**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 70681

**Manuscript Type:** MINIREVIEWS

**Artificial intelligence in the diagnosis and management of colorectal cancer liver metastases**

Rompianesi G *et al*. AI in CRLM diagnosis and management

Gianluca Rompianesi, Francesca Pegoraro, Carlo DL Ceresa, Roberto Montalti, Roberto Ivan Troisi

**Gianluca Rompianesi, Francesca Pegoraro, Roberto Ivan Troisi,** Division of Hepato-Bilio-Pancreatic, Minimally Invasive and Robotic Surgery, Department of Clinical Medicine and Surgery, Federico II University Hospital, Naples 80125, Italy

**Carlo DL Ceresa,** Department of Hepato-Pancreato-Biliary Surgery, Oxford University Hospitals NHS Foundation Trust, Oxford OX3 9ES, United Kingdom

**Roberto Montalti,** Division of Hepato-Bilio-Pancreatic, Minimally Invasive and Robotic Surgery, Department of Public Health, Federico II University Hospital, Naples 80125, Italy

**Author contributions:** Rompianesi G conceptualized the manuscript; Rompianesi G and Montalti R wrote the manuscript; Pegoraro F performed the literature search and the data analysis and extraction; Ceresa CDL and Troisi RI reviewed and edited the manuscript; and all authors have read and approve the final manuscript.

**Corresponding author: Gianluca Rompianesi, FEBS, MD, PhD, Assistant Professor, Surgeon,** Division of Hepato-Bilio-Pancreatic, Minimally Invasive and Robotic Surgery, Department of Clinical Medicine and Surgery, Federico II University Hospital, *via* Pansini 5, Naples 80125, Italy. gianlucarompianesi@gmail.com

**Received:** August 13, 2021

**Revised:** October 12, 2021

**Accepted: December 25, 2021**

**Published online:**

**Abstract**

Colorectal cancer (CRC) is the third most common malignancy worldwide, with approximately 50% of patients developing colorectal cancer liver metastasis (CRLM) during the follow-up period. Management of CRLM is best achieved *via* a multidisciplinary approach and the diagnostic and therapeutic decision-making process is complex. In order to optimize patients’ survival and quality of life, there are several unsolved challenges which must be overcome. These primarily include a timely diagnosis and the identification of reliable prognostic factors. Furthermore, to allow optimal treatment options, a precision-medicine, personalized approach is required. The widespread digitalization of healthcare generates a vast amount of data and together with accessible high-performance computing, artificial intelligence (AI) technologies can be applied. By increasing diagnostic accuracy, reducing timings and costs, the application of AI could help mitigate the current shortcomings in CRLM management. In this review we explore the available evidence of the possible role of AI in all phases of the CRLM natural history. Radiomics analysis and convolutional neural networks (CNN) which combine computed tomography (CT) images with clinical data have been developed to predict CRLM development in CRC patients. AI models have also proven themselves to perform similarly or better than expert radiologists in detecting CRLM on CT and magnetic resonance scans or identifying them from the noninvasive analysis of patients’ exhaled air. The application of AI and machine learning (ML) in diagnosing CRLM has also been extended to histopathological examination in order to rapidly and accurately identify CRLM tissue and its different histopathological growth patterns. ML and CNN have shown good accuracy in predicting response to chemotherapy, early local tumor progression after ablation treatment, and patient survival after surgical treatment or chemotherapy. Despite the initial enthusiasm and the accumulating evidence, AI technologies’ role in healthcare and CRLM management is not yet fully established. Its limitations mainly concern safety and the lack of regulation and ethical considerations. AI is unlikely to fully replace any human role but could be actively integrated to facilitate physicians in their everyday practice. Moving towards a personalized and evidence-based patient approach and management, further larger, prospective and rigorous studies evaluating AI technologies in patients at risk or affected by CRLM are needed.

**Key Words:** Colorectal cancer; Liver metastases; Artificial intelligence; Machine learning; Deep learning; Neural networks; Radiomics

Rompianesi G, Pegoraro F, Ceresa CD, Montalti R, Troisi RI. Artificial intelligence in the diagnosis and management of colorectal cancer liver metastases. *World J Gastroenterol* 2021; In press

**Core tip:** The digitalization of healthcare generating huge amount of data set the ground for the progressive ubiquitous application of artificial intelligence (AI) technologies in healthcare. AI analyses can assist clinicians in all phases of colorectal liver metastases natural history: From predicting their occurrence, to increasing diagnostic accuracy or estimating recurrence risk after treatment and patient outcome. The implementation of AI resources supports the contemporary paradigm shift that sees healthcare focus moving from a generalized, disease-oriented to an individual, patient-centered, precision medicine approach.

**INTRODUCTION**

***Colorectal cancer liver metastases***

Colorectal cancer (CRC) is the most common gastrointestinal cancer, the third most frequently diagnosed malignancy (10.0%) overall, and the second highest cause of cancer-related deaths (9.4%), with incidences varying significantly worldwide[1,2]. CRC development is predominantly sporadic, with patient age, environmental and genetic factors associated with a significantly increased risk[3,4]. Over 20% of newly diagnosed CRC patients have distant metastases at presentation[5], with estimated 5-year survival dropping from 80%-90% in patients with local disease to a dismal 10%-15% in those with metastatic spread[6]. The liver is the preferential metastatic site, due to its anatomical proximity and the portal systemic circulation. This results in 25%-50% of CRC patients developing liver metastasis during the course of the disease[7,8]. In cases of synchronous resectable colorectal cancer liver metastasis (CRLM), the treatment options range from the traditional staged approach, where the primary tumor is resected prior to systemic chemotherapy and liver metastasis resection, to the combined approach of bowel and liver resection during the same procedure, or the “liver first” approach[9]. Irrespective of the timing of the surgical resection, surgery in combination with chemotherapy is the optimal treatment for CRLM, but only 25% of patients are suitable candidates for resection at diagnosis[8,10]. In patients not amenable to surgery, chemotherapy is the usual treatment of choice, with the potential to render 10%-30% of tumors technically resectable through a good response and downsizing[11]. CRLM management is multidisciplinary, with oncologists, surgeons, radiologists and pathologists playing pivotal roles in the complex diagnostic and therapeutic decision-making processes aimed to achieve the best possible outcome for the patient[12]. In such a complex oncological scenario, with unsolved challenges in timely diagnosis, reliable prognostic factor identification and optimal treatment selection, there is a strong need for a precision-medicine, personalized approach in order to optimize patients’ survival and quality of life. The recent progressive implementation of artificial intelligence (AI) in healthcare has been welcomed with enthusiasm by both healthcare professionals and the general public; however, there remain several issues which are yet to be solved. AI has the potential to overcome some of the current practice limitations, and to play a crucial role in all steps of the management of CRLM but its clinical benefits have yet to be clearly established and validated.

The aim of this review is to summarize and analyze the available evidence on the application of AI technologies in the diagnosis and management of patients affected by CRLM.

***AI***

The term AI encompasses all the possible applications of technologies in simulating and replicating human intelligence[13]. These endless applications range from everyday life to finance and economics[14] or various medical fields, thanks to the advances in computational power and the collection and storage of large amounts of data in healthcare. After being adequately programmed and trained, AI has the potential to outperform clinicians in some tasks in terms of accuracy, speed of execution and reduced biases[15]. AI has therefore progressively demonstrated its potential across all human lifespan; from the optimization of embryo selection during *in vitro* fertilization[16] to the prediction of all-cause mortality[17]. The revolutionary potential of these technologies in healthcare has generated great interest in researchers, professionals and industries, with currently over 450 AI-based medical devices approved in Europe or the United States[18]. Nevertheless, the surge of AI and its implementation in clinical practice has been accompanied by several issues including legal considerations regarding security and data, software transparency, flawed algorithms and inherent bias in the input data[13,19].

***Machine learning***

The replication of human intelligence by AI with the utilization of data-driven algorithms that have been instructed and self-train through experience and data analysis is generally defined as machine learning (ML)[13]. After been programmed, ML can find recurrent patterns in large amount of appropriately engineered data and progressively learn and independently improve performance accuracy without human intervention. The ML algorithms are generally classified in supervised learning (the most frequent one, which utilizes classified data), unsupervised learning (where algorithms can independently identify patterns in data without previous classification), semi-supervised learning (can use a combination of both labelled and unlabeled data) and reinforcement learning (uses estimated errors as proportional rewards or penalties to teach algorithms). Deep learning (DL) is a class of ML techniques that has the ability to directly process raw data and perform detection or classification tasks automatically without the need for human intervention. The sets of algorithms utilized by DL are generally artificial neural networks (ANNs) constituted by several layers that elaborate inputs with weights, biases (or thresholds) and deliver an output. ML models can be combined with the large amount of qualitative and quantitative information mined from medical images (radiomics) and clinical data to assist clinicians in evidence-based decision making processes[20].

**PREDICTIVE AI MODELS FOR THE DEVELOPMENT OF CRLM**

A significant proportion of patients affected by CRC will develop CRLM during the follow-up period[21], but only about a quarter of them will be eligible for surgical resection and therefore potential cure[22]. Being able to identify the subgroup of patients at higher risk of CRLM development could allow the adoption of individualized and more intense screening protocols and adjuvant therapies.

