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Advancing Hepatocellular Carcinoma Management Through Peritumoral Radiomics: Enhancing Diagnosis, Treatment, and Prognosis

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Abstract: Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is associated with high mortality rates due to late detection and aggressive progression. Peritumoral radiomics, an emerging technique that quantitatively analyzes the tissue surrounding the tumor, has shown significant potential in enhancing the management of HCC. This paper examines the role of peritumoral radiomics in improving diagnostic accuracy, guiding personalized treatment strategies, and refining prognostic assessments. By offering unique insights into the tumor microenvironment, peritumoral radiomics enables more precise patient stratification and informs clinical decision-making. However, the integration of peritumoral radiomics into routine clinical practice faces several challenges. Addressing these challenges through continued research and innovation is crucial for the successful implementation of peritumoral radiomics in HCC management, ultimately leading to improved patient outcomes.

Keywords: hepatocellular carcinoma, peritumoral radiomics, diagnostic Imaging, artificial intelligence, precision medicine

Introduction and Background

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the third leading cause of cancer-related death worldwide.[1] The high mortality rate associated with HCC is primarily due to its late detection and the aggressive nature of the disease, which often leads to early metastasis and recurrence.[2,3] Despite advances in therapeutic approaches, including surgical resection, liver transplantation, locoregional therapies, and systemic treatments such as tyrosine kinase inhibitors and immune checkpoint inhibitors, the overall prognosis for patients with HCC remains poor. This underscores the critical need for early detection, accurate prognostic assessment, and personalized treatment strategies.[4]

Radiomics, an emerging field that involves the extraction of large amounts of quantitative features from medical images using data-characterization algorithms, offers a promising approach to address these needs.[5] By converting imaging data into high-dimensional mineable data, radiomics has the potential to uncover disease characteristics that fail to be appreciated by the naked eye, thereby enhancing decision support in oncology.[6] In the context of HCC, radiomics has shown promise in improving diagnostic accuracy, predicting treatment response, and assessing prognosis.[7–9]

Early radiomics research predominantly focused on intratumoral radiomics, which analyzes the internal features of the tumor, such as shape, texture, and intensity. Studies have shown that these intratumoral features can be used to predict clinical outcomes, including overall survival, recurrence, and response to treatment in HCC patients.[10] For instance, magnetic resonance imaging (MRI) based radiomics has been widely applied to assess tumor characteristics and predict molecular markers such as PD-L2 expression, providing valuable information for guiding treatment strategies in HCC.[11] However, while intratumoral radiomics provides critical insights into the tumor itself, it does not account for the tumor microenvironment, which plays a vital role in cancer progression.

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While much of the early work in radiomics focused on the analysis of intratumoral regions, recent studies have highlighted the significance of peritumoral tissue—the area surrounding the tumor—in influencing tumor behavior and patient outcomes.[12,13] The peritumoral region is commonly defined as the area surrounding the tumor that expands outward from the tumor boundary, typically within 5–30 mm.[14,15] The peritumoral microenvironment is increasingly recognized as a critical component of cancer progression, involving complex interactions between the tumor and its surrounding tissues, including inflammation, angiogenesis, fibrosis, and immune response. For instance, Yu et al[16] demonstrated that radiomics in the peritumoral region were strong predictors of vessels encapsulating tumor clusters (VETC). Numerous studies, as summarized in Table 1, further highlight the significance of the peritumoral region in capturing key elements of the tumor microenvironment. These insights enhance our understanding of tumor aggressiveness, prognosis, and response to treatment, making peritumoral radiomics a promising tool for improving patient outcomes.[17]

The Significance of Peritumoral Radiomics in Hepatocellular Carcinoma

The peritumoral region is a dynamic zone where the tumor interacts with the surrounding normal liver parenchyma and the body's immune and vascular systems.[39,40] This area is often the site of critical processes such as tumor invasion, neovascularization, and immune evasion, which are essential for tumor growth and metastasis.[41] As such, the characteristics of the peritumoral tissue can provide valuable information about the aggressiveness of the tumor and the likelihood of metastasis or recurrence. A recent study by Zhang et al[42] explored the concept of "habitat imaging", focusing on the peritumoral microenvironment and its role in predicting recurrence-free survival (RFS) in HCC. By analyzing the spatial distribution and characteristics of various habitats within the tumor and its surrounding tissue, they identified specific peritumoral habitats that were strongly associated with early recurrence. Notably, the proportion of a particular habitat in the peritumoral tissue emerged as a significant factor, emphasizing that detailed analysis of the peritumoral region is not just supplementary but plays an active role in shaping the tumor's clinical behavior.

