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RESPONSIBLE EDITORS FOR THIS ISSUE

Is precision medicine for colorectal liver metastases still a utopia? New perspectives by modern biomarkers, radiomics, and artificial intelligence

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Abstract

The management of patients with liver metastases from colorectal cancer is still debated. Several therapeutic options and treatment strategies are available for an extremely heterogeneous clinical scenario. Adequate prediction of patients' outcomes and of the effectiveness of chemotherapy and loco-regional treatments are crucial to reach a precision medicine approach. This has been an unmet need for a long time, but recent studies have opened new perspectives. New morphological biomarkers have been identified. The dynamic evaluation of the metastases across a time interval, with or without chemotherapy, provided a reliable assessment of the tumor biology. Genetics have been explored and, thanks to their strong association with prognosis, have the potential to drive treatment planning. The liver-tumor interface has been identified as one of the main determinants of tumor progression, and its components, in particular the immune infiltrate, are the focus of major research. Image mining and analyses provided new insights on tumor biology and are expected to have a relevant impact on clinical practice. Artificial intelligence is a further step forward. The present paper depicts the evolution of clinical decision-making for patients affected by colorectal liver metastases, facing modern biomarkers and innovative opportunities that will characterize the evolution of clinical research and practice in the next few years.

Key Words: Colorectal liver metastases; Biomarkers; Genetics; Immune infiltrate; Radiomics; Artificial Intelligence

Core Tip: The management of patients with colorectal liver metastases is challenging because the choice among different therapeutic options and strategies is not supported by strong evidence. A precision medicine approach has been an unmet need for a long time, but recent studies have opened new perspectives. In this paper, we will discuss new morphological approaches to assess tumor biology, the promising data from genetic analyses, the raising clinical relevance of the liver-tumor interface, and the potentialities of advanced imaging analysis and artificial intelligence. These are the keys to reach an effective personalized treatment in the near future.

INTRODUCTION

During the last decades, the surgeons and medical oncologists drove the multidisciplinary teams to the ambitious aim of curing patients with colorectal liver metastases [1]. Systemic therapy had a progressively increasing effectiveness[2,3]. To date, the median life expectancy of patients receiving state-of-the-art treatment exceeds 30 mo[1, 2]. The new immunotherapies could further raise the bar. Liver surgery has been the game-changer: It rapidly became the standard thanks to its proven safety (mortality risk lower than 2%) and oncological effectiveness (actual 5- and 10-year survival rates of about 50% and 20%, respectively)[1,4-6]. All patients with technically resectable disease, sufficient future liver remnant volume, and disease control by chemotherapy are now considered for surgery[1,7]. The liver surgeons pursued aggressive indications and developed complex techniques to maximize the resectability rate, even considering liver transplantation in the most recent years[7-9]. However, this generated a paradox: We are now searching for criteria to identify patients that are technically resectable but do not benefit from surgery because of their unfavorable tumor biology (10%-15% of patients have an early recurrence and early cancer-related death after surgery)[10]. Finally, thermal ablation gained momentum. After having demonstrated its effectiveness in patients with hepatocellular carcinoma, radiofrequency and microwave ablation have been successfully applied to patients with colorectal liver metastases, achieving adequate disease control[11,12]. Percutaneous treatments are now even tested as alternative to surgery in randomized trials[13,14].

The management of such a complex scenario should rely on an adequate understanding of tumor biology and several decisions need for a precision medicine approach (*e.g.*, the identification of the most appropriate schedule of systemic therapy, the selection of candidates to surgery, the indication to perioperative chemotherapy, the timing of colorectal and hepatic surgery in patients with synchronous metastases, and the choice between surgery and ablation). However, a recent study demonstrated that hepatobiliary surgeons have a huge heterogeneity in the treatment planning and surgical indications, the choice among different options being almost a throw of the dice[15]. Reliable biomarkers are urgently needed to drive a patient-tailored evidence-based approach.

In 2012, we depicted an evolving scenario with some preliminary evidence[16]. Where do we stand almost a decade later? In the present paper, we will provide a critical overview of traditional biomarkers, new proposals, and future perspectives (Figure 1 and Table 1).

MORPHOLOGY: AN OUTDATED BIOMARKER?

