



Macrotrabecular-Massive Hepatocellular Carcinoma: Light and Shadow in Current Knowledge

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Abstract: The subject of this narrative review is macrotrabecular-massive hepatocellular carcinoma (MTM-HCC). Despite their rarity, these tumours are of general interest because of their epidemiological and clinical features and for representing a distinct model of the interaction between the angiogenetic system and neoplastic cells. The MTM-HCC subtype is associated with various adverse biological and pathological parameters (the Alfa-fetoprotein (AFP) serum level, tumour size, vascular invasion, and satellite nodules) and is a key determinant of patient prognosis, with a strong and independent predictive value for early and overall tumour recurrence. Gene expression profiling has demonstrated that angiogenesis activation is a hallmark feature of MTM-HCC, with overexpression of both angiopoietin 2 (ANGPT2) and vascular endothelial growth factor A (VEGFA).

Keywords: hepatocellular carcinoma, macrotrabecular, angiopoietin 2 inhibitors, TP53, immunotherapy

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world, with 841100 new cases in 2018, and it is the second leading cause of cancer death, with a 5-year survival of 18%. In terms of sex, HCC is the fifth most common cancer in males and the ninth most common cancer in females worldwide.¹ It has been reported that approximately 80% of HCC cases occur in developing countries. HCC appears frequently in patients with cirrhosis, and the most common risk factors include alcohol consumption, hepatitis B (HBV) or hepatitis C (HCV) virus infection and nonalcoholic steatohepatitis (NASH).^{2,3}

HCC is a major health problem, and the majority of patients are diagnosed at an advanced stage, resulting in poor treatment outcomes.⁴

According to EASL and AASLD guidelines, current HCC diagnosis does not require histological confirmation due to excellent reported diagnostic performance of imaging procedures.^{4,5}

In patients with cirrhosis, HCC may be diagnosed noninvasively using multiphasic computed tomography (CT) or dynamic contrast material-enhanced magnetic resonance imaging (MRI) using the Liver Imaging Reporting and Data System (LI-RADS), which standardizes HCC imaging acquisition and terminology and enables accurate stratification of the probability of HCC and overall malignancy.^{4,6-8}

Although numerous histological tumour variants have been reported over the last decades, there has been no robust determination of the clinical impact of pathological classification to date; therefore, a liver biopsy is needed to obtain more information on the clinical implications of the HCC histological subtype.

HCC is a highly heterogeneous cancer at both molecular and histological levels. The HCC phenotype appears to be closely related to particular gene mutations, tumour subgroups and/or oncogenic pathways. Several HCC subtypes characterized by histological features and growth patterns have been identified, including solid (compact), pseudoglandular/acinar, and trabecular patterns, as described in the current WHO classification.⁹

These subtypes correlate with clinical features and prognosis but have not been thoroughly tested as predictors of a response to local or systemic therapies, which explains their limited clinical usefulness.¹⁰

Recent studies have shown that the macrotrabecular-massive subtype of HCC (MTM-HCC) has distinct molecular features and poor prognosis among the aforementioned subtypes.¹¹

The subject of this review is this aggressive subtype of HCC: the diagnostic, associated clinicopathological and imaging features are analysed, and treatment is discussed with particular emphasis on actual knowledge and a brief parenthetical consideration of angiopoietin 2 inhibitors, an ongoing subject of discussion.

Histological Definition: Origins to the Present

The most common growth pattern of HCC is a trabecular form that mimics normal hepatic cord plates. This growth pattern has been referred to as “macrotrabecular” (MT) when the trabeculae become >6 cells thick,^{12,13} and HCC in which the MT pattern constitutes >50% of the entire tumour is considered a subtype: macrotrabecular-massive hepatocellular carcinoma (MTM-HCC).^{11–17}

MT-HCC was first recognized as a distinct growth pattern in 1983,¹² but no studies supporting this observation have since been performed. There are only a few citations of MT-HCC in the literature.^{11,18,19}

The MTM-HCC subtype was first defined in a French collaborative study conducted by Calderaro.¹⁷

In this systematic analysis of more than 340 HCCs, the cut-off for defining HCC as MTM-HCC was the presence of more than 50% of the MT pattern in a tumour, which in turn was defined as a hepatic cord thickness >6 cells.¹⁷ Using biopsy samples, cases are classified as MTM-HCC if at least one focus of the macrotrabecular pattern is identified, without taking into account the areal percentage occupied by the pattern.¹¹

Compared to the results reported by the French group, Jean et al reported a lower cut-off of a $\geq 30\%$ MTM pattern as a diagnostic criterion,¹⁵ which needs to be validated by further studies (Figure 1).

