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

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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

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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

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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.

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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 being 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 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 microbiota 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 ra-diomics 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 [$TBS^2 = (\text{maximum tumor diameter})^2 + (\text{number of liver lesions})^2$]. 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

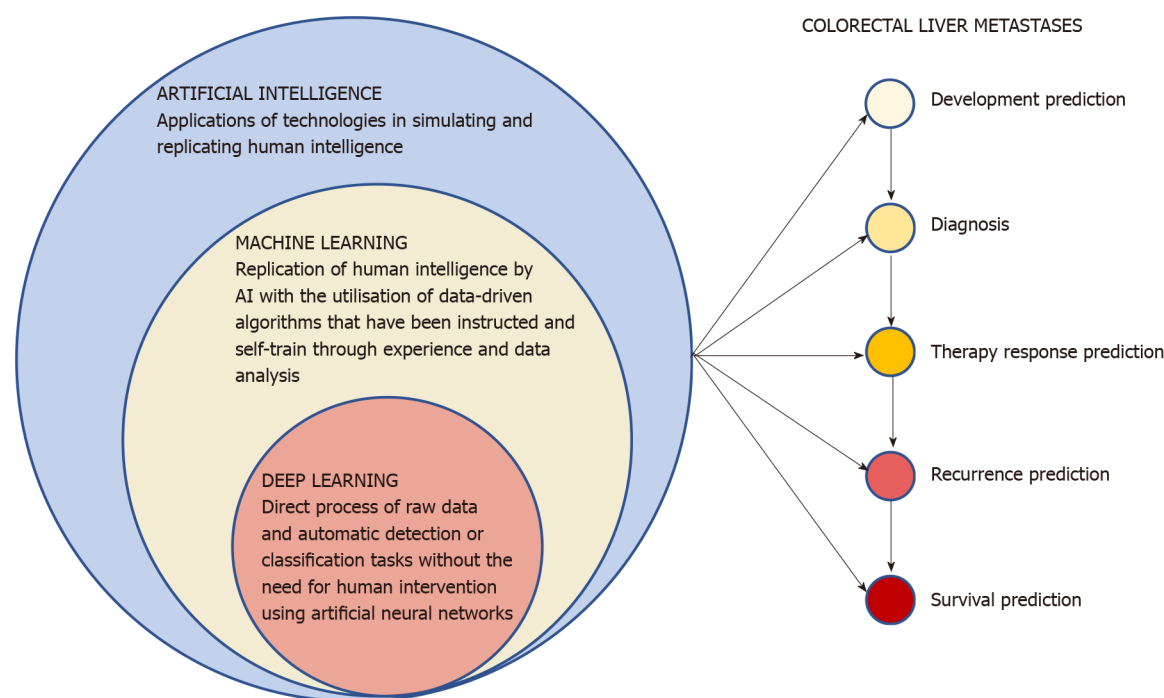


Figure 1 Possible applications of artificial intelligence technologies in the diagnosis and management of colorectal liver metastases. AI: Artificial intelligence.

