimator, and differences in survival rates were compared by means of the log-rank test. For all analyses, $P \leq .05$ was considered statistically significant. Analyses were carried out using the Statistical Package for the Social Sciences (SPSS) software, version 25 (IBM Corporation, New York, NY, USA)

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## 3. Results

### *3.1. Baseline Characteristics*

Fifty-six patients were treated with sorafenib due to HCC recurrence. Among these, 38 patients (67.9%) continued treatment with sorafenib only; the remaining 18 patients (32.1%) were converted to regorafenib. Ten of these 18 patients (17.9%) were subsequently converted to nivolumab.

Baseline characteristics are summarized in Table 1. No donors had a history of hypertension or diabetes. Donor sex, donor age, and donor body mass index (BMI) were not different among the three groups. These recipient characteristics did not differ among the groups: sex: age; BMI; presence of hypertension or diabetes; etiology of the HCC; presence of varix bleeding or ascites; Child-Pugh class; presence of hepatorenal syndrome or spontaneous bacterial peritonitis; MELD score; tumor markers, including AFP and PIVKA-II. None had hepatic encephalopathy or intensive care during the pre-transplant period.

**Table 1.** Baseline characteristics.

| | **Sorafenib group (n = 38)** | **Regorafenib group (n = 8)** | **Nivolumab group (n = 10)** | **P-value** |
|---|---|---|---|---|
| Sex (male) | 34 (89.5%) | 6 (75.0%) | 9 (90.0%) | 0.513 |
| Age (years) | 54 (20-68) | 58 (42-66) | 55 (42-64) | 0.400 |
| BMI | 21.8 (17.4-29.3) | 23.2 (17.1-29.1) | 23.0 (17.2-37.1) | 0.447 |
| Hypertension | 3 (7.9%) | 1 (12.5%) | 0 (0%) | 0.563 |
| Diabetes | 8 (21.1%) | 2 (25.0%) | 2 (20.0%) | 0.963 |
| Etiology for HCC | | | | |
| HBV | 36 (94.8%) | 8 (100%) | 9 (90.0%) | 0.932 |
| HCV | 1 (2.6%) | 0 (0%) | 1 (10.0%) | |
| NBNC | 1 (2.6%) | 0 (0%) | 0 (0%) | |
| Varix bleeding | 2 (5.3%) | 0 (0%) | 1 (10.0%) | 0.644 |
| Ascites | | | | |
| None | 26 (68.4%) | 5 (62.5%) | 9 (90.0%) | 0.669 |
| Controlled | 8 (21.1%) | 2 (25.0%) | 1 (10.0%) | |
| Uncontrolled | 4 (10.5%) | 1 (12.5%) | 0 (0%) | |
| Child-Pugh class | | | | |
| A | 19 (50.0%) | 6 (75.0%) | 4 (40.0%) | 0.739 |
| B | 12 (31.6%) | 1 (12.5%) | 5 (50.0%) | |
| C | 7 (18.4%) | 1 (12.5%) | 1 (10.0%) | |
| Hepatorenal syndrome | 1 (2.6%) | 0 (0%) | 0 (0%) | 0.786 |
| SBP | 2 (5.3%) | 0 (0%) | 0 (0%) | 0.612 |
| MELD score | 10 (6-40) | 8 (6-36) | 10 (7-23) | 0.267 |
| AFP (ng/mL) | 91 (1-17,774) | 271 (3-1,297) | 177 (5-2,297) | 0.890 |
| PIVKA-II (mAU/mL) | 203 (16-75,000) | 25 (14-70,609) | 58 (18-2,302) | 0.410 |
| | | | | |
| Donor sex (male) | 26 (68.4%) | 4 (50%) | 8 (80%) | 0.396 |
| Donor age (years) | 31 (18-58) | 39 (22-61) | 27 (18-82) | 0.581 |
| Donor BMI | 22.4 (19.4-29.2) | 21.7 (18.6-27.2) | 23.6 (22.0-32.5) | 0.130 |

* BMI, body mass index; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B non-C; SBP, spontaneous bacterial peritonitis; MELD, Model for End-stage Liver Disease; AFP, alpha-fetoprotein; PIVKA-II, prothrombin in vitamin K absence-II.

