Different applications of Artificial Intelligence in liver cancer: a scoping review – part II, from treatment planning and efficacy assessment to prognosis prediction and follow-up.

Andrea Chierici, Fabien Lareyre, Benjamin Salucki, Antonio Iannelli, Lisa Guzzi, Sebastien Goffart, Hervé Delingette, Juliette Raffort

Submitted to: Journal of Medical Internet Research
on: February 25, 2024

Table of Contents

Different applications of Artificial Intelligence in liver cancer: a scoping review – part II, from treatment planning and efficacy assessment to prognosis prediction and follow-up.

Andrea Chierici[1, 2]; Fabien Lareyre[3, 4]; Benjamin Salucki[2]; Antonio Iannelli[1, 5]; Lisa Guzzi[6]; Sebastien Goffart[6]; Hervé Delingette[6, 7]; Juliette Raffort[4, 7, 8]

[1]Department of Digestive Surgery, University Hospital of Nice, Nice, France Nice FR
[2]Department of Digestive Surgery, Hospital of Antibes Juan-les-Pins, Antibes, France Antibes FR
[3]Department of Vascular Surgery, Hospital of Antibes Juan-les-Pins, Antibes, France Antibes FR
[4]Université Côte d'Azur, Inserm U1065, C3M, Nice, France Nice FR
[5]Université Côte d'Azur, Inserm U1065, Team 8 “Hepatic complications of obesity and alcohol”, Nice, France Nice FR
[6]Université Côte d'Azur, Inria, Epione Team, Sophia Antipolis, France Sophia Antipolis FR
[7]University Hospital of Nice, Nice, France; 3IA Institute, Université Côte d'Azur, Nice, France Nice FR
[8]Université Côte d'Azur, Inserm U1065, C3M, Nice, France; Clinical Chemistry Laboratory Nice FR

Corresponding Author:
Andrea Chierici
Department of Digestive Surgery, University Hospital of Nice, Nice, France
151, route Saint Antoine de Ginèstiere
Nice
FR

Abstract

Artificial Intelligence (AI) plays a pivotal role in early detection and personalized treatment of liver cancer. The integration of AI in screening and diagnosis enhances detection accuracy and aids in formulating effective treatment strategies. AI-driven tools offer predictive analytics for prognosis, treatment planning, and efficacy assessment, aiming to optimize patient outcomes. In liver cancer management, AI assists in treatment planning, such as liver resection and radioembolization, by improving preoperative mapping and predicting therapeutic response. Additionally, AI models predict chemotherapy efficacy based on patient-specific factors, facilitating tailored treatment approaches. Moreover, leveraging AI models, integrating clinical, biochemical, radiological, and histological data, enables accurate prognostication at diagnosis and post-treatment. Key factors such as microvascular invasion, tumor capsule integrity, and grade significantly influence liver cancer prognosis, often assessed using AI-driven predictive models. Imaging modalities, coupled with AI algorithms, exhibit high accuracy in predicting microvascular invasion, aiding treatment planning and prognosis assessment.
Following treatment, AI plays a crucial role in prognosis assessment. For patients undergoing liver resection, machine learning models predict disease-free survival, aiding decisions regarding adjuvant chemotherapy. Similarly, models for thermoablation and liver transplantation provide insights into recurrence risk, guiding post-treatment follow-up. In patients receiving systemic treatment like immunotherapy, AI-based models predict cancer-related mortality and overall survival, facilitating treatment response assessment and patient stratification.
Despite promising advancements, challenges remain, including the need for external validation and adaptation to diverse patient populations. Further research is essential to realize the full potential of AI in liver cancer management and translate it into clinical impact.

(JMIR Preprints 25/02/2024:57728)
DOI: https://doi.org/10.2196/preprints.57728

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users. Only make the preprint title and abstract visible.

No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✔ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**

Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v

Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

Different applications of Artificial Intelligence in liver cancer: a scoping review – part II, from treatment planning and efficacy assessment to prognosis prediction and follow-up.

Andrea Chierici, MD[1,2], Fabien Lareyre, PhD, MD[3,4], Benjamin Salucki, MD[2], Antonio Iannelli, PhD, MD[1,5,6], Lisa Guzzi[7], Sebastien Goffart[7], Hervé Delingette, PhD[7], Juliette Raffort-Lareyre, PhD, MD[8].

[1] Department of Digestive Surgery, University Hospital of Nice, Nice, France

[2] Department of Digestive Surgery, Hospital of Antibes Juan-les-Pins, Antibes, France

[3] Department of Vascular Surgery, Hospital of Antibes Juan-les-Pins, Antibes, France

[4] Université Côte d'Azur, Inserm U1065, C3M, Nice, France

[5] Université Côte d'Azur, Inserm U1065, Team 8 “Hepatic complications of obesity and alcohol”, Nice, France

[6] ADIPOCIBLE Study Group

[7] Université Côte d'Azur, Inria, Epione Team, Sophia Antipolis, France

[8] Université Côte d'Azur, Inserm U1065, C3M, Nice, France; Clinical Chemistry Laboratory, University Hospital of Nice, Nice, France; 3IA Institute, Université Côte d'Azur, Nice, France

Corresponding author:

Andrea Chierici, MD

Department of Digestive Surgery, University Hospital of Nice, Nice – France.

Hopital l’Archet 2 – 151, route Saint’Antoine de Ginèstiere, 06200 Nice – France.

chierici.ap@chu-nice.fr

Number of words: 6333.

Number of Tables: 2.

Number of references: 55.

Abstract

Artificial Intelligence (AI) plays a pivotal role in early detection and personalized treatment of liver cancer. The integration of AI in screening and diagnosis enhances detection accuracy and aids in formulating effective treatment strategies. AI-driven tools offer predictive analytics for prognosis, treatment planning, and efficacy assessment, aiming to optimize patient outcomes. In liver cancer management, AI assists in treatment planning, such as liver resection and radioembolization, by improving preoperative mapping and predicting therapeutic response. Additionally, AI models predict chemotherapy efficacy based on patient-specific factors, facilitating tailored treatment approaches. Moreover, leveraging AI models, integrating clinical, biochemical, radiological, and histological data, enables accurate prognostication at diagnosis and post-treatment. Key factors such as microvascular invasion, tumor capsule integrity, and grade significantly influence liver cancer prognosis, often assessed using AI-driven predictive models. Imaging modalities, coupled with AI algorithms, exhibit high accuracy in predicting microvascular invasion, aiding treatment planning and prognosis assessment.

Following treatment, AI plays a crucial role in prognosis assessment. For patients undergoing liver resection, machine learning models predict disease-free survival, aiding decisions regarding adjuvant chemotherapy. Similarly, models for thermoablation and liver transplantation provide insights into recurrence risk, guiding post-treatment follow-up. In patients receiving systemic treatment like immunotherapy, AI-based models predict cancer-related mortality and overall survival, facilitating treatment response assessment and

patient stratification.

Despite promising advancements, challenges remain, including the need for external validation and adaptation to diverse patient populations. Further research is essential to realize the full potential of AI in liver cancer management and translate it into clinical impact.

Introduction

Artificial Intelligence (AI) is a field focused on developing computer systems capable of performing tasks that typically require human intelligence, achieved through iterative learning. This technology is increasingly being applied across various domains, with its impact on medicine growing rapidly and significantly. AI encompasses a broad spectrum of subsets, each differing in structure, function, and application.

