Use of $^{18}$F-choline and $^{11}$C-choline as contrast agents in positron emission tomography imaging–guided stereotactic biopsy sampling of gliomas

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Object. Neuroimaging-guided stereotactic biopsy procedures are commonly used for diagnosis of gliomas. A number of the imaging modalities currently in use are not reliable enough in depicting these tumors. The authors developed $^{18}$F-choline and $^{11}$C-choline as tumor imaging agents for positron emission tomography (PET) scanning, and used them to visualize gliomas prior to stereotactic biopsy procedures.

Methods. The PET studies were performed in 12 patients who were thought to be affected by gliomas observed on computerized tomography and magnetic resonance images. The $^{18}$F- and $^{11}$C-choline were injected separately, and the PET scanning was started 5 and 20 minutes postinjection. The PET scans gave quantitative information about the distribution of $^{18}$F- and $^{11}$C-choline in the brain. The tumor uptake was constant between 5 and 20 minutes with both agents. Stereotactic biopsy sampling was performed to obtain tissues from the most radioactive areas on the PET scan; histological diagnoses were made using these tissues. The results were as follows: oligodendroglioma was found in two patients, astrocytoma in one, anaplastic astrocytoma in two, and glioblastoma in seven.

Conclusions. The uptake of contrast agents was always low in low-grade gliomas, and the uptake in high-grade glioma was always high. The tumor/normal (T/N) ratio of $^{18}$F-choline was 10.5:12 in anaplastic astrocytoma and 13.2:21 in glioblastoma. The $^{18}$F-choline yielded slightly superior results compared with $^{11}$C-choline with regard to the T/N ratio. In one case of oligodendroglioma the tumor showed no uptake of $^{18}$F- and $^{11}$C-choline. With this exception, the PET scans of gliomas in which $^{18}$F- and $^{11}$C-choline contrast agents were added would guide the approach to the most malignant areas for stereotactic biopsy sampling.

Key Words • glioma • positron emission tomography • contrast agent • standardized uptake value

Clinical Material and Methods

Patient Population

Twelve patients with untreated gliomas, including two with oligodendroglioma (Grade II), one with astrocytoma (Grade II), two with anaplastic astrocytoma (Grade III), and seven with glioblastoma (Grade IV), were studied using PET scanning before stereotactic biopsy sampling was performed. At first, a presumptive diagnosis of glioma was made based on the CT and MR imaging findings. Then, PET scanning was performed using $^{18}$F-choline and $^{11}$C-choline contrast agents on two consecutive days. Finally, stereotactic biopsy sampling was performed to obtain tissues from the areas with the highest uptake of $^{18}$F- and $^{11}$C-choline observed on PET scans (if PET scans were positive), or from the areas of abnormal findings on CT or MR images (if PET scans were negative). A histological diagnosis was made based on the biopsy specimens, and confirmed, in selected cases, after surgery. This study was approved by the Institutional Review Board, and the patients gave their informed consent.

Abbreviations used in this paper: CT = computerized tomography; FDG = 2-fluoro-2-deoxy-D-glucose; MR = magnetic resonance; PET = positron emission tomography; T/N = tumor/normal tissue ratio.
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**Positron Emission Tomography Scanning Procedure**

The $^{18}$F-choline and $^{11}$C-choline contrast agents were prepared using the previously reported methods. The PET camera (Headtome IV, 6-mm spatial resolution; Shimadzu, Kyoto, Japan) was used for data acquisition. The PET scans were produced as follows: first a transmission scan was performed, then $^{18}$F- or $^{11}$C-choline (370 MBq each) was injected intravenously. At 5 and 20 minutes postinjection, the first and second emission scans were started; the data acquisition time was 3 minutes each. Finally, the computer displayed the radioactivity distribution image on the scale of the standardized uptake value in color, where this value was calculated as follows: (regional radioactivity concentration)/(total injected dose/body weight). One pixel corresponded to a tissue volume of $4 \times 4 \times 9.5$ mm. The computer showed alternatively a numerical value of the standardized uptake value within a selected region of interest.

**Quantification of PET Data**

The area of highest uptake in the brain was enclosed within a region of interest of approximately 12 pixels, and its standardized uptake value was calculated (to equal tumor uptake). Normal gray matter of the contralateral posterior temporal lobe was used as a reference, and its standardized uptake value was calculated (to equal normal uptake). The T/N ratio was defined as the ratio of tumor uptake to normal tissue uptake of contrast material.