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*3.2. Perioperative and HCC Characteristics*

About 90% of LDLT cases were used, and a right lobe graft was used in LDLT cases. Perioperative characteristics are outlined in Table 2. Warm ischemic time, cold ischemic time, graft-to-recipient weight ratio (GRWR), donor and recipient operation time, post-transplant intensive care unit stay, post-transplant complications, and donor and recipient hospitalization were not different among the three groups. In addition, the history of HCC treatments in the pre-transplant period and explant pathology were not different among the three groups (Table 3)

**Table 2.** Perioperative characteristics after liver transplantation.

| | **Sorafenib group (n = 38)** | **Regorafenib group (n = 8)** | **Nivolumab group (n = 10)** | **P-value** |
|---|---|---|---|---|
| Type of LT (LDLT) | 36 (94.7%) | 7 (87.5%) | 9 (90.0%) | 0.715 |
| Warm ischemic time (min) | 87 (45-282) | 95 (73-241) | 91 (55-261) | 0.731 |
| Cold ischemic time (min) | 33 (13-65) | 40 (19-60) | 35 (21-58) | 0.580 |
| GRWR | 1.09 (0.9-3.0) | 1.1 (1.0-2.3) | 1.2 (1.0-1.5) | 0.487 |
| Recipient operation time (min) | 531 (240-929) | 468 (356-631) | 508 (360-735) | 0.604 |
| ICU stay in post-transplant (days) | 6 (3-17) | 6 (3-7) | 6 (4-7) | 0.402 |
| Complications within 30 days | 20 (52.6%) | 3 (37.5%) | 4 (40.0%) | 0.627 |
| Clavien-Dindo class | | | | |
| II | 2 | 1 | 1 | 0.279 |
| IIIa | 12 | 2 | 2 | |
| IIIb | 6 | 0 | 1 | |
| Recipient hospitalization (days) | 28 (18-126) | 22 (19-43) | 23 (16-65) | 0.119 |
| | | | | |
| Donor operation time (min) | 364 (235-491) | 290 (187-453) | 371 (237-526) | 0.293 |
| Macrosteatosis (%) | 5 (0-20) | 5 (3-25) | 5 (5-15) | 0.468 |
| Microsteatosis (%) | 5 (0-25) | 5 (3-75) | 10 (5-60) | 0.484 |
| Donor hospitalization (days) | 12 (6-36) | 10 (6-13) | 10 (7-21) | 0.462 |

*LDLT, living donor liver transplantation; GRWR, graft-to-recipient weight ratio.

**Table 3.** HCC characteristics.

| | **Sorafenib group (n = 38)** | **Regorafenib group (n = 8)** | **Nivolumab group (n = 10)** | **P-value** |
|---|---|---|---|---|
| **Pre-transplant** | | | | |
| Liver resection in pre-LT | 12 (31.6%) | 3 (37.5%) | 2 (20.0%) | 0.695 |
| RFA in pre-LT | 11 (28.9%) | 4 (50%) | 4 (40%) | 0.335 |
| TACE in pre-LT | 21 (65.6%) | 7 (87.5%) | 7 (87.5%) | 0.275 |
| Radiation in pre-LT | 7 (18.4%) | 1 (12.5%) | 2 (20.0%) | 0.907 |
| | | | | |
| **Pathology** | | | | |
| Within Milan criteria | 22 (59.5%) | 7 (87.5%) | 6 (60.0%) | 0.316 |
| Tumor size (cm) | 3.5 (1.0-10.0) | 3.7 (1.5-8.0) | 4.0 (1.0-5.5) | 0.821 |
| Tumor number (Multiple) | 20 (52.6%) | 7 (87.5%) | 6 (60.0%) | 0.190 |
| Microvascular invasion | 29 (76.3%) | 8 (100%) | 8 (80.0%) | 0.309 |
| PVTT | 10 (26.3%) | 1 (12.5%) | 3 (30.0%) | 0.659 |
| BDTT | 2 (5.3%) | 1 (12.5%) | 0 (0%) | 0.504 |
| Intrahepatic metastasis | 21 (55.3%) | 7 (87.5%) | 6 (60.0%) | 0.237 |
| Multicentric occurrence | 7 (18.4%) | 1 (12.5%) | 1 (!0.0%) | 0.777 |

