PERFUSION AND DIFFUSION MRI OF GLIOBLASTOMA PROGRESSION IN A FOUR-YEAR PROSPECTIVE TEMOZOLOMIDE CLINICAL TRIAL

THESE

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par

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IRM DE PERFUSION ET DE DIFFUSION DE LA PROGRESSION DU GLIOBLASTOMÈRE DANS UN ESSAI CLINIQUE PROSPECTIF DE 4 ANS DU TEMOZOLOMIDE

RESUME

BUT

Cette étude a été menée sur le suivi de patients traités pour un glioblastome nouvellement diagnostiqué. Son objectif a été de déterminer l’impact des séquences de perfusion et de diffusion en imagerie par résonance magnétique (IRM). Un intérêt particulier a été porté au potentiel de ces nouvelles techniques d’imagerie dans l’anticipation de la progression de la maladie. En effet, l’intervalle de temps libre de progression est une mesure alternative de pronostic fréquemment utilisée.

MATERIEL ET METHODE

L’étude a porté sur 41 patients participant à un essai clinique de phase II de traitement par temozolomide. Leur suivi radiologique a comporté un examen IRM dans les 21 à 28 jours après radiochimiothérapie et tous les 2 mois par la suite. L’évaluation des images s’est faite sur la base de l’évaluation de l’effet de masse ainsi que de la mesure de la taille de la lésion sur les images suivantes : T1 avec produit de contraste, T2, diffusion, perfusion. Afin de déterminer la date de progression de la maladie, les critères classiques de variation de taille adjoints aux critères cliniques habituels ont été utilisés.

RESULTAT

311 examens IRM ont été revus. Au moment de la progression (32 patients), une régression multivariée selon Cox a permis de déterminer deux paramètres de survie : diamètre maximal en T1 (p>0.02) et variation de taille en T2 (p<0.05). L’impact de la perfusion et de la diffusion n’a pas été démontré de manière statistiquement significative.

CONCLUSION

Les techniques de perfusion et de diffusion ne peuvent pas être utilisées pour anticiper la progression tumorale. Alors que la prise de décision au niveau thérapeutique est critique au moment de la progression de la maladie, l’IRM classique en T1 et en T2 reste la méthode d’imagerie de choix. De manière plus spécifique, une prise de contraste en T1 supérieure à 3 cm dans son plus grand diamètre associée à un hypersignal T2 en augmentation forment un marqueur de mauvais pronostic.
PERFUSION AND DIFFUSION MRI OF GlioblastOMA PROGRESSION IN A FOUR-YEAR PROSPECTIVE TEMOZOLOMIDE CLINICAL TRIAL

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Purpose: This study was performed to determine the impact of perfusion and diffusion magnetic resonance imaging (MRI) sequences on patients during treatment of newly diagnosed glioblastoma. Special emphasis has been given to these imaging technologies as tools to potentially anticipate disease progression, as progression-free survival is frequently used as a surrogate endpoint.

Methods and Materials: Forty-one patients from a phase II temozolomide clinical trial were included. During follow-up, images were integrated 21 to 28 days after radiochemotherapy and every 2 months thereafter. Assessment of scans included measurement of size of lesion on T1 contrast-enhanced, T2, diffusion, and perfusion images, as well as mass effect. Classical criteria on tumor size variation and clinical parameters were used to set disease progression date.

Results: A total of 311 MRI examinations were reviewed. At disease progression (32 patients), a multivariate Cox regression determined 2 significant survival parameters: T1 largest diameter (p < 0.02) and T2 size variation (p < 0.05), whereas perfusion and diffusion were not significant.

Conclusion: Perfusion and diffusion techniques cannot be used to anticipate tumor progression. Decision making at disease progression is critical, and classical T1 and T2 imaging remain the gold standard. Specifically, a T1 contrast enhancement over 3 cm in largest diameter together with an increased T2 hypersignal is a marker of inferior prognosis. © 2005 Elsevier Inc.

