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A Novel Model of Intramedullary Spinal Cord Tumors in Rats: Functional Progression and Histopathological Characterization

INTRODUCTION: Intramedullary spinal cord tumors (IMSCTs) are difficult lesions to treat given their recurrence rate and limited treatment options. Absence of an adequate animal model, however, has hindered the development of new treatment paradigms. In this study we describe the technique for intramedullary injection of two experimental rodent gliomas (9L and F98), and present the methodology for functional and histopathological analysis of tumor progression.

METHODS: F344 rats (n = 24) were randomized into three groups. Group 1 (n = 8) received a 5µl intramedullary injection of Dulbecco's modified Eagle medium (DMEM), Group 2 received a 5µl intramedullary injection of 9L gliosarcoma (100, 000) cells and Group 3 received a 5µl intramedullary injection of F98 glioma (100, 000) cells. Animals were anesthetized, a 2 cm incision was made in the dorsal mid-thoracic region, and the spinous process of the T5 vertebrae was removed to expose the intervertebral space. The ligamentum flavum was removed and an intramedullary injection was made into the spinal cord. Animals were evaluated daily for signs of paralysis using the Basso, Beattie, and Bresnahan (BBB) scale and euthanized after onset of deficits for histopathological analysis.

RESULTS: Animals injected with 9L-gliosarcoma had a median onset of hind limb paresis at 12 ± 2.9 days. Animals injected with F98 glioma had a median onset of hind limb paresis at 19 ± 3 days. Animals injected with DMEM did not show neurological deficits. H & E cross sections confirmed the presence of intramedullary 9L and F98 tumor invading the spinal cord. Control animals had no significant histopathological findings.

CONCLUSIONS: Animals injected with 9L or F98 consistently develop hind limb paresis in a reliable and reproducible manner. The progression of neurological deficits is similar to that seen in patients with IMSCTs. These findings suggest that this model mimics the behavior of IMSCTs in humans and may be used to examine the efficacy of new treatment options for both low and high grade intramedullary tumors.

KEY WORDS: Intramedullary Spinal Cord Tumor; Animal Model; 9L gliosarcoma; F98 glioma

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INTRODUCTION

The prognosis of intramedullary spinal cord tumors (IMSCTs) remains poor (9) mainly due to their infiltrative nature, high recurrence rate, and limited treatment options (13, 38, 41, 42). These lesions, generally arise from glial or ependymal cells, represent 5–25% of all intraspinal tumors, and are more prevalent in children than adults (1, 19, 32).

Surgical resection still remains the standard of care for these patients, with total gross resection as the operative aim (9, 20, 23, 32, 37, 38). Complete gross resection, however, can be difficult given the infiltrative nature of IMSCTs, the presence of surrounding normal cord and the absence of clear surgical planes between cancerous and normal spinal cord tissue (23, 32). While surgical intervention is aimed at preventing further progression of neurological deficits, deterioration eventually occurs (37).

The use of radiotherapy or chemotherapy for the treatment of IMSCT remains controversial. Radiotherapy is often used as an adjunct to

surgical resection for high grade tumors (37). The reported efficacy of this strategy, however, varies significantly between centers and is influenced strongly by tumor grade (20, 23, 38). Ten year survival rates for patients with low-grade astrocytomas, receiving postoperative radiation therapy is as low as 40–50% (11, 17, 40) and as high as 89–91% (25, 27). Two year survival rates for patients with high-grade astrocytoma, receiving postoperative radiation therapy is often 0% (12, 14, 25, 27, 29), but some centers have reported rates as high as 40% (40).

The current role of chemotherapy is also limited (32). Physiological barriers like the blood brain barrier (BBB), formed by tight junctions of the cerebral capillary endothelial cells, the blood-cerebrospinal fluid barrier, and the blood tumor barrier (26, 33) limit the permeability of drugs delivered to the central nervous system (CNS). To circumvent these barriers, several methods have been developed to deliver therapeutics directly to the site of the tumor and are currently used in the treatment of malignant brain tumors and other malignancies (26). In order to adequately test the safety and efficacy of these and other novel approaches in the setting of IMSCTs a reliable and readily reproducible animal model must be developed.