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| | | | | |
|---|---|---|---|---|
| **Recurrence** | | | | |
| Time from LT to HCC recurrence > 12 months | 13 (34.2%) | 1 (12.5%) | 5 (50.0%) | 0.137 |
| Recurrence sites | | | | |
| Liver | 20 (52.6%) | 3 (37.5%) | 6 (60%) | 0.627 |
| Lung | 26 (68.4%) | 5 (62.5%) | 7 (70%) | 0.936 |
| Peritoneum | 4 (10.5%) | 1 (12.5%) | 2 (20.0%) | 0.723 |
| Lymph node | 9 (23.7%) | 2 (25.0%) | 4 (40.0%) | 0.580 |
| Bone | 17 (44.7%) | 2 (25.0%) | 3 (30.0%) | 0.468 |
| Brain | 2 (5.3%) | 0 (0%) | 0 (0%) | 0.612 |
| Adrenal gland | 5 (13.2%) | 0 (0%) | 0 (0%) | 0.272 |
| Others | 2 (5.3%) | 0 (0%) | 0 (0%) | 0.612 |
| AFP at HCC recurrence >20 ng/mL | 17 (44.7%) | 4 (50%) | 6 (60%) | 0.481 |
| PIVKA-II at HCC recurrence > 45 mAU/mL | 24 (63.2%) | 6 (62.5%) | 4 (40%) | 0.541 |

*LT, liver transplantation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; PVTT, portal vein tumor thrombosis; BDTT, bile duct tumor thrombosis; HCC, hepatectomy carcinoma; AFP, alpha-fetoprotein; PIVKA-II, prothrombin in vitamin K absence-II.

*3.3. Outcomes*

Median LT follow-up duration was 24.7 months (range, 3.4-141.0 months) in the Sorafenib group, 39.9 months (range, 14.1-98.6 months) in the Regorafenib group, and 54.3 months (range, 10.7-113.4 months) in the Nivolumab group. Follow-up duration was not different among the groups (P = 0.096).

Median time from LT to HCC recurrence was 8.5 months (range, 1.5-45.2 months) in the Sorafenib group, 8.3 months (range, 3.8-50.8 months) in the Regorafenib group, and 12.6 months (range 1.0-44.1 months) in the Nivolumab group (P = 0.332). Median AFP and PIVKA-II at HCC recurrence were 17.1 (range, 1-4,209) and 62 (range, 1-66,556), respectively, in the Sorafenib group; 8 (range, 1-577) and 62 (range, 10-1,477), respectively, in the Regorafenib group; and 111 (range, 1-15,929) and 51 (range, 12-178), respectively, in the Nivolumab group (P = 0.203 and P = 0.536, respectively). HCC recurrence sites are summarized in Table 3. Nineteen patients (33.9%) developed HCC recurrence one year after LT, mainly in the lung, liver, and bone (Table 3).

The median duration of sorafenib use was 151 days (range, 32-2,178 days) in the Sorafenib group, 216 days (range, 32-1,301 days) in the Regorafenib group, and 108 days (range, 50-2,269 days) in the Nivolumab group (P = 0.285). The median duration of regorafenib use was 102 days (range, 31-221 days) in the Regorafenib group and 84 days (range, 32-232 days) in the Nivolumab group (P = 0.575). The median duration of the nivolumab use was 71 days (range, 31-847 days).

Five patients (13.2%) in the Sorafenib group and two patients (25.0%) in the Regorafenib group were diagnosed with acute cellular rejection. These patients responded well to increased tacrolimus dose. Three patients (30%) developed acute cellular rejection in the Nivolumab group, but only one of these patients was diagnosed with antibody-mediated rejection with severe cholestasis. His bilirubin level was high, his liver graft failed, and he died.

*3.4. Survival*

The cumulative disease-free survival and overall survival rates at 1-year, 2-year, and 3-year after LT were 34.2%, 21.1%, and 5.3%, respectively, and 81.6%, 57.4%, and 36.9%, respectively, in the sorafenib group; 12.5%, 12.5%, and 12.5%, respectively, and 100%, 75%, and 62.5%, respectively, in the regorafenib group; and 50.0%, 20%, and 10%, respectively, and 90.0%, 90.0%, and 60.0%, respectively, in the nivolumab group (P = 0.230) (Figure 1). The cumulative overall survival from

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HCC recurrence, sorafenib use, and each systemic treatment showed no statistically significant differences among the three groups (Figure 2).