The Radiomics Intelligent Analysis Toolkit-based analysis platform built by Li *et al*[23] allowed the construction of individualized nomograms able to combine maximum-level enhanced computed tomography (CT) images in the portal venous phase and patients’ clinical information [age, sex, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9] to predict the development of CRLM in patients with CRC. The area under the receiver operating characteristic (AUROC) score obtained from the analysis of 100 patients (50 with CRLM and 50 controls) was 0.899 [95% confidence interval (CI): 0.761-1.000] on the test set in a total execution time of 270 s. The ML predictive models built by Taghavi[24] including radiomics and a combination of radiomics with clinical features (contrast-enhanced portal venous phase CT of the liver or abdomen with age, sex, primary tumor site, tumor stage, nodal stage, CEA at primary diagnosis, administration of adjuvant/neoadjuvant chemotherapy) of 91 patients (24 of which developed metachronous CRLM), both presented an area under the curve (AUC) in the validation cohort of 86% (95%CI: 85%-87%) in predicting the development of CRLM within 24 mo. The convolutional neural network (CNN) model developed by Lee *et al*[25] in their retrospective, cross-sectional study in 2019 patients who underwent curative colectomy for stage I-III CRC was able to predict 5-year metachronous liver metastasis occurrence with a mean AUC of 0.747 when combining the analysis of the abdominal CT scan taken before the colectomy for clinical staging and clinical features (age, sex, tumor stage, nodal stage).

**AI MODELS FOR THE DIAGNOSIS OF CRLM**

Prompt diagnosis of CRLM at an early stage gives patients the best chances of effective treatment and a superior outcome. One of the key steps in the diagnostic process is tumor segmentation, with nodule volume being a better predictor than diameter[26]. This process is usually done manually but requires a significant expertise, is operator-dependent and time-consuming. In this setting, semiautomatic tumor segmentation methods based on texture analysis have been developed[26] in order to take full advantage of AI’s unique potential to increase sensitivity and specificity of metastatic tumor detection[27].

***CT radiomics models***

Starting with a manual tumor/nontumor class prediction voxel classification, a deformable surface model fitting the tumor boundaries is instigated[27]. A multilayer perceptron feed-forward neural network model concurrently learns per-voxel image features and classifications and, after being trained, it performs a semiautomatic per-tumor segmentation on CT scans. The accuracy of the model resulted in 0.88 ± 0.11, with a sensitivity of 0.84 ± 0.13 and a specificity of 0.92 ± 0.16. The same group in 2019 published the results of a retrospective analysis of a fully CNN for liver lesion detection and segmentation on CT scans with a sensitivity of 71% and 85% and a positive predictive value of 83% and 94% for lesions bigger than 10 mm and 20 mm in diameter, respectively[28]. CRLM is most commonly diagnosed in the venous phase of contrast-enhanced CT scan, as it appears hypodense, with or without peripheral rim enhancement and calcification. Portal-venous phase scans are most reliable in the detection of CRLM, with a sensitivity of approximately 85% for helical CT[29], and such diagnostic power lies in an optimal timing of image acquisition after a delay following contrast intravenous injection. Different equipment, protocols, patient’s body habitus and cardiovascular system function result in high variability and impact on measurement accuracy in the absence of reliable automatic timing quantification. Ma *et al*[30] designed a fully automatic DL CNN that in a 3-s timespan can recognize the optimal portal venous phase acquisitions on CT scans with an AUC of 0.837 (95% CI: 0.765-0.890) in the validation set and an AUC of 0.844 (95% CI: 0.786-0.889) in the external validation set. This is aimed to improve image quality, which is crucial for the detection and characterization of liver lesions and the evaluation of parameters identified as predictors of treatment response and outcome, such as the tumor size, enhancement and vascularity[30]. The DL-based algorithm of Kim *et al*[31] aimed at detecting CRLM without human manipulation and fed by raw data from CT images, showed a sensitivity of 81.82%, comparable to that of radiologists (80.81%, *P* = 0.80), but with significantly more false positives per patient (1.330 *vs* 0.357, *P* < 0.001).

A challenging scenario that can occur in 16%-26% of patients with CRC is when the staging CT scan shows small hypoattenuating hepatic nodules defined as too small to characterize. Further imaging such as magnetic resonance (MR), repeat CT after a time interval, or performing a biopsy can delay treatment, increase costs, remain inconclusive, or have the risk of complications and tumor seeding. However, obtaining a diagnosis is of paramount importance given that 9%-14% of these nodules will prove to be malignant[32,33]. CNN could represent a useful adjunct in the characterization of small hypoattenuating liver lesions, and the model developed by Khalili *et al*[34] presents an AUROC similar to the one of expert radiologists, with better diagnostic confidence (significantly lower proportion of nodules rated in the low confidence zone, 19.6 *vs* 38.4%).

***MR radiomics models***

Despite CT imaging being the most widely used modality in detecting metastatic liver tumors, it can still miss up to 25% of CRLM[35] and MR has progressively gained an established role thanks to the high sensitivity and specificity and absence of ionizing radiations[36,37]. AI utilizing CNN for liver segmentation and CRLM detection could assist radiologists in this complex task and potentially reduce the manual liver lesion detection failure rate of 5%-13%[38]. The CRLM detection method developed by Jansen *et al*[38] is based on a fully CNN with an automatic liver segmentation and the analysis of both dynamic contrast-enhanced and diffusion-weighted MR images in 121 patients. It resulted in an impressive a high sensitivity of 99.8% and a low number of false positives.

***Volatile-organic-compound-based models***

Interestingly, a ML model has been used by Steenhuis *et al*[39] to analyze data from a retrospective cohort of 62 patients following curative CRC resection to detect CRLM development or local recurrence. The volatile organic compounds (VOCs) from patients’ exhaled air are gaseous products of metabolism known to be altered by pathological processes, such as abnormal cell growth, necrosis or intestinal microbioma alteration, and have been evaluated by ML techniques for pattern recognition. This pilot study, despite the limitations due to the small sample size and lack of histological confirmation in about a quarter of patients, showed that the noninvasive, repeatable, and easily applicable eNose analysis was able to identify CRLM or local recurrence with a sensitivity of 0.88 (95% CI: 0.69-0.97), specificity of 0.75 (95% CI: 0.57-0.87), and an overall accuracy of 0.81. Miller-Atkins *et al*[40] combined VOC analysis and demographic data (age and sex) in a predictive model developed using random forest ML and cross-validation that was able to identify patients with CRLM from healthy controls with a classification accuracy of 0.86, specificity of 0.94 but a sensitivity limited to 0.51.

***Histology-based models***

The applications of AI and ML in diagnosing CRLM have been extended to histopathological examination in order to rapidly and accurately identify CRLM tissue. A probe electrospray ionization-mass spectrometry and ML model was able to distinguish CRLM (103 samples) from noncancer liver parenchyma (80 control samples) with an accuracy rate of 99.5% and a AUROC of 0.9999[41]. CRLM patients are a heterogeneous group with considerable variations, including histopathological growth patterns (HGPs) and corresponding microvasculature[42]. The two predominant types of HGPs are the desmoplastic and replacement, with the pushing and mixed types being far less common. Once accurately determined by analyzing the interface between the tumor cells and the nearby normal liver, HGPs can represent a useful prognostic and predictive biomarker for response to therapy and overall survival[43-46]. The MR-based radiomics model developed by Han *et al*[47] aims at preoperatively identifying HGP of CRLM with an AUC of 0.906 in the internal validation cohort when the analysis is performed on the tumor-liver interface zone.

**AI MODELS FOR TREATED CRLM**

Surgical resection offers patients presenting with synchronous or metachronous CRLM the only potential for cure and a superior long-term survival[48] but unfortunately only a fraction of newly diagnosed patients are suitable for surgery. Liver-directed ablative therapies have progressively gained a role in treating nonsurgical candidates with acceptable safety and efficacy profiles[49]. In spite of this, recurrence after CRLM treatment represents a major problem, with an overall risk of local or distant tumor development after surgical resection or ablation as high as 70%-80%, with early recurrences being associated with a poorer prognosis[50,51]. Chemotherapy is of paramount importance in determining outcome of patients with either resectable or unresectable CRLM[8] and can convert up to one third of initially unresectable patients to receive potentially curative treatment[52].

***AI models predicting response to chemotherapy***

A reliable assessment of response to chemotherapy is of paramount importance for the personalized treatment decision-making process to determine eligibility for surgery, or the need for second-line treatments[53]. Discriminating responsive from unresponsive nodules or new lesions on the CT scan often represents a challenging task for radiologists, therefore Maaref *et al*[54] developed a fully automated framework based on DL CNN that achieved an accuracy of 0.91 (95% CI: 0.88-0.93) for differentiating treated and untreated lesions, and 0.78 (95% CI: 0.74-0.83) for predicting the response to a FOLFOX + bevacizumab-based chemotherapy regimen. Similarly, the DL radiomics model by Wei *et al*[55] was able to predict response to chemotherapy (CAPEOX, mFOLFOX6, FOLFIRI or XELIRI regimens) of CRLM based on contrast-enhanced CT according to the response evaluation criteria in solid tumors with an AUC in the validation cohort of 0.820 (95% CI: 0.681-0.959) that increases to 0.830 (95% CI: 0.688-0.973) combining the DL-based model with the CEA serum level. Human epidermal growth factor receptor 2 amplification or overexpression is found in 2%-6% of stage 2/3 CRC patients and treatment with trastuzumab and lapatinib has proven to be beneficial in the 70% of metastatic cases[56]. Giannini *et al*[57] published the results of an ML algorithm predicting the therapeutic response in such a subgroup of patients with an overall sensitivity of 92% (95% CI: 75%-99%) and specificity of 86% (95% CI: 42%-100%). The radiomics-based prediction model for the response of CRLM to oxaliplatin-based chemotherapy developed by Nakanishi *et al*[58] with radiomics features extracted from the pre-treatment CT scans, significantly discriminated good responders (AUC: 0.7792, 95% CI: 0.618-0.941).

