Selection criteria of living donor liver transplantation for hepatocellular carcinoma developed in Korean transplant centers

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With accumulated experience on living donor liver transplantation (LDLT) for hepatocellular carcinoma (HCC), several major Korean transplant centers presented institutional or multicenter selection criteria of LDLT for HCC based on their own experience. This study intended to review the selection criteria of LDLT for HCC developed in the major Korean LT centers. Extended criteria for primary liver transplantation (LT) were developed in Asan Medical Center (AMC) in 2008, the Catholic University of Korea in 2012, Samsung Medical Center in 2014, National Cancer Center Korea in 2016, the model to predict tumor recurrence after LDLT (MoRAL) in three centers in 2016, A-P 200 criteria in Pusan National University in 2016, patient selection by tumor markers in LT for advanced HCC in eight centers, composite criteria using clinical and PET factors in two centers in 2019, tumor size and number, AFP, PIVKA-II, PET (SNAPP) score in AMC in 2021, and quantitative prognostic prediction using AFP-PIVKA-II-tumor volume (ADV) score in AMC in 2021. The criteria for salvage LT were developed from a multicenter study involving three centers in 2014 and from AMC in 2020. Posttransplant prognostic prediction models for early or non-viable HCC were developed in AMC for super-selection criteria in 2011 and pretransplant treatment-induced complete tumor necrosis in 2017. The importance of tumor biology in HCC treatment has been emphasized more than before. The expression of serum tumor markers is a surrogate biomarker reflecting the tumor biology. Pretransplant radiological assessment of HCC combined with tumor marker expression or PET finding will provide reliable information that will assist the decision to perform LDLT in patients with HCC of various stages.

Keywords: Hepatocellular carcinoma; Tumor marker; Tumor biology; Prognosis; Prediction

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths, and the treatment of HCC

remains an ongoing challenge, especially in Asian countries because of the high prevalence of viral hepatitis B and C [1,2]. Surgical resection has been considered the preferred treatment for patients with resectable HCC and preserved

hepatic reserve function. However, it is often limited due to impaired liver function [3,4]. Liver transplantation (LT) has been accepted as an effective treatment modality for selected patients with HCC because it can treat liver cirrhosis and HCC concurrently [5,6]. LT for HCC is limited by the shortage of available donor livers worldwide. Compared with patients in Western countries, those with HCC in Asian countries, where the number of deceased donors is much lower for the high prevalence rate of HCC, have a low probability of undergoing deceased donor LT in time and thus, have a higher risk of dropout because of tumor progression [7,8]. To cope with the donor shortage, living donor liver transplantation (LDLT) has been frequently performed in patients with liver cirrhosis and HCC in Asian countries. In Korea, half of the adult LDLT cases were diagnosed with HCC before LT [9]. With the accumulated experience on LDLT for HCC, several major Korean LT centers presented institutional or multicenter selection criteria for HCC, which are usually extended selection criteria compared to those developed in Western countries, based on their own experience. In this study, we reviewed the selection criteria of LDLT for HCC developed in Korean LT centers.

EXTENDED CRITERIA FOR PRIMARY LIVER TRANSPLANTATION

Expanded Criteria for LDLT in Asan Medical Center (Asan Medical Center Criteria, 2008) [10]

On the basis of the single-center results from 221 HCC

patients undergoing LDLT from 1997 to 2004, the authors proposed modified criteria for LDLT to expand recipient selection without increasing the posttransplant recurrence of HCC. The expanded criteria based on explant pathology were the largest tumor diameter ≤ 5 cm, HCC number ≤ 6 , and no gross vascular invasion. One hundred eighty-six of the 221 HCC patients (84.2%) met the Asan Medical Center criteria, 10% and 5.5% more than those that met the Milan and University of California at San Francisco (UCSF) criteria, respectively. The 5-year overall patient survival (OS) rates were 76.0% and 44.5% within and beyond the Milan criteria, respectively; 75.9% and 36.4% within and beyond the UCSF criteria, respectively; and 76.3% and 18.9% within and beyond the Asan Medical Center criteria, respectively (Fig. 1). Although these three sets of criteria had similar prognostic prediction power, the Asan Medical Center criteria had the highest discriminatory power. The authors concluded that the expanded criteria for LDLT eligibility of HCC patients broadened the indications for patient selection and could more accurately identify patients who would benefit from LDLT [10].

This is the first indication criteria of LDLT for HCC based on a high-volume single-institution LDLT cohort in Korea. It adopted three radiological components including tumor size and number, and gross vascular invasion. The basic concept of the Asan Medical Center criteria was similar to that of the Milan criteria. However, the authors did not include α -fetoprotein (AFP) as a main component of the selection criteria due to difficulty in determining the cutoff

Fig. 1. Hepatocellular carcinoma recurrence and patient survival curves for 206 surviving patients after application of the Asan Medical Center criteria based on explant pathology. (A) Hepatocellular carcinoma recurrence curves showed 1-year, 3-year, and 5-year recurrence rates of 5.8%, 13%, and 15%, respectively, within the criteria and 43.3%, 73.6%, and 73.6%, respectively, beyond the criteria ($p < 0.001$). (B) The overall patient survival curves showed 1-year, 3-year, and 5-year survival rates of 94.3%, 87.5%, and 81.6%, respectively, within the criteria and 71.9%, 37.2%, and 20.7%, respectively, beyond the criteria ($p < 0.001$) [10].

values of pretransplant AFP concentration.

