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Limitation of non-transplant treatment and proper timing for liver transplantation in patients with hepatocellular carcinoma considering long-term survival

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Abstract

In this study, we investigated the long-term survival of patients with hepatocellular carcinoma (HCC) after conventional treatment other than liver transplantation (LT) in our institute and discuss the limitation of non-transplant treatment for HCC and the proper indictors of LT in the recent comprehensive era.

Between 2003 and 2016, 181 patients with HCC aged ≤70 years received active treatment including liver resection, radiofrequency ablation (RFA), and transcatheter arterial chemoembolization (TACE). We analyzed the factors associated with overall survival and proposed new priority for the indicators of LT in HCC patients according to the extracted factors by comparing the survival with 39 transplanted patients with HCC.

Child-Turcotte-Pugh (CTP) score (HR: 1.276; 95% CI: 1.049–1.552, $P = .015$), and number of tumors (HR: 1.238; 95% CI: 1.112–1.377, $P < .001$) were selected as significant factors associated with the survival after active treatments for HCC. Patients with LT had significantly better long-term survival compared with those with non-transplant patients regardless of aforementioned factors. However, regarding relatively short survival (3 years), patients with CTP score of ≥9 and/or ≥3 tumors with non-transplant treatment had poorer survival compared with those of transplanted patients ($P < .05$).

We propose that CTP score of 9 and/or 3 tumors before non-transplant, intensive treatment might be a new priority for considering indicators of LT in patients with HCC.

Abbreviations: AASLD = American Association of Liver Disease, AFP = serum alphafetoproetein, APASL = Asian Pacific Association for the Study of Liver diseases, BCLC = Barcelona Clinic Liver Cancer, CTP = Child-Turcotte-Pugh, DCP = des-gamma carboxy prothrombin, EASL = European Association for the Study of Liver, EORTC = European Organisation for Research and Treatment of Cancer, HCC = hepatocellular carcinoma, HCV = Hepatitis C virus, JSH = Japanese Society of Hepatology, LT = liver transplantation, MELD = model of end-stage liver disease, NCCN = National Comprehensive Cancer Network, PIVKA-II = protein induced by vitamin K absence or antagonists II, RFA = radiofrequency ablation, TACE = transcatheter arterial chemoembolization.

Keywords: HCC, indication, liver transplantation, long-term survival, treatment

1. Introduction

Recent advances in treatment for hepatocellular carcinoma (HCC) such as perioperative surgical management,[1,2] the establishment of techniques and improvements of devices for radiofrequency ablation (RFA)[3,4] or transcatheter arterial chemoembolization (TACE)[5,6]—all have contributed to a better prognosis. However, needless to say, HCC is a malignant tumor and shows high recurrence rate,[7,8] and such an intensive approach usually does not help many patients recover.

One curative option for patients with HCC is liver transplantation (LT).[9–11] This treatment is ideal because the entire liver, which is the origin of the tumors, is completely replaced unless the patients have extrahepatic metastasis or vascular invasion. In 1996, Mazzaferro et al proposed the indications for LT for patients with HCC (termed Milan criteria): patients with a single tumor <5 cm or up to 3 tumors with a maximum diameter of 3 cm, showed better overall and recurrence free survival compared with those beyond this tumor scope.[12] Since then, the Milan criteria have been considered as the gold standard for the indicators for LT in patients with HCC and have been applied in some guidelines for HCC treatment.[7,13–17]

Considering the treatment for HCC, the remnant liver functional reserve should be kept in mind along with the tumor characteristics. Several guidelines such as the American Association of Liver Disease/Barcelona Clinic Liver Cancer (AASLD/BCLC) staging system,[7,13,14] the Asian Pacific Association for the Study of Liver diseases (APASL)[15,16] and the Japanese Society of Hepatology (JSH)[17] include liver functional reserve for selecting treatment in each decision tree. Thus, considering liver functional reserve in treating HCC is an important concept almost universally.

In the present study, we investigated the long-term survival of patients with HCC who received active treatment including resection, RFA, and/or TACE initial treatment to evaluate the limits of non-transplant treatment with good prognoses n the recent era with the improvement of treatment for HCC. In addition, we discuss the appropriate indicators of LT in patients with HCC by comparing the survival of transplant and non-transplant patients.

2. Patients and methods

2.1. Inclusion and exclusion criteria of non-transplant patients with HCC who received active treatment in this study

Between 2003 and 2016, 542 patients were admitted to our hospital for the treatment of HCC, excluding LT. Patients were basically treated according to the consensus algorithms of treatment for HCC from JSH.[17] The inclusion and exclusion criteria for this study are shown in Figure 1.