Magnetic resonance imaging, Perfusion, Diffusion, Glioblastoma, Progression.

INTRODUCTION

Glioblastoma (GBM) is the most frequent primary brain tumor among adults (1, 2). Despite surgery, radiotherapy, and adjuvant chemotherapy (3, 4), this tumor almost invariably recurs at its initial site. Disease progression usually occurs within 3 to 6 months and rapidly leads to death. New treatments for patients with this malignant neoplasm have recently been developed. Among these treatments, temozolomide, an alkylating agent, has shown activity against GBM (5–8). In the phase II trial on which this study is based, we have shown the feasibility and promising survival of the administration of temozolomide chemotherapy with concomitant radiotherapy followed by up to 6 cycles of adjuvant treatment (8). This approach has recently been shown to improve progression-free and overall survival in a randomized phase III trial (9).

In parallel to the recent use of temozolomide, several advanced imaging technologies have become more readily available in cancer centers and hospitals. Thus, the frequent use of magnetic resonance imaging (MRI) has set standards in the brain imaging of tumors by allowing better topographic diagnosis and delineation of tumor extension. T1 gadolinium-enhanced imaging is used to assess the leakage of contrast agent through the blood–brain barrier, commonly disrupted in high-grade glioma, and T2-weighted imaging is used to estimate edema development. However, because of the inherent difficulty in measuring response to treatment or assessing true disease progression in the brain (10), complementary imaging techniques may be of great clinical significance. MRI diffusion and perfusion imaging—in contrast to more complex and expensive techniques such as PET with amino acid tracers and thallium 201 SPECT—can be used to supplement routine MRI investigations without excessive time and cost increase (11, 12). Furthermore, both diffusion and perfusion imaging techniques can be helpful and potentially superior to T1 and T2 in the management of tumor evolution. For example, diffusion imaging reflects cellularity (13, 14), and perfusion imaging may give information on vascular density and...
angio genesis (15–17). These advanced MRI techniques may improve radiologic prediction of response or progression and thus be helpful for the accurate treatment adjustment for an individual patient.

In this study, we aimed to evaluate and confirm the added value of perfusion and diffusion MRI sequences in patients treated at a single institution within a prospective clinical trial. Thus, evolution of GBM in a homogeneous patient population was carefully monitored by a close medical and radiologic follow-up, with classical T1-weighted and T2-weighted MRI, as well as diffusion and perfusion imaging. This study analyzes in particular the behavior of T2, perfusion, and diffusion at disease progression. Special attention has been given to the use of these imaging technologies as tools to potentially anticipate disease progression. Furthermore, multivariate survival analysis has been carried out to establish which radiologic criteria could be especially useful for neuroradiologists and oncologists who examine MRIs of patients with glioblastoma.

METHODS AND MATERIALS

Patients and therapy

Patients with newly diagnosed and histologically confirmed glioblastoma were enrolled in a prospective phase II clinical trial. Treatment after biopsy or surgery consisted of radiotherapy and concomitant temozolomide during 6 weeks, followed after a 4 week interval by up to 6 monthly cycles of adjuvant temozolomide (8). Among the 64 patients enrolled in this trial, 41 patients treated at a single institution and for whom MRI documentation was available were considered for this radiologic ancillary study. Thirty-five patients (85%) received at least 1 cycle of adjuvant therapy, and 19 patients (46%) received all 6 cycles of adjuvant temozolomide. Twenty-three patients (56%) were male and 26 patients (63%) were at least 50 years of age. Concomitant medication and, in particular, corticosteroid and antiepileptic drugs were carefully recorded.