Extended Criteria for LDLT in Seoul St. Mary's Hospital, The Catholic University of Korea (2012) [11]

The authors intended to evaluate the possibility of expanding the selection criteria of LDLT to treat HCC. From 2000 to 2010, the authors retrospectively analyzed 71 patients who had undergone LDLT beyond the Milan criteria among the entire cohort of 199 patients with HCC. They evaluated the tumor biology as well as the OS and disease-free survival (DFS), seeking to identify the risk factors for tumor recurrence. Among the 71 patients beyond the Milan criteria, there were 18 recurrences and 30 deaths. Their 5-year OS and DFS rates were 52.3% and 67.7%, respectively. In multivariate analysis, tumor diameter, tumor number, and Edmondson-Steiner grade significantly

influenced the OS and DFS. According to their new criteria including tumor size ≤ 7 cm and number ≤ 7 , 86% of the patients would be included, compared to 64% using the Milan criteria. The 5-year DFS and OS rates according to the new criteria were comparable to those of the Milan criteria at 86.8% and 72.3% versus 86.8% and 73.4%, respectively (Fig. 2). The authors concluded that their new criteria appeared to achieve useful cut-off values beyond the Milan criteria [11].

Expanded Criteria for LT in Samsung Medical Center (2014) [12]

The authors aimed to evaluate the risk factors for HCC recurrence and proposed new criteria for LT based on pretransplant findings. One hundred eighty patients who underwent LT for HCC between 2002 and 2008 were re-

Fig. 2. Disease-free and overall survival comparison based on the Milan criteria and Catholic Medical Center (CMC) criteria. (A) Disease-free survival. (B) Overall patient survival [11].

viewed retrospectively. The outcome measures included the maximal tumor size and number of tumors revealed by radiological studies before transplantation, demographics, and tumor recurrence. Maximal tumor size >6 cm, >7 tumors, and AFP levels >1,000 ng/mL were identified as the independent prognostic factors of HCC recurrence in univariate and multivariate analyses. The DFS rates in patients with a maximal tumor size ≤6 cm, ≤7 tumors, and/or AFP levels ≤1,000 ng/mL at 1 year, 3 years, and 5 years were 97.9%, 91.5%, and 90.0%, respectively; however, the 1-year, 3-year, and 5-year DFS rate of patients who had a maximal tumor size >6 cm, >7 tumors, and/or AFP levels >1,000 ng/mL were 61.9%, 47.6%, and 47.6%, respectively ($p<0.001$, Fig. 3). The authors concluded that LT could improve the survival of patients with advanced HCC if they had a maximal tumor size ≤6 cm, tumor number ≤7, and/or AFP levels ≤1,000 ng/mL [12].

The Samsung Medical Center criteria added a cutoff value of AFP levels ≤1,000 ng/mL to the conventional radiological finding-based criteria. LDLT comprised 87% of the study cohort.

Expanded Criteria for LT in National Cancer Center Korea (2016) [13]

The authors aimed to expand the LDLT pool of eligible patients with HCC using new morphological and biological criteria. A total of 280 patients with HCC who underwent LDLT from 2005 to 2013 were enrolled. OS and DFS analyses were performed in the patients to evaluate the usefulness of the new criteria using 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and total tumor size of 10 cm. The 5-year OS and DFS rates for patients

who fulfilled the criteria were 85.2% and 84.0%, respectively, and were significantly higher than those beyond the new criteria (60.2% and 44.4%, respectively; $p<0.001$; Fig. 4). The correlation analysis between the preoperative imaging tests and the pathologic reports using Cohen's kappa demonstrated better results using the new criteria than when using the Milan criteria (0.850 vs 0.583). The authors concluded that the new criteria using a hybrid concept of both morphological and biological parameters showed excellent agreement between the preoperative imaging and pathological results, and favorable survival outcomes. These new criteria might be helpful in selecting the optimal patients with HCC awaiting LDLT and expanding the selection pool.

The National Cancer Center Korea included FDG-PET findings as a biological parameter of tumor biology because positive FDG-PET findings in patients with HCC predicted prognosis and tumor recurrence after LT [14].

Model to Predict Tumor Recurrence after LDLT (MoRAL) in Three Centers Including Seoul National University, National Cancer Center Korea and Samsung Medical Center (2016) [15]

The authors intended to develop and validate a model to predict tumor recurrence after LDLT (MoRAL) for HCC beyond the Milan criteria. This multicenter study included a total of 566 consecutive patients who underwent LDLT in the beyond-Milan criteria cohort ($n=205$, the derivation [$n=92$] and validation [$n=113$] sets) and the within-Milan criteria cohort ($n=361$). The primary endpoint was time-to-recurrence. Using the multivariate Cox proportional hazards model, they derived the MoRAL score using serum levels

Fig. 3. Disease-free survival curves according to the Samsung Medical Center (SMC) criteria based on (A) radiological and (B) pathological findings [12].