Liver cancer represents a major global health challenge. It ranks as the seventh most commonly diagnosed cancer but is the second leading cause of cancer-related deaths following lung cancer (1). Despite the availability of various interventions, procedures, and systemic therapies, and the continuous development of new ones, liver cancer, including both Hepatocellular Carcinoma (HCC) and Intrahepatic Cholangiocarcinoma (ICC), continues to have high mortality rates (2). The first part of this review concentrated on the challenges in screening and diagnosing primary liver cancer. It examined how AI is integrated into current strategies and tests to detect the disease early, aiming to establish the most effective treatments at initial stages for optimal outcomes. AI's potential extends beyond early detection; it can also be utilized in subsequent stages of primary liver cancer management to create personalized treatment plans based on the specific characteristics of the cancer and the individual. AI enables the development of tools for prognosis prediction, treatment planning, efficacy assessment, and optimized follow-up. These advancements

aim to enhance both disease-free and overall survival rates by delivering tailored treatments and precisely monitoring cancer recurrence.

In the second part of this review, we explore the current implementations of AI in addressing these aspects of liver cancer management.

Treatment planning and efficacy assessment

The treatment of HCC and ICC depends on tumor staging and the possibility to perform resection with a favorable benefit-risk balance. When resection or ablation is feasible, the association of a systemic therapy before and/or after the invasive procedure can sometimes improve cancer-free survival and overall survival. When the cancer is unresectable or the patient cannot undergo the operation, management mainly consists in chemotherapy and best supportive care. HCC and ICC treatments are well codified, based on the above mentioned elements, in different specific guidelines which are constantly updated (3,4). To correctly manage liver primary cancer, a meticulous preoperative planning strategy is of paramount importance to avoid complications that can affect early patient's life expectancy and to guarantee cancer treatment at the same time. Furthermore, through specimen analysis and biochemical and imaging tests, treatments' efficacy must be assessed to eventually perform complementary procedures or intensify follow-up exams in order to cope with cancer recurrence.

Despite being a primary topic in research nowadays, only a few publications focused on the application of AI for liver cancer treatment specifically. Moreover, HCC represents the principal subject for this kind of papers while our research identified only one manuscript including cases of ICC in the study cohort (5). Details concerning the studies on this topic

included in this review are available in Table 3.

Liver cancer treatment can be realized through procedures with a different degree of invasiveness, such as liver resection, cancer radiofrequency or microwave thermoablation, trans-arterial chemoembolization, trans-arterial radioembolization, and stereotactic body radiotherapy among others. For most of them, preoperative planning is mainly based on liver static or dynamic 2D imaging. However, recent research has shown the interest of the application of AI to improve preoperative planning.

Concerning radioembolization, a radiological/nuclear medicine procedure consisting in delivering microspheres containing a radioactive nucleotide into tumor-feeding hepatic arteries, Chaichana et al. (6) proposed a FCN model capable of producing liver parenchyma and liver tumor segmentation in order to guide the nuclear medicine procedure. Indeed, the goal of radioembolization is to specifically deliver microspheres to the tumor while sparing normal liver parenchyma; this must be done by calculating the absorbed dose of radiation of both normal and pathological liver tissue and it is normally planned using particles mimicking the radioactive microspheres that can be detected through single-photon emission CT-scan. In this research, automated segmentation performed on groundwork CT-scan images was compared with manual segmentation which is normally performed in clinical practice. The proposed model showed a 0.91 and 0.85 Dice's score in liver and tumor segmentation, respectively. However, when considering physicians' evaluation of the segmentation for radioembolization planning, manual segmentation was mostly chosen as the preferred one for liver segmentation while for tumor segmentation there was heterogeneity between physicians; thus, the results of the automated segmentation model seemed to perform worse than the manual one. Similarly, Plachouris et al. (5) proposed a CNN to accurately predict how the radiopharmaceutical will be distributed in the liver tissue after radioembolization for HCC, ICC, and liver metastases.

While for normal liver parenchyma the difference between predicted and real average absorbed dose was very precise (0.44 ± 1.64%), for tumoral tissue this was more inaccurate (5.42 ± 19.31%) with some important model dose underestimation reported by the authors.

Liver tumor ablation represents a valid alternative to liver resection in case of HCC with the largest diameter ≤ 3 cm (7) as it confers comparable results in terms of overall survival with limited post-procedural complications, while it is not recommended for ICC at any stage (4). Clear tumor visualization is of paramount importance for lesion targeting and treatment deliverance. The more precisely the lesion is achieved by the source of energy and the more effective will be the ablation with less thermal damage to the surrounding healthy liver tissue. This is normally obtained through US and/or CT-scan, with some well-known limitations such as poor image-quality and low soft tissue contrast for US and patient irradiation, lower real-time capability, and respiration motion issues for the latter. To address this issue, Wei et al. (8) used a DL approach to perform hepatic and portal vein segmentation and estimation of the US probe plane using 2D US and 3D CT-scan images. Although the authors reported elevated values of segmentation accuracy (99% for the hepatic veins and 98% for the portal veins) and Dice's score (0.8 for the combined hepatic and portal veins model), any detail or perspective was given to show how this model could facilitate the targeting process of laser ablation in practice. De Landro et al. (9), on the other hand, produced a tool to build a peak temperature prediction model that can create maps holding thermal liver laser-induced damage information for patients undergoing liver cancer needle-delivered laser ablation. The prediction is performed by a CNN model exploiting hyperspectral 3D images which are an optical tool used to identify energy distribution in the liver tissue at the moment of ablation. The model is designed to classify liver tissue in non-damaged tissue, ablated tissue (where the peak of the temperature is reached), and an

intermediate surrounding zone where treatment is delivered without complete tissue ablation; liver biopsies were sampled at the spot of laser ablation at the end of the procedure in order to obtain the histological feedback to assess liver thermal damage. Moreover, a regression CNN was also trained to predict the peak temperature at a given pixel and the results merged with the first model to predict ablation's margins. A Dice's score of 0.94 was reported concerning the ability of the model to classify liver tissue in the non-damaged zone. When considering the ablated zone, acceptable values of Dice's score (0.86) were obtained only when the delivered energy heated the liver tissue at a minimum temperature of 80°C. For the intermediate zone, the highest Dice's score (0.92) was obtained at 70°C and then decreased for higher temperatures, thus showing better model's performance when the damage is generated and progress. Dice's score ranged between 0.76 and 0.8 when predicting ablation margins with images taken at 80°C and 70°C.

Lv et al. (10), instead, focused their research on the evaluation of the accuracy of a liver resection simulation system in predicting postoperative liver volume and surgical margins based on preoperative CT-scan through machine learning. When performing surgery for liver cancer, one of the most important challenges is to realize liver resection with sufficiently wide margins from the cancer avoiding the risk of post-hepatectomy liver failure due to an insufficient volume of residual liver parenchyma after operation. The balance between adequate resection margins and sufficient residual liver volume is quite labile and it is affected by many different factors (11). The proposed model achieved an area under the curve of 0.71 on the test dataset in predicting postoperative liver volume and resection margins. However, scarce information was given concerning how the simulation system performed liver segmentation and proposed the operation method on whom depended the liver volume and margin calculation. In a similar optic, Takamoto et al. (12) compared an automated CNN-based model to a manual tracking algorithm to perform liver, vascular and

tumor segmentation and liver and tumor-containing segment volume calculation from CT-scan images. The two models showed superposable performance except from portal vein and hepatic vein segmentation where misclassifications and misconnections were frequent (42% of patients) for the AI-driven model. On the other hand, the automated model performed all the tasks in a mean time of 2.1 minutes while for the manual method this was performed in 35 minutes. Another instrument commonly used to evaluate functional liver reserve to plan surgical resection is the indocyanine green retention rate at 15 minutes. Compared to volume based planning, indocyanine green retention is preferred in Japan and other Asian countries to assess preoperative liver function in order to predict post-hepatectomy liver failure, a highly morbid complication of major hepatectomies (13). The above mentioned machine learning model based on liver CT-scan and MR radiomics proposed by Zhu et al. (14) has the objective of evaluating functional liver reserve in HCC patients using indocyanine green retention as a reference for preoperative planning. Despite showing high accuracy, the authors did not mention if the model managed to overcome the limitations of indocyanine green retention test, notably in case of biliary obstruction, intrahepatic shunts, portal hypertension, and portal thrombosis. Furthermore, neither the model was tested only against one method for liver reserve assessment which is not proven to be superior to others (clinic-biochemical scores, liver volume assessment, liver scintigraphy), nor it was described to be used in the clinical setting.