Imaging and follow-up

Baseline tumor imaging with MRI and CT was performed in our institution and in outside hospitals, and follow-up MRIs were performed solely in our institution. Thus, adequate MRI baseline tumor imaging was available for 28 patients. Subsequently, follow-up included MRI 21 to 28 days after the end of radiochemotherapy and every 2 months thereafter, until disease progression. Progression was usually confirmed with a second MRI after an interval of 4 to 8 weeks but without histologic confirmation. Second surgery for recurrence was usually not recommended. MR examinations were elaborated at 1.5 Tesla, T1-weighted sagittal and T2-weighted transverse spin-echo images were obtained first. Diffusion-weighted images were acquired by application of a spin-echo echoplanar technique in which a diffusion weighted b factor of 1,000 s/mm² in 3 orthogonal directions was used that allowed the computation of trace diffusion-weighted images. Twenty 5-mm thick slices with an interslice gap of 1.5 mm were used to cover the entire brain. Perfusion data were achieved with a gradient-echo echoplanar technique that allowed the acquisition of 10 5-mm thick slices (gap 1.5 mm) in the transverse orientation centered on the lesion. One stack of images was acquired every 1.2 seconds during the first pass of a bolus of contrast agent injected in an antecubital vein through a power injector (0.1 mmol/kg at a rate of 4 mL/s, followed by the injection of 20 mL of saline water at the same injection rate). Postcontrast T1-weighted images in the sagittal and transverse orientation were then obtained.

Perfusion series were processed on commercially available software (Functool; General Electric Medical Systems, Milwaukee, WI). Two different color-coded perfusion maps were produced. The first map was based on the maximum slope of decrease of the MR signal during the first pass of the contrast agent through the brain. The second map displayed the negative-enhancement integral of the MR signal along time during this same first pass. These 2 maps measure the cerebral blood flow (CBF) and the cerebral blood volume (CBV), respectively.

All imaging was acquired over a 40-month period between April 1998 and August 2001. Survival data have been considered up to March 2002, with a median number of MRI examinations per patient of 6 (range, 1–21) and a median follow-up of 15.2 months (range, 5.3–46.5 months).

Image review process

Complete MRI records of each patient from study entry until death or until the cutoff date (August 2001) were prepared for a second reading. Two neuroradiologists who were unaware of the patients’ outcome reviewed and scored the images in agreement.

Six categories of radiologic criteria have been scored: localization (lobe and hemisphere), mass effect, T1 contrast enhancement, T2 hypersignal, diffusion hypervascular, and perfusion hypervascular. Mass effect was reported as none, local, moderate midline shift, or severe midline shift. T1 contrast enhancement was described as absent, linear, nodular, or multiple nodular. T2 hypervascular was assigned a morphologic code: none, limited to a lobe, extension to more than a lobe, or contralateral extension. Signs of leucoencephalopathy (diffuse T2 hypervascular that span the white matter, accompanied by shrinkage of overall brain volume) were also recorded. On diffusion-weighted images, the presence or absence of hypervascular was assessed, and perfusion hypervascular was graded on maximum slope of decrease and negative integral enhancement maps.

The images were compared with the previous examination and variations of each criterion graded as increased, stable, or decreased. T1 contrast enhancement sizes were measured in millimeters, by use of largest diameter and orthogonal diameter (18). T2, diffusion, and perfusion hypervasculars were measured in the same way. Mass-effect variation was graded according to the evolution of 3 classical criteria: sulcus and cisterns vanishing, ventricles shift and deformation, and median line shift.

Disease progression

Disease progression was assessed by the tumor size variation on T1 contrast enhancement and clinical parameters according to the Macdonald criteria (19). An increase greater than or equal to 25% in size, an increase in corticosteroid consumption, or a deteriorating neurologic function was defined as disease progression.

Time reference

For the purpose of this paper, the images acquired at the time of disease progression are designated $t_p$, a reference in time used to monitor the disease’s evolution. The behavior of T2, mass effect, perfusion, and diffusion imaging at $t_p$ but also at the previous ($t_{p-1}$)
and at the following MRI examination \( t_{on} \), were compared with the classical WHO criteria and to the Macdonald criteria \((18, 19)\).

**Statistics**

Overall survival was evaluated from study entry to death or censored on March 15, 2002, according to the Kaplan-Meier method \((20)\).

