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REVIEW

Evaluation of immune microenvironment in hepatocellular carcinoma: current advances in CT and MRI imaging techniques

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide with a high mortality. Tumor immune microenvironment (TIM) plays an important role in the progress of tumorigenesis, progression, and anti-tumor therapy of HCC. The advent of immunotherapy agents has provided new opportunities and options for HCC patients. The immunotherapeutic efficacy is closely associated with the TIM status of HCC patients, which currently relies on postoperative pathological examination. Preoperative non-invasive evaluation of TIM is of great clinical significance in guiding treatment strategies and predicting the response to immunotherapy. This article summarizes the recent research progress in CT and MRI-based imaging techniques for the preoperative non-invasive assessment of TIM in HCC patients.

Keywords Hepatocellular carcinoma · Computed tomography · Magnetic resonance imaging · Tumor immune microenvironment

Introduction

Primary liver cancer is one of the most prevalent malignancies. According to the 2020 global cancer data released by the World Health Organization, primary liver cancer has become the third leading cause of cancer-related deaths worldwide [1], with 75–85% of patients histologically classified as hepatocellular carcinoma (HCC) [2]. In China, over half of HCC patients are diagnosed at an advanced or metastatic stage [3]. Systemic therapy, including multitargeted kinase inhibitors (MKIs), such as Sorafenib, that target tumor cells and angiogenesis, has been the primary treatment strategy for unresectable advanced-stage HCC. Despite achieving certain efficacy, MKIs have not yielded satisfactory objective response rates and overall survival rates [4].

With the advancement of research on immune checkpoint inhibitors (ICIs), the combination of anti-angiogenic drugs and ICIs has brought about new opportunities for patients with unresectable HCC, which has improved HCC patients' survival and now become the first-line treatment strategy [4]. In the systematic treatment guidelines for HCC published by the National Comprehensive Cancer Network (NCCN) in 2021, Atezolizumab combined with Bevacizumab has been recommended as a first-line systemic treatment option [5]. Additionally, the combination therapy has demonstrated significant clinical benefits in the Chinese population, with a 47% reduction in the risk of death and a 40% reduction in the risk of disease progression compared to the sorafenib treatment group [6, 7]. In the 2022 primary liver cancer diagnosis and treatment guidelines of China, combination therapy has been included as a primary anti-tumor treatment option for patients with unresectable HCC [8, 9].

ICIs assist immune cells in recognizing and eliminating tumor cells [10]. However, not all HCC patients could benefit from ICIs. The efficacy of immunotherapy in HCC patients is closely related to the tumor immune microenvironment (TIM). TIM is formed based on the interactions and effects of various immune cells and tumor cells within the tumor. Hedge et al. [11] classified TIM into three types: "immune-infiltrated," "immune-excluded," and "immune-desert". Among them, "immune-infiltrated" means that

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immune cells can infiltrate into the tumor; "immune-excluded" means that although the tumor has a high degree of immune cell infiltration, most of them gathered in the periphery of the tumor; "immune-desert" means that the tumor has very little immune cells' infiltration. Patients with different types of TIM have different prognoses and responses to immunotherapy. Targeted modulation of TIM represents an effective approach in anticancer treatment [4]. Although TIM comprises a diverse range of immune components, such as tumor-infiltrating lymphocytes, immune checkpoint molecules, tumor-associated macrophages, tumor-associated neutrophils, myeloid-derived suppressor cells, etc., they can be broadly classified into those that promote tumor-killing and those that inhibit it. Certain cells, including T cells, NK cells, and MDSCs, exert activating and suppressing dual effects depending on specific conditions [12]. Apart from the complexity of immune components, TIM also exhibits heterogeneity in terms of immune cell abundance and distribution within and around the tumor. Moreover, TIM undergoes dynamic changes in response to different treatment regimens and alterations in the patient's immune status [13]. Evaluating TIM is crucial for predicting HCC patient prognosis and guiding clinical strategy. However, current assessment methods rely on postoperative histological tissue, which cannot achieve dynamic monitoring and fails to address the issue of tumor heterogeneity. With the deepening research on TIM and targeted immunotherapy drugs emerging, accurate evaluation and dynamic monitoring of TIM are becoming urgent challenges in the management of HCC patients.