***AI models predicting recurrence after local ablative therapies***

In order to predict early local tumor progression after ablation treatment of up to five nodules per patient with a maximum diameter of 30 mm, Taghavi *et al*[59] developed a ML-based radiomics analysis of the pretreatment CT scan combined with patients’ clinical features that showed a concordance index in the validation cohort of 0.79 (95% CI: 0.78-0.80).

**AI MODELS PREDICTING SURVIVAL IN CRLM PATIENTS**

***AI models predicting overall survival***

The systematic comparative analysis of quantitative imaging biomarkers based on the geometric and radiomics analysis of the liver tumor burden by Mühlberg *et al*[60], performed on a retrospective cohort of 103 patients with CRLM with automated segmentation of baseline contrast-enhanced CT images, showed that the tumor burden score (TBS) had the best discriminative performance for 1-year survival (AUC: 0.70; 95% CI: 0.56-0.90). The TBS[61] is calculated combining tumor number and maximum diameter through the Pythagorean theorem [TBS2 = (maximum tumor diameter)2 + (number of liver lesions)2]. An ML method has been used by Hao *et al*[62] to analyze whole-genome methylation data to predict cancer *versus* normal tissue of four common tumors (including 29 of 30 CRLMs) with > 95% accuracy and patient prognosis and survival through DNA methylation analysis.

***AI models predicting survival after chemotherapy***

Anti-epidermal growth factor receptor (EGFR) therapies are an effective option for RAS wild-type mutational status CRLM, but there is a need for reliable biomarkers that can estimate the balance between risks and clinical benefits of such therapies in individual patients[63]. Dercle *et al*[64] developed an AI model that through ML could create a signature that evaluated a change in tumor phenotype on interval CT scan images (baseline to 8 wk). The resultant model was able to successfully predict both sensitivity to anti-EGFR therapy (0.80; 95% CI: 0.69-0.94) and overall survival (*P* < 0.05).

***AI models predicting survival after surgical resection of CRLM***

The ANN model constructed by Spelt *et al*[65] retrospectively analyzed a single-center cohort of 241 patients who underwent liver resection for CRLM. Six of the 28 potential risk variables (age, preoperative chemotherapy, size of largest metastasis, hemorrhagic complications, preoperative CEA level and number of metastases) were selected by the ANN model to predict survival more accurately than the Cox regression model, with C-index of 0.72 *versus* 0.66. Paredes *et al*[66] in 2020 published the results of their ML recurrence-free prediction model for patients with CRLM undergoing curative-intent resection using clinical, pathological and morphological tumor characteristics with genetic Kirsten rat sarcoma 2 viral oncogene homolog information. The model, built on the analysis of 1406 multi-institutional patients undergoing liver resection, showed a discriminative ability to predict the recurrence risk at 1, 3 and 5 years (AUROC of 0.693, 0.669 and 0.669, respectively) more accurate than the ones of Fong[67] and Vauthey[68] scores.

**LIMITATIONS**

In spite of AI’s clear potential there remain several unresolved issues and limitations. These include the potential for artefacts in radiomics analyses to affect the results, the ethical and legal considerations, the definition of minimal accuracy rates and safeguards necessary to ensure public safety. Privacy, sensitive data protection and confidentiality need to remain the unmovable cornerstone of patient rights even in the digitalized era, but at the same time, some limitations on data utilization may affect the necessary linkages to prevent biases or errors in AI-driven analyses. There is a strong need from regulatory bodies for clear guidance during the AI-driven transformation of healthcare in order to take full advantage of the potential major improvements in individual and public health, while ensuring trust, safety and transparency. There is a significant variability in the algorithms investigated so far, as well as heterogeneity in the relatively small sample size of the population on which they have been trained and tested (Table 1). Analyses on large registries or national and international collaborations with data sharing could overcome part of the current limitations that limit the formal recognition of AI as a reliable and reproducible application in clinical scenarios.

**CONCLUSION**

The progressive widespread availability of high-performance computing, together with the accessibility to a large amount of data constantly generated as the result of the increase in the digitalization, set the ground for the ubiquitous implementation of AI technologies in contemporary healthcare. The fields of medical and surgical oncology have welcomed with enthusiasm the advent of augmented medicine with numerous studies investigating its potential, also given the high complexity and diversity of cancer patients. CRC makes no exception and still represents a leading cause of cancer-related death due to its high incidence, rapid progression potential and biological heterogeneity that advocate the need for reliable and individualized diagnostic, prognostic and treatment selection tools. Recent years have seen AI technologies tested by researchers in all phases of the CRLM natural history, aiming at overcoming the current difficulties and limitations faced by the multidisciplinary team responsible of the patients’ care (Figure 1). The possibility of identifying the subgroup of patients at higher risk of CRLM development before the occurrence of the disease from the radiomics baseline CT scan analysis with high accuracy (AUC ≥ 0.75) and in less than 5 min could give such patients the best chances of an early diagnosis, more effective treatment, and therefore, a better outcome thanks to a personalized approach[23-25]. Radiomics has also demonstrated a great potential in assisting the radiologists in diagnosing CRLM from CT and MRI scans also by optimizing the identification of the optimal phases for lesions recognition and characterizing small nodules of uncertain nature[27-31,34,38]. A more efficient diagnostic process would help reduce timings and costs, resulting in a potential benefit for both patients and healthcare systems. AI application in order to rapidly and accurately identify CRLM tissue and its different histopathological growth patterns[41,47] could give a significant contribution towards a rapid oncological individualized approach and treatments. AI technologies have also shown potential as a prognostic and outcome tool, predicting with good accuracy response to chemotherapy[54,55,57,58], early local tumor progression after ablation treatment[59], and patient survival after surgery or chemotherapy[60,64-66].

The possibility of reducing human factors and error, increase accuracy and contain timings and costs while adopting a personalized medicine approach is undoubtedly fascinating and appealing, but despite showing promising results, the role of AI in CRLM patients has not yet been fully elucidated. The implementation of AI resources supports the contemporary paradigm shift that sees healthcare focus moving from a generalized, disease-oriented to an individual, patient-centered, precision medicine approach. The effectiveness of ML models lie on a rigid framework in which a well-defined problem and ground truth along with quantitative objective measures to train and validate the algorithm are needed, making the process efficient but rigid. There is also a balance to be struck between the accuracy and artificial logic and the risk of AI becoming less intelligible and explainable. On the other hand, AI medical technologies could represent a way to enable patients to take ownership of their own care, increasing participation and autonomy for a more personalized approach.

AI will likely affect the immediate future of medicine and patients’ management, but rather than replacing the human roles, it will probably be aimed to assist and facilitate physicians in their practice, while being supervised to ensure maximum safety. This could be in the context of diagnostic uncertainty or to assist in planning optimal treatment strategies. A possible future development would be to improve diagnosis and management through the AI analysis and integration of clinical information, radiomic and genetic data thanks to the recent developments in gene sequencing and liquid biopsies, that have showed great potential in gastrointestinal tumors including CRLM[69-72]. A personalized holistic approach providing reliable data for the diagnosis, management and outcome estimation of cancer patients would assist clinicians in the prevention as well as selecting the most appropriate individualized treatment that would grant the patient the best outcome as well as helping patients to make fully informed decisions.

In order to continue to pursue the ambitious goal of improving patients’ care through AI healthcare technologies, further larger, prospective, randomized controlled and rigorous studies are needed.

