Validation for models for tumor recurrence after liver transplantation in hepatectomy patients

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Purpose: Early recurrence of hepatocellular carcinoma (HCC) remains a challenging issue after hepatic resection (HR) because of the associated poor prognosis. Models for tumor recurrence after liver transplantation (MoRAL) have been designed to predict tumor recurrence in HCC patients in the liver transplantation setting. This study aimed to validate the predictability of MoRAL for HCC recurrence or patient death and to evaluate the predictors of early HCC recurrence in hepatectomy patients with treatment-naïve solitary HCC.

Methods: This study included 443 patients with HCC recurrence after HR from January 2005 to December 2011. Patients were stratified into early recurrence (n = 312) and late recurrence (n = 131) groups according to the development of recurrence either within or more than 2 years after hepatectomy.

Results: The median levels of alpha-fetoprotein and protein induced by vitamin K absence-II and the median MoRAL score were significantly higher in the early recurrence group than in the late recurrence group. Regarding pathologic characteristics, the median tumor size, prevalence of tumor grade 3 or 4, microvascular invasion, presence of tumor necrosis, and macrovascular invasion in the early recurrence group were greater than those in the late recurrence group. Multivariate analysis showed that tumor grade 3 or 4, microvascular invasion, and high preoperative MoRAL score were predisposing factors for early HCC recurrence after HR.

Conclusion: The MoRAL score can be used to predict early recurrence in patients with HCC who undergo curative HR. Using this model, other treatments could be considered for patients with early recurrence predicted after HR.

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Key Words: Biochemical tumor markers, Hepatocellular carcinoma, Neoplasm recurrence, Prognosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide [1,2]. Although various treatment strategies have been developed for HCC, hepatic resection (HR) is considered the initial curative treatment strategy for HCC, along with liver transplantation (LT) in especially early HCC [3]. However, HCC recurrence after HR is the primary limitation reducing the effectiveness of HCC treatment because of its high incidence [4]. In particular, early recurrence leads to a worse survival rate among patients [5,6]. Traditionally, serum tumor markers including α-FP and
protein induced by vitamin K absence-II (PIVKA-II) have been considered monitoring factors or potential predictors of poor prognosis after multimodal treatments for HCC as they are indirect indicators of tumor aggressiveness [7-10].

A tumor recurrence prediction model based on a combination of PIVKA-II and α-FP for HCC patients after living donor LT (LDLT) beyond the Milan criteria was previously introduced for predicting HCC recurrence [11]. The models for tumor recurrence after liver transplantation (MoRAL) score (\(11 \times \sqrt{\text{PIVKA-II}} + 2 \times \sqrt{\alpha\text{-FP}}\)) employs 2 tumor markers [11]. A previous study reported that a low MoRAL score (<314.8 points) was closely associated with better recurrence-free survival and overall survival after LDLT compared with a high MoRAL score because MoRAL score reflects tumor aggressiveness and biology [11].

However, no study employing the MoRAL score in HR in HCC patients has been reported. On the basis of the usefulness of the MoRAL score in predicting tumor aggressiveness, we hypothesized that the MoRAL score can predict patient prognosis following HR for treatment-naïve solitary HCC. The purpose of this study is to validate the predictability of MoRAL for HCC recurrence or patient death and to evaluate the predictors of early HCC recurrence after HR in patients with treatment-naïve solitary HCC.

**METHODS**

**Patients**

This study included patients with recurrent HCC after HR, which was diagnosed on the basis of several guidelines and histologically confirmed after HR at Seoul National University Hospital (SNUH; n = 938) or Samsung Medical Center (SMC; n = 1,382) from January 2005 to December 2011 [12,13].

This study was approved by the Institutional Review Boards (IRBs) at 2 participating centers (No. 1807-084-059 from SNUH and No. 2019-09-069-003 from SMC). The need for informed consent was waived by the IRBs because of the retrospective investigation.

Solitary HCC patients with Child-Pugh class A and preoperative α-FP and PIVKA-II records who underwent curative HR were included. Patients with the following characteristics were excluded: no preoperative data on either α-FP or PIVKA-II, R1 resection, ruptured HCC, non-Korean status, history of malignancy other than HCC, under 18 years of age, history of adjuvant therapy after HR, or loss to follow-up after HR. Finally, 443 patients were identified for inclusion in our study. Patient medical information was retrospectively investigated.