The tumor morphology is still the basis of several clinical decisions. The tumor burden defines the resectability of patients, and, in resectable ones, the need for perioperative

Table 1 Characteristics of different biomarkers of colorectal liver metastases.

	Biomarker characteristics					
	Standardized	Reproducibility	Robustness (across series)	Early assessment	Reliability in prediction	(Potential) Clinical impact
Morphology and clinical data	d	e	c	e	b	c
Dynamic evaluation	d	e	e	b	d	e
Genetics	c	d	d	e	e	e
Peritumoral tissue data	c	d	c	a	d	d
Radiomics	b	c	c	e	c	d
Artificial intelligence	a	a	b	d	d	e

The performances of every biomarker are evaluated by a score, ranging from "a" if very low to "e" if very high.
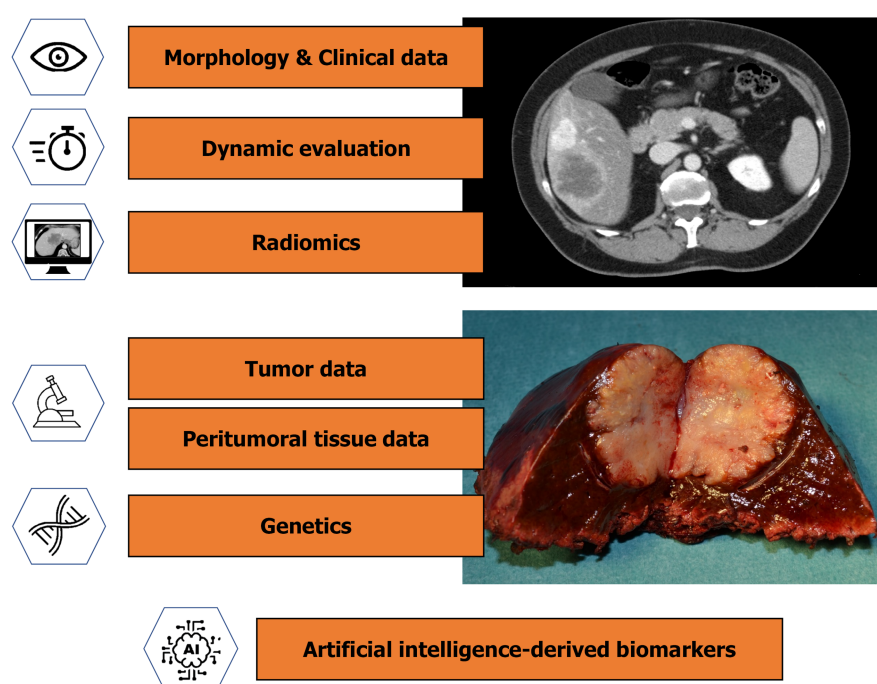
Figure 1 Available biomarkers for patients affected by colorectal liver metastases. A biomarker is defined as any parameter (molecular, cellular, clinical, imaging or identified by an artificial intelligence process) having a clinical role in narrowing or guiding treatment decisions and contributing to the estimation of the overall patient prognosis (prognostic biomarker), the clinical outcome after a treatment (predictive biomarker), or the properties of a clinical condition /disease (diagnostic biomarker).

chemotherapy[1,7]. The size of liver metastases determines the indication to thermal ablation (effective in nodules ≤ 30 mm)[17]. Several morphological parameters, including primary tumor data and tumor markers, have a prognostic value, and they have been combined into multiple scores to optimize their prognostic performance (Table 2)[18-23].

Recent studies reaffirmed the role of tumor morphology as a biomarker and determinant of the treatment strategy. First, Sasaki *et al*[24] proposed to combine the number and size of metastases into a "Tumor Burden Score", mimicking the Metroticket evidence for hepatocellular carcinoma[25]. They classified the patients into three groups and achieved a good stratification of survival, better than the stratification achieved by the size or the number of metastases when separately considered. Nevertheless, the Tumor Burden Score failed to select the candidates to surgery, the patients of the high-risk group (score ≥ 9) having an expected 5-year survival rate over 20%. Second, the primary tumor site has gained momentum. In comparison with patients having a left colonic tumor, those having a right colonic tumor are characterized by a lower response to chemotherapy, survival after surgery, and effectiveness

