Featured Article

Correlation of Molecular Genetics with Molecular and Morphological Imaging in Gliomas with an Oligodendroglial Component

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ABSTRACT

Purpose: Since the recognition that oligodendrogliomas may be chemosensitive, their diagnosis and clinical management has become highly controversial. Histopathology diagnosis remains challenging and new tools such as molecular genetics or molecular imaging require evaluation.

Experimental Design: In a single-center, population-based prospective study, allelic imbalance in chromosomes 1p36, 19q13, 17p12–15, and 10p12–15 has been investigated in 19 oligodendroglioma WHO grade 2 (OII), 20 oligoastrocytoma WHO grade 2 (OII), 8 oligodendroglioma WHO grade 3 (OIII), and 12 oligoastrocytoma WHO grade 3 (OIII), and compared with pretherapy histopathology, computed tomography and/or magnetic resonance imaging (CT and/or MR), [fluorine-18]fluoro-2-deoxyglucose (18F-FDG), and thallium-201 single-photon emission computed tomography (201Tl SPECT).

Results: In 50 cases, 18F-FDG uptake correlated with 201Tl uptake; however, 8 cases had increased 201Tl uptake but were hypometabolic for 18F-FDG, and 1 case was hypermetabolic with normal 201Tl uptake. Sixteen cases enhanced on CT/MR but failed to show 201Tl uptake; and 2 low-grade non-enhancing oligodendrogliomas had increased 201Tl uptake. Increased metabolism was more likely in high-grade cases, with 201Tl uptake more strongly correlated with grade than was 18F-FDG uptake. Tumors with 1p/19q loss were more likely to show increased 201Tl uptake and, to a lesser degree, increased 18F-FDG uptake than those with these losses. Elevated metabolism in 28% of low-grade tumors was significantly more common in tumors with 1p/19q loss, and increased uptake of both 18F-FDG and 201Tl in low-grade cases was found only in those with 1p/19q loss.

Conclusions: In this study, dissociation of uptake of contrast agents and radiotracers suggests independent deregulation of the blood–brain barrier breakdown and metabolism during disease progression of oligodendroglial neo-plasms, and the association of elevated metabolism with 1p/19q loss, particularly in low-grade tumors, may have implications for clinical management.

INTRODUCTION

Gliomas arise in around 5 to 10 per 100,000 of the general population, with an increasing incidence in the elderly (1, 2). These tumors are notoriously refractory to conventional radiotherapy and chemotherapy, and the prognostic outlook for patients with high-grade gliomas is usually dismal (3). In addition, many patients present initially with a low-grade glioma that, in the majority of cases, progresses with time to high-grade. Since the discovery that a high proportion of oligodendrogliomas, are responsive to polychemotherapy with procarbazine, vincristine, and lomustine (PCV), the diagnosis and therapeutic management of gliomas with an oligodendroglial component has become highly controversial (4–8).

Gliomas are classified, according to their histologic features, into three major types: astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas based on similarities to mature glial cells. Traditionally oligodendrogliomas were thought to make up ~4% of all gliomas but recently the reported incidence has risen to as much as 33% in some studies, with concomitant decrease in the incidence of astrocytomas (7, 9). This rise may be due to increased awareness of the need to recognize oligodendrogliomas for therapeutic purposes, relaxation of the WHO histopathologic criteria for the diagnosis of oligodendrogliomas and earlier diagnosis through advances in magnetic resonance imaging techniques (8–11). Many gliomas that were previously diagnosed as astrocytomas are now classified by using the revised World Health Organization (WHO) criteria (12) as oligodendrogliomas or oligoastrocytomas, which are "mixed" gliomas with features of both astrocytic and oligodendroglial differentiation. Although oligodendrogliomas that display "classic" oligodendroglial features are readily recognized, for many cases, particularly low-grade gliomas, the presence of "astrocytic" or "oligodendroglial" differentiation is ambiguous,
making precise histopathologic classification impossible. As in other gliomas, clear distinction between low-grade “benign” and the more aggressive high-grade tumors is also difficult, with concomitant implications for clinical management (13). For example, “watch and wait” may be recommended for low-grade gliomas with therapy given at transformation to high-grade (14). These factors make more objective means to diagnose the subtype and grade of glioma essential for accurate prognostication and prediction of response to therapy.

