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Project for interventional Oncology LArge-database in liveR Hepatocellular carcinoma – Preliminary CT-based radiomic analysis (POLAR Liver 1.1)

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Abstract. – OBJECTIVE: The objective of this study is to find a contrast-enhanced CT-radiomic signature to predict clinical incomplete response in patients affected by hepatocellular carcinoma who underwent locoregional treatments.

PATIENTS AND METHODS: 190 patients affected by hepatocellular carcinoma treated using focal therapies (radiofrequency or microwave ablation) from September 2018 to October 2020 were retrospectively enrolled. Treatment response was evaluated on a per-target-nodule basis on the 6-months follow-up contrast-enhanced CT or MR imaging using the mRECIST criteria. Radiomics analysis was performed using an in-house developed open-source R library. Wilcoxon-Mann-Whitney test was applied for univariate analysis; features with a p-value lower than 0.05 were selected. Pearson correlation was applied to discard highly correlated features (cut-off=0.9). The remaining features were included in a logistic regression model and receiver operating characteristic curves; sensitivity, specificity, positive and negative predictive value were also computed. The model was validated performing 2000 bootstrap resampling.

RESULTS: 56 treated lesions from 42 patients were selected. Treatment responses were: complete response for 26 lesions (46.4%), 18 partial responses (32.1%), 10 stable diseases (17.9%), 2 progression diseases (3.6%). Area-Under-Curve value was 0.667 (95% CI: 0.527-0.806); accuracy, sensitivity, specificity, positive and negative predictive values were respectively 0.66, 0.85, 0.50, 0.59 and 0.79.

CONCLUSIONS: This contrast-enhanced CT-based model can be helpful to early identify poor responder's hepatocellular carcinoma patients and personalize treatments.

Key Words:
Radiomic, Hepatocellular carcinoma, Ablation, Interventional oncology, Personalized medicine.

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Abbreviations

Intraoperative neuromonitoring = IONM; recurrent laryngeal nerve = RLN; electromyography = EMG; intensive care unit = ICU; twitch = TW; mean arterial pressure = MAP; heart rate = HR; time of flight = TOF.

Introduction

In the last decade, remarkable advances in cancer care have created new challenges leading the clinical practice towards personalized medicine. Hepatocellular carcinoma (HCC) is one of the most common cancers in the world, frequently complicating the clinical course of liver cirrhosis[1]. HCC prognosis is poor due to its rapidly infiltrating growth[1]. A careful multidisciplinary assessment of tumor characteristics, liver function, and physical status is required for proper therapeutic management[2-4].

HCC patients are a very inhomogeneous mix of patients, with multiple etiologies, different cirrhosis stratification, clinical conditions, comorbidities, compliance, surgical risk and decompensation risk, different genomic and histopathological tumor variants, tumor load, and life expectancy.

In this scenario, surgical and systemic options are combined with locoregional percutaneous or intra-arterial treatments, based on new devices and techniques[5].

Locoregional therapies represent emerging and promising treatments against primary and secondary liver tumors with both a curative, or palliative intent[6].

In this scenario, treatment allocation is extremely complex, also using a stage hierarchy approach as proposed by the Barcelona Clinic Liver Cancer (BCLC) scheme, or a therapeutic hierarchy as suggested by Asia-Pacific treatment algorithm and by the recent Italian multi-society guidelines[7-9]. However, a practical clinical approach needs more "plasticity" and "adaptability", refining treatment indications and considering multimodal approaches to increase treatment effectiveness in multiple HCC stages[10].

Multimodal approaches, based on multidisciplinary selection, can increase treatment efficacy, preventing the incomplete necrosis and improving patient survival, without increasing treatment complications[11,12]. The biological heterogeneity of the HCC can represent a key factor for a tailored clinical approach and for personalized treatments[13,14]. In fact, although HCC heterogeneity can lead to patient's stratification in different risk classes, there are no adequate tools to identify the subgroups burdened with an increased probability of local recurrence. An early identification of this subgroup could lead to the proposal of alternative and multimodal treatments[15-17].

Based on this background, it would be useful to identify different imaging biomarkers that could aid assessment of prognosis, treatment response prediction, and disease status monitoring. The aim of the study is to develop the tools for liver radiological imaging analysis, creating a radiomics model based on dynamic contrast-enhanced CT images which can predict incomplete response in patients with a single HCC lesion after locoregional treatments. This model could grant early identification of poor responder patients.

