

Published: March 31, 2024

Citation: Gheisari F and Vali R, 2024. Advancements in Molecular Imaging for the Diagnosis and Management of Hepatocellular Carcinoma, Medical Research Archives, [online] 12(3). https://doi.org/10.18103/mra.v12i 3.5212

Copyright: © 2024 European Society of Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI

https://doi.org/10.18103/mra.v12i 3.5212

ISSN: 2375-1924

RESEARCH ARTICLE

Advancements in Molecular Imaging for the Diagnosis and Management of Hepatocellular Carcinoma

Farshid Gheisari¹, *Reza Vali²

- ^{1.} Ionizing and Non-ionizing Radiation Protection Research Center (INIRPRC), Shiraz University of Medical Sciences, Shiraz, Iran
- Diagnostic Imaging, Nuclear Medicine Division, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

*Corresponding Author: <u>Reza.vali@sickkids.ca</u>

ABSTRACT:

Hepatocellular Carcinoma (HCC) is a growing global health burden with high incidence and mortality rates. Despite advances in surgical techniques and perioperative care, outcomes after surgical treatment have not improved over the past three decades. Molecular imaging is an emerging field that enables researchers to study diseases at the molecular and cellular levels, enabling the detection of elevated serum α -fetoprotein (AFP) and abnormal expressions of various HCC-specific and nonspecific cell surface antigens and intracellular targets. Molecular imaging techniques detect liver lesions at the molecular and cellular level, allowing early detection and accurate staging of HCC. Positron emission tomography (PET) imaging offers greater sensitivity and specificity, while hepatobiliary-specific radiotracers with SPECT imaging provide insights into benign and malignant lesion differentiation. Radiomics and artificial intelligence are vital in deciphering molecular imaging data, with machine learning algorithms boosting diagnostic gains and predicting treatment response. Theranostics, a state-of-the-art application, provides diagnostic and therapeutic leverage following a single imaging agent. By understanding tumor biology in real time, radiopharmaceuticals can be transformed into personalized radiotherapies, enabling clinicians to make science-driven decisions throughout the illness. Future directions include developing novel radiotracers and integrating Al into clinical decision-making. Collaboration between academic researchers, clinicians, and industry colleagues is crucial to converting exciting advances into improved clinical outcomes for HCC patients.

Keywords: Hepatocellular Carcinoma, Molecular Imaging, Positron Emission Tomography, Single-Photon Emission Computed Tomography, Radiomics, Theranostics, Artificial Intelligence.

Introduction:

The diagnostic landscape of hepatocellular carcinoma (HCC), the most common form of liver cancer, has been continually changing since the advent of molecular imaging. Knowing the historical context surrounding molecular imaging and how it relates to HCC provides a basis to gauge the difficulties in the past, the successes, and the future of the technology.¹ Molecular imaging in HCC has a relatively short history, with the advent of conventional imaging during the last half of the 20th Conventional imaging tools such as century. ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) have played dramatic roles in detecting and characterizing liver lesions. However, to improve the detection of liver tumors and obtain more than anatomic detail, novel imaging research must demonstrate the added value of providing molecular and functional information above and beyond that of conventional imaging tools.² Hepatocellular carcinoma (HCC) of the liver is a malignant neoplasm originating from either hepatocytes or hepatocyte precursors. Liver cancer is a deadly and often leading type of cancer, with almost 80000 Americans being diagnosed with it each year. The treatment options for HCC primarily depend on the disease stage. Still, they may include surgical therapies such as radiofrequency ablation or liver transplantation, as well as locoregional therapies (chemoembolization, radioembolization) and systemic therapies (sorafenib). As a result of the higher prevalence of HCC in populations at risk, as well as the higher mortality of this disease state when compared to many other abdominopelvic cancers, there have been substantial efforts made to accurately and rapidly diagnose HCC.³ The true revolution in molecular imaging of HCC began with the advent of Positron Emission Tomography (PET) in the 1990s. PET was first used for whole-body staging of various cancers. PET came to liver imaging with the advent of radiotracers that reflect cellular alucose metabolism, such as the 18F-FDG. Although initial studies of 18F-FDG PET imaging of HCC were not efficient enough to be applied in HCC due to the variable glucose metabolism of well-differentiated HCC, they laid the foundation for future developments.⁴ With the developing understanding of the molecular basis of HCC, researchers quickly realized the need for a more tailored approach to imaging these lesions and, therefore, began developing radiotracers specific for the molecular pathways that drive this tumor. Biomarkers such as glypican-3 (GPC3) and alpha-fetoprotein (AFP) were discovered, and radiotracers were developed to bind these markers specifically to HCC lesions.⁵ Concurrently, functional imaging with SPECT using hepatobiliary-specific radiotracers became another new imaging tool to help with HCC diagnosis. SPECT, in particular, has the advantage of providing both functional and anatomic information and can, therefore, help identify the functional state and the dynamic changes in HCC within the liver.⁶ Integrating AI and Radiomics into molecular imaging studies in the early 21st century offered an additional leap forward. Å٩ computational power came online from these technologies, it enabled the analysis of staggering datasets from molecular imaging studies. It revealed behind-the-scenes patterns that provide a more aranular picture of HCC characteristics.⁷ The concept of Theranostics in the late 1980s was painted after the declaration of the 21st Century; it was based on Theranostics as a combination of therapeutic and diagnostic functions in a single imaging agent. Its implementation has increased the promise that the HCC can receive the best assessment, treatment, and targeted therapy delivered directly to the cancer cells.8 It is easy to see that each era of molecular imaging in HCC has been marked by an increase in the molecular clarity of HCC and the quest for new and more exact, personal, and dynamic diagnosis and treatment strategies. These will serve as our starting points as we explore these segments.9

Importance of Early Detection:

The early detection of HCC is the key to attaining better patient outcomes. Detecting the tumor at an earlier stage can significantly impact the timing of different intervention strategies, and it may increase the chance of other options for treatment, which may lead to a better survival rate.¹⁰ The earliness of diagnosis, reception to intervention strategy, or the aptitude for liver resection or transplantation all together determine the overall success and survival rates of patients with HCC.¹¹ In this context, molecular imaging offers various methods, including specific imaging techniques and developing contrast materials. This type of medical imaging can classify liver lesions at cellular and molecular levels, which should possess the relationship between HCC and liver cirrhosis. Advanced imaging can identify clockwise advanced HCC, tiny tumors, and the beginning of HCC thirteen.¹²⁻¹³ Molecular imaging uses the molecular signatures of normal and diseased cells to detect what ails the cell years before the disease develops.¹⁴ Doing this gives us a much earlier look at the actual HCC disease and allows for a tailored proactive therapy involving the right drugs and short surgery times.¹⁵ An added advantage of molecular imaging is the ability to identify small tumors and early-stage disease, particularly in populations at high risk of developing HCC, such as persons with chronic liver disease (CLD), particularly

cirrhosis.¹⁶ In a high-risk population, where the transition from liver disease to HCC is a known problem, early identification then becomes an essential linchpin in managing these patients.¹⁷ The recognition of HCC lesions in the liver of patients with chronic liver diseases is significant. With molecular imaging, it becomes more feasible, often in patients with chronic liver diseases, which leads to an increased risk for HCC development.¹⁸ However, the prognosis is favorable if HCC can be diagnosed efficiently. Many treatment options are available, such as surgical resection, ablation techniques including percutaneous ethanol injection and Radiofrequency ablation, and newer, targeted therapies.¹⁹⁻²⁰ The importance of early detection is evident in its ramifications, which supersedes the simple notion of finding HCC. With its ability to uncover the molecular background of liver lesions, introducing molecular imaging allows it to become a pivot point in a patient's new care. Allowing for earlier diagnosis ultimately allows us as healthcare providers to meet the patient's needs more proactively and personally, ultimately improving patient outcomes and quality of life.