Recent research has shown that oligodendrogliomas are typified by loss of heterozygosity of chromosomes 1p and 19q and that these genetic losses may be considered as the molecular hallmark of the oligodendroglial lineage (11, 15–17), indicative of good prognosis (18) and responsiveness to chemotherapy (4, 19, 20). Astrocytomas are more likely to have loss of chromosome 17p and mutation in the p53 gene, whereas oligoastrocytomas show either loss of 1p and 19q typical of oligodendrogliomas or loss of 17p and p53 mutation as in astrocytomas (13, 21–23). Thus, molecular genetic analysis is becoming increasingly important to assist in the diagnosis of gliomas with an oligodendrogial component.

Alternatively molecular and physiologic imaging techniques show promise for the noninvasive characterization of gliomas. Metabolic imaging with radiolabelled tracers such as 201Thallium or [18F]fluorodeoxyglucose has been used in a number of studies, to yield diagnostic or prognostic information (24–27), to guide biopsy (28), to distinguish recurrent tumor from radiation necrosis (29), or to monitor response to therapy (30–33). In addition, it has been suggested that increased metabolism may be related to therapeutic responsiveness (31, 34). However, there is no reported comprehensive study comparing morphologic and metabolic imaging with molecular genetic information in a large series of gliomas with an oligodendrogial component.

Future improvements in therapeutic outcome from conventional therapeutic modalities rely on appropriate choice and delivery of therapy to individual patients based on knowledge of the biology and physiology of the tumor. Accordingly, we have established a multidisciplinary approach in a prospective study of oligodendroglial neoplasms undergoing therapy at a single United Kingdom treatment center. In this paper, we report the pretherapy molecular genetic and morphologic or metabolic imaging characteristics of a series of gliomas with an oligodendrogial component, that are potentially eligible for PCV chemotherapy.

MATERIALS AND METHODS

Case Selection and Histopathology. Fifty-nine adult patients with supratentorial gliomas undergoing assessment at The Walton Centre for Neurology and Neurosurgery between June 2000 and April 2003 were investigated. These cases had magnetic resonance/computed tomography (MR and/or CT) and nuclear medicine imaging investigations pre- or postsurgery and before radiotherapy or chemotherapy, a histopathological diagnosis of oligodendroglioma or oligoastrocytoma WHO grade 2 or 3, and had given informed consent for research. The study was approved by the relevant ethics committees. Pathological diagnosis was based on examination of the morphology of the most aggressive neoplastic tissue present in specimens obtained by surgical resection, image-guided biopsy, or serial stereotactic biopsy. Immunocytochemistry was performed when necessary for phenotyping (glial fibrillary acidic protein expression) and assessment of proliferation [Ki67 expression]. The histopathology of these cases was classified according to current WHO criteria (10). Tumors with an overall diagnosis of oligoastrocytoma contained at least 25% oligodendrogial elements, whether distinct or admixed. The series comprised 19 oligodendroglioma WHO grade 2 (OII), 20 oligoastrocytoma WHO grade 2 (OAI), 8 oligodendroglioma WHO grade 3 (OIII), and 12 oligoastrocytoma WHO grade 3 (OAIII).

Imaging. Thallium-201 single-photon emission computed tomography (201TI SPECT) and 2-[18F]fluoro-2-deoxy-d-glucose ([18F-FDG]) SPECT scans were obtained with a dual-headed collimated gamma camera (DSTXL GESMVI 1998, GE Medical Systems, Slough, United Kingdom). Tomographic images were acquired 20 minutes after intravenous injection of 148 MBq [201TI]thallous chloride with low-energy high-resolution collimators (LEHR) and selection of 20% windows centered on the 72-keV and 167-keV photopeaks of 201TI. On the same or following day, 53 of 59 patients had 18F-FDG SPECT; the remaining 6 patients had scans within 2 weeks. Patients fasted for at least 6 h before intravenous injection of 400 MBq 18F-FDG and rested in a darkened room before and after injection. Imaging was carried out 50 minutes after administration, and the same acquisition conditions applied as for 201TI SPECT, except super-high energy collimators (SHEGP) were fitted and a 20% window selected on the 511-keV peak. Images were reconstructed with filtered back projection and were rotated to be parallel to the orbitomeatal line. No correction was made for attenuation, and a high-resolution Metz filter and Hermes Software (Nuclear Diagnostics Ltd., Northfleet, United Kingdom) were used to reconstruct images in the coronal, sagittal, and transaxial projections for visual reporting by an experienced nuclear medicine consultant (S. V.). [18F-FDG] uptake was assessed as normal, hypermetabolic, or hypometabolic, if the intensity of signal within the known site of tumor was equivalent to, greater than, or less than the equivalent site in the contralateral hemisphere, respectively. Similarly, scans were reported as having either increased or normal 201TI uptake at the site of the tumor, compared with the contralateral hemisphere.

