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CREATING A POTENTIAL PROGNOSTIC IMAGING FEATURE FOR AFTER SURGERY SURVIVAL OF SOLITARY HCC PATIENTS BY RADIOMICS SCORE

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Abstract:
In this study, we aimed at developing a rad-score derived from the preoperative CECT of solitary HCC patients, based on the assumption that such rad-score may help to identify patients who were at high risk of postoperative recurrence and death and improve clinical decision making for solitary HCC patients

Keywords: HCC patients

BACKGROUND

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most common cause of cancer-related death worldwide [1]. Current HCC staging systems, like Barcelona Clinic Liver Cancer (BCLC) staging system, indicate that hepatectomy is a potentially curative treatment for patients with early-stage HCC [2]. However, postoperative recurrence is high, with 5-year rates reaching 70% [3, 4], suggesting that even in the same early-stage, patients have a diverse postoperative prognosis. Thus, the current staging systems still need improvement, for example, incorporating new risk factors for a better stratification of postoperative outcome. In fact, traditional staging systems mainly consist of pathological factors, like tumor size and vascular invasion, while tremendous information in preoperative computed tomography (CT) or magnetic resonance imaging (MRI) reflecting tissue intrinsic characters and heterogeneity [5,6,7,8] remains untapped. Recently, it has been reported that various imaging features were associated with pathological features and prognosis of the tumor and complementary to current staging systems, like rectal cancer and bladder cancer [9, 10]. As such, new prognostic factors, like those derived from CT and MRI images, to identify patients with high risk of postoperative recurrence and death are urgently needed, which could help to select patients who are more likely to benefit from surgery.

Radiomics, an emerging and promising field, hypothesizes that medical images, including CT and MRI, could provide vivid and crucial information on tumor [11]. By converting medical images into high-dimensional, mineable and quantitative features via high-throughput data extraction, radiomics method provides an unprecedented opportunity to improve decision-support in oncology at low cost and noninvasively. Currently, image examinations are routinely conducted for cancer patients, including HCC [12]. Compared to developing new molecular biomarkers, radiomics method may not require additional physical or molecular tests and thus not increase the economic burden of patients. In addition, previous studies have demonstrated that quantitative radiomics features were associated with clinical prognosis and underlying genomic patterns across a range of cancer types, such as non-small cell lung cancer [1] and advanced nasopharyngeal carcinoma [1]. In HCC, contrast-enhanced computed tomography (CECT) has been widely used in the diagnosis due to its high specificity and sensitivity [12]. Meanwhile, it had been reported that the characteristics of tumor CT images were associated with gene expression profiles, pathological features, and prognosis of HCC [11,]. As far as we are concerned, image features could be divided into semantic features and agnostic features. Semantic features are commonly used in the radiology lexicon to describe regions of interest, including internal arteries, hypodense halos and so on, while agnostic features, like texture features, attempt to capture lesion heterogeneity though quantitative descriptors [11]. Previous studies preferred the clinical application of semantic features, as they were easy to acquire. Recently, growing concerns have been paid on the potential clinical application of agnostic features. For instance, Fu et al. investigated the prognostic significance of CT image texture features for advanced HCC patients receiving TACE (transarterial chemoembolization) [1]. Another study has suggested that texture analysis was promising for HCC patient

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stratification for determining the suitability of liver resection vs. TACE [11]. Furthermore, texture analysis has been reported for the potential for predicting postoperative hepatic insufficiency and assessing fibrosis. However, the prognostic significance of radiomics feature has been rarely investigated in HCC patients receiving hepatectomy.

In this study, we aimed at developing a rad-score derived from the preoperative CECT of solitary HCC patients, based on the assumption that such rad-score may help to identify patients who were at high risk of postoperative recurrence and death and improve clinical decision making for solitary HCC patients

METHODS

Patient selection and data collection

Patient recruitment, as well as the inclusion and exclusion criteria, were presented in Additional file 1: Figure S1. A total of 119 patients were enrolled and randomly divided into a training cohort (n = 80) and validation cohort (n = 39). The pathological diagnoses on all cases were reviewed and confirmed independently by two expert pathologists.