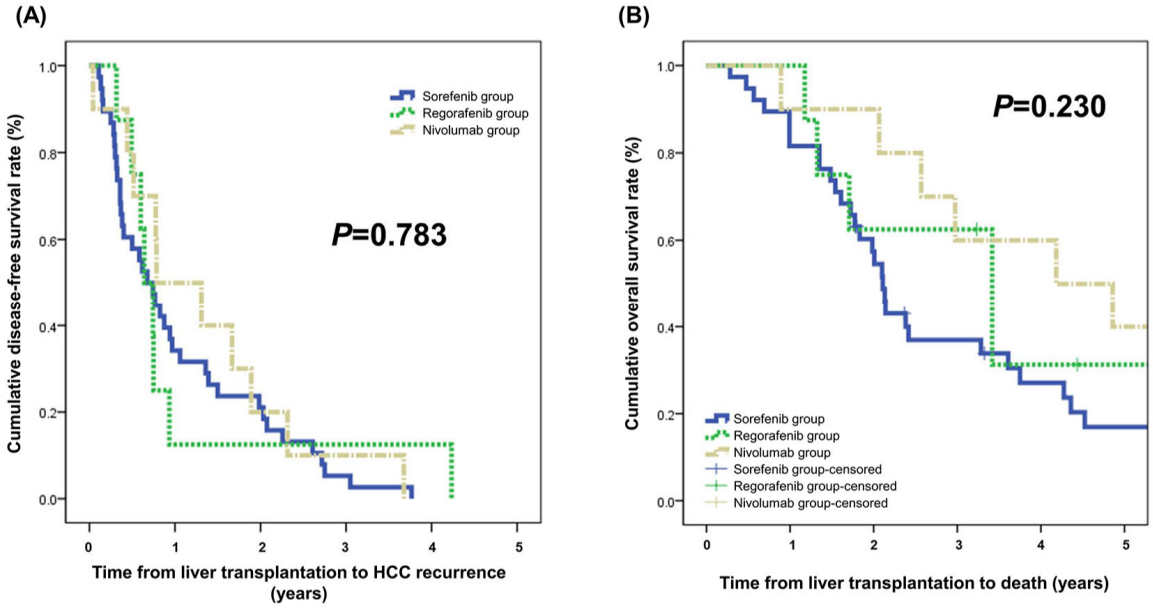


**Figure 1.** Survival from liver transplantation. (A) Disease-free survival and (B) Overall survival.

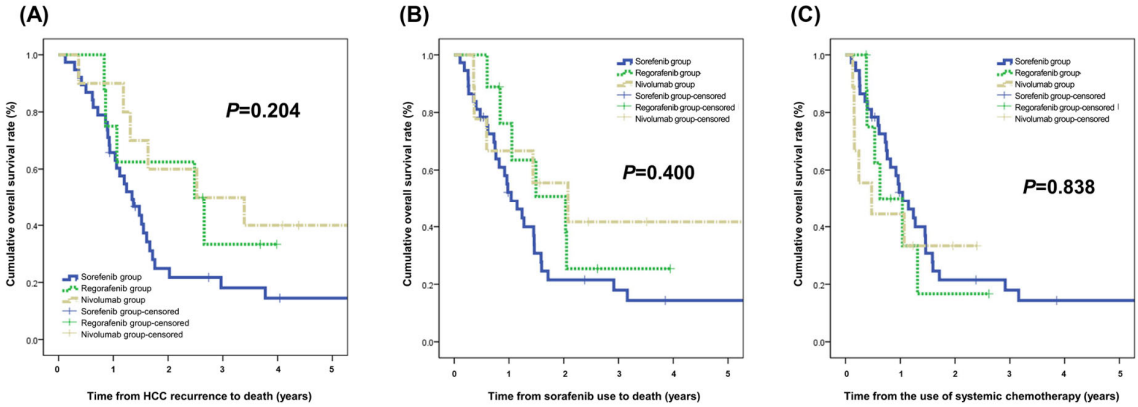


**Figure 2.** Overall survival after HCC recurrence (A), with sorafenib use (B), and with each systemic chemotherapeutic agent (C).