Fig. 4. Overall and disease-free survival rates according to the National Cancer Center Korea (NCCK) criteria with preoperative imaging findings (A) and explant pathology (B) [13].

of protein induced by vitamin K absence or antagonist II (PIVKA-II) and AFP, which provided a good discriminant function for time-to-recurrence (concordance index=0.88). The concordance index was maintained similarly on both internal and external validations (mean 0.87 and 0.84, respectively). At a cutoff of 314.8 (75th percentile value), a low MoRAL score (≤ 314.8) was associated with significantly longer DFS (vs >314.8 , HR [hazard ratio]=5.29, $p<0.001$) (Fig. 5) and OS (HR=2.59, $p=0.001$) in the beyond-Milan criteria cohort. The 5-year DFS and OS rates of the beyond-Milan criteria patients with a low MoRAL score were as high as 66.3% and 82.6%, respectively. The within-Milan criteria patients with a high MoRAL score showed a higher risk of recurrence than the beyond-Milan criteria patients with a low MoRAL score (HR=2.56, $p=0.035$). The MoRAL score was significantly correlated with the explant histology. The authors concluded that this model using PIVKA-II and AFP provided refined prognostication. Among the beyond-Milan

criteria HCC patients, those with a MoRAL score ≤ 314.8 and without extrahepatic metastasis might be potential candidates for LDLT [15].

The MoRAL score added the concept of serum tumor markers to the conventional radiological finding-based criteria, focused on the discrimination of high-risk patients beyond the Milan criteria.

AFP-PIVKA-II 200 Criteria in Pusan National University (2016) [16]

The Milan criteria have been widely accepted for indicating patients with HCC suitable for LT. However, a 7% to 20% possibility of HCC recurrence remains, even among patients who fulfill the Milan criteria. The authors reviewed 88 patients with HCC who underwent LT from 2010 to 2014. The risk factors for HCC recurrence were analyzed, and the OS and DFS rates were calculated based on each risk factor. Seventeen patients (19.3%) experienced HCC recur-

rence. Multivariate analyses revealed that the independent risk factors for HCC recurrence were PIVKA-II >200 mAU/mL, levels of >200 for AFP (ng/mL) or PIVKA-II (mAU/mL), and microvascular invasion. The authors defined the AFP-PIVKA-II 200 (A-P 200) criteria as simultaneously exhibiting AFP ≤200 ng/mL and PIVKA-II ≤200 mAU/mL. The 3-year OS rates among patients who fulfilled or exceeded the A-P

200 criteria were 89.2% and 80.0%, respectively ($p=0.79$). The 3-year DFS rates among patients who fulfilled or exceeded the A-P 200 criteria were 89.9% and 43.1%, respectively ($p<0.001$) (Fig. 6). The authors concluded that these findings confirm that the A-P 200 criteria could be used to predict recurrence after LT among patients with HCC [16].

The A-P 200 criteria adopted only serum tumor markers without radiological findings of tumor size and number.

Fig. 5. The cumulative risk of tumor recurrence according to the Milan criteria (MC) and the model to predict tumor recurrence after living donor liver transplantation (MoRAL) score using a cut off of 314.8. The risk of recurrence decreased in the following order: beyond MC/high MoRAL score > within MC/high MoRAL score > beyond MC/low MoRAL > within MC/low MoRAL score ($p<0.001$). The patients within MC with high MoRAL score experienced higher recurrence than the patients beyond MC with low MoRAL score (hazard ratio=2.56, $p=0.035$) [15].

Patient Selection by Tumor Markers in LT for Advanced HCC in 8 Centers Including Seoul National University Hospital, Seoul National University Bundang Hospital, Seoul National University Boramae Medical Center, Asan Medical Center, Samsung Medical Center, National Cancer Center Korea, Yonsei University Severance Hospital, and Korea University Anam Hospital (2018) [17]

Far advanced HCC is generally considered a contraindication for LT, but the biologically favorable tumors among them could show acceptable results. However, it is still unclear which tumors can be treated with LT. Data were collected on adult patients who underwent LT for HCC beyond the Milan criteria in 8 Korean LT centers between 2000 and 2013. Far advanced HCC was defined as HCC with the largest tumor ≥10 cm, 10 or more tumor nodules, or accompanying macrovascular invasion. A total of 688 patients, including 169 with far advanced HCC, were enrolled in the study. The 5-year OS and DFS rates were 60.4% and 55.1% respectively for all patients, but only 28.7% and 24.8% respectively for patients with far-advanced HCC ($p<0.001$). Both preoperative AFP and PIVKA-II were significant risk

