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Mechanistic Study of PD-1 Inhibitors in the Immune Microenvironment of Liver Metastases: A Comprehensive Analysis Based on Radiomics

(Kajian Mekanistik Perencat PD-1 dalam Persekitaran Mikro Imun Metastasis Hati: Analisis Komprehensif Berdasarkan Radiomik)

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ABSTRACT

Liver metastases are a common and clinically challenging type of tumor. Their poor prognosis has prompted researchers to seek new treatments. The immune microenvironment of liver metastases is complex and critical. It involves interactions among various immune cells, cytokines, and signaling pathways that influence tumor growth, metastasis, and treatment efficacy. In recent years, PD-1 inhibitors have emerged as a major breakthrough in immunotherapy, showing promise in treating liver metastases. However, accurately predicting patient responses to PD-1 inhibition remains a pressing challenge. Radiomics is a non-invasive tool that analyzes features from medical images to show how tumor biology affects treatment responses. This article reviews the features of the immune microenvironment in liver metastases, how PD-1 inhibitors work, and the advancements in radiomics for predicting treatment responses in liver metastases. It aims to offer useful insights for clinical practice and point out future research directions to further improve treatment outcomes and accurate treatment evaluations for patients with liver metastases.

Keywords: Immune microenvironment; liver metastases; PD-1 inhibitors; radiomics

ABSTRAK

Metastasis hati merupakan sejenis tumor yang biasa dan mencabar secara klinikal. Prognosisnya yang buruk telah mendorong para penyelidik untuk mencari rawatan baharu. Persekitaran mikro imun metastasis hati adalah kompleks dan kritikal. Ia melibatkan interaksi antara pelbagai sel imun, sitokin dan laluan isyarat yang mempengaruhi pertumbuhan tumor, metastasis dan keberkesanan rawatan. Dalam beberapa tahun kebelakangan ini, perencat PD-1 telah muncul sebagai satu kejayaan besar dalam imunoterapi, menunjukkan potensi dalam merawat metastasis hati. Walau bagaimanapun, meramalkan tindak balas pesakit dengan tepat terhadap perencatan PD-1 masih menjadi cabaran. Radiomik ialah alat bukan invasif yang menganalisis ciri daripada imej perubatan untuk menunjukkan bagaimana biologi tumor mempengaruhi tindak balas rawatan. Kertas ini mengulas ciri persekitaran mikro imun dalam metastasis hati, bagaimana perencat PD-1 berfungsi dan kemajuan dalam radiomik untuk meramalkan tindak balas rawatan dalam metastasis hati. Ia bertujuan untuk menawarkan pandangan berguna untuk amalan klinikal dan menunjukkan hala tuju penyelidikan masa depan untuk meningkatkan lagi hasil rawatan dan penilaian rawatan yang tepat untuk pesakit dengan metastasis hati.

Kata kunci: Metastasis hati; perencat PD-1; persekitaran mikro imun; radiomik

INTRODUCTION

The liver frequently serves as the primary site for cancer metastasis, especially in common malignancies like colorectal cancer, which often have a poor prognosis. Liver metastases affect both patient survival and significantly reduce their quality of life. Furthermore, liver metastatic tumors often develop resistance to various treatment options, resulting in poor treatment outcomes (Ren et al. 2020). Therefore, patients with liver metastases need effective treatment strategies and evaluation tools.

The immune microenvironment of liver metastases is complex and important. It involves interactions among various immune cells, cytokines, and signaling pathways that collectively influence tumor growth, metastasis, and treatment responses. In the immune microenvironment, immune cells, like tumor-infiltrating lymphocytes, play key roles, while the expression of immune checkpoint molecules like PD-L1 is closely linked to tumor immune evasion.