**REFERENCES**

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

2 **Global Burden of Disease Cancer Collaboration.**, Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, Abdelalim A, Abdoli A, Abdollahpour I, Abdulle ASM, Abebe ND, Abraha HN, Abu-Raddad LJ, Abualhasan A, Adedeji IA, Advani SM, Afarideh M, Afshari M, Aghaali M, Agius D, Agrawal S, Ahmadi A, Ahmadian E, Ahmadpour E, Ahmed MB, Akbari ME, Akinyemiju T, Al-Aly Z, AlAbdulKader AM, Alahdab F, Alam T, Alamene GM, Alemnew BTT, Alene KA, Alinia C, Alipour V, Aljunid SM, Bakeshei FA, Almadi MAH, Almasi-Hashiani A, Alsharif U, Alsowaidi S, Alvis-Guzman N, Amini E, Amini S, Amoako YA, Anbari Z, Anber NH, Andrei CL, Anjomshoa M, Ansari F, Ansariadi A, Appiah SCY, Arab-Zozani M, Arabloo J, Arefi Z, Aremu O, Areri HA, Artaman A, Asayesh H, Asfaw ET, Ashagre AF, Assadi R, Ataeinia B, Atalay HT, Ataro Z, Atique S, Ausloos M, Avila-Burgos L, Avokpaho EFGA, Awasthi A, Awoke N, Ayala Quintanilla BP, Ayanore MA, Ayele HT, Babaee E, Bacha U, Badawi A, Bagherzadeh M, Bagli E, Balakrishnan S, Balouchi A, Bärnighausen TW, Battista RJ, Behzadifar M, Behzadifar M, Bekele BB, Belay YB, Belayneh YM, Berfield KKS, Berhane A, Bernabe E, Beuran M, Bhakta N, Bhattacharyya K, Biadgo B, Bijani A, Bin Sayeed MS, Birungi C, Bisignano C, Bitew H, Bjørge T, Bleyer A, Bogale KA, Bojia HA, Borzì AM, Bosetti C, Bou-Orm IR, Brenner H, Brewer JD, Briko AN, Briko NI, Bustamante-Teixeira MT, Butt ZA, Carreras G, Carrero JJ, Carvalho F, Castro C, Castro F, Catalá-López F, Cerin E, Chaiah Y, Chanie WF, Chattu VK, Chaturvedi P, Chauhan NS, Chehrazi M, Chiang PP, Chichiabellu TY, Chido-Amajuoyi OG, Chimed-Ochir O, Choi JJ, Christopher DJ, Chu DT, Constantin MM, Costa VM, Crocetti E, Crowe CS, Curado MP, Dahlawi SMA, Damiani G, Darwish AH, Daryani A, das Neves J, Demeke FM, Demis AB, Demissie BW, Demoz GT, Denova-Gutiérrez E, Derakhshani A, Deribe KS, Desai R, Desalegn BB, Desta M, Dey S, Dharmaratne SD, Dhimal M, Diaz D, Dinberu MTT, Djalalinia S, Doku DT, Drake TM, Dubey M, Dubljanin E, Duken EE, Ebrahimi H, Effiong A, Eftekhari A, El Sayed I, Zaki MES, El-Jaafary SI, El-Khatib Z, Elemineh DA, Elkout H, Ellenbogen RG, Elsharkawy A, Emamian MH, Endalew DA, Endries AY, Eshrati B, Fadhil I, Fallah Omrani V, Faramarzi M, Farhangi MA, Farioli A, Farzadfar F, Fentahun N, Fernandes E, Feyissa GT, Filip I, Fischer F, Fisher JL, Force LM, Foroutan M, Freitas M, Fukumoto T, Futran ND, Gallus S, Gankpe FG, Gayesa RT, Gebrehiwot TT, Gebremeskel GG, Gedefaw GA, Gelaw BK, Geta B, Getachew S, Gezae KE, Ghafourifard M, Ghajar A, Ghashghaee A, Gholamian A, Gill PS, Ginindza TTG, Girmay A, Gizaw M, Gomez RS, Gopalani SV, Gorini G, Goulart BNG, Grada A, Ribeiro Guerra M, Guimaraes ALS, Gupta PC, Gupta R, Hadkhale K, Haj-Mirzaian A, Haj-Mirzaian A, Hamadeh RR, Hamidi S, Hanfore LK, Haro JM, Hasankhani M, Hasanzadeh A, Hassen HY, Hay RJ, Hay SI, Henok A, Henry NJ, Herteliu C, Hidru HD, Hoang CL, Hole MK, Hoogar P, Horita N, Hosgood HD, Hosseini M, Hosseinzadeh M, Hostiuc M, Hostiuc S, Househ M, Hussen MM, Ileanu B, Ilic MD, Innos K, Irvani SSN, Iseh KR, Islam SMS, Islami F, Jafari Balalami N, Jafarinia M, Jahangiry L, Jahani MA, Jahanmehr N, Jakovljevic M, James SL, Javanbakht M, Jayaraman S, Jee SH, Jenabi E, Jha RP, Jonas JB, Jonnagaddala J, Joo T, Jungari SB, Jürisson M, Kabir A, Kamangar F, Karch A, Karimi N, Karimian A, Kasaeian A, Kasahun GG, Kassa B, Kassa TD, Kassaw MW, Kaul A, Keiyoro PN, Kelbore AG, Kerbo AA, Khader YS, Khalilarjmandi M, Khan EA, Khan G, Khang YH, Khatab K, Khater A, Khayamzadeh M, Khazaee-Pool M, Khazaei S, Khoja AT, Khosravi MH, Khubchandani J, Kianipour N, Kim D, Kim YJ, Kisa A, Kisa S, Kissimova-Skarbek K, Komaki H, Koyanagi A, Krohn KJ, Bicer BK, Kugbey N, Kumar V, Kuupiel D, La Vecchia C, Lad DP, Lake EA, Lakew AM, Lal DK, Lami FH, Lan Q, Lasrado S, Lauriola P, Lazarus JV, Leigh J, Leshargie CT, Liao Y, Limenih MA, Listl S, Lopez AD, Lopukhov PD, Lunevicius R, Madadin M, Magdeldin S, El Razek HMA, Majeed A, Maleki A, Malekzadeh R, Manafi A, Manafi N, Manamo WA, Mansourian M, Mansournia MA, Mantovani LG, Maroufizadeh S, Martini SMS, Mashamba-Thompson TP, Massenburg BB, Maswabi MT, Mathur MR, McAlinden C, McKee M, Meheretu HAA, Mehrotra R, Mehta V, Meier T, Melaku YA, Meles GG, Meles HG, Melese A, Melku M, Memiah PTN, Mendoza W, Menezes RG, Merat S, Meretoja TJ, Mestrovic T, Miazgowski B, Miazgowski T, Mihretie KMM, Miller TR, Mills EJ, Mir SM, Mirzaei H, Mirzaei HR, Mishra R, Moazen B, Mohammad DK, Mohammad KA, Mohammad Y, Darwesh AM, Mohammadbeigi A, Mohammadi H, Mohammadi M, Mohammadian M, Mohammadian-Hafshejani A, Mohammadoo-Khorasani M, Mohammadpourhodki R, Mohammed AS, Mohammed JA, Mohammed S, Mohebi F, Mokdad AH, Monasta L, Moodley Y, Moosazadeh M, Moossavi M, Moradi G, Moradi-Joo M, Moradi-Lakeh M, Moradpour F, Morawska L, Morgado-da-Costa J, Morisaki N, Morrison SD, Mosapour A, Mousavi SM, Muche AA, Muhammed OSS, Musa J, Nabhan AF, Naderi M, Nagarajan AJ, Nagel G, Nahvijou A, Naik G, Najafi F, Naldi L, Nam HS, Nasiri N, Nazari J, Negoi I, Neupane S, Newcomb PA, Nggada HA, Ngunjiri JW, Nguyen CT, Nikniaz L, Ningrum DNA, Nirayo YL, Nixon MR, Nnaji CA, Nojomi M, Nosratnejad S, Shiadeh MN, Obsa MS, Ofori-Asenso R, Ogbo FA, Oh IH, Olagunju AT, Olagunju TO, Oluwasanu MM, Omonisi AE, Onwujekwe OE, Oommen AM, Oren E, Ortega-Altamirano DDV, Ota E, Otstavnov SS, Owolabi MO, P A M, Padubidri JR, Pakhale S, Pakpour AH, Pana A, Park EK, Parsian H, Pashaei T, Patel S, Patil ST, Pennini A, Pereira DM, Piccinelli C, Pillay JD, Pirestani M, Pishgar F, Postma MJ, Pourjafar H, Pourmalek F, Pourshams A, Prakash S, Prasad N, Qorbani M, Rabiee M, Rabiee N, Radfar A, Rafiei A, Rahim F, Rahimi M, Rahman MA, Rajati F, Rana SM, Raoofi S, Rath GK, Rawaf DL, Rawaf S, Reiner RC, Renzaho AMN, Rezaei N, Rezapour A, Ribeiro AI, Ribeiro D, Ronfani L, Roro EM, Roshandel G, Rostami A, Saad RS, Sabbagh P, Sabour S, Saddik B, Safiri S, Sahebkar A, Salahshoor MR, Salehi F, Salem H, Salem MR, Salimzadeh H, Salomon JA, Samy AM, Sanabria J, Santric Milicevic MM, Sartorius B, Sarveazad A, Sathian B, Satpathy M, Savic M, Sawhney M, Sayyah M, Schneider IJC, Schöttker B, Sekerija M, Sepanlou SG, Sepehrimanesh M, Seyedmousavi S, Shaahmadi F, Shabaninejad H, Shahbaz M, Shaikh MA, Shamshirian A, Shamsizadeh M, Sharafi H, Sharafi Z, Sharif M, Sharifi A, Sharifi H, Sharma R, Sheikh A, Shirkoohi R, Shukla SR, Si S, Siabani S, Silva DAS, Silveira DGA, Singh A, Singh JA, Sisay S, Sitas F, Sobngwi E, Soofi M, Soriano JB, Stathopoulou V, Sufiyan MB, Tabarés-Seisdedos R, Tabuchi T, Takahashi K, Tamtaji OR, Tarawneh MR, Tassew SG, Taymoori P, Tehrani-Banihashemi A, Temsah MH, Temsah O, Tesfay BE, Tesfay FH, Teshale MY, Tessema GA, Thapa S, Tlaye KG, Topor-Madry R, Tovani-Palone MR, Traini E, Tran BX, Tran KB, Tsadik AG, Ullah I, Uthman OA, Vacante M, Vaezi M, Varona Pérez P, Veisani Y, Vidale S, Violante FS, Vlassov V, Vollset SE, Vos T, Vosoughi K, Vu GT, Vujcic IS, Wabinga H, Wachamo TM, Wagnew FS, Waheed Y, Weldegebreal F, Weldesamuel GT, Wijeratne T, Wondafrash DZ, Wonde TE, Wondmieneh AB, Workie HM, Yadav R, Yadegar A, Yadollahpour A, Yaseri M, Yazdi-Feyzabadi V, Yeshaneh A, Yimam MA, Yimer EM, Yisma E, Yonemoto N, Younis MZ, Yousefi B, Yousefifard M, Yu C, Zabeh E, Zadnik V, Moghadam TZ, Zaidi Z, Zamani M, Zandian H, Zangeneh A, Zaki L, Zendehdel K, Zenebe ZM, Zewale TA, Ziapour A, Zodpey S, Murray CJL. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* 2019; **5**: 1749-1768 [PMID: 31560378 DOI: 10.1001/jamaoncol.2019.2996]