Histological Prevalence

An MTM-HCC incidence rate of approximately 10–15% has been reported in different studies.^{11–16}

Ziol et al¹¹ identified the macrotrabecular-massive subtype in 12% of cases in a cohort of 237 HCC surgical samples and 284 HCC liver biopsies. Rastogi performed a retrospective study on 217 HCC patients in which MT-HCC was diagnosed in 20/218 (9.2%) cases, with coexistence of macrotrabecular and pseudoglandular patterns in 18% of cases.²¹

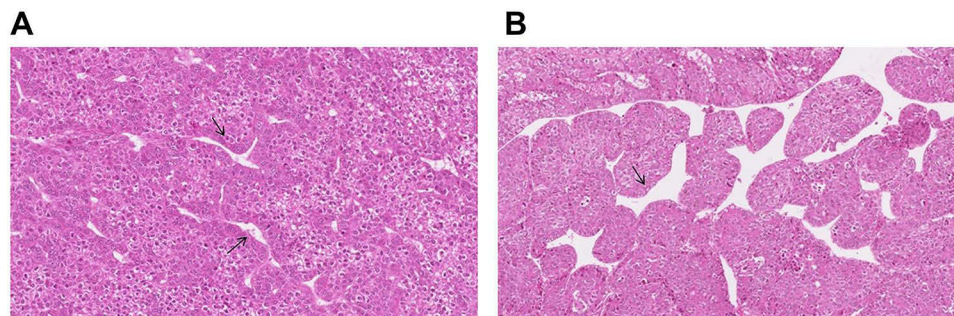


Figure 1 Histological imaging of MTM-HCC. (A) Microscopic examination show a macrotrabecular architectural pattern with thick trabecular or more than 6 cells (black arrows). (B) Trabeculae are separated by dilated vascular spaces (black arrow). Figure provided courtesy of Julien Calderaro.

By comparison, Lauwers et al²⁵ noted a macrotrabecular-predominant architecture in a higher number of cases (26.6% of 425 HCC resections).

In the study by Renne et al, MTM-HCC was identified in 7.8% of 541 resected HCCs from Italy, Korea and Japan,²⁰ whereas Feng et al reported MTM-HCC in 38% of 170 resected HCCs in China.²²

Coherently with Renne, Cannella et al found MTM-HCC in 7.8% of 295 HCCs cases.²³

In a recent American study,²⁴ MTM-HCC was reported in 7.1% of 378 HCC. However, the macrotrabecular pattern was more commonly seen in HCCs arising in non-fibrotic liver tissues compared with HCCs in cirrhosis (13.68% vs 4.95%) (Table 1).

Pathological Features

MTM patterns were found to be significantly correlated with the pathological features of aggressiveness, such as Edmondson grades III–IV ($P = 0.001$), and less pseudoglandular pattern.²⁰

In the Calderaro study,¹⁷ the pathological features associated with the MTM-HCC subtype were satellite nodules and vascular invasion.