CT and MRI-based imaging techniques have played an indispensable role in diagnosing, staging, evaluating treatment efficacy, and monitoring processes in HCC patients [14]. The emergence of novel imaging technologies and contrast agents further enhances diagnostic accuracy. Imaging techniques offer advantages of preoperative non-invasiveness and dynamic monitoring, enabling comprehensive evaluation within and around the tumor. Medical imaging plays a crucial role in evaluating various aspects of the TIM, such as cell density, angiogenesis, etc. Diffusion-weighted imaging (DWI) primarily focuses on evaluating the movement and restriction of water molecules within the tissue. In general, the active proliferation of tumor cells leads to an increase in tissue density, thereby restricting the movement of water molecules. Additionally, perfusion imaging can assess the vascular characteristics of tumors by calculating parameters such as blood flow perfusion velocity and perfusion peak. Perfusion imaging techniques provide valuable information about tumor blood supply. In recent years, the integration and application of traditional radiomics, deep learning networks, and other technologies have significantly contributed to the extraction of information from CT and MRI images [15]. In addition, the progress of advanced medical imaging techniques, such as dual-source CT, MRI functional imaging, diffusion-weighted imaging (DWI), perfusion imaging, and dynamic contrast enhancement magnetic resonance imaging (DCE-MRI), has also provided a solid foundation for applying CT and MRI-based imaging techniques to evaluate TIM in HCC patients. This article summarizes the recent research progress in CT and MRI-based imaging techniques for the preoperative non-invasive assessment of TIM in HCC patients.

CT evaluation of TIM in HCC patients

In the selection of imaging techniques for diagnosis and treatment process for HCC patients, CT has better diagnostic accuracy compared to ultrasound [16], fewer usage restrictions, and a faster imaging speed compared to MRI. Dynamic contrast-enhanced CT images provide crucial information on the lesion's location, morphology, and blood supply. Moreover, CT perfusion imaging not only provides information regarding the perfusion information of HCC lesion and the liver, but also give insights into cellular-level features, such as microvascular density (MVD) [17], VEGF-2 expression [18], and TIM-related information [19]. Studies have indicated that CT signs, such as the sharpness of tumor margins, can serve as an indicator for evaluating tumor MVD. Furthermore, both the perfusion parameters obtained from CT and the histopathological examination of tumors have demonstrated variations in MVD among tumors with different margin morphologies [17]. However, CT lacks high soft-tissue resolution, and the assessment of gross features is inevitably affected by subjective factors. CT evaluation of TIM in HCC patients now primarily relies on radiomics, which involves utilizing machine learning approaches to delineate the regions of interest (ROIs) and extract features from CT images of HCC.

Previous studies have indicated that CT-based imaging techniques present a promising opportunity for the non-invasive preoperative evaluation of TIM in HCC patients [6, 7, 19]. The radiomics approach enables the development of predictive models for various aspects of TIM, such as predicting the infiltration of T cells in TIM based on CT images [19], classifying the immune status of HCC patients into distinct types ("immune-infiltrated type", "immune-excluded type", or "immune-desert type") [6], and the immunotherapeutic efficacy in HCC patients [6, 7].

Based on new techniques, such as radiomics and deep learning networks, studies have made non-invasive predictions of single indicators in TIM at the cellular and gene levels [20–22]. The study used self-supervised learning to predict PD-1 and PD-L1 expression based on CT images, showing an AUC of 86.56% for PD-1 expression and an AUC of 83.93% for PD-L1 expression [22]. Neutrophil