PD-1 inhibitors represent an important advancement in immunotherapy. They block the PD-1/PD-L1 pathway, lifting the tumor's suppression of the immune system. This enhancement of immune responses leads to better treatment outcomes for patients (Abaza et al. 2023). PD-1 inhibitors not only restore T cell function but also promote immune surveillance and the clearance of metastatic liver tumors, showing promise in treating liver metastases. However, accurately predicting patient responses to this treatment remains a critical challenge. To address this challenge, radiomics serves as a non-invasive assessment tool. By analyzing multidimensional features extracted from medical images, radiomics can show how tumor behavior relates to treatment response (Wang et al. 2023). In the clinical prediction of response to PD-1 inhibitor treatment for liver metastases, extracting and analyzing radiomic features, building predictive models, and their potential application in clinical practice all show great value. Through steps like standardizing high-quality image segmentation, extracting and cleaning features, and building predictive models with machine learning algorithms, radiomics can really help with clinical decision-making, optimize treatment options, and ultimately improve patient survival and quality of life.

This paper reviews the immune microenvironment in liver metastases, explains the function of PD-1 inhibitors, and summarizes the use of radiomics in predicting treatment responses. Future research should focus on several key areas: improving data standardization and imaging quality control, conducting large-scale multicenter studies, and encouraging the development of new technologies and interdisciplinary teamwork. Additionally, exploring how new technologies like spectral CT can enhance the assessment of liver metastases will be crucial for improving treatment outcomes and accurately evaluating efficacy in patients with liver metastasis.

FEATURES OF THE IMMUNE MICROENVIRONMENT IN LIVER METASTASES

COMPOSITION OF IMMUNE CELLS

Tumor-infiltrating lymphocytes (TILs) play a crucial role in the immune microenvironment of liver metastases. Studies indicate that TILs not only detect and attack tumor cells but also regulate the immune response by releasing cytokines, influencing tumor growth and prognosis. For instance, the presence of CD8+ T cells is often associated with a favorable prognosis. In contrast, a higher number of regulatory T cells (Tregs) typically suggests increased immune suppression and tumor growth (Qin et al. 2022). Furthermore, myeloid-derived suppressor cells (MDSCs) exert strong immunosuppressive effects in liver metastases by inhibiting T cell activity and promoting the expansion of Tregs, thereby enhancing the tumor's ability to evade the immune system (Hagenstein et al. 2024). Therefore, the composition of immune cells in liver metastases is complex and dynamic, influencing the tumor's biological characteristics and response to treatment.

MECHANISMS OF IMMUNE SUPPRESSION IN THE LIVER

The immune microenvironment of liver metastases shows significant expression of immune checkpoint molecules, particularly programmed death-ligand 1. PD-L1 inhibits T cell activity by binding to programmed death 1, allowing tumor cells to evade immune detection (Tu et al. 2020). Research indicates that high levels of programmed death-ligand 1 in liver metastases correlate with poor prognosis (Xiong et al. 2023). Moreover, the balance between pro-inflammatory and anti-inflammatory cytokines significantly influences immune suppression in liver metastases. High levels of pro-inflammatory cytokines like IL-6 and TNF-α boost tumor immune evasion, while anti-inflammatory cytokines such as IL-10 make immune suppression worse by inhibiting T cell activity and encouraging Tregs to differentiate (Zhou, Li & Pathak 2019). This cytokine balance affects tumor progression and presents potential targets for immunotherapy.

DYNAMIC CHARACTERISTICS OF THE IMMUNE MICROENVIRONMENT

The immune microenvironment of liver metastases is dynamic and closely related to the progression of metastatic lesions. Research indicates that changes in the tumor microenvironment affect tumor growth and spread. For instance, the types and functions of cells in the immune microenvironment of liver metastases can vary with the tumor burden (Han et al. 2023). Recent advances in genomics have enhanced our understanding of the interactions between tumor cells and the immune microenvironment. The application of single-cell RNA sequencing technology has showed the heterogeneity and functional diversity of immune cells in liver metastases, opening up new possibilities for personalized treatment (Chen et al. 2023). Additionally, changes in immune phenotypes may be associated with genetic mutations and epigenetic alterations in tumor cells. These factors collectively influence the immune microenvironment of liver metastases and their clinical manifestations (Xu et al. 2024).