Radiomics provides a powerful tool for quantifying these microenvironmental changes in the peritumoral region.[43] By extracting features related to texture, shape, and intensity from medical images, peritumoral radiomics can capture the heterogeneity and complexity of the tumor microenvironment.[44] These radiomics features can then be correlated with clinical outcomes, providing non-invasive biomarkers for tumor aggressiveness and helping to stratify patients according to their risk of recurrence or metastasis.[45] For instance, texture analysis of the peritumoral region on contrast-enhanced computer tomography (CT) or MRI has been shown to correlate with various adverse clinical outcomes, such as early recurrence and poor overall survival.[46] These correlations underscore the critical role that the peritumoral microenvironment plays in determining the clinical behavior of HCC. By providing a detailed quantitative analysis of the peritumoral region, peritumoral radiomics enables a deeper understanding of the tumor microenvironment, which is pivotal in driving tumor aggressiveness and recurrence. As research in this field progresses, the integration of peritumoral radiomics into routine clinical practice could significantly enhance the precision of diagnosis, prognosis, and personalized treatment strategies for HCC patients, ultimately leading to better management of this challenging disease.

Comparison and Integration of Peritumoral and Tumor Radiomics

Both intratumoral and peritumoral radiomics offer unique and complementary insights into the biology of HCC. Recent studies have shown that peritumoral radiomics—analyzing the tissue surrounding the tumor—can achieve comparable predictive performance.[31] Peritumoral radiomics is not merely an adjunct to intratumoral analysis; rather, it captures distinct and complementary information that is not available from tumor-based models alone.[18]

The combination of intratumoral and peritumoral radiomics has been shown to further enhance predictive accuracy.[37] However, the integration of these two approaches requires careful consideration. Simply combining the regions as a single ROI is not sufficient.[31,38] Instead, advanced methods that leverage the distinct information from each region should be employed to maximize predictive performance.[31] For instance, Wang et al[36] demonstrated that a combined model integrating radiomics features from both the tumor and a 5-mm peritumoral region significantly improved the prediction of microvascular invasion (MVI) in HCC patients with small tumors (≤ 5 cm).