Univariate analyses were conducted as a step toward multivariate analysis. Patients at \( t_{on} \) were segregated in 2 groups, according to a criterion such as T1 largest diameter, T2 hypersignal, mass effect, surgery vs. biopsy, or age. A log-rank test was performed to compare the survival curves of the 2 groups. A \( p \) value less than or equal to 0.05 was considered significant.

Significant criteria for survival established by univariate analyses were used in a multivariate Cox model of proportional hazards \((21)\). Criteria were included one at a time in the model, from the lowest log-rank \( p \) value to the highest. A \( p \) value less than or equal to 0.05 was considered significant.

**RESULTS**

**Patients, tumor location, and imaging**

A total of 311 MRI examinations from 41 patients were reviewed. The 41 patients included in this radiologic ancillary study are representative of the whole study population with regard to demographics, progression-free survival, and overall survival (data not shown) \((8)\). Adequate MRI baseline tumor imaging was available for 28 patients. Perfusion and diffusion data were available in 71\% (220 examinations) and 77\% (240 examinations), respectively.

Most tumors had an extension in the frontal lobe (46\%) compared with the temporal or parietal lobes (25\%). In 3 patients (7\%), the tumor was located in the occipital lobe, whereas in 6 patients (15\%), a bilateral butterfly-like tumor extension was present. Some tumors (7\%) extended deeper into the central region of the brain.

**Time to disease progression and survival**

At the time of completion of the review process, a total of 32 patients (78\%) had demonstrated disease progression on the basis of radiologic and clinical signs. At the first examination with disease progression \(( t_{on} \), 22 out of the 32 patients (69\%) were still in treatment (4-week intervals or adjuvant). Progression-free survival was computed at 6.9 months (95\% CI, 5.3 to 8.5 months). Overall survival was 15.7 months (95\% CI, 14.3 to 17 months), survival after progression was 6.6 months (95\% CI, 4.6 to 8.6 months).

**T1 contrast enhancement and T2 hypersignal**

At disease progression, we noted nodular contrast enhancement in all patients. Twenty-two out of the 28 patients with postoperative baseline MR imaging available presented also a nodular contrast enhancement at baseline, and 4 patients presented a linear and 2 patients presented no contrast enhancement.

During the follow-up, T2-weighted imaging of the 41 patients showed 2 different patterns of evolution. The hypersignal was often focalized in the vicinity of the lesion

<table>
<thead>
<tr>
<th>( t_{on} )</th>
<th>T1 contrast enhancement</th>
<th>T2 hypersignal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative baseline (( n = 28))</td>
<td>None (( n = 10))</td>
<td>25% (( n = 7))</td>
</tr>
<tr>
<td>Disease progression (( t_{on} )</td>
<td>Local (( n = 4))</td>
<td>39% (( n = 9))</td>
</tr>
<tr>
<td>( t_{on} )</td>
<td>Moderate (( n = 7))</td>
<td>25% (( n = 2))</td>
</tr>
<tr>
<td>( t_{on} )</td>
<td>Severe (( n = 1))</td>
<td>100% (( n = 1))</td>
</tr>
</tbody>
</table>

| \( p \) value to the highest. A \( p \) value less than or equal to 0.05 was considered significant. |
and showed an alteration caused by the tumor. By contrast, 9 patients in this cohort showed leuкоencephalopathy signs (overall brain volume shrinkage accompanied by a hyperintense T2 signal that spanned the white matter). These patients had a median survival time of 26.7 months (95% CI, 6.9 to 46.5 months). Leuкоencephalopathy is a known late complication in patients treated for malignant glioma and occurs 18 to 24 months after radiotherapy. Table 1 offers a summary of the findings and scores at postoperative baseline and at disease progression.