While many intracranial animals models exist (10, 18, 21, 36, 45), a search of the literature reveals only one previous attempt to create an animal IMSCT model (35). In this study Salcman et al.injected adult mongrel dogs with an intramedullary tumor cell suspension of a canine gliosarcoma and measured the time to onset of paresis. Absence of a detailed standardized record of motor function and the use of dogs, which are expensive and limited experimental subjects, have limited the applicability of this model in pre-clinical testing.

We have previously developed a model of IMSCT in rabbits (28). This model is suitable for dose escalation/toxicity studies but the limited availability of monoclonal antibodies for histopathological and molecular analysis, higher cost, and the existence of only one non-glial transplantable tumor cell line (VX2 carcinoma) constitute limiting factors.

Development of a rodent model of IMSCT using glial cell lines would facilitate biological and histopathological studies, lower cost, and increase accessibility to the model. Established rodent tumor lines of intracranial glial tumors commonly used, such as the 9L gliosarcoma and the F98 glioma that are syngeneic to Fischer 344 rats are ideal candidates for intramedullary implantation given their predictable growth rate and their aggressive nature (4).

In this study, we present a novel rat model of IMSCTs using 9L gliosarcoma and F98 glioma and discuss the methodology, histopathological features, and functional correlation of spinal cord invasion with the loss of hind limb motor function after tumor implantation.

MATERIALS AND METHODS

Experimental Design

Twenty-four Fisher 344 rats were randomized into 3 experimental groups. Animals in the first group (n = 8) received a 5-µl intramedullary injection containing Dulbecco's modified Eagle medium (DMEM) and were used as controls. Animals in the second group (n = 8) received a 5-µl intramedullary injection containing 100, 000 9L gliosarcoma cells in 5-µl media. Animals in the third group (n = 8) received a 5-µl intramedullary injection containing 100, 000 F98 glioma cells in 5-µl media. The hind limb motor function of the animals was assessed as described below and animals were sacrificed after onset of paraparesis for histopathological analysis.

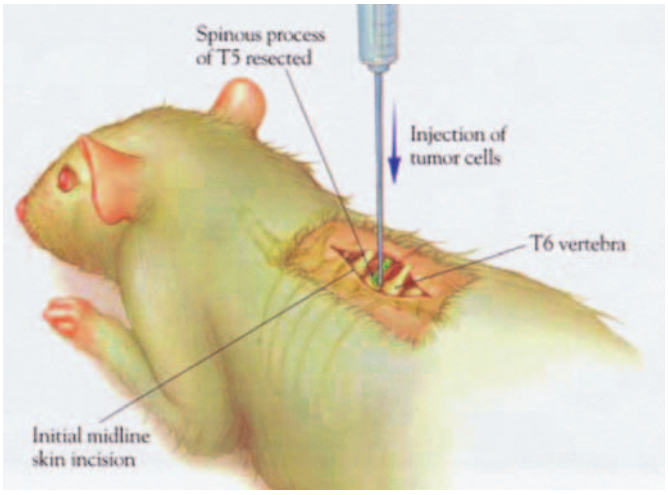

FIGURE 1. *Artist's illustration depicting the incision and surgical approach for intramedullary tumor injection in the rat. The positioning of the animal as well as the adequate angle of needle penetration for the Hamilton syringe containing the tumor cell suspension is shown. The spinous process of the T5 vertebrae removed during the approach is illustrated in green and shown in detail in Figure 2.*

Animals

Female Fischer 344 rats weighing 150–200 g were obtained from Charles River Laboratories (Wilmington, MA). They were housed in standard facilities and given free access to water and rodent chow. All of the rats were treated in accordance with the policies and principles of laboratory animal care of the Johns Hopkins University School of Medicine Animal Care and Use Committee.

Tumor Lines

The 9L gliosarcoma was obtained from Dr. M. Barker at the University of California-San Francisco Brain Tumor Research Center (San Francisco, CA). The F98 glioma was obtained from Dr. R. Barth (Ohio State University, Columbus, OH). Cell lines were grown in DMEM (Gibco, Invitrogen Corporation, Grand Island, NY) with 4.5 g/L glucose, supplemented with 10% fet al. bovine serum and penicillin/streptomycin. A tumor suspension was prepared by suspending 100, 000 cells in 5-µl DMEM.