Table 2 Some of the available scores for outcome prediction of patients with colorectal liver metastases candidates to surgery

	Morphology-based scores				Morphology- and Genetics-based scores		
	Nordlinger *et al*[18], 1996	CRS, Fong *et al*[19], 1999	Iwatsuki *et al*[20], 1999	Rees *et al* [21], 2008	RAS Mutation CRS, Brudvik *et al*[60] 2017	GAME score, Margonis *et al*[61] 2018	Extended CRS, Lang *et al*[65], 2019
Morphological parameters							
Age	Yes (60 yr)						
Primary tumor							
Extension into the serosa	Yes						
N status primary tumor	Yes	Yes		Yes	Yes	Yes	Yes
Grading primary tumor				Yes			
Liver metastases							
Number	Yes (3)	Yes (1)	Yes (2)	Yes (3)		Yes (TBS)	
Size	Yes (50 mm)	Yes (50 mm)	Yes (80 mm)	Yes (50 mm)	Yes (50 mm)		Yes (50 mm)
Bilobar			Y				
DFI	Yes (24 mo)	Yes (12 mo)	Yes (30 mo)				
Surgical margin	Yes (10 mm)						
Extrahepatic disease				Yes		Yes	
CEA value		Yes (200 ng/mL)		Yes (60 ng/mL)		Yes (20 ng/mL)	
Genetic parameters							
RAS					Yes	Yes[1]	
RAS/RAF pathway							Yes
SMAD							Yes

[1]KRAS status.

DFI: Disease-free interval from primary to metastases; CEA: Carcinoembryonic antigen; CRS: Clinical risk score; GAME: Genetic and morphological evaluation; TBS: Tumor Burden Score.

of thermal ablation[26-29]. The embryological origin of the two parts of the colon (midgut for the right colon and hindgut for the left one) and the different genetic profiles of the tumors could explain such results. However, the impact of the primary tumor side on the treatment strategy is still to be defined, and, in this distinction (right *vs* left colonic cancer), the rectal cancers remain a blurred entity to elucidate. Third, a recent study based on the LiverMetSurvey data suggested that patients with synchronous multiple bilobar metastases should undergo a liver-first approach because this strategy achieves better survival than the alternative ones (*i.e.* the simultaneous and primary tumor-first approaches)[30]. This evidence could lead to a major change in current practice and definitively prioritizes the treatment of liver metastases in presence of a severe hepatic tumor burden. Fourth, in patients with liver and lung metastases, the pulmonary disease has shown a limited prognostic relevance [31]. Such data should be paired with those provided by Viganò *et al*[32], who demonstrated that the pathological response of colorectal metastases to systemic therapy changes according to the involved organ, being low in the lung and lymph nodes metastases, intermediate in the hepatic ones, and high in the peritoneal ones. The inhomogeneous prognostic relevance and chemosensitivity of the different tumor sites open new perspectives in treatment strategies and oncological research.

Despite its extensive adoption in current practice, tumor morphology is not a robust biomarker for several reasons. First, in patients undergoing systemic therapy,

morphology gives a limited prediction of the response to treatment. Second, in resectable patients, it does not allow for an adequate selection of candidates. The number of colorectal metastases and the presence of extrahepatic disease are paradigmatic examples. Even if the number of nodules is a strong prognostic factor, there is not a numeric cut-off value beyond which resection is contraindicated, and some patients with numerous metastases may benefit from surgery[33-35]. Similarly, the presence of extrahepatic disease contraindicates surgery in a limited proportion of patients (unresectable lesions, distant lymph node metastases, and diffuse peritoneal disease combined with multiple hepatic metastases)[36-38]. Third, different morphological parameters have been reported by different studies, and none has been confirmed by all authors. Fourth, morphological criteria can be modified by chemotherapy (*e.g.*, the tumor size), and it is unclear which value (before or after treatment) should be considered. Finally, tumor morphology offers a snapshot of the tumor and misses its evolution.

