Prediction of recurrence and survival using big data analytics and machine learning in patients with hepatocellular carcinoma after curative surgery: abridged secondary publication

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KEY MESSAGES

1. A deep-learning model was developed using preoperative computed tomography to predict hepatocellular carcinoma recurrence.
2. Compared with microvascular invasion, Recurr-NET demonstrated superior risk stratification in predicting hepatocellular carcinoma recurrence.
3. Recurr-NET can be used for preoperative prognostication in hepatocellular carcinoma.

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Introduction

Despite curative surgery, early recurrence of hepatocellular carcinoma (HCC) within 2 years remains common. Histological microvascular invasion (MVI) is strongly associated with early recurrence.[1] HCC is typically diagnosed via computed tomography (CT) or magnetic resonance imaging (MRI); the role of advanced imaging metrics for prediction of postoperative recurrence is important. Deep-learning techniques can automatically identify complex patterns and provide quantitative assessments of radiological findings. A CT-based deep-learning algorithm capable of predicting longitudinal, clinically relevant outcomes could substantially enhance HCC prognostication and management. We developed a deep-learning model using preoperative CT to predict HCC recurrence after curative surgery.

Methods

Consecutive patients diagnosed with resectable HCC at four medical centres in Hong Kong (internal cohort, December 2008 to December 2019) and one medical centre in Taiwan (external cohort, May 2006 to August 2019) were included. All patients were Chinese, aged ≥18 years, and underwent hepatic resection with histologically confirmed HCC. MVI was defined as tumour cells located in intra- or extra-tumoural blood vessels covered by endothelial cells, observable only via microscopy.[2] After curative surgery, all patients underwent contrast-enhanced CT of the liver with serum alpha-fetoprotein monitoring every 6 months. Recurrence was based on CT or MRI findings of LI-RADS (liver imaging reporting and data system) category 5 lesions or histological or mortality data recorded.

The internal cohort was randomly divided into training and internal validation groups at an 8:2 ratio. Deep learning was conducted using PyTorch 1.12.1. Processed triphasic CT scans and preoperative clinical data were used to develop Recurr-NET, which is a multimodal, multiphasic residual-network random survival forest deep-learning model designed to predict the risk of HCC recurrence within 5 years. Recurr-NET consists of two components: an image model based on the residual network (ResNet) structure and a random survival forest model. A 64-dimensional vector derived from the image model was combined with patients' clinical data in the random survival forest model to calculate a risk score. Three versions of the deep-learning model were trained: Recurr-NET^{CT}, Recurr-NET^{LITE}, and Recurr-NET. Recurr-NET^{CT} incorporated only CT images, whereas Recurr-NET^{LITE} incorporated CT images and basic clinical parameters (age, sex, hepatitis B surface antigen, hepatitis C virus antibody, history of fatty liver on imaging, alpha-fetoprotein levels, and the Model for End-stage Liver Disease score). Recurr-NET, the full model, incorporated both CT images and comprehensive clinical parameters including those listed above as well as smoking status, comorbidities, use of antiviral therapy for hepatitis B, and baseline blood test results. All three models were applied to the internal validation and external testing cohorts.

The diagnostic accuracy of Recurr-NET for predicting HCC recurrence was stratified by year and presented as the area under the receiver operating characteristic curve (AUROC), positive predictive value, and negative predictive value. Bootstrapping was performed to calculate 95% confidence intervals. The AUROC of Recurr-NET was compared with that of MVI using the Delong's test. Cumulative