Age is an important factor in considering LT and in consensus algorism for the treatment of HCC in Japan; it is one of the including factors indicating LT.[17,18] Hence, our initial study population numbered 265 patients with age ≤70 years, the upper limit of recipient age in most transplant centers in Japan. Following, we selected a few exclusion criteria from among the several established, extended criteria of LT for HCC[19–22]; maximum tumor number being ≥10, size of ≥50 mm, serum alphafetoproetein (AFP) of ≥500 ng/mL, or protein induced by vitamin K absence or antagonists II (PIVKA-II; DCP = des-gamma carboxy prothrombin) of ≥500 IU/mL. And also, we excluded the patients with Child-Turcotte-Pugh (CTP) class C, which was beyond the standard for active treatment of HCC other than LT.

Consequently, 84 patients were excluded. Finally, 181 patients were included in this study; 131 males and 50 females with a median age of 62 years. HCV was the dominant etiology (118/182; 65.2%) and initial treatments were 51 received RFA, 80 TACE, 19 RFA + TACE, and 31 had surgical resections (Table 1).

2.2. Transplant patients with HCC

Forty-eight patients with HCC received LT during the same period as non-transplant patients as described above. Indicators of LT during this period was as follows; not expecting good survival after non-transplant treatment (as per the JSH guideline[17]) and whose ages were ≤70 years old. Patients who did not meet Milan criteria were not excluded unless they had extrahepatic or macrovascular invasion in preoperative imaging study. Among these, 9 patients were excluded because of the exclusion criteria in non-transplant patients, as described above. Preoperative backgrounds are shown in Table 2; 30 males
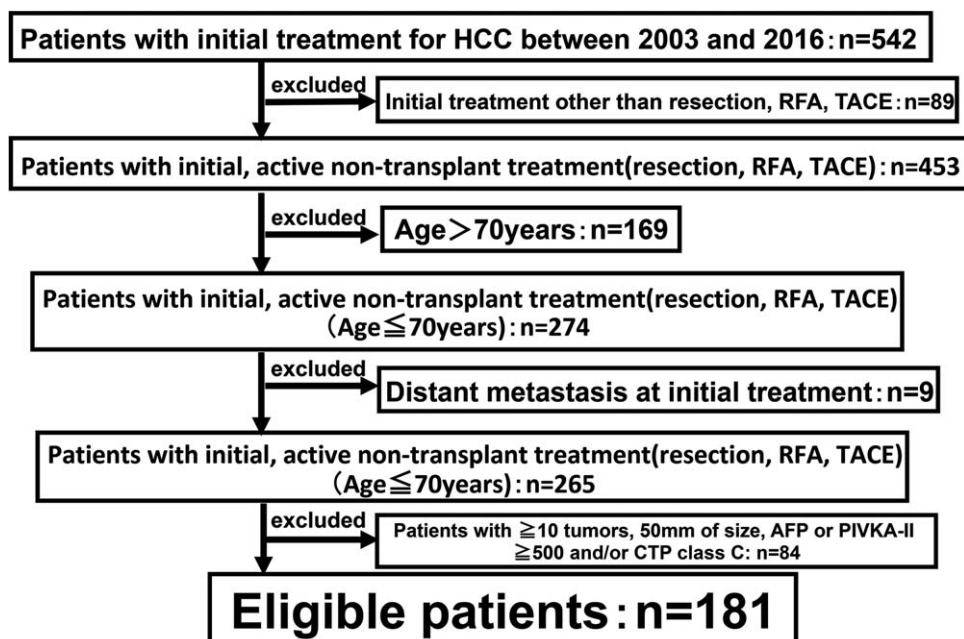

Figure 1. Schema of the inclusion and exclusion criteria in this study. RFA = radiofrequency ablation, TACE = transcatheter arterial chemoembolization.

Table 1

Backgrounds of non-transplant patients with age ≤70 years who received active treatment for HCC.

n	181
Age (years old)	62 (40–70)
Sex (male/female)	131/50
Etiology (HCV/HBV/HCV + HBV/EtOH/AIH//NBNC)	118/32/1/15/1/14
Child-Turcotte-Pugh score	6 (5–9)
MELD score	9 (6–20)
Number of tumors	1 (1–10)
Maximum size of tumors (mm)	18.0 (7.0–48.0)
AFP (ng/mL)	14.3 (1.0–485.3)
PIVKA-II (DCP; mIU/mL)	28.0 (5.0–149.0)
Initial treatment (RFA/TACE/RFA + TACE/resection)	51/80/19/31

AFP = alphapfetoprotein, AIH = autoimmune hepatitis, DCP = des-γ-carboxy prothrombin, EtOH = alcoholic, HBV = hepatitis B virus, HCV = hepatitis C virus, NBNC = non-B, non-C, PBC = primary biliary cholangitis, PIVKA-II = protein induced by vitamin K absence or antagonist, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.