HOW PD-1 INHIBITORS AFFECT THE LOCAL IMMUNE MICROENVIRONMENT IN LIVER METASTASES

MECHANISM OF ACTION OF PD-1

PD-1 inhibitors boost T cell activity by blocking the PD-1/PD-L1 pathway, thereby restoring the body's anti-tumor immune response. PD-1 is an important immune checkpoint that stops T cells from multiplying and being effective by binding to PD-L1. Studies indicate that PD-1 inhibitors effectively lift this inhibitory effect, promote T cell activation and proliferation, and enhance their ability to recognize and combat liver metastases (Han, Liu & Li 2020). Furthermore, PD-1 inhibitors promote immunogenic cell death (ICD), a process that activates the immune system to induce tumor cell death. ICD releases antigens that attract more immune cells into the tumor microenvironment, enhancing tumor-specific immune responses (Zhou et al. 2022b). Through these mechanisms, PD-1 inhibitors not only restore T cell function but also aid in the detection and elimination of liver metastases.

REMODELING OF THE IMMUNE MICROENVIRONMENT

PD-1 inhibitors significantly reshape the immune microenvironment in liver metastases. PD-1 inhibitors alter the infiltration of immune cells, leading to an increased presence of effector T cells and anti-tumor immune cells at the tumor site. This alteration enhances the immune response against the tumor and suppresses tumor growth (Jiang et al. 2019). In addition, PD-1 inhibitors can trigger local inflammation, enhance tumor metabolism, and increase the sensitivity of liver metastases to immunotherapy. This inflammation not only aids in killing tumor cells but also improves immune cell function by altering metabolic pathways within the tumor microenvironment. This creates a more favorable environment for anti-tumor immune responses (Hirano et al. 2021).

CLINICAL OUTCOMES REFLECTION

In clinical practice, the effectiveness of PD-1 inhibitors in treating liver metastases is evaluated using metrics such as the objective response rate (ORR) and disease control rate (DCR), which can be assessed through imaging in various malignant tumors. Studies show that PD-1 inhibitors can significantly improve the ORR and DCR in patients with liver metastases from certain primary tumor types (He et al. 2020). The effectiveness of PD-1 inhibitors varies widely among liver metastases from different primary tumors. For instance, some liver metastases respond positively to PD-1 inhibitors, while others show resistance to treatment. This variability may be related to factors such as the tumor's immune microenvironment, levels of PD-L1 expression, and other mechanisms of immune evasion (Zheng, Fang & Li 2019). Therefore, in clinical practice, personalized treatment plans and evaluations of the patient's immune microenvironment are especially crucial.

HOW RADIOMICS CAN HELP PREDICT CLINICAL RESPONSES TO PD-1 INHIBITORS

EXTRACTION AND ANALYSIS METHODS OF RADIOMIC FEATURES

Extracting and analyzing radiomic features is essential for radiomics research, especially for predicting clinical responses to PD-1 inhibitors. We can extract features such as shape, texture, and intensity from imaging technologies like CT and MRI. These technologies provide valuable insights into tumors and their microenvironments, serving as important predictive indicators for immunotherapy (Ahn et al. 2022; Ho et al. 2019). PET-CT examinations offer unique benefits in assessing the activity of malignant tumor cells (Palumbo et al. 2020). To predict clinical responses to PD-1 inhibitors in liver metastases, we begin by standardizing high-quality image segmentation to identify areas of interest. Various methods, such as pyradiomics are used to extract radiomic features, which are then cleaned, filtered, and simplified to enhance the accuracy and efficiency of the model. Studies have shown that CT radiomic analysis can act as a biomarker for evaluating clinical efficacy (Ebrahimpour et al. 2024). Next, we employ machine learning algorithms to develop predictive models that integrate radiomic features with clinical variables, thereby enhancing prediction accuracy (Saravi et al. 2024). Finally, we validate the model's performance using both internal and external validation sets to assess its ability to predict responses to PD-1 inhibitor treatment in patients with liver metastasis (Huang et al. 2024). This process helps support clinical decision-making, optimizing treatment options, and improving patient survival and quality of life.