Semiquantitative data for the uptake of 201TI and 18F-FDG were obtained for 57 and 59 cases, respectively, by importing the reconstructed transverse slices in interfile format into NIH Image (http://rsb.info.nih.gov/nih-image).5 201TI scans for two patients were excluded for technical reasons. The tumor was located by comparison with the known tumor site from MR or CT images, and regions of interest (ROI) with the greatest difference in signal intensity within the tumor were identified by an experienced consultant neurosurgeon (P. C. W.). These ROI were considered to be representative of the most aggressive biology and were chosen for quantitation. Uptake of 201TI or 18F-FDG was measured in an axial slice containing the selected ROI and expressed as the ratio of the mean tumor counts in the

5 Internet address: http://rsb.info.nih.gov/nih-image.
ROI and the mean activity in an equivalent ROI mirrored in the contralateral supratentorial hemisphere. With this approach, normal brain tissue or tumor tissue with $^{201}$Tl or $^{18}$F-FDG uptake equivalent to that of normal brain would have a ratio of 1. The percentage error in the estimation of semiquantitative data for $^{18}$F-FDG and $^{201}$Tl uptake, based on replicate analyses, was calculated as $3.4 \pm 3.3\%$ and $3.0 \pm 2.4\%$ (mean $\pm$ SD), respectively.

MR or CT images, taken for clinical management purposes or to guide stereotactic biopsy, were retrieved from the Neuroradiology files. CT and MR scans were performed with standard protocols before and after the administration of contrast material. Gadolinium–EDTA [Magnevist (Schering AG, Berlin, Germany) (dimethylglucamine gadopentetate)] was administered to a concentration of 0.1 mmol/kg body weight for MR scanning. On hundred milliliters of iodinated contrast [Ultravist (Schering AG, Berlin, Germany) (ipromide)] with a concentration of 300 mg of iodine/mL was used for CT. Pretherapy scans, taken immediately before or just after the date of the nuclear medicine scan, were chosen for examination. Axial CT and MR T1-weighted images for 58 cases were examined, and contrast enhancement was scored as present, absent, equivocal, or not assessable. Tumors showing faint, patchy, or focal enhancement were noted. These scans were obtained, on average, 16 days before the first nuclear medicine scan, and 93% were within a month.

**Laser Capture Microdissection.** Tissue specimens for molecular genetic analysis were obtained from the histopathology archives. Regions of tumor histology in resected tumors or stereotactic biopsy specimens representative of the most aggressive tissue available and the overall pathology diagnosis were selected for study. Laser capture microdissection of hematoxylin and eosin (H&E)-stained formalin-fixed paraffin-embedded sections or EtOH-fixed intra-operative smear preparations was used to enrich the tumor component in the samples for analysis with multiple simultaneous PCR amplification procedure and microsatellite markers, followed by capillary electrophoresis as described previously (36, 37). The microsatellite panel included the polymorphic markers: chromosome 1, D1S2667, D1S508, D1S214 (1p36); chromosome 19, D19S412, D19S112, D19S596 (19q13); chromosome 17, D17S796, D17S1176, D17S1353 (17p13); chromosome 10, D10S689, D10S179 (10p12–10p15); chromosome 10q, D10S1687, D10S2491, D10S583, D10S587, D10S212 (10q22–10q26). Additional markers, D1S468, D1S2795 (1p36) and D19S217, D19S572 (19q13) were used for cases that lacked informativity for given loci.

After electrophoresis, data analysis was carried out with Genetic Profiler (Molecular Dynamics, Amersham Bioscience, Chalfont St. Giles, Buckinghamshire, United Kingdom) and EXCEL (Microsoft Corporation, Reading, United Kingdom) software to calculate peak height ratios. When allelic imbalance was observed rather than complete loss, the ratio of the mean peak heights of the two alleles was calculated for normal (N1: N2) and tumor (T1:T2). Allelic imbalance was calculated from the ratio of the tumor signal to that of the normal signal T1:T2 over N1:N2. Complete loss or ratios of $<0.33$ indicated loss of heterozygosity at that locus. Partial loss was indicated if significant skewing occurred (ratio, $>0.33$ to $<0.75$) and $P < 0.05$ when tested by the Mann–Whitney test (36, 37).