Table 1 Studies Based on Peritumoral Radiomics in HCC

Author	Year	Sample Size	Imaging Modality	Peritumoral Region Size	Predictive Outcome	Segmentation Method	Feature Extraction Method	AUC*
Shan et al[18]	2019	156	CT	2cm	Recurrence	Manually, A.K. software	A.K. software	0.79
Song et al[19]	2020	184	MRI	1mm, 3mm, and 5mm	RFS with TACE	Manually, ITK-SNAP	A.K. software	1mm, 0.658; 3mm, 0.714; 5mm, 0.707
Nebbia et al[20]	2020	99	MRI	1cm	MVI	Manually, not known	PyRadiomics	0.846
Dong et al[21]	2020	322	US	Uniform dilated half of the tumor radius	MVI	Manually, MITK	PyRadiomics	MVI – vs MVI +: 0.71; M1 vs M2: 0.752
Zhang et al[22]	2021	132	MRI	5mm	Recurrence after curative ablation	Manually, ITK-SNAP	PyRadiomics	0.549
Zhang et al[23]	2021	153	MRI	2mm and 5mm	RFS with surgical resection	Manually, ITK-SNAP	PyRadiomics	2mm: 0.657; 5mm: 0.657
Yu et al[16]	2022	182	MRI	1cm	VETC	Manually, 3D Slicer	PyRadiomics	0.972
Chen et al[24]	2021	595	CT	5mm, 1cm, and 2cm	OR to TACE	Manually, 3D Slicer	PyRadiomics	5mm, 0.55; 1cm, 0.53; 2cm, 0.52
Yang et al[25]	2021	201	MRI	1cm	MVI	Manually, A.K. software	A.K. software	0.714
Gao et al[15]	2022	115	MRI	5mm	MVI	Manually, 3D Slicer	PyRadiomics	0.796
Liu et al[26]	2022	267	CT	3mm, 5mm	OS after hepatectomy	Manually, 3D Slicer	PyRadiomics	3mm: 0.785; 5mm: 0.734
Dong et al[27]	2022	100	US	5mm	MVI	Manually, 3D Slicer	PyRadiomics	0.8
Jiang et al[28]	2023	102	MRI	0–10mm	MVI	Manually, ITK-SNAP	PyRadiomics	2mm: 0.835
Kang et al[29]	2023	160	CT	1–5mm	ER	Manually, ITK-SNAP	A.K. software	3mm: 0.807
Zhao et al[30]	2023	138	MRI	3mm, 5mm, and 1cm	Response to TACE	Manually, ITK-SNAP	A.K. software	3mm: 0.823; 5mm: 0.823; 1cm: 0.793
Qian et al[31]	2023	118	US	2cm	Ki-67	Manually, ITK-SNAP	PyRadiomics	0.772
Dong et al[32]	2024	221	MRI	1cm	VETC	Manually, 3D Slicer	PyRadiomics	0.844
Shi et al[33]	2024	164	CT	5mm, and 1cm	Response to TACE	Manually, 3D Slicer	PyRadiomics	5mm: 0.936; 1cm: 0.940
Qian et al[17]	2024	153	US	2cm	Differentiation, CK7, Ki67, and p53	Manually, ITK-SNAP	PyRadiomics	Differentiation: 0.815; CK7: 0.922; Ki67: 0.762; p53: 0.849
Yang et al[34]	2024	219	MRI	1cm	VETC and MVI	Manually, 3D Slicer	PyRadiomics	0.82
Hashimoto et al[35]	2024	71	CT	5mm	Recurrence after TACE	Manually, 3D Slicer	PyRadiomics	0.773
Wang et al[36]	2024	206	CT	5mm, and 1cm	MVI	Semi-automatic, Radiomics software platform	Radiomics software	5mm: 0.759; 1cm: 0.693
Zhang et al[37]	2024	190	CT	1cm	VETC	Manually, Radcloud platform	Radcloud platform	0.788
Liu et al[38]	2024	265	MRI	5mm, 1cm, and 2cm	Differentiation	Manually, ITK-SNAP	PyRadiomics	5mm: 0.84; 1cm: 0.87; 2cm:0.73

Abbreviations: AUC, area under curve; CT, computer tomography; MRI, magnetic resonance imaging; RFS, recurrence-free survival; MVI, microvascular invasion; US, ultrasound; VETC, vessels encapsulating tumor clusters; OR, objective response; OS, overall survival; ER, early recurrence; TACE, transarterial chemoembolization; CK7, cytokeratin 7; *: best AUC in the test/validation/external validation group.

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By combining both peritumoral and intratumoral radiomics with appropriate methods, we can achieve more accurate diagnostic and prognostic predictions, ultimately leading to improved patient stratification and personalized treatment strategies.

Diagnostic Applications of Peritumoral Radiomics

Peritumoral radiomics has emerged as a valuable tool in the diagnosis and differential diagnosis of HCC. Traditional imaging modalities, such as contrast-enhanced CT and MRI, primarily focus on visualizing the tumor itself, often overlooking the surrounding tissue. However, by incorporating peritumoral analysis, clinicians can gain additional diagnostic information that enhances the accuracy of HCC diagnosis and helps differentiate it from other liver lesions, such as intrahepatic cholangiocarcinoma or benign liver nodules.[47] The ability of peritumoral radiomics to assess subtle differences in tissue characteristics around the tumor contributes to more precise and earlier detection of HCC.[48]

