CHAPTER THIRTEEN

Advanced multimodal imaging in differentiating glioma recurrence from post-radiotherapy changes

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Contents

Abstract

Gliomas are the most common malignant primary brain tumor, and their prognosis is extremely poor. Radiotherapy is an important treatment for glioma patients, but the changes caused by radiotherapy have brought difficulties in clinical image evaluation because differentiating glioma recurrence from post-radiotherapy changes including pseudo-progression (PD) and radiation necrosis (RN) remains a challenge. Therefore,

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accurate and reliable imaging evaluation is very important for making clinical decisions. In recent years, advanced multimodal imaging techniques have been applied to achieve the goal of better differentiating glioma recurrence from post-radiotherapy changes for minimizing errors associated with interpretation of treatment effects. In this review, we discuss the recent applications of advanced multimodal imaging such as diffusion MRI sequences, amide proton transfer MRI sequences, perfusion MRI sequences, MR spectroscopy and multinuclides PET/CT in the evaluation of post-radiotherapy treatment response in glioma patients and highlight their potential role in differentiating post-radiotherapy changes from glioma recurrence.

1. Introduction

Glioma accounts for about 30% of primary tumors in the central nervous system and is one of the most common primary brain tumors (Ostrom et al., 2018). The treatment of glioma is very difficult, especially for the high-grade glioma like the most malignant glioma subtype glioblastoma multiforme (GBM), even with standardized treatment including surgery, radiotherapy and chemotherapy, the median survival time of patients with GBM is only about 14–16 months (Wen & Kesari, 2008). This poor prognosis is largely due to the near universal recurrence of tumors after initial treatment because of GBM has the capacity to invade surrounding normal brain tissue making true complete removal of the tumor by surgery cannot be achieved. However, when to recurrence and the pathological type of the recurrent tumor is highly variable and cannot be predicted. Especially the changes in brain blood vessels and the destruction of the blood-brain barrier after radiotherapy also be considered to result in post-radiotherapy imaging performance (like pseudo-progression or RN) which can be manifested as intensified lesions on MRI like recurrent glioma, making it difficult to distinguish. However, differentiating true tumor recurrence from post-radiotherapy changes is crucial for how to choose the treatment options for patients with recurrent glioma. The widely used RANO criteria are a valuable tool using radiologic and clinical features aimed to correctly classify patients into progressive or non-progressive disease evaluation, both in the clinical setting and in the clinical trials (Ellingson, Chung, Pope, Boxerman, & Kaufmann, 2017). But it is still difficult to distinguish whether glioma recurrence is real or not because of the RANO assessment criteria have certain image evaluated limitations that emerging image techniques have tried to overcome. Recent years, under the need for advanced

radiologic techniques, like specific diffusion and perfusion MRI sequences, MR spectroscopy, which seem to play a role in distinguishing these phenomena. Considering MR and PETCT are the most commonly used imaging methods in glioma diagnosis and treatment follow-up, in this review we discussed recent applications of advanced MR imaging such as APT, diffusion-weighted and perfusion-weighted imaging and advanced PETCT with multiple nuclides in the evaluation of treatment response, and highlight their potential role in differentiating post-radiotherapy changes from true glioma recurrence.

2. Advanced MR imaging in identifying glioma recurrence and post-radiotherapy changes

The T1/T2/flair and enhancement MR sequences are often used in the follow-up of glioma patients during their treatment. MRI typically reveal an irregularly ring-enhancing lesion with surrounding edema, which is also consistent with tumor recurrence or post-radiotherapy changes. Diagnosing post-radiotherapy changes is difficult because of low rates of re-operation, autopsy or biopsy, which is the gold standard, and few studies correlate imaging performance with pathological. But some special sequences of MR play an important role in identifying glioma recurrence and changes after radiotherapy and also have an important role in clinical treatment (Fig. 1).

