Modification of glucose metabolism in brain tumors by using cervical spinal cord stimulation

Bernardino Clavo, M.D., Ph.D., Francisco Robaina, M.D., Ph.D., Ricardo Montz, M.D., Ph.D., Marta Domper, M.D., Miguel A. Caramés, M.D., Jesús Morea, M.D., Beatriz Pinar, M.D., Ph.D., María A. Hernández, M.D., Victoria Santullano, M.D., and José Luis Carreras M.D., Ph.D.

Departments of Radiation Oncology—Research, Functional and Stereotactic Neurosurgery, and Neuro-Radiology, Dr. Negrin University Hospital, Las Palmas; PET FOCUSCAN Institute, Madrid; Canary Islands Institute for Cancer Research, Las Palmas; and Grupo de Investigación Clínica en Oncología Radioterápica, Madrid, Spain

Object. In previous studies the authors have shown potential increases in locoregional blood flow and oxygenation in tumors by using electrical cervical spinal cord stimulation (SCS). In the present report they demonstrate the effect of cervical SCS on brain tumor metabolism, as assessed using \[^{18}\text{F}]\text{fluorodeoxyglucose–positron emission tomography (FDG-PET).}

Methods. Cervical devices were inserted in 11 patients who had high-grade gliomas, six of which had recurrent. While the SCS device was deactivated, each patient underwent an initial FDG-PET study to clarify the clinical status. A second FDG-PET study was performed later the same day while the stimulation device was activated to determine the effect of cervical SCS on glucose metabolism.

All 11 patients were evaluable for this PET study. Basal glucose metabolism was higher in the tumor than in the peritumoral areas (p = 0.048). There was a significant increase in glucose uptake during cervical SCS in both the tumor (p = 0.035) and the peritumoral (p = 0.001) areas, with measured increases of 43 and 38%, respectively. The estimated potential maximal residual activity of the first FDG dose’s contribution to the activity on the second scan was 18.5 ± 1% or less.

Conclusions. This PET study is the first in which is described the effect of cervical SCS on glucose metabolism in brain tumors and supports previous study data indicating a modification of locoregional blood flow and oxygenation by cervical SCS. These results open up new approaches to modifying the effect of radiochemotherapy in the treatment of malignant brain tumors.

Key Words • brain tumor • high-grade glioma • spinal cord stimulation • fluorine-18–labeled fluorodeoxyglucose–positron emission tomography • cerebral blood flow • glucose metabolism

Generally, areas with malignant brain tumors have lower perfusion than peritumoral and healthy tissues.2,3,11 This characteristic may result in the reduced delivery of chemotherapy and oxygen, causing additional tumor hypoxia.2,3,14 Furthermore, hypoxia will select more aggressive cells6 with altered apoptosis and, consequently, resistance to radio- and chemotherapy. Additionally, restricted blood flow induces decreased delivery of nutrients such as glucose and decreases the rate of elimination of metabolites such as lactate. All of these factors create an adverse microenvironment. Increasing the locoregional blood flow and modifying the tumor microenvironment could optimize treatment conditions and change the biological response to radiochemotherapy in these tumors. The most widely evaluated method for accomplishing such modifications—the administration of nicotinamide—has not demonstrated significant changes in the blood flow in brain tumors, however.8

Electrical cervical SCS is a neurosurgical technique usually used to treat ischemic syndromes. In previous studies we have shown that cervical SCS can increase locoregional blood flow2 and tumor oxygenation1 in patients with HGGs. Our aim in the present prospective study was to extend these findings by assessing the effect of cervical SCS on glucose metabolism in brain tumors with the aid of FDG-PET.