3 **Chan AT**, Giovannucci EL. Primary prevention of colorectal cancer. *Gastroenterology* 2010; **138**: 2029-2043.e10 [PMID: 20420944 DOI: 10.1053/j.gastro.2010.01.057]

4 **Kastrinos F**, Syngal S. Inherited colorectal cancer syndromes. *Cancer J* 2011; **17**: 405-415 [PMID: 22157284 DOI: 10.1097/PPO.0b013e318237e408]

5 **van der Pool AE**, Damhuis RA, Ijzermans JN, de Wilt JH, Eggermont AM, Kranse R, Verhoef C. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer: a population-based series. *Colorectal Dis* 2012; **14**: 56-61 [PMID: 21176063 DOI: 10.1111/j.1463-1318.2010.02539.x]

6 **Miller KD**, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, Jemal A, Kramer JL, Siegel RL. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin* 2019; **69**: 363-385 [PMID: 31184787 DOI: 10.3322/caac.21565]

7 **Sheth KR**, Clary BM. Management of hepatic metastases from colorectal cancer. *Clin Colon Rectal Surg* 2005; **18**: 215-223 [PMID: 20011304 DOI: 10.1055/s-2005-916282]

8 **Chow FC**, Chok KS. Colorectal liver metastases: An update on multidisciplinary approach. *World J Hepatol* 2019; **11**: 150-172 [PMID: 30820266 DOI: 10.4254/wjh.v11.i2.150]

9 **Lillemoe HA**, Vauthey JN. Surgical approach to synchronous colorectal liver metastases: staged, combined, or reverse strategy. *Hepatobiliary Surg Nutr* 2020; **9**: 25-34 [PMID: 32140476 DOI: 10.21037/hbsn.2019.05.14]

10 **Arshad U**, Sutton PA, Ashford MB, Treacher KE, Liptrott NJ, Rannard SP, Goldring CE, Owen A. Critical considerations for targeting colorectal liver metastases with nanotechnology. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 2020; **12**: e1588 [PMID: 31566913 DOI: 10.1002/wnan.1588]

11 **Ismaili N**. Treatment of colorectal liver metastases. *World J Surg Oncol* 2011; **9**: 154 [PMID: 22115124 DOI: 10.1186/1477-7819-9-154]

12 **Weledji EP**. Centralization of Liver Cancer Surgery and Impact on Multidisciplinary Teams Working on Stage IV Colorectal Cancer. *Oncol Rev* 2017; **11**: 331 [PMID: 28814999 DOI: 10.4081/oncol.2017.331]

13 **Topol EJ**. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* 2019; **25**: 44-56 [PMID: 30617339 DOI: 10.1038/s41591-018-0300-7]

14 **Moloi T**, **Marwala**, T. Artificial Intelligence in Economics and Finance Theories. In: Introduction to Artificial Intelligence in Economics and Finance Theories. 2020: 1-12 [DOI:10.1007/978-3-030-42962-1\_1]

15 **Matheny ME**, Whicher D, Thadaney Israni S. Artificial Intelligence in Health Care: A Report From the National Academy of Medicine. *JAMA* 2020; **323**: 509-510 [PMID: 31845963 DOI: 10.1001/jama.2019.21579]

16 **Xi Q**, Yang Q, Wang M, Huang B, Zhang B, Li Z, Liu S, Yang L, Zhu L, Jin L. Individualized embryo selection strategy developed by stacking machine learning model for better in vitro fertilization outcomes: an application study. *Reprod Biol Endocrinol* 2021; **19**: 53 [PMID: 33820565 DOI: 10.1186/s12958-021-00734-z]

17 **Ulloa Cerna AE**, Jing L, Good CW, vanMaanen DP, Raghunath S, Suever JD, Nevius CD, Wehner GJ, Hartzel DN, Leader JB, Alsaid A, Patel AA, Kirchner HL, Pfeifer JM, Carry BJ, Pattichis MS, Haggerty CM, Fornwalt BK. Deep-learning-assisted analysis of echocardiographic videos improves predictions of all-cause mortality. *Nat Biomed Eng* 2021; **5**: 546-554 [PMID: 33558735 DOI: 10.1038/s41551-020-00667-9]

18 **Muehlematter UJ**, Daniore P, Vokinger KN. Approval of artificial intelligence and machine learning-based medical devices in the USA and Europe (2015-20): a comparative analysis. *Lancet Digit Health* 2021; **3**: e195-e203 [PMID: 33478929 DOI: 10.1016/S2589-7500(20)30292-2]

19 **Benjamens S**, Dhunnoo P, Meskó B. The state of artificial intelligence-based FDA-approved medical devices and algorithms: an online database. *NPJ Digit Med* 2020; **3**: 118 [PMID: 32984550 DOI: 10.1038/s41746-020-00324-0]

20 **Gillies RJ**, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. *Radiology* 2016; **278**: 563-577 [PMID: 26579733 DOI: 10.1148/radiol.2015151169]

21 **Hackl C**, Neumann P, Gerken M, Loss M, Klinkhammer-Schalke M, Schlitt HJ. Treatment of colorectal liver metastases in Germany: a ten-year population-based analysis of 5772 cases of primary colorectal adenocarcinoma. *BMC Cancer* 2014; **14**: 810 [PMID: 25369977 DOI: 10.1186/1471-2407-14-810]

22 **Engstrand J**, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal cancer liver metastases — a population-based study on incidence, management and survival. *BMC Cancer* 2018; **18**: 78 [PMID: 29334918 DOI: 10.1186/s12885-017-3925-x]

23 **Li M**, Li X, Guo Y, Miao Z, Liu X, Guo S, Zhang H. Development and assessment of an individualized nomogram to predict colorectal cancer liver metastases. *Quant Imaging Med Surg* 2020; **10**: 397-414 [PMID: 32190566 DOI: 10.21037/qims.2019.12.16]

24 **Taghavi M**, Trebeschi S, Simões R, Meek DB, Beckers RCJ, Lambregts DMJ, Verhoef C, Houwers JB, van der Heide UA, Beets-Tan RGH, Maas M. Machine learning-based analysis of CT radiomics model for prediction of colorectal metachronous liver metastases. *Abdom Radiol (NY)* 2021; **46**: 249-256 [PMID: 32583138 DOI: 10.1007/s00261-020-02624-1]

25 **Lee S**, Choe EK, Kim SY, Kim HS, Park KJ, Kim D. Liver imaging features by convolutional neural network to predict the metachronous liver metastasis in stage I-III colorectal cancer patients based on preoperative abdominal CT scan. *BMC Bioinformatics* 2020; **21**: 382 [PMID: 32938394 DOI: 10.1186/s12859-020-03686-0]

26 **Vorontsov E**, Tang A, Roy D, Pal CJ, Kadoury S. Metastatic liver tumour segmentation with a neural network-guided 3D deformable model. *Med Biol Eng Comput* 2017; **55**: 127-139 [PMID: 27106756 DOI: 10.1007/s11517-016-1495-8]

27 **Zheng Q**, Yang L, Zeng B, Li J, Guo K, Liang Y, Liao G. Artificial intelligence performance in detecting tumor metastasis from medical radiology imaging: A systematic review and meta-analysis. *EclinicalMedicine* 2021; **31**: 100669 [PMID: 33392486 DOI: 10.1016/j.eclinm.2020.100669]

28 **Vorontsov E**, Cerny M, Régnier P, Di Jorio L, Pal CJ, Lapointe R, Vandenbroucke-Menu F, Turcotte S, Kadoury S, Tang A. Deep Learning for Automated Segmentation of Liver Lesions at CT in Patients with Colorectal Cancer Liver Metastases. *Radiol Artif Intell* 2019; **1**: 180014 [PMID: 33937787 DOI: 10.1148/ryai.2019180014]

29 **Schima W**, Kulinna C, Langenberger H, Ba-Ssalamah A. Liver metastases of colorectal cancer: US, CT or MR? *Cancer Imaging* 2005; **5 Spec No A**: S149-S156 [PMID: 16361131 DOI: 10.1102/1470-7330.2005.0035]

30 **Ma J**, Dercle L, Lichtenstein P, Wang D, Chen A, Zhu J, Piessevaux H, Zhao J, Schwartz LH, Lu L, Zhao B. Automated Identification of Optimal Portal Venous Phase Timing with Convolutional Neural Networks. *Acad Radiol* 2020; **27**: e10-e18 [PMID: 31151901 DOI: 10.1016/j.acra.2019.02.024]