Rastogi et al²¹ performed a study series in which it showed that the macrotrabecular pattern was often associated with poor grades of differentiation, the pT3 stage, tumour sizes of 2–5 cm and >5 cm, and high AFP levels.²¹

In the Renne study, the MTM-HCC subtype was significantly enriched by vessels that encapsulated tumour clusters (VETC phenotype), which was defined as enrichment of $\geq 55\%$ of the tumour area by CD34 immunostaining ($P = 0.006$).²⁰

Molecular Biology

Hepatocellular carcinoma cells accumulate somatic DNA alterations. The most frequent genetic alterations are mutations in the TERT promoter, accounting for approximately 60% of cases, followed by mutations in TP53 in approximately

Table 1 Macrotrabecular Tumour Incidence

Authors, Journal	Country-Population	Year	Individual Numbers	Incidence	
				%	N
Kirchi, <i>Cancer</i> ¹²	Japan	1983	57	31.6	18
Lauwers, <i>Am J Surg Pathol</i> ²⁵	USA	2002	425	26.6	113
Ziol, <i>Hepatology</i> ¹¹	France	2018	556	12	62
Jeon, <i>Am J Surg Pathol</i> ¹⁵	France	2019	231	1.7	4
Mule, <i>Radiology</i> ¹⁶	France	2020	152	17	26
Renne, <i>Hepatology</i> ²⁰	Italy, Korea, Japan	2020	541	7.8	42
Rastogi, <i>Pathol Res Pract</i> ²¹	India	2021	218	9.2	20
Rhee, <i>J Hepatol</i> ¹⁴	Korea	2021	476	17.6	84
Zhu, <i>Abdo rad</i> ³⁷	China	2021	88	36.4	32
Feng, <i>Radiology</i> ²²	China	2021	170	38	65
Jain, <i>Am J Clin Pathol</i> ²⁴	USA	2021	378	7.1	27
Cannella, <i>JHEP REPORT</i> ²³	Italy, French	2021	295	7.8	23

Notes: All reference citations included in the table are reported in the manuscript references (Arabic numbers above journal names correspond to the reference numbers in the text).

Abbreviations: Am J Surg Path, American Journal of Surgical Pathology; Abdo Rad, Abdominal Radiology; Path Res Pract, Pathology - Research and Practice; J Hepatol, Journal of Hepatology; Am J Clin Pathol, American Journal of Clinical Pathology.

30% of cases, WNT signalling (CTNNB1 and AXIN1 in approximately 40% and 10% of cases, respectively), or chromatin remodelling (ARID1A and ARID2 in approximately 10% and 5% of cases, respectively).²⁶

Calderaro et al¹⁷ was the first to show that a TP53 mutation and FGF19 amplification were associated with the MTM-HCC subtype. A strong association with the G3 transcriptomic subgroup, a subclass linked to cell cycle activation and chromosomal instability, was also observed.¹⁷

Interestingly, Li Li Liu et al²⁷ reported a higher expression of tumoral programmed death-ligand 1/chemokine-like factor (CKLF)-like MARVEL transmembrane domain containing 6 (PD-L1/CMTM6) and a higher inflammatory cell density in the MTM-HCC subtype compared to other subtypes. CMTM6 belongs to the chemokine-like factor (CKLF)-like MARVEL transmembrane domain-containing (CMTM) family and is a key regulator of PD-L1; that is, CMTM6 is an important immune checkpoint inhibitor that promotes PD-L1 expression in tumour cells in the defence against T cells.²⁸ In the Renne study, compared to other subtypes, the MTM-HCC subtype was significantly more frequent in p53+ and double-positive phenotypes (P53+ and β -catenin/GS+, with $P < 0.001$ and $P = 0.046$, respectively) and less frequent in the β -catenin/GS+ phenotype ($P = 0.006$).²⁰

The Role of Biopsy

The role of tumour biopsies in the management of patients with HCC is one of the most actively debated subjects in the liver cancer community.^{29–31}

MTM-HCC can be accurately diagnosed in biopsy samples through the identification of MTM patterns.¹¹

Using biopsies to identify morphology and molecular alterations is critically important for elucidating the mechanisms of carcinogenesis, improving diagnosis and prognostication, and finally facilitating the development of personalized medicine by identifying tumour entities with overexpressed PDL-1 that respond to immunotherapy.