When HCC is not eligible for surgery, trans-arterial chemoembolization is one of the most common procedures realized to obtain cancer control or remission and extend patients survival. Moreover, this procedure can be repeated and, when it allows to achieve tumor regression, it can be followed by other procedures such as surgery, thermoablation and/or stereotactic body radiotherapy to improve oncological results. However, when multiple interventions are combined in a large period, it is hard to foresee which patient will benefit

from a specific strategy and which one will not respond and should be addressed to systemic therapy or best supportive care avoiding unbeneficial invasive procedures. For this reason, Mo et al. (15) elaborated an AI-based model to identify which patients can benefit from stereotactic body radiotherapy or thermoablation after trans-arterial chemoembolization for HCC. The variables mostly influencing progression-free and overall survival in the training dataset of patients were the cause of cirrhosis, the cancer stage, and the albumin-bilirubin (ALBI) score (a biochemical score reflecting liver function). Once the model was built, a deep feedforward neural network was used to evaluate how progression-free and overall patients' survival was modified if the therapeutical attitude post-trans-arterial chemoembolization changed when compared with the procedure each patient actually received. The proposed model suggested that a change in the treatment strategy could bring some benefit to 33% of patients. Through DL simulation, a significant gain in progression-free survival (HR=0.5) was highlighted by changing the treatment following the machine-learning model suggestion, while no significant difference was found when considering overall survival. Although this research represents an interesting example of AI-guided decision-making tool, some common limits in this kind of works such as the absence of an external validation and of a real clinical application reduce the reliability of the results. Although transarterial chemoembolization is the most frequently performed procedure in case of unresectable HCC, an elevated percentage of patients does not respond to this treatment and experiments tumor progression (16). Boldanova et al. (17) built different machine-learning models including clinical, radiological, and transcriptomics features to identify responders and non-responders for transarterial chemoembolization. Most of clinical and radiological features did not permit to make this distinction with elevated accuracy. The best model created exploited logistic regression and was based on the tumor area at CT-scan and the tumor expression of FAM111B and HPRT1, a tripsin-like peptidase

and an enzyme involved in purine recycling, respectively. This model permitted to achieve a ~90% accuracy in discriminating treatment responders and non-responders. However, as the validation cohort came from the same center and consisted in only 7 patients, further external validation would be useful to assert if this model is useful to avoid transarterial chemoembolization to patients who will not take any advantage. With a similar aim, Sun et al. (18) used machine-learning and multiparameter-MR radiomics features obtaining 70.6% accuracy. As for the previous study, the absence of external validation represents an important drawback for the general applicability of this model.

AI can also be used to perform prediction on the efficacy of chemotherapy in order to evaluate if one treatment will give the attended results and evaluate other available alternatives if this drug is likely to be ineffective in a specific patient. Hsu et al. (19) analyzed treatment outcomes of Lenvatinib, a kinase inhibitor, in the setting of unresectable HCC based on serum biomarkers such as alpha-fetoprotein, ALBI grade, and circulating angiogenic factors. Their research focused on tumor objective response rate, progression-free survival, and overall survival. Using a decision tree model the authors highlighted the importance of alpha-fetoprotein as a marker for tumor response. A reduction of > 40% of alpha-fetoprotein was associated with an increased objective response rate. Moreover, the association of circulating angiogenic factors FGF21 and ANG2 and alpha-fetoprotein concentrations permits to classify patients undergoing Lenvatinib in a low, intermediate, and high-risk groups corresponding to 84.6%, 21.7%, and 0% of objective response rate, respectively. Although this could represent a useful tool to predict the efficacy of chemotherapy based on individual data, it was performed and tested on Asian patients only who represent a cohort whose genetic and environmental characteristics that may differ from Western population, thus introducing an important bias for the general reliability of the model. On the other hand, it represents a primary example of how biochemical markers that

are known to be modified by tumor response can be exploited to foresee treatment efficacy and modify the therapeutical attitude. Luo et al. (20), instead, exploited the association of genomics/transcriptomics and AI to predict HCC sensitivity to chemotherapeutic drugs. They used machine learning and ANN to identify genes mutations responsible for cancer-associated fibroblast activation. Based on the presence of mutations, the authors defined low and high fibroblasts activation classes and, on this variable, they analyzed HCC sensitivity to chemotherapy. Their results showed that patients with high activation of cancer-associated fibroblasts had increased response to chemotherapy.

It is also worth to say that many authors have recently published different DL models to perform segmentation of liver cancer and vacularization with the aim to develop a tool useful for physicians to plan liver cancer treatment (21–30). However, their results are limited to a comparison of accuracy between the proposed model and manual segmentation or segmentation performed by other models, without any proposed practical applications in clinical setting. For this reason, their results were not extensively included in this review.

Author	Country	Data	Patients (n)	Model	Objective
Plachouris, 2021[5]	Greece	SPECT/CT-scan	19	CNN, automatic	Prediction of microspheres biodistribution for TARE (HCC, ICC, Met)
Chaichana, 2021[6]	Thailand	SPECT/CT-scan	56	CNN, automatic	Segmentation for liver TARE planning (HCC)
Wei, 2021[8]	Germany/China	US/CT-scan	52	CNN, automatic	Probe plane identification for liver TA planning (HCC)
De Landro, 2021[9]	Italy	HSI	-	CNN, automatic	Prediction of ablation margins for LA planning (HCC)
Lv, 2021[10]	China	CT-scan	50	ML	Liver remnant volume and resection plane prediction (HCC)
Takamoto, 2022[12]	Japan	CT-scan	144	CNN, automatic	Liver and tumor segmentation and volume calculation (HCC, ICC, Met, benign lesions)
Zhu, 2023[14]	China	MR/CT-scan radiomics, IGC	190	ML	Liver functional reserve evaluation (HCC)
Mo, 2022[15]	USA	clinical, biochemical	237	ML	Treatment planning (SBRT vs. TA) after TACE (HCC)
Boldanova, 2021[17]	Switzerland	clinical, radiological, transcriptomics	33	ML	Prediction of TACE outcome (HCC)
Sun, 2020[18]	China	MR radiomics	84	ML	Prediction of TACE outcome (HCC)
Hsu, 2022[19]	Taiwan	biochemical	82	ML	Prediction of Lenvatinib response (HCC)
Luo, 2022[20]	China	genomics/transcriptomics	450	ANN, ML	Prediction of chemotherapy response (HCC)

Table 3: characteristics of the studied describing AI-driven models to perform planning and efficacy assessment of primary liver cancer therapy. SPECT: single-photon emission computed tomography; CT: computed tomography; MR: magnetic resonance; US: ultrasonography; HSI: hyperspectral imaging; IGC: indocyanine-green clearance; ML: machine learning; CNN: convolutional neural network; ANN: artificial neural network; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; Met: liver metastases; TARE: transarterial radio-embolization; TA: thermoablation; LA: laser ablation; SBRT: stereotactic body radiotherapy; TACE: transarterial chemoembolization.

Liver cancer prognosis prediction and follow-up

The prognosis of patients affected by primary liver cancer depends on a combination of multiple cancer- and patient-related features.

In the era of personalized medicine, the possibility to precisely identify patients at low- and high-risk of recurrence allows to establish a specific treatment and follow-up strategy. The diagnosis of primary liver cancer is based on a combination of clinical, biochemical, radiological, and histological data that can be extensively exploited to build prognostic predictive models through AI at the moment of diagnosis. Furthermore, the same tests are repeated after the patient underwent cancer treatment; thus, the same amount data can be used to produce a tool capable of predicting prognosis after a specific procedure such as liver resection, termoablation, transarterial chemoembolization, and others. In this chapter we resume the recent literature concerning AI applied to prognosis prediction in liver cancer at the moment of diagnosis and post-treatment (Table 4).