### *3.5. Risk Factors for Death from HCC Recurrence*

Univariate analysis showed that MELD score, male donor, tumor size, and DFS >1 year were closely associated with death from HCC recurrence. Only DFS > 1 year was a powerful predisposing protective factor for death from HCC recurrence in multivariate analysis (Table 4).

**Table 4.** Risk factors for death from HCC recurrence in liver transplant patients.

| | OR | 95% CI | P-value |
|---|---|---|---|
| **Univariate** | | | |
| Recipient sex (male) | 0.835 | 0.351-1.988 | 0.684 |
| Recipient age | 1.011 | 0.979-1.045 | 0.492 |
| MELD score | 1.046 | 1.003-1.091 | 0.038 |
| Hospitalization | 1.005 | 0.992-1.018 | 0.450 |
| Donor sex (male) | 0.520 | 0.277-0.978 | 0.042 |
| Donor age | 1.019 | 0.995-1.043 | 0.123 |

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| | | | |
|---|---|---|---|
| GRWR | 1.653 | 0.779-3.509 | 0.191 |
| Beyond Milan criteria | 1.730 | 0.878-3.409 | 0.114 |
| Tumor size | 1.233 | 1.039-1.463 | 0.017 |
| Microvascular invasion | 1.210 | 0.548-2.671 | 0.637 |
| PVTT | 1.774 | 0.909-3.461 | 0.093 |
| Intrahepatic metastasis | 1.255 | 0.670-2.353 | 0.478 |
| Multicentric occurrence | 0.822 | 0.345-1.958 | 0.659 |
| DFS > 1 year | 0.403 | 0.197-0.823 | 0.013 |
| Group | | | |
| Sorafenib group | 1 | 1 | 0.206 |
| Regorafenib group | 0.608 | 0.251-1.471 | 0.270 |
| Nivolumab group | 0.492 | 0.202-1.195 | 0.117 |
| AFP at HCC recurrence >20 ng/mL | 1.256 | 0.684-2.309 | 0.462 |
| PIVKA-II at HCC recurrence >45 mAU/mL | 1.849 | 0.960-3.559 | 0.066 |
| | | | |
| **Multivariate** | | | |
| DFS > 1 year | 0.389 | 0.176-0.860 | 0.020 |

* GRWR, graft-to-recipient weight ratio; PVTT, portal vein tumor thrombosis; DFS, disease-free survival; AFP, alpha-fetoprotein; PIVKA-II, prothrombin in vitamin K absence-II.

## 4. Discussion

Treatment of recurrent HCC after LT is challenging, and the evidence to establish a management algorithm is lacking. Our study aimed to determine the potential value of regorafenib or nivolumab for survival of patients in whom HCC recurred during sorafenib therapy. However, we did not demonstrate effectiveness of either regorafenib or nivolumab in these recurrent HCC LT patients in whom sorafenib had failed. The improvement in survival was neither statistically nor clinically meaningful when compared with patients with similar characteristics who received sorafenib. OS from LT and HCC recurrence were better in the Regorafenib or Nivolumab groups than the Sorafenib group, but the differences did not reach a statistical significance.

Chemotherapeutic drugs kill rapidly dividing cells, including cancer cells; but these drugs can also affect normal cells. This can cause side effects such as fatigue, nausea, hair loss, and an increased risk of infection. In liver transplant patients, systemic chemotherapy can also potentially interact with the immunosuppressive medications used to prevent organ rejection and thereby increase the risk of side effects.

Sorafenib is a targeted therapy that inhibits the growth of cancer cells by blocking specific proteins involved in tumor growth and angiogenesis. The safety profile and effectiveness of sorafenib in patients with recurrent HCC after LT has been confirmed by small cohort studies [4]. These findings and the lack of alternative effective systemic treatment options made sorafenib the standard of care in HCC recurrence after LT [4, 9]. In our study, we first treated all recurrent HCC patients received with sorafenib as the standard of care in unresectable, recurrent HCC from 2007 to 2015 [3, 10, 11]. Patients received only sorafenib in our center because of no available alternative drugs. Since regorafenib or nivolumab was introduced in the global market, sorafenib failure patients received regorafenib or nivolumab.