**Definition**

The early recurrence group was defined as patients with HCC recurrence within 2 years after HR and the late recurrence group was defined as patients with HCC recurrence more than 2 years after HR. Surgical HR of more than 3 segments was defined as major resection. In addition, when HCC recurrence was diagnosed by radiologic imaging, the presence of 10 or more intrahepatic tumor numbers was defined as diffuse intrahepatic tumor recurrence.

**Surgery and surveillance**

The surgical procedure of HR and the histological evaluation of specimens have been previously described [8,9]. All patients who underwent HR visited outpatient services one month after their surgery and then every 2 or 3 months thereafter. At the outpatient visit, the patients were evaluated for blood tests, liver function tests, α-FP, PIVKA-II, and radiologic tests. Liver CT and liver MRI were alternately examined every 3 months for 2 years after surgery.

**Treatment of recurrence**

When HCC recurrence was detected during follow-up after HR, patients were treated within 2 months after HCC recurrence. Solitary intrahepatic recurrent HCC patients with Child-Pugh class A underwent re-resection. Radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI) was considered in cases of solitary HCC measuring less than 3 cm when re-resection was difficult or dangerous to conduct. Transarterial chemoembolization (TACE) was considered when multiple intrahepatic recurrences were detected or when re-resection, RFA, or PEI was difficult. Salvage LDLT was considered if decompensated liver function and potential living liver donors were present. Combined TACE and RFA (TACE-RFA) was performed in SMC in intrahepatic small solitary HCC when the approach of the percutaneous RFA needle was difficult due to tumor location. Systemic chemotherapy was not initially considered as a treatment in patients with intrahepatic HCC recurrence.

**Statistical analysis**

Categorical variables are expressed as numbers and percentages, and continuous variables are described as medians and ranges. Comparisons of categorical variables were performed using the chi-square test or Fisher exact test. The Mann-Whitney U-test was used for continuous variables. Disease-free survival (DFS) was considered as the period from the operation date to HCC recurrence date, and patient survival (PS) was defined as the period from the operation date to death date. Survival rates were analyzed using the Kaplan-Meier method with a log-rank test. All significant predictors of early recurrence in bivariate analysis were analyzed in a binary logistic regression model to show independent values by multivariate analysis. All tests were 2-sided, and statistical significance was defined as P < 0.05. All statistical analyses
were performed using IBM SPSS Statistics ver. 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

The baseline characteristics of the early and late recurrence groups are summarized in Table 1. Of the 443 study participants, 312 (70.4%) were included in the early recurrence group. Median α-FP and PIVKA-II levels were 61 ng/mL (range, 2–356,800 ng/mL) and 143 mAU/mL (range, 2–48,000 mAU/mL) respectively, in the early recurrence group and 12 ng/mL (range, 2–21,137 ng/mL) and 44 mAU/mL (range, 2–9,030 mAU/mL) in the late recurrence group. Accordingly, the median MoRAL score in the early recurrence group was significantly higher than that in the late recurrence group (182.8 points vs. 97.2 points, P < 0.001). There were no significant differences in sex, age, etiology, body mass index, hemoglobin concentration, hemoglobin concentration, platelet count, total bilirubin, AST, ALT, albumin, creatinine, INR, and ICG-R15 between the two groups. However, the early recurrence group had a significantly higher proportion of patients with an α-FP level ≥40 ng/mL and a MoRAL score >314.8 points.