31 **Kim K**, Kim S, Han K, Bae H, Shin J, Lim JS. Diagnostic Performance of Deep Learning-Based Lesion Detection Algorithm in CT for Detecting Hepatic Metastasis from Colorectal Cancer. *Korean J Radiol* 2021; **22**: 912-921 [PMID: 33686820 DOI: 10.3348/kjr.2020.0447]

32 **Jang HJ**, Lim HK, Lee WJ, Lee SJ, Yun JY, Choi D. Small hypoattenuating lesions in the liver on single-phase helical CT in preoperative patients with gastric and colorectal cancer: prevalence, significance, and differentiating features. *J Comput Assist Tomogr* 2002; **26**: 718-724 [PMID: 12439304 DOI: 10.1097/00004728-200209000-00009]

33 **Lim GH**, Koh DC, Cheong WK, Wong KS, Tsang CB. Natural history of small, “indeterminate” hepatic lesions in patients with colorectal cancer. *Dis Colon Rectum* 2009; **52**: 1487-1491 [PMID: 19617765 DOI: 10.1007/DCR.0013e3181a74d5e]

34 **Khalili K**, Lawlor RL, Pourafkari M, Lu H, Tyrrell P, Kim TK, Jang HJ, Johnson SA, Martel AL. Convolutional neural networks versus radiologists in characterization of small hypoattenuating hepatic nodules on CT: a critical diagnostic challenge in staging of colorectal carcinoma. *Sci Rep* 2020; **10**: 15248 [PMID: 32943654 DOI: 10.1038/s41598-020-71364-5]

35 **Xu LH**, Cai SJ, Cai GX, Peng WJ. Imaging diagnosis of colorectal liver metastases. *World J Gastroenterol* 2011; **17**: 4654-4659 [PMID: 22180707 DOI: 10.3748/wjg.v17.i42.4654]

36 **Böttcher J**, Hansch A, Pfeil A, Schmidt P, Malich A, Schneeweiss A, Maurer MH, Streitparth F, Teichgräber UK, Renz DM. Detection and classification of different liver lesions: comparison of Gd-EOB-DTPA-enhanced MRI versus multiphasic spiral CT in a clinical single centre investigation. *Eur J Radiol* 2013; **82**: 1860-1869 [PMID: 23932636 DOI: 10.1016/j.ejrad.2013.06.013]

37 **Mao Y**, Chen B, Wang H, Zhang Y, Yi X, Liao W, Zhao L. Diagnostic performance of magnetic resonance imaging for colorectal liver metastasis: A systematic review and meta-analysis. *Sci Rep* 2020; **10**: 1969 [PMID: 32029809 DOI: 10.1038/s41598-020-58855-1]

38 **Jansen MJA**, Kuijf HJ, Niekel M, Veldhuis WB, Wessels FJ, Viergever MA, Pluim JPW. Liver segmentation and metastases detection in MR images using convolutional neural networks. *J Med Imaging (Bellingham)* 2019; **6**: 044003 [PMID: 31620549 DOI: 10.1117/1.JMI.6.4.044003]

39 **Steenhuis EGM**, Schoenaker IJH, de Groot JWB, Fiebrich HB, de Graaf JC, Brohet RM, van Dijk JD, van Westreenen HL, Siersema PD, de Vos Tot Nederveen Cappel WH. Feasibility of volatile organic compound in breath analysis in the follow-up of colorectal cancer: A pilot study. *Eur J Surg Oncol* 2020; **46**: 2068-2073 [PMID: 32778485 DOI: 10.1016/j.ejso.2020.07.028]

40 **Miller-Atkins G**, Acevedo-Moreno LA, Grove D, Dweik RA, Tonelli AR, Brown JM, Allende DS, Aucejo F, Rotroff DM. Breath Metabolomics Provides an Accurate and Noninvasive Approach for Screening Cirrhosis, Primary, and Secondary Liver Tumors. *Hepatol Commun* 2020; **4**: 1041-1055 [PMID: 32626836 DOI: 10.1002/hep4.1499]

41 **Kiritani S**, Yoshimura K, Arita J, Kokudo T, Hakoda H, Tanimoto M, Ishizawa T, Akamatsu N, Kaneko J, Takeda S, Hasegawa K. A new rapid diagnostic system with ambient mass spectrometry and machine learning for colorectal liver metastasis. *BMC Cancer* 2021; **21**: 262 [PMID: 33691644 DOI: 10.1186/s12885-021-08001-5]

42 **Vermeulen PB**, Colpaert C, Salgado R, Royers R, Hellemans H, Van Den Heuvel E, Goovaerts G, Dirix LY, Van Marck E. Liver metastases from colorectal adenocarcinomas grow in three patterns with different angiogenesis and desmoplasia. *J Pathol* 2001; **195**: 336-342 [PMID: 11673831 DOI: 10.1002/path.966]

43 **Nielsen K**, Rolff HC, Eefsen RL, Vainer B. The morphological growth patterns of colorectal liver metastases are prognostic for overall survival. *Mod Pathol* 2014; **27**: 1641-1648 [PMID: 24851832 DOI: 10.1038/modpathol.2014.4]

44 **van Dam PJ**, van der Stok EP, Teuwen LA, Van den Eynden GG, Illemann M, Frentzas S, Majeed AW, Eefsen RL, Coebergh van den Braak RRJ, Lazaris A, Fernandez MC, Galjart B, Laerum OD, Rayes R, Grünhagen DJ, Van de Paer M, Sucaet Y, Mudhar HS, Schvimer M, Nyström H, Kockx M, Bird NC, Vidal-Vanaclocha F, Metrakos P, Simoneau E, Verhoef C, Dirix LY, Van Laere S, Gao ZH, Brodt P, Reynolds AR, Vermeulen PB. International consensus guidelines for scoring the histopathological growth patterns of liver metastasis. *Br J Cancer* 2017; **117**: 1427-1441 [PMID: 28982110 DOI: 10.1038/bjc.2017.334]

45 **Stremitzer S**, Vermeulen P, Graver S, Kockx M, Dirix L, Yang D, Zhang W, Stift J, Wrba F, Gruenberger T, Lenz HJ, Scherer SJ. Immune phenotype and histopathological growth pattern in patients with colorectal liver metastases. *Br J Cancer* 2020; **122**: 1518-1524 [PMID: 32205863 DOI: 10.1038/s41416-020-0812-z]

46 **Frentzas S**, Simoneau E, Bridgeman VL, Vermeulen PB, Foo S, Kostaras E, Nathan M, Wotherspoon A, Gao ZH, Shi Y, Van den Eynden G, Daley F, Peckitt C, Tan X, Salman A, Lazaris A, Gazinska P, Berg TJ, Eltahir Z, Ritsma L, Van Rheenen J, Khashper A, Brown G, Nystrom H, Sund M, Van Laere S, Loyer E, Dirix L, Cunningham D, Metrakos P, Reynolds AR. Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases. *Nat Med* 2016; **22**: 1294-1302 [PMID: 27748747 DOI: 10.1038/nm.4197]

47 **Han Y**, Chai F, Wei J, Yue Y, Cheng J, Gu D, Zhang Y, Tong T, Sheng W, Hong N, Ye Y, Wang Y, Tian J. Identification of Predominant Histopathological Growth Patterns of Colorectal Liver Metastasis by Multi-Habitat and Multi-Sequence Based Radiomics Analysis. *Front Oncol* 2020; **10**: 1363 [PMID: 32923388 DOI: 10.3389/fonc.2020.01363]

48 **Abdalla EK**, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, Hess K, Curley SA. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004; **239**: 818-25; discussion 825-7 [PMID: 15166961 DOI: 10.1097/01.sla.0000128305.90650.71]

49 **Di Martino M**, Rompianesi G, Mora-Guzmán I, Martín-Pérez E, Montalti R, Troisi RI. Systematic review and meta-analysis of local ablative therapies for resectable colorectal liver metastases. *Eur J Surg Oncol* 2020; **46**: 772-781 [PMID: 31862133 DOI: 10.1016/j.ejso.2019.12.003]

50 **Sorbye H**. Recurrence patterns after resection of liver metastases from colorectal cancer. *Recent Results Cancer Res* 2014; **203**: 243-252 [PMID: 25103010 DOI: 10.1007/978-3-319-08060-4\_17]

51 **Bredt LC**, Rachid AF. Predictors of recurrence after a first hepatectomy for colorectal cancer liver metastases: a retrospective analysis. *World J Surg Oncol* 2014; **12**: 391 [PMID: 25528650 DOI: 10.1186/1477-7819-12-391]

52 **Folprecht G**, Gruenberger T, Bechstein W, Raab HR, Weitz J, Lordick F, Hartmann JT, Stoehlmacher-Williams J, Lang H, Trarbach T, Liersch T, Ockert D, Jaeger D, Steger U, Suedhoff T, Rentsch A, Köhne CH. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). *Ann Oncol* 2014; **25**: 1018-1025 [PMID: 24585720 DOI: 10.1093/annonc/mdu088]

53 **Bonanni L**, de’Liguori Carino N, Deshpande R, Ammori BJ, Sherlock DJ, Valle JW, Tam E, O’Reilly DA. A comparison of diagnostic imaging modalities for colorectal liver metastases. *Eur J Surg Oncol* 2014; **40**: 545-550 [PMID: 24491289 DOI: 10.1016/j.ejso.2013.12.023]