One of the critical areas where peritumoral radiomics has shown significant promise is in the detection of MVI, a major prognostic factor in HCC.[36] MVI is typically classified based on the extent of vascular invasion from the tumor margin, with categories such as ≤1cm or >1cm. Tumors with MVI located within 1cm of the tumor boundary are generally associated with more aggressive behavior and a higher likelihood of recurrence.[49] MVI is associated with a higher risk of recurrence and poorer overall survival, making its early detection crucial for guiding treatment decisions.[50,51] However, conventional imaging techniques often struggle to identify MVI preoperatively.[52] Peritumoral radiomics offers a non-invasive and highly accurate method to predict MVI, enhancing the diagnostic capabilities beyond what is achievable with traditional biomarkers.[28] Several studies have demonstrated that radiomics models incorporating peritumoral features can significantly improve the predictive performance compared to those relying solely on intratumoral characteristics.[21,36,53] In peritumoral radiomics, the size of the peritumoral region is crucial for predicting MVI. Larger regions (eg, 15–30mm) are often analyzed to capture broader microenvironmental changes, while smaller regions closer to 1cm have been shown to offer the most specific insights into microvascular invasion. Evidence suggests that the peritumoral region around 1cm is most suitable for MVI prediction, as it effectively captures both local invasion and critical tissue interactions near the tumor boundary.[54,55]

In addition to improving the detection of MVI, peritumoral radiomics also plays a crucial role in assessing pathological outcomes.[31,56] Our previous study highlights the potential of ultrasound-based radiomics models to predict important biological characteristics of HCC, such as tumor differentiation, cytokeratin 7 (CK7) expression, Ki67 proliferation index, and p53 mutation status.[17] These models demonstrated impressive predictive performance, with AUC values of 0.815 (0.683–0.948) for differentiation, 0.922 (0.785–1) for CK7 expression, 0.762 (0.618–0.906) for Ki67 expression, and 0.849 (0.667–1) for p53 mutation status. Each of these biological markers carries significant clinical implications. Tumor differentiation reflects the grade of the cancer, with poorly differentiated tumors typically exhibiting more aggressive behavior and worse prognosis.[57] CK7 is a crucial immunohistochemical marker used to determine the origin of liver tumors and to assess the potential for intrahepatic metastasis.[58] The Ki67 index is a marker of cellular proliferation, where higher levels indicate more rapid tumor growth and, consequently, a more aggressive disease course.[59] Finally, p53 is a tumor suppressor gene, and mutations in p53 are often associated with poor outcomes, including resistance to therapy and higher rates of recurrence.[60] The ability of peritumoral radiomics to accurately predict these markers preoperatively can greatly enhance personalized treatment planning, allowing for better stratification of patients according to their risk profiles and tailoring of therapeutic strategies accordingly.

Treatment Applications of Peritumoral Radiomics

Peritumoral radiomics is increasingly being recognized for its potential to guide and optimize treatment strategies in HCC.[61] The heterogeneity and dynamic nature of the peritumoral microenvironment play a crucial role in determining the tumor's response to various treatments.[62] By analyzing radiomics features from the peritumoral region, clinicians can gain insights into the likely efficacy of therapeutic approaches, leading to more personalized and effective treatment plans.

One of the key areas where peritumoral radiomics has shown promise is in predicting the outcomes of surgical interventions. Surgery remains a primary curative option for HCC, especially in early-stage patients. However, recurrence rates after surgery are high due to the aggressive nature of the disease.[63] Recent studies have demonstrated that

radiomics features from the peritumoral region can help predict the likelihood of recurrence following resection, providing valuable information for risk stratification and post-operative management.[18,29,48]

In addition to surgery, peritumoral radiomics has been particularly valuable in predicting the response to transarterial chemoembolization (TACE), a widely used locoregional therapy for intermediate-stage HCC. TACE works by delivering chemotherapy directly to the tumor while simultaneously blocking its blood supply, but its effectiveness can vary widely among patients.[64] Peritumoral radiomics offers a non-invasive method to predict which patients are likely to respond well to TACE. Zhao et al[30] developed a model based on MRI-derived radiomics features from the intratumoral and peritumoral regions, which accurately predicted TACE response and helped identify patients who would benefit most from this treatment. Additionally, Wang et al[65] demonstrated that a deep learning model incorporating both intratumoral and peritumoral radiomics features could effectively predict both time-to-progression (TTP) and overall survival (OS) in patients undergoing TACE, further validating the utility of peritumoral radiomics in optimizing TACE outcomes.