extracellular traps (NETs), which are extracellular web-like structures of DNA chromatin complexes extruded from dying neutrophils, were once thought to mainly function as snares that caught and killed harmful microorganisms. NETs play an important role in promoting metastasis [20]. The study extracted radiomic features from CT images and grouped NETs into high- and low-NETs. Based on the grouping result, the prognosis of HCC patients and the efficacy of immunotherapy were predicted [20]. The low-NETs were associated with better survival and higher levels of immune cell infiltration. A radiomics signature (RNETS) was found to be an independent risk factor for progression-free survival (PFS). In addition, the objective response rate of HCC patients treated with PD-1 inhibitor was significantly higher in the low-RNETS group (27.8%) than in the high-RNETS group (10.8%). Radiomics features extracted from CT images can also be used to predict the expression of immune-related indicators in HCC patients at the gene level such as ribonucleotide reductase regulatory subunit M2 (RRM2) [21]. The result showed that high RRM2 expression acted as a risk factor for overall survival (OS) [hazard ratio (HR) = 2.083] and was implicated in the regulation of the immune response.

In addition to utilizing machine learning methods to extract radiomic features from CT images for modeling and prediction of TIM and patients' prognosis [7, 19], a retrospective multicenter study [6] proposed an integrated prediction model by combining the acquired CT radiomic features with the corresponding tumor CD8+ T-cell gene expression profiles. The model was independently validated using public genetic data, immune status classification data, and immunotherapeutic efficacy data. Validation results using the public genetic database demonstrated an area under the curve (AUC) of 0.67 (95% CI 0.57–0.77, $P = 0.0019$). Validation results using immune status classification data demonstrated an AUC of 0.76 (95% CI 0.66–0.86, $P < 0.0001$) in differentiating "immune-infiltrated type" and "immune-desert type" HCC patients. The validation of immunotherapeutic efficacy data in HCC patients demonstrated a higher proportion of patients achieving objective response after 3 months of immunotherapy in the high radiomic feature score group, accompanied by an improved overall survival rate.

Furthermore, based on contrast-enhanced CT, a study [23] was conducted to evaluate the relative Hounsfield unit attenuation index (rHUAI) on contrast-enhanced computed tomography (CECT) for predicting systemic treatment response in HCC patients. rHUAI obtained from CECT has the potential as a non-invasive tool for predicting tumor response in advanced HCC patients who have received combined ICI and anti-angiogenesis. Another study based on the dual-source CT technique has found that with the increase in the number and size of mouse HCC lung metastases, there would be more formation of blood vessels and CXCR4+, which is involved in the chemotaxis of leukocytes in the corresponding metastatic tumors [24].

Although the combination of CT imaging and radiomics techniques provides a novel approach for non-invasively evaluating TIM, the tissue resolution of CT images is relatively inferior to that of MRI. Moreover, CT is unable to acquire information regarding the hepatocyte's function, resulting in a relatively limited availability of cellular-level features in comparison to MRI imaging.

In addition to the above aspects, positron emission tomography–computed tomography (PET–CT) combines positron emission tomography (PET) and CT technologies, providing comprehensive metabolic and anatomical information throughout the body. This combination offers an important tool for the evaluation and monitoring of TIM. In recent years, researchers have utilized PET–CT technology to assess the efficacy and prognosis of immunotherapy [25–30]. ^{18}F-FDG PET–CT reflects the level of tumor glucose metabolism. Some studies have used ^{18}F-FDG PET–CT to evaluate tumor metabolic activity and immune cell infiltration, demonstrating a correlation between high ^{18}F-FDG uptake, immune cell infiltration, favorable response to immunotherapy, and prognosis [25, 26]. Additionally, researchers are developing other radiotracers to enable a more comprehensive evaluation of tumor immunity. For instance, ^{89}Zr has been used to label CD8+ T cells, allowing for the assessment of their distribution and quantity within the tumor [30]. Furthermore, specific radiotracers can bind to PD-L1, enabling the quantitative evaluation of PD-L1 expression levels in tumors through PET–CT imaging. This technique holds the potential for selecting appropriate immunotherapy strategies and predicting therapeutic efficacy. These novel radiotracers contribute to improved quantitative assessment and monitoring of tumor immune cells [27–29]. PET–CT provides more comprehensive information and tools for the individualization and precision of tumor immunotherapy. With ongoing technological developments and innovations, the application of PET–CT in the field of tumor immunity holds great promise, supporting the optimization of immunotherapy and personalized management of cancer patients.