### RESULTS

**Clinicopathologic Characteristics.** The cases investigated in this single-center study were gliomas with an oligodendrogial component referred for nuclear medicine imaging after

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinicopathologic characteristics</th>
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<tbody>
<tr>
<td></td>
<td>WHO grade 2</td>
</tr>
<tr>
<td>No. of cases</td>
<td>39</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>19:20</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td></td>
</tr>
<tr>
<td>At first referral</td>
<td>(25–62)</td>
</tr>
<tr>
<td>At study</td>
<td>(27–63)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Craniotomy *</td>
<td>2</td>
</tr>
<tr>
<td>Image-guided biopsy</td>
<td>2</td>
</tr>
<tr>
<td>Serial stereotactic biopsy</td>
<td>35</td>
</tr>
<tr>
<td>Newly diagnosed (pathology diagnosis)</td>
<td>30</td>
</tr>
<tr>
<td>Previous therapy</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>5</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0</td>
</tr>
<tr>
<td>-1p/-19q Genotype</td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>12/19 (63%)</td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td>7/20 (35%)</td>
</tr>
</tbody>
</table>

* With residual tumor evaluable by MR after surgical resection.
† Time interval between nuclear medicine imaging studies and start of previous radiotherapy; median, 70 months (range, 13–166 months).
‡ Anaplastic oligodendroglioma treated 58 months previously by PCV chemotherapy for an earlier low-grade oligodendroglioma.
histopathology diagnosis and before further therapy (Table 1). The majority of cases were newly diagnosed after serial stereotactic biopsy with no previous therapy.

**201Tl and 18F-FDG Uptake.** 201Tl-SPECT scans were reported as either normal or increased; 18F-FDG SPECT scans were either hypometabolic or hypermetabolic and none were normal (Fig. 1). Cases with high uptake of 18F-FDG were more likely to have high uptake of 201Tl also; conversely, tumors hypometabolic for 18F-FDG were more likely to show normal 201Tl uptake (Table 2). However, 8 cases were hypometabolic but had increased uptake of 201Tl, and one low-grade tumor was hypermetabolic in the absence of increased 201Tl uptake. Semi-quantitative data, expressed as a ratio of uptake in regions of the most aggressive biology (i.e., regions of greatest difference in signal intensity), relative to the contralateral brain, also showed a significant correlation between 18F-FDG and 201Tl uptake (Spearman correlation: low-grade rho = 0.35, P = 0.034; high-grade rho = 0.485, P = 0.03; whole series rho = 0.481, P = 0.000). The median value for 18F-FDG uptake in the 19 cases reported as hypermetabolic was 1.55 (range, 1.11–2.4); and in the 40 cases reported as hypometabolic, the median value was 0.75 (range, 0.51–0.93). Semi-quantitative 201Tl data were available for 26 cases reported to have increased 201Tl uptake and 31 cases with normal uptake. Median values for uptake of 201Tl in increased and normal cases was 3.3 (range, 1.30–9.60) and 1.01 (range, 0.81–1.12), respectively.

**201Tl and 18F-FDG Uptake and Histopathology.** The relationship between histopathology and uptake of 18F-FDG or 201Tl is shown in Fig. 2 and Table 3A. Oligodendrogliomas showed no difference in the uptake of 18F-FDG or 201Tl compared with oligoastrocytomas with semi-quantitative data (Fig. 2). However, low-grade oligodendrogliomas were significantly more likely to be reported as having increased uptake of 201Tl but not of 18F-FDG (Table 3A).

### Table 2 18F-FDG SPECT and 201Tl SPECT

<table>
<thead>
<tr>
<th></th>
<th>18F-FDG, hypometabolic</th>
<th>18F-FDG, hypermetabolic</th>
<th>18F-FDG, hypometabolic</th>
<th>18F-FDG, hypermetabolic</th>
<th>P  *</th>
</tr>
</thead>
<tbody>
<tr>
<td>201Tl, normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO grade 2</td>
<td>72% (28/39)</td>
<td>3% (1/39)</td>
<td>5% (2/39)</td>
<td>20% (8/39)</td>
<td>0.000</td>
</tr>
<tr>
<td>WHO grade 3</td>
<td>20% (4/20)</td>
<td>0% (0/20)</td>
<td>30% (6/20)</td>
<td>50% (10/20)</td>
<td>0.087</td>
</tr>
<tr>
<td>All cases</td>
<td>54% (32/59)</td>
<td>2% (1/59)</td>
<td>14% (8/59)</td>
<td>30% (18/59)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

NOTE. Figures in parentheses (number of cases/cases evaluable).