Hepatic arterial infusion chemotherapy (HAIC) is another locoregional therapy where radiomics and deep learning has shown promise in improving treatment predictions.[66] Studies focusing on tumor-based radiomics features have demonstrated significant success in predicting HAIC outcomes.[67] For example, tumor radiomics has been effective in stratifying patients based on their response to HAIC, helping to tailor more personalized treatment plans.[68] While the role of peritumoral radiomics in HAIC remains underexplored, future research may investigate whether incorporating features from the peritumoral region could enhance predictive performance, particularly in identifying patients most likely to benefit from this therapy. However, current evidence is limited, and further studies are needed to validate these potential applications.

Similarly, peritumoral radiomics has been explored as a tool for predicting the efficacy of radiofrequency ablation (RFA), another locoregional therapy commonly used in HCC.[18,22] RFA destroys tumor tissue through heat, but its success depends on complete ablation of both the tumor and surrounding peritumoral tissue.[69,70] Radiomics features that reflect the degree of fibrosis, inflammation, and tissue heterogeneity in the peritumoral region have been associated with better RFA outcomes, guiding patient selection and treatment planning.[61,71]

Beyond locoregional therapies, peritumoral radiomics is also being investigated for its role in predicting the efficacy of targeted and immunotherapies, which are increasingly used in HCC.[72,73] Targeted therapies, such as sorafenib, and immune checkpoint inhibitors have shown promise, but not all patients respond to these treatments.[74–76] The ability to stratify patients based on radiomics features from the peritumoral microenvironment could help in selecting those most likely to benefit from these therapies. Recent studies have found that certain peritumoral radiomics features, such as angiogenesis and immune cell infiltration patterns, correlate with improved responses to targeted agents and immunotherapies.[7,77]

Prognostic Applications of Peritumoral Radiomics

Prognostication is a critical aspect of HCC management, as it directly influences decisions regarding treatment intensity, follow-up schedules, and patient counseling. Traditional prognostic models for HCC often rely on clinical factors such as tumor size, number of lesions, serum alpha-fetoprotein levels, and liver function status.[78,79] While these factors are important, they do not fully capture the biological heterogeneity of HCC, which is a key determinant of patient outcomes.[80] Peritumoral radiomics offers a novel approach to enhancing prognostic assessments by incorporating information about the tumor microenvironment, which plays a crucial role in disease progression.

Several studies have demonstrated the prognostic value of peritumoral radiomics in predicting OS, disease-free survival (DFS), and RFS in HCC patients.[81] Liu et al[26] developed a radiomics nomogram that integrated both intratumoral and peritumoral radiomics features with clinical data, significantly improving the prediction of OS in patients undergoing hepatectomy compared to traditional models. The integration of peritumoral radiomics features allowed for a more refined stratification of patients, significantly improving the prediction of survival outcomes compared to traditional models.[44] And a recent study by Jingyu Wen et al[82] utilized dual-area CT radiomics to predict the expression levels of fatty acid-binding protein 4 in HCC, which is associated with tumor aggressiveness and patient survival.

Furthermore, the integration of peritumoral radiomics with molecular and genomic data holds promise for refining prognostic models in HCC. Combining radiomics features with molecular profiles allows for the development of comprehensive models that account for both imaging phenotypes and underlying tumor biology, thereby enhancing the precision of prognostic predictions. Chen et al demonstrated how radiomics combined with FOXM1 gene expression data

could serve as a powerful prognostic tool, linking radiomic features with specific molecular signatures and patient outcomes.[83] This integrated approach can significantly contribute to personalized medicine in HCC, enabling more tailored treatment strategies based on a patient's unique tumor characteristics.