RADIOMICS PREDICTION MODEL

The application of radiomics in predicting clinical responses to PD-1 inhibitors in liver metastases demonstrates significant potential. Constructing the prediction model requires several steps: collecting baseline imaging data from patients, performing image segmentation and reconstruction, gathering high-throughput radiomic features, transforming medical images into detailed, analyzable data, and selecting features with the LASSO model. Subsequently, a prediction model is developed using neural networks or other machine learning algorithms, such as support vector machines and decision trees. To evaluate the model's ability to predict treatment response, we determine the optimal cutoff value using the receiver operating characteristic (ROC) curve. Research indicates that radiomics-based prediction models are likely to help predict how well liver metastasis patients will respond prior to receiving PD-1 inhibitor treatment, assisting doctors in creating more precise treatment plans (Hectors et al. 2020). Moreover, radiomics technology can extract more precise information from images than is perceptible to the naked eye, thereby creating imaging biomarkers to predict

PD-L1 expression levels. By analyzing everything together, it can boost the model's accuracy and show how imaging features relate to the tumor's immune environment.

APPLICATION POTENTIAL IN CLINICAL PRACTICE

The potential of radiomics in clinical practice is significant, particularly for developing personalized treatment plans and monitoring treatment effects in real-time. Analyzing radiomic features allows doctors to assess how patients respond to PD-1 inhibitors. This assessment helps them create more precise treatment plans. This precision in treatment planning not only enhances effectiveness but may also reduce unnecessary side effects (Yamaguchi et al. 2024). Additionally, radiomics allows for real-time monitoring of treatment responses. This capability enables doctors to quickly adjust treatment strategies by regularly checking changes in imaging features, optimizing patient outcomes. Research shows that radiomics offers valuable insights throughout various stages of tumor treatment, helping doctors make better-informed decisions (Liu, He & Li 2022; Patel et al. 2024). The application prospects of radiomics in PD-1 inhibitor therapy look promising and warrant further research and exploration.

CURRENT CHALLENGES AND FUTURE RESEARCH DIRECTIONS

CHALLENGES IN EVALUATING IMMUNOTHERAPY EFFICACY AND NEW OPPORTUNITIES IN MOLECULAR IMAGING

The diverse response patterns and immune-related adverse events (irAE) experienced by patients undergoing immunotherapy make it challenging for imaging physicians to accurately assess these responses (Borcoman et al. 2019; Nishino, Hatabu & Hodi 2019). After receiving immunotherapy for malignant tumors, imaging tests may show that tumor lesions grow or treatment, lesions may shrink and tumor markers may decrease, a phenomenon known as pseudo progression (Park et al. 2020). The traditional efficacy evaluation criteria for solid tumors specifically, the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) rely on changes in lesion size and effectively assess the efficacy of cancer treatments. However, during immunotherapy, pseudo progression renders these traditional criteria inadequate, highlighting the need for new standards to accurately assess immunotherapy efficacy. Scholars have proposed immune-related response criteria (irRC), immune-related efficacy evaluation criteria for solid tumors, immune response evaluation criteria in solid tumors (iRECIST), and modified immune efficacy evaluation criteria for solid tumors based on relevant clinical trial data (Costa et al. 2021). However, evaluating efficacy with these standards usually means waiting at least four weeks to confirm if the disease has progressed, which causes a big delay in getting patients the information they need about how well the treatment is working (Billan, Kaidar-Person & Gil 2020; Saida et al. 2021). In the process of tumor immunotherapy, telling the difference between real progression from tumor cell growth and pseudo progression from immune cell buildup poses a significant challenge for radiomics. We still need to figure out how the radiomic features of lesions relate to immune responses, actual response status, and prognosis in larger-scale prospective studies in the future. Current research indicates that identifying new targets and developing innovative molecular imaging probes aimed at T cell activation can create new opportunities for precise tumor immunotherapy. This approach will enhance

