·Special Lectures·

Current concepts in glioblastoma imaging

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Keywords

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Abstract

Glioblastoma (GBM, WHO grade Ⅳ) is the most common and the most malignant primary brain tumor occurring during adulthood, with an annual incidence of 5 cases per 100 000. Treatment involves surgical resection, followed by radiotherapy and concomitant and adjuvant temozolomide. Despite multimodality treatment, the median survival time is 15 months. Herewith we discuss the value of neuroimaging in differentiating GBM from other types of brain tumors, in guiding tumor biopsy, in making non-invasive assessment of tumor's aggressiveness, in estimating overall prognosis, in differentiating treatment-induced brain necrosis from tumor recurrence and in assessing response to treatment.

Glioblastoma (GBM, WHO grade Ⅳ) is the most common and the most malignant primary brain tumor occurring during adulthood, with an annual incidence of 5 cases per 100 000 [1-2]. Despite multimodality treatment consisting of gross surgical resection, radiotherapy and concomitant and adjuvant temozolomide, the median survival is 15 months [3-4]. Several prognostic factors have been identified so far including younger age, Karnofsky performance score over 80, total surgical resection, O^6-methylguanine DNA methyltransferase (MGMT) promoter, epidermal growth factor receptor (EGFR) amplification, Ki-67 index, *PTEN*, multidrug resistance proteins expression and polymorphisms in the *LIG4*, *BTBD2*, *HMGA2*, and *RTEL1* genes[1, 3-5].

The major neuroimaging techniques used in patients with GBM are magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Advanced MRI techniques, including diffusion, perfusion and spectroscopy, offer important diagnostic advantages over conventional imaging in the assessment of patients with GBM (Fig. 1). Diffusion MRI measures the mobility of water within tissues. Diffusion tensor imaging (DTI) permits the mapping of the diffusion process of water molecules. Fractional anisotropy (FA), a measure of diffusion directionality, provides a quantitative estimate of the degree of diffusion anisotropy. Perfusion MRI measures the vascularity within a tumor. The dynamic susceptibility contrast (DSC) imaging produces maps of relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), and mean transit time (MTT, Fig. 2). MR spectroscopy (MRS) can measure important tumor metabolites such as N-acetyl aspartate (NAA), choline (Cho), creatine (Cr), myoinositol (mI), lactate (Lac), mobile lipids (Lip) and other macromolecules. Yet no tumor-specific metabolite has been recognized to date. In brain tumors there is usually an increased signal of Cho, whereas NAA and Cr are reduced [6-7]. Nuclear medicine scintigraphic techniques, namely PET and SPECT, have also been employed towards the evaluation of brain tumors. Various radiotracers are currently used with different indications. Compared to PET, SPECT has the advantage of lower cost and wider availability, nevertheless PET has better spatial resolution, sensitivity and specificity[8-9].

The role of these imaging modalities focus on the differentiation of GBM from other types of brain tumors, in guiding tumor biopsy, in the non-invasive assessment of tumor aggressiveness, in the estimation of prognosis, in the differentiation of treatment-induced necrosis from tumor recurrence and in the assessment of response to treatment.

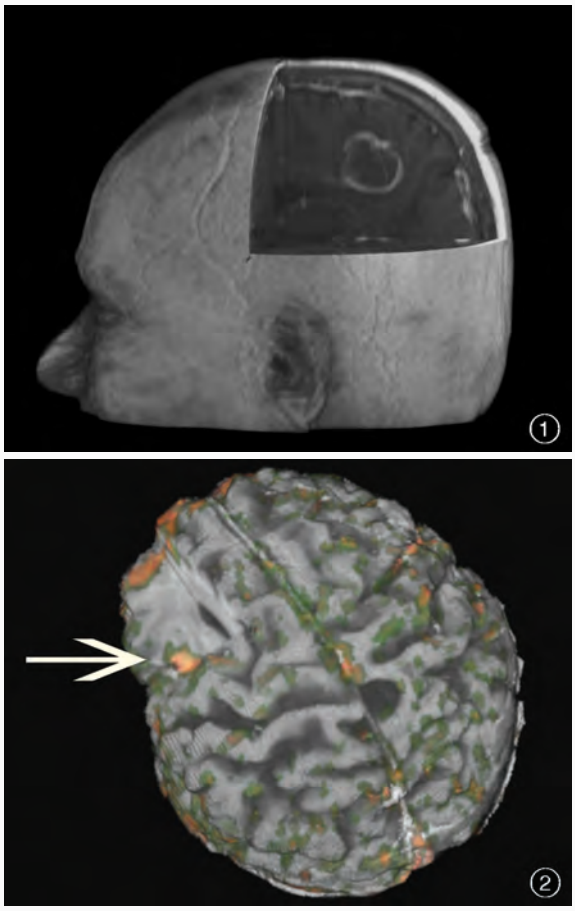

Figure 1 Volume rendering 3D T_1-weighted image of a glioblastoma **Figure 2** 3D perfusion rCBV map in a case of recurrent glioblastoma (arrow indicates)