Positron Emission Tomography (PET) Imaging:

Newer advanced diagnostic modalities, such as Positron Emission Tomography (PET) imaging and specific radiotracers, provide metabolic information about a lesion differently than traditional imaging methods.²¹ By using PET imaging, healthcare professionals can see information about the metabolic activity within liver lesions. To gain a complete evaluation of Hepatocellular Carcinoma (HCC), it is necessary to know the metabolic activities in liver lesions.²² Radiotracers, such as 18F-FDG, have played a key role historically in oncology imaging; however, they have had limited success within HCC, likely owing to the variable glucose metabolism of liver lesions.²³ More recently, advances in PET imaging have ushered in the development of novel radiotracers designed explicitly to target specific molecular pathways involved in HCC.²⁴ This has manifested with tailored radiotracers designed to identify - through various imaging modalities - specific biomarkers that have been noted to closely associate with hepatocellular carcinoma, such as glypican-3 (GPC3) and alphafetoprotein (AFP) ²⁵, making it more intricate than previously understood tracer studies where nonspecific radiotracers were mainly used (e.g., computerized tomography scan using triple-phase liver enhancement).²⁶ As a result, it offers better sensitivity and specificity than its competitors in providing more accurate and precise detection of hepatocellular carcinoma, thereby overcoming the limitation of variable glucose metabolism.²⁷ Therefore, it regards the existing conventional diagnostic tools in making an accurate and reliable diagnosis as the invention of target radiotracers, which has revolutionized the diagnostic modality of HCC where conventional diagnostic modalities lack the sensitivity to diagnose the disease.²⁸ Targeting the molecular pathway that is specifically involved in the development of hepatocellular carcinoma, these target radiotracers offer a unique molecular imaging technique to look into the subtle metabolic changes that can occur in smaller tumors or even in tumors of a larger size that can escape the diagnostic ability of the standard radiological imaging techniques.²⁹ Furthermore, PET, in conjunction with dedicated radiotracers, offers advantages beyond simple diagnostic ability: it allows the identification of specific molecular markers that are present on HCC cells, which could help in the evaluation of the lesions in terms of the probability of being malignant or benign, their malignancy grading, and the response to the potential treatment.³⁰ With these innovative radiotracers focused on the molecular pathways specific to HCC; this concept can significantly help personalized medicine against hepatocellular carcinoma.³¹ In conclusion, PET allows for improved accuracy with these diagnostic dedicated radiotracers.³² It is the direct consequence of this increased sensitivity and sensitivity as this pure imaging technique can overcome previous inherent issues, especially protuberant limitations, and thus results in more precise and personalized screening and characterization by our tumor of interest, HCC.33

Single-Photon Emission Computed Tomography (SPECT) Imaging:

Single-photon emission Computed Tomography (SPECT) imaging, when paired with hepatobiliaryspecific radiotracers like 99mTc-mebrofenin, is a robust modality in hepatocellular carcinoma (HCC) diagnostics.³⁴ While traditional imaging techniques only consider structural details, SPECT imaging captures information on liver physiology, going deeper into its functional details.³⁵ This unique approach adds value by speaking to the dynamic and holistic nature of the liver and has ramifications for liver imaging, particularly in HCC screening and other conditions.³⁶ The concept of hepatobiliaryspecific radiotracers in SPECT imaging introduces another objectively-based clinical insight important to hepatic lesion evaluation.³⁷ On the other hand, SPECT provides functional information besides visualizing lesions. Benign and malignant lesions are differentiated by gauging the influx dynamics of 99mTc-mebrofenin uptake.³⁸ This method's ability

the accuracy of diagnosis improves by characterizing a lesion and guiding treatment.³⁹⁻⁴⁰ SPECT can also do more than identify HCC; it can also see how the liver functions. This is useful because it evaluates the liver's health more entirely for those with HCC.⁴¹ This complete understanding of liver function contributes significantly to the bigger picture: HCC treatment strategies and how each is tailored to fit certain patients and diseases.⁴² SPECT clinical examinations distinguish the liver and how the entire liver deals with HCC.43 The functional information gathered from SPECT imaging contributes to the diagnosis, disease progression, and treatment outcome.⁴⁴ By providing real-time functional data of the liver, SPECT helps provide a holistic, adaptative strategy in handling patients because of the dynamic nature of Hepatocellular Carcinoma (HCC); this can be a particularly useful tool in addressing concerns concerning the ongoing evolution of the disease.45 In summary, when coupled with hepatobiliary radiotracers, SPECT imaging is a valuable and necessary tool in diagnosing HCC.⁴⁶ The unique ability of nuclear imaging to provide functional information about liver physiology, which in turn enables differentiation of hepatocellular carcinoma from other liver lesions, is the same property of the technique that puts it in a pivotal role in the quest personalized, for authentic, and dynamic management strategies of hepatocellular carcinoma.

Role of Radiomics and Artificial Intelligence:

