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Research Progress on the Prediction of BRAF Gene Mutation in Papillary Thyroid Carcinoma by Artificial Intelligence Combined with Medical Imaging

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Abstract: The global incidence of papillary thyroid carcinoma has been exhibiting an upward trend, with the BRAF gene serving as a specific molecular marker that is closely associated with the aggressiveness and lymph node metastasis of this malignancy. In recent years, radiomics and deep learning methodologies based on medical imaging have emerged as innovative approaches for predicting molecular markers, enabling the extraction of subvisual information that transcends human perceptual capabilities. These advanced techniques provide novel predictive tools for identifying BRAF gene mutations in papillary thyroid carcinoma. This article aims to comprehensively review the applications and research advancements of machine learning and deep learning approaches based on medical imaging in predicting BRAF gene mutations in papillary thyroid carcinoma.

1. Introduction

Papillary thyroid carcinoma (PTC) is the most common pathological type of thyroid tumors, accounting for approximately 80-90% of all thyroid tumors. Its incidence has been increasing globally year by year, while the mortality rate remains stable. The 10-year survival rate is greater than 90%[1]. The pathogenesis of PTC involves the interaction between genetic and environmental factors, mainly including ionizing radiation, high-iodine diet, genetic factors, hormonal influences, etc[2].

At the molecular mechanism level, abnormal activation of the MAPK signaling pathway is a core driving factor of PTC. As a key molecular event in this pathway, BRAF mutation promotes cell proliferation, inhibits apoptosis, and induces tumor dedifferentiation by persistently activating ERK protein. Studies have shown that BRAF mutations are significantly associated with the invasiveness of PTC (such as lymph node metastasis and extrathyroidal invasion) and poor prognosis (increased recurrence rate and iodine therapy resistance). The BRAF gene is an important tool for the diagnosis and prognostic evaluation of this disease[3, 4]. Traditional methods for BRAF gene detection include detecting tissues obtained by fine-needle aspiration biopsy (Fineneedle Aspiration Biopsy, FNAB) or surgical resection through methods such as PCR sequencing and FISH detection of rearrangements[5]. However, the above-mentioned procedures have limitations such as high cost

and long time consumption, and are invasive operations that may require anesthesia when necessary, carrying risks of injuring surrounding blood vessels and nerves and leaving complications. In addition, due to the small amount of tissue samples obtained by some methods, molecular information in important areas may be lost, so they cannot fully represent the biological characteristics of the entire tumor. In recent years, many studies have confirmed the correlation between BRAF gene mutations in PTC and imaging features, with the hope of providing a new non-invasive molecular marker examination method. Artificial intelligence (AI) has recently risen rapidly and become widely popular in medical image analysis, prediction of molecular markers, and other aspects, playing an important role in the medical field. It can achieve non-invasive and efficient prediction by integrating multimodal data (ultrasound, CT, MRI)[6]. This article mainly summarizes the research progress of artificial intelligence based on medical imaging in predicting BRAF gene mutations in papillary thyroid carcinoma, so as to achieve precision medicine.

2. Principles of BRAF Gene Mutation in Papillary Thyroid Carcinoma

PTC is a mitogen-activated protein kinase (MAPK)-driven cancer, with over 80% of PTC cases exhibiting alterations in genes related to the MAPK signaling pathway, including BRAF, RAS, and RET rearrangements. The mutation rate of BRAF in PTC ranges from 45% to 60%, making it the most common and critical molecular marker. The BRAF gene is located on chromosome 7 (7q34) and encodes a serine-threonine kinase, serving as a core member of the RAS/MAPK signaling pathway. This pathway regulates cell proliferation, differentiation, migration, and apoptosis through a cascade reaction (RAS→RAF→MEK→ERK)[7, 8]. Most BRAF gene mutation sites are point mutations at BRAF T1799A, which lead to the substitution of glutamic acid for valine at residue 600 of the BRAF protein, causing a conformational change in the BRAF kinase, known as the BRAF V600E mutation[9]. It can make extracellular regulated protein kinases insensitive, thereby leading to continuous and highly activated MAPK signaling, resulting in abnormal cell proliferation and differentiation disorders. Therefore, BRAF V600E is associated with the malignant phenotype, invasiveness, iodine refractoriness, and recurrence risk of PTC.

3. Correlation between medical imaging features and BRAF mutation in papillary thyroid carcinoma

Different medical imaging modalities play a role in predicting BRAF gene mutations in papillary thyroid carcinoma (PTC).