Prognosis prediction at diagnosis

Among multiple factors influencing the prognosis of liver cancer, microvascular invasion is one of the most important along with tumor capsule integrity and grade (31). For this reason, it represents one of the most frequently evaluated factors in the recently developed AI- models to predict cancer prognosis. Research focusing on microvascular invasion mainly used imaging and radiomic data to feed AI models for the prediction of the outcomes of patients before therapeutic interventions.

CT-scan and MR images of 397 patients affected by HCC were used separately and combined as input for CNN to predict microvascular invasion (32). In this study, the DL multimodal algorithm showed an accuracy of 80%, which was greater than what was reported for the single-modality models based on MR (73%) and CT-scan (73%) only. In addition, employing follow-up data on HCC recurrence of the study cohort as a comparison, the multimodal DL model was also able to predict differences in recurrence-

free survival based on the prediction of microvascular invasion status. Unfortunately, the authors did not report any information regarding the HCC staging of the included patients, which deeply condition tumor recurrence depending on different features (e.g.: single vs. multiple HCC, HCC diameter, etc.), thus reducing the impact of microvascular invasion on the survival results. Based exclusively on contrast-enhanced CT-scan images, Li et al. (33) also used a CNN model to predict the presence or absence of microvascular invasion (the involvement by the lesion of a portal vein, hepatic vein, or a large capsular vessel of the surrounding hepatic tissue lined by endothelium) in patients with resectable HCC undergoing surgery. This model alone reached an AUC of 0.754, 0.782, and 0.767 when using pre-contrast, portal, and delayed-phase images respectively. This predictive model was then implemented in a nomogram with some clinic-radiological factors such as the presence of a tumor peripheral halo, a capsule, and net margins. The resulting nomogram showed an AUC of 0.897 and 83.5% accuracy. Additionally, the authors compared recurrence-free and overall survival data of the cohort with the survival curves based on the microvascular invasion predictions realized with the nomogram showing a significant survival reduction in patients who were predicted to have microvascular invasion compared to those who did not have. Again, the relative heterogeneity of tumor characteristics and the monocentric nature of the included patients introduces a bias for the predictive accuracy of the model. To partially overcome this issue, Liu et al. (34) developed their predictive model using arterial-phase CT-scan images of patients affected by HCC from different hospitals. The CNN model applied to an external dataset showed an AUC of 0.777 in predicting microvascular invasion status. However, in this case, no survival analysis based on model prediction was conducted. Yang et al. (35), instead, to avoid selection bias, focused their research on patients with early stage HCC (1-3 nodules with <3 cm diameter, absence of macrovascular invasion, absence of metastatic disease). Their model was based on radiomics, and DL extracted features from

contrast enhanced CT scan and showed an accuracy of 96.47% in predicting microvascular invasion. The predictive model was then used to explore its prognostication in 5-year recurrence free-survival and overall survival, but it resulted to have low C-index values (0.601 and 0.589 respectively in the test cohort). Similarly, Kucukkaya et al. (36) fed a CNN with contrast enhanced MR images from patients with early stage HCC to predict tumor recurrence. In this case, no specific prognostic factor was investigated but recurrence was directly predicted through image feature extraction by the network. Recurrence prediction was realized on different time frames (1-, 2-, 3-, 4-, 5-, 6-years post-treatment) and the AUC of the proposed model varied from 0.71 to 0.85 in the different time points. Curves were built for recurrence-free survival for the different time points distinguishing patients at high- and low-risk of recurrence based on the model's predictions; except for 1-year post-treatment, a significant difference in survival was identified at each time point.

To improve the prognostic value of their models, some authors exploited imaging to predict not only microvascular invasion, but also other well-known prognostic factors. Chu et al. (37) developed a 3D CNN model capable of predicting HCC microvascular invasion and the presence of vessels encapsulating tumor clusters from 133 pre-operative contrast enhanced MR. The proposed model showed an AUC of 0.917 and of 0.86 for microvascular invasion and vessels encapsulating tumor clusters prediction. The model was also capable of classifying HCC patients in low- and high-risk groups for recurrence-free survival and overall survival based on the prediction of the presence or absence of the two prognostic factors evaluated showing that the absence of prognostic factors was associated to a significant gain in survival.

Radiological data does not represent the only source of information to predict HCC microvascular invasion. Zheng et al. (38) developed a neural network model based on clinical and biological features that were preventively identified through univariate and

multivariate analysis on 1697 patients with HCC. The neural network was fed with data concerning age, percentage of neutrophils, presence of multiple tumors, tumor diameter, and alpha fetoprotein level; the AUC for microvascular invasion was 0.704. When considering early-stage HCC patients only, age, percentage of neutrophils, and alpha fetoproteins levels were independent risk factors for microvascular invasion. The AUC for this predictive model was 0.605.

As it was reported for microvascular invasion in the aforementioned research, contrast enhanced CT-scan was used to predict other prognostic factors. Gu et al. (39), for example, aimed to predict HCC histological grade through a CNN model based on arterial-phase 2D CT-scans. The authors reported an AUC of 0.798 for this model in classifying low- and high-grade HCC.

In most of the previously described models, although sometimes heterogeneous, the authors included only patients with resectable HCC. However, a large number of patients presents advanced stage HCC at the moment of diagnosis that cannot be resected. As many different therapeutical procedures can be performed for this subgroup of patients, predicting their prognosis can be useful to plan a personalized strategy as for those who can undergo liver resection. Kim et al. (40) and Meng et al. (41), aimed to predict the survival of patients undergoing transarterial chemoembolization for unresectable HCC based on pre-procedural CT-scan radiomics. In the first paper, the authors produced a combined clinical and radiological model based on Child-Pugh score, alpha fetoprotein level, HCC size, and 5 radiomics features to classify patients in low- and high-risk groups for survival probability. The survival curves based on the model prediction showed a significant survival difference between the 2 groups with an impressive survival gain for patients in the low-risk group (HR: 19.88). However, when analyzing the characteristics of the 88 patients included for model development, we can notice that there is high heterogeneity in patients' and cancers' characteristics with both small solitary HCC in fully

active and performant individuals and multiple large HCC in frail patients, for whom a difference in survival probability is easily forgone. Moreover, it is not clear if the distinction in low- and high-risk group is based on a predefined time threshold or just on the computed global survival curve of the whole population, thus reducing the informative quality of the model in the clinical setting. Finally, many included patients had early-stage solitary HCC for whom it is not declared why transarterial chemoembolization was preferred to liver resection or liver transplantation. Meng et al. (41) similarly built a clinicoradiological model based on radiomics features and tumor numbers to create a nomogram capable of predicting 1- and 2-years survival probability. C-index reported by the authors for this model was 0.7 in the testing cohort. Moreover, based on the risk stratification of the model, the authors identified two risk classes for whom survival curves were depicted showing a significant survival gain for the low-risk group (median survival: 30.9 months vs. 17 months; HR: 2.43). Compared to what was proposed by Kim et al. (40), the study cohort was more homogeneous with most of the patients being BCLC stage B for whom transarterial chemoembolization represents the main option.