MOVING TOWARD A DYNAMIC VIEW

The tumor behavior is intuitively an effective surrogate biomarker of its biology. In the early 2000s, some authors proposed to adopt a time-test before surgery in patients with resectable colorectal liver metastases (*i.e.* an observation period to evaluate the tumor evolution)[39-41]. One-third to half of the patients developed additional lesions during the time-test and were excluded from resection. This policy has been early abandoned because of the advent of effective chemotherapy regimens, which combine observation and treatment. To date, neoadjuvant systemic therapy is a standard, and the tumor behavior during treatment is one of the most powerful prognostic factors. Since 2004, progression while on chemotherapy is even considered a contraindication to resection in resectable patients with few exceptions[42].

The prognostic role of the response to chemotherapy is indisputable, but three main limitations of this parameter should be highlighted: It excludes from surgery less than 10% of candidates[43]; the pathological evaluation of response has a poor agreement with the radiological one (about one-third of responders at imaging has no tumor regression at the pathology analysis)[44,45]; the no-progression during short chemotherapy (2-3 mo, the present standard) does not necessarily correspond to favorable biology and prognosis (about 15% of patients develop early recurrence after surgery)[10].

There is another time interval during which the tumor behavior can be analyzed. Patients must respect a 4-wk pause between the end of the systemic therapy and surgery (6 wk in case of anti-vascular endothelial growth factor treatment)[46,47]. We observed that about 15% of patients with tumor response or stabilization during chemotherapy have an early tumor progression in the interval between chemotherapy and surgery and an extremely poor outcome (0% survival at 2 years)[48]. Such a progression should contraindicate resection and dictates the need for restaging immediately before surgery.

Finally, percutaneous thermal ablation could contribute to the dynamic evaluation of colorectal liver metastases. It has been proposed as a time-test in patients with a synchronous disease or early recurrence after liver surgery with several benefits: Ablation provided a minimally invasive and effective treatment of the metastases, with high salvageability in case of local failure; avoided futile surgery in some cases; and spared chemotherapy for further disease progression[49,50].

Despite its effectiveness, the dynamic evaluation of colorectal metastases should be applied with caution. First, the time-test must be adequate. Progression during prolonged systemic therapy or after a long chemotherapy-surgery interval represents a loss of chance for resectable patients rather than a selection[48]. Even a disease progression in the interval between the two stages of a staged hepatectomy should not be considered *tout-court* an adequate selection of candidates[51]. Second, selected patients with a dimensional-only progression of the tumor and a limited hepatic tumor burden can be considered for surgery despite progression[52]. Finally, progression is not a definitive contraindication to resection, and surgery can be scheduled if the disease is controlled by a further line of chemotherapy[53,54].

GENETIC DATA: THE PANACEA FOR ALL THE UNCERTAINTIES?

Tumor genetics is the key to design a precision medicine approach. The sequencing of large series of metastases highlighted few high-frequency mutations, which have been extensively investigated for their association with the outcome. Tumor protein p53 (TP53) and APC gene mutations are the commonest ones (65%-75% and 45%-85% of patients, respectively)[55,56], but most studies focused on the RAS genes. KRAS and NRAS mutations are evident in one-third to half of the patients and have an established clinical impact: They preclude anti-epidermal growth factor receptor treatments and are associated with a lower response rate to chemotherapy, poorer survival, and higher risk of pulmonary metastases[57-59]. RAS status has been recently included in two prognostic scores for patients undergoing liver surgery (Table 2): The RAS Mutation Clinical Risk Score that considers the RAS status, metastases size, and N status of the primary tumor[60]; the Genetic And Morphological Evaluation (GAME) score that considers the KRAS status, carcinoembryonic antigen level, N status of the primary tumor, Tumor Burden Score, and presence of extrahepatic disease[61]. Both have been externally validated and outperformed the standard morphology-based scores. The patients with the highest scores had extremely poor outcome (0% recurrence-free survival at 2 years after surgery if RAS Mutation Clinical Risk Score = 3 or GAME score ≥ 6), but they were a marginal part of the cohort (14/564, 2.5%, and 18/1249, 1.4%, respectively).