**Results**

**Typical PET Scans, Histological Characteristics, and CT/MR Images of Low-Grade Glioma and Glioblastoma**

Figure 1 presents typical PET images of low-grade glioma (Grade II astrocytoma, Case 3; arrow). **Upper Row:** Low-grade glioma (Grade II astrocytoma, Case 3; arrow). **Lower Row:** Glioblastoma (Grade IV, Case 12). Images were obtained at 5 and 20 minutes postinjection. Deep black of the halftone images indicates a standardized uptake value of 1 or more.

**Low-Grade Glioma (Pt.3)**

- $^{18}$F-Choline
- $^{11}$C-Choline

5 min 20 min 5 min 20 min

**Glioblastoma (Pt.12)**

- $^{18}$F-Choline
- $^{11}$C-Choline

5 min 20 min 5 min 20 min

**Fig. 1.** Axial $^{18}$F- and $^{11}$C-choline–enhanced PET scans of gliomas before treatment. **Upper Row:** Low-grade glioma (Grade II astrocytoma, Case 3; arrow). **Lower Row:** Glioblastoma (Grade IV, Case 12). Images were obtained at 5 and 20 minutes postinjection. Deep black of the halftone images indicates a standardized uptake value of 1 or more.

**Low-Grade Glioma (Pt.3)**

**Fig. 2.** **Upper:** Photomicrograph showing a section of low-grade glioma obtained in Case 3. Many tumor cells are plump, with copious paranuclear cytoplasm (gemistocytic astrocytoma). **Lower:** Photomicrograph showing a section of glioblastoma obtained in Case 12. Areas of necrosis and blood vessels are surrounded by pseudopalisading tumor cells. H & E, original magnification × 400 (upper); × 200 (lower).

**Glioblastoma (Pt.12)**

**Fig. 2.**

- **Upper:** Photomicrograph showing a section of low-grade glioma obtained in Case 3. Many tumor cells are plump, with copious paranuclear cytoplasm (gemistocytic astrocytoma).
- **Lower:** Photomicrograph showing a section of glioblastoma obtained in Case 12. Areas of necrosis and blood vessels are surrounded by pseudopalisading tumor cells. H & E, original magnification × 400 (upper); × 200 (lower).

**Uptake of $^{18}$F- and $^{11}$C-Choline in Relation to the Histological Type of Glioma**

Table 1 shows patient data, including tumor location, hist-
tological type, and tumor uptake (in standardized uptake values) of 18F- and 11C-choline measured at 5 and 20 minutes postinjection. It also shows normal tissue uptake in the gray matter of the contralateral posterior temporal lobe. With both 18F- and 11C-choline, tumor uptake was low in low-grade glioma (Grade II oligodendroglioma and Grade II astrocytoma), and high in high-grade glioma (Grade III anaplastic astrocytoma and Grade IV glioblastoma). Tumor uptake was almost constant between 5 and 20 minutes with both tracers, whereas normal tissue uptake was very low, resulting in a very high T/N ratio. The 18F-choline uptake, however, decreased gradually in normal tissue, but the 11C-choline uptake did not change with time. The result was an increase of the T/N ratio with 18F-choline (< 10.5–12 in anaplastic astrocytoma, and 13.2–21 in glioblastoma), giving very clear images of tumors with 18F-choline at 20 minutes. The change of T/N ratio with time is shown in Fig. 4.

In one patient with oligodendroglioma (Case 1) no uptake of 18F- and 11C-choline was demonstrated on PET studies.

Table 2 shows the particulars of tumor contour seen on CT, MR, and PET studies with addition of 18F- and 11C-choline in all patients. Glioma was well delineated on PET scans, and the tumor size on PET studies was almost the same as that seen on contrast-enhanced CT and MR images (when the tumor enhanced). There were a few exceptions: PET scans were positive in nonenhanced areas in the patients in Cases 2 and 5, and PET scans were negative in an enhanced area in the patient in Case 8.

In one patient with oligodendroglioma (Case 1) no contrast enhancement was demonstrated on CT and MR images, and this corresponded to the absence of the uptake of 18F- and 11C-choline in PET studies.

The PET studies were always negative in the amorphous edematous area surrounding the tumor.