2.1 DSC-PWI

Glioma is known as its rich in angiogenesis, consisting of irregular glomerular-like newly formed blood vessels which arising from coexisting vessels, while the necrotic region reveals extensive vascular injury and tissue ischemia with vascular endothelial damage and thrombosis (Grossman et al., 1988). The use of MR imaging approach in differentiating post-radiotherapy changes from true glioma recurrence by exploiting tumor angiogenesis and neovascularity has gained interest over the past years. Dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging (DSC-PWI) is one of them and which can reflect the distribution of microcirculation of blood perfusion and generate hemodynamic parameters such as relative cerebral blood volume (rCBV), peak height, and percentage signal intensity recovery. The diagnostic value of DSC-PWI in differentiating glioma recurrence from post-radiotherapy changes has been investigated in several studies. One study showed the rCBV of recurrence

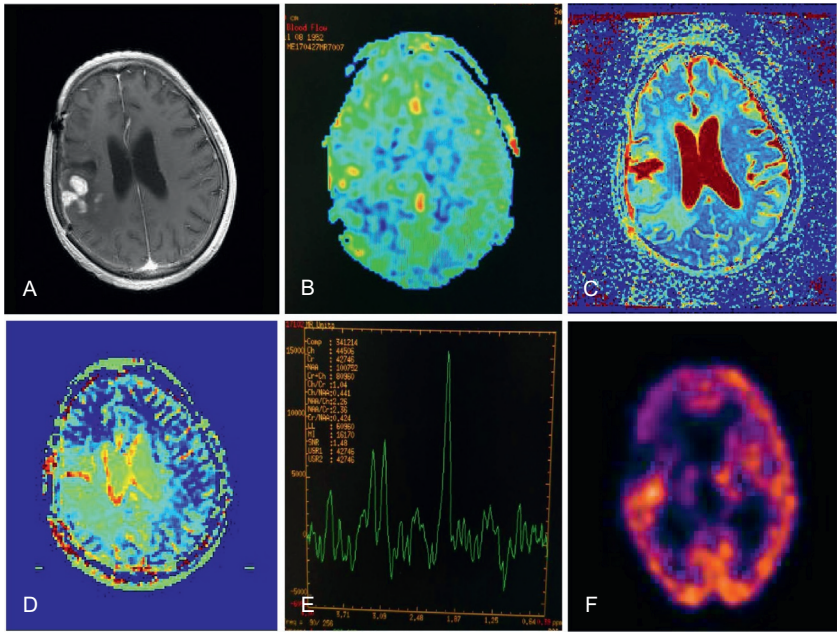

Fig. 1 An example of multimodal imaging evaluation for glioma patients after surgery and radiation therapy. (A) T1-weight MR sequence suggests irregular enhancement lesion behind the residual cavity in the right frontal. (B) Part of right frontal lesion has high perfusion in the DSC-PWI MR sequence. (C) The residual cavity in right frontal is high ADC value because of rich cerebrospinal fluid, while the ADC value at the margin of the lesion is slightly reduced in the DWI MR sequence. (D) In the APT MR sequence, part of lesion has slightly raised signal. (E) In the MRS MR sequence, the right frontal lesion has NAA peaks decreased significantly, and the Cho peak and Cho/Cr increased. (F) The right frontal lesion shows active glucose metabolism with SUV value increased in PET/CT.

group obviously higher than the radiation-induced brain injury group with a statistical significance difference (Zhang, Niu, & Han, 2014). Another study included 56 patients (30 patients were glioma recurrence which confirmed by histopathology, and 26 patients were pseudo-progression) reported that when rCBV > 2.15 was confirmed as the critical value to distinguish the recurrence of glioma, the sensitivity and specificity of the differential diagnosis were 84.5% and 100.0%, respectively (Wang, Wang, Zhang, Yong, & Kuihong, 2017). Kong et al. (2011) found it's likely to be glioma recurrence when rCBV was >1.47 and there was a significant difference in the maximum rCBV ratio between true glioma recurrence and pseudo-progression associated with significant statistical differences ($P = 0.003$). Wang (2009) used the ratio of rCBV > 1.579 as the threshold to indentify glioma

recurrence form post-radiotherapy changes, and the sensitivity and specificity were 74% and 100%, respectively. Bobek-Billewicz, Stasik-Pres, Majchrzak, and Zarudzki (2010) standardized the rCBV (rCBV = CBV affected side/CBV health side) to obtain rCBV threshold. When $rCBV_{max}$ was >1.7 or $rCBV_{mean}$ was >1.25, it means that the glioma has recurred and when the $rCBV_{max}$ was <1.0 or $rCBV_{mean}$ was <0.5, it's highly indicated as post-radiotherapy changes. Furthermore, some studies suggested that the changes in rCBV may be more useful. Mangla et al. (2010) found seven patients with suspected pseudo-progression had a mean decrease in rCBV of 41% after chemo-radiotherapy therapy, while 12 patients with suspected true progression had a mean increase in rCBV of 12%. Boxerman et al. (2017) investigated the value of longitudinal trends in rCBV for predicting pseudo-progression following radiation therapy, and found only the change in rCBV at the first subsequent follow-up and the overall linear trend in rCBV after initial progressive enhancement, but not the mean rCBV at initial progressive enhancement to be significantly different between true glioma recurrence and pseudo-progression. Based on these results, it's concluded that longitudinal trends in rCBV may be more valuable than absolute rCBV in distinguishing them (Table 1).