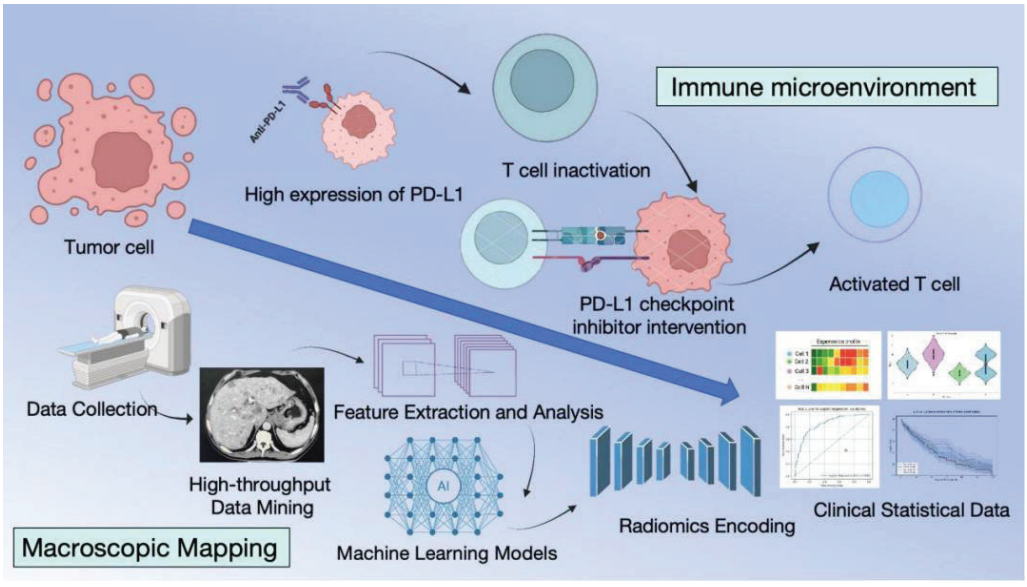

FIGURE 1. A conceptual diagram that links PD-1, the immune microenvironment, and radiomics.

guidance for immunotherapy, improve efficacy evaluation, and aid in risk assessment and clinical decision-making for cancer patients (Zhou et al. 2022a).

DATA STANDARDIZATION AND IMAGE QUALITY CONTROL

Studying the immune microenvironment of liver metastases and the effects of PD-1 inhibitors presents significant challenges in data standardization and image quality control. Radiomics plays an important role in assessing the tumor microenvironment, predicting responses to immunotherapy, and monitoring disease progression, but its effectiveness is highly dependent on the accuracy and consistency of the data. Imaging data is heterogeneous due to varying equipment and scanning parameters used by different medical institutions, complicating later analysis. Therefore, it is essential to establish unified data standards and image quality control processes to ensure effective comparison and analysis of data from different sources. Currently, employing deep learning for automated data quality control shows promise, as it enhances processing efficiency and reduces human error (Pontoriero et al. 2021). Therefore, future research should emphasize the development of standardized data collection and processing protocols, the establishment of large imaging databases, and the adoption of advanced image registration and calibration techniques to enhance data comparability and reliability.

THE NEED FOR LARGE-SCALE MULTICENTER STUDIES

Large-scale multicenter studies are vital in medical research for evaluating disease prevalence and treatment effects. Integrating data from various medical institutions allows researchers to achieve more generalizable results (Marquis-Gravel et al. 2023). Although several studies have examined the immune microenvironment of liver metastases and PD-1 inhibitors, they often depend on small sample sizes or single-center data (DiLorenzo et al. 2024; Sebastian & Peter 2022). Large-scale multicenter studies are essential for understanding the immune mechanisms of liver metastases, evaluating the efficacy of PD-1 inhibitors, and identifying relevant biomarkers for immune therapy responses. Multicenter studies can provide a broader and more diverse patient population, helping to uncover differences and similarities among various populations, thereby developing more precise and effective treatment strategies. Future research should focus more on international collaboration and multicenter teamwork, speeding up scientific discovery through data and resource sharing. Furthermore, more scientifically rigorous study designs are needed, with appropriate control groups, sufficient follow-up periods, and objective assessment criteria to ensure the reliability and reproducibility of research findings.