Table 1. Baseline characteristics between early and late recurrence groups

| Characteristic                  | Early recurrence group (n = 312) | Late recurrence group (n = 131) | P-value |
|---------------------------------|----------------------------------|--------------------------------|---------|
| No. of patients                 | 312                              | 131                            |         |
| Age (yr)                        | 54 (19–82)                       | 57 (34–81)                     | 0.092   |
| Male sex                        | 260 (83.3)                       | 107 (81.7)                     | 0.680   |
| Etiology                        |                                   |                                | 0.726   |
| HBV                             | 254 (81.4)                       | 107 (81.7)                     |         |
| HCV                             | 12 (3.8)                         | 8 (6.1)                        |         |
| NBNC                            | 5 (1.6)                          | 2 (1.5)                        |         |
| Alcohol                         | 3 (1.0)                          | 2 (1.5)                        |         |
| Others                          | 38 (12.2)                        | 12 (9.2)                       |         |
| Body mass index (kg/m²)         | 24.2 (16.7–31.2)                 | 23.6 (14.7–36.3)               | 0.212   |
| Hemoglobin (g/dL)               | 14.3 (8.1–17.7)                  | 14.4 (7.0–17.8)                | 0.218   |
| Platelet (/μL)                  | 152,500 (13,900–547,000)         | 148,000 (12,800–298,000)       | 0.240   |
| Total bilirubin (mg/dL)         | 0.8 (0.2–2.0)                    | 0.8 (0.3–1.9)                  | 0.233   |
| AST (IU/L)                      | 37 (7–466)                       | 34 (10–225)                    | 0.072   |
| ALT (IU/L)                      | 38 (8–290)                       | 35 (7–186)                     | 0.119   |
| Albumin (g/dL)                  | 4.1 (2.8–5.1)                    | 4.1 (3.1–5.0)                  | 0.307   |
| Creatinine (mg/dL)              | 0.9 (0.4–7.3)                    | 0.9 (0.6–5.6)                  | 0.625   |
| INR                             | 1.09 (0.13–1.28)                 | 1.09 (0.76–1.36)               | 0.668   |
| α-FP, ≥40 ng/mL                 | 169 (54.2)                       | 49 (37.4)                      | 0.002   |
| PIVKA-II, ≥100 mAU/mL           | 117 (37.5)                       | 45 (34.4)                      | <0.001  |
| ICG-R15 (%)                     | 10.2 (0.3–73.5)                  | 11.3 (0.3–49.0)                | 0.512   |
| MoRAL score, >314.8 points      | 89 (28.5)                        | 12 (9.2)                       | <0.001  |

Values are presented as number only, median (range), or number (%).

NBNC, non-hepatitis B and non-hepatitis C; INR, international normalized ratio; PIVKA-II, proteins induced by vitamin K absence-II; ICG-R15, indocyanine green clearance rate at 15 minutes; MoRAL, model to predict the tumor recurrence after living donor liver transplantation.

Table 2. Perioperative and pathologic characteristics

| Characteristic                  | Early recurrence group (n = 312) | Late recurrence group (n = 131) | P-value |
|---------------------------------|----------------------------------|--------------------------------|---------|
| Major resection                 | 104 (33.3)                       | 33 (25.2)                       | 0.093   |
| Tumor size (cm)                 | 4.3 (1.0–21.0)                   | 3.0 (1.1–12.0)                  | <0.001  |
| Tumor grade 3 or 4              | 140 (44.9)                       | 32 (24.4)                       | <0.001  |
| Tumor hemorrhage                | 149 (47.4)                       | 51 (38.9)                       | 0.079   |
| Tumor necrosis                  | 178 (57.1)                       | 54 (41.2)                       | 0.003   |
| Microvascular invasion          | 187 (59.9)                       | 48 (36.6)                       | <0.001  |
| Macrovascular invasion          | 23 (7.4)                         | 0 (0)                           | 0.001   |
| Intrahepatic metastasis         | 37 (11.9)                        | 10 (7.6)                        | 0.095   |
| Beyond Milan criteria based on pathology | 138 (44.2) | 29 (22.1) | <0.001 |
| Hospital stay (day)             | 10 (5–92)                        | 9 (6–33)                        | 0.201   |

Values are presented as number (%) or median (range).
platelet count, international normalized ratio, AST level, ALT level, albumin level, total bilirubin level, creatinine level, and indocyanine green retention rate at 15 minutes between the 2 groups.

**Perioperative and pathologic characteristics**

The perioperative and pathologic characteristics of the early and late recurrence groups are outlined in Table 2. The median tumor size and prevalence of tumor grade 3 or 4 in the early recurrence group were significantly greater than those in the late recurrence group. Also, the presence of tumor necrosis in the resected tumor, microvascular invasion, and portal vein tumor thrombosis were significantly more frequent in the early recurrence group than in the late recurrence group. Accordingly, the tumor recurrence rate was significantly higher in the early recurrence group than in the late recurrence group.

