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Advances in Radiomics of the Tumor Microenvironment in Metastatic Lymph Nodes

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Abstract: As one of the main ways of tumor metastasis, the presence or absence of lymph node metastasis is of great significance to the choice of treatment and prognosis of tumor patients. With significant advances in immunotherapy, assessing the tumor microenvironment in metastatic lymph nodes and predicting the efficacy of lymph node immunotherapy has become a hot research topic. In this review, we summarize the recent radiomics studies in assessing the tumor microenvironment of metastatic lymph nodes and predicting the efficacy of immunotherapy. We also discuss the role of metastatic lymph node stromal cells in antitumor immunity.

Keywords: Radiomics; Tumor microenvironment; Metastatic lymph nodes; Immunotherapy; Stromal cells

1. Introduction

As secondary immune organs, lymph nodes are believed a major role in recognizing and delivering antigens, and critical for initiating anti-tumor immune responses. According to the "seed and soil" theory[1], the initiation of metastatic lymph nodes depends on the synergistic effect of tumor cells (seed) and the lymph node microenvironment (soil).

Lymph node metastasis is one of the main ways of tumor metastasis and related to the patient's treatment, prognosis and survival. The dynamic response of CD8+ T cells to cancer immunotherapy in human regional lymph nodes is disrupted in metastatic lymph nodes. This provides new challenges and novel ideas for the treatment of tumors accompanied by lymph node metastasis.

Immunotherapy is the activation of a patient's own immune cells to stimulate a functional immune response against tumor cells. The proposal of lymph node-targeting strategy[2] has drawn our attention to the immune microenvironment of the lymph nodes themselves, especially to the dynamic evaluation of the immune efficacy before and after the treatment. Recent studies have proposed radiomics for predicting response to immunotherapy, which can provide a more comprehensive assessment of a tumor by extracting features of the entire tumor microenvironment (TME) than biophase-based approaches. In addition, radiomics models can be used for multiple scans, allowing clinicians to continuously and non-invasively track changes in tumor phenotype and clinical response[3].

In order to explore the tumor microenvironment in metastatic lymph nodes and to provide better methods for the prediction of immunotherapy response. In this review, we focus on the current advances in radiomics to predict the tumor microenvironment in metastatic lymph nodes.

2. Brief introduction to the TME

Over the past few years, the definition of " tumor" has evolved from a simple aggregation of tumor cells to a complex organ-like structure composed of tumor cells, immune cells, fibroblasts, vascular endothelial cells, and other stromal cells. TME has been one of the research hotspots in oncology[4]. With the development of tumor immunity, TME has been shown to play a decisive role in tumor development, progression, metastasis, recurrence and potential therapeutic targets. The tumor microenvironment consists of two major categories, cellular and non-cellular components[5]. The local microenvironment of the lymph node determines the growth of lymph node metastasis and response to therapeutic interventions, including the growth and immune evasion of immune cells and stromal cells in metastatic lymph nodes, as described in detail in the review[6].

3. Application of radiomics in assessing the tumor microenvironment in metastatic lymph nodes

Radiomics is a recently developed imaging technique that converts radiographic data from a region of interest into high-dimensional feature data that can be analyzed. These features, such as shape, texture, and waveform, are associated with cancer phenotypes and the tumor

microenvironment. When these features are correlated with clinical disease outcomes, they form the basis of specific and reliable clinical evidence. Radiomics can quantify inter- and intra-tumor heterogeneity, accurately determine the status of metastatic lymph nodes, and provide a better basis for clinical decision-making on tumor treatment options[7].

In recent years, most of the radiomics studies on lymph nodes have focused on diagnosing the benign and malignant nature of preoperative lymph nodes, such as XU et al.[8] summarized the application of magnetic resonance imaging radiomics in preoperative lymph node diagnosis of esophageal cancer, magnetic resonance radiomics combines both the high resolution of magnetic resonance and the high throughput of histology, presenting a great advantage in the diagnosis of metastatic lymph nodes.