The difference of GBM from other space-occupying lesions such as solitary metastasis, abscess or lymphoma may be challenging. Measured by MRS the metabolite levels in peritumoral edematous and surrounding apparently normal brain region narrow the differential[10]. Wijnen et al. recently reported that the level of Cho, mI, glycine, NAA and Cr were significantly different in GBM from metastasis and meningioma. Furthermore, perfusion MRI may exclude the presence of lymphoma, given that primary brain lymphoma has higher cellularity and is lack of neoangiogenesis, thus the rCBV is not elevated. DTI has a potential to differentiate abscess from GBM and metastasis[11]. Brain SPECT and PET have been also used to exclude the presence of a brain abscess, an entity exhibiting significantly fainter radiotracer uptake as compared with GBM[12-13]. Besides, all the above imaging modalities can also provide complementary functional information to guide stereotactic biopsy, since the biopsy should be targeted towards a 'hot spot' seen on MRS, perfusion-weighted MR, or SPECT/PET scan (Fig. 3).

On the topic of non-invasive assessment of GBM aggressiveness and patient's prognosis, both MR and nuclear medicine techniques have shown positive results[9]. Law et al[14]. reported that cases exhibiting rCBV over 1.75 were associated with a significantly more rapid time to progression than patients with lower values. In diffusion weighted imaging (DWI) minimum apparent diffusion coefficient (ADC) values were well-negatively correlated with tumor proliferation rate (Ki-67 index), whereas a positive correlation between the FA values, cell density and the MIB-1/Ki-67 index has been reported[15]. Brain SPECT by ^{99m}Tc-Tetrofosmin showed a positive correlation between radiotracer uptake and tumor proliferation assessed by Ki-67 index or flow cytometry[16-17]. Besides, patients with a ^{99m}Tc-Tetrofosmin tumor-to-normal brain uptake exceeding 4.7 had significantly worse survival than patients with a lower uptake (Fig. 4)[18].

Thallium-201 (^{201}Tl) and ^{99m}Tc-Sestamibi (^{99m}Tc-MIBI) may also be acceptable alternatives to SPECT tracers[19]. Nevertheless, ^{99m}Tc-Tetrofosmin has been proven superior to brain tumor imaging since this tracer was not influenced by glioma's multidrug resistance phenotype[20]. Apart from SPECT, similar PET studies have been conducted. Colavolpe et al[21]. reported that pre-treatment PET scanning by fluorine-18 fluorodeoxyglucose (^{18}F-FDG) served as an imaging biomarker in recurrent high-grade glioma for predicting survival following anti-angiogenic therapy with bevacizumab.

The differentiation of treatment induced necrosis (TIN) from glioma recurrence is a common and frequent clinical problem. Chamberlain et al[22]. reported that 14% of GBM patients being treated with concurred radiotherapy and temozolomide developed surgically-confirmed early necrosis. Correct diagnosis is the cornerstone of optimal patient management, since these two entities have different treatment and prognosis. Conventional MRI has several shortcomings for the identification of TIN because both TIN and recurrent tumor may exhibit similar imaging findings. Perfusion MRI may narrow the differential. Recurrent tumor was consistently found to have higher rCBV ratio whereas TIN was seen to have lower rCBV[23]. On diffusion MRI, mean ADC and ADC ratios in glioma recurrence were significantly lower than those in TIN. In a small study, perfusion MRI scan proved superior to ^{18}F-FDG and ^{11}C-methionine (^{11}C-Met) PET for the detection of radiation necrosis[23]. With regards to SPECT, ^{201}Tl proved superior to conventional MRI in differentiating recurrence from TIN. In a systematic review, Vos et al[24]. reported that the sensitivity of ^{201}Tl SPECT in detecting recurrence ranged from 43% to 100% and the specificity from 25% to 100%. Le Jeune et al[25]. found that ^{99m}Tc-MIBI SPECT had 89% sensitivity, 83% specificity and 87% accuracy for the detection of tumor recurrence. ^{99m}Tc-Tetrofosmin was also suitable