Ultrasound, characterized by low cost, non-invasiveness, and radiation-free properties, serves as the first-line examination for thyroid nodules[10]. Numerous studies have explored the relationship between the ultrasonic manifestations of lesions and BRAF gene mutations in PTC. For example, extremely hypoechoic lesions, microcalcifications, an aspect ratio >1, irregular margins, and the absence of a hypoechoic halo are recognized as predictive ultrasonic features of BRAF V600E mutation[11].Russell et al.[12] proposed that the reason might be that BRAF mutations lead to dense proliferation of tumor cells with less stromal components, forming uniform cell masses that reduce the acoustic wave reflection interface, thus appearing as hypoechoic or extremely hypoechoic on ultrasound. Microcalcifications may be related to calcium salt deposition after rapid cell proliferation and apoptosis driven by BRAF mutations. Vertical tumor growth (aspect ratio >1) and blurred or irregular margins may be associated with BRAF mutations promoting changes in cell polarity and invasive growth through activating the MAPK pathway. Studies have also found that PTC patients with BRAF V600E mutations have higher scores in ultrasound elastography, and this score is highly correlated with the diagnosis of BRAF V600E mutations[13].This is because BRAF-mutated tumors exhibit increased hardness in elastography due to fibrous stromal

hyperplasia and high cellular density[12].However, the evaluation of ultrasound images relies too heavily on the personal experience of ultrasound physicians, which is highly subjective and places high demands on the professional capabilities of ultrasound physicians.

There are fewer studies on the relationship between CT features and BRAF gene mutations in papillary thyroid carcinoma (PTC) compared with ultrasound. However, some studies have shown that the maximum tumor diameter on contrast-enhanced CT, normalized iodine concentration (NIC) in the venous phase, spectral curve slope, NIC in the arterial phase, and normalized effective atomic number are independent predictors of BRAF V600E mutation. Among them, NIC in the arterial phase has the highest diagnostic efficiency[14].Tumor size is positively correlated with proliferative activity and invasiveness. For example, papillary thyroid carcinomas with a diameter >1 cm are more likely to be malignant or highly invasive. BRAF mutations promote cell proliferation through the MAPK pathway, leading to rapid tumor growth and an increase in maximum diameter. NIC (normalized iodine concentration) reflects tumor blood supply and iodine metabolism capacity. Venous-phase NIC is associated with microvascular density (MVD), while arterial-phase NIC reflects early tumor blood supply and neovascularization capacity. On one hand, BRAF mutations increase angiogenesis through VEGF (thereby increasing NIC), and on the other hand, they inhibit NIS (sodium-iodide symporter), leading to iodine metabolic disorders (potentially decreasing NIC). The comprehensive effect is heterogeneity in venous-phase NIC. BRAF mutations promote angiogenesis through factors such as VEGF, resulting in elevated arterial-phase NIC. Studies have shown that arterial-phase NIC is significantly associated with microvascular invasion in BRAF-mutated liver cancer[15].The slope of the spectral curve reflects the heterogeneity of tissue components. A high slope indicates dense tissue or rich in high atomic number elements (such as calcification or high cellular density). BRAF mutations lead to disordered arrangement of tumor cells and increased nuclear atypia, which may be manifested as an increase in the slope of the spectral curve. In addition, BRAF mutation-related abnormal angiogenesis may affect tissue perfusion and further alter the curve morphology[16].The normalized effective atomic number reflects the elemental composition of tissues (such as iodine, calcium, and proteins). Tumors with lower differentiation have a higher normalized effective atomic number. BRAF mutations lead to increased cellular atypia and enlarged cell nuclei, which may increase the normalized effective atomic number. In addition, BRAF mutation-related abnormal angiogenesis (such as hemorrhage and calcification) may further affect the value of the normalized effective atomic number[17].CT can examine retrosternal thyroid lesions that are difficult to detect by ultrasound and some cervical lymph nodes, and can provide a more comprehensive observation of the relationship between the thyroid gland and surrounding tissue structures. In addition, CT examination is less dependent on the operator's experience and has stronger reproducibility[18].However, affected by its resolution, CT is only suitable for larger nodules.