Table 2

Backgrounds of transplant patients with HCC.

n	39
Age (years old)	58 (35–63)
Sex (male/female)	30/9
Etiology (HCV/HBV/NBNC)	19/15/5
Child-Turcotte-Pugh score	10 (5–13)
MELD score	15 (8–28)
*Number of tumors	2 (0–10)
*Maximum size of tumors (mm)	18.0 (0–50.0)
AFP (ng/mL)	22.0 (2.0–495.0)
PIVKA-II (DCP; mIU/mL)	34.0 (7.0–362.0)
Milan criteria (within/without)	31/8

AFP = alphapfetoprotein, DCP = des-γ-carboxy prothrombin, HBV = hepatitis B virus, HCV = hepatitis C virus, NBNC = non-B, non-C, PIVKA-II = protein induced by vitamin K absence or antagonist, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.

* Patients with curative treatment were included, and 0 means no viable tumors at the liver transplantation.

and 9 females of recipients with a median age of 58 years. HCV was also dominant as the etiology in this cohort (19/39; 48.7%) and 20.5% of patients (9/38) had HCC beyond Milan criteria.

2.3. Statistical analysis

Data were collected at initial treatment in non-transplant patients and preoperative data in transplant patients as the investigated factors associated with patients' survival including age, sex, etiology of background liver disease, maximum size and number of tumors, CTP score, the model of end-stage liver disease (MELD) score, serum AFP and PIVKA-II. To investigate the factors associated with patient survival in non-transplant patients, the Cox proportional hazard model was employed. The log-rank test was conducted to compare the survival among each consequent values of factors associated with survival of non-transplant patients and to compare the survival of transplant and non-transplant patients. Additionally, to compare the survival

and calculate the hazard ratio between non-transplant and transplant patients, the Cox-proportional Hazard models was conducted. A P value of $<.05$ was considered as statistically significant. All statistical analysis was performed using SPSS ver. 24.0 (IBM Corporation, Armonk, NY).

3. Results

3.1. Factors associated with survival after active treatment in non-transplant patients

First, we investigated the factors associated with survival after active treatment in non-transplant patients with HCC. In univariate analysis, the CTP score ($P = .043$), number ($P < .001$), maximum size ($P = .034$) of tumors, serum AFP ($P = .020$), and PIVKA-II ($P = .029$) were the significant factors associated with the survival after active treatment in non-transplant patients. In multivariate analysis, the CTP score (HR: 1.276; 95% CI: 1.049–1.552, $P = .015$), and number (HR: 1.238; 95% CI: 1.112–1.377,

Table 3

Factors associated with survival after initial treatment in non-transplant patients with age ≤70 years who received active treatment.

	Univariate analysis	P	Multivariate analysis	P
Age	1			
1 year older	1.022 (0.982–1.064)	.281		
Sex				
male	1			
female	1.214 (0.719–2.048)	.468		
Etiology				
NBNC	1			
HBV	0.447 (0.171–1.167)	.100		
HCV	1.042 (0.514–2.115)	.909		
Child-Turcotte-Pugh score	1		1	
1 point higher	1.223 (1.007–1.485)	.043	1.276 (1.049–1.552)	.015
MELD score	1			
1 point higher	1.057 (0.954–1.170)	.289		
Number of tumor	1		1	
1 more tumor	1.273 (1.156–1.403)	<.001	1.238 (1.112–1.377)	<.001
Maximum size of tumor	1			
1 mm larger	1.029 (1.002–1.057)	.034		
AFP	1			
1 ng/mL higher	1.003 (1.000–1.006)	.020		
PIVKA-II (DCP)	1			
1mIU/ml higher	1.003 (1.000–1.006)	.029		