Although it represents a first-level diagnostic test that is implemented with CT-scan and MR in the suspicion of malignant liver mass(es), US is one of the main tools used for liver cancer diagnosis and follow-up, as it is easily available, reliable, low-cost, and non-irradiant. Thus, Huang et al. (42) aimed to develop a recurrence prediction model based exclusively on contrast-enhanced US images. Ultrasonic features from 215 patient with HCC were extracted from the manually delineated regions of interest taken from the US exams. Then, through machine learning, the model was trained to classify patients in low- and high-risk classes of recurrence which resulted to have 9.5% and 76.5% of cumulative 2-years recurrence probability and 37.6 (2 – 85) months and 12.8 (1.6 – 60.5) months of median recurrence time respectively. Although recurrence time was significantly different, large time ranges highlights a practical low difference in recurrence time prediction. In

addition, it is not clear on which basis the authors set the cut-off for a priori definition of low- and high-risk recurrence classes definition.

Although most of the AI-driven models to perform prognostic prediction for patients with liver cancer are based on radiological data, some research has been conducted focusing on other features with the same aim.

One astute and simple mean to perform prediction is exploiting biochemical and clinical data as reported by Liu et al. (43). Through regression analysis, age, white blood cell count, creatinine levels, total bilirubin levels, gamma glutamyl transferase levels, lactate dehydrogenase levels, albumin levels, tumor size ≥ 5 cm, tumor number ≥ 2, portal vein tumoral thrombosis, alpha fetoprotein levels ≥ 400ng/ml, antiviral therapy, T cells count, and CD8+ T cells count were identified as risk or protective factors affecting survival in 3427 patients with HCC. This data was fed to ANN to produce a 1-, 3-, and 5-years overall survival prediction model. The AUC of the model was 0.871, 0,831, and 0.848 in the validation cohort for the three time points respectively, with a global C-index of 0.773. The model was also used to identify three risk classes of survival and survival curves built on model predictions showed a significant difference between low-, intermediate-, and high-risk groups (overall survival: 98.5 months vs. 26.9 months vs. 5.2 months; progression-free survival: 33.4 months vs. 13.5 months vs. 3.8 months). The heterogeneity in patients' and cancers' characteristics of this large study population makes the proposed tool a useful mean to predict the evolution of the disease at the moment of diagnosis.

As we previously discussed for HCC diagnosis, the association of omics and AI in cancer research is gaining increasing interest. Thus, some researchers proposed AI-driven models to predict liver cancer prognosis based on genomics and transcriptomics exploiting public datasets. Luo et al. (20) focused their research on genes expressed by cancer-associated fibroblasts as these cells play a key role in promoting tumor proliferation and immune exclusion. In this study, 12 prognostic genes were identified through machine

learning and then fed to ANN to finally identify 3 mutated genes involved in high cancer-associated fibroblasts activation. The definition of a cancer-associated fibroblasts activation score with some clinical features such as age, gender, and cancer stage, permitted to build a nomogram to realize 1-, 3-, and 5-years survival prediction that showed an AUC ≈ 0.7 for the three time points. Tohme et al. (44) also developed a prognostic model for HCC which was, instead, only based on genomics and transcriptomics. ANN and a classification tree algorithm were used to identify 3 genes which were the strongest independent predictors for disease-free and overall survival. The machine learning algorithm also allowed to identify cutoff values for RNA expression to define 4 classes of risk with different survival. Regression analysis confirmed significant different disease-free and overall survival curves depending on the risk class compared to the group with the lower risk score (disease-free survival HR: 3.41, 5.54, 6.36; overall survival HR: 1.95, 2.46, 2.92). With an akin method, Zhou et al. (45) also used AI to identify genes' expression associated to poorer prognosis for HCC to build a risk score to classify patients with HCC in high- and low-risk classes related to different prognosis. AUC was 0.736, 0.668, and 0.73 for 1-, 3-, and 5-years survival prediction respectively. Then, this risk score was used to constitute a nomogram together with the presence of vascular tumor invasion and TNM stage in order to more precisely predict 1-, 3-, and 5-years survival; no significant difference was found in nomogram prediction and real data concerning survival at any time point. Cheng et al. (46), also exploited ML to isolate 12 genes differentially expressed between HCC and non-cancer tissue, that resulted to be associated with early tumorigenesis and cancer progression. Based on this panel of genes' expression, two classes of different HCC-related prognosis were built that resulted in a significant different survival (HR: 2.59). Finally, Owens et al. (47) applied a deep learning algorithm to the same multi-omics public datasets to identify clusters of patients with homogenous cancer biology and survival. The neural network selected 377 mRNAs, 15

miRNAs, and 328 methylation features reunited in 7 pathways differentiating prognostic clusters. The clustering function permitted to identify 2 different prognostic groups based on 5 different multi-omics features and classification based on each feature individually was associated with a significant difference in survival probability.

Although prognostic prediction based on omics is at its first step of development and has already shown important potentiality, real-life clinical setting is far from being capable of exploiting these tools at the moment as genomics and transcriptomics analysis are expensive, time consuming, and not reimbursed by national health systems.

Post-treatment prognosis prediction

Although prognosis can be predicted on the basis of clinical, biochemical, radiological, and omics data at the moment of diagnosis, once patients affected by liver primary cancer receive their first line of treatment, additional data concerning tumor characteristics and treatment efficacy can be additionally exploited to perform a more accurate forecast.

Different prognostic models have been developed depending on the type of treatment performed. Gu et al. (48) analyzed data from 2778 patients with early stage HCC who underwent liver resection to create a machine learning model to predict 10-year disease-free survival with the aim to guide clinical decisions regarding the need of an adjuvant chemotherapy. The covariates used for the model development were age, race, alpha fetoprotein levels, tumor size, multifocality, vascular invasion, histological grade and fibrosis score. C-statistic for 10-year disease-free survival was 0.721. Then, the authors identified through machine learning 3 classes of patients with different probabilities of post-resection survival, allowing to allocate a specific patient to a group of low (63.8 - 74.6%), intermediate (29.3 - 49.2%), or high (0.8 – 29.7%) risk for 10-year disease-free survival. Wang et al. (49) aimed to perform a predictive model with the same objective but focusing on patients with HBV-related solitary HCC who underwent liver resection. The authors

created nomograms predicting 1-, 2-, and 5- years recurrence-free survival and 1-, 3-, and 5- years overall survival based on tumor size, differentiation, microscopic vascular invasion, preoperative alpha-fetoprotein, neutrophil-to-lymphocyte ratio, albumin-to-bilirubin ratio, and blood transfusion. The C-index were 0.83 and 0.87 respectively. Finally, Sun et al. (50) also built a prognosis prediction model for patients who underwent liver resection for HCC but including also advanced TNM stages, with the exclusion of metastatic disease. In this case, the machine learning model was trained to predict tumor recurrence and resulted to have an AUC of 0.8877 in the validation cohort. The model was also able to classify patients in low and high recurrence risk who showed significantly different disease-free survival and overall survival curves (HR: 9.437 and 24.73, respectively).

When HCC treatment consists in thermoablation, data concerning the whole specimen microscopic analysis cannot be obtained and exploited for prognostic model development as reported in the previous described studies. Wang et al. (51) built a feedforward neural network model fed with pre-procedural MR images, intraoperative CT-scan images and thermal dose information, and postoperative MR images of patients treated with radiofrequency thermoablation after a pre-treatment tumor freezing process for HCC. This model could predict recurrence with a C-index of 0.855. Moreover, the algorithm could identify two classes of patients with low and high recurrence risk whose survival curves were significantly different.

Liver transplantation is one of the recommended treatments for early and intermediate stage HCC conferring an expected > 5 years survival (3). However, tumor recurrence occurs in 10-15% of patients; thus, it is important to identify those patients at higher risk of recurrence to adapt post-liver transplant follow-up. Based on HCC pathomics features coming from liver transplant specimens fed to a CNN, Qu et al. (52) produced a tool to predict HCC recurrence. One-, 2-, and 3-years recurrence free survival were delineated by

the model with an AUC of 0.779, 0.828, and 0.814 respectively on the validation cohort. Tumor size, microvascular invasion, and tumor differentiation grade mainly contributed to increased recurrence risk. Similarly to other reported prognostic models, low- and high-recurrence risk classes were identified by the model, which resulted to have significantly different recurrence curves. Also, the authors did not report how the risk cut off was set and model validation was not performed on an external cohort.