Signs of disease progression

The first examination with disease progression (t₀) was monitored in comparison with its preceding (t₋₁) and following (t₊₁) examinations. Five main radiologic parameters were monitored: T1 contrast enhancement, T2 hypersignal, mass effect, perfusion hypersignal, and diffusion hypersignal. At t₀, all patients demonstrated an increase in T1 contrast enhancement. At examination t₋₁, no parameter presented a clear variation that predicted this progression. Specifically, no perfusion and diffusion image could anticipate disease progression. Both perfusion postprocessing methods on cerebral blood flow (CBF) and cerebral blood volume (CBV) led to the same conclusion in methods on cerebral blood flow (CBF) and cerebral blood volume (CBV). A clear variation that predicted this progression was confirmed. (Table 2, Fig. 1).

Of the other parameters, only T2 hypersignal showed a clear tendency to increase at t₀, which thus suggests disease progression. On an MRI performed 2 months after first progression (t₊₁), the delayed tendency of the parameters to increase was confirmed. (Table 2, Fig. 1).

Warning signs at disease progression

At t₀, univariate log-rank analysis was completed to identify potential prognostic factors for a multivariate model. Each radiologic parameter and the clinical prognostic factors age, performance status, and debulking surgery (8) have been analyzed for survival. Size of T1 contrast enhancement, variation of T2 hypersignal and of mass effect, debulking surgery, and age were retained in this order for the multivariate model (Table 3).

The multivariate analysis used a Cox model. It was performed in an ascending manner; that is by addition of 1 parameter from Table 3 at a time. Only 2 parameters, namely, largest diameter of T1 contrast enhancement and variation in T2 hypersignal, remained statistically significant in the analysis (p < 0.05) (Table 4). Because this

![Fig. 1. Potential markers of disease progression increase from first follow-up examination to time t₋₁, t₀ or t₊₁. White indicates perfusion hypersignal. Light gray indicates diffusion hypersignal. Gray indicates mass effect. Dark gray indicates T2 hypersignal. Black indicates T1 contrast enhancement. Values are displayed in percent of the examinations available, as an examination before t₋₁ is not always available to evaluate the variation at t₋₁. Abbreviations: t₀, first examination graded as disease progression; t₋₁, t₀, examination preceding and following, respectively, after t₀.](image-url)
Table 3. Univariate log-rank survival analysis

<table>
<thead>
<tr>
<th>Grouping parameter*</th>
<th>p Value at ( t_0 )</th>
<th>Median survival in months (95% CI)</th>
<th>Median progression-free survival in months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 largest diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 3 ) cm</td>
<td>( &lt;0.001 ) (( n = 16 ) vs. 16)</td>
<td>13.6 (6.3-20.9)</td>
<td>6.1 (4.3-7.9)</td>
</tr>
<tr>
<td>(&lt; 3 ) cm</td>
<td></td>
<td>26.8 (14.6-39.0)</td>
<td>8.7 (0-20.7)</td>
</tr>
<tr>
<td>T2 hypersignal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>( &lt;0.005 ) (( n = 21 ) vs. 11)</td>
<td>14.3 (10.4-18.2)</td>
<td>6.3 (5.7-6.9)</td>
</tr>
<tr>
<td>No increase</td>
<td></td>
<td>42.7 (30.7-54.7)</td>
<td>18.2 (0-39.6)</td>
</tr>
<tr>
<td>Mass effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>( &lt;0.02 ) (( n = 12 ) vs. 20)</td>
<td>8.8 (5.3-12.3)</td>
<td>6.3 (5.7-6.9)</td>
</tr>
<tr>
<td>No increase</td>
<td></td>
<td>17.1 (6.5-27.7)</td>
<td>18.2 (0-39.6)</td>
</tr>
<tr>
<td>Debulking surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full or partial</td>
<td>( &lt;0.02 ) (( n = 25 ) vs. 7)</td>
<td>16.7 (16.1-17.3)</td>
<td>8.7 (8.5-8.9)</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>10.6 (3.0-18.2)</td>
<td>5.5 (4.3-6.7)</td>
</tr>
<tr>
<td>Age at diagnostic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 50 ) y</td>
<td>( &lt;0.05 ) (( n = 21 ) vs. 11)</td>
<td>12.1 (5.2-19.0)</td>
<td>6.1 (5.3-6.9)</td>
</tr>
<tr>
<td>(&lt; 50 ) y</td>
<td></td>
<td>26.8 (10.7-42.9)</td>
<td>13.7 (7.4-20.0)</td>
</tr>
</tbody>
</table>

* Each grouping parameter splits the patients in two subsets. Survival of the first subset was tested against the survival of the second subset. The two values of \( n \) are the number of patients in each two subsets.