**Fig. 1.** Comparison of hepatocellular carcinoma (HCC) recurrence and death after hepatic resection between early and late recurrence groups.

**Table 3.** Characteristics at HCC recurrence

| Characteristic                              | Early recurrence group (n = 312) | Late recurrence group (n = 131) | P-value |
|--------------------------------------------|---------------------------------|--------------------------------|---------|
| First HCC recurrence                       |                                 |                                |         |
| Time from HR to first HCC recurrence (mo)  | 8 (1–24)                        | 39 (25–116)                    | <0.001  |
| Tumor size at 1st HCC recurrence (cm)      | 1.5 (0.5–9.2)                   | 1.3 (0.2–3.8)                  | 0.089   |
| α-FP at first HCC recurrence (ng/mL)       | 9 (1–200,000)                   | 4 (2–15,912)                   | <0.001  |
| PIVKA-II at first HCC recurrence (mAU/mL)  | 25 (8–24,000)                   | 22 (9–699)                     | 0.018   |
| MoRAL score at first HCC recurrence        | 62.6 (34.0–1,786.2)             | 57.1 (35.8–297.4)              | 0.001   |
| Extrahepatic recurrence                    | 3 (1.0)                         | 1 (0.8)                        | 0.841   |
| Diffuse intrahepatic recurrence            | 21 (6.7)                        | 2 (1.5)                        | 0.032   |
| Beyond Milan criteria                      | 62 (19.9)                       | 10 (7.6)                       | 0.001   |
| Treatments                                 |                                 |                                |         |
| TACE                                        | 184 (59.0)                      | 58 (44.3)                      |         |
| RFA                                         | 74 (23.7)                       | 47 (35.9)                      |         |
| PEI                                         | 12 (3.8)                        | 4 (3.1)                        |         |
| Re-resection                                | 22 (7.1)                        | 16 (12.2)                      |         |
| LDLT                                        | 13 (4.2)                        | 2 (1.5)                        |         |
| Others                                      | 1 (0.3)                         | 1 (0.8)                        |         |
| TACE and RFA                                | 6 (1.9)                         | 3 (2.3)                        |         |
| Second HCC recurrence                       |                                 |                                |         |
| Time from first to second HCC recurrence (mo)| 13 (1–110)                     | 17 (1–73)                      | 0.359   |
| Extrahepatic recurrence at 2nd recurrence  | 6 (1.9)                         | 1 (0.8)                        | 0.679   |
| Follow-up after HR (mo)                     | 37 (4–115)                      | 68 (28–115)                    | <0.001  |

Values are presented as number (%) or median (range).

HCC, hepatocellular carcinoma; HR, hepatic resection; PIVKA-II, proteins induced by vitamin K absence-II; MoRAL, model to predict the tumor recurrence after living donor liver transplantation; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; LDLT, living donor liver transplantation.
the proportion of cases beyond Milan criteria based on pathology in the early recurrence group was higher than that in the late recurrence group (44.2% vs. 22.1%, \( P < 0.001 \)). There were no significant differences in the incidence of major resection, the presence of tumor hemorrhage, intrahepatic metastasis, or hospitalization between the 2 groups.

**Hepatocellular carcinoma recurrence and survival**

The median follow-up duration after HR for treatment-naïve solitary HCC was significantly shorter in the early recurrence group (37 months vs. 68 months, \( P < 0.001 \)). Both DFS and PS were worse in the early recurrence group than in the late recurrence group (\( P < 0.001 \) and \( P < 0.001 \), respectively) (Fig. 1). The median time from HR to first HCC recurrence was 8 months (range, 1–24 months) in the early recurrence group and 39 months (range, 25–116 months) in the late recurrence group (Table 3).

When HCC recurrence was diagnosed, the median \( \alpha \)-FP level, PIVKA-II level, and MoRAL score were significantly higher in the early recurrence group than in the late recurrence group. Accordingly, the incidence of a MoRAL score greater than 314.8 points was 14.1% in the early recurrence group (\( n = 29 \)) but 0% in the late recurrence group. Patients with MoRAL scores greater than 314.8 points before HR presented worse DFS and PS compared with patients with MoRAL scores of 314.8 points or less (Fig. 2). The incidence rates of diffuse intrahepatic recurrence and beyond Milan criteria based radiologic images were also higher in the early recurrence group than in the late recurrence group (6.7% vs. 1.5%, \( P = 0.032 \)). TACE was widely used in both groups as a treatment for recurrent HCC, but RFA or re-resection was more often used in the late recurrence group than in the early recurrence group.