Finally, prognostic prediction models can be developed not only to foresee the risk of HCC recurrence in patients treated with invasive procedures, but also for those who undergo systemic treatment. These patients mainly present advanced HCC which is associated with low long-term survival. Immunotherapy has shown encouraging results in prolonging patients survival but non-responders are not rare (53). To identify survival differences in patients receiving immunotherapy for advanced HCC, Lui et al. (54) used 47 clinical variables of 395 patients to predict 1-year cancer related mortality through machine learning. Through the random forest algorithm, the authors created a predictive model with an AUC of 0.92, 2% of false positive rate, and 5.2% false negative rate. The three main risk factors associated with 1-year cancer-related mortality were elevated baseline alpha-fetoprotein, bilirubin, and alkaline phosphatases levels. The research by Hsu et al. (19), already mentioned above, also gives an insight on prognosis prediction after systemic treatment for HCC, showing how circulating angiogenic factors FGF21 and ANG2 and alpha-fetoprotein concentrations permits to classify patients undergoing Lenvatinib in a low, intermediate, and high-risk group that cannot only predict tumor response rate to chemotherapy, but also overall survival. As a matter of fact, the authors showed significant survival differences between the high-, intermediate, and low-risk classes.

As we reported in the other paragraphs, reports on AI-driven models focusing on ICC are rarer than those for HCC. Although anecdotal for the moment, Alaimo et al. (55) used the optimal survival and optimal policy tree machine learning models to predict overall survival

using data from 600 patients who underwent liver resection for ICC. Based on tumor size, carbohydrate antigen 19-9 levels, nodal status, margin width, and age, they identified 5 different 5-years overall survival subgroups with an AUC of 0.69 on the test dataset. However, the lack of an external validation reduces the reliability of their results.

Author	Country	Data	Patients (n)	Model	Setting	Outcome		
						Accuracy (%)	c-index	AUC
At diagnosis								
Cheng, 2022[46]	China	genomics	-	ML	OS prediction (HCC)			
Luo, 2022[20]	China	Clinical, genomics, transcriptomics	450	ANN, ML	OS prediction (HCC)			0.7
Wang, 2022[32]	China	MR/CT-scan	397	CNN, automatic	MI and RFS prediction (HCC)	80		
Li, 2022[33]	China	clinical, CT-scan	1116	CNN, automatic	MI, RFS, and OS prediction (HCC)	83.5		0.897
Liu, 2021[34]	Taiwan	CT-scan	473	CNN, automatic	MI prediction (HCC)	71		0.78
Yang, 2021[35]	China	clinical, CT-scan radiomics	283	DL	MI, RFS, and OS prediction (HCC)	96.5		0.909
Kucukkaya, 2023[36]	Germany	MR	120	CNN, automatic	RFS prediction (HCC)			0.71-0.85
Chu, 2022[37]	China	MR	133	CNN, automatic	MI, VET, RFS, and OS prediction (HCC)			0.86-0.92
Zheng, 2023[38]	China	clinical, biochemical	1687	NN	MI prediction (HCC)			0.704
Gu, 2021[39]	China	CT-scan	455	CNN, automatic	Histological grade prediction (HCC)			0.798
Kim, 2018[40]	Korea	clinical, CT-scan radiomics	88	ML	OS prediction (HCC)			
Meng, 2020[41]	China	clinical, CT-scan radiomics	162	ML	OS prediction (HCC)		0.7	
Huang, 2022[42]	China	CEUS radiomics	215	ML	RFS prediction (HCC)			0.845
Liu, 2022[43]	China	clinical, biochemical	3427	ANN	RFS and OS prediction (HCC)		0.773	0.83-0.87
Tohme, 2021[44]	USA	genomics, transcriptomics	363	ML	RFS and OS prediction (HCC)			
Zhou, 2021[45]	China	genomics, transcriptomics	-	ML	OS prediction (HCC)			0.67-0.74
Owens, 2021[47]	UK	genomics, transcriptomics	452	ANN	OS prediction (HCC)			
After treatment								
Hsu, 2022[19]	Taiwan	biochemical	82	ML	OS prediction after Lenvatinib (HCC)			
Ji, 2021[48]	China	clinical, biochemical, histological	2778	ML	RFS prediction after LR (HCC)		0.721	
Wang, 2020[49]	China	clinical, biochemical, histological	1081	ML	RFS and OS prediction after LR (HCC)		0.83-0.87	
Sun, 2023[50]	China	clinical, biochemical, histological	1854	ML	RFS after LR (HCC)			0.888
Wang, 2022[51]	China	MR/CT-scan	25	FNN	RFS after TA (HCC)		0.855	
Qu, 2023[52]	China	pathomics	380	CNN	Tumor recurrence after LT (HCC)			0.78-0.83
Lui, 2022[54]	China	clinical	395	ML	OS prediction after immunotherapy (HCC)			0.92
Alaimo, 2023[55]	International	clinical, biochemical, pathological	600	ML	OS prediction (ICC)			0.69

Table 4: characteristics of the studies describing AI-driven models to perform prognosis prediction of primary liver cancer at the moment of diagnosis or after treatment. CT: computed tomography; MR: magnetic resonance; CEUS: contrast-enhanced ultrasonography; ML: machine learning; CNN: convolutional neural network; ANN: artificial neural network; NN: neural network; FNN: feedforward neural network; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; OS: overall survival; RFS: recurrence-free survival; MI: microvascular invasion; VET: vessel encapsulating tumor; LR: liver resection; TA: thermoablation; LT: liver transplantation.

Conclusion

AI-driven models, from machine learning to DL, represent one major subject of research development in many medical fields at the moment. The applications of AI in the setting of primary liver cancer are multiple and authors are constantly developing tools that can assist or even substitute clinicians in their daily practice. The results reported concerning models' performance are impressive and it is hard to imagine that future clinical practice could not rely on this technology.

However, as we pointed out in the first part of this review, many limitations still exist when analyzing research on this subject.

Although more pronounced in research concerning AI models for screening and diagnostics, model development and real-life implementation are quite distant also for what it concerns treatment and post-treatment management phasis. In particular, when considering prediction models based on genomics and transcriptomics, most of the models are based on data whose access is not available easily worldwide and with costs far too expensive to allow a routine usage.

Secondly, when an example of clinical application is provided, this is frequently affected by the intention of the authors to produce a highly performing model to the detriment of its actual interest in clinical practice. For example, this issue becomes manifest in prognosis prediction models when patients risk classes of survival are built depending on statistics rather than on time thresholds on whom different therapeutical attitudes can be planned. In addition, we frequently noticed that patients included for models training have characteristics that make models' purpose nonsuitable for a part of patient's cohort. This happens, for instance, when developing a model for treatment planning and efficacity assessment on a cohort that includes patients for whom this treatment is not recommended in first place or at all.

Thirdly, as already highlighted for screening and diagnosis, models frequently lack

full validation processes, in particular with the absence of an external validation. As populations on whom models are developed frequently come from one or a restricted number of centers and are not representative of the general population, the absence of the implementation of the proposed tools on a test population prevent from reducing the influence of selection bias.

Finally, for treatment planning, prognosis prediction, and follow-up, models development is highly affected by different therapeutical indications, treatment delivery and follow-up strategies applied in different countries, as well as organization of health systems and economical resources that can be spent in the different phasis of liver cancer management. For example, patients in non-Western countries may not be treated and followed with the same protocols as in Western countries, thus making models not comparable and impossible to implement on a global scale.