Given the cellular heterogeneity within tumors, Tsien et al. hypothesized that the parametric response map (PRM) of rCBV at week 3 during

Table 1 A summary of the diagnostic performance of DSC-PWI MR imaging parameters in some studies.

Nation	Study/year	Parameter	Cutoff	Sensitivity (%)	Specificity (%)
China	Wang et al. (2017)	rCBV	2.15	84.5	100.0
China	Zhang et al. (2014)	Mean rCBV	2.17	NA	NA
Korea	Kong et al. (2011)	rCBV	1.47	81.5	77.8
China	Wang (2009)	rCBV	1.58	74	100
Poland	Bobek-Billewicz et al. (2010)	rCBVmax/ rCBVmean	1.70/1.25	NA	NA
USA	Boxerman et al. (2017)	Change in rCBV at first subsequent follow-up	0.84	NA	NA

chemo-radiotherapy would better distinguish pseudo-progression from glioma recurrence in patients with high-grade glioma, as compared with standard imaging methods including percent change of rCBV and relative cerebral blood flow (rCBF). According to PRM analysis, a significantly decreased blood volume at week 3 was noted in patients with progressive disease as compared with those with pseudo-progression ($P<0.001$) (Tsien et al., 2010). However, this method was based on early perfusion data acquired at week 3 during chemo-radiotherapy, which is not a standard time for follow-up MR imaging. In addition, histogram analyses of perfusion data have been undertaken in a few studies. Song et al. (2013) analyzed predictive values of the 70th, 90th, and 95th percentile points from cumulative nCBV (relative CBV of the tumor normalized with respect to the contralateral normal white matter) histograms as well as the mean and peak height from nCBV histograms. However, there was no significant differentiating parameter on the nCBV histograms. Baek, Kim, Kim, Choi, and Kim (2012) found that percent change of kurtosis and skewness of nCBV between the first and second post-concurrent chemotherapy and radiation therapy follow-up in patients with newly diagnosed glioblastomas may serve as an imaging predictor for early treatment response. They think the histographic pattern of nCBV was the best independent predictor for early tumor progression, rather than each percent change of skewness or kurtosis, with a sensitivity of 85.7% and a specificity of 89.2%. Predictive values of other parameters such as relative peak height (rPH) and percent signal change (PSR) correlate with rCBV have also been investigated in some reports. The rPH, known to correlate with rCBV, is defined as the maximal change in signal intensity (Barajas et al., 2009). And the PSR is influenced by the size of the extravascular space and contrast leakage. Therefore, lower PSR implies delayed return of the perfusion curve to baseline and thus higher vascular permeability (Mangla et al., 2011). Young et al. reported that pseudo-progression showed significantly lower median rCBV and rPH and higher PSR than true progression. This observation is thought to reflect the reduced or absent neoangiogenesis as well as low-grade leakiness attributable to inflammation and edema in pseudo-progression (Young et al., 2013).

2.2 DWI

Diffusion-weighted imaging (DWI) is an advanced imaging technique to evaluate the molecular function and to detect microscopic water diffusion