* Fisher’s exact test (two-tailed significance).
Low-grade tumors (OII+OAI) were more likely to be reported as hypometabolic after 18F-FDG SPECT or normal after 201Tl SPECT, compared with high-grade tumors (OIII+OAIII; Table 3A). Similarly, with semiquantitative data, the high-grade tumors were more likely to have higher 201Tl uptake than did low-grade tumors, but comparisons of 18F-FDG uptake in low- and high-grade cases did not reach statistical significance (Fig. 2). Measurement of 201Tl uptake, therefore, showed a stronger correlation with histopathological grade than did 18F-FDG.

For individual histologic subtypes, oligodendrogliomas showed no difference in 18F-FDG or 201Tl uptake with grade, (Fig. 2; Table 3A). In contrast, high-grade oligoastrocytomas were more likely to show greater 201Tl uptake (Fig. 2) and to be reported as increased, compared with low-grade oligoastrocytomas (Fisher’s exact test, $P = 0.000$). High-grade oligoastrocytomas were also more likely to be reported as hypermetabolic (Fisher’s exact test, $P = 0.03$), but this did not reach significance if semiquantitative data were considered.

201Tl and 18FDG Uptake and Contrast Enhancement. Contrast enhancement on MR or CT scans was present in 13 of 19 OII, 10 of 19 OAI, 6 of 6 OIII, and 11 of 11 OAIII. Tumors in the series with contrast enhancement were more likely to have increased 201Tl uptake (Table 3B; Fig. 2D), but not when only pathologically low-grade cases were included. Increased 18F-FDG uptake was less strongly associated with contrast enhancement, being significant only when semiquantitative data were considered (Mann-Whitney $P = 0.036$). In 33% of cases, 201Tl uptake was not directly associated with contrast enhancement. Six OII, 9 OAI, and 1 OAIIII had normal 201Tl uptake despite the presence of contrast enhancement; in 12 of these, contrast enhancement was faint, patchy, or focal, but in 4, the enhancement was distinct and measurable. Two OII had increased 201Tl uptake in the absence of contrast enhancement; in both of these, 201Tl uptake was focal, and assessment of contrast enhancement was considered technically difficult. Oligodendrogliomas were as likely as oligoastrocytomas to show contrast enhancement.

Molecular Genetics and Histopathology. The relationship between allelic losses in chromosomes 1p36, 19q13, 17p13, 10p12–15, and 10q22–26, and histopathological diagnosis is illustrated in Table 1 and Fig. 3. Twelve of 19 OII, 7 of 20 OAI, 8 of 8 OIII, and 4 of 12 OAIII had loss of both 1p36 and 19q13. Chromosome 10 loss was found only in high-grade tumors.

201Tl and 18FDG Uptake and Molecular Genetics. In low-grade tumors and in the series as a whole, tumors with loss of both 1p36 and 19q13 were more likely to have increased uptake of 201Tl than those without loss of 1p36 and 19q13 (Fig. 4; Table 3C). Similarly, tumors with loss of 1p36 and 19q13 were more likely to be hypermetabolic for 18F-FDG uptake (Table 3C), but this did not reach significance when semiquan-
titative data were used (Fig. 4). One anaplastic oligoastrocytoma had loss of 1p36 but not of 19q13; analysis of 18F-FDG and 201Tl uptake in tumors with and without loss of 1p36 gave results similar to those described above. Thus, allelic loss of 1p/19q or 1p only was associated in this study with a greater likelihood of increased metabolism.

In the low-grade tumors without loss of 1p36 and 19q13, 18 of 20 (6 OII and 12 OAII) were hypometabolic and had

![Fig. 3](image-url)  
Fig. 3 Allelic losses in chromosomes 1p36, 19q13, 17p13, 10p12–15, and 10q22–26 and histopathologic diagnoses.
normal 201Tl uptake. Of these, two cases had loss of 19q13, seven had loss of 17p13, three had loss of 17p13 and 19q13, and six had no detectable loss of any of the loci investigated; eight showed features of elevated metabolism; 8 (7 OII, 1 OAII) were hypermetabolic and had increased 201Tl uptake, of which 6 showed contrast enhancement, and 1 (OII) was hypometabolic with increased 201Tl uptake and was enhancing.