Fig. 6. Overall survival and disease-free survival according to the A-P 200 criteria. (A) The 3-year overall survival rates for patients who were within and patients who exceeded the A-P 200 criteria were 89.2% and 90.3%, respectively ($p=0.92$). (B) The 3-year disease-free survival rates for the patients who were within and patients who exceeded the A-P 200 criteria were 89.0% and 43.6%, respectively ($p<0.001$) [16].

factors for HCC recurrence after LT. In particular, combined AFP+PIVKA-II was a better predictor than either marker alone. Of all far advanced HCC patients with available AFP and PIVKA-II levels, 45 (30.8%) had low AFP+PIVKA-II (≤ 300) and their 5-year DFS and OS rates were 47.8% and 53.4%, respectively, which were acceptable and significantly superior to those of patients with AFP (ng/mL)+PIVKA-II (nAU/mL) >300 (21.0% and 10.8%, respectively; $p<0.001$) (Fig. 7). The authors concluded that the patients with favorable HCC had acceptable outcomes after LT even when their tumors were extremely advanced. The AFP+PIVKA-II sum provided reliable information on the tumor biology of far-advanced HCC [17].

This study suggested that the degree of serum tumor marker expression was closely associated with posttransplant HCC recurrence in patients with HCC far beyond the

Milan criteria.

Composite Criteria Using Clinical and FDG PET Factors in Seoul National University Hospital and Samsung Medical Center (2019) [18]

The authors retrospectively enrolled 239 patients who underwent LDLT between 2005 and 2013. On PET, maximum tumor-to-background ratio (TBRmax) was measured. Significant predictors for recurrence were selected by logistic regression and survival analyses. With varying cutoff values for the selected factors, composite criteria were designed to maximize the predictive performance for recurrence, and tenfold cross-validation was performed. Tumor size, number, AFP, and TBRmax were selected as significant predictors in both logistic regression and multivariate survival analyses. In combination of these factors,

Fig. 7. Recurrence-free survival after liver transplantation (LT) in subgroups with far advanced hepatocellular carcinoma. (A) Comparison of tumor markers in only patients with tumor size ≥ 10 cm. (B) Comparison of tumor markers in only patients with 10 or more tumors. (C) Comparison of tumor markers in only patients with macrovascular invasion. (D) Comparison of macrovascular invasion for all patients with far advanced hepatocellular carcinoma. There were significant differences between the low-risk (AFP+PIVKA-II ≤ 300) and high-risk (AFP+PIVKA-II >300) patients in all subgroups. The presence of macrovascular invasion was not as effective as the sum of AFP+PIVKA-II to predict tumor recurrence in the far advanced group [17].

the highest diagnostic performance was sensitivity of 75.7% and specificity of 88.5% with cutoff values of tumor size <6.0 cm, tumor number <8, alpha-fetoprotein <465 ng/mL, and TBRmax <2.8. The composite criteria exhibited the

highest performance for predicting tumor recurrence and DFS among the tested criteria including conventional ones (Fig. 8). The authors concluded that the composite criteria adding FDG PET findings to clinical factors are effective in

Fig. 8. Kaplan-Meier survival curves according to each patient selection criteria. In comparison with other criteria (A–E), the composite criteria exhibited the highest predictive value for recurrence-free survival (RFS) (F) [18].

Fig. 9. Kaplan-Meier probability of hepatocellular carcinoma (HCC) recurrence within 5 years for living donor liver transplant recipients in the development and validation groups [19].

selecting appropriate liver cancer patients who are candidates for LT.

This study suggested that hypermetabolic uptake of FDG PET is a significant risk for tumor recurrence in addition to the conventional risk factors.

Tumor Size and Number, AFP, PIVKA-II, FDG PET (SNAPP) Score in Asan Medical Center (2021) [19]

The authors aimed to develop and validate the new score system by using morphologic and biologic data. Predictors for HCC recurrence after LDLT were developed (n=627) and validated (n=806) in 1,433 patients between 2007 and 2016 to create the SNAPP score (tumor Size and

Number, AFP, PIVKA-II, and PET). On logistic regression based on 3-year DFS, the SNAPP factors were independently associated with HCC recurrence. The SNAPP score was highly predictive of HCC recurrence (C statistic, 0.920), and 5-year post-LT recurrence rates were significantly different between low, intermediate, and high SNAPP score groups. The performance of the SNAPP score (C-index [95% confidence interval], 0.840 [0.801–0.876]) on predicting tumor recurrence after LDLT was better than that of the New York/California, the Risk Estimation of Tumor Recurrence After Transplant, and MoRAL score (Fig. 9). The authors concluded that the SNAPP score provides excellent prognostication after LDLT for HCC patients.

Fig. 10. Tumor recurrence and patient survival according to the pretransplant ADV scores in the treatment-naïve (TN) and pretransplant-treated (PT) groups. (A) Tumor recurrence (left) and overall patient survival (right) curves according to the pretransplant ADV scores in the TN group. (B) Tumor recurrence (left) and overall patient survival (right) curves according to the explant ADV scores in the TN group [20].

This study also suggested that hypermetabolic uptake of FDG PET is a significant risk for tumor recurrence in addition to the conventional risk factors.