TABLE 1. Characteristics of patients

Characteristic	All (n=1231)*	Training (n=536)*	Internal validation (n=135)*	External testing (n=560)*
Age, y	62.4±10.7	62.5±9.3	63.0±9.1	62.1±12.2
Male sex	1023 (83.1)	465 (86.8)	107 (79.3)	451 (80.5)
Ever-smoker	-	244 (45.5)	60 (44.4)	-
Liver disease				
Viral hepatitis	1068 (86.8)	478 (89.2)	120 (88.9)	470 (83.9)
Hepatitis B	943 (76.6)	445 (83.0)	109 (80.7)	389 (69.5)
Hepatitis C	144 (11.7)	35 (6.5)	11 (8.1)	98 (17.5)
Alcohol-related liver disease	-	35 (6.5)	9 (6.7)	-
Non-alcoholic fatty liver	-	6 (1.1)	1 (0.7)	-
Other liver diseases/cryptogenic	-	82 (15.3)	19 (14.1)	-
Barcelona Clinic Liver Cancer stage				
0	167 (13.6)	95 (17.7)	26 (19.3)	46 (8.2)
A	857 (69.6)	337 (62.9)	88 (65.2)	432 (77.1)
B	176 (14.3)	79 (14.7)	15 (11.1)	82 (14.6)
C	31 (2.5)	25 (4.7)	6 (4.4)	0
D	0	0	0	0
Blood tests				
Model for End-Stage Liver Disease score	8.0±2.2	8.2±2.2	8.0±2.0	7.9±2.3
Platelets, 10^9/L	176.6±78.0	173.5±75.1	177.1±86.4	179.3±78.7
Prothrombin time, s	11.6 (10.9-12.5)	12.2 (11.4-13.0)	12.2 (11.5-13.0)	11.1 (10.6-11.5)
Albumin, g/L	41.0 (38.0-44.0)	42.0 (38.0-44.0)	42.0 (38.0-44.0)	40.0 (38.0-43.0)
Alpha fetoprotein, ng/mL	15.7 (4.0-178.5)	15.0 (4.0-152.0)	10.0 (3.8-108.3)	18.4 (4.8-325.0)
Comorbidities				
Diabetes mellitus	303 (24.6)	155 (28.9)	32 (23.7)	116 (20.7)
Hypertension	511 (41.5)	231 (43.1)	59 (43.7)	221 (39.5)
Hyperlipidaemia	119 (9.7)	76 (14.2)	13 (9.6)	30 (5.4)
Chronic kidney disease	38 (3.1)	18 (3.4)	5 (3.7)	15 (2.7)
Ischaemic heart disease	56 (4.5)	25 (4.7)	7 (5.2)	24 (4.3)
Computed tomography findings				
No. of radiological lesions	1.6±1.0	2.0±1.2	2.0±1.2	1.2±0.5
Multiple lesions	441 (35.8)	281 (52.4)	68 (50.3)	92 (16.4)
Size of dominant lesion, cm	5.0±3.6	4.3±3.3	4.9±3.7	5.6±3.7
Major vessel involvement	52 (4.2)	18 (3.4)	3 (2.2)	31 (5.5)
Features of portal hypertension	264 (21.4)	141 (26.3)	35 (25.9)	88 (15.7)
Histological findings				
No. of hepatocellular carcinoma nodules	1.3±0.7	1.3±0.8	1.3±0.9	1.2±0.5
Multifocal hepatocellular carcinoma	206 (16.7)	102 (19.0)	19 (14.1)	85 (15.2)
Size of dominant lesion, cm	5.1±3.7	4.5±3.3	5.0±4.0	5.6±3.8
Microvascular invasion	591 (48.0)	159 (29.7)	35 (25.9)	397 (70.9)
Portal vein invasion	31 (2.5)	25 (4.7)	6 (4.4)	0
Margin involvement	85 (6.9)	38 (7.1)	5 (3.7)	42 (7.5)
Tumour differentiation				
Well differentiated	101 (8.2)	61 (11.4)	21 (15.6)	19 (3.4)
Moderately differentiated	716 (58.2)	334 (62.3)	79 (58.5)	303 (54.1)
Poorly differentiated	388 (31.5)	128 (23.9)	32 (23.7)	228 (40.7)
Undifferentiated	26 (2.1)	13 (2.4)	3 (2.2)	10 (1.8)
Cirrhosis in surrounding liver	501 (40.7)	270 (50.4)	61 (45.2)	170 (30.4)
Steatosis in surrounding liver	377 (30.6)	137 (25.6)	34 (25.2)	206 (36.8)

* Data are presented as mean ± standard deviation, median (range), or No. (%) of patients

recurrence risks predicted by Recurr-NET and MVI were plotted on Kaplan-Meier curves and compared in terms of survival difference at fixed time points.