AI-driven models have the potential to improve the management of liver cancer, but many efforts still have to be realized to obtain well-structured and reliable models.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Rumgay H, Arnold M, Ferlay J, Lesi O, Cabasag CJ, Vignat J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. J Hepatol [Internet]. 2022;77(6):1598–606. Available from: https://doi.org/10.1016/j.jhep.2022.08.021
3. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol [Internet]. 2022;76(3):681–93. Available from: https://doi.org/10.1016/j.jhep.2021.11.018

4. Rushbrook S, Kendall T, Zen Y, Albazaz R, Manoharan P, Pereira SP, et al. British Society of Gastroenterology Guidelines for the Diagnosis and Management of Cholangiocarcinoma. Gut. 2023;In press:1–31.
5. Plachouris D, Tzolas I, Gatos I, Papadimitroulas P, Spyridonidis T, Papathanasiou N, et al. A deep-learning-based prediction model for the biodistribution of 90 Y microspheres in liver radioembolization.
6. Chaichana A, Frey EC, Teyateeti A, Rhoongsittichai K, Tocharoenchai C, Pusuwan P, et al. Automated segmentation of lung , liver , and liver tumors from Tc-99m MAA SPECT / CT images for Y-90 radioembolization using convolutional neural networks. 2021;(August):7877–90.
7. Shin SW, Ahn KS, Kim YSW, Kim TS, Kim YH, Kang KJ. Liver Resection Versus Local Ablation Therapies for Hepatocellular Carcinoma within the Milan Criteria A Systematic Review and Meta-analysis. Ann Surg. 2021;273(4):656–66.
8. WEI W, Haishan X, Alpers J, Rak M, Hansen C. A deep learning approach for 2D ultrasound and 3D CT/MR image registration in liver tumor ablation. Comput Methods Programs Biomed [Internet]. 2021;206:106117. Available from: https://doi.org/10.1016/j.cmpb.2021.106117
9. De Landro M, Felli E, Collins T, Nkusi R, Baiocchini A, Barberio M, et al. Prediction of in vivo laser-induced thermal damage with hyperspectral imaging using deep learning. Sensors. 2021;21(20):1–19.
10. Lv S, Li S, Yu Z, Wang K, Qiao X, Gong D, et al. Application of the Preoperative Assistant System Based on Machine Learning in Hepatocellular Carcinoma Resection. 2021;2021.
11. Merath K, Tiwari A, Court C, Parikh A, Dillhoff M, Cloyd J, et al. Postoperative Liver Failure: Definitions, Risk factors, Prediction Models and Prevention Strategies. J Gastrointest Surg. 2023;2640–9.

12. Takamoto T, Ban D, Nara S, Mizui T, Nagashima D, Esaki M. Automated Three - Dimensional Liver Reconstruction with Artificial Intelligence for Virtual Hepatectomy. J Gastrointest Surg [Internet]. 2022;2119–27. Available from: https://doi.org/10.1007/s11605-022-05415-9

13. Nishio T, Taura K, Koyama Y, Ishii T, Hatano E. Current status of preoperative risk assessment for posthepatectomy liver failure in patients with hepatocellular carcinoma. Ann Gastroenterol Surg. 2023;(May):871–86.

14. Zhu L, Wang F, Chen X, Dong Q, Xia N, Chen J, et al. Machine learning-based radiomics analysis of preoperative functional liver reserve with MRI and CT image. 2023;1–10.

15. Mo A, Velten C, Jiang JM, Tang J, Ohri N. Improving Adjuvant Liver-Directed Treatment Recommendations for Unresectable Hepatocellular Carcinoma : An Artificial Intelligence – Based Decision-Making Tool. JCO Clin cancer informatics. 2022;6:1–9.

16. Lu L, Zeng J, Wen Z, Tang C, Xu N. Transctheter arterial chemoembolisation followed by three-dimensional conformal radiotherapy versus transcatheter arterial chemoembolisation alone for primary hepatocellular carcinoma in adults (Review). Cochrane Clin Answers. 2019;(2).

17. Boldanova T, Fucile G, Vosshenrich J, Suslov A, Ercan C, Coto-Llerena M, et al. Supervised learning based on tumor imaging and biopsy transcriptomics predicts response of hepatocellular carcinoma to transarterial chemoembolization. Cell Reports Med [Internet]. 2021;2(11):100444. Available from: https://doi.org/10.1016/j.xcrm.2021.100444

18. Sun Y, Bai H, Xia W, Wang D, Zhou B, Zhao X, et al. Predicting the Outcome of Transcatheter Arterial Embolization Therapy for Unresectable Hepatocellular Carcinoma Based on Radiomics of Preoperative Multiparameter MRI. J Magn Reson

Imaging. 2020;52(4):1083–90.

19. Hsu P-Y, Liang P-C, Chang W-T, Lu M-Y, Wang W-H, Chuang S-C, et al. Artificial intelligence based on serum biomarkers predicts the efficacy of lenvatinib for unresectable hepatocellular carcinoma. Am J Cancer Res [Internet]. 2022;12(12):5576–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/36628276%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC9827079
20. Luo Y, Tan H, Yu T, Tian J, Shi H. A Novel Artificial Neural Network Prognostic Model Based on a Cancer-Associated Fibroblast Activation Score System in Hepatocellular Carcinoma. Front Immunol. 2022;13(July):1–14.
21. Ansari MY, Yang Y, Balakrishnan S, Abinahed J, Al-Ansari A, Warfa M, et al. A lightweight neural network with multiscale feature enhancement for liver CT segmentation. Sci Rep [Internet]. 2022;12(1):1–12. Available from: https://doi.org/10.1038/s41598-022-16828-6
22. Said D, Carbonell G, Stocker D, Hectors S, Vietti-Violi N, Bane O, et al. Semiautomated segmentation of hepatocellular carcinoma tumors with MRI using convolutional neural networks. Eur Radiol [Internet]. 2023;33(9):6020–32. Available from: https://doi.org/10.1007/s00330-023-09613-0
23. Zang L, Liang W, Ke H, Chen F, Shen C. Research on liver cancer segmentation method based on PCNN image processing and SE-ResUnet. Sci Rep [Internet]. 2023;13(1):1–14. Available from: https://doi.org/10.1038/s41598-023-39240-0
24. Jiang L, Ou J, Liu R, Zou Y, Xie T, Xiao H, et al. RMAU-Net: Residual Multi-Scale Attention U-Net For liver and tumor segmentation in CT images. Comput Biol Med [Internet]. 2023;158(September 2022):106838. Available from: https://doi.org/10.1016/j.compbiomed.2023.106838
25. Liu J, Yan Z, Zhou C, Shao L, Han Y, Song Y. mfeeU-Net: A multi-scale feature

extraction and enhancement U-Net for automatic liver segmentation from CT Images. Math Biosci Eng. 2023;20(5):7784–801.

26. Kushnure DT, Talbar SN. HFRU-Net: High-Level Feature Fusion and Recalibration UNet for Automatic Liver and Tumor Segmentation in CT Images. Comput Methods Programs Biomed [Internet]. 2022;213:106501. Available from: https://doi.org/10.1016/j.cmpb.2021.106501
27. Hille G, Agrawal S, Tummala P, Wybranski C, Pech M, Surov A, et al. Joint liver and hepatic lesion segmentation in MRI using a hybrid CNN with transformer layers. Comput Methods Programs Biomed. 2023;240.
28. Gong Z, Guo C, Guo W, Zhao D, Tan W, Zhou W, et al. A hybrid approach based on deep learning and level set formulation for liver segmentation in CT images. J Appl Clin Med Phys. 2022;23(1):1–11.
29. Wu Y, Shen H, Tan Y, Shi Y. Automatic liver tumor segmentation used the cascade multi-scale attention architecture method based on 3D U-Net. Int J Comput Assist Radiol Surg [Internet]. 2022;17(10):1915–22. Available from: https://doi.org/10.1007/s11548-022-02653-9
30. Shao HC, Huang X, Folkert MR, Wang J, Zhang Y. Automatic liver tumor localization using deep learning-based liver boundary motion estimation and biomechanical modeling (DL-Bio). Med Phys. 2021;48(12):7790–805.
31. Nevola R, Ruocco R, Criscuolo L, Villani A, Alfano M, Beccia D, et al. Predictors of early and late hepatocellular carcinoma recurrence. World J Gastroenterol. 2023;29(8):1243–60.
32. Wang F, Chen Q, Chen Y, Zhu Y, Zhang Y, Cao D, et al. A novel multimodal deep learning model for preoperative prediction of microvascular invasion and outcome in hepatocellular carcinoma. Eur J Surg Oncol [Internet]. 2023;49(1):156–64. Available from: https://doi.org/10.1016/j.ejso.2022.08.036

33. Li X, Qi Z, Du H, Geng Z, Li Z, Qin S, et al. Deep convolutional neural network for preoperative prediction of microvascular invasion and clinical outcomes in patients with HCCs. Eur Radiol. 2022;32(2):771–82.