Quantitative Prognostic Prediction Using AFP-PIVKA-II-Tumor Volume (ADV) Score in Asan Medical Center (2021) [20]

The authors assessed the prognostic impact of AFP-des- γ -carboxyprothrombin [DCP or PIVKA-II]-tumor volume (ADV) score for predicting HCC recurrence and OS after LDLT. This study included 843 patients who underwent LDLT for HCC between 2006 and 2015. These cases were divided into the treatment-naïve (n=256) and pretransplant-treated (n=587 [69.6%]) groups. There was weak or nearly no correlation between AFP, PIVKA-II and tumor volume. There were high correlations between the pretransplant and explant findings regarding tumor number, size, and ADV score. HCC recurrence and all-cause patient death occurred in 182 (15.9%) and 126 (15.0%) patients respectively, during the follow-up period of 75.6 ± 35.5 months. The 5-year tumor recurrence and OS rates were 21.5% and 86.2%, respectively. The pretransplant-treated group showed higher tumor recurrence ($p < 0.001$) and lower overall survival rates ($p < 0.001$). Tumor recurrence and OS were closely correlated with both the pretransplant and explant ADV scores in the treatment-naïve and pretransplant-treated groups (Fig. 10). The ADV score enabled further prognostic stratification of the patients within and beyond the Milan, UCSF, and Asan Medical Center criteria. Compared to the 7 pre-existing selection criteria, ADV score with a cutoff of 5log showed the highest prognostic contrast regarding

tumor recurrence and OS (Fig. 11). Prognostic prediction diagrams using pretransplant ADV scores were visualized to present the tumor recurrence and OS at 5 years (Fig. 12). The authors concluded that this prognostic prediction model using ADV scores was an integrated, quantitative surrogate biomarker for posttransplant prognosis in HCC patients and could provide reliable information to assist in the decision-making for LDLT.

The majority of the currently available selection criteria for HCC involve yes-or-no dual concepts and their cutoffs are derived from statistical analyses. In contrast, the ADV score is an integrated surrogate marker enabling the reliable prediction of posttransplant prognosis in a quantitative manner. Currently, there are only two selection criteria enabling quantitative prognostic prediction, Metroticket 2.0 criteria [21] and ADV score [20]. The posttransplant prognosis of HCC patients according to the Metroticket 2.0 criteria (tumor diameter+number) ≤ 7 & AFP $\leq 200/400/1,000$ ng/mL is comparable to that of ADV score < 5 log [20]. The ADV score appears to be intuitive in assessing prognosis because there is only one continuous value.

SELECTION CRITERIA FOR SALVAGE LIVER TRANSPLANTATION

Prognostic Prediction Model with Time of Post-resection HCC Recurrence, Milan Criteria and AFP in 3 Centers Including Samsung Medical Center, Ajou University and Seoul National University (2014) [22]

Salvage LT is considered a feasible option for the treatment of recurrent HCC. The authors performed a multi-

Fig. 11. Tumor recurrence and patient survival curves according to the pretransplant ADV score with a cutoff of 5log. (A) Tumor recurrence. (B) Overall patient survival [20].

Fig. 12. Prognostic prediction diagrams according to the ADV scores. Diagrams showing the probability of tumor recurrence (A) and overall patient survival (B) at posttransplant 5 years according to the prediction model using pretransplant ADV scores [20].

center study to assess the risk factors associated with HCC recurrence and OS after salvage LT. Between 2000 and 2011, 101 patients who had previously undergone liver resection for HCC underwent LT at 3 transplant centers. The data of 69 patients were retrospectively reviewed for analysis. HCC recurrence was diagnosed at a median of 10.6 months after the initial liver resection, and the patients underwent salvage LT. Recurrences were within the Milan

criteria in 48 cases and were outside the Milan criteria in 21 cases. After salvage LT, 31 patients had HCC recurrence during a median follow-up period of 24.5 months. There were 24 deaths, and 20 were due to HCC recurrence. The 5-year OS rate was approximately 54.6%, and the 5-year DFS rate was 49.3%. HCC recurrence within 8 months after liver resection [HR=3.124, p=0.009], AFP >200 ng/mL (HR=2.609, p=0.02), and HCC outside the Milan criteria at salvage LT

(HR=2.219, $p=0.03$) were independent risk factors for poor DFS after salvage LT (Fig. 13). The authors concluded that the timing and extent of HCC recurrence after primary liver resection both played significant roles in the outcome of salvage LT [22].

This guideline was accepted as reasonable selection criteria for salvage LDLT after its publication. However, the treatment response for post-resection tumor recurrence was not taken into account in the analysis; thus, further validation studies were necessary. Early tumor recurrence after liver resection was not a significant risk factor for posttransplant tumor recurrence in a recent high-volume study [23].