Patients and Methods

Study Design and Patient Selection

Patients affected by HCC undergoing focal nodule ablative therapies (radiofrequency ablation – RFA, microwave ablation – MWA) from September 2018 to October 2020 were considered for this monocentric study and retrospectively enrolled. The inclusion and exclusion criteria are reported in Table I.

Staging, Imaging Modalities and Technique

Data regarding sex, age, lesion size and location, Child-Pugh class, bilirubin, albumin, treatment modalities and treatment response was acquired. Before the treatment, all patients underwent a staging CT using a 64-channel multidetector-row CT scanner (Lightspeed VCT XT, GE Medical Systems, USA) at 120 kV tube voltage and 100 mA tube current. All studies were acquired from the diaphragm to the pelvic floor, with 1.25 mm-slice thickness reconstruction. 0.4 gI/kg of iodinate low-osmolar non-ionic contrast medium (Iopromide, 370 mgI/mL, Ultravist, Bayer, Germany) were injected at a 4 mL/s flow-rate, followed by a flush of 60 mL of saline. Arterial phase was acquired with a bolus-tracking technique, an 18 second diagnostic-delay after the threshold of 150 Hounsfield Units (HU) was reached in a Region of Interest (ROI) placed at the thoraco-abdominal aortic passage; the venous and delayed phases were acquired at 70 and 180 seconds respectively.

Table I. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Age > 18 years	Oral anticoagulant drugs in the 5 days before the procedure
Signed informed consent	Known allergy to iodinated contrast medium
Single or multiple HCC lesions with multidisciplinary indication to treatment with locoregional ablative techniques	Kidney function impairment (Glomerular Filtration Rate < 60 mL/min/1.73 m^2)
Contrast-enhanced CT examination performed 1 month or less prior to locoregional treatment	Pregnant or lactating women
6-month Contrast-enhanced CT or MRI follow-up examination	Platelet count < 50,000/mm^3
	International Normalized Ratio < 1.5
	Thromboplastin time < 45 s
	Prothrombin time < 15 s

HCC = Hepatocellular Carcinoma; CT = Computed Tomography; MRI = Magnetic Resonance Imaging.

All tumors were classified as perivascular or non-perivascular HCC based on CT findings (perivascular if with any contact with first- or second-degree branches of a portal or hepatic vein that are 3 mm or greater in axial diameter).

Pre-treatment images were evaluated by one experienced radiologist with more than 10 years of experience in interpreting abdominal images and was blinded to clinical outcomes.

Treatment Modalities

All patients underwent locoregional ablative treatments (RFA, MWA)[6,10]. All ablation procedures were performed percutaneously with real-time ultrasound (US) guidance. Deep sedation and local anesthesia at the electrode entry point were established before each treatment. A MWA needle was used in case of tumor 3 cm in diameter or larger, or with a perivascular location. Aim of the ablation was to obtain a safety tumor-free margin of at least 0.5 cm in the healthy liver parenchyma surrounding the tumor. Strategies for ablation concerning optimal electrode type and ablation technique were officially discussed at multidisciplinary tumor board meetings and were decided by matching pre-procedural CT findings with the planning US findings before each treatment. All procedures were performed by the same operator, with more than 15 years of experience in ablative therapies.

Treatment Response and Follow-Up

Treatment response to ablation was evaluated on a per-target nodule basis on the 6-months follow-up CT or MR imaging using the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[18]. Treatment response was independently evaluated by 2 experienced radiologists with >5 years of experience, and conflicting results were evaluated by a third radiologist with over 10 years of experience.

Considering the patient's sample dimension, a binary outcome for the radiomics study has been evaluated. Treatment response was distinguished in two main classes: class 1 including complete response (CR), and class 0 including incomplete response (partial response – PR, stability of disease – SD, progression of disease – PD).

Radiomics Analysis

The whole gross tumor volume (GTV) of treated lesions was contoured by a radiologist and independently evaluated and validated by an expert radiologist as defined in International Commission on Radiation Units and Measurements [ICRU] No. 83[19].

Due to the retrospective nature of the study, ethical approval was waived by the local Ethical Committee. The radiomics analysis was performed in R (version 3.4.1) using an in-house developed open-source R library for radiomics analysis called Moddicom[20]. The radiomics software was validated as part of the Image Biomarker Standardization Initiative, which allowed verification and calibration of different radiomics software implementations for the extraction of standardized and reproducible radiomic features[21].