THE IMPORTANCE OF NEW TECHNOLOGY DEVELOPMENT AND INTERDISCIPLINARY COLLABORATION

With rapid technological advancements, more innovative tools are being utilized in cancer research and treatment. In the field of studying the immune microenvironment of liver metastases and the effects of PD-1 inhibitors, new technologies such as high-throughput sequencing, single-cell sequencing, and advanced imaging techniques offer fresh insights and ways to dive deep into the complexity of the tumor environment and how immunotherapy works (Nguyen, Xu & Robinson 2020). However, these technologies present several challenges, including technical costs, operational complexity, and data interpretation difficulties. Working together across disciplines is key to tackling these challenges. Integrating knowledge and technologies from fields such as biology, medicine, computer science, and statistics can lead to a deeper understanding of the immune microenvironment of liver metastases. This, in turn, will help identify new treatment targets and biomarkers, as well as optimize immunotherapy strategies (Liu, He & Li 2022). Future research should prioritize forming interdisciplinary teams to drive innovation in liver metastases immunotherapy by leveraging research resources and technological strengths from various fields.

FUTURE RESEARCH DIRECTIONS FOR SPECTRAL CT IN EVALUATING LIVER METASTASES

Spectral CT, an advanced imaging technology, provides detailed information about tissue composition. Spectral CT offers multi-parameter imaging and material analysis capabilities, including material density, hemodynamic parameters, and effective atomic number, which reflect the biological characteristics of tumors in greater depth (Liu, He & Li 2022). In the assessment of liver metastases, spectral CT can quantify the iodine content, fat content, and other parameters within the tumor, which may relate to the tumor's biological characteristics and its response to immunotherapy. For example, changes in iodine content may indicate changes in the tumor's vascular structure, which may be linked to tumor responses following immunotherapy. Additionally, spectral CT shows potential in predicting treatment responses to PD-1 inhibitors. By monitoring changes in internal tumor parameters before and after treatment, spectral CT can assess the tumor's response to therapy, thereby guiding treatment plan adjustments (Liu, He & Li 2022). Spectral CT's multi-parameter quantitative imaging capability captures subtle changes in the tumor microenvironment and immune status. This opens new avenues for assessing immune status in liver metastases through radiomics and provides fresh research perspectives for evaluating immunotherapy efficacy, highlighting directions for future exploration.

In the current context of medical research, radiomics, as an emerging technological approach, is significantly enhancing our predictive capabilities for liver metastasis patients undergoing PD-1 inhibitor treatment. By analyzing in depth multi-parameter imaging data, radiomics can extract multi-dimensional information closely related to the biological characteristics of tumors, offering robust support for personalized treatment plans, thereby improving predictive accuracy and potentially optimizing existing treatment strategies to enhance patient survival rates and quality of life. When exploring the link between radiomics and PD-1 inhibitor treatment outcomes, it is crucial to consider the variability in research results. This variability stems from the lack of uniformity in feature extraction methods, analysis models, and patient selection criteria across different studies. Additionally, challenges such as insufficient generalization and poor interpretability of artificial intelligence models must be addressed. Additionally, the complex biological characteristics of liver metastases create challenges for applying radiomics. Future research must focus on controlling and standardizing these variables to enhance the reproducibility and broader applicability of findings.

As data science and artificial intelligence technologies advance, the future applications of radiomics in precision medicine appear very promising. We aim to create a comprehensive multi-omics research system that integrates radiomics, genomics, transcriptomics, and other omics data. This system will help us better understand the occurrence and development of liver metastases, decode biological information, and significantly improve predictive capabilities for immunotherapies like PD-1 inhibitors. Consequently, the use of radiomics in treating liver metastases with PD-1 inhibitors is eagerly anticipated. However, to foster further progress in this field, we need to find a balance between research rigor and diversity. Ultimately, radiomics will provide a strong foundation for precision medicine, enabling us to offer more personalized and accurate treatment plans for each patient.

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