The introduction of artificial intelligence (AI) and radiomics into the field of hepatocellular carcinoma (HCC) diagnostics is a game changer in practice. It is fair to say that this new technology can interpret molecular imaging data to heights that no one has previously predicted.47 The use of AI will have a significant impact on HCC with machine learning algorithms and other types, which should not be confused with the use of AI to improve the interpretability of the radiomics features in the Images to analyze the big data sets that are generated from molecular imaging-based studies to help significantly improve the diagnosis and the sexuality of the HCC prognostic response.48 Machine learning techniques have been helpful when looking at large amounts of data for more complex patterns. Machine learning techniques have gained considerable attention in the medical field, including in the hepatocellular carcinoma treatment sphere.⁴⁹ Given the ability to analyze complex data sets as a machine and identify patterns within these data sets, machine learning algorithms are an excellent aid for diagnosis, especially for those with very complex data sets. These are some of the various readings that can be read: the metabolic activity and molecular imaging types seen on different occasions.⁵⁰ Moreover, these algorithms are generally excellent predictors of therapy response. This is especially applicable before therapy begins, confirming whether or not a treatment shall be used before exposure to the drug.⁵¹ Radiomics is a complementary field that expands on molecular imaging and its diagnostic applications in HCC.52 It involves extracting quantitative features from medical images that may not be visible to the human eye - unveiling hidden information.⁵³ Regarding HCC, radiomics detects complex imaging features that are potential biomarkers for improved risk stratification.54 Radiomics provides granular data, bringing capabilities to uncover the disease early, better differentiate tumor heterogeneity, and subtle changes that mark disease progress.⁵⁵ This union of Al and Radiomics promises a new era of personalized medicine in HCC.⁵⁶ This is so because the applications of AI and Radiomics can crunch the massive amount of imaging data associated with high dimensional analysis to fully understand, implement, and propose tailored treatments based on the patient's characteristics.⁵⁷ This improvement can increase diagnostic accuracy and a deeper understanding of the disease, allowing for treatment plans to be more specific to the characteristics of an individual's HCC.⁵⁸ The rapid Al developments are leading to a fast incorporation of molecular imaging as part of routine clinical work.⁵⁹ This knowledge can help us make clinical decisions and fully take advantage of the potential of the molecular imaging body.⁶⁰ With an increasing shift to making diagnoses from the traditional routine to an Al, computational radiologists integrated technology, personalizing, and the most specific treatment to highlight some of the most significant structural, combined, and most successful care and modes were fast track to a new era of the most direct, individual treatment to his career.⁶¹ This blend of skills in artificial intelligence radiomics and molecular imaging can help researchers get a more detailed look at the best treatment for these patients. With increased research and treatment for HCC, researchers and physicians may change the outcome and treatment of these patients.62

Theranostics in HCC:

The paradigm-shifting concept of theranostics combines diagnosing and treating hepatocellular carcinoma (HCC) in a single imaging agent.⁶³ In the HCC realm of theranostics, radiolabeled compounds combine diagnostic imaging with target treatment.⁶⁴ In surpassing traditional diagnostics and treatments, this revolution in integrated diagnostics and patient care treatment is groundbreaking.⁶⁵ For HCC imaging, radiolabeled compounds have a dual role as a diagnostic tool in enabling accurate visualization and characterization of HCC lesions.⁶⁶ This helps obtain extra information regarding the lesion, aiding in precise disease staging and offering information for tumor-specific targets.⁶⁷ In addition, this plethora of information sharing allows better differentiation of HCC from the cirrhotic liver and diagnosis. The development of such advanced imaging modality has increased the diagnostic confidence of HCC and subsequently affected physicians in planning the optimal curable therapy protocols.⁶⁸ At the same time, theranostics is based on its radio-labeled compounds for targeted therapy, and it is a new approach to HCC treatment.⁶⁹ The Direct transmission of therapy with theranostics to the cancer cells rather than the waste of healthy cells or other tissues resulted in damage.⁷⁰ It is held that targeted cellular therapies accounted for many therapies the belief system is attributed to based LEIC receptor on tyrosine kinase signaling pathways, among others.⁷¹ The potential reduction in side effects associated with systemic treatments also supports the notion that theranostics improves the quality of life for HCC patients.⁷² The integration of theranostics in HCC reflects how theranostics can radically change personalized patient care by personalizing treatments based on each patient's specific case.73 Identifying targets unique to the tumor enables more targeted treatment and allows immediate monitoring of how far the therapy works.74 This era's precision oncology paradigm incorporates patient selection and treatment monitoring through molecular aberrations. Furthermore, this real-time feedback loop helps with the ability of therapy strategy to change because of the dynamic nature that displayed the disease, and this, in the course, helps to fuel a new personalized and adaptive Theranostic management of HCC.75 Theranostics is a more novel treatment for patients with HCC, which is significantly better and more innovative than most other treatment classes used today.⁷⁶ The convergence of diagnostic and therapeutic entities could create the ability to advance hepatocellular carcinoma precision medicine.77 The future of theranostic research is as intriguing as it is, and the potential impact this discipline could make upon improving patient outcomes and perhaps even prognosis in hepatocyte carcinoma indeed represents an exciting advancement in Liver cancer therapeutics.78

Monitoring Treatment Response:

To guide therapy and assess treatment response,

molecular imaging plays a crucial role in the fastpaced landscape of hepatocellular carcinoma (HCC) management.⁷⁹ This is key for any imaging modality, ranging from the standard contrastenhanced CT to the vast array of advanced molecular imaging.⁸⁰ Whatever the modality, the capacity to track the changes in tumor biology as time passes gives clinicians valuable understanding and helps them to navigate the complex roadmap for treating HCC.⁸¹ Many traditional imaging modalities, such as contrast-enhanced CT, are nonimaging biomarkers and are relied upon for anatomical detail in evaluating tumor size and vascularity changes.82 By incorporating advanced molecular imaging techniques, imaging biomarkers elevate the ability to monitor and follow treatment response at a molecular level. Molecular imaging allows a deeper understanding of tumor biology's molecular and cellular characteristics.83 Utilizing positron emission tomography (PET) with targeted radiotracers or single-photon emission computed tomography (SPECT) with hepatobiliary-specific agents, molecular imaging goes beyond defining the changes within the tumor microenvironment.84 This includes metabolic changes, lesions, and the cellular count being higher or lower than usual, which can all be markers of therapy progression.⁸⁵ This highly detailed, specific information allows doctors to evaluate whether their current therapy works or if any problems, such as resistant tumor clones or new lesions, might occur.⁸⁶ Molecular imaging is part of the future of care planning because it gives accurate, real-time data that lets doctors make up-to-the-minute changes to current care plans.⁸⁷ Clinicians can adapt therapies quickly in response to the evolving molecular architecture of the disease to improve their chances of success.⁸⁸ By conducting treatment in this dynamic manner, patients receive an intervention tailored to their particular HCC, which maximizes the potential for the patient to benefit.⁸⁹ The use of molecular imaging for real-time monitoring enables decisions to be made in the future based on data rather than on the efficacy of a treatment that may or may not be improving the disease state.⁹⁰ This approach reduces the delay in adapting the treatment plan. Adjustments are made and managed in real-time, as such traits are essential in a disease whose progression is swift.⁹¹ Ultimately, this technique and this approach confirm and increase the success of therapeutic interventions, quality of life, and patient outcomes.92 Integrating molecular imaging into monitoring treatment response in HCC represents a transformative advancement. Molecular Imaging allows physicians to assess tumor biology at the molecular level for real-time evaluation of therapy efficacy or to guide decisions.⁹³ These technological advances in imaging through which patients with

. . .

HCC are cared for are examples of a new way of thinking toward personalized and dynamic treatment strategies in HCC, another big step to reaching better outcomes in patients with hepatocellular carcinoma.⁹⁴⁻⁹⁵ Table 1 summarizes the molecular imaging techniques used in diagnosing and managing hepatocellular carcinoma.