Follow-up time \( t_0 \) is the first examination graded as disease progression.

Analysis identified only 2 parameters as significant, an overall score at disease progression could not be proposed. However, at first progression (\( t_0 \)), the subset of 14 patients with a T1 contrast enhancement largest diameter above 3 cm in size and simultaneously a T2 hypersignal that increased since last examination (\( t_{-1} \)) had a median survival of 13.6 months (95% CI, 5.8 to 21.4 months) compared with a median survival of 28.2 months (95% CI, 10.8 to 45.6 months) for the other 18 patients. This difference in survival time was significant (log-rank \( p < 0.001 \)), which demonstrated that these 2 parameters are crucial radiologic warning signs at progression.

**DISCUSSION**

Over the past 10 years, MRI has become the principal imaging modality on which clinicians base the follow-up and the evaluation of brain tumors. MRI and assessment of clinical parameters such as neurologic function and corticosteroid use are integral parts of the widely used MacDonald's response criteria for primary brain tumors (19). However, some specific aspects of the follow-up, such as response assessment and tumor-specific imaging, increasingly challenge radiologists (22). Delayed morphologic changes caused by treatment and contrast uptake on blood–brain barrier disruption after surgery or radiotherapy are difficulties that may obscure the picture. For these reasons, additional imaging techniques may be of help (22). In specific situations, positron emission tomography (PET) that use amino acids tracers and \(^{201}\)TI single-photon emission computed tomography (SPECT) have demonstrated additional value for the imaging of brain tumors (11,12). These techniques are nonetheless far from being commonly available in health centers, and performing an additional examination is a burden to the patients and the health-care system.

Recent works have shown the potential of perfusion and diffusion imaging in assessment of tumor development. Histologic changes such as angiogenesis are evaluated by perfusion and cellularity is evaluated by diffusion imaging (13, 15–17). We assessed in a group of 41 homogeneously treated patients with glioblastoma (GBM) whether these techniques would allow us to anticipate disease progression. In particular, for the evaluation of new treatment or new chemotherapy agents, progression-free survival is frequently used as a surrogate endpoint (23). To our knowledge, few reports on gliomas specifically focus on Grade IV astrocytoma, and none includes a homogeneous set of patients comparable with ours. In our study, despite careful,

Table 4. Multivariate Cox model (proportional hazards) of survival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( p ) Value</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>( p ) Value</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 largest diameter</td>
<td>(&lt;0.02)</td>
<td>5.7</td>
<td>1.5–22</td>
<td>(&lt;0.05)</td>
<td>3.9</td>
<td>1.0–15</td>
</tr>
<tr>
<td>T2 hypersignal</td>
<td>(&lt;0.05)</td>
<td>3.0</td>
<td>1.0–8.9</td>
<td>(&lt;0.05)</td>
<td>5.7</td>
<td>1.0–31</td>
</tr>
</tbody>
</table>

Follow-up time \( t_0 \) is the first examination graded as disease progression; \( t_{+1} \) examination follows \( t_0 \).
consistent, and frequent (every 2 months) evaluation, we
could not show that perfusion and diffusion techniques
added valuable information. These 2 techniques did not
anticipate disease progression.

Other reports in animal models are consistent with the
results of our clinical trial. In effect, on GL261 implanted
mouse gliomas, T1 contrast enhancement has been shown to
be present before evidence of angiogenesis (17). Thus,
blood–brain barrier disruption is not necessarily caused by
neovascularization. Furthermore, for GBM in humans, per­
fusion is not positively correlated with tumor growth. Pos­
ibly, the microvasculature of such hypercellular glioma
cannot meet the metabolic demands of the growing tumor.
Ischemic necrosis is then the logical outcome of this pecu­
liar unstable state (16).