Multivariate analysis revealed that tumor grade 3 or 4, microvascular invasion, and MoRAL score greater than 314.8 points before HR were strongly associated with early HCC recurrence following curative HR in solitary treatment-naïve HCC patients (Table 4).

There were no statistically significant differences in the median time from first HCC recurrence to second HCC recurrence and presence of extrahepatic recurrence between the 2 groups. However, DFS from first HCC recurrence to second HCC recurrence and PS from first HCC recurrence to death were significantly worse in the early recurrence group and in patients with MoRAL score greater than 314.8 points before HR lower than in the late recurrence group or in patients with MoRAL score of 314.8 points or less before HR (Figs. 3, 4).

**DISCUSSION**

The present study revealed that a preoperative MoRAL score greater than 314.8 points is closely associated with worse DFS and PS and can predict early recurrence. The time from first HCC recurrence to second HCC recurrence and the time from first HCC recurrence to patient death were correlated with a preoperative MoRAL score greater than 314.8 points.

### Table 4. Risk factors for early recurrence within 2 years after curative liver resection

| Risk factor             | OR (95% CI)         | P-value |
|-------------------------|---------------------|---------|
| Tumor grade 3 or 4      | 2.069 (1.277–3.351) | 0.003   |
| Tumor size, >5 cm       | 1.495 (0.870–2.568) | 0.146   |
| Tumor necrosis          | 1.240 (0.792–1.943) | 0.347   |
| Microvascular invasion  | 1.712 (1.077–2.272) | 0.023   |
| MoRAL score, >314.8 points | 2.229 (1.093–4.547) | 0.027   |

OR, odds ratio; CI, confidence interval; MoRAL, model to predict the tumor recurrence after living donor liver transplantation.

![Fig. 2. Comparison of hepatocellular carcinoma (HCC) recurrence and death from first HCC recurrence between the early and late recurrence groups.](image-url)
Preoperative serum α-FP level is a prognostic factor correlated with oncological outcomes [11]. The expression of α-FP in HCC tissues was shown to be closely associated with biological aggressiveness and tumor differentiation of HCC because the serum α-FP level reflects tumor necrosis and tumor cell proliferation or regeneration of the underlying liver [14,15].

PIVKA-II level for detection or diagnosis of HCC has been demonstrated and widely used in Asian countries, but experiences using PIVKA-II as a screening diagnostic tool in European countries remain limited in number [14]. PIVKA-II has been proven to act not only as a diagnostic biomarker but also as an independent prognostic factor in HCC patients [8-10]. Also, PIVKA-II has been reported to be another independently predisposing factor of intrahepatic recurrence; a high serum PIVKA-II level was closely associated with tumor recurrence by intrahepatic metastasis of tumor cells via the portal vein because of the increased biological invasiveness to the vessel [16]. Thus, serum PIVKA-II has been demonstrated to be strongly associated with extrahepatic metastasis and microvascular invasion, even in early HCC [17,18].

These observations suggest that serum α-FP and PIVKA levels have a significant association with a high rate of HCC recurrence after surgery [8-10]. Our study also demonstrated that the early recurrence group presented significantly higher preoperative α-FP and PIVKA-II levels than the late recurrence group. Early recurrence of HCC is known to shorten the survival time after HR [6], which implies that early recurrent HCC cases are biologically more aggressive than late recurrent HCC cases [14].

The MoRAL score is a model that involves PIVKA-II and α-FP as components. Accordingly, MoRAL scores in the early recurrence group were significantly higher than those in the late recurrence group. Early recurrence of HCC is known to shorten the survival time after HR [6], which implies that early recurrent HCC cases are biologically more aggressive than late recurrent HCC cases [14].