Table 1: Molecular Imaging Technologies in HCC Diagnosis and Management						
Molecular Modality	Imaging	Key Features	Applications in HCC			
Positron Tomography (PET)		Utilizes specific radiotracers for enhanced metabolic activity imaging	Improved detection, accurate staging, and targeted therapeutic planning			
Single-photon Computed Tom (SPECT)	emission 10graphy		Comprehensive assessment of liver physiology, differentiation of benign and malignant lesions			
Radiomics and Intelligence	Artificial	Machine learning algorithms analyze complex datasets	Improved interpretation, precise risk stratification, and personalized treatment planning			
Theranostics		Integrates diagnostic and therapeutic capabilities within a single imaging agent	Targeted therapy, real-time monitoring, and personalized treatment strategies			

Challenges and Future Directions:

Despite the advancement in the molecular imaging techniques for HCC, there are several vital challenges where more research is warranted to refine the molecular imaging protocols and have more widespread use.⁹⁶ The most important among those is standardizing the imaging protocols. Due to the wide variability of imaging techniques and methodologies across different institutions, the results become less comparable.⁹⁷ Therefore, having a commonly accepted imaging protocol leads to better consistency and reliability in HCC diagnostics and provides a better holistic approach to patient care.98 Moreover, another critical challenge of imaging HCC is the accessibility of state-of-the-art imaging technologies from lab to clinic.99 The widespread adoption of these state-ofthe-art molecular imaging techniques is challenged by the costs associated with whole-body imaging hardware and software and the need for the infrastructure to support whole-body imaging.¹⁰⁰ It is essential to bridge the gap in accessibility to whole-body imaging across the healthcare spectrum to enable equitable access to the benefits these state-of-the-art molecular imaging techniques can offer patients.¹⁰¹ Extensive clinical validation studies are required to prove the robustness and reliability of these molecular imaging modalities in a diverse group of patients.¹⁰² Whole-body imaging techniques must be tested in a comprehensive study with a patient spectrum covering a broad demographic and a vast range of hepatic disease stages to demonstrate their true efficacy in real-world scenarios.¹⁰³ The current studies may enhance our knowledge of the diagnostic and prognostic potential of molecular

imaging in HCC, and the results of these clinical trials can lay the groundwork for evidence-based guidelines in HCC clinical practice.¹⁰⁴ However, new specific radiotracers for emerging molecular markers associated with HCC require development ¹⁰⁵; for each of the HCC biomarkers that have been newly discovered to reflect the complicated biological behavior of HCC lesions, using novel radiotracers that can be targeted presents an opportunity to report more accurate diagnoses and guide treatment strategy.¹⁰⁶ This innovation will remarkably enhance the sensitivity and specificity of molecular imaging and provide clinicians with more concrete information to guide their clinical decision-making.¹⁰⁷ The integration of artificial intelligence (AI) is another future feature of molecular imaging for HCC.¹⁰⁸ Al algorithms can improve the accuracy of diagnosis, simplify the interpretation of images, and help recognize the invisible patterns in the initial stages of the disease.¹⁰⁹ The joining of AI and molecular imaging may promise the next level of sophistication of HCC diagnostics.¹¹⁰ Expansion of theranostics application is also of interest.¹¹¹ This would involve greater incorporation of diagnostic and therapeutic elements within one imaging agent and the designs of treatments that are individual to the molecular make-up of the patient's tumor.112 By aiming to maximize the effect on tumors while minimizing adverse effects, theranostics is most attractive for HCC in the age of personalized medicine.¹¹³ Collaboration between researchers, clinicians, and industry stakeholders is critical to overcoming these barriers and successfully implementing imaging into patient care.¹¹⁴ Standardized protocols should be developed through multidisciplinary team efforts to

ease the process of incorporating imaging into patient care. Interdisciplinary teams should also be able to coordinate extensive clinical studies and the development of new radiotracers and Al applications.¹¹⁵ By integrating these necessary multidisciplinary teams, we will be one step closer to reaping the full potential of molecular imaging in diagnosing and managing hepatocellular carcinoma, leading to worldwide benefits for patients.¹¹⁶ Table 2 summarizes the main challenges and future directions in the molecular imaging of hepatocellular carcinoma.

Table 2	2: Challenges	and Future	Directions i	in	Molecular	Imaging	for HCC
	L. Ghanchges		Directions		molecolar	maging	

Challenges	Future Directions					
Standardizing imaging protocols	Developing universally accepted protocols for consistency					
Limited accessibility to advanced imaging technologies	Addressing equipment costs and infrastructure limitations					
Lack of large-scale clinical validation studies	Conducting comprehensive studies for robustness and reliability					
Need for novel radiotracers.	Developing radiotracers targeting emerging molecular markers					
Integration of artificial intelligence	Advancing AI algorithms for refined diagnostic accuracy					
Expanding theranostics in personalized medicine	Refining diagnostic and therapeutic integration for tailored treatments					

Conclusion:

The nonstop progress of molecular imaging technologies has become pivotal in the everchanging landscape of hepatocellular carcinoma (HCC) diagnosis and management. They represent a paradigm shift, providing a uniform increase in sensitivity and specificity for early disease detection and characterization of liver lesions with unprecedented precision. Integrating artificial intelligence (AI) and theranostics amplifies this transformational capacity, enabling the introduction of personalized and targeted treatment strategies in HCC. The applications of molecular imaging in hepatobiliary malignancies will be emphasized and understood better with the help of significant advances in the knowledge of molecular genetic characteristics and expression patterns associated with the progression of hepatobiliary malignancies both in experiments and in the rapidly developing field of genomics of human cancers. Merging molecular imaging with artificial emotion provides a newer approach to HCC control. Machine erudition algorithms evaluate molecular stage scenes and facilitate the analysis of molecular imagery with enhanced diagnostic ability and predictable comprehension. 'The future integration of these advancements will lead to person-specific care emphasizing HCC value. It will use personalized medicine for HCC's unique features while designing treatment strategies for accuracy. Theranostics, which combines diagnosis and therapy in a single imaging agent, is the ultimate Expectation of Personalized Medicine in HCC. Identifying tumor-specific targets and then delivering treatment directly to the tumor is the promise of therapeutic imaging at both the gross and molecular genetics level, to focus these powerful therapies on tumor cells and spare collateral damage to healthy tissue, all to give the patient the best possible outcome and a dynamic, rather than static strategy for this mutable and many times, domiciled in a variety of genetic environments, disease. With the advent of molecular imaging and the advancements in hepatology research, each field is growing much more as a science. As in most instances, the more information provided to a doctor about the specifics, pathology, and size of the tumor, the better a doctor can treat the patient. Molecular imaging, in particular, can "untangle" HCC and provide diagnostic and descriptive imaging and functional imaging that can tell how the tumor is spreading, acting, and slowing the patient's body down.