The value of the diffusion technique is subject to much
debate. Diffusion hypersignal on diffusion-weighted trace
images increases with cellularity (14), whereas it decreases
during edema development (24). A consequence of this
condition is a rather complex behavior in tumors in which
both increased cellularity and increased edema are present.
Indeed, as the tumor grows and its cellularity tends to
increase, disruption of the blood–brain barrier will lead to
edema. These factors then have radiologic effects on diffu­
sion behavior that tend to counteract each other. A recent
study on patients with various brain tumors and treatments
has shown the potential of diffusion variation to delineate
tumor regions that respond to treatment at a very early
timepoint during radiation therapy (25). Compared with that
study, our work focuses on diffusion variation in relation
with disease progression at a longer time scale in a homo­
geneous population of GBM. In this setting, diffusion vari­
ation was not able to anticipate disease progression. In a
similar way, the 8 patients with progressive disease of the
Moffat et al. (25) study presented only minor changes in
ADC. Indeed, because diffusion imaging reflects his­
topathological changes, further studies should focus on ho­
mogenous populations in terms of pathology and treatment.
For example, lower-grade gliomas show different his­
topathological patterns that will lead to other imaging ef­
effects, whereas nonenhancing malignancies would certainly
benefit on follow-up techniques that do not rely on contrast­
enhancement techniques.

Hence, perfusion and diffusion showed a rather complex
behavior and did not enable us to foresee disease progress­
sion. Classical parameters, thus, remain the imaging refer­
eence. A T1 contrast enhancement of over 3 cm in largest
diameter together with the increase of T2 hypersignal is
proposed as a marker of inferior prognosis. Conventional
clinical and radiologic parameters of tumor progression
have confirmed their usefulness in our study. Moreover, our
MRI follow-up scheme, with simple time course denomin­
atiosn such as t−1, t0, and t+1 and multivariate analysis, has
demonstrated its pertinence and could easily be transposed
to other brain tumors and treatments. When used on large
cohorts, this statistical approach would certainly lead to the
identification of more parameters that could then be brought
together in useful prognostic scoring functions.

In conclusion, our work showed that although elaborate
imaging techniques such as perfusion and diffusion MRI are
becoming standardized in many medical centers, they do
not enable the radiologist to anticipate disease progression.
Classical T1 imaging remains the gold standard in the
follow-up of tumor growth. Together with T2 imaging, this
technique is accurate in reflecting the current evolution of
the brain tumor. The quest for more precise imaging tech­
niques to monitor biologic effects of treatment for high­
grade gliomas continues (22).

REFERENCES

2. Stupp R, Hegi ME. Recent developments in the management of
malignant glioma. ASCO 2003 Educational Book. Alexandria;
forme and anaplastic astrocytoma: Pathologic criteria and
isons of radiotherapy and nitrosoureas for the treatment of
phase II trial of temozolomide in patients with glioblastoma
developments in the use of temozolomide for the treatment of
Cross Hospital experience with temozolomide in patients with
survival for patients with newly diagnosed glioblastoma mul­
tiforme treated with concurrent radiation plus temozolomide
followed by adjuvant temozolomide. J Clin Oncol 2002;
20:1375–1382.
plus concomitant and adjuvant temozolomide for gliobla­
ability in the radiological assessment of response to chemother­
11. Benard F, Ronza J, Hustin X. Imaging gliomas with positron
emission tomography and single-photon emission computed
photon emission computed tomography as an early predictor of
weighted MRI with echo-planar technique in the evaluation of
weighted imaging in patients with brain tumors. AJNR Am J
15. Lev MH, Hochberg F. Perfusion magnetic resonance imaging
to assess brain tumor responses to new therapies. Cancer
Control 1998;5:115–123.