Compared with the first two imaging examinations, MRI has higher soft tissue resolution and includes multiple imaging modes that reflect different characteristics of lesions. Among them, diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) can also reflect the microstructure of lesion tissues, such as cell density and membrane integrity, which have significant advantages for the diagnosis of PTC[19].BRAFV600 mutations in papillary thyroid carcinoma are associated with MRI manifestations such as delayed enhancement morphology, ADC signal, and delayed enhancement in enhancement curve types[20].Delayed enhancement typically reflects tumor stromal fibrosis or abnormal vascular maturity. Activation of the MAPK pathway causes uneven distribution of microvessels and incomplete basement membranes of new blood vessels, leading to slow extravasation of contrast agents and manifested as delayed enhancement. The ADC value reflects the degree of water molecule diffusion restriction. BRAF mutations promote cell proliferation, resulting in close arrangement of tumor cells that restrict water molecule diffusion,

thereby reducing ADC signal values. Delayed enhancement occurs because fibrosis and extracellular matrix remodeling delay the outflow of contrast agents, forming sustained enhancement[21].

4. The Current Application Status of Artificial Intelligence in Medical Imaging Analysis

Artificial Intelligence (AI) aims to develop systems that can simulate, expand, or extend human intelligence, enabling them to perceive the environment, acquire knowledge, reason and make decisions, and complete complex tasks just like humans[22].Machine learning (ML), an important branch of AI, learns patterns from data through algorithms and makes predictions. Its core lies in feature engineering, which requires manually extracting data features (such as shape and texture), and then completing tasks through classification or regression models. Core algorithms include support vector machines (SVM), random forest, K-means clustering, etc[23].

In medical imaging, ML is widely used in basic tasks such as image segmentation and object detection. Its advantages include strong adaptability to small sample sizes, low hardware requirements, and high model interpretability. However, it requires manual segmentation of lesions, and model performance may suffer due to labeling errors or biases. Additionally, it faces issues such as poor interpretability and limited generalization capabilities. Deep Learning (DL), an advanced form of ML, primarily includes Convolutional Neural Networks (CNN), Recurrent Neural Networks (RNN), etc. Its core lies in constructing multi-layered Artificial Neural Networks (ANN) to automatically learn and extract more complex features from data. Compared with traditional machine learning, DL is more intelligent in feature extraction: it does not rely on manual delineation but can automatically filter and obtain more relevant imaging features meaningful for research[24].Its advantages lie in processing complex, high-dimensional data (such as CT and MRI images), being able to capture subtle lesions and global features, and achieving high-precision disease monitoring (such as breast cancer, thyroid cancer screening, and pulmonary nodule identification, etc.)[25, 26],and Integrating multimodal data to predict patient prognosis, provide personalized treatment plans, and achieve precision medicine.[27], However, it requires a large number of samples to train models, has high requirements for hardware facilities, and model decisions are not transparent. Through the dual-track development of ML and DL, artificial intelligence is bringing revolutionary changes to the medical industry. In the future, with algorithm optimization, multidisciplinary integration, and policy support, AI in medical imaging will unleash greater potential in fields such as early disease screening and personalized treatment.

5. Research Progress of Artificial Intelligence Based on Medical Imaging in Predicting BRAF Gene Mutation in Papillary Thyroid Carcinoma

5.1 Ultrasound

Scholars such as Kwon[28] were among the first to conduct research in this field. They retrospectively included 96 thyroid nodules from papillary thyroid carcinoma patients, dividing them into BRAF mutation-positive and negative groups. After manually delineating the regions of interest (ROI) of the nodules, extracting effective features, and constructing three different machine learning models, they evaluated the performance of these models, including accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and the area under the receiver operating characteristic curve (AUC). The results showed that all classification models exhibited moderate performance in predicting the presence of BRAF mutations in papillary thyroid carcinoma, with an AUC of 0.651, an accuracy of 64.3%, a sensitivity of 66.8%, and a specificity of 61.8%. This confirms the feasibility of using ultrasound images for analysis.Yoon et al.[29]

analyzed ultrasound images using a CAD program developed with deep learning CNN and calculated the malignant risk degree of each thyroid nodule based on the ultrasound images. Although the performance was moderate (AUC=0.706), it also demonstrated the potential of such research.

Wu et al.[30] established machine learning models, deep transfer learning models, and a combined machine learning-deep transfer learning model using two-dimensional ultrasound images, and compared the performance of these three models. The results showed that the AUC value of the combined model was higher than that of the deep transfer learning model and the machine learning model, with AUC, accuracy, sensitivity, and specificity reaching 0.833, 80.6%, 76.2%, and 81.7%, respectively. It can be seen that in terms of two-dimensional ultrasound images, the deep learning combined with machine omics model performs better than standalone deep learning or machine learning models in predicting BRAFV600E gene mutations in papillary thyroid carcinoma, and deep learning performs slightly better than machine learning.