Calderaro et al³² used a molecular-driven selection of biomarkers to implement the diagnosis of HCC morphomolecular subtypes and identified ESM1 (endothelial specific molecule 1) as a reliable microenvironment immunohistochemical marker of MTM-HCC.³²

The very aggressive MTM-HCC subtype may lead to a reconsideration of the role of biopsy for HCC diagnosis because the identification of this subtype during pretherapeutic work-up may have strong prognostic implications. Indeed, patients may benefit from adjuvant therapies and/or upfront registration on the liver transplant waiting list after resection or RFA. However, no data are available on the prognostic value of the MTM-HCC subtype regarding recurrence after liver transplantation.

Clinical Features

Calderaro et al showed that the MTM-HCC subtype was characterized by HBV infection, a higher level of alpha-fetoprotein, early relapse and poor survival. Subsequent work by the same group also showed that this subtype was associated with advanced tumour stages, vascular invasion, and poor prognosis.¹⁷

MTM-HCC is associated with poor survival in all studies. For example, Calderaro et al reported that the survival rate was 40% at 24 months in INSERM U1162 cohort and 60% at 24 months in validation cohort.¹⁷

Although the available data are coherent, additional study series are needed to investigate the clinical impact of MTM-HCC.

Radiological Features of Macrotrabecular-Massive Hepatocellular Carcinoma

To date, few analyses have been performed on the radiological features of histologically confirmed MTM-HCC (Table 2). Most of these have focused on MRI presentations.

Macrotrabecular-massive HCC has been reported to be associated with a peculiar microvascular pattern described as a sinusoid-like microvascular pattern or “vessels that encapsulate tumour clusters” (VETC) pattern, appear as a cobweb-like network encapsulating individual HCC clusters.^{33–35}

Table 2 Imaging Features of Macrotrabecular-Massive HCC Subtype

Authors, Journal	Image Analysis	Year	Individual Numbers	Principal Imaging Features	P value	Specificity (%)
Mule, <i>Radiology</i> ¹⁶	MRI 1.5 Tesla	2020	152	Substantial necrosis**	< 0.001***	93
Zhu, <i>Abdominal Radiology</i> ³⁷	MRI 3 Tesla	2021	88	Intratour fat Size > 50 mm Substantial necrosis**	0.014 [‡] 0.005 [‡] 0.01 [‡]	84
Rhee, <i>J Hepatol</i> ¹⁴	Gadoxetic Acid-Enhanced MRI	2021	476	≥50% hypovascular component and ≥ 2 ancillary findings*	NA	94 in training cohort
Feng, <i>Radiology</i> ²²	CT	2021	170	Main tumour size > 5 cm Intratour necrosis Intratour haemorrhage	0.005 [‡] < 0.001 [‡] 0.005 [‡]	NA
Cannella, <i>JHEP REPORT</i> ²³	CT MRI	2021	295	Tumor in vein LR-M feature Infiltrative [°] appearance Necrosis Larger size Tumor in vein Larger size	< 0.001 [‡] < 0.010 [‡] 0.032 [‡] 0.038 [‡] < 0.006 [‡] 0.052 [‡] 0.011 [‡]	NA

Notes: *Intratour arterial, arterial phase peritoural enhancement, and nonsmooth tumour margin. **Substantial necrosis, visually defined as tumour necrosis occupying at least 20% of the tumour. ***Multivariable logistic regression analysis. °LI-RADS major features ie non-rim APHE, non-peripheral “washout”, and enhancing “capsule”. Univariate analysis. †Multivariate analysis. All reference citations included in the table are reported in the manuscript references (Arabic numbers above journal names correspond to the reference numbers in the text).

Abbreviations: MRI, magnetic resonance imaging; J Hepatol, Journal of Hepatology; CT, computed tomography.

HCCs with such vascular patterns exhibit a low microvascular density and frequent tumour necrosis, and low microvascular density is highly correlated with low arterial enhancement on MRI.³⁶

In line with these results, Rhee et al¹⁴ used MRI data to show that the internal or diffuse hypovascular component (≥50% of the hypovascular component) of the arterial phase combined with two or more ancillary findings (intratumour artery, arterial phase peritoural enhancement, and nonsmooth tumour margin) was significantly associated with MTM-HCC and was associated with a poor prognosis.