Quantitative Prognostic Prediction Using ADV Score in Asan Medical Center (2020) [23]

The prognostic accuracy of ADV score was assessed in patients undergoing salvage LDLT and their outcomes were compared with patients undergoing primary LDLT. Tumor recurrence and OS outcomes were compared in 125 patients undergoing salvage LDLT from 2007 to 2018 and in 500 propensity score-matched patients undergoing primary LDLT. In the patients undergoing salvage LDLT, the median intervals between hepatectomy and tumor recurrence, between the first HCC diagnosis and salvage LDLT, and between hepatectomy and salvage LDLT were 12.0,

Fig. 13. Survival analyses of patients after salvage liver transplantation according to the number of risk factors (tumor recurrence within 8 months after liver resection, serum AFP levels >200 ng/mL at transplantation, beyond the Milan criteria at transplantation). (A) Recurrence-free survival was significantly decreased with an increasing number of risk factors ($p<0.001$) except between the subgroups with 1 and 2 risk factors (not significant). (B) The overall survival did not differ between subgroups with 1, 2 or 3 risk factors; however, the survival for all these subgroups was significantly decreased in comparison to the survival of the subgroup with no risk factors ($p<0.001$) [22].

Fig. 14. Posttransplant disease-free survival (DFS) curves according to (A) the duration of disease-free survival period after hepatectomy and (B) the interval between hepatectomy and living donor liver transplantation [23].

37.2, and 29.3 months, respectively. DFS ($p=0.98$) and OS ($p=0.44$) rates did not differ significantly in patients undergoing salvage and primary LDLT. Pretransplant and explant ADV scores were significantly predictive of DFS and OS in patients undergoing salvage LDLT ($p<0.001$) (Fig. 14). The DFS after prior hepatectomy ($p=0.52$) and interval between hepatectomy and LDLT ($p=0.82$) did not affect DFS after salvage LDLT (Fig. 15). The Milan criteria and ADV score were independently prognostic of DFS and OS following salvage LDLT, and the prognosis of the patients within and beyond the Milan criteria could be further stratified by ADV score (Fig. 16). The authors concluded that the risk factors and posttransplant outcomes were similar in patients undergoing salvage and primary LDLT. The ADV score is a surrogate biomarker for posttransplant prognosis in both salvage and primary LDLT recipients. Prognostic models incorporating ADV scores can help determine whether to perform salvage LDLT [23].

The ADV score alone or in combination with the Milan criteria enables the reliable prediction of the posttransplant prognosis following salvage LDLT, as in primary LDLT.

POSTTRANSPLANT PROGNOSTIC PREDICTION OF EARLY OR NON-VIABLE HCC

Super-selection Criteria from Asan Medical Center (2011) [24]

The majority of patients with HCC undergoing LT meet the Milan criteria, which are regarded as the narrowest criteria for LT. The prognostic analysis of incidentally detected HCC after LT suggested that a subgroup of HCC patients was at very low risk of recurrence. To determine the criteria defining this super-selection group, the authors retrospectively analyzed the survival data of 593 adult LDLT recipients with HCC in the explanted liver. The tumor features of incidental HCC in 38 patients not showing recurrence

Fig. 15. Disease-free survival (DFS) and overall survival (OS) in 125 patients who underwent salvage living donor liver transplantation. The patients were also stratified by 1log intervals of pretransplant ADV scores (A, B) and by pretransplant ADV score cutoffs of 4.0 log and 6.0 log (C, D) [23].

Fig. 16. Disease-free survival (DFS) in (A, B) 86 patients within the Milan criteria (C, D) and in 39 patients beyond the Milan criteria stratified according to 1log intervals of explant ADV scores (A, C) and by two explant ADV score cutoffs of 4.0 log and 6.0 log (B, D) [23].

were analyzed. Of these patients, 34 (89.5%) each had ≤2 tumors and tumors ≤2.0 cm in size. Applying these criteria to 555 patients with pretransplant known HCC allowed to identify 79 patients with untreated pretransplant known HCCs ≤2.0 cm in size. Only two of these patients showed recurrence, making the conditions for super-selection the presence of tumors ≤2.0 cm in size, ≤2 tumors, AFP ≤ 200 ng/mL, and no pretransplant treatment. In 87 patients satisfying these criteria, the 10-year tumor recurrence and OS rates were 1.3% and 92.1%, respectively (Fig. 17). After excluding patients meeting these criteria, the 5-year recurrence rates in patients satisfying the Milan, UCSF, and Asan Medical Center criteria were increased by 2.9%–4.0%. The authors concluded that this super-selection or super-Milan category may be used for validating the assessment of various indication criteria and for developing cost-effective posttransplant HCC surveillance protocols [24].

Fig. 17. Cumulative tumor recurrence rates in patients with incidentally diagnosed hepatocellular carcinoma (iHCC) and untreated small pre-transplant known hepatocellular carcinoma (pkHCC) ≤2.0 cm in size (p=0.27) [24].

Fig. 18. Comparison of tumor recurrence and patient survival curves after hepatic resection (HR) and liver transplantation (LT). (A) Comparison of the tumor recurrence curves showed $p < 0.001$ between the HR groups and $p = 0.019$ between the LT groups. (B) Comparison of the patient survival curves showed $p < 0.001$ between the HR groups and $p = 0.11$ between the LT groups [25].