The CT images and the corresponding segmented ROIs, namely the GTV, were imported in Moddicom.

208 radiomic features were extracted from each GTV. These included 17 first order statistics, 14 morphological and 177 texture features. Each feature was normalized with its maximum value.

Radiomics features selection process based on the Wilcoxon-Mann-Whitney test and the Pearson correlation coefficient was then applied to reduce their dimensionality. We used the Wilcoxon-Mann-Whitney test to evaluate the association between each radiomics feature with the binary outcome in a univariate analysis. We considered features with *p*-values lower than 0.05 as statistically significant. We computed the Pearson correlation coefficient between the statistically significant features and set a cut-off value of 0.9 to discard highly correlated and redundant features.

A logistic regression model was then set up using only the selected features. The model performance was evaluated using the receiver operating characteristic (ROC) curve. We selected the optimal threshold on the ROC curve as the best cut-off according to the Youden index method. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated based on the optimal threshold. We computed the 95% confidence intervals of the metrics by performing 2000 bootstrap resampling.

Results

From an initial database of 190 patients affected by HCC treated with locoregional therapies from September 2018 to October 2020, 53 patients undergoing ablative treatments were selected and finally, according to the inclusion and exclusion criteria, 42 patients were retrospectively included in the study, with 11 patients being affected by multiple lesions, for a total of 56 treatments (Figure 1). Patients' characteristics are reported in Table II.

A total of 56 GTVs were considered for the analysis: 25 (44.6%) lesions were treated with RFA, and 31 (55.4%) with MWA. For 26 lesions (46.4%) a CR occurred, for 18 lesions (32.1%) PR, for 10 patients (17.9%) SD, for 2 lesions (3.6%) a PD occurred.

No significant differences were observed in the baseline characteristics of patients treated with RFA or MWA, with different tumour location (perivascular/non-perivascular). No significant differences were obtained in terms of complete/incomplete response based on ablation technique used or tumor location.

When considering radiomics analysis, two radiomics features resulted statistically significant with the Wilcoxon-Mann-Whitney test:

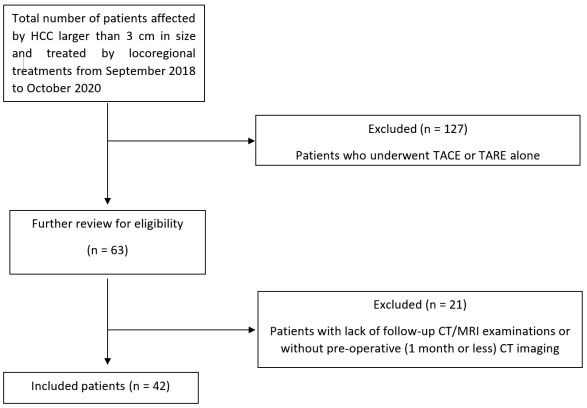

Figure 1. Flow diagram of the patient selection progress. Abbreviations: HCC hepatocellular carcinoma, TACE transarterial chemoembolization, TARE transarterial radioembolization, CT computed tomography.

F_cm.clust.shade (p = .032) and F_cm_merged.clust.shade (p = .035); these features have been named according to the nomenclature proposed

Table II. Patients' and lesions' characteristics.

Sex	8 F (19%)
Age	67.5 ± 11
Lesion size	3.4 ± 0.7 (2.2-4.7)
Lesion Number	
- 1	31 (73.9%)
- 2	8 (19%)
- 3	3 (7.1%)
Lesion Location	
Perivascular	41 (73.2%)
Non-Perivascular	15 (26.8%)
Child-Pugh class	
- A5	22 (52.4%)
- A6	9 (21.4%)
- B7	5 (11.9%)
- B8	4 (9.5%)
- B9	1 (2.4%)
- C	1 (2.4%)
Cirrhosis etiology	
- Viral (HBV / HCV)	29 (69%)
- Alcohol	9 (21.5%)
- Metabolic (NASH/NAFLD)	4 (9.5%)
Bilirubin (mg/dL)	1.21 ± 0.69
Albumin (g/dL)	6.9 ± 10
Treatment modality (%)	
- RFA	25 (44.6%)
- MWA	31 (55.4%)
Treatment response (%)	
- CR	26 (46.4%)
- PR	18 (32.1%)
- SD	10 (17.9%)
- PD	2 (3.6%)

HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; NASH = Non-Alcoholic Steato-Hepatitis; NAFLD = Non-Alcoholic Fatty Liver Disease; RFA = Radiofrequency Ablation; MWA = Micro-wave Ablation; CR = Complete Response; PR = Partial Response; SD = Disease Stability; PD = Disease Progression.