Mulé et al¹⁶ performed a retrospective study on 189 patients, in which MTM-HCCs were classified as LIRADS-5 on multiphase contrast-enhanced MRI and presented substantial necrosis that may help to identify the MTM-HCC subtype with high specificity.

Feng et al²² confirmed previously reported results on MRI and were the first to report that substantial necrosis on CT was related to the presence of VETC.²²

Recently, Zhu et al³⁷ reported that for 88 patients with histologically confirmed HCC, intratumour fat was determined to be an independent predictor of MT-HCC, whereas necrosis was not.³⁷

A macrotrabecular area has also been more frequently observed in HCCs with arterial phase rim-like enhancement on gadoxetic acid-enhanced MRI.¹⁵

Hence, the presence of substantial necrosis on imaging may lead to consideration for lesion biopsy with therapeutic and prognostic intent, especially as the MTM-HCC subtype can be accurately diagnosed in biopsy samples.¹¹

In a recent Italo-French study,²³ the larger size, the presence of tumor in vein (TIV), at least 1 LR-M feature (LI-RADS major features, ie non-rim APHE, non-peripheral “washout”, and enhancing “capsule”), infiltrative appearance and necrosis or severe ischaemia were significantly more frequent in MTM-HCCs than in other subtypes on contrast-enhanced CT).

In addition, TIV and larger size tended to be more frequent in MTM-HCCs on MRI too.²³

Imaging findings of MTM-HCC could help select HCC patients who show poor outcomes after curative treatment as potential candidates for clinical trials of neoadjuvant strategies (Figure 2).

Treatment

According to the Barcelona Clinic Liver Cancer (BCLC), the only curative treatments for HCC to date – whatever the histological subtype (including MTM) – are liver transplantation, resection and in some cases thermal ablation. Compared to the standard surgical approach in HCC, there are no dedicated technical strategies allowing to improve survival outcomes. Systemic treatment is the only option for advanced HCC.⁴ Sorafenib was the first agent shown to improve the survival of patients with advanced HCC or in cases of intermediate-stage disease despite progression with transarterial therapies.³⁸ Treatment practices have changed in recent years with the advent of Lenvatinib³⁹ as another first-line treatment choice and Regorafenib,⁴⁰ Ramucirumab,⁴¹ and Cabozantinib⁴² as second-line treatment options. Checkpoint-blockade immunotherapy targeting programmed cell death protein 1 (PD-1) has recently shown promising efficacy for HCC. In May 2020, the FDA approved a combination treatment of Atezolizumab and Bevacizumab for patients with unresectable or metastatic HCC who have not received prior systemic therapy based on the primary analysis results of the IMbrave150 study.⁴³

Li Li Lu et al²⁷ reported that the MTM-HCC subtype was characterized by a high expression of CMTM6/PD-L1, suggesting that MTM-HCC patients are suitable candidates for tumour immunotherapy.

Targeting particular subsets of tumours remains a promising approach, as shown by the recent success of the REACH-2 trial⁴¹ that assessed the efficacy of Ramucirumab, an anti-angiogenic drug, in patients with elevated alpha-fetoprotein serum levels. Interestingly, MTM-HCC is characterized by increased levels of alpha-fetoprotein and activation of angiogenesis; the antitumour effect of Ramucirumab or other anti-angiogenic drugs in patients with this subtype of HCC should be assessed.⁴¹

During trans-arterial chemoembolization (TACE), the ischemic damage caused by the arterial occlusion induces the production of the hypoxia-inducible factor (HIF)-1 α , a known modulator of PD-L1 expression, decreased the percentage of T-regs and increased the CD4+/CD8+ ratio.⁴⁴

In particular, Montasser et al in their series with 11 cases of MTM-HCC demonstrated an increase of PD-1 and PD-L1 expression in HCC following TACE that supported the use of TACE in combination with immunotherapy.⁴⁵

This rationale guided the design of trials testing the combination of TACE and anti-PD-1 mAb (like, in NCT03397654 trial – pembrolizumab after TACE- or NCT03143270 trial – nivolumab with drug-eluting bead-TACE). More data are needed to evaluate the benefits of treatment combining TACE and checkpoint inhibitors in MTT-HCC.