34. Liu SC, Lai J, Huang JY, Cho CF, Lee PH, Lu MH, et al. Predicting microvascular invasion in hepatocellular carcinoma: a deep learning model validated across hospitals. Cancer Imaging. 2021;21(1):1–16.

35. Yang Y, Zhou Y, Zhou C, Ma X. Deep learning radiomics based on contrast enhanced computed tomography predicts microvascular invasion and survival outcome in early stage hepatocellular carcinoma. Eur J Surg Oncol [Internet]. 2022;48(5):1068–77. Available from: https://doi.org/10.1016/j.ejso.2021.11.120

36. Kucukkaya AS, Zeevi T, Chai NX, Raju R, Haider SP, Elbanan M, et al. Predicting tumor recurrence on baseline MR imaging in patients with early-stage hepatocellular carcinoma using deep machine learning. Sci Rep [Internet]. 2023;13(1):1–9. Available from: https://doi.org/10.1038/s41598-023-34439-7

37. Chu T, Zhao C, Zhang J, Duan K, Li M, Zhang T, et al. Application of a Convolutional Neural Network for Multitask Learning to Simultaneously Predict Microvascular Invasion and Vessels that Encapsulate Tumor Clusters in Hepatocellular Carcinoma. Ann Surg Oncol [Internet]. 2022;29(11):6774–83. Available from: https://doi.org/10.1245/s10434-022-12000-6

38. Zheng J, Wei X, Wang N, Pu X, Yang J, Jiang L. A new method for predicting the microvascular invasion status of hepatocellular carcinoma through neural network analysis. BMC Surg. 2023;23(1):1–7.

39. Gu D, Guo D, Yuan C, Wei J, Wang Z, Zheng H, et al. Multi-scale patches convolutional neural network predicting the histological grade of hepatocellular carcinoma. Proc Annu Int Conf IEEE Eng Med Biol Soc EMBS. 2021;2584–7.

40. Kim J, Choi SJ, Lee S-H, Lee HY, Park H. Predicting Survival Using Pretreatment CT

for Patients With Hepatocellular Carcinoma Treated With Transarterial Chemoembolization: Comparison of Models Using Radiomics. Am J Roentgenol. 2018;211(November):1026–34.

41. Meng XP, Wang YC, Ju S, Lu CQ, Zhong BY, Ni CF, et al. Radiomics Analysis on Multiphase Contrast-Enhanced CT: A Survival Prediction Tool in Patients With Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization. Front Oncol. 2020;10(July):1–12.
42. Huang H, Ruan SM, Xian MF, Li M De, Cheng MQ, Li W, et al. Contrast-enhanced ultrasound–based ultrasomics score: a potential biomarker for predicting early recurrence of hepatocellular carcinoma after resection or ablation. Br J Radiol. 2022;95(1130).
43. Liu X, Wang X, Yu L, Hou Y, Jiang Y, Wang X, et al. A Novel Prognostic Score Based on Artificial Intelligence in Hepatocellular Carcinoma: A Long-Term Follow-Up Analysis. Front Oncol. 2022;12(May).
44. Tohme S, Yazdani HO, Rahman A, Handu S, Khan S, Wilson T, et al. The Use of Machine Learning to Create a Risk Score to Predict Survival in Patients with Hepatocellular Carcinoma: A TCGA Cohort Analysis. Can J Gastroenterol Hepatol. 2021;2021.
45. Zhou X, Dou M, Liu Z, Jiao D, Li Z, Chen J, et al. Screening Prognosis-Related lncRNAs Based on WGCNA to Establish a New Risk Score for Predicting Prognosis in Patients with Hepatocellular Carcinoma. J Immunol Res. 2021;2021.
46. Cheng B, Zhou P, Chen Y. Machine-learning algorithms based on personalized pathways for a novel predictive model for the diagnosis of hepatocellular carcinoma. BMC Bioinformatics [Internet]. 2022;23(1):1–19. Available from: https://doi.org/10.1186/s12859-022-04805-9
47. Owens AR, McInerney CE, Prise KM, McArt DG, Jurek-Loughrey A. Novel deep

learning-based solution for identification of prognostic subgroups in liver cancer (Hepatocellular carcinoma). BMC Bioinformatics [Internet]. 2021;22(1):1–22. Available from: https://doi.org/10.1186/s12859-021-04454-4

48. Ji G-W, Fan Y, Sun D-W, Wu M-Y, Wang K, Li X-C, et al. Machine Learning to Improve Prognosis Prediction of Early Hepatocellular Carcinoma After Surgical Resection [Corrigendum]. J Hepatocell Carcinoma. 2021;Volume 8:1297–8.
49. Wang X-H, Liao B, Hu W-J, Tu C-X, Xiang C-L, Hao S-H, et al. Novel Models Predict Postsurgical Recurrence and Overall Survival for Patients with Hepatitis B Virus-Related Solitary Hepatocellular Carcinoma ≤10 cm and Without Portal Venous Tumor Thrombus. Oncologist [Internet]. 2020;25(10):e1552–61. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2005777956&from=export
50. Sun LY, Ouyang Q, Cen WJ, Wang F, Tang WT, Shao JY. A Model Based on Artificial Intelligence Algorithm for Monitoring Recurrence of HCC after Hepatectomy. Am Surg. 2023;89(5):1468–78.
51. Wang X, Li W, Zhang K, Sun J, Yang J, Zhang A, et al. A Novel Tumor Progression Prediction Method for Multimode Ablation Treatment. IEEE Trans Biomed Eng. 2022;69(4):1386–97.
52. Qu WF, Tian MX, Lu HW, Zhou YF, Liu WR, Tang Z, et al. Development of a deep pathomics score for predicting hepatocellular carcinoma recurrence after liver transplantation. Hepatol Int [Internet]. 2023;17(4):927–41. Available from: https://doi.org/10.1007/s12072-023-10511-2
53. Rizzo A, Brandi G. Biochemical predictors of response to immune checkpoint inhibitors in unresectable hepatocellular carcinoma. Cancer Treat Res Commun [Internet]. 2021;27:100328. Available from: https://doi.org/10.1016/j.ctarc.2021.100328

54. Lui TKL, Cheung KS, Leung WK. Machine learning models in the prediction of 1-year mortality in patients with advanced hepatocellular cancer on immunotherapy: a proof-of-concept study. Hepatol Int [Internet]. 2022;16(4):879–91. Available from: https://doi.org/10.1007/s12072-022-10370-3

55. Alaimo L, Moazzam Z, Endo Y, Lima HA, Butey SP, Ruzzenente A, et al. The Application of Artificial Intelligence to Investigate Long-Term Outcomes and Assess Optimal Margin Width in Hepatectomy for Intrahepatic Cholangiocarcinoma. Ann Surg Oncol. 2023;30(7):4292–301.