Surgical Technique

Rats were anesthetized with an intraperitoneal (i.p.) injection (0.4–0.6ml) of a stock solution containing ketamine hydrochloride (25 mg/ml) (Hospira, Inc.LAe Forest IL), xylazine (2.5

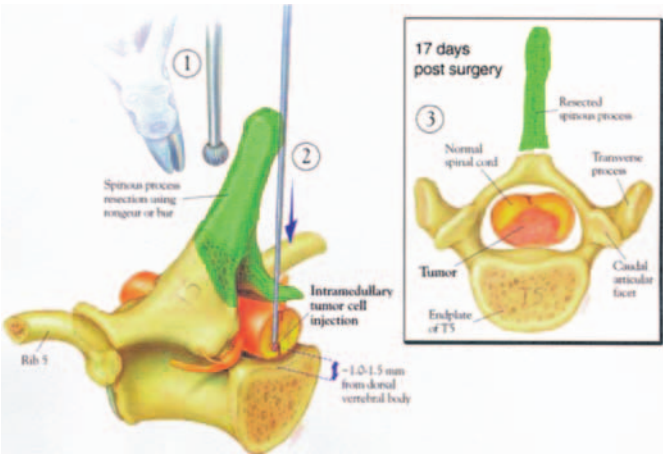

FIGURE 2. *Artist's illustration depicting 1) removal of T5 spinous process highlighted in green using rongeurs or drill. 2) Intramedullary injection of tumor cell suspension, please not the relationship between the tip of the needle and the posterior wall of the vertebral body, and the indicated distance for needle retraction after contact with the vertebral body. 3) Cross sectional view that represents a specimen 17 days after tumor implantation, the invasion and compression of the normal spinal cord at this time point is represented.*

mg/ml, Phoenix Pharmaceutical, Inc., St. Joseph MO), and 14.25% ethanol in normal saline. Animals were placed on a sterile field and their backs were shaved and prepared with a betadine solution. The spinous process of T5 was identified, and a 2-cm longitudinal incision was made over the dorsal midthoracic region. The underlying fascia and the paravertebral muscles were retracted laterally, the spinous process of T5 was removed with rongeurs, and the ligamentum flavum was removed exposing the intervertebral space. The cell suspension was injected through the dorsal intervertebral space with a 26 gauge Hamilton syringe (Hamilton Company, Reno, NV). The needle was advanced until the dorsal aspect of the vertebral body was felt and then retracted slightly (1–2mm). Penetration of the spinal cord was confirmed by monitoring a lower extremity motor reflex after needle insertion. Wounds were closed with surgical staples and analgesia was provided with an intraperitoneal (i.p.) injection of 0.2 ml of 0.02 mg/ml buprenorphine (Abbott Laboratories, North Chicago, IL) in saline.

Functional Testing

Functional testing of hindlimb strength was assessed using the Basso, Bresnahan and Beattie (BBB) scale (5, 6). Briefly, rats were placed in an open field testing area and allowed to adapt. Once the animal walked continuously, it was observed for 4 minutes and locomotion was rated using the BBB locomotor scale. The BBB scale is a 22 point scale ranging from 21 (consistent plantar stepping and coordinated gait, consistent toe clearance, predominant paw position is parallel thoughout stance, consistent trunk stability, tail consistently up) to 0 (no observable hindlimb movement). All animals were tested preoperatively to ensure a baseline locomotor rating of 21. Postoperatively, animals were tested at least once every other day. Two different observers were randomly assigned to score the animal's motor function.

Euthanasia

Once the functional BBB score of an animal was less than or equal to 5 (slight movement of two joints and extensive movement of the third), euthanasia was performed by CO_2 overexposure. The experiment was concluded at Day 60 and all animals in the DMEM only (control) group were sacrificed at this time.

Histopathological Analysis

After sacrifice, the spinal column of each animal was exposed and a segment encompassing all macroscopically visible tumor was excised *en bloc* and placed in 4% formalin in PBS. At the completion of the study all spines were placed in hydrochloric acid for decalcification. Collected specimens included the surgical level and two vertebral segments above and below the level of tumor implantation. Thee decalcified thoracic spine stions (2-mm each) were sliced axially (2 stions though visible tumor, 1 stion though normal tissue) and embedded in paraffin. Five slides (10-µm thick) were obtained from each stion for H & E staining.