Clinical Material and Methods

Patient Population

Between March 2000 and December 2004, we enrolled in the present study 11 consecutive patients in whom HGGs
had been diagnosed and who had been referred to our unit for evaluation for radiochemotherapy. Of these 11 tumors, six were glioblastomas multiforme and five were recurrent anaplastic gliomas. There were two women and nine men with a mean mean age of 49 years (range 30–68 years). The cervical SCS electrodes were usually inserted 2 to 3 weeks postsurgery, and the FDG-PET study was performed 1 to 2 weeks later, before the administration of the scheduled radiochemotherapy. For inclusion in the study, patients were required to meet the following criteria: an age of at least 18 years, a Karnofsky Performance Scale score of 60% or better, and the elective use of PET was approved by our health service 1.27-mm-diameter tetrapolar electrode percutaneously inserted on the posterior surface of the spinal cord at C2–4, in the epidural space and slightly displaced toward the tumorous side. The electrode was connected to a subcutaneous impulse generator that delivered an adjustable range of pulse width, intensity, and frequency of stimulation. These parameters were individually adjusted for each patient to produce mild paresthesia in the upper limbs: intensity, 1 to 3 V; pulse width, 200 μsec; pulse rate, 80 to 100 Hz. Following electrode insertion, the cervical SCS device was maintained in the off position until the PET study.

**Positron Emission Tomography Studies**

We used a C-PET 250 device (Philips-ADAC-UGM, Philadelphia, PA) to measure the levels of FDG. Patients were evaluated twice on the same day: in basal conditions and following SCS. The baseline FDG-PET study was conducted following the intravenous injection of FDG (1 MBq/kg body weight) with the patient supine and calm in a dimly lit room. Patients were advised to fast for a minimum of 6 hours before the exploratory study. Images were acquired 45 minutes after the injection of FDG by using a C-PET camera equipped with six curved sodium iodide detector crystals arranged in full ring array. Attenuation correction was performed with a postinjection quasisimultaneous transmission scan using a 137Cs rotating source. The second FDG-PET study commenced approximately 2 hours later. Patients were instructed to switch on the SCS device approximately 10 minutes before the intravenous injection of the second FDG dose (2 MBq/kg body weight) and to keep it on for the next 20 to 30 minutes; thus, stimulation was turned off for approximately 20 minutes after the second injection and before the second FDG-PET scan. Images were acquired with exactly the same protocol as that used to obtain the first PET study.

### TABLE 1

| Case No. | Age (yrs), Sex | Lesion Location | Type of Resection | Tumor Grade* | % Max Residual Activity† | SUVmax Tumor Area | SUVmax Peritumoral Area |
|----------|---------------|-----------------|-------------------|--------------|-----------------|-----------------|----------------|----------------|----------------|
| 1§       | 45, M         | frontal         | none              | III          | 10              | 18              | 32.4            | 80             | 18             | 32.4            | 80             | 6.40            | 11.5            | 79.69          |
| 2§       | 30, F         | frontoparietal  | near-total        | III          | 17              | 7.6             | 7.7             | 1.32           | 1.32           |
| 3§       | 31, M         | temporal        | subtotal           | III          | 20              | 1               | 2.5             | 150            | 150            |
| 4         | 55, M         | multifocal      | biopsy            | IV           | 21              | 6.8             | 8.8             | 29.41          | 29.41          |
| 5         | 68, M         | temporal, multifocal | biopsy          | IV           | 18              | 4.22            | 5.01            | 18.72          | 18.72          |
| 6         | 64, M         | frontoparietal  | biopsy            | IV           | 23              | 4.99            | 8.52            | 70.74          | 70.74          |
| 7§       | 38, M         | parietal        | none              | III          | 19              | 7.95            | 10.8            | 35.85          | 35.85          |
| 8§       | 48, M         | frontal         | none              | III          | 20              | 4.56            | 6.13            | 34.43          | 34.43          |
| 9         | 50, M         | temporal        | subtotal           | IV           | 21              | 7.21            | 10.12           | 40.36          | 40.36          |
| 10        | 62, M         | temporal        | subtotal           | IV           | 18              | 7.82            | 9.42            | 20.46          | 20.46          |
| 11§       | 51, F         | frontal         | none              | III          | 16              | 4.07            | 4.72            | 15.97          | 15.97          |