Ten of 12 high-grade tumors with loss of 1p36 and 19q13, and the anaplastic oligoastrocytoma with loss of 1p36 only, had features of elevated metabolism; 7 cases (4 OIII, 3 OAIII) were hypermetabolic and had increased uptake of 201Tl, and 4 cases (2 OIII, 2 OAIII) had increased 201Tl uptake but were hypometabolic. Two cases (one OIII in which enhancement was equivocal and one OIII in which enhancement was not assessable) had normal 201Tl uptake and were hypometabolic. Of the seven anaplastic oligoastrocytomas with intact 1p36, three cases (1 with loss of 17p13 and 10q22–26, 1 with loss of 17p13, 10p12–15, and 10q22–26, and 1 with loss of 19p13) were hypermetabolic with increased 201Tl uptake, and 2 cases (1 with loss of 17p13 and 19p13, 1 with loss of 10p12–15 and 10q22–26) were hypometabolic but had increased 201Tl uptake, and 2 cases (with loss of 17p13) were hypometabolic with normal 201Tl uptake. All of the cases with chromosome 10 loss showed features of elevated metabolism.

Prior Therapy. One OAII, four OII, three OIII, and four OAIII had previous therapy before this study. Seven of these had loss of 1p36 and 19q13, and all showed contrast enhancement. Six cases had increased 201Tl uptake and were hypermetabolic, four had increased 201Tl uptake but were hypometabolic, and two had normal uptake of 201Tl and were hypometabolic. These trends are similar to those for the series as a whole (Table 2), suggesting that previous therapy did not necessarily influence features of hypermetabolism.

DISCUSSION

In this study, we have used a multidisciplinary approach to characterize a series of gliomas with an oligodendroglial component. Important findings of the study include the following: the lack of association of elevated 201Tl uptake with hypermetabolism for 18F-FDG in 15% of cases examined, and with contrast enhancement in 33% cases; and the association of genetic losses in chromosomes 1p and 19q with features of elevated metabolism.

Uptake of the radiotracers used in this study reflects the complex biology of these tumors. Thallium-201, which is administered as a chloride and emits X-rays, behaves like potassium and is rapidly distributed through, and cleared from, the body, with low uptake in normal cerebral tissue (38) because of restricted passive diffusion across the blood–brain barrier. Its uptake in gliomas is thought to depend on a combination of factors, including alterations to the blood–brain barrier, the activity of the Na/K ATPase pump indicating cell viability, and, to a lesser extent, blood flow (38, 39). Thallium-201 uptake has been correlated in gliomas with histopathological grade (26, 40) and cellular proliferation (41–43). 18F-FDG is the most commonly used positron-emitting radiotracer in oncology. FDG, an analogue of glucose, is transported into the cell by facilitated normal 201Tl uptake. Of these, two cases had loss of 19q13, seven had loss of 17p13, three had loss of 17p13 and 19q13, and six had no detectable loss of any of the loci investigated; eight showed features of elevated metabolism; 8 (7 OII, 1 OAII) were hypermetabolic and had increased 201Tl uptake, of which 6 showed contrast enhancement, and 1 (OII) was hypometabolic with increased 201Tl uptake and was enhancing.

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Uptake of the radiotracers used in this study reflects the complex biology of these tumors. Thallium-201, which is administered as a chloride and emits X-rays, behaves like potassium and is rapidly distributed through, and cleared from, the body, with low uptake in normal cerebral tissue (38) because of restricted passive diffusion across the blood–brain barrier. Its uptake in gliomas is thought to depend on a combination of factors, including alterations to the blood–brain barrier, the activity of the Na/K ATPase pump indicating cell viability, and, to a lesser extent, blood flow (38, 39). Thallium-201 uptake has been correlated in gliomas with histopathological grade (26, 40) and cellular proliferation (41–43). 18F-FDG is the most commonly used positron-emitting radiotracer in oncology. FDG, an analogue of glucose, is transported into the cell by facilitated
diffusion; in the cell, it is subsequently phosphorylated by hexokinase to fluorodeoxyglucose-6-phosphate; however, unlike glucose, it is not a substrate for further metabolism. De-phosphorylation is slow in tissues with low levels of glucose-6-phosphatase and fluorodeoxyglucose-6-phosphate becomes “trapped” intracellularly (44). Malignant cells are characterized by high rates of glucose consumption, reflecting increased energy demand related to proliferation, increased expression of glucose transporters, or deregulation of hexokinase activity, and show elevated uptake of $^{18}$F-FDG (25, 38). Increased uptake can also occur in nonmalignant tissues including inflammatory tissue and normal brain, with greater uptake in gray compared with white matter (45, 46). Cell density and anaplasia are major determinants of glucose uptake in gliomas (47, 48); thus, low-grade gliomas may be hypometabolic, whereas more aggressive gliomas may show hypermetabolism (49, 50). Although lower in spatial resolution than dedicated positron emission tomography, the adaptation of conventional nuclear medicine cameras with high-energy collimators to image positron-emitting radiotracers has permitted successful $^{18}$F-FDG SPECT imaging of gliomas and other tissues (51–53).