54 **Maaref A**, Romero FP, Montagnon E, Cerny M, Nguyen B, Vandenbroucke F, Soucy G, Turcotte S, Tang A, Kadoury S. Predicting the Response to FOLFOX-Based Chemotherapy Regimen from Untreated Liver Metastases on Baseline CT: a Deep Neural Network Approach. *J Digit Imaging* 2020; **33**: 937-945 [PMID: 32193665 DOI: 10.1007/s10278-020-00332-2]

55 **Wei J**, Cheng J, Gu D, Chai F, Hong N, Wang Y, Tian J. Deep learning-based radiomics predicts response to chemotherapy in colorectal liver metastases. *Med Phys* 2021; **48**: 513-522 [PMID: 33119899 DOI: 10.1002/mp.14563]

56 **Meric-Bernstam F**, Hurwitz H, Raghav KPS, McWilliams RR, Fakih M, VanderWalde A, Swanton C, Kurzrock R, Burris H, Sweeney C, Bose R, Spigel DR, Beattie MS, Blotner S, Stone A, Schulze K, Cuchelkar V, Hainsworth J. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol* 2019; **20**: 518-530 [PMID: 30857956 DOI: 10.1016/S1470-2045(18)30904-5]

57 **Giannini V**, Rosati S, Defeudis A, Balestra G, Vassallo L, Cappello G, Mazzetti S, De Mattia C, Rizzetto F, Torresin A, Sartore-Bianchi A, Siena S, Vanzulli A, Leone F, Zagonel V, Marsoni S, Regge D. Radiomics predicts response of individual HER2-amplified colorectal cancer liver metastases in patients treated with HER2-targeted therapy. *Int J Cancer* 2020; **147**: 3215-3223 [PMID: 32875550 DOI: 10.1002/ijc.33271]

58 **Nakanishi R**, Oki E, Hasuda H, Sano E, Miyashita Y, Sakai A, Koga N, Kuriyama N, Nonaka K, Fujimoto Y, Jogo T, Hokonohara K, Hu Q, Hisamatsu Y, Ando K, Kimura Y, Yoshizumi T, Mori M. Radiomics Texture Analysis for the Identification of Colorectal Liver Metastases Sensitive to First-Line Oxaliplatin-Based Chemotherapy. *Ann Surg Oncol* 2021; **28**: 2975-2985 [PMID: 33454878 DOI: 10.1245/s10434-020-09581-5]

59 **Taghavi M**, Staal F, Gomez Munoz F, Imani F, Meek DB, Simões R, Klompenhouwer LG, van der Heide UA, Beets-Tan RGH, Maas M. CT-Based Radiomics Analysis Before Thermal Ablation to Predict Local Tumor Progression for Colorectal Liver Metastases. *Cardiovasc Intervent Radiol* 2021; **44**: 913-920 [PMID: 33506278 DOI: 10.1007/s00270-020-02735-8]

60 **Mühlberg A**, Holch JW, Heinemann V, Huber T, Moltz J, Maurus S, Jäger N, Liu L, Froelich MF, Katzmann A, Gresser E, Taubmann O, Sühling M, Nörenberg D. The relevance of CT-based geometric and radiomics analysis of whole liver tumor burden to predict survival of patients with metastatic colorectal cancer. *Eur Radiol* 2021; **31**: 834-846 [PMID: 32851450 DOI: 10.1007/s00330-020-07192-y]

61 **Sasaki K**, Margonis GA, Andreatos N, Zhang XF, Buettner S, Wang J, Deshwar A, He J, Wolfgang CL, Weiss M, Pawlik TM. The prognostic utility of the “Tumor Burden Score” based on preoperative radiographic features of colorectal liver metastases. *J Surg Oncol* 2017; **116**: 515-523 [PMID: 28543544 DOI: 10.1002/jso.24678]

62 **Hao X**, Luo H, Krawczyk M, Wei W, Wang W, Wang J, Flagg K, Hou J, Zhang H, Yi S, Jafari M, Lin D, Chung C, Caughey BA, Li G, Dhar D, Shi W, Zheng L, Hou R, Zhu J, Zhao L, Fu X, Zhang E, Zhang C, Zhu JK, Karin M, Xu RH, Zhang K. DNA methylation markers for diagnosis and prognosis of common cancers. *Proc Natl Acad Sci U S A* 2017; **114**: 7414-7419 [PMID: 28652331 DOI: 10.1073/pnas.1703577114]

63 **Martinelli E**, Ciardiello D, Martini G, Troiani T, Cardone C, Vitiello PP, Normanno N, Rachiglio AM, Maiello E, Latiano T, De Vita F, Ciardiello F. Implementing anti-epidermal growth factor receptor (EGFR) therapy in metastatic colorectal cancer: challenges and future perspectives. *Ann Oncol* 2020; **31**: 30-40 [PMID: 31912793 DOI: 10.1016/j.annonc.2019.10.007]

64 **Dercle L**, Lu L, Schwartz LH, Qian M, Tejpar S, Eggleton P, Zhao B, Piessevaux H. Radiomics Response Signature for Identification of Metastatic Colorectal Cancer Sensitive to Therapies Targeting EGFR Pathway. *J Natl Cancer Inst* 2020; **112**: 902-912 [PMID: 32016387 DOI: 10.1093/jnci/djaa017]

65 **Spelt L**, Nilsson J, Andersson R, Andersson B. Artificial neural networks—a method for prediction of survival following liver resection for colorectal cancer metastases. *Eur J Surg Oncol* 2013; **39**: 648-654 [PMID: 23514791 DOI: 10.1016/j.ejso.2013.02.024]

66 **Paredes AZ**, Hyer JM, Tsilimigras DI, Moro A, Bagante F, Guglielmi A, Ruzzenente A, Alexandrescu S, Makris EA, Poultsides GA, Sasaki K, Aucejo FN, Pawlik TM. A Novel Machine-Learning Approach to Predict Recurrence After Resection of Colorectal Liver Metastases. *Ann Surg Oncol* 2020; **27**: 5139-5147 [PMID: 32779049 DOI: 10.1245/s10434-020-08991-9]

67 **Fong Y**, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; **230**: 309-18; discussion 318-21 [PMID: 10493478 DOI: 10.1097/00000658-199909000-00004]

68 **Brudvik KW**, Jones RP, Giuliante F, Shindoh J, Passot G, Chung MH, Song J, Li L, Dagenborg VJ, Fretland ÅA, Røsok B, De Rose AM, Ardito F, Edwin B, Panettieri E, Larocca LM, Yamashita S, Conrad C, Aloia TA, Poston GJ, Bjørnbeth BA, Vauthey JN. RAS Mutation Clinical Risk Score to Predict Survival After Resection of Colorectal Liver Metastases. *Ann Surg* 2019; **269**: 120-126 [PMID: 28549012 DOI: 10.1097/SLA.0000000000002319]

69 **Qi ZH**, Xu HX, Zhang SR, Xu JZ, Li S, Gao HL, Jin W, Wang WQ, Wu CT, Ni QX, Yu XJ, Liu L. The Significance of Liquid Biopsy in Pancreatic Cancer. *J Cancer* 2018; **9**: 3417-3426 [PMID: 30271504 DOI: 10.7150/jca.24591]

70 **Mason MC**, Tzeng CD, Tran Cao HS, Aloia TA, Newhook TE, Overman MJ, Kopetz SE, Vauthey JN, Chun YS. Preliminary Analysis of Liquid Biopsy after Hepatectomy for Colorectal Liver Metastases. *J Am Coll Surg* 2021; **233**: 82-89.e1 [PMID: 33667566 DOI: 10.1016/j.jamcollsurg.2021.02.011]

71 **Saini A**, Pershad Y, Albadawi H, Kuo M, Alzubaidi S, Naidu S, Knuttinen MG, Oklu R. Liquid Biopsy in Gastrointestinal Cancers. *Diagnostics (Basel)* 2018; **8** [PMID: 30380690 DOI: 10.3390/diagnostics8040075]

72 **Rompianesi G**, Di Martino M, Gordon-Weeks A, Montalti R, Troisi R. Liquid biopsy in cholangiocarcinoma: Current status and future perspectives. *World J Gastrointest Oncol* 2021; **13**: 332-350 [PMID: 34040697 DOI: 10.4251/wjgo.v13.i5.332]

**Footnotes**

**Conflict-of-interest statement:** No Author has any conflict of interest to disclose.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** August 13, 2021