Baseline clinicopathological data were derived from medical records. Tumor differentiation was graded by the Edmondson grading system [21]. Postoperative follow-up strategy and treatment strategy were according to a uniform guideline as we previously described [22, 23], and were listed in the Additional file 2. Ethical approval was obtained from the institutional review board of our Hospital, and the informed consent requirement was waived. Time to recurrence (TTR) was defined as the interval between surgery and recurrence or the last observation for surviving patients without recurrence. Overall survival (OS) was defined as the interval between surgery and death or the last observation for surviving patients. The data were censored at the last follow-up for living patients.

Statistical analysis

Statistical analyses were performed using SPSS software (20.0; SPSS, Inc., Chicago, IL, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) with the "rms" package (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were compared using the Mann-Whitney U, while category variables were compared using Chi-squared or Fisher's exact tests. X-tile (Yale University, New Haven, CT, USA) software was used to determine the optimal cut-off value of the rad-score, which is a graphical method that illustrates the presence of substantial tumor subpopulations and shows the robustness of the relationship between a biomarker and outcome by construction of a two-dimensional projection of every possible subpopulation. Survival curves were depicted using Kaplan–Meier analysis (log-rank test). The Cox's proportional hazards regression model was applied for univariate and multivariate analyses. "Rms" package was used to build nomogram models. The Harrell's concordance index (C-index) and calibration curves were used to evaluate the nomogram models. Details of nomogram models were listed in the Additional file 2. A two-sided value of $p < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of the patients

No significant differences in clinicopathological features were observed between the two cohorts (Table 1). All patients were solitary HCC and received R0 resection. The mean follow-up time in training and validation cohorts was 52.7 ± 21.6 months and 54.5 ± 22.1 months, respectively. Overall survival rates at 1, 3, and 5 years after operation was 87, 76 and 69% for training cohort and 88, 75 and 72% for validation cohort, respectively.

Variable	Training cohort	Validation cohort	*p*
Median(range) age, y	55(24–85)	55(13–83)	0.93
Gender (male/female)	175/37	88/19	0.95
Tumor size(≤3,> 3), cm	76/133	38/69	0.82
Vascular invasion(Present/Absent)	22/190	12/95	0.82
Microvascular invasion(Present/Absent)	68/144	29/78	0.36
Tumor differentiation (III-IV/I-II)	16/193	6/101	0.46
Liver cirrhosis(Present/Absent)	166/46	87/20	0.53
HbsAg (Positive/Negative)	178/34	85/22	0.32
Tumor encapsulation (Present/ Absent)	112/110	59/48	0.70
Preoperative blood test			
DBIL(mean ± SD), μmol/L	6.9 ± 11.9	7.3 ± 16.4	0.45

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Variable	Training cohort	Validation cohort	*p*
TBIL(mean ± SD), μmol/L	14.8 ± 14.5	15.04 ± 19.2	0.94
ALT(mean ± SD), U/L	40.1 ± 31.3	46.1 ± 69.2	0.91
AST(mean ± SD), U/L	38.7 ± 27.3	453.6 ± 66.3	0.67
AFP(mean ± SD), ng/ml	4460 ± 13,186	3800 ± 12,646	0.60
ALB(mean ± SD), g/L	40.7 ± 7.0	39.8 ± 3.6	0.06
GGT(mean ± SD), U/L	84.3 ± 98.8	80.8 ± 83.5	0.38

(Table 1).

Low rad-score correlated with poor survival in solitary HCC patients

In the training cohort, low rad-score were significantly associated with shorter TTR (median TTR [95% confident interval (CI)] for low [$n = 49$] versus high rad-score [$n = 163$]: 38 [28.2–47.1] versus 53 [48.0–58.4] months; $p = 0.005$, Fig. 1a). In the validation cohort, no significance was observed in recurrence between the two groups with the p value of 0.054 (Fig. 1b), suggesting that the rad-score was slightly over-fitted to the training cohort. As for OS, low rad-score significantly correlated with shorter postoperative survival in both training cohort (median OS [95% CI] for low [n = 49] versus high rad-score [n = 163]: 54.9[45.4–64.5] versus 70.5 [66.6–74.5] months; $p = 0.003$, Fig. 1c) and validation cohort (median OS [95%CI] for low [$n = 37$] versus high [$n = 70$]: 50.9[38.5–63.3] versus 82.2 [75.6–88.8] months; $p = 0.003$, Fig. 1d).

