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Radiomics in gliomas: A promising assistance for glioma clinical research

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ABSTRACT Gliomas are the most common brain primary tumors worldwide, which is the earliest sequenced cancer gene in the Cancer Genome Atlas (TCGA) project. The World Health Organization Classification Update of Central Nervous System (CNS) Tumors 2016 highlights that glioma is the first tumor classified based on both of the molecular markers and histology. Radiomics is an extraction approach for high-throughput data which collects the quantitative image information appearing. Combined imaging data with genomics and proteomics, radiomics show promising prediction for cancer diagnosis, treatment, and prognosis. In this review, the radiomic analysis methods applied in gliomas are highlighted. Some remarkable findings confirm the considerable potential of radiomics in clinical cancer research.

KEY WORDS radiomics; gliomas; molecular marker; diagnosis; treatment; prognosis

影像组学在胶质瘤临床研究中的应用进展

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[摘要] 胶质瘤是世界上最常见的原发性脑肿瘤，也是美国癌症和肿瘤基因图谱(the Cancer Genome Atlas，TCGA)工程中最早完成基因测序的恶性肿瘤。2016年更新的WHO中枢神经系统肿瘤分型中，胶质瘤是所有肿瘤疾病之中第一种通过基因表达水平与病理表现相结合的方法进行分型的肿瘤。影像组学是一种新兴的高通量定量影像数据信息提取分析方法。影像组学是影像特征与基因组学、蛋白质组学的融合，因此在肿瘤诊断、预后及治疗方案选择的临

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床研究中拥有巨大潜力，对于胶质瘤的研究有着极大帮助。

[关键词] 影像组学；胶质瘤；分子标志物；诊断；治疗；预后

Gliomas are the most common brain primary tumors worldwide[1-2]. The latest report indicates the brain tumor ranks 10th among all types of malignant tumors[3]. In China gliomas account for 32% of all primary central nervous system (CNS) tumors and 81% of malignant tumors in the CNS. The incidence rate of malignant glioma is 5–8 cases per million, and the mortality rate in 5 years is only second to pancreatic cancer and lung cancer, ranking 3rd overall[4]. Gliomas can be classified according to the morphology, the malignancy and the location of the tumor. The most widely used classification system is developed by the WHO. According to this classification system, glioma is divided from I level (the lowest malignancy and best prognosis) to the IV level (the highest malignancy and worst prognosis). However, the classical pathologic classification based on morphology cannot reflect the biological characteristics of some gliomas. For instance, some gliomas relapse and develop in the short term while they were pathologically diagnosed at the low level (benign). On the contrary, some high-grade (malignant) gliomas can remain stable for a long time. The similar phenotype gliomas show totally dissimilitude sensitivity in chemoradiotherapy. To sum up, the present clinical research for glioma focuses on how to precisely predict the prognosis and choose the appropriate treatment strategy[5], in which understanding of gliomas in molecular level plays a critical role.

1 Molecular markers in gliomas

Researchers have already spent years of time digging out the mutation in the gliomas progression. The gene atlas of gliomas was the first tumor gene atlas accomplished by the Cancer Genome Atlas (TCGA) group genome mapping. The TCGA data indicate that there are 5 gene mutations in one gliomas in average. This research promotes the appearance of new classification method for gliomas, from phenotype level to gene level. The expression level and mutation of EGFR, NF1, IDH1/2, TP53, and PTEN drives various signal pathways and constitutes the basis of gliomas development[6]. IDH1/2 mutation was the first confirmed gene which can make an effect on genetic, biochemical, and clinical changes in oncogene database[7-8]. IDH1 mutation is associated with the increase of survival time. And for more than 70% of level II–III glioma patients, the ID1/2 mutation can be detected.