Statistical Analysis

In this study, a BBB functional score of less than 5 was the primary end point, and thus the threshold for sacrifice. Survival times were compared between groups using the log-rank (Mantel-Cox) test in Kaplan-Meier nonparametric analysis of survival. SPSS 8.0 (SPSS Inc., Chicago, IL) software for Windows was used for the statistical analyses. Results of the BBB score are expressed as mean ± standard error of the mean (Mean ± SEM). Results for median survival are reported as median ± SEM. Euthanized animals in each group were recorded as a "zero" as its functional score for each day post-sacrifice.

RESULTS

Functional Progression

A total of 24 rats received a 5-µl intramedullary injection. Animals in the first group (controls) had no significant functional deficits through the course of the study (Day 60). On postoperative Day 11, control animals had a BBB score of 18.25 ± 0.25, animals from the second group (9L) had a mean score of 8.4 ± 2.68, and animals in the third group (F98) had a mean score of 9.5 ± 0.68 (*Fig. 3*).

Animals receiving 9L had a median survival of 12 ± 2.9 days. Animals receiving F98 had a median survival of 19 ± 3.4 days. There was a significant difference between median survival of the 9L and F98 groups ($P = 0.034$, Mantel-Cox log-rank test). There was no mortality among control animals (9L versus Controls $P < 0.0001$, F98 versus Controls $P = 0.0001$) (*Fig. 4*).

Histopathology

Examination of control animals revealed no significant findings (*Fig. 5*). Histopathological examination of those animals

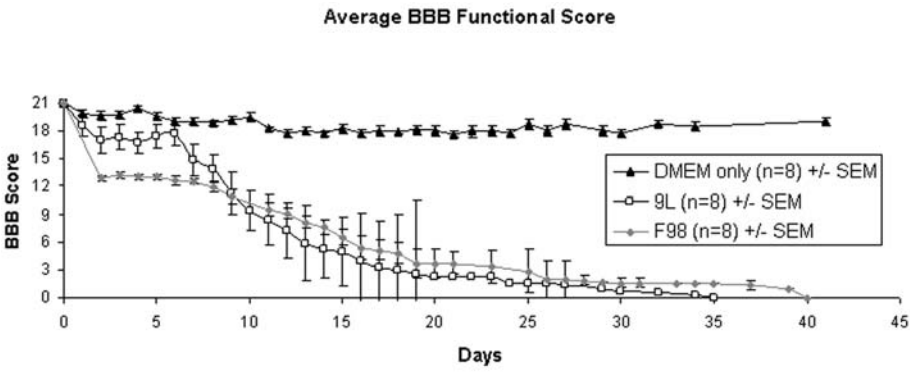

FIGURE 3. *Line graph depicting the mean BBB score of each group over time in days. Control animals are represented by solid circles and show a sustained BBB score throughout the study. Animals implanted with 9L gliosarcoma are represented by empty squares and show a progressive decline in motor function that starts approximately 7 days after implantation. Animals implanted with F98 glioma are represented by solid triangles and show a progressive but slower decrease in motor function when compared to 9L animals. Error bars are ± SEM.*

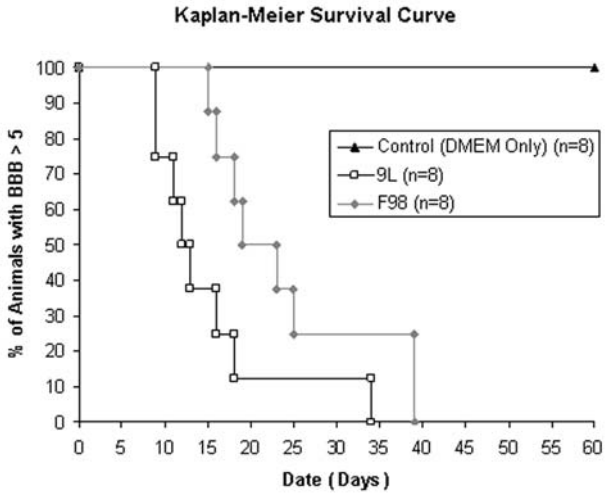

FIGURE 4. *Kaplan-Meier graph showing onset of paralysis (BBB function score < 5). Control animals are represented by solid circles and did not show onset of paralysis throughout the study. Animals implanted with 9L are represented by empty squares and show a faster onset of paralysis when compared to the animals implanted with F98, represented by solid triangles.*