Results

In total, 1231 patients with hepatic resection and histologically confirmed HCC were included in the analysis (Table 1). Among these, 536 (43.5%), 135 (11.0%), and 560 (45.5%) patients comprised the training, internal validation, and external testing cohorts, respectively. Overall, the median follow-up duration was 65.1 (range, 35.7-101.2) months. Cumulative probabilities of recurrence at 2 and 5 years were 41.8% and 56.4%, respectively. Overall, 568 (46.1%) patients died at a median interval of 35.0 (range, 17.0-64.7) months. In the internal cohort, 247 (36.8%) patients died of liver-related causes at a median interval of 32.6 (range, 16.3-61.8) months.

Recurr-NET achieved AUROCs of 0.770 to 0.857 in the internal validation cohort and 0.758 to 0.798 in the external testing cohort, significantly outperforming MVI in the respective cohorts (0.518 to 0.590 and 0.557 to 0.615) for predicting HCC recurrence from years 1 to 5 (all P<0.001, Table 2). The AUROCs for Recurr-NET^{LITE} and Recurr-NET^{CT} were also superior to those for MVI (all P<0.001) but remained numerically lower than those of the full Recurr-NET model.

Compared with MVI, Recurr-NET demonstrated superior risk stratification for recurrence at year 2 in the internal validation cohort (72.5% vs 50.0%, P<0.001) and external testing cohort (65.3% vs 46.6%, P<0.001) as well as for recurrence at year 5 in the respective cohorts (86.4% vs 62.5%, P<0.001 and 81.4% vs 63.8%, P<0.001) [Fig].

Patients identified as high-risk by Recurr-NET, compared with those identified by MVI, exhibited significantly higher liver-related mortality rates at year 2 (28.3% vs 11.8%, P<0.001) and year 5 (69.1% vs 29.9%, P<0.001). Similarly, Recurr-NET outperformed MVI in predicting all-cause mortality at year 2 in the internal validation cohort (31.9% vs 14.3%, P<0.001) and external testing cohort (32.7% vs 18.9%, P<0.001) as well as all-cause mortality at year 5 in the respective cohorts (72.9% vs 34.3, P<0.001 and 66.8% vs 37.9%, P<0.001).

Discussion

We developed, validated, and externally tested Recurr-NET, a multimodal multiphasic CT-based deep-learning model for predicting HCC recurrence and mortality after curative surgery. Recurr-NET demonstrated superior risk stratification compared with MVI, the principal histological predictor of aggressive tumour behaviour, for both early and late recurrence of HCC. Notably, the performance of Recurr-NET remained robust in external testing and across diverse patient subgroups stratified by age, viral hepatitis status, cirrhosis, and steatosis. A key advantage of Recurr-NET over MVI is its exclusive reliance on preoperative CT and clinical variables, facilitating prognostication before surgery.