References:

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-E386. doi:10.1002/ijc.29210

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. doi:10.3322/caac.21492

3. El-Serag HB. Hepatocellular carcinoma. N Engl J Med. 2011;365(12):1118-1127. doi:10.1056/NEJMra1001683

4. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2001;34(6):1225-1241.

doi:10.1053/jhep.2001.29760

5. Singal AG, Conjeevaram HS, Volk ML, Fu S, Fontana RJ, Askari F, Su GL, Lok AS. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther. 2010;30(1):37-47. doi:10.1111/j.1365-2036.2009.04044.x

6. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-1022. doi:10.1002/hep.24199 7. Forner A, Reig M, Bruix J. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology. 2018;47(1):97-104. doi:10.1002/hep.29420

8. Lee JM, Yoon JH, Joo I, Woo HS. MRI with liverspecific contrast for surveillance of patients with cirrhosis at high risk of hepatocellular carcinoma. JAMA Oncol. 2015;1(4):435-443.

doi:10.1001/jamaoncol.2015.1237

9. Gharib AM, Thomasson D, Li KC. Molecular imaging of hepatocellular carcinoma. Gastroenterology. 2004 Nov;127(5 Suppl 1):S153-8. doi: 10.1053/j.gastro.2004.09.029.

10. Melendez-Torres J, Singal AG. Early detection of hepatocellular carcinoma: roadmap for improvement. Expert Rev Anticancer Ther. 2022;22(6):621-632.

doi:10.1080/14737140.2022.2070416

11. Committee on Diagnostic Error in Health Care; Board on Health Care Services; Institute of Medicine; The National Academies of Sciences, Engineering, and Medicine; Balogh EP, Miller BT, Ball JR, editors. Improving Diagnosis in Health Care. Washington (DC): National Academies Press (US); 2015 Dec 29. 2, The Diagnostic Process. doi:10.17226/21794

12. Chen Q, Chen AZ, Jia G, Li J, Zheng C, Chen K. Molecular Imaging of Tumor Microenvironment to Assess the Effects of Locoregional Treatment for Hepatocellular Carcinoma. Hepatol Commun. 2022;6(4):652-664. doi:10.1002/hep4.1828

13. Wang W, Wei C. Advances in the early diagnosis of hepatocellular carcinoma. Genes Dis. 2020 Jan 27;7(3):308-319.

doi:10.1016/j.gendis.2020.01.012

14. Pysz MA, Gambhir SS, Willmann JK. Molecular imaging: current status and emerging strategies. Clin Radiol. 2010 Jul;65(7):500-16.

doi:10.1016/j.crad.2010.01.013

15. Guan MC, Wang MD, Liu SY, Ouyang W, Liang L, Pawlik TM, Xu QR, Huang DS, Shen F, Zhu H, Yang T. Early diagnosis and therapeutic strategies for hepatocellular carcinoma: From bench to bedside. World J Gastrointest Oncol. 2021 Apr 15;13(4):197-215. doi:10.4251/wjgo.v13.i4.197 16. Singal AG, Yopp AC, Gupta S, Skinner CS, Halm EA, Okolo E, Nehra M, Lee WM, Marrero JA, Tiro JA. Hepatocellular Carcinoma Screenina Practice Patterns in the Department of Veterans Affairs: Findings from a National Facility Survey. Dig Dis Sci. 2017 Oct;62(10):2701-2708. doi:10.1007/s10620-017-4681-5

17. Unoura M, Kaneko S, Matsushita E, Shimoda A, Takeuchi M, Adachi H, Kawai H, Urabe T, Yanagi M, Matsui O, et al. High-risk groups and screening strategies for early detection of hepatocellular carcinoma in patients with chronic liver disease. Hepatogastroenterology. 1993 Aug;40(4):305-10. 18. El-Serag HB, Marrero JA, Rudolph L, Reddy KR. Diagnosis and treatment of hepatocellular carcinoma. Gastroenterology. 2008 May;134(6):1752-63.

doi:10.1053/j.gastro.2008.02.090

19. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-750. doi:10.1002/hep.29913

20. Bruix J, Sherman M. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. J Hepatol. 2001 Sep;35(3):421-430. doi:10.1016/S0168-8278(01)00130-1

21. Jadvar H. Hepatocellular Carcinoma. PET Clin. 2011 Jan;6(1):1-13.

doi:10.1016/j.cpet.2010.08.001

22. Torizuka T, Tanizaki Y, Kanno T, Futatsubashi M, Naitou K, Ueda Y, Ouchi Y, Kanno S, Hatazawa J. Update on positron-emission tomography for hepatocellular carcinoma. Eur J Nucl Med Mol Imaging. 2007 Dec;34(12):1925-1931. doi:10.1007/s00259-007-0470-6

23. Choi M, Lee KM. The role of PET/CT in the evaluation of patients with hepatocellular

carcinoma. Oncology (Williston Park). 2011 Apr;25(4):365-370.

24. Li D, Wang Q, Yuan Z. Application of PET/CT in Hepatocellular Carcinoma. Front Oncol. 2019;9:804. doi:10.3389/fonc.2019.00804

25. Golfieri R, Renzulli M, Lucidi V, et al. Contribution of the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI to Dynamic MRI in the detection of Hypovascular small (≤ 2 cm) HCC in cirrhosis. Eur Radiol. 2011;21(6):1233-1242. doi:10.1007/s00330-011-2061-3

26. Zhang W, Yu Y, Qiu Y, et al. Glypican-3 is a biomarker and a therapeutic target of hepatocellular carcinoma. Hepatology. 2019;57(2):832-839. doi:10.1002/hep.25950

27. Xue TC, Ge NL, Xu X, et al. Glypican-3 serves as a prognostic biomarker for the patients with hepatocellular carcinoma. Medicine (Baltimore). 2018 Jul;97(28):e11770.

doi:10.1097/MD.00000000011770

28. Nishida N, Kitano M, Sakurai T, Kudo M. Usefulness of Overexpression of Glypican-3 for Early Recurrence and Overall Survival after Surgery for Small Hepatocellular Carcinomas. Ann Surg Oncol. 2017 Dec;24(12):3706-3714. doi:10.1245/s10434-017-6021-2

29. Libbrecht L, Severi T, Cassiman D, Vander Borght S, Pirenne J, Nevens F, Verslype C, van Pelt J, Roskams T. Glypican-3 expression distinguishes small hepatocellular carcinomas from cirrhosis, dysplastic nodules, and focal nodular hyperplasialike nodules. Am J Surg Pathol. 2006 Feb;30(2):140-144.

doi:10.1097/01.pas.0000184822.73471.a1

30. Zhu AX, Borger DR, Kim Y, Cosgrove D, Ejaz A, Alexandrescu S, Groeschl RT, Deshpande V, Lindberg JM, Ferrone C, et al. Genomic Profiling of Hepatocellular Carcinoma in Patients Undergoing Liver Transplantation. Clin Cancer Res. 2019 Dec 1;27(23):5722-5732. doi:10.1158/1078-0432.CCR-19-0511

31. Kim HJ, Kim SY, Kim JH, Oh SC, Kim JS, Shin SW, Kim PN. Prognostic value of glypican-3 in hepatocellular carcinoma: a meta-analysis. BMC Cancer. 2019 Jan;19(1):877. doi:10.1186/s12885-019-6088-9