injected with 9L gliosarcoma revealed highly cellular, well circumscribed lesions invading the white matter with finely fibrillary backgrounds, and compression of the grey matter (*Fig. 6*). Within the tumors cellular nuclei were polymorphic with bizarre nuclear patterns; occasional multinucleated cells were observed, with clearly identified mitotic figures. Endothelial proliferation was evident and alternating areas of angiogenesis and necrosis were frequently observed. Histopathological examination of animals injected with F98 glioma revealed infiltrative lesions, with a high degree of white and grey matter invasion (*Fig. 7*), abundant necrosis was consistently observed with replacement of normal structures with scar tissue. Endothelial proliferation was scarce with limited angiogenesis.

DISCUSSION

In this study we present a novel model of intramedullary spinal cord tumors in rats, using two rodent glioma cell lines, describe the methodology for tumor implantation, and define its functional and histopathological progression. We found that animals implanted with 9L and F98 had a median onset of hind limb paresis of 12 and 19 days respectively. The progression of hind-limb deficits observed in the animals implanted with tumor adequately correlates with the decline in function observed in patients with IMSCTs. Animals undergoing sham surgery recovered without incidents and displayed no significant decline in hind limb function.

The 9L gliosarcoma is one of the most popular rat brain tumor models (2, 3). It was developed by Benda (7), Schmidek (39), and colleagues in CD Fischer (CDF) rats through weekly i.v. injections of MNU for 26 weeks, and is typically described as a sarcomatous well circumscribed lesion (3) with highly immunogenic potential (8, 15, 31) and marked angiogenic activity (44). The F98 glioma is also widely used in neuro-oncology for intracranial implantation in syngeneic rats. It was developed by Wechsler and colleagues in CDF rats using a single i.v. injection of ENU administered to a pregnant animal on the 20th day of gestation (24). F98 develops as an infiltrative tumor with low immunogenic potential (43) and moderate angiogenic activity. Both cell lines are considered good models of anaplastic glioma (4).

The aggressive behavior displayed by 9L and F98 after intramedullary implantation correlates well with their progression in intracranial models (16, 22, 34). Animals receiving 9L exhibit a more rapid onset of paraparesis after an intramedullary challenge, and have lower median survival rates after intracranial implantation, when compared to animals implanted with F98 under the same experimental settings. The availability of two different tumor lines with different progression rates gives the investigator the option of selecting the model that best suits the needs of the experimental design.

Furthermore, the different histopathological presentation of these tumors provides a better representation of the variability observed in the human disease. Whereas the 9L is typically well circumscribed and grows with an expansive pattern that causes rapidly progressive cord ischemia, edema, and subsequent necrosis, the F98 is very infiltrative, causes extensive necrosis and disruption of the normal cytoarchitecture (43), and exhibits a significantly slower rate of decline in motor function when compared with 9L . Such pathological differences have obvious implications for evaluating treatment options, and this model offers the opportunity to explore the efficacy of treatments against two distinctive, yet commonly seen pathological characterizations.

Given the diverse cellular populations present in the normal spinal cord, it can harbor the full spectrum of CNS neoplasms,

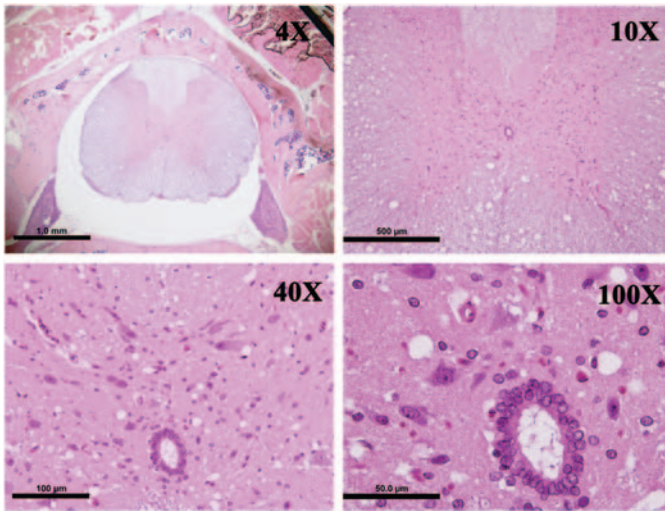

FIGURE 5. *Microphotographs of a cross section of the spinal cord of a rat injected with DMEM (control) and stained with H & E. The top left image shows the normal spinal cord in situ at a 4X magnification. Image sizes are present in the top right corners.*