**Discussion**

It is our understanding that the definite diagnosis of glioma should be made only after biopsy sampling and histological examination. When a stereotactic biopsy procedure is intended, 18F- and 11C-choline PET scanning seems to be very helpful in determining the most malignant areas of gliomas, in which various grades of malignant tissues may be present heterogeneously.

Another application of 18F- and 11C-choline PET scanning would be for the differential diagnosis of previously treated gliomas to distinguish among tumor recurrence, inflammation, necrosis, and scar formation. In this case, both CT and MR images are poorly informative, because the information in contrast-enhanced CT and MR images may be seriously compromised by the reactive inflammatory changes. After surgery, the enhancement occurs in a few days at the site of treatment, and it may persist for several months. The enhancement may occur after a delay of several months following radiation therapy and it may be located adjacent to necrotic tissues or remotely as a consequence of radiation-induced telangiectasia.

Previously, when we introduced 11C-choline for brain tumor imaging with PET, we found that untreated and recurrent high-grade gliomas were always visualized clearly with sharp delineation, and were devoid of the influence of reactive inflammatory changes.

We have now introduced 18F-choline, and it is an improvement on the images obtained with 11C-choline. The agent 18F-choline was developed by us and by DeGrado, et al.; our preparation was [18F-fluoroethyl]fluoroethylcho-

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**Tumor Contour Revealed by CT, MR, and PET Studies**

**Low-Grade Glioma (Pt. 3)**

**Glioblastoma (Pt. 12)**

Fig. 3. Axial CT and MR imaging studies of low-grade glioma (Case 3) and glioblastoma (Case 12). The images consist of CT scans without contrast enhancement (A), CT scans with contrast enhancement (B), T1-weighted MR images without contrast enhancement (C), T1-weighted MR images with contrast enhancement (D), and T2-weighted MR images (E).
Use of $^{18}$F- and $^{11}$C-choline in PET scanning of gliomas

The uptake is given as a standardized uptake value; the values for normal gray matter are in parentheses. — = not measured.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs), Sex</th>
<th>Tumor Location</th>
<th>Histological Diagnosis†</th>
<th>$^{18}$F-Choline</th>
<th>$^{11}$C-Choline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29, M</td>
<td>lt frontal</td>
<td>oligodendroglioma, Grade II</td>
<td>invisible (0.077)</td>
<td>invisible (0.046)</td>
</tr>
<tr>
<td>2</td>
<td>42, M</td>
<td>rt parietal</td>
<td>oligodendroglioma, Grade II</td>
<td>0.251 (0.053)</td>
<td>0.280 (0.054)</td>
</tr>
<tr>
<td>3</td>
<td>23, M</td>
<td>rt frontal</td>
<td>astrocytoma, Grade II</td>
<td>0.274 (0.090)</td>
<td>0.286 (0.060)</td>
</tr>
<tr>
<td>4</td>
<td>17, M</td>
<td>rt frontal</td>
<td>anaplastic astrocytoma, Grade III</td>
<td>0.544 (0.061)</td>
<td>0.565 (0.047)</td>
</tr>
<tr>
<td>5</td>
<td>50, M</td>
<td>rt frontal</td>
<td>anaplastic astrocytoma, Grade III</td>
<td>0.556 (0.071)</td>
<td>0.620 (0.059)</td>
</tr>
<tr>
<td>6</td>
<td>54, F</td>
<td>lt thalamic</td>
<td>glioblastoma, Grade IV</td>
<td>0.427 (0.041)</td>
<td>0.410 (0.031)</td>
</tr>
<tr>
<td>7</td>
<td>59, F</td>
<td>lt temporal</td>
<td>glioblastoma, Grade IV</td>
<td>0.531 (0.065)</td>
<td>0.527 (0.032)</td>
</tr>
<tr>
<td>8</td>
<td>69, M</td>
<td>rt frontal</td>
<td>glioblastoma, Grade IV</td>
<td>0.577 (0.065)</td>
<td>0.633 (0.046)</td>
</tr>
<tr>
<td>9</td>
<td>34, F</td>
<td>rt occipital</td>
<td>glioblastoma, Grade IV</td>
<td>0.799 (0.063)</td>
<td>0.783 (0.050)</td>
</tr>
<tr>
<td>10</td>
<td>68, F</td>
<td>lt occipital</td>
<td>glioblastoma, Grade IV</td>
<td>0.910 (0.084)</td>
<td>0.920 (0.059)</td>
</tr>
<tr>
<td>11</td>
<td>65, M</td>
<td>lt temporooccipital</td>
<td>glioblastoma, Grade IV</td>
<td>1.388 (0.127)</td>
<td>1.282 (0.074)</td>
</tr>
<tr>
<td>12</td>
<td>47, F</td>
<td>bilat frontal</td>
<td>glioblastoma, Grade IV</td>
<td>1.710 (0.177)</td>
<td>1.751 (0.083)</td>
</tr>
</tbody>
</table>

