MINI REVIEW

Perspective: Imaging for Gliomas

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The 2016 World Health Organization classification of tumors of the central nervous system broadly employs genetic alterations for diagnostic criteria including isocitrate dehydrogenase-1 (IDH1) mutation or IDH2 mutation, and 1p/19q codeletion,[1] with the goal of creating more homogeneous disease categories with greater prognostic value.[2-5] Molecular diagnostics is becoming an increasingly important aspect of clinical oncologic neuropathology practice. However, genetic analyses are time consuming and costly. It is hoped that further accumulation of research work will help to clarify the correlations and discrepancies between the findings of molecular testing, conventional microscopic morphological examination of hematoxylin and eosin staining, and diagnostic imaging in clinical practice, despite potential conflicts.[2] Some investigations have tried to clarify the correlation between pre-operative imaging and genetic status. Leu *et al*.[6] reported that the combination of perfusion and diffusion-weighted magnetic resonance imaging (MRI), especially the combination of regional cerebral blood volume, apparent diffusion coefficient, T2 hyperintense volume, and presence of contrast enhancement may aid in non-invasively identifying genetic subtypes of diffuse gliomas. Brendle *et al*.[7] evaluated perfusion, dynamic contrast-enhanced (DCE) perfusion imaging, and arterial spin labeling (ASL). DCE and ASL perfusion were reported to be complementary in the differentiation of gliomas.

Genetic analyses are time consuming and costly. More time is necessary than before between the acquisition of specimens at the surgical intervention and completion of their investigation including genetic alterations. The decision-making regarding the indications for placement of a nitrosourea wafer on the surgical operative field to cover the interval between the surgical intervention and beginning of drug therapy based on the definite diagnosis of malignant glioma usually has to be made based on the pre-operative imaging findings and quick histological diagnosis of frozen sections. It is hoped that a new regimen can be devised that will be able to considerably shorten this interval. It is also hoped that the optimal integration of genetic features, surface markers, HE histological morphological characteristics, and imaging findings including promising molecular and functional imaging will allow appreciable cost savings.[8]

Arai *et al*.[9] presented a case of glioblastoma, with atypical findings on MRI, arising during treatment with lenvatinib for thyroid cancer. MRI revealed a slightly high-intensity lesion in the left frontal base area on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images, and the lesion showed only faint enhancement on T1-weighted images, after gadolinium administration. Although the histopathological diagnosis was glioblastoma, Grade IV histology was observed in only a limited area and the majority of the specimen showed lower grade histology. They warned that molecular targeting agents used for other preexisting neoplasms might modify the imaging findings of brain tumors. The number of patients treated with chronic antineoplastic drugs is increasing. Opportunities to encounter such patients who developed brain tumors while receiving molecular targeting drugs are also likely increasing. In such patients not only the imaging findings but also the clinical course may be affected. They described that in patients receiving molecular target therapy for other diseases, it is necessary to consider a more aggressive pathology than indicated by the images. It is well known that antiangiogenic agents often produce a rapid decrease in contrast enhancement because of reduced vascular permeability despite not having a true antitumor effect. It is always difficult to distinguish a decrease in contrast enhancement due to reduced vascular permeability by antiangiogenic agents from true antitumor effects. Actually bevacizumab is used not only for its antitumor effects but also for antiangiogenic ones to reduce peritumoral brain parenchymal edema and improve patient symptoms in the postradiotherapy period.[10] Furthermore,

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pseudoprogression is sometimes clinically observed during follow-up after chemotherapy for gliomas and radiation necrosis after radiotherapy, both of which would show enhancement by contrast medium on imaging. Besides at the initial diagnosis of diffuse glioma, during evaluation of the treatment results, for example, associated with RANO criteria[11] after chemotherapy, particular care has to be taken in observing the follow-up imaging findings.

Modification of the imaging findings by previously administered drugs may be problematic in radiotherapy for glial tumors. During treatment planning of recent intensity modulated radiation therapy (IMRT) for glial tumors, pseudonormalization of images, resulting in underestimation of tumor volume, may interfere with the appropriate delineation of the target volumes. Target volumes would be defined based on the gadolinium enhancement area and surrounding T2-weighted or FLAIR high-intense area in IMRT with simultaneous integrated boost (SIB).[12] For example, Iuch *et al*.[13] employed three-layered planning target volumes (PTVs) in a hypofractionated schedule. PTV1 was the surgical cavity and residual tumor on T1-weighted MRI with 5-mm margins, PTV2 was the area with 15-mm margins surrounding the PTV1, and PTV3 was the high-intensity area on FLAIR images. Irradiation was performed in eight fractions at total doses of 68, 40, and 32 Gy for PTV1, PTV2, and PTV3, respectively. They used concurrent temozolomide (TMZ) given at 75 mg/sq m/day for 42 consecutive days. Adjuvant TMZ was given at 150–200 mg/sq m/day for 5 days every 28 days. We also performed IMRT with SIB using three PTVs with a more conventional fraction schedule by TrueBeam STx (Varian, Tokyo) linear accelerator with an ExacTrac (BrainLAB, Tokyo) patient positioning system. PTV1 is the surgical cavity and residual tumor on T1-weighted magnetic resonance images with 2-mm margins, PTV2 is the high-intensity area on pre-operative FLAIR with 2-mm margins, and PTV3 is the area surrounding the PTV2 with 15-mm margins. Irradiation was performed in 30 fractions at total doses of 69, 60, and 48-54 Gy for PTV1, PTV2, and PTV3, respectively (unpublished data). We also used concurrent and adjuvant TMZ. Planning of these IMRT depends entirely on the pre-operative and post-operative MRI findings.

Understanding is achieved by higher detailed research datum accumulation of the associations among genetic features, surface markers, HE histological morphological characteristics, and imaging findings including molecular imaging and contrast enhancement depending on blood–brain barrier conditions affected by not only tumor infiltration but also drug-induced alterations. It is hoped that greater advances in both molecular imaging and functional imaging will aid in the identification of the genetic characteristics affecting prognosis.

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