MRI evaluation of TIM in HCC patients

MRI is more accurate in diagnosing HCC compared with CT and ultrasound. Besides, functional MRI can directly acquire information at the cellular level, such as the restricted state of water molecules within the tumor on DWI. DCE-MRI enables the acquisition of consecutive MRI images [16], acquiring the perfusion parameters from ROIs. The evolution of free-breathing sequences further improved image quality [31]. With the application of the hepatobiliary-specific

contrast agent (Gd-EOB-DTPA) and the advancements in MRI functional imaging techniques, MRI has demonstrated better accuracy in detecting HCC lesions than CT in a cirrhotic liver background. MRI achieves a high specificity of 94% in the diagnosis of HCC regardless of tumor size [32]. In addition to showing the morphology and location information of HCC lesions, Gd-EOB-DTPA MRI can evaluate the status of liver function. The process of TIM evaluation of HCC patients based on MRI, some of the methods are similar to those used to evaluate TIM in HCC patients based on CT images, involved in the utilization of machine learning for lesion identification and radiomics feature extraction analysis [33–35].

In previous studies, machine learning methods extract radiomic features from MRI and predict TIM in HCC patients. The AUC for predicting PD-L1 positive expression ranged from 0.794 to 0.897 [33]. The correlation coefficients between radiomic features and PD-L1 expression at the protein and mRNA levels reached 0.41–0.47 and − 0.48 to 0.47, respectively [34]. A correlation analysis [34] was conducted between the qualitative/quantitative imaging features on MRI and the counts of CD3, CD68, and CD31 cells in the TIM of HCC patients, the correlation coefficients (r) ranging from − 0.41 to 0.40 and − 0.52 to 0.45. Based on the radiomics method, there is study that extracted the radiomic features from MRI images and established non-invasive prediction of immunotherapy target PD-L2 expression in HCC [36]. The T2-weighted, arterial-phase, and portal venous-phase and combined MRI radiomic models showed AUCs of 0.789 (95% CI 0.702–0.875), 0.727 (95% CI 0.632–0.823), 0.770 (95% CI 0.682–0.875), and 0.871 (95% CI 0.803–0.939), respectively. In addition, there is a study that extracts radiomic features based on DCE-MRI and predicts Ang-2 expression in HCC patients. The AUCs for the radiomics, clinic-radiologic, and combined models for predicting Ang-2 expression were 0.800, 0.874, and 0.933, respectively [37]. Moreover, a model was established to predict the total RPS6K expression in HCC patients based on different radiomic features extraction methods [38]. Radiomic features were extracted from T2-weighted and diffusion-weighted images. Machine learning algorithms, including multiple logistic regression (MLR), supporting vector machine (SVM), random forest (RF), and artificial neural network (ANN), were applied to construct the predictive model. Among all built models, the ANN-based hybrid model exhibited the best predictive ability with AUC of 0.887 and 0.826 in training and validation cohorts.