The analysis of BRAF mutations generated a major interest despite their low frequency (4%-10%)[56,62]. The oncologists reported extremely poor survival of BRAF mutated patients, raising doubts about their candidacy to surgery[57,62]. Nevertheless, surgical series achieved an adequate outcome in selected BRAF mutated patients, suggesting that this genetic profile is a strong prognostic factor but should not be an absolute contraindication when the disease is adequately controlled by chemotherapy [63,64]. Additional mutations have been associated with prognosis, such as those of the TP53, PIK3CA, APC, and SMAD genes[65]. The Mainz group suggested that the performances of the aforementioned RAS score can be improved by replacing the RAS with the RAS-RAF pathway and adding the SMAD family (Table 2)[65]. The patients with all four negative prognostic factors (metastasis size > 50 mm, N+ primary tumors, and double mutation of the RAS-RAF pathway and SMAD family) had an extremely low median survival (1 year after surgery), but they were very few (only 5 out of 123, 4%). The MD Anderson Cancer Center group reported a cumulative negative prognostic impact of the mutations of TP53, RAS, and SMAD4: Survival progressively decreased with the increase in the number of the altered genes[66].

Those are the first steps of genetic-based precision medicine, but we have still to face some major challenges: Evidence is preliminary and needs robust validation to drive clinical practice; some criteria to select the candidates to surgery have been proposed, but they concern a minimal proportion of patients (< 5%)[60,61,65]; the discordance of the genetic profile between the primary tumor and metastases and their corresponding prognostic impact remain to be elucidated; tumor heterogeneity may lead to clonal populations with different mutations into a single metastasis, but their assessment is not yet standardized.

THE SOLUTION COULD BE OUTSIDE THE TUMOR

The liver-tumor interface could be the true battlefield where the interaction between the neoplastic cells and the "host" determines the prognosis. Several data are in favor of this hypothesis.

First, the pathology analysis of the peritumoral parenchyma highlighted the presence of the micrometastases (*i.e.* vascular and lymphatic tumoral emboli, perineural tissue infiltration, and satellite nodules)[44]. They are mainly localized within the first 2 mm of tissue surrounding the tumor, are reduced by chemotherapy, and negatively impact prognosis[44,67,68]. Micrometastases are the true determinants of the local recurrence risk after resection and thermal ablation.

Second, the profile of liver metastases has prognostic relevance. In 2009, Mentha *et al*[69] depicted the so-called "dangerous-halo" (*i.e.* a neoplastic regrowth at the tumor periphery due to an early reactivation of the metastases after the end of chemotherapy). This could represent the pathology counterpart of the radiological tumor progression that we observed in the interval chemotherapy-surgery. To date, the metastases' profile has been named "tumor growth pattern" and has been distinguished into three types: Pushing, desmoplastic, and replacement[70]. The types

correspond to different growing modalities: The metastases with a replacement pattern grow by co-opting the stroma and sinusoids; those with a pushing pattern have signs of active hypoxia-induced angiogenesis[71,72]. The replacement pattern is the most aggressive one and is associated with a lower response rate to chemotherapy, higher recurrence risk, and poorer survival[73-75]. In patients with a replacement pattern, we also observed an increased risk of local recurrence after surgery and the need for a wider surgical margin (unpublished data).

Third, a growing interest concerns the peri-tumoral immune infiltrate, especially after the introduction of modern immunotherapies. As for the primary colorectal cancers, an immunoscore, based on the presence of CD3+ and CD8+ cells in the core of liver metastases and at their invasion margin, achieved a good stratification of prognosis[76]. Additional cell populations have been investigated for their association with the outcome, such as the macrophages[77], but data are still preliminary.

Unfortunately, the biomarkers of the liver-tumor interface can be assessed only by the pathologist on the surgical specimen. The lack of an adequate non-invasive evaluation strongly reduces their clinical relevance. In addition, a comprehensive overview of the liver-tumor interface, merging the different pathology details, is still lacking, precluding a definitive understanding of the tumor-host interaction.

A further aspect deserves consideration; some features of the non-tumoral liver parenchyma could impact prognosis. Chemotherapy-associated sinusoidal injuries have been associated with the tumor response to chemotherapy; the more severe the sinusoidal dilatation the lower the response rate[44,78]. Nevertheless, the response to therapy and not the sinusoidal dilatation impacted survival[44]. In contrast, Viganò *et al*[44] depicted moderate/severe steatosis as a positive prognostic factor after surgery (5-year survival rate 53% *vs* 35%). These results have been confirmed by a subsequent analysis of the LiverMetSurvey database[79] and are in line with some studies reporting a favorable association between body mass index and prognosis[80,81]. We are still far from conclusive evidence and reliable explanation, but further investigations should be performed to potentially outline new therapeutic approaches.