Although 85% of cases in this study showed a close association between $^{18}$F-FDG and $^{201}$Tl uptake, $^{201}$Tl uptake did not correlate with $^{18}$F-FDG uptake in the remainder. In addition, 39% of low-grade cases and one high-grade glioma were enhancing on MR or CT but failed to show $^{201}$Tl uptake; and in 5% of low-grade cases, $^{201}$Tl uptake was increased in the absence of definitive detectable enhancement. Although there was an association in the series as a whole between enhancement and increased $^{201}$Tl uptake, there was no relationship between contrast enhancement and $^{18}$F-FDG uptake. Although each imaging modality differs in spatial resolution and sensitivity, these results are not accountable simply through differences in instrumentation. Although small foci of enhancement seen on MR may be missed with the lower resolution of the gamma camera, some tumors that had clearly measurable contrast enhancement on MR and/or CT failed to show $^{201}$Tl uptake. In addition, faint enhancement seen in a region greater than 1 cm$^2$ would be expected to be clearly evident in the more sensitive $^{201}$Tl-SPECT images. These findings suggest that in oligodendroglial neoplasms, uptake of the two radiotracers and the contrast enhancing agent reflect separate facets of the biology of these tumors. Neither contrast agents nor $^{201}$Tl cross the intact blood–brain barrier, but, whereas uptake of contrast agents and $^{201}$Tl through the impaired blood–brain barrier is passive, $^{201}$Tl is actively taken up by tumor cells via the Na/K ATPase pump, which results in additional intracellular trapping. Our results suggest that the blood–brain barrier breakdown, which occurs during neoplastic transformation of low-grade gliomas as a result of angiogenesis (54, 55), is temporally dissociated from cell cycle deregulation that is associated with increased proliferation in some oligodendroglial tumors. Interestingly, all but one of the tumors that were enhancing in the absence of $^{201}$Tl uptake were also hypometabolic. In contrast, the foci of high metabolic activity for both $^{201}$Tl and $^{18}$F-FDG detected in two non-enhancing oligodendrogliomas may be due to the increased sensitivity of $^{201}$Tl-SPECT. Alternatively, this may reflect differential permeability in the blood–brain barrier breakdown, allowing passage of $^{201}$Tl but not contrast agents because of differences in molecular size and charge. As described above, uptake of $^{18}$F-FDG and $^{201}$Tl in gliomas depends on different aspects of tumor biochemistry; and the differing spectra of molecular genetic alterations and gene expression changes giving rise to individual tumors may contribute to the dissociation of $^{18}$F-FDG and $^{201}$Tl uptake seen in 15% of cases. These observations of dissociation in some tumors between uptake of contrast agents, $^{18}$F-FDG and $^{201}$Tl are supported in other studies of gliomas and astrocytomas (39, 43, 56–58) but have not previously been described in a substantial series of gliomas with an oligodendroglial component.