**First decision:** October 2, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** International

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

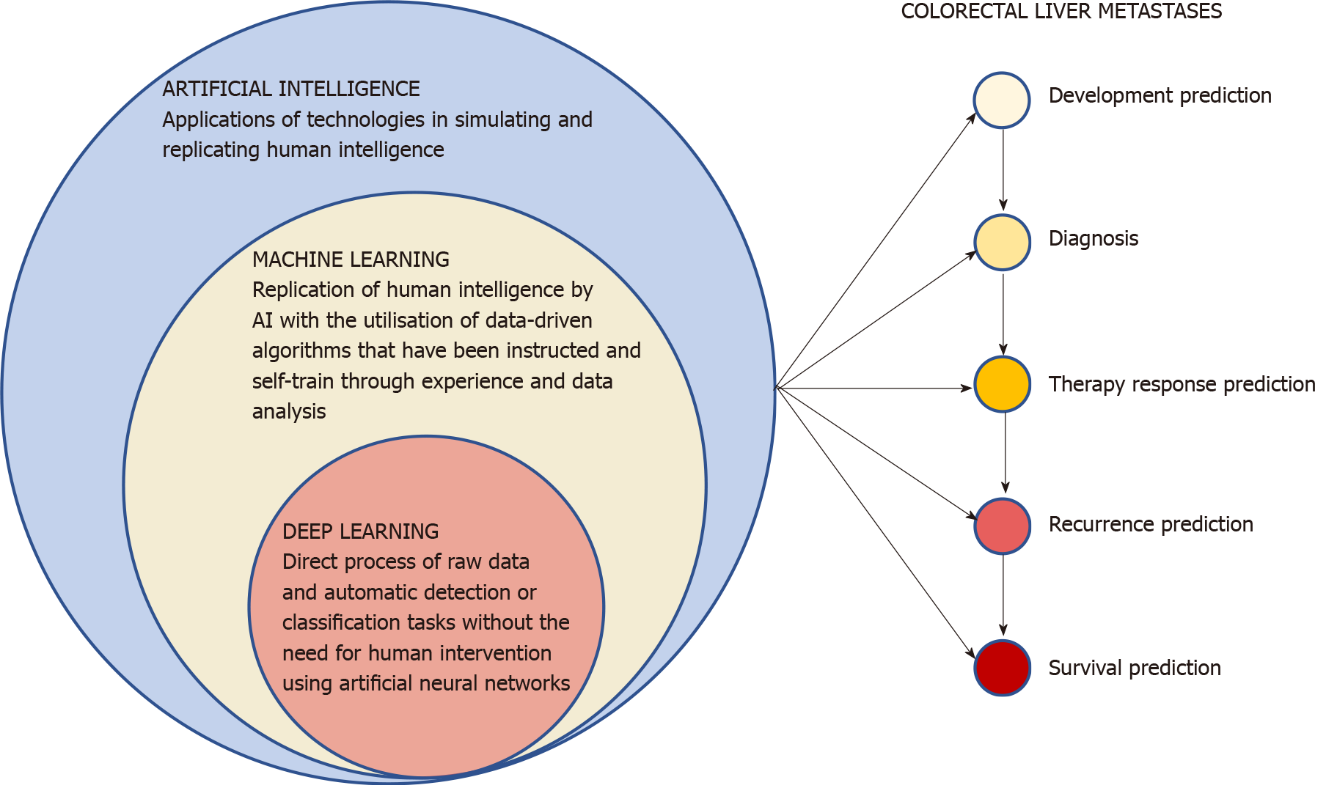
Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Liu Y **S-Editor:** Wang JJ **L-Editor:** Kerr C **P-Editor:**

**Figure Legends**



**Figure 1** **Possible applications of artificial intelligence technologies in the diagnosis and management of colorectal liver metastases.** AI: Artificial intelligence.

**Table 1 Summary of the studies considered in this review**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Study design** | **AI model type** | **Data source** | **Total sample size/training cohort/validation cohort** | **AUC training/AUC validation** | **Sensitivity/specificity** | **PPV/NPV** | **Accuracy** |
| CRLM development | | | | | | | | |
| Li *et al*[23] (2020) | Retrospective; Single center | Radiomics/ML | CT images ± clinical data | 100/NA/80 | 0.90/0.906 | 81%/84% | 85%/79% | NA |
| Taghavi *et al*[24] (2021) | Retrospective; Multicenter | Radiomics/ML | CT images ± clinical data | 91/70/21 | 0.952-0.683-0.954/0.862-0.713-0.864 | NA/NA | NA/NA | NA |
| Lee *et al*[25] (2020) | Retrospective; Single center | Radiomics/CNN | CT images ± clinical data | 2019/1413/606 | NA/0.6062-0.7093-0.7474 | NA/NA | NA/NA | NA |
| Diagnosis | | | | | | | | |
| Vorontsov *et al*[26] (2017) | Retrospective; Single center | Radiomics/CNN | CT images | 40/32/8 | NA/NA | 84%/92% | NA/NA | 88% |
| Vorontsov *et al*[28] (2019) | Retrospective; Single center | Radiomics/CNN | CT images | 156/115/15 | NA/NA | 59%5/NA | 80%5/NA | NA |
| Ma *et al*[30] (2020) | Retrospective; Multicenter | CNN | CT images | 909/479/202 (2286) | NA/0.837-0.8446 | 82%6/74%5 | 75%6/81%6 | NA |
| Kim *et al*[31] (2021) | Retrospective; Single center | DL | CT images | 587/502/85 | NA/0.631 | 81.82%/22.22% | NA/NA | NA |
| Khalili *et al*[34] (2020) | Retrospective; Single center | CNN | CT images ± liver metastatic status | 199/150/49 | NA/0.84-0.957 | (81.5%-81.5%7)/(76.2%-96.4%7) | NA/NA | 78.3%; 90.6%6 |
| Jansen *et al*[38] (2019) | Retrospective; Single center | CNN | MRI images | 121/3341/861 | NA/NA | 99.8%/NA | NA/NA | NA |
| Steenhuis *et al*[39] (2020) | Retrospective; Single center | ML | VOCs | 62/NA/NA | NA/0.86 | 88%/75% | 72%/90% | 81% |
| Miller-Atkins *et al*[40] (2020) | Prospective; Single center | ML | VOCs | 296/284/NA | NA/NA | 51%/94% | NA/NA | 86% |
| Kiritani *et al*[41] (2021) | Retrospective; Single center | ML | Histologic markers | 183/NA/40 | NA/0.999 | 100%/99% | NA/NA | 99.5% |
| Han *et al*[47] (2020) | Retrospective; Single center | Radiomics/ML | MRI images ± clinical data | 107/611/311 | 0.9742-0.6593-0.9714/0.9122-0.6763-0.9094 | 95.2%2-57.1%3-95.2%4/80.0%2-70.0%3-70.0%4 | NA/NA | 90.3%2; 61.3%3; 87.1%4 |
| Chemotherapy response | | | | | | | | |
| Maaref *et al*[54] (2020) | Retrospective; Single center | DL CNN | CT images | 202/70%/10% | 0.97/0.88 | 98%/54% | NA/NA | 91%8; 78%9 |
| Wei *et al*[55] (2021) | Retrospective; Single center | Radiomics/DL | CT images ± CEA | 192/144/48 | 0.90310-0.93511/0.82010-0.83011 | 90.9%/73.3% | 88.2%/78.6% | 85.4% |
| Giannini *et al*[57] (2020) | Retrospective; Multicenter | Radiomics/ML | CT images | 38/28/10 | NA/NA | 92%/86% | 96%/75% | NA |
| Nakanishi *et al*[58] (2021) | Retrospective; Single center | Radiomics | CT images | 42/941/321 | 0.8512/0.7792 | NA/NA | NA/NA | NA |
| Local ablative therapies efficacy | | | | | | | | |
| Taghavi *et al*[59] (2021) | Retrospective; Single center | Radiomics/ML | CT images | 90/63/27 | NA/0.782-0.563-0.794 | NA/NA | NA/NA | NA |
| Survival prediction | | | | | | | | |
| Mühlberg *et al*[60] (2021) | Retrospective; Single center | Radiomics/ML | CT images ± WLTB ± TBS | 103/NA/NA | NA/0.7012-0.7313-0.7614 | NA/NA | NA/NA | NA |
| Hao *et al*[62] (2017) | Retrospective; Multicenter | ML | DNA methylation | 17921/NA/8841 (7181,6) | NA/NA | NA/NA | NA/NA | 98.4% |
| Dercle *et al*[64] (2020) | Retrospective; Multicenter | ML | CT images | 667/438/229 | 0.83/0.80 | 80%/78% | NA/NA | NA |
| Spelt *et al*[65] (2013) | Retrospective; Single center | ANN | Clinical variables | 241/NA/NA | NA/NA | NA/NA | NA/NA | 72% |
| Paredes *et al*[66] (2020) | Retrospective; Multicenter | ML | Clinical variables | 1406/703/703 | 0.52715-0.52516-0.69317/0.52415-0.50116-0.64217 | NA/NA | NA/NA | NA |

1Number of lesions.

2Model based on radiomics data only.

3Model based on clinical data only.

4Model based on both radiomics and clinical data.

5Per patient values.

6Values calculated on the external validation set.

7Model based on both convolutional neural network and liver metastatic status.

8For differentiating treated and untreated lesions.

9For predicting the response to a FOLFOX + bevacizumab-based chemotherapy regimen.

10Model based on both deep learning and radiomics signature.

11Model based on deep learning and radiomics signature considering carcinogenic embryonic antigen values.

12Model based on tumor burden score.

13Model based on geometric metastatic spread of whole liver tumor burden.

14Model based on the Aerts radiomics prior model.

15Model based on Fong/Blumgart clinical risk score for predicting 1-year recurrence.

16Model based on Brudvik-Vauthey clinical risk score for predicting 1-year recurrence.

17Model based on Paredes-Pawlik clinical risk score for predicting 1-year recurrence.

AI: Artificial intelligence; ANN: Artificial neural network; AUC: Area under the curve; CEA: Carcinogenic embryonic antigen; CNN: Convolutional neural network; CRLM: Colorectal cancer liver metastases; DL: Deep learning; ML: Machine learning; NPV: Negative predictive value; PPV: Positive predictive value; TBS: Tumor burden score; VOCs: Volatile organic compounds; WLTB: Whole liver tumor burden.