Agyekum et al.[31] utilized ultrasonic elastography to create six different machine learning algorithms for predicting BRAFV600E mutations. The results showed that the AUC values of all six machine learning models were higher than 0.8, with the best performance achieved by the SVM_RBF algorithm, reaching an AUC of 0.98. This further indicates that the novel ultrasonic imaging technique of elastography also has good value for predicting BRAF V600E mutations. Wang et al.[32] also demonstrated high value in predicting BRAF V600E mutations using a combined imaging model of ultrasonic elastography and grayscale ultrasound images. The AUC values of the training set and test set were 0.985 and 0.931, respectively. It can be seen that the performance of a single ultrasound image model is comparable to that of the combined model.

5.2 CT

Dong Yongxiu et al.[33] included 52 patients with papillary thyroid carcinoma confirmed by surgery and with BRAFV600E mutation results. They used MaZda software to perform texture analysis on the venous phase images of preoperative contrast-enhanced CT scans of the patients, and then used three feature selection algorithms to predict BRAFV600E mutations. The results showed that among the three feature selection algorithms, NDA had very high diagnostic performance, with misjudgment rates all below 10%; multiple combinations had misjudgment rates <20%, indicating good diagnostic performance; the combination with the lowest misjudgment rate was POE+ACC+NDA, with an area under the ROC curve (AUC) of 0.969. Although this study did not use artificial intelligence, it further demonstrates that BRAFV600E mutations can be analyzed using CT images.Ge Zhao et al.[34] retrospectively collected enhanced CT imaging data and pathological results of 84 PTC patients. After feature engineering and feature selection, four machine learning models were established. Finally, 16 features were extracted from enhanced CT images to predict BRAFV600E mutations in papillary thyroid carcinoma. The results showed that the mLP model performed most prominently, with an accuracy of 0.882 and an AUC of 0.883. In summary, in terms of CT images, radiomics and texture analysis have both demonstrated good performance in predicting BRAFV600E mutations.

5.3 MRI

Zheng et al.[35] extracted texture features from T2-weighted imaging (T2WI) and contrast-enhanced T1-weighted imaging (CE-T1WI), and constructed three models (T2WI, CE-T1WI, and combined model) to predict BRAFV600E mutations. The results showed that the AUC values of the T2WI model, CE-T1WI model, and combined model were 0.83 (95% CI: 0.75-0.91), 0.83 (95% CI: 0.73-0.90), and 0.88 (95% CI: 0.81-0.94), respectively. At a cutoff value

of 0.674, the T2WI model had an accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 0.776, 0.679, 0.905, 0.905, and 0.679, respectively; the CE-T1WI model had values of 0.755, 0.750, 0.762, 0.808, and 0.696 at a cutoff value of 0.573; and the combined model had values of 0.816, 0.893, 0.714, 0.806, and 0.833 at a cutoff value of 0.420. These findings indicate that MRI-based texture analysis may be a potential method for preoperatively predicting BRAFV600E mutations in PTC.

6. Future Challenges and Prospects

In summary, the application of artificial intelligence (AI) for preoperative prediction of BRAF V600E mutation in papillary thyroid carcinoma (PTC) using medical imaging is becoming increasingly prevalent. Both machine learning (ML) and deep learning (DL) demonstrate considerable development potential and clinical value; however, several limitations persist in this field. Regarding AI: both ML and DL require extensive datasets for training, with model performance significantly declining when data is insufficient. In ML, manual data annotation and region of interest (ROI) delineation inevitably introduce inter-operator variability and subjectivity, while DL models suffer from opaque decision-making ("black box" nature), poor interpretability compromising trustworthiness, and limited generalizability, necessitating validation through prospective multi-center studies. Furthermore, AI technology presents high technical barriers and rapid obsolescence, demanding high-performance computing hardware and interdisciplinary expertise in mathematics and programming. For medical imaging: current ultrasound applications remain confined to static single-layer images, though future integration of dynamic videos could optimize AI model performance. Additionally, research should explore novel ultrasound techniques (e.g., contrast-enhanced ultrasound) or multimodal ML/DL models to predict BRAF mutation. Studies utilizing CT or MRI for BRAF mutation prediction in PTC remain scarce, representing significant research opportunities. Beyond BRAF, other molecular markers (e.g., RAS mutations, RET rearrangements) contribute to PTC pathogenesis; future studies should investigate whether these influence tumor morphology and if AI can predict their expression. Despite existing limitations, AI demonstrates superior diagnostic accuracy over traditional methods and is expected to provide a cost-effective solution for precision medicine.

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