Some studies in the evaluation of TIM based on MRI can directly establish a prediction model through imaging manifestations, quantitative/semi-quantitative parameters, and parameters from functional MRI sequences [39–42]. The predictive models derived from these studies were utilized to predict the individual immune markers within the tumor, composite immune scores, and the efficacy of immunotherapy in HCC patients. A study [43] has shown that the enhancement degree of intrahepatic lesions based on MRI images (evaluated by relative enhancement rate) can be used to predict the response of immunotherapy in HCC patients. The disease control rate was 37.5% (3/8) versus 70.0% (7/10), respectively, in patients with or without higher enhancement intrahepatic HCC nodules. Imaging manifestations involved in these studies include irregular tumor margins, hypo-intensity in the hepatobiliary phase surrounding the tumor, enhanced capsule, incomplete tumor capsule, signal heterogeneity on T2-weighted images, tumor number, intra-tumoral vessels, rim enhancement, and tumor size [39–41]. Quantitative/semi-quantitative parameters involved in these studies include lesion signal intensity during the hepatobiliary phase, enhancement rate, arterial contrast-to-noise ratio, apparent diffusion coefficient (ADC), and T1 values [40–43]. These research findings indicate that MRI can be utilized for analyzing the immune components in HCC patients and predicting their response to immunotherapy. Another study [39] demonstrated that independent predictive factors for PD-L1 positive expression included irregular tumor margins ($P = 0.008$), and low signal intensity in the peritumoral liver parenchyma in the hepatobiliary phase ($P < 0.001$). Independent predictive factors for high CD8 cell density included enhanced tumor capsule ($P = 0.001$) and low signal intensity in the peritumoral liver parenchyma ($P = 0.025$). The predictive models for PD-L1 positive expression, high CD8 cell density, and their combination achieved AUCs of 0.810 and 0.809, 0.740 and 0.728, and 0.809 and 0.874 in the training and validation sets, respectively. Moreover, irregular tumor margins, low signal intensity in the peritumoral liver parenchyma, and enhanced tumor capsules were associated with objective responses to immunotherapy in patients. Another study [40] demonstrated that incomplete tumor capsules, heterogeneous signals on T2-weighted images, and arterial contrast-to-noise ratio were able to predict the immunotherapeutic efficacy for HCC patients. A histogram-based approach using multiple imaging features (tumor number, intra-tumoral vessels, capsule, rim enhancement, and T1 values) enables the prediction of the immune scores of HCC patients [41]. The C-index reached 0.737 and 0.726 in the training and validation sets, respectively.

However, although MRI has the advantage of preoperative dynamic non-invasive evaluation of TIM, the TIM components, and the interactions among these components are complex. There is still a lot to improve in the evaluation of TIM by MRI. There is still a lack of prospective study cohorts with large samples to verify the efficacy of these models.

Summary and prospect

In conclusion, with the increasing use of immunotherapy in HCC patients in recent years, there has been a progressive growth in research focused on evaluating the TIM, which was associated with immunotherapeutic efficacy in HCC patients. Medical imaging techniques provide a preoperative non-invasive approach to assess TIM in HCC patients. Meanwhile, studies have reported that in addition to the tumor itself, individual factors such as fat quantification also affect the efficacy of immunotherapy [44, 45]. Imaging techniques can simultaneously evaluate both tumor lesions and individual factors, which may be a potential research direction in the future. CT and MRI-based imaging techniques have shown feasibility and good accuracy in predicting immune markers within TIM and evaluating the immunotherapeutic efficacy in HCC patients. However, most existing studies are retrospective and have only focused on predicting immune markers within specific subsets of TIM. To comprehensively analyze TIM, further in-depth research and exploration with advanced medical imaging techniques is needed. Some advanced MRI imaging techniques, such as magnetic resonance metabolic imaging and ultra-high magnetic field MRI imaging, have also emerged, bringing new opportunities to solve the problems currently encountered in TIM preoperative evaluation.

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Declarations

Conflict of interest All authors have no relevant financial or non-financial interests to disclose.