AFP = alphapfetoprotein, DCP = des-γ-carboxy prothrombin, HBV = hepatitis B virus, HCV = hepatitis C virus, NBNC = non-B, non-C, PIVKA-II = protein induced by vitamin K absence or antagonist.
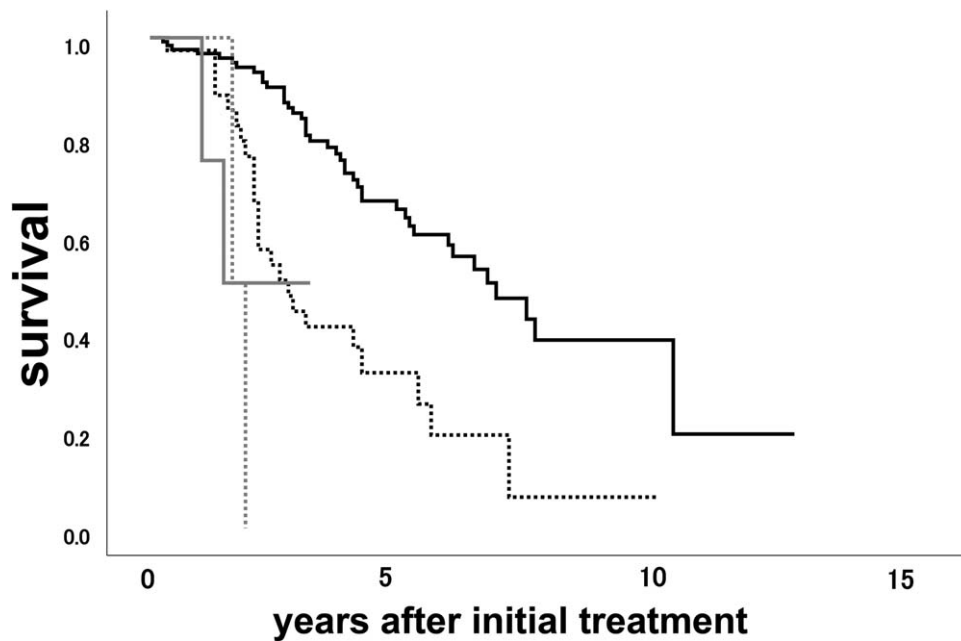
Figure 2. Comparison of the long-term survival in non-transplant patients with HCC divided by a CTP score of 9 and tumor number of 3. (A) Black solid line represents the survival in patients with CTP scores of ≦8,numbers of ≦2 (1 year: 96.8%, 5 years: 61.6%), (B) black broken line represents the survival in those with CTP scores of ≦8, numbers of ≧3 (1 year: 97.4%, 5 years: 31.7%), (C) gray solid line represents the survival of those with CTP scores of ≧9, numbers of ≦2 (1 year: 80.0%, 5 years: 57.1%), and (D) gray broken line represents the survival in those with CTP scores of ≧9, numbers of ≧3 (1 year: 80.0%, 5 years: 0%). Log-rank test: $P < .001$.

$P < .001$) were selected as statistically significant and independent factors (Table 3).

3.2. Long-term survival of non-transplant patients with HCC according to CTP score and number of tumors

According to the data as described above, we attempted to investigate the proper threshold to find the maximum limit for good survival after non-transplant treatment and to consider the priority of the indicators of LT in patients with HCC, considering long-term survival in recent era.

Investigating the survival regarding each CTP score, we found that a CTP score of 9 was a good indicator for the survival of the patients with HCC after initial treatment (Supplemental Table 1, http://links.lww.com/MD/E515). Comparing the survival of patients divided by CTP score of 9, those with CTP score of ≧9 were significantly worse than those with CTP score of ≦8 (Supplemental Figure 1A, http://links.lww.com/MD/E512, $P = .003$). Regarding survival as per tumor numbers, 3 tumors appeared to be a good indicator of patient survival (Supplemental Table 2, http://links.lww.com/MD/E516). Comparing the survival of patients divided by tumor number of 3, those with ≧3 tumors were significantly worse than those with 1 or 2 tumors (Supplemental Figure 1B, http://links.lww.com/MD/E512, $P < .001$).

3.3. What factors determine a good prognosis for non-transplant treatment based on CTP score and number of tumors?

Next, we divided the patients into 4 groups according to threshold levels of Child-Pugh score of 9, numbers of 3, statistically significant discrimination was shown for survival

after initial treatment for HCC (Fig. 2, $P < .001$), especially for patients with CTP score of ≦8 and ≦2 tumors (Group A, Table 4), who had a significantly better survival compared with all other groups ($P < .05$).

These data suggested that patients had a CTP score of 8 and with 2 tumors may be the best indicators of good survival after initial active treatment.

3.4. Comparison of survival of HCC patients with or without LT-superiority of LT in HCC patients and how to make a decision for priority of indicators during initial treatment

Comparing the long-term survival between transplant and non-transplant patients with HCC, the former showed better survival than the latter according to each category of CTP scores (Supplemental Figure 2A, http://links.lww.com/MD/E513), number of tumors (Supplemental Figure 2B, http://links.lww.com/MD/E513), though not surprisingly.

Table 4

P values for the log-rank test between each class of non-transplant patients with HCC according to CTP class, number and maximum size of tumors.