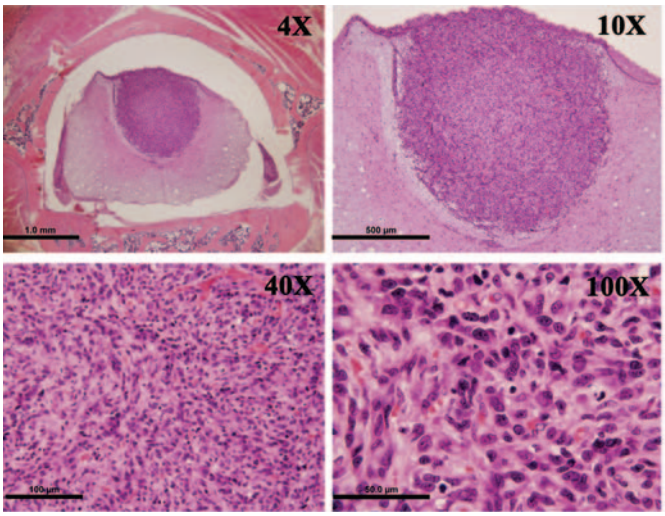

FIGURE 6. *Microphotographs of a cross section of the spinal cord of a rat injected with 9L gliosarcoma and stained with H & E. The concentric nature of the 9L gliosarcoma is readily apparent, and compression of normal spinal cord tissue can be appreciated. The size of the images is shown in the top right corner.*

including astrocytomas, oligodendrogliomas, ependymomas, mixed gliomas, and mixed glial-neuronal tumors. The frequency and behavior of these tumors, however, tends to differ in the spinal cord when compared to the brain. For instance, myxopapillary ependymomas and gangliocytic paragangliomas, which are typically found in the cauda equina, are very rarely found in the brain as primary lesions, and the relative frequency of certain primary spinal cord tumors differs from the frequency reported for the same tumors in the brain. Major differences can also be found in the type of IMSCTs present in pediatric patients

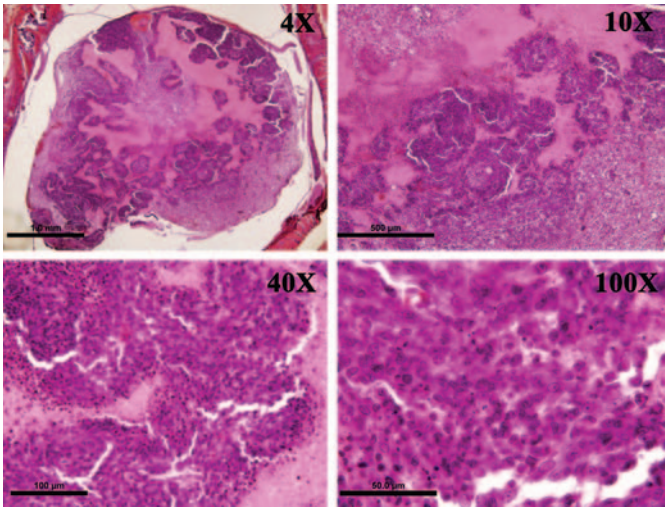

FIGURE 7. *Microphotographs of a cross section of the spinal cord of a rat injected with F98 glioma and stained with H & E. The highly infiltrative nature of this tumor is shown, extensive loss of normal cytoarchitecture is observed. Image sizes are shown in the top right corner.*

when compared to adults. A comprehensive study on the surgical pathology of IMSCTs (30) showed that although ependymomas account for over half of all IMSCTs in adults, the represent only 16% of IMSCTs in children, in whom fibrillary astrocytomas appear to be the most common type. Gangliogliomas and related neuronal-glial tumors are also common in children (35%), but are rare in adults (6%). Pilocytic astrocytomas, oligodendrogliomas and mixed gliomas with oligodendrogliomatous characteristics seem to be unusual IMSCT for both children and adults. This variability in histopathological presentation must be addressed when designing experimental studies to assess novel interventions and must be considered in the development of an adequate animal model of the disease. The use of 9L and F98 provides biological and histopathological variability and using the same methodology other cell lines can be implanted, including human tumors in nude rodents.