The super-selection criteria are regarded as the narrowest criteria for LT ever presented. They can be used for predicting the prognosis of the incidentally detected HCC in the explanted livers.

Prognostic Impact of Pretransplant Treatment-induced Complete Tumor Necrosis from Asan Medical Center (2017) [25]

Transarterial chemoembolization (TACE)-induced complete tumor necrosis is known to improve the postresection outcomes of HCC. The authors aimed to assess the prognostic effects of complete tumor necrosis after preoperative TACE for HCC in patients who underwent LT. The clinical outcomes of patients showing complete tumor necrosis after LT ($n = 233$) were analyzed. The control groups comprised patients with minimal recurrence risk as naïve one or two HCCs ≤ 2 cm for LT ($n = 184$). The 1-year, 3-year, and 5-year tumor recurrence rates were 4.1%, 7.9%, and 7.9%, respectively, which were higher than those of the controls ($p = 0.019$). The 1-year, 3-year, and 5-year OS rates were 92.7%, 89.2%, and 86.9%, respectively, which were not different than those of controls ($p = 0.11$) (Fig. 18). The LT recipients had lower recurrence and higher OS rates compared to the hepatic resection patients ($p < 0.001$). The authors concluded that the prognostic effect of TACE-induced complete tumor necrosis for HCC patients appeared to be limited to downstaging. The LT recipients benefited more from complete tumor necrosis than the hepatic resection patients [25].

Complete tumor necrosis is defined as the absence of viable HCC in the explanted liver; however, risk of HCC

recurrence still exists because it appears to be a downstaging of the disease. An ADV score of 0 can theoretically be obtained in patients showing complete tumor necrosis, in which the prognosis of these patients was quite comparable to that of patients with ADV scores < 2 log [20].

DISCUSSION

It is difficult to predict the posttransplant prognosis of patients who have undergone LT for the treatment of HCC because the tumor burden at LT varies widely, HCC tumor biology is heterogeneous, and there are potential influences of continued immunosuppression. To reduce the risk of posttransplant HCC recurrence, many selection criteria have been proposed since the publication of the Milan criteria in 1996 [26].

The selection criteria of LT for HCC in Asian countries are different from those in Western countries because the indication of the former is LDLT whereas that of the latter is deceased donor LT. Considering the features of LDLT with a close relationship between the donor and recipient, the target survival rates in LDLT can be lower than those of deceased donor LT. In clinical practice, LDLT has occasionally been directed to a certain recipient with advanced HCC far beyond the eligible criteria [17]. Because of the unique features of LDLT, the indeterminate survival outcome, such as the 5-year OS rate of 50%, can be rationalized without a critical impairment of donor ethics [27]. However, early HCC recurrence leading to futile LT can evoke serious psychosocial issues with respect to living donors [27,28]. Because more than a negligible proportion of patients beyond

the Milan or UCSF criteria survived for a long time, it is not reasonable to decisively reject the patients with advanced HCC who earnestly want to receive LDLT with the expectation of faint but prolonged survival. Thus, there is a real need to modify the existing indication criteria to effectively exclude truly high-risk HCC patients [10].

The majority of conventional selection criteria for LT for HCC are based on tumor size and number, and some also include the AFP or DCP values. From the viewpoint of HCC biology, the tumor size and number are quantitative components of tumor burden, whereas tumor marker expression can be a qualitative component of tumor burden. In a cohort including 1,176 cases of liver resection for HCC, there was no significant correlation between the combinations AFP and tumor volume ($r^2=0.125$, $r=0.353$, $p<0.001$), AFP and tumor diameter ($r^2=0.079$, $r=0.281$, $p<0.001$), PIVKA-II and tumor volume ($r^2=0.237$, $r=0.486$, $p<0.001$), PIVKA-II and tumor diameter ($r^2=0.217$, $r=0.465$, $p<0.001$), and AFP and PIVKA-II ($r^2=0.082$, $r=0.287$, $p<0.001$) [29]. Tumor size and number, tumor volume, AFP and PIVKA-II are independent prognostic factors. Therefore, the quantitative and qualitative components of HCC should be taken into account concurrently for the prognostic prediction of HCC.

Recent trends in developing prognostic prediction models of LT for HCC include the Milan criteria as the quantitative component and the expression of AFP and/or PIVKA-II as the qualitative component. The expression of tumor markers can be used as a complementary guideline in patients beyond the Milan criteria [12,15,17]. Various combinations of the expression levels of AFP and PIVKA-II were used as simple addition or the addition of the square root to determine the cutoff values in the development cohorts. Such calculation methods for tumor markers also have a definite limitation of a yes-or-no dual concept, as does the Milan criteria. Although both AFP and PIVKA-II are significant risk factors, the selection criteria in Western countries use only AFP because PIVKA-II is not routinely measured [21,30]. In contrast, the Kyoto criteria include tumor size, number and PIVKA-II, but the AFP level is omitted [31]. Because the measurement of both AFP and PIVKA-II has been routinely performed in Korea, the selection criteria developed in Korea usually include these two tumor markers at to enhance the predictive power [12,15,16,20]. A retrospective data analysis of the Japanese nationwide survey established new expanded criteria for LDLT candidates with HCC, the 5-5-500 rule (nodule size ≤ 5 cm in diameter, nodule number ≤ 5 , and AFP value ≤ 500 ng/mL), which showed a 5-year tumor recurrence rate of 7.3% [32].