	A	B	C	D
A				
B	<0.001			
C	**0.039**	0.818		
D	<0.001	**0.035**	0.730	

A: CTP score ≦8, number <3, B: CTP score ≦8, number ≧3, size <30 mm, C: CTP score ≧9, number <3, D: CTP score ≧9, number ≧3.
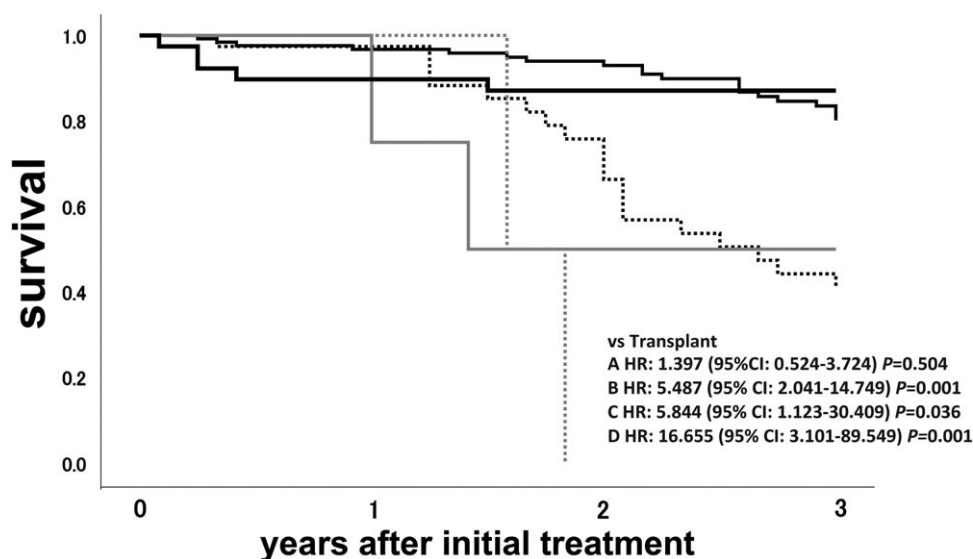Log-rank test. Bold letters: $P < .05$.

Figure 3. Comparison of the relatively short-term (3 years) survival between non-transplant patients with HCC divided by CTP score of 9 and a tumor number of 3 and transplant patients with HCC. (A) Black solid line represents the survival in patients with CTP scores of ≤8 and tumor numbers of ≤2 (1 year: 96.8%, 3 years: 80.1%), (B) black broken bar represents the survival in those with CTP scores of ≤8 and tumor numbers of ≥3 (1 year: 97.4%, 3 years: 41.0%), (C) gray solid line represents the survival in those with CTP scores of ≥9 and tumor numbers of ≤2 (1 year: 75.0%, 3 years: 50.0%), and (D) gray broken line represents the survival in those with CTP score of ≥9 and tumor number of ≥3 (1 year: 100%, 3 years: 0%). Black bold line represents 3-year survival of transplant patients with HCC (1 year: 89.7%, 3 years: 87.1%).

Next, we investigated the relatively short-term (3 years) survival and compared transplant and non-transplant patients according to CTP score and number of tumors. CTP score of 9 (Supplemental Figure 3A, http://links.lww.com/MD/E514) and tumor number of 3 (Supplemental Figure 3B, http://links.lww.com/MD/E514) seemed to be the best cut-off points. Hence, we divided the four groups according to the thresholds of CTP score and tumor number of tumors. As described above, the survivals of patients receiving non-transplant treatment with CTP score of ≥9 and/or tumor number of ≥3 were significantly worse than those who received transplantation (P < .05), while the survival of those with CTP score of ≤8 and tumor number of ≤2 was not statistically different in patients receiving non-transplant treatment (P = .504) compared with those who received transplantation (Fig. 3).

3.5. Comparison of the survival between transplant and non-transplant patients according to the treatment other than LT

To evaluate long-term survival of patients with HCC, initial treatment might be the important factor. So, we investigated the survival according to each non-transplant treatments and compared with post-transplant survival. The survivals of the patients who received TACE as the initial treatment, including combination with RFA were significantly worse compared with those of transplant patients (TACE only; P < .001, TACE + RFA; P = .001, Fig. 4). In contrast, the survivals of patients who received resection (P = .269) and RFA (P = .144) showed no statistical difference compared with those of transplant patients (Fig. 4). Then, we finally compared the background of non-transplant between patients who received TACE and non-TACE treatment. Background of patients with TACE, including combination treatment with RFA, showed significantly worse

liver function (CTP score, P = .001, MELD score, P = .024) and tumor biology (number and size, P < .001) compared with those without TACE (Supplemental Table 3, http://links.lww.com/MD/E517).

Collectively, our data suggested that LT for patients with HCC is confirmed as the ideal treatment considering long-term survival. Furthermore, those with CTP score of ≥9 and/or tumor number of ≥3 may indicate priority for LT in HCC patients especially in patients who should be considered TACE, taking into account both short-term and long-term survivals.

4. Discussion

Recent advances of the treatment for patients with HCC have resulted in an improved prognosis. However, even in the recent era, the survival of patients with HCC is not good enough, with many patients still dying as the disease progression.