RADIOMICS: IMAGING BEYOND THE VISIBLE DATA

Radiomics, or texture analysis, uses mathematical formulas to extract from medical imaging modalities invisible-to-the-eye patterns, which correlate with the biological properties of the analyzed tissue[82,83]. The complexity of analyses progressively increased, moving from histogram-based values to different types of matrices, filters, and transforms[84,85]. In patients with colorectal liver metastases, several potential applications of radiomics have been proposed[86]. First, it can predict the effectiveness of chemotherapy[87-95]. The decrease in entropy and increase in homogeneity of liver lesions after chemotherapy have been associated with the radiological tumor response. Some authors even reported the possibility to predict response to systemic therapy by analyzing the images at diagnosis before chemotherapy; higher entropy and lower homogeneity of liver metastases were associated with a subsequent higher response rate. When compared with the standard RECIST criteria, texture analysis achieved earlier and more accurate prediction. Second, radiomics have been associated with patients' prognosis, metastases with higher entropy and lower homogeneity having a better survival[88,90,96]. The comparative analysis of the imaging modalities before and after chemotherapy further refined the prediction of the long-term outcome[89,91, 92,94], and there is accumulating evidence that both radiomic scores and combined clinical-radiomic models outperform traditional predictors of survival[92]. Third, textural features of the tumor before thermal ablation can predict the risk of local recurrence[97]. Fourth, radiomics are associated with the pathology data (*e.g.*, tumor grading, growth pattern, and regression grade after chemotherapy[88,98,99]). Finally, texture analysis has the potential to provide a non-invasive evaluation of the chemotherapy-associated liver injuries, which at present are poorly evaluated by standard imaging modalities[46,100].

The strength of radiomics relies on its capability to provide early prediction of the outcome and to reach a non-invasive estimation of the pathology details of colorectal metastases, anticipating data that are usually collected only after surgery. Further, the possibility to interpret the biological value of some radiomic features facilitates their implementation into clinical practice. For instance, entropy and heterogeneity, especially after contrast enhancement, clearly suggest the presence of active disease with heterogeneous clones, while homogeneity after chemotherapy reflects tumor necrosis due to a response to treatment. Finally, the development of technological tools

to perform automatic segmentation of liver tumors will enable easier extraction of radiomic features, contributing to the spread of such data. However, the texture analysis suffers from some limitations: Some features, in particular the second-order ones, lack interpretability; radiomics has instability across different devices and acquisition protocols, especially for magnetic resonance images; studies differ in terms of software packages, analyzed phases, and reported features; and reliable cut-off values of radiomic parameters are lacking. Those issues have to be solved to speed up the application of radiomics into clinical practice.

## ARTIFICIAL INTELLIGENCE: WHERE DO WE STAND?

In the most recent years, the so-called "artificial intelligence" (AI) is the object of major interest and investments, with a consequent spike of AI-related publications[101]. Introduced in the 1950s, the term AI defines a computer program that, in a very specific setting, can "learn" and self-improve over time[102,103]. A demonstration of its potentialities took place in 1997, when a chess-playing AI, named Deep Blue, was able to beat the world champion Kasparov[104]. In medicine, AI is expected not only to optimize the prediction of an outcome by combining all available variables but also to update and improve continuously prediction according to the experienced results (Figure 2). AI can represent a major support to the decision-making processes, especially in the clinical scenarios with several therapeutic and strategical options and lack of consensus among experts, exactly as occurs for colorectal metastases[15]. In this sense, AI is not *per se* a biomarker but maximizes the profitability of all available data. However, AI may also have an additional role. It can be applied to medical imaging to identify new patterns that can contribute to diagnosis or prediction[105]. Such patterns, extractable from any type of imaging modality in a completely unbiased and unsupervised way, can be considered AI-derived biomarkers, subject to clinical validation[106]. Analogously, AI can identify biomarkers from any source of data, including clinical charts, medical reports, and images scan.