By incorporating comprehensive preoperative imaging and clinical data, Recurr-NET demonstrated excellent performance in predicting both early and late recurrence, as well as liver-related and all-cause mortality. From a clinical perspective, Recurr-NET may assist in identifying patients at high risk of late recurrence, enabling clinicians to consider liver transplantation as an alternative to resection for these individuals.[3]

This study had some limitations. First, no centralised histological review was conducted; pathology findings were derived from reports generated by pathologists at each participating hospital. Second, because Recurr-NET was developed using CT data,

TABLE 2. Diagnostic accuracy of Recurr-NET^{CT}, Recurr-NET^{LITE}, Recurr-NET, and microvascular invasion for hepatocellular carcinoma recurrence

Model	Year 1					Year 2					Year 3					Year 4					Year 5				
	AUROC	PPV	NPV	SEN	SPE	AUROC	PPV	NPV	SEN	SPE	AUROC	PPV	NPV	SEN	SPE	AUROC	PPV	NPV	SEN	SPE	AUROC	PPV	NPV	SEN	SPE
Internal validation																									
Recurr-NET	0.843	0.659	0.868	0.692	0.849	0.857	0.744	0.807	0.653	0.866	0.838	0.857	0.739	0.610	0.915	0.809	0.884	0.607	0.535	0.911	0.770	0.884	0.543	0.507	0.898
Recurr-NET^{LITE}	0.811	0.769	0.821	0.513	0.935	0.762	0.828	0.755	0.490	0.939	0.760	0.893	0.667	0.424	0.958	0.742	0.906	0.558	0.408	0.946	0.757	0.939	0.516	0.413	0.959
Recurr-NET^{CT}	0.796	0.720	0.804	0.462	0.925	0.776	0.767	0.743	0.469	0.915	0.770	0.862	0.663	0.424	0.944	0.761	0.917	0.582	0.465	0.946	0.756	0.944	0.534	0.453	0.959
Microvascular invasion	0.590	0.441	0.755	0.385	0.796	0.570	0.500	0.670	0.347	0.793	0.547	0.545	0.577	0.305	0.789	0.541	0.636	0.468	0.296	0.786	0.518	0.636	0.407	0.280	0.755
External testing																									
Recurr-NET	0.798	0.488	0.882	0.729	0.726	0.781	0.668	0.789	0.699	0.764	0.759	0.749	0.683	0.637	0.785	0.758	0.817	0.604	0.613	0.812	0.760	0.863	0.513	0.556	0.841
Recurr-NET^{LITE}	0.760	0.570	0.844	0.563	0.848	0.740	0.708	0.718	0.505	0.858	0.711	0.788	0.610	0.439	0.881	0.740	0.861	0.556	0.479	0.894	0.752	0.890	0.486	0.474	0.894
Recurr-NET^{CT}	0.755	0.600	0.852	0.583	0.860	0.706	0.686	0.709	0.486	0.849	0.693	0.786	0.608	0.435	0.881	0.720	0.858	0.559	0.489	0.889	0.734	0.915	0.500	0.490	0.918
Microvascular invasion	0.615	0.327	0.888	0.875	0.354	0.605	0.476	0.769	0.833	0.377	0.590	0.565	0.654	0.798	0.383	0.568	0.623	0.546	0.792	0.343	0.557	0.678	0.459	0.784	0.329

Abbreviations: AUROC=area under receiver operating characteristic curve, NPV=negative predictive value, PPV=positive predictive value, SEN=sensitivity, SPE=specificity