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References

1. International Agency for Research on Cancer. Globocan. 2020. https://www.gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49. https://doi.org/10.3322/caac.21660.
3. Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int. 2015;35(9):2155–66. https://doi.org/10.1111/liv.12818.
4. Zhang DZ, Niu JQ. Clinical advances in targeted therapy and immunotherapy for hepatocellular carcinoma. Chin J Hepatol. 2019;27(11):834–7. https://doi.org/10.3760/cma.j.issn.1007-3418.2019.11.005.
5. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet (Lond, Engl). 2022;400(10360):1345–62. https://doi.org/10.1016/S0140-6736(18)30010-2.
6. Sun R, Limkin EJ, Vakalopoulou M, Dercle L, Champiat S, Han SR, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. Lancet Oncol. 2018;19(9):1180–91. https://doi.org/10.1016/S1470-2045(18)30413-3.
7. Yuan G, Song Y, Li Q, Hu X, Zang M, Dai W, et al. Development and validation of a contrast-enhanced CT-based radiomics nomogram for prediction of therapeutic efficacy of anti-PD-1 antibodies in advanced HCC patients. Front Immunol. 2020. https://doi.org/10.3389/fimmu.2020.613946.
8. National Health Commission of the People's Republic Of C. Chinese guidelines for diagnosis and treatment of breast cancer 2018 (English version). Chin J Cancer Res. 2019;31(2):259–77. https://doi.org/10.21147/j.issn.1000-9604.2019.02.02.
9. Yang Y, Sun J, Wu M, Lau WY, Zheng S, Wang XH, et al. Chinese expert consensus on immunotherapy for hepatocellular carcinoma (2021 edition). Liver cancer. 2022;11(6):511–26. https://doi.org/10.1159/000526038.
10. Sangro B, Chan SL, Meyer T, Reig M, El-Khoueiry A, Galle PR. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol. 2020;72(2):320–41. https://doi.org/10.1016/j.jhep.2019.10.021.
11. Hegde PS, Karanikas V, Evers S. The where, the when, and the how of immune monitoring for cancer immunotherapies in the era of checkpoint inhibition. Clin Cancer Res. 2016;22(8):1865–74. https://doi.org/10.1158/1078-0432.CCR-15-1507.
12. Santhakumar C, Gane EJ, Liu K, McCaughan GW. Current perspectives on the tumor microenvironment in hepatocellular carcinoma. Hep Intl. 2020;14(6):947–57. https://doi.org/10.1007/s12072-020-10104-3.
13. Dagogo-Jack I, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol. 2018;15(2):81–94. https://doi.org/10.1038/nrclinonc.2017.166.
14. Zhang Y, Wei Y, Ye Z, Wei H, Zhang Z, Chen J, et al. Imaging diagnosis and differential diagnosis of hepatocellular carcinoma. Chin J Radiol. 2020;54(8):5. https://doi.org/10.3760/cma.j.cn112149-20200528-00751.
15. Wu J, Mayer AT, Li R. Integrated imaging and molecular analysis to decipher tumor microenvironment in the era of immunotherapy. Semin Cancer Biol. 2022;84:310–28. https://doi.org/10.1016/j.semcancer.2020.12.005.
16. Chartampilas E, Rafailidis V, Georgopoulou V, Kalarakis G, Hatzidakis A, Prassopoulos P. Current imaging diagnosis of