To date, World Health Organization Classification Update of the CNS Tumors 2016 is the first tumor classification based on both the molecular markers and histology[9-10]. In this update, main molecular markers of gliomas (Table 1) were highlighted as IDH, 1p19qdeletion, MGMT, TERT, ATRX, and p53[9-10]. Those molecular changes were observed in various signaling pathways which participant the regulation of tumor behavior. After 9-year research from the CNS Tumors 2007, IDH1/2 still keep the title of "star molecule" in glioma.

IDH1/2 are enzymes in Krebs cycle which catalyzes the conversion of isocitrate to alpha-ketoglutarate. IDH1 mutations in the active site of codon 132 (R132H) result in the abnormal production of 2-hydroxyglutarate, which causes histone and DNA methylation, hence promoting tumorigenesis. IDH2 mutations occur in codon 172. Mutations in IDH2 are associated with 2-hydroxyglutaric aciduria, which results in seizures, hypotonia, and progressive damage to the cerebrum. As the most important diagnostic marker distinguishing glioma from gliosis, IDH is positive in astrocytoma, oligodendroglioma, and even in 10% glioblastoma, especially secondary[9].

Table 1 Molecular markers in different levels of glioma[9]

Tumors	Molecular markers
Astrocytoma	IDH1/2, TP53, ATRX
Oligodendroglioma	IDH1/2, 1p/19q co-deletion, TERT
Glioblastoma	IDH1/2, TERT, MGMT methylation
Diffuse midline glioma, H3 K27M-mutant	H3 K27M, ATRX, TP53

IDH: Isocitrate dehydrogenase; TP53: Tumor protein p53; ATRX: Alpha-thalassemia/mental retardation syndrome X-linked; MGMT: O^6-methylguanine-DNA methyltransferase

2 Radiomics and gliomas

The accomplishment of TCGA project drives the cancer management to a new era of precision oncology[11]. Making right treatment plan in right time requires robust, validated biomarkers, which offers an opportunity for radiomics blossom. Radiomics is an extraction approach of high-throughput data which collects the quantitative image information and cluster into radiomic feature[12]. Combined with genomic, proteomic, histology, and clinical data, the radiomics is in the bud. Tumor characters become measurable by quantitative imaging approach and radiomic features provide useful information for disease diagnosis, treatment, and prognosis[13-17]. The traditional method of pathologic sampling is not able to provide a "panoramic view" of tumor and not repeatable for a certain point[18-19]. Although some researchers made effort to dig out the correlation between images and histology of gliomas, the lack of accuracy methods leads to that the results are not so precise[20]. Here radiomics offers a new direction that can be noninvasive and consecutive through the course of gliomas. Radiomics analysis can provide valuable diagnostic and prognostic information by building up the relationship between gene expression patterns and image features[21-22]. If the IDH1/2 mutation can be indirectly observed by changes in radiomics features, the evaluation of gliomas may become more convenient and rapid.

3 Workflow of radiomics

Proliferating results prove that radiomics is an approach which can be applied in a variety of researches such as genomic, proteomic, clinical outcome, and treatment assessment. Twenty-six radiomic features emerged significant changes, which were not visible to human eyes, related to gene induction in tumor cell with radiotherapy in tumors with similar volumes. Radiomics broadens the research field from patients to tumor models[23].

With the hypothesis that radiomic data can be used for tumor character research, a routine workflow of radiomics was depicted by Lambin et al[24], which is used by most researchers to conduct radiomic analysis. The first step is the acquisition of image from computed tomography, magnetic resonance imaging (MRI), positron emission tomography (PET), or other imaging devices. After segmenting into tumor regions and normal tissues, the quantitative data of interesting region are extracted. Researchers sum up the image data into quantitative image features describing the intensity distribution, spatial relationships, texture, and shape character of tumor[13]. Combined with genomic, proteomic, and clinical information, the selected features are analyzed. As quantitative data giving more information than image, imaging approaches have prodigious potential in diagnosis, treatment decision, and prognosis of cancer[25-28].