of the human body, which is a method of signal contrast generation based on the differences in Brownian motion. Generally speaking, the cell density is high in recurrent glioma tumors and low in the post-radiotherapy changes. Then the diffusivity of water molecules is expected to be decreased due to relative reductions in extracellular space of recurrent glioma tumors. Due to apparent diffusion coefficient (ADC) values from DWI are believed to reflect the cellularity in tumors, which means it's may valuable in differentiating post-radiotherapy changes from glioma recurrence. Various parameters from ADC histograms, such as the fifth percentile of cumulative ADC histograms, the mean, kurtosis, and skewness, have been previously investigated. Also there are some other parameters such as the ADC or FA ratio, the minimum or maximum ADC, and rADC in parametric response maps. The fifth percentile has been confirmedly shown to be helpful in distinguishing true glioma tumors or pseudo-progression or RN (Chu et al., 2013; Song et al., 2013). Chu et al. (2013) reported that the fifth percentiles of cumulative ADC histograms at both standard and high b values were significantly lower in the true progression group than in the pseudo-progression group. Another study by Song et al. (2013) has shown that true relapsed glioma could be differentiated from pseudo-progression with a sensitivity of 90% and a specificity of 90% using a cut off fifth percentile ADC value as 892×10^{-6} mm^2/s. The mean ADC value has been found to have the discriminative ability to identify the relapsed glioma from post-radiotherapy changes in some studies (Lee et al., 2012), but not in others (Chu et al., 2013; Song et al., 2013). With regard to some other histogram parameters such as kurtosis, skewness, there was no significant difference was showed between this two groups (Lee et al., 2012). Some reports explained the results of the mean ADC value and the fifth percentiles of the cumulative ADC histograms by showing that real relapsed glioma consists of more cellular components, as reflected by a higher relative frequency at low ADC values than post-radiotherapy changes, even though both true progression and pseudo-progression comprise variable portions of viable tumors and post-radiotherapy necrosis (Kong et al., 2011; Wen et al., 2010).

As for the value of ADC ratio or FA ratio, there were some paradoxical results too. Some previous report suggested that the ADC ratio of true glioma progression was lower than that of radiation necrosis. Li et al. (2013) reported that the ADC ratio of the lesion enhanced area in the true progression group was lower than that in the radiation necrosis group, and the FA ratio in the real relapsed glioma group was higher than that in the

radiation necrosis group. There was no significant difference in the above two indexes between the edema of the two groups. The results of ROC curve analysis showed that the diagnostic sensitivity, specificity and accuracy of were 85%, 86.7% and 85.7% when the ADC ratio was <1.65 and (or) FA ratio was >0.36. However, some other study showed the contrary result that the ADC ratio of glioma recurrence was higher than that of radiation necrosis. Sundgren et al. (2006) analyzed that the reason for the high ADC value of true progression might be related to the expansion of the extracellular space and the predilection of necrosis in high-grade glioma, while the reduced diffusion of radiation necrosis might be related to the glial hyperplasia and fibrosis in the lesion surrounding area, which limited the diffusion of water molecules. As for FA value which has been shown to be valuable in previous histological types and grading diagnosis of gliomas (Beppu et al., 2003; Sinha, Bastin, Whittle, & Wardlaw, 2002), but the value of FA ratio in differentiating glioma recurrence from post-radiation changes has only been reported in a few cases (Hiroshi, 2007), not by enough research to support it. A report suggested (Wang et al., 2012) that the mean and maximum ADC values of the true glioma recurrence group were smaller than those of the post-radiation changes group, but the difference was not statistically significant. While the minimum ADC of the true glioma recurrence group was significantly lower than that of the post-radiation changes group implying the result that the minimum ADC has certain significance in differentiating the two groups.

There was a study used the parametric response map which is a newly introduced post-processing tool to investigate whether a voxel-wise analysis of ADC values to distinguish the glioma recurrence and post-radiation changes of high-grade glioma. In this study (Reimer et al., 2017), rADC voxels showed a decrease of 59.2% above 0.25 in patients with true glioma recurrence and 18.6% in patients with pseudo-progression. This feasibility study suggests that the assessment of rADC using parametric response maps might be an approach to identify the two groups.

2.3 APT

Amide proton transfer (APT) imaging is a new MRI technique that detects endogenous mobile proteins and peptides in tissue via saturation of the amide protons in the peptide bonds. APT is a safe, non-invasive technology which can be easily performed using existing hardware for clinical neuroimaging of gliomas. It was suggested to be able to provide more brain tumor

contrast massage (Jones et al., 2006; Zhou et al., 2008; Zhou, Lal, Wilson, Laterra, & van Zijl, 2003) based on the increased cellular content of proteins and peptides in malignant tumors (Hobbs et al., 2003; Howe et al., 2003).