hepatocellular carcinoma. Cancers. 2022. https://doi.org/10.3390/cancers14163997.
17. Bai RJ, Li JP, Ren SH, Jiang HJ, Liu XD, Ling ZS, et al. A correlation of computed tomography perfusion and histopathology in tumor edges of hepatocellular carcinoma. Hepatobiliary Pancreatic Dis Int HBPD INT. 2014;13(6):612–7. https://doi.org/10.1016/s1499-3872(14)60298-8.
18. Thaiss WM, Kaufmann S, Kloth C, Nikolaou K, Bösmüller H, Horger M. VEGFR-2 expression in HCC, dysplastic and regenerative liver nodules, and correlation with pre-biopsy dynamic contrast enhanced CT. Eur J Radiol. 2016;85(11):2036–41. https://doi.org/10.1016/j.ejrad.2016.09.012.
19. Liao H, Zhang Z, Chen J, Liao M, Xu L, Wu Z, et al. Preoperative radiomic approach to evaluate tumor-infiltrating CD8(+) T cells in hepatocellular carcinoma patients using contrast-enhanced computed tomography. Ann Surg Oncol. 2019;26(13):4537–47. https://doi.org/10.1245/s10434-019-07815-9.
20. Xin H, Lai Q, Zhou Y, He J, Song Y, Liao M, et al. Noninvasive evaluation of neutrophil extracellular traps signature predicts clinical outcomes and immunotherapy response in hepatocellular carcinoma. Front Immunol. 2023. https://doi.org/10.3389/fimmu.2023.1134521.
21. Li Q, Long X, Lin Y, Liang R, Li Y, Ge L. Computed tomography radiomics signature via machine learning predicts RRM2 and overall survival in hepatocellular carcinoma. J Gastrointest Oncol. 2023;14(3):1462–77. https://doi.org/10.21037/jgo-23-460.
22. Xie T, Wei Y, Xu L, Li Q, Che F, Xu Q, et al. Self-supervised contrastive learning using CT images for PD-1/PD-L1 expression prediction in hepatocellular carcinoma. Front Oncol. 2023. https://doi.org/10.3389/fonc.2023.1103521.
23. Feng Y, Zhang H, Ren Q, Li C, Liu S, Zheng C, et al. Contrast-enhanced CT parameters predict short-term tumor response in patients with hepatocellular carcinoma who received sequential combined anti-angiogenesis and immune checkpoint inhibitor treatment. Eur J Radiol. 2023. https://doi.org/10.1016/j.ejrad.2023.110784.
24. Ko SF, Yip HK, Zhen YY, Lee CC, Li JH, Lee CC, et al. Cancer patient-derived circulating microparticles enhance lung metastasis in a rat model: dual-source CT, cellular, and molecular studies. Mol Imag Biol. 2016;18(4):490–9. https://doi.org/10.1007/s11307-015-0923-8.
25. Annovazzi A, Vari S, Giannarelli D, Pasqualoni R, Sciuto R, Carpano S, et al. Comparison of 18F-FDG PET/CT criteria for the prediction of therapy response and clinical outcome in patients with metastatic melanoma treated with ipilimumab and PD-1 inhibitors. Clin Nucl Med. 2020;45(3):187–94. https://doi.org/10.1097/RLU.0000000000002921.
26. Seban RD, Nemer JS, Marabelle A, Yeh R, Deutsch E, Ammari S, et al. Prognostic and theranostic 18F-FDG PET biomarkers for anti-PD1 immunotherapy in metastatic melanoma: association with outcome and transcriptomics. Eur J Nucl Med Mol Imaging. 2019;46(11):2298–310. https://doi.org/10.1007/s00259-019-04411-7.
27. Niemeijer AN, Oprea-Lager DE, Huisman MC, Hoekstra OS, Boellaard R, de Wit-van der Veen BJ, et al. Study of (89)Zr-pembrolizumab PET/CT in patients with advanced-stage non-small cell lung cancer. J Nucl Med. 2022;63(3):362–7. https://doi.org/10.2967/jnumed.121.261926.
28. Huisman MC, Niemeijer AN, Windhorst AD, Schuit RC, Leung D, Hayes W, et al. Quantification of PD-L1 expression with (18) F-BMS-986192 PET/CT in patients with advanced-stage non-small cell lung cancer. J Nucl Med. 2020;61(10):1455–60. https://doi.org/10.2967/jnumed.119.240895.
29. Smit J, Borm FJ, Niemeijer AN, Huisman MC, Hoekstra OS, Boellaard R, et al. PD-L1 PET/CT imaging with radiolabeled durvalumab in patients with advanced-stage non-small cell lung cancer. J Nucl Med. 2022;63(5):686–93. https://doi.org/10.2967/jnumed.121.262473.
30. Kist-de-Ruijter L, van de Donk PP, Hooiveld-Noeken JS, Giesen D, Elias SG, Lub-de-Hooge MN, et al. Whole-body CD8(+) T cell visualization before and during cancer immunotherapy: a phase 1/2 trial. Nat Med. 2022;28(12):2601–10. https://doi.org/10.1038/s41591-022-02084-8.