Compared with the patients undergoing liver resection for HCC, those undergoing LDLT have unique tumor features such as a higher incidence of multiple tumors and a more frequent history of pretransplant treatment [25]. In clinical practice for LDLT in Korea, the incidence of upfront LDLT for HCC has been decreasing because the treatment response is regarded as a reliable parameter to assess the tumor aggressiveness. At this time, a question exists regarding the posttransplant prognosis of patients with down-staged HCC compared to those with treatment-naïve HCC. In the prognostic prediction model using ADV scores, comparable outcomes were obtained if the ADV scores of down-staged and treatment-naïve HCCs were similar [20]. When HCC exceeds the institutional selection criteria during pretransplant evaluation for LDLT, various locoregional treatments including TACE and radiofrequency ablation have been performed to see the treatment responses. If noticeable down-staging effects occurred, the patients might be selected for LDLT. Otherwise, the majority of the patients might be dropped from LDLT consideration and treated with non-surgical therapeutic modalities.

How to assess the degree of the down-staging effects is a matter of major concern. The expression of AFP and PIVKA-II is simple to use to assess the treatment response because they are continuous variables. Regarding tumor size and number, it is reasonable to use Modified Response Evaluation Criteria In Solid Tumors (mRECIST) because it includes only the viable portion of the HCC [33]. It has been reported that there exists a reliable correlation between the results of pretransplant imaging and explant/resection pathology regarding the size of the viable tumors [34-36]. In patients who have undergone TACE before LT, the tumor size and number can be estimated by measuring the contrast-enhancing portions of the tumors, and lipidolized zones were considered non-enhancing lesions as adopted in the mRECIST criteria, which can offset the different therapeutic effects of the preceding HCC treatments. In real-world situations involving LDLT, most of the prior HCC treatments have been performed with curative intent, rather than as a down-staging intervention or neoadjuvant therapy. Such locoregional treatments have been repeatedly performed to control the recurrence of HCC lesions, and patients would ultimately face the situation of choosing LDLT or the best supportive care with or without systemic chemotherapy. Since the pretransplant clinical course of HCC is often complex, it is difficult to predict the posttransplant prognosis of patients with HCC. Treatment response is one of the important parameters for predicting the post-

transplant prognosis of HCC patients.

FDG PET is reported to be an effective method of predicting HCC recurrence after LT [13,14,18,19,37-39]. However, the definition of hypermetabolic uptake in FDG PET findings is widely variable in the studies reported in the literature, thus a consensus concept is necessary to determine the FDG PET finding as a major component of prognostic prediction model. In addition, significant changes in hypermetabolic FDG PET findings after locoregional therapies remain an issue of validation.

The majority of the currently available selection criteria for HCC involve yes-or-no dual concepts and their cutoffs are derived from statistical analysis of the development cohort. Currently, there are only two selection criteria enabling quantitative prognostic prediction, Metroticket 2.0 criteria [21] and ADV score [20]. The Metroticket version 1.0 model was updated to version 2.0 by addition of AFP and removal of microvascular invasion [21,40]. One difference between ADV score-based prognostic prediction and Metroticket version 2.0 study was the integration of PIVKA-II. The prognostic predictive powers of the ADV score-based model and the Metroticket 2.0 criteria were similar [20], but the former provides more detailed prognostic information, especially in patients with high PIVKA-II expression or multiple tumors ≥ 10 . Furthermore, the cutoff values of the ADV score are not fixed and detailed prognostic information can therefore be obtainable in patients with any range of ADV scores. These features of the two models enabling quantitative prognostic prediction appear to be helpful in selecting patients with advanced HCC not satisfying the pre-existing selection criteria.

Recently, the incidence of salvage LDLT has gradually increased along with the increase in the number of liver resections for HCC [41]. A Korean multicenter study proposed a 3-factor prognostic prediction model including HCC recurrence within 8 months after liver resection, AFP >200 ng/mL and HCC outside the Milan criteria at salvage LT. This guideline has been accepted as reasonable selection criteria for salvage LDLT. However, various treatment responses for post-resection tumor recurrence were not taken into account; thus, further validation study was necessary. A recent high-volume single-institution study demonstrated that early tumor recurrence after liver resection was not a significant risk factor for posttransplant tumor recurrence, in which a 2-factor prognostic prediction model with the Milan criteria and the ADV score at a cutoff of 4 log was proposed [23].

The importance of tumor biology in the treatment of

HCC has been emphasized more than before. The expression of AFP and PIVKA-II is a surrogate biomarker demonstrating tumor biology. Pretransplant radiological assessment of HCC combined with tumor marker expression or PET finding will provide reliable information that will assist in the decision to perform LDLT in patients with HCC of various stages.

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