An animal study showed that the amide protons detected by APT could distinguish tumor and radiation necrosis in animal study through non-invasive methods (Zhou et al., 2011). Another animal study also suggested that the APT imaging based on CEST method could not only identify glioma and post-radiation changes, but also detect the post-chemotherapy changes of glioblastoma in orthotopic transplantation (Sagiyama et al., 2014). Su, Zhang, and Zhang (2017) showed that APT imaging can provide excellent results in differentiating glioma recurrence and post-radiation changes when combine with the routine MRI images. The magnetization transfer ratio (MTR) as well as the relative MTR (rMTR) between glioma and post-radiation changes was significantly different. The MTR and rMTR are able to differentiate the two groups with high sensitivity and specificity. Both MRT and rMRT exhibited diagnostic performance with the AUC of 0.986 and 0.943. Ma et al. (2016) reported that the APT is hyperintensity in real glioma recurrence, while pseudo-progression was associated with APT isointensity to mild hyperintensity. The cut off APTmean and APTmax to distinguish between this two groups were 2.42% and 2.54%, respectively. Some further study suggested that APT imaging can predict the WHO grades of adult diffuse gliomas. The mean APT signal intensity values were 2.1 + 0.4% in grade II gliomas, 3.2 + 0.9% in grade III gliomas, and 4.1 + 1.0% in grade IV gliomas (Togao et al., 2014). Togao et al. (2017) also found that APT imaging is useful in discriminating HGGs from LGGs among diffuse gliomas, the APT90 and APTmean were significantly higher in the HGGs compared to the LGGs.

2.4 MRS

Magnetic resonance spectroscopy (MRS) is based on metabolite detection by measurement of the spectra of specific isotopes, for example, ^{1}H, ^{13}C or ^{31}P which is one of the MR methods plays an important non-invasive and safe role in determining brain tumor types and grades. Concentrations of the metabolites are relatively steady for normal brain tissue but they may change due to disturbances in metabolism during different tumor grades. There are lots of metabolites that can be identified by MRS, but only a few of them has clinical significance in diagnosis of gliomas, including *N*-acetylaspartate, choline, creatine, myo-inositol, lactate, and lipids.

And metabolites' levels are often expressed as ratios, rather than as absolute concentrations (Li, Wang, & Gonen, 2003). A study (Sakata et al., 2017) showed that there were significant correlations between metabolite concentrations and ratios on MRS and APT values, suggesting that both MRS and APT imaging could play potential roles for quantitatively assessing similar biological characteristics in brain tumors on MRI imaging. Another study found validated thresholds for the main metabolite concentrations obtained by MRS and the values of ADC to distinguish glioma recurrence from pseudo-progression. Glioma recurrence was observed for the total choline (tCho) to total *N*-acetylaspartate (tNAA) concentration ratio with the threshold $\geq$1.3 and the ADCmean value higher than 1313×10^{-6} mm^2/s was identified to pseudo-progression. The combination of MRS focused on the tCho/tNAA concentration ratio and the ADCmean value could applicable to early non-invasive and high significant sensitivity and specificity to differentiated between glioma recurrence and pseudo-progression (Kazda et al., 2016). Some other study showed that MRS alone could moderately differentiate glioma recurrence from radiation necrosis using metabolite ratios like Cho/Cr and Cho/NAA ratio. Quantitative analysis showed that the sensitivity and specificity for Cho/Cr ratio both were 0.83 and the AUC under the characteristic curve was 0.9001. The sensitivity and specificity for Cho/NAA ratio were 0.88 and 0.86, respectively. The AUC under the characteristic curve was 0.9185 (Zhang et al., 2014). Some other studies suggest that the MRS should be combined with other advanced imaging technologies to improve accuracy of non-invasive differential diagnosis. Fink et al. (2012) believed that a 3T DSC-PWI and multi-voxel MRS Cho/Cr peak-area and Cho/NAA peak-height seem to exceed DWI for distinguishing glioma recurrence from post-treatment effects. And single-voxel MRS parameters do not appear to reliably distinguish glioma recurrence from post-treatment effects, and should not be used in place of multi-voxel MRS.