4 Radiomic analysis in gliomas: Image combined with "-omics" data in clinical oncology

4.1 Tumor classification and phenotypic difference identification

The 2016 CNS tumor classification standard showed the new method which is based on the combination of histopathology and molecular characters of tumor, which will provide great help to guide clinical diagnosis and treatment and to predict prognosis. In addition, it will provide a theoretical basis for the study of molecular subtype correlation between image features and glioma[4]. Radiomics is applied to identify tumor phenotype, gene expression pattern, and classification. Cho's group has presented a radiomic method to grade the glioma[29]. A total of 45 radiomics features form 180 features extracted from T1, T2, FLAIR and contrast help to make sense to quantify the phenotype of gliomas. After treated with L1-norm regularization, a score was gotten to predict whether the glioma is high-grade or low-grade and this method leads to the accuracy of 0.8981. The IDH1 mutation in low-grade glioma was demonstrated to play critical role in prognosis and diagnosis[8, 30]. The new idea of deep learning also improves the accuracy of radiomics analysis. All the features can be directly extracted from the deep neural network, which avoids introducing extra errors to the analysis system. Deep learning based radiomics method was applied to predict the mutation status of IDH1[31]. In this research the area under receiver operating characteristic curve(AUC) of IDH1 was 95% estimated, increased 9% compared with 86% of that using normal radiomics method. Another research highlighted MRI features and found that sharp tumor

margins, homogeneous signal intensity and less contrast enhancement are associated with IDH mutation[32]. This analysis included 193 patients with astrocytic neoplasms, in which 57.5% were detected IDH1 mutation and 3.1% IDH2 mutation. And the IDH1/2 mutations are also related to the location of tumor.

4.2 Prognostic biomarker for clinically-relevant factors

As a noninvasive method, radiomics can get dynamical and serial information. Big advantages in monitoring the behavior of tumor make radiomic researches move from bench to bedside[33-35]. The important hypothesis of radiomics to be clinical biomarkers for diagnosis, prognosis, treatment response and outcome prediction leads to the spring up of related researches[36]. Researchers get more information than the pictures from the data, while quantitative methods make the data more reliable[37]. A research with 55 glioblastoma patients has displayed that 3 enhanced MRI features are significantly related to survival of the patients[38]. PET features also can be applied to radiomics research[15, 39-40]. By extraction of tumor-to-background ratio and higher-order textural features of 70 L-S-methyl-11C-methionine (11C-MET)-PET positive glioma patients, 3 models were built up and got high accurate prediction results for survival[41].

4.3 Treatment monitoring and outcome prediction

Radiomics features gotten during tumor process or treatment course make noninvasive detection possible. Functional MRI was used to analyze survival of bevacizumab-treated patients. Low apparent diffusion coefficient from the lower curve (ADC-L) is associated with poor outcome, which was confirmed by the multi-center brain study[42]. As these studies are mainly working for clinic, both convenience and cost are taken into consideration. Software development plays a critical role for radiomics research progression. Radiomic research process is simplified by the invention of specialized software IBEX[43]. Workflows are running automatically after inputting information and setting parameters, which offers great convenience for researchers. Semi-automated tumor segmentation software helps to make the image features more objective[44]. Combined effective hardware (advanced imaging devices) with software, radiomics will contribute to develop new profile of tumor with molecular tumor characters.

5 Conclusion and promising future of radiomics

Radiomics, radiogenomics, and molecular imaging consist the coming generation of imaging. As a high-throughput noninvasive approach, radiomics offers a new choice for cancer research. With the same extraction data, both macro and micro analysis from genome to clinically relevant factors can be conducted. With the tumor heterogeneity on different levels such as genome, cells, tissues, and individuals, radiomics gives a noninvasive and dynamic monitoring way which is convenient and low costs[45-46].

There are a few of exciting findings in this field. However, most of the studies only demonstrated the association between tumor phenotype and image features, instead of the gene level. That means these studies did not tell a whole story.

To summary, studies on radiomics are pushing the understanding of gliomas by providing information for better clinical classification and prognosis. As a new field, the radiomics research in gliomas still has a long way to go[47-48].

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