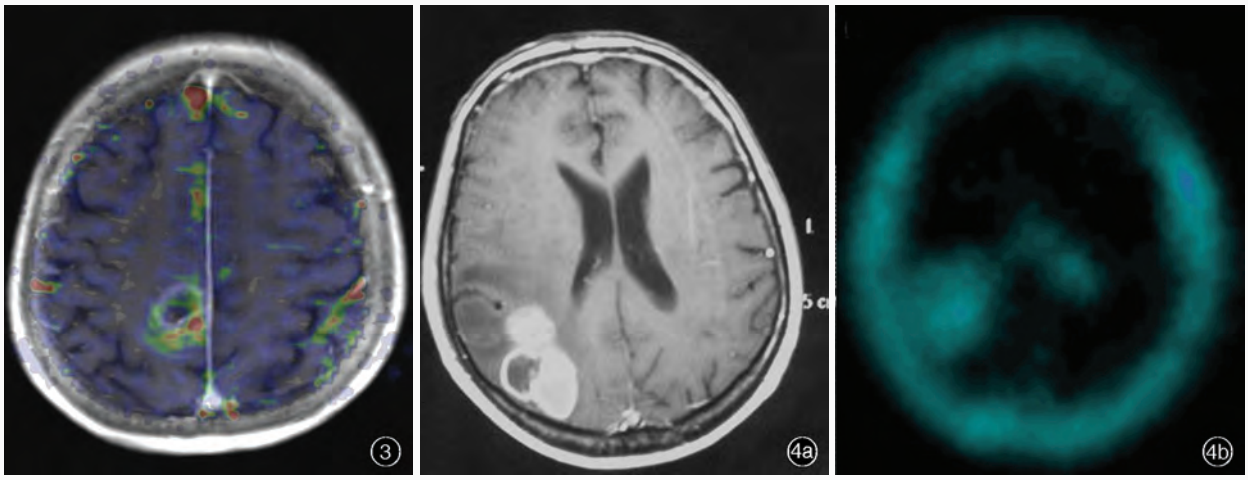

Figure 3 rCBV map superimposed on T_1WI with gadolinium enhanced revealing the tumor´s ´hot spot´ in which a stereotactic biopsy should be performed **Figure 4** A case of glioblastoma exhibits profound tracer uptake in ^{99m}Tc-Terofosmin brain SPECT. Axial enhanced T_1WI (Panel 4a). SPECT (Panel 4b)

for the detection of recurrent tumor. In a recent study this tracer proved to have similar accuracy to perfusion MRI[26 and unpublished data].

Apart from the standard GBM treatment consisting of neurosurgery, radiotherapy and chemotherapy with temozolomide (TMZ), the approval of bevacizumab, an anti-vascular endothelial growth factor (VEGF) agent for recurrent GBM, increased the need for timely detection of response to treatment. Conventional MRI detected size alterations or changes in the pattern of contrast enhancement, but these findings were not conclusive. Perfusion MRI provided valuable information on vascular remodeling in anti-angiogenic therapy and has been proposed as an indicator of response to treatment[27]. Given that SPECT and PET evaluate the tumor's metabolic activity, response to treatment could be identified earlier than that with conventional MRI. ^{99m}Tc-MIBI proved superior to conventional MRI during estimating response to treatment[28]. Hutterer et al[29]. compared conventional MRI with ^{18}F-fluoroethyl-L-tyrosine (FET) PET for the assessment of response to anti-angiogenic treatment in patients with recurrent high-grade gliomas. ^{18}F-FET PET proved superior to MRI, since it allowed for an earlier detection of tumor progression.

In conclusion, the current imaging modalities provide important information for proper patient management. Among MR techniques, perfusion MRI and MRS seem to be more accurate for the identification of tumor aggressiveness, estimation of overall prognosis, biopsy guidance, differentiation of TIN from tumor recurrence and assessment of tumor response to treatment. Nuclear medicine modalities provide also important information. In healthcare units without an on-site PET facility, SPECT by ^{99m}Tc-Tetrofosmin or ^{99m}Tc-MIBI could also render useful metabolic information.

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·小词典·

中英文对照名词词汇(一)

癌胚抗原 carcinoembryonic antigen(CEA)
靶控输注 target-controlled infusion(TCI)
胞嘧啶脱氨酶 cytosine deaminase(CD)
尺神经 ulnar nerve(UN)
磁共振波谱 magnetic resonance spectroscopy(MRS)
磁共振静脉血管造影术 magnetic resonance venography(MRV)
磁共振血管造影术 magnetic resonance angiography(MRA)
磁敏感加权成像 susceptibility-weighted imaging(SWI)
刺激间歇时间 inter-stimulus interval(ISI)
刺激强度 stimulus intensity(SI)
大脑胶质瘤病 gliomatosis cerebri(GC)
单纯疱疹病毒胸苷激酶 herpes simplex virus-thymidine kinase(HSV-tk)
单光子发射计算机体层摄影术 single photon emission computed tomography(SPECT)
胆碱 choline(Cho)
多发性硬化 multiple sclerosis(MS)
多形性胶质母细胞瘤 glioblastoma multiforme(GBM)
耳蜗电图 electrocochleogram(ECochG)
二氨基联苯胺 diaminobenzidine(DAB)
C-反应蛋白 C-reactive protein(CRP)
5-氟胞嘧啶 5-fluorocytosine(5-FC)
5-氟尿嘧啶 5-fluorouracil(5-FU)
复合动作电位 compound action potential(CAP)
复合肌肉动作电位 compound muscle action potential(CMAP)
复合神经动作电位 compound nerve action potential(CNAP)
钆喷替酸葡甲胺 gadolinium-diethylenetriaminepentaacetic acid(Gd-DTPA)
高压氧 hyperbaric oxygen(HBO)
更昔洛韦 ganciclovir(GCV)
功能磁共振成像 functional magnetic resonance imaging(fMRI)
骨髓间充质干细胞 bone marrow-derived mesenchymal stem cells(BM-MSCs)
寡克隆区带 oligoclonal bands(OCB)
灌注成像 perfusion-weighted imaging(PWI)
国际标准化组织 International Standard Organized(ISO)
红细胞沉降率 erythrocyte sedimentation rate(ESR)