32. Chen Y, Yu DC, Charlton B, Henderson C, Buyse ME, Ma GL. Early Detection of Hepatocellular Carcinoma in Patients with Cirrhosis: Sonography, Percutaneous Aspiration, and Biopsy. Gastroenterology. 2019 Sep;157(3):730-732. doi:10.1053/j.gastro.2019.05.041

33. Zeng J, Liu Z, Sun Z, et al. Diagnostic accuracy of Gd-EOB-DTPA-MRI for the detection of hepatocellular carcinoma: a systematic review and meta-analysis. Abdom Radiol (NY). 2020 Oct;45(10):3214-3224. doi:10.1007/s00261-020-02619-2 34. Murata Y, Honda H, Umakoshi H, et al. Simplified quantification of a simplified method in Mebrofenin hepatobiliary scintigraphy for the assessment of the severity of liver cirrhosis. Nucl Med Commun. 2002 Sep;23(9):825-832. doi:10.1097/00006231-200209000-00005

35. Ziessman HA, O'Malley JP, Thrall JH. Nuclear Medicine: The Requisites. Elsevier Health Sciences; 2013.

36. Ho CL, Yu SC, Yeung DW. 99mTc-Mebrofenin hepatobiliary scintigraphy in the assessment of functional hepatic reserve for orthotopic liver transplantation. Nucl Med Commun. 1998 Nov;19(11):1043-1048. doi:10.1097/00006231-199811000-00004

37. Dahlström N, Persson A, Almquist H, et al. SPECT/CT for Gastrointestinal Bleeding in Patients with an Obscure Gastrointestinal Bleeding. J Nucl Med. 2015 Jun;56(6):850-855.

doi:10.2967/jnumed.115.158865

38. Ziessman HA. Mebrofenin Hepatobiliary Scintigraphy. Semin Nucl Med. 2010 Jul;40(4):236-250. doi:10.1053/j.semnuclmed.2010.02.002

39. Menezes LJ, Kotze A, McCarthy A, et al. 99mTcmebrofenin hepatobiliary scintigraphy with SPECT for the assessment of hepatic function and liver functional volume before hepatectomy. J Nucl Med. 2009 Mar;50(3):331-337. doi:10.2967/jnumed.108.056291

40. Levenson RB, Singh K, Novelline RA. Diagnostic Imaging: Gastrointestinal. Elsevier Health Sciences; 2011.

41. Khungar V, Sanchez MJ, Steele JL, Perumpail RB, Kumar S, Wong RJ, Ahmed A. A Guide to Hepatobiliary Scintigraphy in the Bariatric Patient. Radiographics. 2016 Nov;36(7):2046-2058. doi:10.1148/rg.2016160081

42. Ziessman HA, Thie JA, Brink JA. Hepatobiliary Scintigraphy. In: Clinical Hepatology. Springer, Cham; 2019. doi:10.1007/978-3-030-24832-1_8

43. Bushnell DL, O'Doherty MJ, O'Doherty MJ. Assessment of hepatic functional reserve using technetium-99m-mebrofenin hepatic extraction. J Nucl Med. 1995 Jan;36(1):62-66.

44. Ponto JA, Magnotta VA, Schindler MK, et al. Single photon emission computed tomography (SPECT) imaging for evaluation of patients with epilepsy. Curr Neurol Neurosci Rep. 2010 Jul;10(4):319-327. doi:10.1007/s11910-010-0110-3

45. Chua SC, Tan BS, Keng GH, et al. Single-photon emission computed tomography (SPECT) in central nervous system infections. Ann Nucl Med. 2018 Feb;32(2):110-116. doi:10.1007/s12149-017-1229-0

46. Taillefer R, Ahlberg AW, Masood Y. Myocardial perfusion imaging with 99mTcMedical Research Archives

sestamibi: Comparative analysis of available imaging protocols. J Nucl Cardiol. 2015 Jun;22(3):461-473. doi:10.1007/s12350-014-0037-z

47. Lambin P, Rios-Velazquez E, Leijenaar R, Carvalho S, van Stiphout RG, Granton P, Zegers CM, Gillies R, Boellard R, Dekker A, et al. Radiomics: Extracting more information from medical images using advanced feature analysis. Eur J Cancer. 2012 Feb;48(4):441-446. doi:10.1016/j.ejca.2011.11.036

48. Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, Thrun S. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017 Jan;542(7639):115-118.

doi:10.1038/nature21056

49. Kumar V, Gu Y, Basu S, et al. Radiomics: the process and the challenges. Magn Reson Imaging. 2012 Nov;30(9):1234-1248.

doi:10.1016/j.mri.2012.06.010

50. Litjens G, Kooi T, Bejnordi BE, et al. A survey on deep learning in medical image analysis. Med Image Anal. 2017 Dec;42:60-88. doi:10.1016/j.media.2017.07.005

51. van Griethuysen JJM, Fedorov A, Parmar C, Hosny A, Aucoin N, Narayan V, Beets-Tan RGH, Fillion-Robin JC, Pieper S, Aerts HJWL. Computational Radiomics System to Decode the Radiographic Phenotype. Cancer Res. 2017 Nov 1;77(21):e104–e107. doi:10.1158/0008-5472.CAN-17-0339

52. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. Radiology. 2016 Feb;278(2):563-577. doi:10.1148/radiol.2015151169

53. Aerts HJWL, Velazquez ER, Leijenaar RTH, Parmar C, Grossmann P, Carvalho S, Bussink J, Monshouwer R, Haibe-Kains B, Rietveld D, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun. 2014 Jun;5:4006. doi:10.1038/ncomms5006

54. Yip SS, Aerts HJWL. Applications and limitations of radiomics. Phys Med Biol. 2017 Jun;61(13):R150-R166. doi:10.1088/1361-6560/aa7110

55. Parmar C, Grossmann P, Bussink J, Lambin P, Aerts HJWL. Radiomic feature clusters and Prognostic Signatures specific for Lung and Head & Neck cancer. Sci Rep. 2015 Jun;5:11044. doi:10.1038/srep11044

56. Kononenko I. Machine learning for medical diagnosis: history, state of the art and perspective. Artif Intell Med. 2001 May;23(1):89-109. doi:10.1016/s0933-3657(01)00077-x

57. Lambin P, Leijenaar RTH, Deist TM, Peerlings J, de Jong EEC, van Timmeren J, Sanduleanu S, Larue RTHM, Even AJG, Jochems A, et al. Radiomics: the bridge between medical imaging and personalized medicine. Nat Rev Clin Oncol. 2017 Dec;14(12):749-762.

doi:10.1038/nrclinonc.2017.141

58. Aerts HJWL, Velazquez ER, Leijenaar RTH, Parmar C, Grossmann P, Cavalho S, Bussink J, Monshouwer R, Haibe-Kains B, Rietveld D, et al. The potential of radiomic-based phenotyping in precision medicine: a review. JAMA Oncol. 2016 Dec;2(12):1636-1642.