31. Cannella R, Sartoris R, Grégory J, Garzelli L, Vilgrain V, Ronot M, et al. Quantitative magnetic resonance imaging for focal liver lesions: bridging the gap between research and clinical practice. Br J Radiol. 2021;94(1122):20210220. https://doi.org/10.1259/bjr.20210220.
32. Zhao C, Dai H, Shao J, He Q, Su W, Wang P, et al. Accuracy of various forms of contrast-enhanced MRI for diagnosing hepatocellular carcinoma: a systematic review and meta-analysis. Front Oncol. 2021. https://doi.org/10.3389/fonc.2021.680691.
33. Tian Y, Komolafe TE, Zheng J, Zhou G, Chen T, Zhou B, et al. Assessing PD-L1 expression level via preoperative MRI in HCC based on integrating deep learning and radiomics features. Diagnostics. 2021. https://doi.org/10.3390/diagnostics11101875.
34. Hectors SJ, Lewis S, Besa C, King MJ, Said D, Putra J, et al. MRI radiomics features predict immuno-oncological characteristics of hepatocellular carcinoma. Eur Radiol. 2020;30(7):3759–69. https://doi.org/10.1007/s00330-020-06675-2.
35. Chen S, Feng S, Wei J, Liu F, Li B, Li X, et al. Pretreatment prediction of immunoscore in hepatocellular cancer: a radiomics-based clinical model based on Gd-EOB-DTPA-enhanced MRI imaging. Eur Radiol. 2019;29(8):4177–87. https://doi.org/10.1007/s00330-018-5986-x.
36. Tao YY, Shi Y, Gong XQ, Li L, Li ZM, Yang L, et al. Radiomic analysis based on magnetic resonance imaging for predicting PD-L2 expression in hepatocellular carcinoma. Cancers. 2023. https://doi.org/10.3390/cancers15020365.
37. Zheng J, Du PZ, Yang C, Tao YY, Li L, Li ZM, et al. DCE-MRI-based radiomics in predicting angiopoietin-2 expression in hepatocellular carcinoma. Abdom Radiol (New York). 2023;48(11):3343–52. https://doi.org/10.1007/s00261-023-04007-8.
38. Yang F, Wan Y, Shen X, Wu Y, Xu L, Meng J, et al. Application of multi-modality MRI-based radiomics in the pre-treatment prediction of RPS6K expression in hepatocellular carcinoma. Mol Biomed. 2023;4(1):22. https://doi.org/10.1186/s43556-023-00133-3.
39. Sun L, Mu L, Zhou J, Tang W, Zhang L, Xie S, et al. Imaging features of gadoxetic acid-enhanced MR imaging for evaluation of tumor-infiltrating CD8 cells and PD-L1 expression in hepatocellular carcinoma. Cancer Immunol Immunother CII. 2022;71(1):25–38. https://doi.org/10.1007/s00262-021-02957-w.
40. Sheng R, Zeng M, Jin K, Zhang Y, Wu D, Sun H. MRI-based nomogram predicts the risk of progression of unresectable hepatocellular carcinoma after combined lenvatinib and anti-PD-1 antibody therapy. Acad Radiol. 2022;29(6):819–29. https://doi.org/10.1016/j.acra.2021.09.004.
41. Tang M, Zhou Q, Huang M, Sun K, Wu T, Li X, et al. Nomogram development and validation to predict hepatocellular carcinoma tumor behavior by preoperative gadoxetic acid-enhanced MRI. Eur Radiol. 2021;31(11):8615–27. https://doi.org/10.1007/s00330-021-07941-7.
42. Huang MQ, Song CY, Lin YY, Feng ST, Peng ZP. Apparent diffusion coefficient of MRI in predicting the immune microenvironment of HCC. J Sun Yat-sen Univ (Med Sci). 2021;42(2):242–9.
43. Aoki T, Nishida N, Ueshima K, Morita M, Chishina H, Takita M, et al. Higher enhancement intrahepatic nodules on the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI as a poor responsive marker of anti-PD-1/PD-L1 monotherapy for unresectable hepatocellular carcinoma. Liver Cancer. 2021;10(6):615–28. https://doi.org/10.1159/000518048.

44. Yan SY, Yang YW, Jiang XY, Hu S, Su YY, Yao H, et al. Fat quantification: Imaging methods and clinical applications in cancer. Eur J Radiol. 2023. https://doi.org/10.1016/j.ejrad.2023.110851.
45. Xiao LS, Li RN, Cui H, Hong C, Huang CY, Li QM, et al. Use of computed tomography-derived body composition to determine the prognosis of patients with primary liver cancer treated with immune checkpoint inhibitors: a retrospective cohort study. BMC Cancer. 2022;22(1):737. https://doi.org/10.1186/s12885-022-09823-7.