* World Health Organization tumor classification.
† Percentage of the estimated potential maximal residual activity of the first FDG dose carried over to the activity on the second scan.
‡ Percentage of change (increase): (SUVmax post-SCS − SUVmax pre-SCS) × 100/SUVmax pre-SCS.
§ Relapsed patients. Case 1: local progression after previous subtotal resection and radiotherapy; diagnosis by MR imaging and FDG-PET. Case 2: previous biopsy and radiotherapy for Grade I oligodendroglioma; recurrent as Grade III oligodendroglioma with macroscopic resection but higher uptake on PET. Case 3: local recurrence with component of Grade III astrocytoma after two previous complete resections for gemistocytic astrocytoma. Case 7: two meningeal implants after resection of local recurrence (with previous surgery and radiotherapy); implants did not undergo biopsy and diagnosis was made using MR imaging and FDG-PET. Case 8: recurrence after complete surgery and radiotherapy; FDG-PET assessment was performed before confirmatory surgery. Case 11: local recurrence of Grade III mixed oligodendroglioma (with previous radiotherapy); recurrence did not undergo biopsy and diagnosis was made using MR imaging and FDG-PET.
# Surgery was not performed before PET assessment.
tain the first scan, including reconstruction with an iterative algorithm (slice thickness 2 mm), reorientation parallel to the bases of frontal and occipital cerebral lobes, and display in transversal, sagittal, and coronal views. Semiquantitative measurements of glucose uptake and metabolism in the brain were evaluated. The SUV\textsubscript{max} were calculated in both PET studies in regions of interest: tumor and peritumoral areas defined with visual reference to a pretreatment computerized tomography scan and/or MR image. The SUV\textsubscript{max} were estimated as a semiquantitative measurement calculated with the following equation: \( \frac{Q\textsubscript{max} \times W}{Q\textsubscript{inj}} \), where \( Q\textsubscript{max} \) is the maximal FDG uptake in the tumor or peritumoral area (MBq/L), \( W \) represents body weight (kg), and \( Q\textsubscript{inj} \) is the activity of the dose of injected FDG.

Additionally, in applying this procedure, the maximal residual activity of the first FDG dose, which could potentially contribute to the increase in activity on the second scan, was calculated for each patient. The PET studies pre- and post-SCS were performed by the same three specialists in Nuclear Medicine who were not blinded to patient data.

**Statistical Analysis**

The SPSS (version 7.0 for Windows; SPSS Ibérica, Madrid, Spain) was used throughout. The two-tailed paired t-test was applied to compare values between different areas pre- and post-SCS. Measured data are expressed as the means ± standard deviations. The percentage of increase is expressed as the means and 95% CIs. All probability values of 0.05 or less were considered statistically significant.

**Results**

All 11 patients were evaluable for this PET study. There was a clear increase in glucose metabolism in the tumor and peritumoral areas in eight (73%) of 11 patients. In the tumors, SUV\textsubscript{max} pre- and post-SCS were 6.75 ± 1.3 and 9.65 ± 2.4, respectively (\( p = 0.035 \)), representing an increase of 43\% (95% CI 4–82\%). In peritumoral areas, the SUV\textsubscript{max} pre- and post-SCS were 4.53 ± 0.68 and 6.27 ± 0.88, respectively (\( p = 0.001 \)), representing an increase of 38\% (95% CI 19–58\%). Before SCS, SUV\textsubscript{max} were higher in the tumor than in peritumoral areas (\( p = 0.048 \); Fig. 1). Representative images are featured in Fig. 2. Table 1 shows the individual values of SUV\textsubscript{max} pre- and post-SCS.

The estimated potential maximal residual activity of the first FDG dose contributing to the activity on the second scan was less than 2\%.

We found no significant difference in glucose metabolism or in the percentage of modification in relation to the tumor grade or tumor status as a new or recurrent lesion. Individual PET measurement data are presented in Table 1.