![Comparison of hepatocellular carcinoma (HCC) recurrence and death from first HCC recurrence according to the models for tumor recurrence after liver transplantation (MoRAL) score.](image1)

![Comparison of hepatocellular carcinoma (HCC) recurrence and death after hepatic resection according to the models for tumor recurrence after liver transplantation (MoRAL) score.](image2)
late recurrence group. The MoRAL score was developed for predicting early recurrence after LDLT in HCC patients [11]. Clinicians could use this approach to identify patients beyond the Milan criteria who are at low risk of tumor recurrence after LDLT. Higher MoRAL scores are associated with cytokeratin 19 expression, which is a stemness-related marker and indicates tumor aggressiveness or tumor invasiveness [15]. A previous study reported that a low MoRAL score (<314.8 points) was closely associated with a significantly lower risk of both tumor recurrence and overall death than was a high MoRAL score (>314.8 points) [19]. Therefore, the predictability and statistical usefulness of the MoRAL score were demonstrated in an LT setting [20]. Recently, another study validated use of the MoRAL score in RFA patients [21]. However, LDLT is not always an option in solitary HCC patients [12]. If liver function is preserved and adequate living liver donors are not available, HR is more highly recommended than LDLT in patients with solitary HCC. In our study, the MoRAL score was significantly associated with DFS and PS after HR. Our study also demonstrated that high MoRAL scores were consistent with the findings of previous studies [11,19,21]. The cut-off value of 314.8 points was statistically useful in the case of HR as was true in the case of LDLT. The MoRAL score was statistically meaningful not only in univariate analysis but also in multivariate analysis. Interestingly, the MoRAL score can predict the development of early HCC recurrence within 2 years after HR. In addition, a high MoRAL score predicted early recurrence within 2 years after HR and the chance for the second recurrence after the first recurrence.

The biggest factor that impacts survival after treatment of HCC is early recurrence, based on the present study. Appropriate treatments for early recurrence improve the survival rate of patients [5]. Using the MoRAL score model, we can discern patients in the early recurrence risk group in the preoperative stage. Therefore, we cautiously suggest that regular or frequent surveillance for the development of early recurrence by liver radiologic images might be necessary among patients with high MoRAL scores. The risk of developing early recurrence after HR for treatment-naïve solitary HCC seemed to be quite high among patients with high MoRAL scores. Early detection of early recurrent HCC improves the survival rate by facilitating the earlier introduction of appropriate treatments such as PEI, RFA, TACE, re-resection, and LDLT [5].

Our study has several limitations. First, there is a potential risk for selection bias because of its retrospective design. In addition, our study included only recurrent hepatectomy patients with HCC. Second, as our study population reflects the epidemiology of HCC in South Korea, most of our patients had chronic hepatitis B. Third, it was not easy to gather detailed information from 2 hospitals. The type of liver resection, intraoperative blood loss and transfusion during the surgical procedure, and postoperative complications were not investigated. Further studies validating the prognostic role of the MoRAL score in HCC patients with different etiologies in Western countries are warranted to generalize our results.

In conclusion, we validated the MoRAL score for prediction of oncological outcome after HR in patients with treatment-naïve solitary HCC. Patients with MoRAL scores of 314.8 points or less demonstrated better outcomes in comparison with patients with high MoRAL scores. Patients with high MoRAL scores (>314.8 points) might require frequent regular surveillance regarding the development of early tumor recurrence, and MoRAL scoring is an easily performed, widely available, objective, and reproducible means by which to identify patients at greater potential risk of recurrence.

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Conflict of Interest
The authors have no competing interests to declare.