LT is one of the curative options, as a tumor producing liver is replaced with a healthy liver, yielding an ideal treatment unless patients have extrahepatic metastasis or vascular invasion and additionally whether patients receive appropriate donor livers. LT for HCC patients was first reported by Starzl et al,[23] and since then, most transplant centers have performed LT for patients with HCC. The present study showed that the long-term survival of transplant patients was significantly better than that of non-transplant patients with HCC, though not surprisingly (Supplemental Figure 2, http://links.lww.com/MD/E513).

However, the donor source is not inexhaustible, hence, we focused on the "maximum-limit" of non-transplant treatment, possibly considered as the point when LT yields better prognosis for patients with HCC. Among these populations, CTP score of 9 and/or tumor number of 3 were identified as the best predictors of survival of patients with HCC by non-transplant treatment. In other words, patients with CTP score of ≥9 and/or tumor number
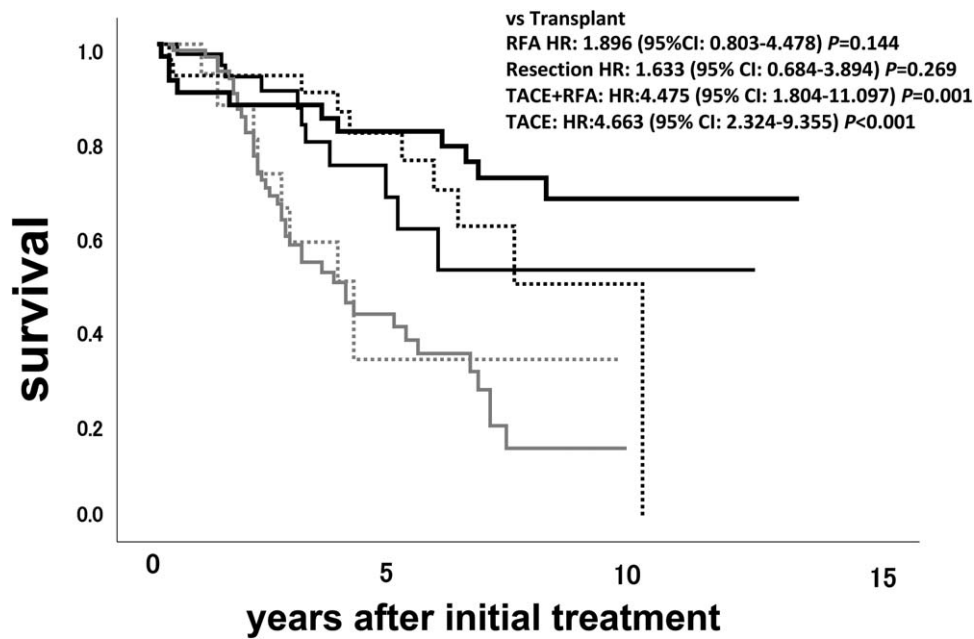
Figure 4. Comparison of the long-term survival between non-transplant patients with HCC according to the initial treatment and transplant patients with HCC. (A) Black solid line represents the survival in patients who received RFA (1 year: 97.9%, 5 years: 60.8%), black broken bar represents the survival in those who received resection (1 year: 93.3%, 5 years: 81.2%), gray solid line represents the survival in those who received RFA + TACE (1 year: 93.8%, 5 years: 33.2%), and gray broken line represents the survival in those who received TACE (1 year: 97.3%, 5 years: 40.1%) in non-transplant patients. Black bold line represents the survival of transplant patients with HCC (1 year: 89.7%, 5 years: 81.5%).

of ≥3 before treatment cannot expect a good outcome by active treatments with curative intent, such as resection, ablation, or TACE, and LT as the first treatment might be the best option for improving their prognosis, considering long-term survival.

The selection of treatment for HCC in patients with CTP class B is sometimes difficult and controversial.[24] Overall, resection would be recommended only in patients with CTP class A, normal bilirubin levels, and absence of portal hypertension according to AASLD/EASL guidelines.[24] However, according to APASL,[15,16] JSH,[17] The National Comprehensive Cancer Network (NCCN),[25] and the South Korean guidelines,[26] CTP class B patients were not excluded based on the indication of resection. Local ablation is one of the good options for CTP class B patients, not suitable for resection unless the patients have significant ascites or uncorrected coagulopathy,[24,27,28] though these populations were negatively associated with overall survival after treatment.[29] In contrast, patients with initial complete response showed good survival even in CTP class B patients.[29] For TACE, according to the EASL-EORTC guidelines, CTP class B and C patients are not good candidates,[30] however, in the NCCN[25] and JSH[17] guidelines, CTP class B patients were not excluded, and a Japanese multicenter study reported that the survival was 82% at 1 year, 43% at 3 years, and 22% at 5 years with a periprocedural mortality of 0.62%.[31]