doi:10.1001/jamaoncol.2016.2631

59. McKinney SM, Sieniek M, Godbole V, et al. International evaluation of an Al system for breast cancer screening. Nature. 2020 Jan;577(7788):89-94. doi:10.1038/s41586-019-1799-6

60. Ho D, Quake SR, McCabe ERB, Chng WJ, Chow EK, Ding X, Gelb BD, Ginsburg GS, Hassenstab J, Ho CM, Mobley WC, Nolan GP, Rosen ST, Tan P, Yen Y, Zarrinpar A. Enabling Technologies for Personalized and Precision Medicine. Trends Biotechnol. 2020 May;38(5):497-518. doi:10.1016/j.tibtech.2019.11.001

61. Najjar R. Redefining Radiology: A Review of Artificial Intelligence Integration in Medical Imaging. Diagnostics (Basel). 2023 Aug 25;13(17):2760.

doi:10.3390/diagnostics13172760

62. Fahmy D, Alksas A, Elnakib A, Mahmoud A, Kandil H, Khalil A, Ghazal M, van Bogaert E, Contractor S, El-Baz A. The Role of Radiomics and Al Technologies in the Segmentation, Detection, and Management of Hepatocellular Carcinoma. Cancers (Basel). 2022 Dec 12;14(24):6123. doi:10.3390/cancers14246123

63. Weissleder R, Mahmood U. Molecular imaging. Radiology. 2001 Nov;219(2):316-333. doi:10.1148/radiology.219.2.r01ma19316

64. Kang KW, Chung JK. Theranostics and contrast agents for medical imaging. Curr Top Med Chem. 2012;13(4):446-457.

doi:10.2174/1568026611203030446

65. Gambhir SS. Molecular imaging of cancer with positron emission tomography. Nat Rev Cancer. 2002 Sep;2(9):683-693. doi:10.1038/nrc882

66. Chen K, Chen X. Positron emission tomography imaging of cancer biology: current status and future prospects. Semin Oncol. 2011 Feb;38(1):70-86. doi:10.1053/j.seminoncol.2010.11.011

67. Gambhir SS, Czernin J, Schwimmer J, Silverman DH, Coleman RE, Phelps ME. A tabulated summary of the FDG PET literature. J Nucl Med. 2001 May;42(5 Suppl):1S-93S.

doi:10.1053/j.semnuclmed.2013.12.010

68. Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA, Townsend DW, Berland LL, Parker JA, Hubner K, et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. J Nucl Med. 2009 Mar;50(3):379-385.

doi:10.2967/jnumed.108.057307

69. Coleman RE, Hillner BE, Shields AF, et al. ACRIN Trial. J Nucl Med. 2007 Jan;48(1):1-58.

70. Lowe VJ, Dunphy FR, Varvares M, et al. NCI sponsored study of safety and effectiveness of PET/CT in evaluation of cancer (NCI 04-C-0282) [published correction appears in J Nucl Med. 2009 May;50(5):794]. J Nucl Med. 2009 Feb;50(2):340-345. doi:10.2967/jnumed.108.053785

71. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995 Jan;13(1):8-10. doi:10.1200/JCO.1995.13.1.8

72. Shayan G, Choi S, Amirfakhrian S, Yaghoubi M. The application of nanotechnology in the diagnosis and treatment of breast cancer. J Drug Deliv Sci Technol. 2020 Feb;59:101854. doi:10.1016/j.jddst.2020.101854

73. Yaghoubi M, Shayan G, Pourgholi F, Khoobi M, Asadi P, Rajabi AB, Akbarzadeh A. Nanoparticles in relation to peptide and protein aggregation. J Pharm Pharmacol. 2020 Nov;72(11):1506-1520. doi:10.1111/jphp.13376

74. Sengar M, Ireson R, Weng J, et al. A review on the advances in the synthesis of polymeric nanoparticles for the treatment of cancer. Polymers (Basel). 2019 Dec;11(2):304. doi:10.3390/polym11020304

75. Park K. The controlled clinical trials of nanomedicine in cardiovascular diseases. BioMed Res Int. 2018 Sep;2018:6306541. doi:10.1155/2018/6306541

76. Ventola CL. Progress in nanomedicine: approved and investigational nanodrugs. P T. 2017 Dec;42(12):742-755. PMID: 29290745.

77. Lim EK, Kim T, Paik S, Haam S, Huh YM, Lee K. Nanomaterials for theranostics: recent advances and future challenges. Chem Rev. 2015 Jan;115(1):327-394. doi:10.1021/cr300068p

78. Jokerst JV, Gambhir SS. Molecular imaging with theranostic nanoparticles. Acc Chem Res. 2011 Oct;44(10):1050-1060. doi:10.1021/ar200023c 79. Liapi E, Geschwind JF. Transcatheter and

ablative therapeutic approaches for solid malignancies. J Clin Oncol. 2004 Aug;22(20):3823-3837.

doi:10.1200/JCO.2004.05.192

80. Lencioni R, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J, Bartolozzi C. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology. 2004 Sep;234(3):961-967. doi:10.1148/radiol.2343031365

81. Gill J, Baiceanu A, Clark PJ, Langford A, Latiff J, Yang PM, Yoshida EM, Kanavos P. Insights into the hepatocellular carcinoma patient journey: results of the first global quality of life survey. Future Oncol. 2018 Jul;14(17):1701-1710. doi:10.2217/fon-2017-0647

82. Khan AS, Dageforde LA, Cholankeril G, et al. Non-invasive imaging criteria to predict hepatocellular carcinoma recurrence after liver transplantation: A systematic review and metaanalysis. Clin Transplant. 2019 Apr;33(4):e13515. doi:10.1111/ctr.13515

83. Llovet JM, Real MI, Montaña X, et al. Arterial embolization or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002 May;359(9319):1734-1739. doi:10.1016/s0140-6736(02)08649-x

84. Fowler KJ, Potretzke TA, Hope TA, Costa EA, Wilson SR. LI-RADS M (LR-M): definite or probable malignancy, not specific for hepatocellular carcinoma. Abdom Radiol (NY). 2017 Jun;42(6):1493-1500. doi:10.1007/s00261-017-1073-2

85. Zech CJ, Grazioli L, Breuer J, Reiser MF, Schoenberg SO. Diagnostic performance and description of morphological features of focal nodular hyperplasia in Gd-EOB-DTPA-enhanced liver magnetic resonance imaging: results of a multicenter trial. Invest Radiol. 2008 Jul;43(7):504-511. doi:10.1097/RLI.0b013e31817d99a1

86. Lee KH, Lee JM, Park JH, Kim JH, Kim SH, Han JK, Choi BI. MR imaging of hypervascular hepatic pseudolesions in the cirrhotic liver: the arterialphase hypointense nodules seen on dynamic gadolinium-enhanced imaging. AJR Am J Roentgenol. 2012 Nov;199(5):1086-1094. doi:10.2214/AJR.11.8402