A first attempt in using AI-based therapy guidance dates to 2005, when a decision matrix platform, named OncoSurge, was introduced to help clinicians deciding the best treatment of patients at first diagnosis of colorectal liver metastases (*i.e.* when the treatment planning has the greatest impact)[107]. This method was later validated against the multidisciplinary team meeting achieving an almost perfect agreement [108]. Since then, few studies have been published, but they outlined a progressive increase in AI performances[109-113]. The AI predicted the recurrence risk after surgery by taking into account clinical, pathology, and laboratory data[110,112]. The addition of radiomic features into the machine learning models further optimized and anticipated the prediction[109,111]. Wei *et al*[113] compared a clinical, radiomic, and AI-based model to predict response to first-line chemotherapy; the deep-learning model had the best results, outperforming not only the model based on clinical parameters but also the one including texture analysis.

So far, the AI implementation into everyday practice is a priority to fill the quantum leap toward personalized computer-assisted medicine and will probably become a standard for clinical decision-making in the near future. It will allow merging all biomarkers, from morphological criteria to radiomics and genetic ones, weighing their prognostic role. Nevertheless, some current limitations of AI should be kept in mind. First, it needs training on large datasets, as Deep Blue did analyzing data from millions of chess matches[104]. Big data are crucial, but their availability is still limited by legal constraints and privacy policies. Shared databases and advanced interlinked frameworks could be the starting point. Second, AI supports decisions and does not replace clinical judgment yet, but computer-derived recommendations could lead to some legal and insurance critical issues. Finally, several technical and technological obstacles currently relegate AI-based approaches to highly specialized centers into a research setting.

CONCLUSION

To date, we are still far from a solid precision medicine for patients affected by colorectal liver metastases because of the limited capability of the available biomarkers to predict survival, response to chemotherapy, and the effectiveness of loco-regional therapies. Nevertheless, major (r)evolutions are ongoing, and the clinical approach to patients with metastatic colorectal cancer is going to change in the near future. The
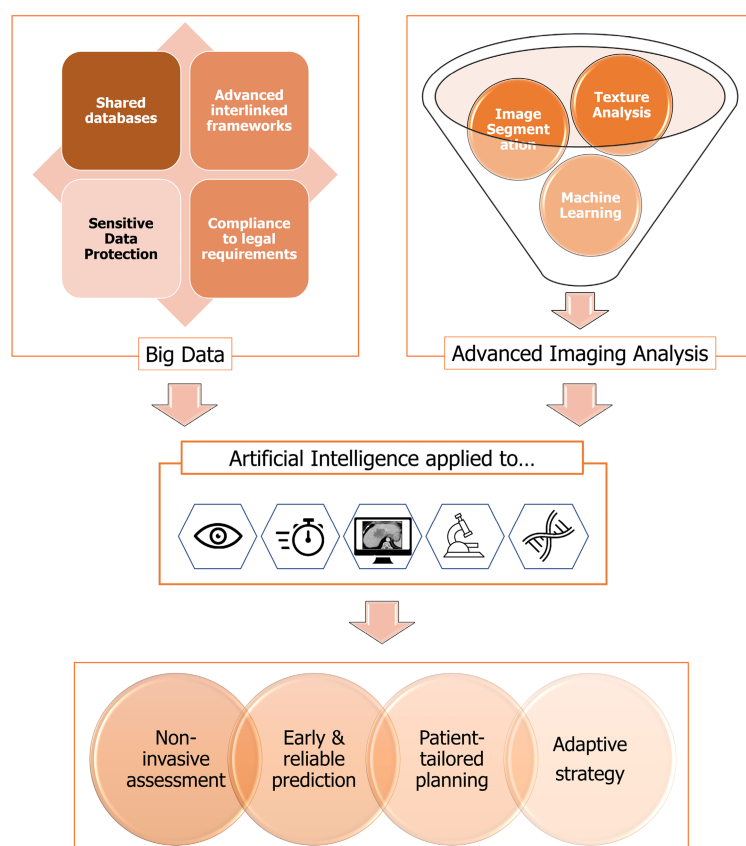
Figure 2 Future developments in the treatment planning for patients with colorectal liver metastases based on radiomics, big data, and artificial intelligence.

genetic analyses will definitively unveil the tumor biology, becoming the consistent basis of treatment planning; new biomarkers, based on radiomics and liver-tumor interface characteristics, will further enrich our comprehension and prediction of the tumor evolution; AI will merge and balance all data to drive decision-making processes.

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