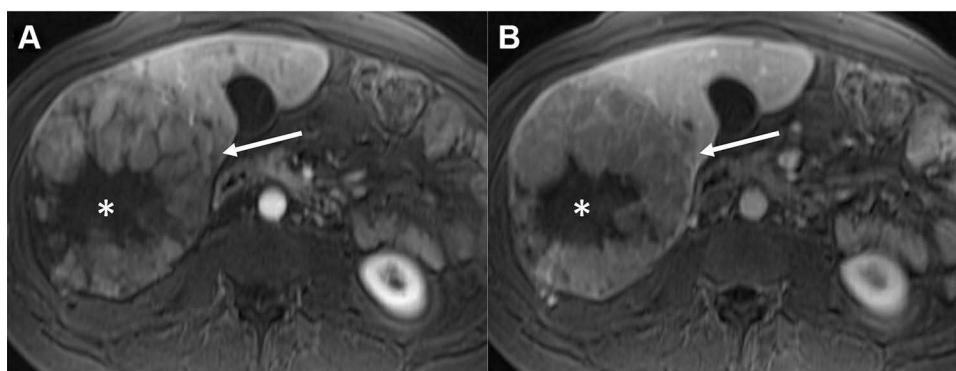


Figure 2 Radiological imaging of MTM-HCC. MR images in a 39-year-old woman with 13-cm heterogeneous macrotrabecular-massive hepatocellular carcinoma (MTM-HCC) in right liver lobe (arrow). Note the presence of a large central area without enhancement on late arterial (A) and venous (B) phases images, corresponding to substantial necrosis (*). Figure provided courtesy of Sébastien Mulé.

Prognosis

HCC is a highly malignant tumour associated with a poor prognosis, and only a subset of patients are eligible for curative treatment options. Moreover, the recurrence rate is high.⁵ The tumour size, vascular invasion, grading and staging are important variables for predicting HCC prognosis.⁴⁶

Although the MTM-HCC subtype is more prevalent in intermediate or advanced HCC, MTM-HCC represented a significant fraction (10%) of tumours classified as very early or early HCC (BCLC 0/A) in a cohort studied by Zioli et al.¹¹

Macrotrabecular-massive HCC (MTM-HCC) appears to be associated with early relapse after resection or percutaneous ablation, independent of classical clinical and radiological prognostic factors.³⁴

The MTM-HCC pattern was found to promote the metastatic potential of a mouse HCC cell line *in vivo* through the release of tumour clusters into the bloodstream in an epithelial-to-mesenchymal transition-independent manner.³⁴

In the same line, in a recent American study,⁴⁷ the authors identified the MTM subtype as the most common histomorphologic features in primary tumors associated with metastasis amongst 39 HCC cases studied.

Calderaro et al¹⁷ observed an association between MTM-HCC and poor prognosis (early relapse and poor survival). Major aggressiveness of this HCC subtype (major incidence of vascular invasion and satellite nodules) was also reported.

These features were confirmed in a report by Zioli et al¹¹ of a significantly higher recurrence rate and worse overall survival in patients with this HCC subtype compared to other subtypes. Similar results were found by Jeon et al¹⁵ for patients who underwent liver resection/transplantation. Li Li Liu et al²⁷ showed that at the molecular level, CMTM6/PD-L1 expression was an independent prognostic factor for patient survival in the MTM-HCC subtype population, with increased risk of HCC progression and death.

The above-mentioned reported data are in line with those of Zhu et al,⁴⁸ showing that elevated expression of CMTM6 in a cohort of HCC cases was frequently accompanied by worsening of malignant phenomena, including high AFP levels, large tumour sizes, advanced TNM stages, and vascular invasion.

This association between macrotrabecular-massive growth pattern and higher AFP expression was recently confirmed by the recent studies of Cannella et al²³ Ridder et al⁴⁹ ([Supplementary Material Figure S1](#)).