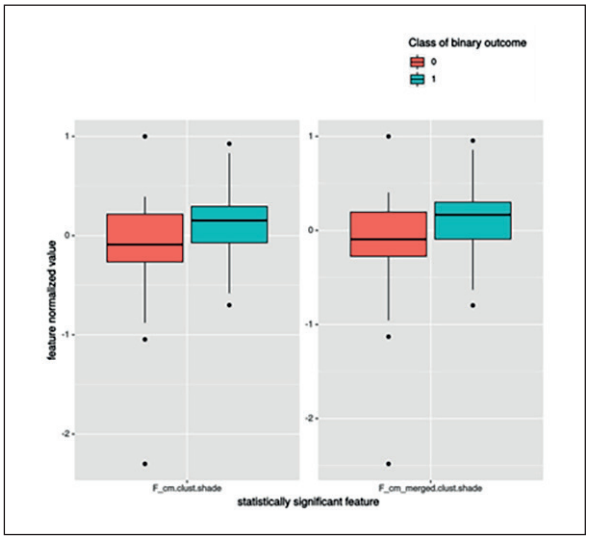

Figure 2. Boxplots of the statistically significant features resulted from the Wilcoxon-Mann-Whitney test for the two classes of the binary outcome. Class 1 includes complete response (CR), class 0 includes incomplete response (PR, SD, PD).

by the Image Biomarker Standardization Initiative based on the grey level co-occurrence matrix (GLCM)[21]. Figure 2 shows the boxplots of the statistically significant features subdivided in the two classes of the binary outcome. The Pearson correlation coefficient between the two statistically significant features was equal to 1. Considering a cut-off value of 0.9 for the correlation coefficient, only one of the highly correlated features was considered. In particular, we selected the feature with the lowest *p*-value, namely F_cm.clust.shade, to build the radiomic model.

Table III reports the results of the logistic regression model. The covariate F_cm.clust.shade showed an estimated regression coefficient significantly different from 0 ($p < .05$). The residual deviance of the logistic regression model was equal to 72.27, while the null deviance of a model that contains only the intercept was equal to 77.35.

Figure 3 shows the ROC curve of the model including the 95% confidence intervals (CI). The area under the curve (AUC) value was 0.667 with a 95% CI of 0.527-0.806. The optimal threshold on the ROC curve according to the Youden index method was equal to 0.42. Based on this threshold, we evaluated the model performance obtaining the following results: accuracy 0.66 (95% CI: 0.52-0.78), sensitivity 0.85 (95% CI: 0.69-0.96), specificity 0.50 (95% CI: 0.33-0.67).

The positive predictive value (PPV) and the negative predictive value were 0.59 and 0.79, respectively.

Discussion

In recent years, a combination of interventional therapies has been widely applied in the HCC treatment[6,22,23]. The aim should be to expand the indication for locoregional treatments. Percutaneous ablation is a curative treatment indicated for nodules smaller than 3 cm. Combining percutaneous approach with other locoregional approach, such as transarterial chemoembolization (TACE), radiotherapy and Interventional Radiotherapy (IRT, also called brachytherapy), electro-

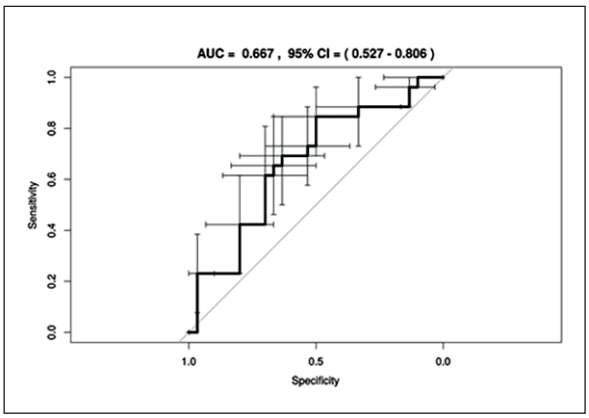

Figure 3. ROC curve with 95% confidence intervals (CI) of the sensitivity and specificity represented as bars. The AUC value and corresponding 95% CI are also reported.

Table III. Results of the logistic regression model.