3. PET/CT

Positron emission tomography and computed tomography better known as PET/CT is a nuclear medicine technique which combines, in a single gantry, a positron emission tomography (PET) scanner and an X-ray computed tomography (CT) scanner, to acquire sequential images from both devices in the same session, which are combined into a single co-registered superposed image. Thus, PET/CT not only can depicts the

spatial distribution of metabolic or biochemical activity in the body but also can be more precisely aligned or correlated with anatomic imaging obtained by CT scanning. PET/CT has the advantage of providing both functions as stand-alone examinations. There are many radiopharmaceuticals used for PET/CT imaging, liking radioactive fluorine-18 (18F) fluorodeoxyglucose (FDG) used to trace glucose metabolism making it has certain clinical value to the diagnosis of glioma grading. But 18F-FDG accumulate largely in normal brain tissue, leading to the small difference between glioma lesions and normal brain tissue (Singhal, Narayanan, Jain, Mukherjee, & Mantil, 2008). So it is not good for glioma display, especially for low-grade glioma with low metabolism and lesions close to gray matter.

A study suggested that PET/CT using radio-labeled amino acids such as O-(2-[18F]fluoroethyl)-L-tyrosine (FET), allows imaging of amino acid transport in brain tumors and is potential in distinguishing pseudo-progression from true glioma recurrence (Galldiks et al., 2015). Some static and dynamic PET features have been shown to be strongly related to pseudo-progression. As to static PET parameters, 6wparticularly the maximum tumor-to-normal brain ratio (TNRmax) at an optimal cutoff of 1.9 has been shown to be helpful with a high sensitivity and specificity in detecting glioma recurrence. The results of this pilot study suggested that textural FET-PET feature analysis might lend itself as a novel useful non-invasive tool, besides the frequently used TNRmax to distinguish pseudo-progression from true tumor recurrence in patients with HGG (Kebir et al., 2016).

11C-MET is an amino acid PET imaging agent, which can reflect the transport and metabolism of amino acids and widely used in diagnosis and differential diagnosis of brain tumors. It has important clinical value in differentiating glioma recurrence and post-radiation changes, predicting tumor recurrence, etc. (Weber et al., 2000). A study showed that the metabolic characteristic of pseudo-progression includes negative or moderately increased uptake of 11C-MET with UI of less than 1.9 in accordance with the location of a positive contrast lesion in the MRI scan. The threshold UI value of more than 1.9 enabled differentiation between continued tumor growth and its pseudo-progression with the sensitivity of 83.5% and the specificity of 97.0% (Skvortsova, Brodskaya, & Gurchin, 2014). This means 11C-MET is well useful in differentiating glioma recurrence and post-radiation changes.

13N-NH3 is another commonly used PET imaging agent, which is low fat soluble and can't completely uptake by the brain. The diameter

of 13N-NH3 is smaller than iodine or Gd DTPA, making it can penetrate the blood-brain barrier, so the 13N-NH3 has high sensitivity in evaluating blood-brain barrier change (Xiangsong, Xingchong, Chang, Xiaoyan, & Zhifeng, 2011; Zhao et al., 2008). This also means that 13N-NH3 has potential for differential diagnosis glioma recurrence from post-radiation changes.

When it comes to the comprehensive use of the PET/CT imaging agents which we discussed above, a study suggested that the possibility of glioma recurrence was extremely high if all of the 18F-FDG, 11C-MET and 13N-NH3 imaging are positive. When 11C-MET and 13N-NH3 were negative, the possibility of glioma recurrence was small. 13N-NH3 imaging results were helpful for the identification of tumor properties when 18F-FDG imaging was negative and 11C-MET imaging was positive, which indicated the possibility of glioma. But when 11C-MET imaging was negative, it is less likely to be glioma (Rao, Zhang, & Wang, 2013). So the combination of two or more PET/CT imaging agents can improve the sensitivity and specificity of the differential diagnosis of glioma recurrence from post-radiation changes.

4. Discussion

Over the past decade, radiotherapy, like surgery and adjuvant chemotherapy, is considered as an important cornerstone treatment for high-grade gliomas, for example, anaplastic astrocytoma and glioblastoma. Although radiotherapy is demonstrated clinically meaningful and significant survival benefits for glioma patients, it is associated with a high incidence of post-radiotherapy imaging changes because of radiation-related brain injury. Radiation-related brain injury can be acute injury, early delayed injury (well known as pseudo-progression) and late injury (termed radiation necrosis) (Chao et al., 2013). Acute injury occurs during radiotherapy. Pseudo-progression is a form of early delayed injury, which should always be considered in the first 3 months after concurrent chemo-radiation for gliomas (Brandsma, Stalpers, Taal, Sminia, & van den Bent, 2008). On the other end of the spectrum, radiation necrosis is part of late injury that usually appears months to years after radiation treatment. Pseudo-progression will be defined as being reversible and radiation necrosis is permanent radiation injury and defined as being irreversible.