New Perspectives

Angiopoietin 2 Inhibitors, An Ongoing Subject of Discussion

In MTM-HCC, angiopoietin 2 (ANGPT2) mRNA levels are overexpressed, along with a significant almost increasing trend in the vascular endothelial growth factor (VEGF) level.¹⁷

To date, ANGPT2, in cooperation with VEGFA, is known to promote neoangiogenesis and endothelial sprouting in the tumoral environment.⁵⁰

It has also been shown that secretion of ANGPT2 by various primary solid tumours can induce metastasis via the extravasation of circulating tumour cells⁵¹ by loosening endothelial cell junctions and increasing vascular permeability of distant organs.^{34,52}

In HCC, ANGPT2 produced by neoplastic cells may disseminate directly in adjacent liver parenchyma and contribute to the increased frequency of satellite nodules observed in MTM-HCC.

It is reasonable to expect that silencing the expression of ANGPT2 growth factor by neoplastic cells could disrupt the formation of this particular pattern and reduce both intrahepatic neoplasia and extrahepatic metastases.³⁴

Hashizume et al⁵³ have suggested that Ang2 inhibitors and VEGF inhibitors may have complementary antiangiogenic actions and effects on reducing tumour growth.

Ang2 inhibition prevents the growth of new vessels by endothelial sprout formation, whereas VEGF inhibition causes tumour vessel regression, and the formation of empty basement membrane sleeves reduces tumour growth. The combined blockade of Ang2 and VEGF has additive effects on sprouting and vessel regression and decelerates tumour growth.⁵³

Schmittnaegel et al⁵⁴ also demonstrated that blocking angiogenesis using these types of antibodies enhanced antitumour immunity (by increasing extravasation and perivascular accumulation of antitumour CD8+ cells and interferon- γ -producing cytotoxic T lymphocytes).⁵⁴

The synergistic use of ANGPT2 inhibitors and Bevacizumab (anti-VEGF) combined with immunotherapy could open novel therapeutic avenues for this highly aggressive HCC subtype and may represent a new tool for HCC treatment, bringing HCC molecular classification into clinical practice.

Artificial Intelligence: Which Role in the Future for MTM-HCC

The artificial intelligence (AI), computer-based algorithms for data analysis and by the construction of predictive models based on the usage of various imaging techniques, especially in combination with HCC molecular biomarkers, recently used for improving image recognition and representation in HCC diagnosis and prognosis.⁵⁵ For example, in their most recent article that represents a proof-of-principle study, Zeng et al⁵⁶ propose a novel approach using AI to predict activation of inflammatory gene signatures associated with increased sensitivity to immunotherapy, for improving personalized allocation of therapy. In this trend, the combination of artificial intelligence and automated computerized image analysis is likely to provide a new tool for MTM-HCC diagnosis and for characterisation of biomarkers to help in therapy work-up in the near future.

Conclusion

This article is a narrative review of the most recent data in the field of MTM-HCC, and provides insights on future directions and challenges.

In conclusion, MTM-HCC is an aggressive subtype of HCC characterized by vascular invasion, a higher level of alpha-fetoprotein, early relapse and poor survival.

Although the available data are coherent, additional study series are needed to investigate the clinical impact of MTM-HCC on treatment response. The development of particular therapeutic strategies and/or trials focusing on the particularly aggressive subtype of MTM-HCC should be considered. One limitation is the subjective nature of pathology and nonoptimal interobserver agreement among pathologists; however, artificial intelligence and automated computerized image analysis are likely to provide a unique opportunity to achieve consensus in MTM-HCC diagnosis in the near future.

Abbreviations

HCC, hepatocellular carcinoma; MTM-HCC, macrotrabecular hepatocarcinoma; LT, liver transplantation; PD-1, checkpoint-blockade immunotherapy targeting programmed cell death protein 1; CMTM6, chemokine-like factor-like (CKLF) MARVEL transmembrane domain-containing 6; ANGPT2, angiopoietin; VEGF, vascular endothelial growth factor; AFP, alpha-fetoprotein.

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