**Discussion**

Tumor cell metabolism depends on the glycolytic pathway, which is not oxygen dependent but essentially relies
on glucose supply, which, in turn, is dependent on blood flow.²² Hence, in the present study, the increase in glucose uptake in the tumor and peritumoral areas after cervical SCS should be associated with increased glucose availability caused by an increase in blood flow. This result is in agreement with data from our previous studies of cervical SCS in patients with brain tumors, showing blood flow increases in tumors and peritumoral areas (as measured using transcranial Doppler ultrasonography) as well as in tumors (as assessed using SPECT).³ Our hypothesis is further supported by a preliminary report of PET measurements in a vegetative noncancerous patient in whom the pattern of increase in cerebral blood flow was almost the same as that in glucose uptake.¹²

There are several hypotheses regarding the mechanisms responsible for the cervical SCS–induced increase in tumor blood flow and, secondarily, glucose metabolism. The segmental liberation of vasoactive substances and the activation of vasomotor centers in the brainstem¹⁶,¹⁷,²⁰ as well as a sympatholytic effect¹⁰,¹⁵,¹⁶,²⁰ have been described. In addition, preexisting host vessels incorporated into the lesion¹⁸ could explain the tumor blood flow response to cervical SCS, whereas defective self-regulatory mechanisms in tumor vessels²² would not preclude regional blood flow increases in response to SCS. Indeed, nitric oxide mediation of tumor PO₂ increases after electrical nerve stimulation has been reported.⁹

The observed capacity of cervical SCS to increase glucose metabolism in tumors and peritumoral areas is of considerable clinical interest. This modification could result in the recruitment of tumor cells into a more active metabolic state, making them potentially more sensitive to chemotherapy and radiotherapy. This hypothesis is supported by the significant correlation between a better response to temozolomide and microenvironment of the tumor in the course of radiotherapy (as well as for temozolomide) is the hematological toxicity, which would not be increased by the local effect of cervical SCS. Although several authors have described the adverse implications of tumor ischemia/hypoxia and results of a meta-analysis have shown that modification of tumor ischemia/hypoxia does not significantly increase tumor dissemination, thirteen additional studies are needed to establish the implications of tumor microenvironment modification by cervical SCS and to confirm SCS as an adjuvant in the treatment of these tumors.

Finally, we must note that the estimated potential maximal residual activity of the first FDG dose carryover to the second scan was 18.5% or less, which implies that the measured 40% increase in tumor metabolism by cervical SCS (43% in the tumor and 38% in peritumoral areas) must be adjusted for this potential carryover. Probably, a more realistic estimate would be approximately 20%. The percentage of modification described in the present FDG-PET study is similar to that revealed in our previous studies with transcranial Doppler ultrasonography and SPECT.² Furthermore, the percentage of patients with a clear increase in glucose metabolism (taking into account the potential maximal residual activity) is similar to the percentage of patients with a clear increase observed in our previous study of tumor blood flow assessment using SPECT.²

**Conclusions**

To the best of our knowledge, this is the first report of data proving an increase in glucose uptake in brain tumors following cervical SCS. Data in the present study support our previous findings on the potential locoregional blood flow increase in brain tumors after cervical SCS. This result allows the possibility of using cervical SCS to modify the metabolism and microenvironment of the tumor in the course of radiochemotherapy for the treatment of HGGs. Additional research is required to confirm the clinical benefits of using this approach.

**Disclosure**

In the past, F. Robaina has received financial support for research activities and has been an external scientific consultant for Medtronic Ibérica (Madrid, Spain). No other author has any involvement that could be construed as a conflict of interest.

**Acknowledgments**

Editorial assistance was provided by Dr. Peter R. Turner (t-Scientific Ltd, Reus, Spain) and statistical assistance by Dr. Dolores Fiuza (Research Unit, Dr. Negrín University Hospital, Las Palmas, Spain). Scientific supervision was performed by Grupo de Investigación Clínica en Oncología Radioterápica, Spain.
Brain tumor metabolism modification by cervical SCS

References


Manuscript received May 9, 2005. Accepted in final form October 24, 2005.

This work was supported by Grant No. FUNCIS 03/09 from the Health and Research Foundation of the Autonomous Government of the Canary Islands (Spain) and Grant No. ISCiii, RTICCC C03/10 from the Canary Islands Institute for Cancer Research (Las Palmas, Spain).

Address reprint requests to: Bernardino Clavo, M.D., Ph.D., Department of Radiation Oncology and Research Unit, Dr. Negrin Hospital, C/Barranco la Ballena s/n, 35020 Las Palmas, Canary Islands, Spain. email: bernardinoclavo@terra.es.