* The uptake is given as a standardized uptake value; the values for normal gray matter are in parentheses. — = not measured.
† Graded according to Kleihues, et al.

Conclusions

Administration of $^{18}$F- and $^{11}$C-choline before PET scans

Fig. 4. Graph showing the T/N ratio of $^{18}$F- and $^{11}$C-choline in gliomas of different grades. The increase in the T/N ratio of $^{18}$F-choline from 5 to 20 minutes is indicated by arrows.
were obtained was a very effective aid in imaging gliomas. The \( ^{18} \text{F} \)-choline showed a slightly higher T/N ratio than the \( ^{11} \text{C} \)-choline. Use of \( ^{18} \text{F} \)- and \( ^{11} \text{C} \)-choline for PET scanning would help practitioners determine the most appropriate location for stereotactic biopsy sampling of gliomas.

### References


### Table 2

Summary of glioma contours measured using various neuroimaging modalities aided by \( ^{18} \text{F} \)- and \( ^{11} \text{C} \)-choline in 12 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Area of MT (cm)</th>
<th>CT Findings</th>
<th>MR Findings</th>
<th>PET Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5 x 4</td>
<td>LDA w/ calc</td>
<td>hom LIA</td>
<td>het HIA</td>
</tr>
<tr>
<td>2</td>
<td>3.5 x 3.5</td>
<td>LDA w/ calc</td>
<td>het enhanced area</td>
<td>hom HIA &gt; MT</td>
</tr>
<tr>
<td>3</td>
<td>0.3 x 2.5</td>
<td>hom LDA (8 x 8-cm cyst)</td>
<td>rim partially enhanced</td>
<td>hom HIA (cyst)</td>
</tr>
<tr>
<td>4</td>
<td>4 x 4</td>
<td>het LDA w/ calc</td>
<td>het enhanced area</td>
<td>hom HIA (cyst)</td>
</tr>
<tr>
<td>5</td>
<td>2.5 x 3</td>
<td>het LDA</td>
<td>het enhanced area &amp; oval LDA w/ enhancement</td>
<td>hom HIA &amp; oval HIA</td>
</tr>
<tr>
<td>6</td>
<td>3 x 3</td>
<td>isodense-to-HDA</td>
<td>het enhanced area</td>
<td>het low-to-HIA</td>
</tr>
<tr>
<td>7</td>
<td>3.5 x 4</td>
<td>het LDA encircled by amorph LDA</td>
<td>het enhanced area</td>
<td>hom HIA</td>
</tr>
<tr>
<td>8</td>
<td>2.5 x 2</td>
<td>amorph LDA</td>
<td>ring-shaped enhanced area</td>
<td>hom HIA</td>
</tr>
<tr>
<td>9</td>
<td>2 x 5</td>
<td>hom LDA</td>
<td>het enhanced area</td>
<td>hom LIA</td>
</tr>
<tr>
<td>10</td>
<td>1 x 2</td>
<td>isodense sulcal effacement &amp; small LDA (cyst)</td>
<td>hom enhanced area</td>
<td>het low-to-HIA</td>
</tr>
<tr>
<td>11</td>
<td>5 x 5</td>
<td>het LDA encircled by amorph LDA</td>
<td>het enhanced area</td>
<td>hom HIA</td>
</tr>
<tr>
<td>12</td>
<td>5 x 8</td>
<td>hom LDA</td>
<td>hom LIA</td>
<td>MT het enhanced</td>
</tr>
</tbody>
</table>

* amorph = amorphous; calc = calcification; corresp = corresponding; HD = high-density; HDA = HD area; het = heterogeneous; HIA = high-intensity area; hom = homogeneous; LD = low-density; LDA = LD area; LIA = low-intensity area; MT = main tumor.
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