For the majority of cases in this study, serial stereotactic biopsy ensured sampling of the most aggressive tumor tissue on which to base histopathology diagnosis. As in other studies of gliomas in general, or astrocytomas in particular (25, 58, 59), features of elevated metabolism were more likely to be seen in high-grade gliomas with an oligodendroglial component, with $^{201}$Tl uptake being more strongly correlated with histopathological grade than $^{18}$F-FDG uptake. Thus, uptake of $^{201}$Tl being lower in normal brain than uptakes of $^{18}$F-FDG, and requiring blood–brain barrier breakdown, provides a clearer indication of histopathological grade. However, whereas $^{201}$Tl and, to a lesser extent $^{18}$F-FDG uptake correlated with grade in oligoastrocytomas, no correlation between metabolism and grade was observed for the oligodendroglomas. In contrast, Derlon et al. reported greater $^{18}$F-FDG uptake in high-grade oligodendrogliomas in a selected series of 31 “pure” oligodendrogliomas (60). Although $^{18}$F-FDG SPECT and $^{201}$Tl SPECT could not be used to distinguish oligodendrogliomas from oligoastrocytomas in high-grade cases, or in the series as a whole, low-grade oligodendrogliomas were more likely to be reported as having increased $^{201}$Tl uptake than were low-grade oligoastrocytomas.

As in other studies, the classification of these gliomas according to histopathological subtype differed, for many cases, from the classification according to molecular genetics. Loss of 1p and 19q, considered to be the molecular hallmark of oligodendrogliomas (11, 15), was found overall in 74% of oligodendrogliomas and 34% of oligoastrocytomas. The dissociation between pathology and molecular genetics was greatest in low-grade tumors, 100% of anaplastic oligodendrogliomas having a loss of 1p/19q. Occasional gliomas with loss of 1p without concomitant loss of 19q have been reported in other studies (19) and was seen in an anaplastic oligoastrocytoma in this study. Chromosome 10 loss, which is commonly associated with poor prognosis in high-grade astrocytomas and oligoastrocytomas (61, 62) was detected in only 25% of the high-grade cases in this study. Chromosome 10 loss was found in both oligodendrogliomas and oligoastrocytomas and in tumors with 1p/19q loss, as well as in those with loss of 17p or no detectable loss in chromosomes 1p36, 19q13, or 17p13.

Grouping the tumors in this series according to molecular genetics rather than histopathology subtype showed a stronger correlation with metabolism. Tumors with loss of chromosomes 1p36 and 19q13 (or 1p36 only) were more likely to show increased uptake of $^{201}$Tl and with a weaker association to be hypermetabolic for $^{18}$F-FDG than those without these losses. Features of elevated metabolism were seen in 80% of high-grade cases in tumors with or without 1p/19q loss. In contrast, elevated metabolism in 28% of low-grade tumors was signifi-
cantly more common in those with loss of 1p36 and 19q13 than in those without. Furthermore, increased uptake of both \(^{201}\)Tl and \(^{18}\)F-FDG was found only in low-grade tumors with 1p/19q loss, and this did not depend on the presence of contrast enhancement. In this way, our study has identified a subgroup of histopathologically low-grade gliomas typified by 1p/19q loss and whose biochemistry/physiology results in elevated metabolism manifested as increased radiotracer uptake. This is the first report of this phenomenon, but it has some support in the literature. Kaschten et al. (63) noted that low-grade oligodendrogliomas may be FDG avid, Derlon et al. (50) observed more pronounced hypometabolism in astrocytomas compared with oligodendrogliomas, and Kuwert et al. (64) found high uptake of iodine-123 \(\beta\) methyl tyrosine in an oligodendroglioma and an oligoastrocytoma.

In anaplastic oligodendrogliomas, it is thought that 1p/19q loss may be predictive of response to chemotherapy (4, 19), and aspects of their physiology such as blood flow and metabolism may be important factors in drug delivery and chemosensitivity (65, 66). It has been shown that some low-grade oligodendroglial tumors respond to PCV chemotherapy, albeit more indolently (20, 67), but the therapy of these gliomas remains controversial. Means to predict which patients benefit from chemotherapy and an improved understanding of the appropriate timing of therapy during the clinical evolution of these tumors are necessary. It is possible that the subgroup of metabolically active low-grade gliomas with 1p/19q loss identified in this study may be the ones that are responsive to PCV chemotherapy. Further multidisciplinary study is essential to test this hypothesis and to establish the role of molecular imaging and molecular genetics in predicting chemosensitivity.

In summary, dissociation of uptake of contrast agents \(^{201}\)Tl and \(^{18}\)F-fluorodeoxyglucose in some oligodendroglial neoplasms suggests their independent regulation, with imaging techniques providing information on separate aspects of their biology. Elevated metabolism was associated not only with increased grade but also with 1p/19q loss; and a subgroup of histopathologically low-grade gliomas, typified by 1p/19q loss with increased metabolism, has been identified. These findings may have potential implications for the diagnosis and clinical management of gliomas with an oligodendroglial component.

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REFERENCES

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