Regorafenib is the first second-line systemic treatment that improved survival in patients with HCC who tolerated sorafenib with disease progression, as recently shown in the international phase 3, randomized controlled RESORCE trial [5]. However, the effects and safety of regorafenib have not been thoroughly evaluated in LT settings. We recently used regorafenib in sorafenib failure cases. We found that the LT recipient did not exhibit an effective response to the regorafenib treatment after sorafenib failure. Fortunately, the severe side effects of regorafenib are rare because the patient had adequate liver function during treatment; this may have increased his tolerance to the regorafenib treatment.

The immune checkpoint inhibitor nivolumab has been conditionally approved for HCC by the Food and Drug Administration, based on promising results of noncomparative phase I/II trials [12]. A previous systematic review study reported a lesser objective response rate (ORR) in 25 LT recipients who received nivolumab treatment, compared to the ORR of non-transplant patients in the CheckMate-459 trial [33] (8% vs. 15%), indicating an inferior therapeutic benefit [13, 14]. The differences in treatment response in most nivolumab treated patients in our study may be due to nivolumab being used as salvage therapy. Thus these patients were at a high risk of tumor progression. Unfortunately, our cases did not demonstrate high efficacy of nivolumab compared with sorafenib or regorafenib.

We experienced one fatal antibody-mediated rejection, which resulted in graft failure and death. Our team does not use nivolumab. A previous study showed that among the 47 patients treated with ICIs, 31.9% of patients had graft rejection and the median survival time was 6.5 (0.3–48) months [15]. Rejection was often accompanied by high mortality, and 44% of all patients died because of graft failure [15]. The rejection rate of patients treated with nivolumab was the highest (33%, 3/9 cases), which indicated the worst prognosis in those patients [16].

We identified that late recurrence was a strong prognostic factor for survival in recurrent HCC LT patients. The time between transplant and recurrence is important in predicting the outcome after recurrence; worse survival rates occur when recurrence is diagnosed within 12 months from transplantation [17]. Some authors reported that early recurrence after LT is associated with extremely poor prognosis and based their conclusions on the suggestion that the early HCC recurrence is due to aggressive tumor biology [18]. These authors did not clearly identify predictive factors of early recurrence [18].

This study has some limitations, particularly the retrospective design, the lack of randomization, the presence of some undeniable differences among groups, the absence of a control group of patients with similar characteristics, the long enrollment period, the absence of a standardized protocol for the long study period, and heterogeneous immunosuppressive regimen protocols. In addition, we do not know the exact side effects and the adverse events that were related to chemotherapeutic agents because medical records were reviewed retrospectively. Therefore, we could not demonstrate the safety of systemic treatments in our study. Further randomized studies are needed to prospectively confirm the data generated by this and previous studies to assess the effectiveness and safety of sorafenib, regorafenib, and nivolumab in LT settings.

The present study did not demonstrate the effectiveness of regorafenib or nivolumab in recurrent HCC patients with sorafenib failure. The usage of nivolumab can potentially cause rejection of the transplanted liver, so careful monitoring and management of immunosuppressive medications is necessary. Recurrent HCC after LT require timely and appropriate treatment to improve patients' chances of survival. A multidisciplinary team of healthcare professionals, including hepatologists, transplant surgeons, radiologists, and oncologists, should develop an individualized treatment plan for each patient based on his or her specific circumstances. Close monitoring and follow-up are also important for detecting recurrent disease early and initiating treatment as soon as possible.

**Author' contributions:** Jieun Kwon: Data collection, data interpretation, wrote the manuscript. Jongman Kim: Study design, data collection, data analysis, data interpretation, and wrote the manuscript. Sang Oh Yun, Sunghae Park, Manuel Lim, Jaehun Yang, Jinsoo Rhu, Gyu-Seong Choi, and Jae-Won Joh: Data collection and interpretation.

**Institutional Review Board Statement:** The study complied with the Declaration of Helsinki.

**Data Availability Statement:** Additional data is not available.

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**Conflicts of Interest:** The authors of this manuscript have no conflicts of interest to disclose.

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