Assessment of incremental value of rad-score

To investigate the incremental value of rad-score in individual postoperative recurrence and survival prediction, we compared the discrimination performance of clinicopathological nomograms and rad-score based nomograms. The clinicopathological nomograms were established based on independent clinicopathological risk factors, with the C-index of 0.633 (95% CI: 0.571–0.695) for recurrence and 0.554 (95% CI: 0.485–0.623) for postoperative survival in the training cohort. The discrimination performance of the nomogram improved when the rad-score was integrated (recurrence: C-index, 0.639, 95%CI: 0.577–0.701; survival: C-index, 0.714, 95%CI: 0.635–0.793), significantly higher than the discrimination performance of clinicopathological nomogram in the training cohort

DISCUSSION

In this study, a multi-CT-texture feature based rad-score was proposed, which successfully stratified patients into groups with significant differences in TTR and OS, and may be complementary to traditional staging systems.

Radiomics, a promising field of oncological research, assume that image features could predict the prognosis of patients, as they are associated with tumor biological characteristics [11]. Previous studies have supported this hypothesis [17,]. For instance, Banerjee et al. proposed an image features of venous invasion, consisting of three semantic features (internal arteries, hypodense halo, and tumor liver difference), were closely associated with early recurrence and poor survival for HCC. Similarly, the rad-score identified in our study was closely associated with pathological factors of HCC, like larger tumor size and vascular invasion and could be predictive of recurrence and survival.

Previously, several staging systems have been proposed for HCC patients, including TNM, BCLC, and HKLC. Our rad-score based nomograms yielded a better discriminative ability than these traditional staging systems for solitary HCC patients. In addition, our results suggested that the rad-score could complement the TNM and BCLC staging systems in prognostic stratification as the C-index value increased when the rad-score was added to them. This incremental ability indicated the clinical importance of our finding for solitary HCC patients.

In our study, lasso-logistic regression model was performed to select texture features to establish the rad-score, as features obtained from lasso were generally accurate and the regression coefficients of most features were shrunk toward zero during overfitting , making the model easier to interpret and allowing the identification of the most valuable features. Indeed, this method had been widely used in similar studies.

Of note, the C-index values were relatively low for traditional staging systems, this phenomenon may be attributed to the study design. In our study, only solitary HCC patients were included. According to the traditional staging systems, these patients belong to the early or intermediate stages and are appropriate for surgery. Although they share the same or similar stage, a great deal of heterogeneity exists among them and they have a diverse postoperative prognosis. Thus, traditional staging systems could not actually predict recurrence and survival for these patients. In addition, the rad-score proposed also shared a relatively low C-index, but this couldn't affect the clinical significance of rad-score, as it could stratify these patients into groups with different prognosis and improved the prognostic performance of traditional staging systems when being added into them for these patients.

The current study had several limitations. On one hand, the data in this study were derived from only one hepatobiliary center. On the other hand, only solitary HCC patients were included in this study, which may influence the generalization of the conclusion. In addition, this is a retrospective research. Therefore, further perspective multicenter analyses including HCC patients as various tumor stages were needed to validate the prognostic significance of this rad-score.

CONCLUSIONS

In summary, a rad-score derived from CT texture features was proposed in this study, which was an independent prognostic factor for tumor recurrence and survival of solitary HCC patients. In addition, this image score was complementary to the current staging systems of HCC patients. Finally, prognostic nomograms combining this score and clinicopathological features were proposed, which outperformed traditional staging systems and provided a convenient way to predict prognosis for solitary HCC patients, and may influence decision-making on the possible benefit of surgery.

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