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

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 <i>et al</i> [23] (2020)	Retrospective; Single center	Radiomics/ML	CT images ± clinical data	100/NA/80	0.90/0.906	81%/84%	85%/79%	NA
Taghavi <i>et al</i> [24] (2021)	Retrospective; Multicenter	Radiomics/ML	CT images ± clinical data	91/70/21	0.95 ² -0.68 ³ -0.95 ⁴ /0.86 ² -0.71 ³ -0.86 ⁴	NA/NA	NA/NA	NA
Lee <i>et al</i> [25] (2020)	Retrospective; Single center	Radiomics/CNN	CT images ± clinical data	2019/1413/606	NA/0.606 ² -0.709 ³ -0.747 ⁴	NA/NA	NA/NA	NA
Diagnosis								
Vorontsov <i>et al</i> [26] (2017)	Retrospective; Single center	Radiomics/CNN	CT images	40/32/8	NA/NA	84%/92%	NA/NA	88%
Vorontsov <i>et al</i> [28] (2019)	Retrospective; Single center	Radiomics/CNN	CT images	156/115/15	NA/NA	59% ⁵ /NA	80% ⁵ /NA	NA
Ma <i>et al</i> [30] (2020)	Retrospective; Multicenter	CNN	CT images	909/479/202 (228 ⁶)	NA/0.837-0.844 ⁶	82% ⁶ /74% ⁵	75% ⁶ /81% ⁶	NA
Kim <i>et al</i> [31] (2021)	Retrospective; Single center	DL	CT images	587/502/85	NA/0.631	81.82%/22.22%	NA/NA	NA
Khalili <i>et al</i> [34] (2020)	Retrospective; Single center	CNN	CT images ± liver metastatic status	199/150/49	NA/0.84-0.95 ⁷	(81.5%-81.5% ⁷)/(76.2%-96.4% ⁷)	NA/NA	78.3%; 90.6% ⁶
Jansen <i>et al</i> [38] (2019)	Retrospective; Single center	CNN	MRI images	121/334 ¹ /86 ¹	NA/NA	99.8%/NA	NA/NA	NA
Steenhuis <i>et al</i> [39] (2020)	Retrospective; Single center	ML	VOCs	62/NA/NA	NA/0.86	88%/75%	72%/90%	81%
Miller-Atkins <i>et al</i> [40] (2020)	Prospective; Single center	ML	VOCs	296/284/NA	NA/NA	51%/94%	NA/NA	86%
Kiritani <i>et al</i> [41] (2021)	Retrospective; Single center	ML	Histologic markers	183/NA/40	NA/0.999	100%/99%	NA/NA	99.5%
Han <i>et al</i> [47] (2020)	Retrospective; Single center	Radiomics/ML	MRI images ± clinical data	107/61 ¹ /31 ¹	0.974 ² -0.659 ³ -0.971 ⁴ /0.912 ² -0.676 ³ -0.909 ⁴	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 <i>et al</i> [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 <i>et al</i> [55] (2021)	Retrospective; Single center	Radiomics/DL	CT images ± CEA	192/144/48	0.903 ¹⁰ -0.935 ¹¹ /0.820 ¹⁰ -0.830 ¹¹	90.9%/73.3%	88.2%/78.6%	85.4%
Giannini <i>et al</i> [57] (2020)	Retrospective; Multicenter	Radiomics/ML	CT images	38/28/10	NA/NA	92%/86%	96%/75%	NA
Nakanishi <i>et al</i> [58] (2021)	Retrospective; Single center	Radiomics	CT images	42/94 ¹ /32 ¹	0.8512/0.7792	NA/NA	NA/NA	NA
Local ablative therapies efficacy								
Taghavi <i>et al</i>	Retrospective;	Radiomics/ML	CT images	90/63/27	NA/0.78 ² -	NA/NA	NA/NA	NA

<i>al</i> [59] (2021)	Single center				0.56 ³ -0.79 ⁴			
Survival prediction								
Mühlberg <i>et al</i> [60] (2021)	Retrospective; Single center	Radiomics/ML	CT images ± WLTB ± TBS	103/NA/NA	NA/0.70 ¹² -0.73 ¹³ -0.76 ¹⁴	NA/NA	NA/NA	NA
Hao <i>et al</i> [62] (2017)	Retrospective; Multicenter	ML	DNA methylation	1792 ¹ /NA/884 ¹ (718 ^{1,6})	NA/NA	NA/NA	NA/NA	98.4%
Dercle <i>et al</i> [64] (2020)	Retrospective; Multicenter	ML	CT images	667/438/229	0.83/0.80	80%/78%	NA/NA	NA
Spelt <i>et al</i> [65] (2013)	Retrospective; Single center	ANN	Clinical variables	241/NA/NA	NA/NA	NA/NA	NA/NA	72%
Paredes <i>et al</i> [66] (2020)	Retrospective; Multicenter	ML	Clinical variables	1406/703/703	0.527 ¹⁵ -0.525 ¹⁶ - 0.693 ¹⁷ /0.524 ¹⁵ -0.501 ¹⁶ -0.642 ¹⁷	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 Brudevik-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.

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.

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