Challenges and Future Directions of Peritumoral Radiomics

Despite the significant potential of peritumoral radiomics in enhancing HCC diagnosis, treatment prediction, and prognostication, several challenges and limitations hinder its clinical implementation. One of the primary issues is the lack of standardization in imaging protocols and radiomics feature extraction methods across different institutions and imaging modalities.[84,85] This variability can lead to inconsistent radiomics features being extracted from the same imaging data, which in turn limits the reproducibility and generalizability of radiomics models.[86]

Another significant challenge lies in the complexity of interpreting radiomics features. Unlike traditional imaging biomarkers, which are often straightforward (eg, tumor size or enhancement patterns), radiomics features are high-dimensional and may not directly correlate with underlying biological processes.[87] This complexity necessitates the development of advanced machine learning algorithms and statistical models capable of integrating radiomics data with clinical and molecular information to provide interpretable and actionable insights.[88]

Additionally, the integration of radiomics into the clinical workflow remains a hurdle. Currently, the application of radiomics is largely confined to research settings. For it to transition into routine clinical practice, there is a need for robust validation of radiomics models, development of user-friendly software tools, and comprehensive training of healthcare professionals in the interpretation and utilization of radiomics data.[89] Ensuring that these treatment-predictive models are accurate and generalizable across different clinical settings is also essential for their broader adoption.[90,91]

Overcoming these challenges will be critical for the successful implementation of peritumoral radiomics in the clinical management of HCC, ultimately leading to improved patient outcomes. To accelerate the integration of peritumoral radiomics into clinical practice, several key areas require further research and development:

Standardization of Imaging Protocols and Feature Extraction: The variability in imaging protocols across different institutions poses a significant challenge to the reproducibility and generalizability of radiomics models.[92] Establishing standardized imaging protocols, including parameters for image acquisition, preprocessing, and feature extraction, is critical to ensure consistency in radiomics analyses. Collaborative efforts to create universal guidelines, similar to those developed for other imaging modalities, will be instrumental in this regard.[93]

Multicenter Validation Studies: While many radiomics models have shown promise in single-center studies, their applicability across diverse patient populations and clinical settings remains to be confirmed. Large-scale, multicenter studies are needed to validate these models in various demographic groups, different stages of HCC, and across multiple imaging platforms.[94] Such studies will help establish the robustness and clinical utility of peritumoral radiomics in routine practice.

Integration with Genomics and Other Biomarkers: The future of precision oncology lies in the integration of multi-omic data, where radiomics, genomics, proteomics, and other biomarkers are combined to provide a comprehensive understanding of tumor biology.[95] Integrating peritumoral radiomics with molecular and genetic data could lead to the development of highly personalized treatment strategies, tailored to the unique characteristics of each patient's tumor.[96] Research should focus on exploring the synergistic potential of these data types to improve predictive accuracy and treatment outcomes.

Development of Clinically Accessible Tools: For peritumoral radiomics to transition from research into clinical practice, user-friendly software tools and platforms are needed.[97] These tools should be capable of seamlessly integrating radiomics analysis into the clinical workflow, providing real-time decision support for clinicians. Additionally, training programs and educational resources will be necessary to equip healthcare professionals with the knowledge and skills to interpret and apply radiomics data effectively.

Exploring New Imaging Modalities: While much of the current research in peritumoral radiomics focuses on CT and MRI, there is growing interest in exploring other imaging modalities, such as ultrasound and PET-CT.[98,99] Each of these modalities offers unique advantages and could provide complementary information when combined with peritumoral radiomics, further enhancing the accuracy and utility of radiomics models.

Conclusion

Peritumoral radiomics presents a promising advancement in the management of HCC, offering unique insights into the tumor microenvironment. This approach enhances diagnostic accuracy, guides personalized treatment strategies, and improves prognostic assessments, all of which are crucial for advancing precision medicine in HCC. However, to fully unlock the potential of peritumoral radiomics, ongoing challenges must be addressed. Continued efforts in these areas are essential to ensure that this approach becomes a reliable tool in the management of HCC.

Abbreviations

HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; VETC, vessels encapsulating tumor clusters; AUC, area under curve; CT, computer tomography; RFS, recurrence-free survival; MVI, microvascular invasion; US, ultrasound; OR, objective response; OS, overall survival; ER, early recurrence; TACE, transarterial chemoembolization; CK7, cytokeratin 7; TTP, time-to-progression; OS, overall survival; HAIC, hepatic arterial infusion chemotherapy; RFA, radiofrequency ablation; DFS, disease-free survival.

Data Sharing Statement

All data are included in the article.

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