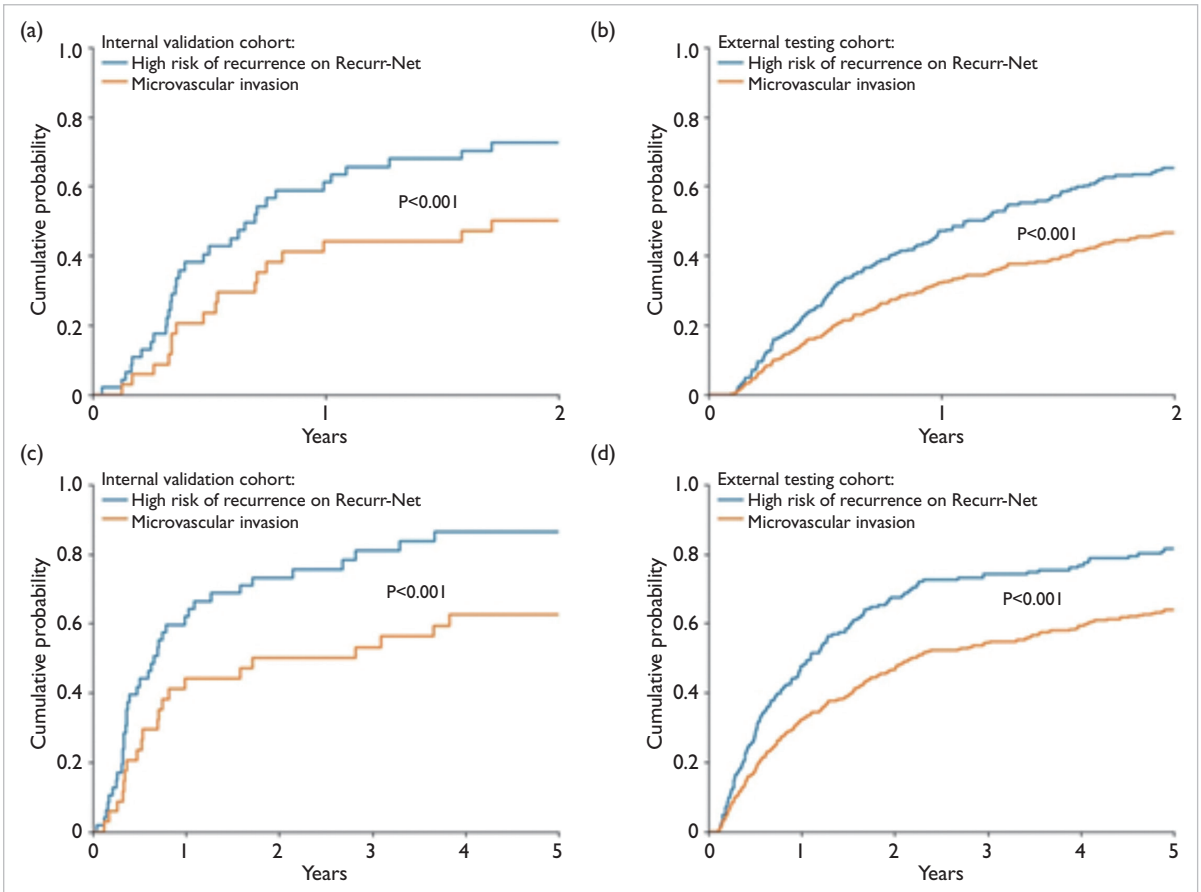

FIG. Comparison of Recurr-NET with microvascular invasion for recurrence risk stratification. Cumulative probabilities of hepatocellular carcinoma recurrence for internal validation and external testing cohorts at (a and b) year 2 and (c and d) year 5 are shown

its findings cannot be directly extrapolated to MRI-based assessments. However, the random survival forest component of Recurr-NET allowed integration of a Kaplan-Meier estimator for survival analysis. This enabled consideration of time as a factor, facilitating the determination of clinically relevant outcomes such as HCC recurrence and mortality. Additionally, we specifically collected longitudinal data over a period of 5 years (median, 65.1 months) to evaluate both early and late HCC recurrence. The use of external testing validated the promising diagnostic and risk stratification performance of Recurr-NET, suggesting that our findings are robust and generalisable.

Conclusions

Recurr-NET, which utilises preoperative CT and clinical parameters, demonstrated robust risk stratification for early and late HCC recurrence and mortality after curative surgery. The model consistently outperformed MVI in recurrence risk stratification, demonstrating its potential use for preoperative prognostication.

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Disclosure

The results of this research have been previously published in:

1. Hui RW, Chiu KW, Lee IC, et al. Multimodal multiphasic pre-operative image-based deep-learning predicts hepatocellular carcinoma outcomes after curative surgery. Hepatology 2024 Dec 2.

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