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REFERENCES

1. Lee YB, Ha Y, Chon YE, Kim MN, Lee JH, Park H, et al. Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B. Clin Mol Hepatol 2019;25:52-64.
2. Sartorius K, Sartorius B, Aldous C, Govender PS, Madiba TE. Global and country underestimation of hepatocellular carcinoma (HCC) in 2012 and its implications. Cancer Epidemiol 2015;39:284-90.
3. Yu SJ. A concise review of updated guidelines regarding the management of hepatocellular carcinoma around the world: 2010-2016. Clin Mol Hepatol 2016;22:7-17.
4. Kim JM, Joh JW, Yi NJ, Choi GS, Kwon C, Lee KW, et al. Living donor liver transplantation should be cautiously considered as initial treatment in recurrent hepatocellular carcinoma within the Milan criteria after curative liver resection. Ann Transl Med 2020;8:288.
5. Shah SA, Greig PD, Gallinger S, Cattral MS, Dixon E, Kim RD, et al. Factors associated with early recurrence after resection for hepatocellular carcinoma and outcomes. J Am Coll Surg 2006;202:275-83.
6. Jung SM, Kim JM, Choi GS, Kwon CH, Yi NJ, Lee KW, et al. Characteristics of early recurrence after curative liver resection for solitary hepatocellular carcinoma. J Gastrointest Surg 2019;23:304-11.
7. Kim JM, Kwon C, Joh JW, Sinn DH, Choi GS, Paik SW. Prognosis of preoperative positron emission tomography uptake in hepatocarcinoma patients. Ann Surg Treat Res 2018;94:183-9.
8. Kim JM, Kwon CH, Joh JW, Park JB, Lee JH, Kim SJ, et al. Outcomes after curative hepatectomy in patients with non-B non-C hepatocellular carcinoma and hepatitis B virus hepatocellular carcinoma from non-cirrhotic liver. J Surg Oncol 2014;110:976-81.
9. Kim JM, Kwon CH, Joh JW, Park JB, Lee JH, Kim SJ, et al. Differences between hepatocellular carcinoma and hepatitis B virus infection in patients with and without cirrhosis. Ann Surg Oncol 2014;21:458-65.
10. Kim JM, Hyuck C, Kwon D, Joh JW, Lee JH, Paik SW, et al. Protein induced by vitamin K antagonist-II (PIVKA-II) is a reliable prognostic factor in small hepatocellular carcinoma. World J Surg 2013;37:1371-8.
11. Lee JH, Cho Y, Kim HY, Cho EJ, Lee DH, Yu SJ, et al. Serum tumor markers provide refined prognostication in selecting liver transplantation candidate for hepatocellular carcinoma patients beyond the Milan criteria. Ann Surg 2016;263:842-50.
12. Korean Liver Cancer Association; National Cancer Center. 2018 Korean Liver Cancer Association-National Cancer Center Korea practice guidelines for the management of hepatocellular carcinoma. Gut Liver 2019;13:227-99.
13. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:5358-80.
14. Trevisani F, D’Intino PE, Morselli-Labate AM, Mazzella G, Accogli E, Caraceni F, et al. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. J Hepatol 2001;34:570-5.
15. Hoshida Y, Toffanin S, Lachenmayer A, Villaneuva A, Minguez B, Llovet JM. Molecular classification and novel targets in hepatocellular carcinoma: recent advancements. Semin Liver Dis 2010;30:35-51.
16. Okuwaki Y, Nakazawa T, Shibuya A, Ono K, Hidaka H, Watanabe M, et al. Intrahepatic distant recurrence after radiofrequency ablation for a single small hepatocellular carcinoma: risk factors and patterns. J Gastroenterol 2008;43:71-8.
17. Poté N, Cauchy F, Albuquerque M, Voitot H, Belgitti J, Castera L, et al. Performance of PIVKA-II for early hepatocellular carcinoma diagnosis and prediction of microvascular invasion. J Hepatol 2015;62:848-54.
18. Bae HM, Lee JH, Yoon JH, Kim YJ, Heo DS, Lee HS. Protein induced by vitamin K absence or antagonist-II production is a strong predictive marker for extrahepatic metastases in early hepatocellular carcinoma: a prospective evaluation. BMC Cancer 2011;11:435.
19. Chang Y, Cho Y, Lee JH, Lee YB, Cho EJ, Yu SJ, et al. Comparison of models for tumor recurrence after liver transplantation for the patients with hepatocellular carcinoma: a multicenter long-term follow-up study. Cancers (Basel) 2019;11:1295.
20. Nam JY, Lee JH, Bae J, Chang Y, Cho Y, Sinn DH, et al. Novel model to predict HCC recurrence after liver transplantation obtained using deep learning: a multicenter study. Cancers (Basel) 2020;12:2701.
21. Yoo J, Lee MW, Lee DH, Lee JH, Han JK. Evaluation of a serum tumour marker-based recurrence prediction model after radiofrequency ablation for hepatocellular carcinoma. Liver Int 2020;40:1189-200.