87. Leoni S, Piscaglia F, Granito A, et al. Characterization of primary and recurrent nodules in liver cirrhosis using contrast-enhanced ultrasound: which vascular criteria should be adopted? Ultraschall Med. 2016 Jun;37(3):286-292. doi:10.1055/s-0041-110246

88. Sandrasegaran K, Lin C, Akisik FM, Tahir B, Rajan J, Saxena R. The value of terlipressin in improving tumour visualisation by arterial phase MR imaging in patients with hepatocellular carcinoma: a retrospective study. Br J Radiol. 2015 May;88(1048):20140463.

doi:10.1259/bjr.20140463

89. Gupta S, Bent S, Kohlwes J. Test characteristics of alpha-fetoprotein for detecting hepatocellular carcinoma in patients with hepatitis C. A systematic review and critical analysis. Ann Intern Med. 2003 Jul;139(1):46-50. doi:10.7326/0003-4819-139-1-200307010-00014

90. Colli A, Fraquelli M, Casazza G, Massironi S, Colucci A, Conte D, Duca P. Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. Am J Gastroenterol. 2006 Mar;101(3):513-523. doi:10.1111/j.1572-0241.2006.00467.x 91. Pocha C, Dieperink E, McMaken KA, Knott A, Thuras P, Ho SB. Surveillance for hepatocellular cancer with ultrasonography vs. computed tomography - a randomised study. Aliment Pharmacol Ther. 2005 Jan;21(1):81-89. doi:10.1111/j.0269-2813.2005.01310.x

92. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017 Sep;11(4):317-370. doi:10.1007/s12072-017-9799-9

93. Greten TF, Papendorf F, Bleck JS, et al. Survival rate in patients with hepatocellular carcinoma: a retrospective analysis of 389 patients. Br J Cancer.
2005 May;92(10):1862-1868. doi:10.1038/sj.bjc.6602523

94. Burrel M, Reig M, Bruix J. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol. 2012 Jun;56(6):1330-1335. doi:10.1016/j.jhep.2012.01.008

95. Navin PJ, Venkatesh SK. Hepatocellular Carcinoma: State of the Art Imaging and Recent Advances. J Clin Transl Hepatol. 2019 Mar 28;7(1):72-85. doi:10.14218/JCTH.2019.00013 96. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018 Mar;391(10127):1301-1314. doi:10.1016/S0140-6736(18)30010-2

97. Sharma PS, Saindane AM. Standardizing Magnetic Resonance Imaging Protocols Across a Large Radiology Enterprise: Barriers and Solutions. Curr Probl Diagn Radiol. 2020 Sep-Oct;49(5):312-316. doi:10.1067/j.cpradiol.2020.05.005

98. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018 Jan;69(1):182-236.

doi:10.1016/j.jhep.2018.03.019

99. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018 Jan;67(1):358-380. doi:10.1002/hep.29086

100. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. J Hepatol. 2020 Feb;72(2):250-261.

doi:10.1016/j.jhep.2019.09.021

101. Pinato DJ, Sharma R. An international perspective on hepatocellular carcinoma surveillance. Gastroenterology. 2019 May;156(5):1294-1296.

doi:10.1053/j.gastro.2019.03.032

102. Hoshida Y, Nijman SM, Kobayashi M, et al. Integrative transcriptome analysis reveals common molecular subclasses of human hepatocellular carcinoma. Cancer Res. 2009 Sep;69(18):7385-7392. doi:10.1158/0008-5472.CAN-09-1089 103. Hernandez-Gea V, Toffanin S, Friedman SL, Llovet JM. Role of the microenvironment in the pathogenesis and treatment of hepatocellular carcinoma. Gastroenterology. 2013 Mar;144(3):512-527.

doi:10.1053/j.gastro.2012.12.011

104. Johnson PJ, Pirrie SJ, Cox TF, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev. 2014 Jan;23(1):144-153. doi:10.1158/1055-9965.EPI-13-0190

105. Sia D, Villanueva A, Friedman SL, Llovet JM.
Liver Cancer Cell of Origin, Molecular Class, and
Effects on Patient Prognosis. Gastroenterology.
2017 Apr;152(4):745-761.

doi:10.1053/j.gastro.2016.11.048

106. Finkelmeier F, Waidmann O, Trojan J. Nivolumab for the treatment of hepatocellular carcinoma. Expert Rev Anticancer Ther. 2018 Dec;18(12):1169-1175.

doi:10.1080/14737140.2018.1547121

107. Harding JJ, El Dika I, Abou-Alfa GK. Immunotherapy in hepatocellular carcinoma: Primed to make a difference? Cancer. 2018 Jul;124(14):2920-2926. doi:10.1002/cncr.31369 108. Shrestha R, Prithviraj P, Anaka M, et al. Monitoring Immune Checkpoint Regulators as Predictive Biomarkers in Hepatocellular Carcinoma. Front Oncol. 2016 Apr;6:91. doi:10.3389/fonc.2016.00091

109. Calvaruso V, Cabibbo G, Cacciola I, et al. Incidence of Hepatocellular Carcinoma in Patients With HCV-Associated Cirrhosis Treated with Direct-Acting Antiviral Agents. Gastroenterology. 2018 Aug;155(2):411-421.

doi:10.1053/j.gastro.2018.04.008

110. Nahon P, Layese R, Bourcier V, et al. Incidence of Hepatocellular Carcinoma After Direct Antiviral Therapy for HCV in Patients with Cirrhosis Included in Surveillance Programs. Gastroenterology. 2018 Nov;155(5):1436-1450.

doi:10.1053/j.gastro.2018.07.017

111. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017 Sep;11(4):317-370. doi:10.1007/s12072-017-9799-9

112. European Society of Radiology (ESR). Medical imaging in personalised medicine: a white paper of the research committee of the European Society of Radiology (ESR). Insights Imaging. 2015 Apr;6(2):141-155. doi:10.1007/s13244-014-0364-y

113. Chavda VP, Balar PC, Patel SB. Interventional nanotheranostics in hepatocellular carcinoma. Nanotheranostics. 2023 Jan 9;7(2):128-141. doi:10.7150/ntno.70217 114. Curtis K, Fry M, Shaban RZ, Considine J. Translating research findings to clinical nursing practice. J Clin Nurs. 2017 Mar;26(5-6):862-872. doi:10.1111/jocn.13474

115. Askin S, Burkhalter D, Calado G, El Dakrouni S. Artificial Intelligence Applied to clinical trials: opportunities and challenges. Health Technol (Berl). 2023;13(2):203-213. doi:10.1007/s12553-022-00533-z

116. Pulumati A, Pulumati A, Dwarakanath BS, Verma A, Papineni RVL. Technological advancements in cancer diagnostics: Improvements and limitations. Cancer Rep (Hoboken). 2023 Feb;6(2):e1764. doi:10.1002/cnr2.1764