And also, number of tumors was the statistically significant factor for predicting survival of patients with non-transplant HCC in our cohort. Tumor number and size are the established factors to select the treatment in non-transplant patients according to most of the guidelines.[7,15,17,25,26] In these guidelines, especially in the indication of locoregional therapy including resection and RFA, number and size are basically restricted as number of ≤3 and size of ≤3 to 5 cm. In fact, in our cohort, resection and local ablation was selected in patients with

relatively better liver function and tumor biology compared with TACE, and it might be affected the good prognosis in patients with resection and RFA as the initial treatment. In contrast, only tumor number was selected as a significant factor associated with long-term survival, though tumor size was not (Table 3). It might be due to the setting of our cohort, that the size was restricted to ≤5 cm, however, the number was extended to ≤10 to aim the comparison of patients with LT according to the several established, extended criteria of LT for HCC.[19–22]

Considering indicators for LT, we should know the "upper limit" for better survival. Milan criteria, described above, have been the gold standard for the indicators of LT for HCC.[12] However, these criteria have recently been recognized as severe; several extended criteria reported by many transplant centers included the extension of tumor size and number of tumors.[19,32–34] Furthermore, in other extended criteria, tumor markers (especially DCP) which reflect the biological character of the tumors, were included.[20,21] Moreover, a recent Japanese multicenter study reported AFP was also the predictive factor of tumor recurrence and prognosis after LT.[22] Some kinds of cap for the "maximum" indication are necessary to avoid unexpected recurrence after LT.

Most of the allocation systems for patients with HCC in the world have applied the "MELD exemption". These allocation systems give 14 to 22 points at listing, and additional points were given according to the waiting time, should patients have less aggressive tumors, considering the size and tumor markers.[35] Considering the prognosis after non-transplant treatment and transplantation in the present study, for example, HCC patients with CTP score of 9 and/or 3 tumors could be given another priority for the indication of LT.

General weak point is that the present study adopts a retrospective, observational approach using a single center. Furthermore, the number of patients included in this study was

quite small and statistical power was relatively weak. In non-transplant patients, we excluded patients with far advanced tumors; maximum tumor number being ≧10, size of ≧50 mm, serum AFP of ≧500 ng/mL, or DCP of ≧500 IU/mL, to compare the survival of transplant patients, whose standard treatment is based on some extended criteria of LT for HCC,[19–22] and age ≤70 years, the upper limit of recipient age in most transplant centers in Japan, so some selection bias might be yielded compared with the real-world data. And we also aimed to exclude Child C patients who is beyond the standard non-transplant treatment according to the JSH guideline.[17] However, because majority of transplanted patients were in Child C status (23/39: 59.0%), so it was difficult to exclude these patients. Therefore, it is also the large limitation of this study, that we have only included the comparison of the standard treatment for non-transplant patients and LT itself as the treatment for HCC. Thus, interpretation of the comparison of survival between transplant and non-transplant patients should be made with caution.

In conclusions, we investigated the long-term prognosis of patients with HCC after conventional treatment (non-transplant) and LT to evaluate the limitation of non-transplant, active treatment and proper indicators of LT in the recent era of improvement for treatment against HCC. A CTP score of 9 and/or tumor number of 3, which is within the levels of indication in some standard treatment algorithms of HCC, especially those who are considered TACE as the initial treatment, could be the limitation of non-transplant treatment and patients with this status could be given the priority for LT treatment for HCC.

Author contributions

MI planned this study, and AN analyzed the data and wrote this manuscript. AN, MI, TH, TK, YI, and TI managed the non-transplant patients, and HK and YO managed the transplant patients. All authors contributed the data collection and critical discussion for submit, and MF organized the study group.

References

[1] Dhir M, Melin AA, Douaiher J, et al. A review and update of treatment options and controversies in the management of hepatocellular carcinoma. Ann Surg 2016;263:1112–25.

[2] Cauchy F, Soubrane O, Belghiti J. Liver resection for HCC: patient's selection and controversial scenarios. Best Prac Res Clin Gastroenterol 2014;28:881–96.

[3] Tiong L, Maddern GJ. Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. Br J Surg 2011;98:1210–24.

[4] Ikeda K, Osaki Y, Nakanishi H, et al. Recent progress in radiofrequency ablation therapy for hepatocellular carcinoma. Oncology 2014;87:73–7.

[5] Pinato DJ, Howell J, Ramaswami R, et al. Review article: delivering precision oncology in intermediate stage liver cancer. Aliment Pharmacol Ther 2017;45:1514–23.