Covariate	Estimated coefficient	Standard error	z-value	*p*-value (>|z|)
(Intercept)	-0.1830	0.2825	-0.648	.517
F_cm.clust.shade	1.4035	0.7066	1.986	.047*

*The covariate F_cm.clust.shade showed a significant estimated coefficient (*p*-value < .05).

chemotherapy, and systemic drug infusion, can increase treatment effectiveness in large HCC nodules[10,24-26].

These approaches could determine an increase of the ablated area, increasing the rate of curative treatment, reducing the number of retreatments, and slowing local tumour progression.

Current clinical data reveal that TACE combined with RFA is superior to RFA or TACE alone in inducing complete necrosis and increasing overall survival rates, with indication for lesions larger than 3 cm[10,24]. However, regardless of tumour size, there is a variety of factors that might affect treatment outcomes, such as tumour location, perivascular or non-perivascular, liver disease etiology, continuous presence of pro-carcinogenic factors that are etiology-related, presence of macro- and micro-vascular invasion, and the assessment of liver disease severity[27-29]. All these different aspects should be evaluated to correctly define the indication for a tailored approach, increasing advantages for combination treatment able to balance disadvantages due to potential increase of procedural complication and procedural cost. This precise assessment cannot be performed on standard imaging even if performed by experienced readers and clinicians.

The use of radiomics in medicine is still in its infancy with a limited number of published papers that used radiomics mainly to investigate the prediction of HCC recurrence after curative ablation[30-43]. However, radiomics could also be very useful to stratify patients with HCC nodules amenable for curative approach into two prognostic subgroups with significantly different treatment responses. The patients for whom a complete response was predicted were advised to be treated with ablation only. Conversely, in patients for whom a complete response was not predicted, treatment efficacy could be significantly improved with combined therapies.

A large number of radiomic features in our study were extracted. As multiple radiomic features could cause overfitting, compared with the number of cases, feature reduction and selection was performed. Accordingly, the radiomics model constructed with optimal features subset achieved satisfying performance.

F_cm.clust.shade is a radiomics textural feature based on the GLCM. The GLCM is a matrix which contains information about the combinations of the grey levels of neighbouring pixels. F_cm.clust.shade gives a measure of the skewness and uniformity of the GLCM. A higher value of F_cm.clust.shade indicates greater asymmetry about the mean.

F_cm.clust.shade resulted as a significant feature in the univariate analysis with the Wilcoxon-Mann-Whitney test, showing statistically significant association with the binary outcome. When used in a logistic regression model, this feature resulted in an estimated regression coefficient significantly different from 0. In the cohort of patients included in this study, the model accuracy was equal to 0.66, with a sensitivity of 0.85 and a negative predictive value of 0.79.

The limitations of the study included the small sample size and the lack of independent validation. Further studies on larger sample sizes and independent cohorts are required to evaluate the predictive performance of the presented model. Future work will address these limitations.

Moreover, according to the opportunity to early identify poor responder patients, an interventional trial could be proposed to intensify treatment with multimodal therapy for high-risk patients, combining different focal approaches, such as radiation therapy (radioembolization, IRT), TACE or electrochemotherapy.

Conclusions

The results of this study are encouraging, but further studies must be performed to confirm and validate the proposed predictive model. We constructed a convenient and feasible radiomics model that could be helpful to identify whether a treatment intensification could modify clinical outcomes. Preoperative treatment response stratification could favorably influence the decision-making process for the best therapeutic strategy for each patient, reducing recurrence rates and improving patient safety and overall survival.

Conflict of Interests

The authors declare that they have no conflict of interest.

Funding

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Ethical Standards

Ethical approval was waived by the local Ethics Committee in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Authors' Contribution

Conceptualization, R.I. and L.T.; methodology, R.I., L.T. and P.C.; software, H.E.T. and L.B.; validation, F.C.; formal analysis, L.B. and P.C.; investigation, R.I, F.C, V.L. and A.T.; resources, F.C, V.L., L.C., F.R.P., A.T., H.E.T. and L.B.; data curation, B.F., F.C. and V.L.; writing—original draft preparation, C.C, A.P. and V.L.; writing—review and editing, R.I. and L.T, .; visualization, A.G. and M.P.; supervision, F.G., G.L.R., A.G., V.V., M.A.G. and R.M.; project administration, V.V., A.G. and R.M. All authors have read and agreed to the published version of the manuscript.

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