The tumor microenvironment in metastatic lymph nodes has been increasingly emphasized as researchers have studied lymph nodes and tumor heterogeneity has been proposed, YU et al. explored the relationship between MRI radiographic features and the tumor microenvironment in 90 breast cancer patients by T1 enhancement and T2WI MRI sequences.

Significant changes in key radiological features after neoadjuvant chemotherapy can be explained by changes in the tumor microenvironment, and the association between MRI radiological features and tumor microenvironmental features may reveal the underlying biological basis of MRI radiology.

Kotaro et al. Retrospectively analyzed 62 patients with surgically resected pathologic N2 lung adenocarcinoma who underwent preoperative PET, that proved tumor-promoting stromal cells αSMA+ CAFs and CD204+ tam were more frequently transferred to metastatic lymph nodes with high FDG uptake, suggesting that metastatic lymph node mesenchymal stromal cells play an important role in tumor immunity, which correlates with poor prognosis.

Despite the growing interest in metastatic lymph node radiomics in various research areas of oncology, most studies have focused almost exclusively on the immune cells of the lymph node and have lacked attention to the mesenchymal cells. Stromal cells were for a long time considered to be merely structural cells that play a supportive and compartmentalized role; however, active interactions between endothelial and fibroblastic stromal cells drive the maturation of the lymphoid ecological niche[9], plays an equally important role in lymph node metastasis.

4. Importance of stromal cells

Cancer cells rely on extensive support from the stroma for survival, proliferation and invasion. Therefore, tumor stroma is an important potential target for anticancer therapy. Fibroblasts are a major cellular component of the tumor microenvironment in many tissues and entities. Normal fibroblasts exhibit an inhibitory effect on pre-tumor cells in their inactivated state. However, fibroblasts are recruited and activated by tumor cells as part of tumor connective tissue formation. Such activated fibroblasts are referred to as cancer-associated fibroblasts (CAFs.) CAFs, as one of the main components of TME, have been shown to interact with tumors through a variety of mechanisms: inducing tumor cell proliferation, affecting tumor angiogenesis, forming an immunosuppressive microenvironment to evade immune surveillance, and promoting tumor formation and drug resistance. Due to their significant role in tumor progression and genetic stability compared to cancer cells, CAFs (cancer-associated fibroblasts) are considered as targets for anti-tumor therapy. Targeting these cells can indirectly affect tumor angiogenesis and drug delivery.

5. Conclusions

As one of the major modes of tumor metastasis, changes in metastatic lymph nodes cannot be assessed without evaluating the efficacy of tumor therapy. Metastatic lymph nodes sometimes provide more information than the primary tumor, and similar observations have been reported in lung cancer, where metastatic lymph node phenotypic information has a better predictive value for pathological response than radiological features of the primary tumor[10].

With the rapid development of immunotherapy, the assessment of immunotherapy is of paramount clinical concern. Biopsy has been used as the gold standard for predicting response to immunotherapy. However, it is difficult to detect geographic heterogeneity using biopsy because a single biopsy may not be representative of the entire metastatic lymph node. Immunotherapy can be predicted by means of radiomics, and since radiomics features reflect cancer biology, such as tumor heterogeneity and microenvironment, these models have great potential to predict immunotherapy response more accurately than current methods. The findings of Trebeschi et al. suggest that radiographic characterization of lesions in standard radiographic imaging can serve as a noninvasive biomarker of response to immunotherapy and may be predictive of lesion response to therapy in neoadjuvant and palliative care, characterization of patient response to therapy and response patterns, show utility in improving patient stratification.

Radiomics can be used not only for the assessment of immunotherapy efficacy, but also to enable the assessment of the tumor microenvironment prior to treatment, to tailor the optimal treatment plan for cancer patients and to achieve precision medicine.

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