[6] Sangiovanni A, Colombo M. Treatment of hepatocellular carcinoma: beyond international guidelines. Liver Int 2016;36:124–9.

[7] Bruix J, Sherman M. American Association for the Study of Liver DiseasesManagement of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–2.

[8] Lin S, Hoffmann K, Schemmer P. Treatment of hepatocellular carcinoma: a systematic review. Liver Cancer 2012;1:144–58.

[9] Menahem B, Lubrano J, Duvoux C, et al. Liver transplantation versus liver resection for hepatocellular carcinoma in intention to treat: An attempt to perform an ideal meta-analysis. Liver Transpl 2017;23:836–44.

[10] Akamatsu N, Cillo U, Cucchetti A, et al. Surgery and hepatocellular carcinoma. Liver Cancer 2016;6:44–50.

[11] Cucchetti A, Vitale A, Cescon M, et al. Can liver transplantation provide the statistical cure? Liver Transpl 2014;20:210–7.

[12] Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.

[13] Silva MF, Sherman M. Criteria for liver transplantation for HCC: what should be the limits be? J Hepatol 2011;55:1137–47.

[14] Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona 2000 EASL conference. J Hepatol 2001;35:421–30.

[15] Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the study of the liver consensus recommendations on hepatocellular carcinoma. Hepatol Int 2010;4:439–74.

[16] Chow PK. Resection for hepatocellular carcinoma: is it justifiable to restrict this to the American Association for the study of the liver/Barcelona Clinic for Liver Cancer criteria? J Gastroenterol Hepatol 2012;27:452–7.

[17] Kudo M. Real practice of hepatocellular carcinoma in Japan: conclusions of the Japan Society of Hepatology 2009 Kobe Congress. Oncology 2010;78:180–8.

[18] Kudo M, Kitano M, Sakurai T, et al. General rules for the clinical and pathological study of primary liver cancer, nationwide follow-up survey and clinical practice guidelines: the outstanding achievements of the Liver Cancer Study Group of Japan. Dig Dis 2015;33:765–70.

[19] Sugawara Y, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. Dig Dis 2007;25:310–2.

[20] Taketomi A, Sanefuji K, Soejima Y, et al. Impact of des-gamma-carboxy prothrombin and tumor size on the recurrence of hepatocellular carcinoma after living donor liver transplantation. Transplantation 2009;87:531–7.

[21] Ito T, Takada Y, Ueda M, et al. Expansion of selection criteria for patients with hepatocellular carcinoma in living donor liver transplantation. Liver Transpl 2007;13:1637–44.

[22] Shimamura T, Akamastu N, Fujiyoshi M, et al. Expanded living-donor liver transplantation criteria for patients with hepatocellular carcinoma based on the Japanese nationwide survey: the 5-5-500 rule-a retrospective study. Transpl Int 2019;32:356–8.

[23] Starzl TE. Experience in Hepatic Transplantation. Philadelphia: W.B. Saunders Co; 1969. pp. 1–553.

[24] Granito A, Bolondi L. Non-transplant therapies for patients with hepatocellular carcinoma and Child-Pugh-Turcotte class B cirrhosis. Lancet Oncol 2017;18:e101–12.

[25] Benson AB, Abrams TA, Ben-Josef E, et al. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. J Natl Compr Canc Netw 2009;7:350–91.

[26] Korean Liver Cancer Study Group (KLCSG), for the National Cancer Center, Korea (NCC)2014 KLCSG-NCC Korea Practice Guideline for the management of hepatocellular carcinoma. Gut Liver 2015;9:267–317.

[27] Kim YS, Lim HK, Rhim H, et al. Ablation of hepatocellular carcinoma. Best Pract Res Clin Gastroenterol 2014;28:897–908.

[28] Dietrich CF, Lorentzen T, Appelbaum L, et al. EFSUMB guidelines on interventional ultrasound (INVUS), part III—abdominal treatment procedures (long version). Ultraschall Med 2016;37:E1–32.

[29] Sala M, Llovet JM, Vilana R, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology 2004;40:1352–60.

[30] European Association for the Study of the Liver; European Organisation for Research and Treatment of CancerEASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–43.

[31] Takayasu K, Arii S, Kudo M, et al. Superselective transarterial chemo-embolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. J Hepatol 2012;56:886–92.

[32] Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394–403.

[33] Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35–43.

[34] Lee S, Ahn C, Ha T, et al. Liver transplantation for hepatocellular carcinoma: Korean experience. J Hepatobiliary Pancreat Sci 2010;17:539–47.

[35] Toso C, Mazzaferro V, Bruix J, et al. Toward a better liver graft allocation that accounts for candidates with and without hepatocellular carcinoma. Am J Transplant 2014;14:2221–7.