Acute injuries seem to be caused by vasodilation, blood–brain-barrier impairment and changes in vascular permeability. Pseudo-progression is

regarded as a subacute form of radiation-related reaction with or without neurological deterioration. It occurs in a reported incidence of 20–30% within the first 3 months after the completion of concurrent chemo-radiotherapy in glioblastoma multiforme (GBM) patients. But the patho-physiology of pseudo-progression and molecular changes associated with it still poorly understood. However, radio-necrosis regarded as a late injuries involve tissue necrosis linked to vessel damage and edema. Vascular injury initiates the process of radiation necrosis. Histologic analyses have shown radiation necrosis occurs in the white matter and is associated with calcification, fibrinoid deposition, vascular hyalinization and endothelial thickening (Schultheiss, Kun, Ang, & Stephens, 1995; Yoshii, 2008).

The typical performance of radiation necrosis in enhanced T1 MRI is irregular circular enhanced lesion, like a cheese or soap bubble. Sometimes it can be asymptomatic, and sometimes it presents as a space occupying necrotic mass provoking neurological deficit. Although pathology is the gold standard in the differential diagnosis of radiation necrosis from true glioma recurrence, it still be challenging in certain cases, because radiation necrosis can contain some portions of viable tumor. However, many patients with recurring glioma are not good candidates for re-operation, so it is particularly important to distinguish the glioma recurrence and radiation necrosis through imaging follow-up. But this identification is difficult, especially when a progressive lesions showed on conventional contrast-enhanced MR imaging and accompany with clinical deterioration it is a diagnostic challenges to clinicians and radiologists. False interpretation of post-radiation change as true glioma recurrence may lead to the cessation of effective first-line therapy and unnecessary re-operation. So better advanced imaging techniques including different sequences of magnetic resonance and PET/CT which may useful in differentiating the post-radiation change from true glioma recurrence is the urgent need for clinicians.

Novel advanced imaging approaches including diffusion, perfusion, and metabolic imaging appear to show promise in accurately identifying post-radiation change from true glioma recurrence. Among diverse advanced MR imaging techniques, perfusion-weighted imaging (PWI) and MRS techniques have been used in the clinic for a long time and considered attractive imaging bio-markers for certain identification of post-radiation change with tumor recurrence in high-grade glioma patients. In addition, advanced MR imaging techniques such as APT and advanced PET/CT have shown promising applications. But even so, there is currently no method to make a very good differential diagnosis. The combination of multiple advanced

MR and PET/CT imaging methods may be helpful to improve the accuracy and specificity of differential diagnosis. However, in the application of these technologies, they may also encounter problems that are inconsistent with measurement variability, false positives, and different interpretations of imaging doctors. These problems and different interpretation currently have high variability and/or imperfect accuracy, which is at least partly attributed to a lack of consensus on standardized approaches for image acquisition, post-processing and analysis. Future efforts need to focus on homogenizing these approaches, which is necessary for more comprehensive and objective evaluation for using in the area of differential diagnosis between post-radiation changes and tumor recurrence. Therefore, there is a need for better imaging tools to determine brain tumor response to therapy based on understanding biological changes within the tumor and minimizing errors associated with evaluation and interpretation of treatment effects. Comprehensive imaging methods, including magnetic resonance and PET/CT, are the research directions with promising prospects.

5. Conclusion

With the standardized application of radiotherapy in high-grade gliomas patients, the probability of post-radiotherapy changes is increasing. However, to date, there is still no established standard imaging method to diagnose post-radiotherapy changes including pseudo-progression and radiation necrosis. Therefore, the hard to distinguish post-radiotherapy changes from glioma recurrence brings significant challenges in clinical treatment. Over the past few years, there are, however, more development of imaging in advanced MR including PWI, MRS, DWI and APT and advanced multinuclides PET/CT including 18F-FDG, 11C-MET and 13N-NH3 showed a certain effect to distinguish post-radiotherapy changes from glioma recurrence, which is of great help to the clinical diagnosis and treatment. But the standard imaging evaluation protocol which could widely used in clinical, more reasonable and accurate for follow-up of glioma patients still needs more research to confirm.

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