Furthermore, as opposed to the usual testing conditions of intracranial tumor models, agents tested for IMSCTs will have to be delivered to the tumors without compromising the integrity of the spinal cord and their impact can be measured by tumor size, survival, as well as by motor function. Similarly, treatment strategies that involve local drug-delivery are limited by the size of the spinal cord which warrants small drug/vehicle sizes/volumes. Moreover, the impact of these strategies is also affected by the nature and degree of surgical manipulation of the spinal cord, which is substantially different from the surgical manipulation that required for intracranial models.

The ease of reproducibility and convenience of rats as the experimental animal make our model ideal for pre-clinical testing of novel therapeutics. Unlike previous IMSCT models whose only functional analysis is time to paralysis, the model presented allows for graded characterization of deficit onset and advanced molecular analysis. A shortcoming was observed in the initial experimental design when despite adequate randomization of

animals allocated to receive either medium or tumor cell injection, the observers assigned to determine BBB scores could not control for the gross differences in motor function present at later stages of the experiments between animals implanted with tumor and controls, which decreased the impact of the blinding, therefore we can't consider the study to be truly blinded. Nonetheless, following the model described in this study we proceeded to test intramedullary cytotoxic agents in our laboratory in a blinded, randomized fashion, and we have found the model to be optimal in differentiating dose-dependent responses, therefore we recommend a blinded, randomized experimental design.

A common observation related to the methodology involves the postoperative drop observed on Day 2 after tumor implantation, which constitutes an artifact of the aforementioned methodology that places animals in the lowest scoring bracket of displayed functions, and represents a weakness of our adaptation of the BBB scoring system. A score of 14 is the highest score which incorporates rotated paw position during locomotion during initial contact with the surface as well as just before it is lifted off at the end of stance, and represents a limitation in the adaptation of the BBB scale to our experimental settings. As such, the drop represents the decrease from the preoperative score, to the post tumor injection score as the result of rotated paws during locomotion, while other higher ranked motor functions were still intact. As the scores do not change appreciably over the first 7 days, this initial decline is likely to be the result of surgical manipulation during tumor implantation, rather than tumor progression, and bears no clinical significance as the scores remained at this level, until tumor growth had progressed to the point of producing observable deficits, at a rate comparable to that of 9L-injected animals. The maintained level of function was high enough that motor deficits which significantly impaired motor function were not present.

We have previously described the technique for intramedullary injections in a rabbit IMSCT model, which given the size of the rabbit spinal cord is ideal for radiographic characterization of IMSCTs and for testing of drug delivery and image guided devices (28). Together, both models facilitate pre-clinical testing of therapeutics and devices, for the treatment of IMSCTs.

In conclusion this new model of intramedullary spinal cord tumors provides reliable and reproducible methodology, correlates well with the human disease, and will be a useful tool in pre-clinical testing of novel treatment options.

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COMMENTS

For much of its history, neurosurgery has been "limited" by the idea that the adult nervous system does not have the ability to repair itself. This has placed obvious constraints on the scope of therapeutic possibilities for our field. Over the course of the past few years, there has been tremendous interest in a "biological" solution to surmount these limitations, with considerable effort and financial resources devoted to "restorative neurosurgery." These efforts have taken the form of stem cell research and attempts to "engineer" cells at the molecular level. In this review, the authors remind us that perhaps a less "biological" approach may ultimately play a role in restoring function to the damaged nervous system. The field of neuroprosthetics is rapidly expanding, and its capabilities, which are intimately dependent upon computational power, will surely broaden with the increasing influence of new technological paradigms such as nanotechnology. This review is timely and of obvious relevance to neurosurgeons.

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Leuthardt et al. provide a general overview of the idea of neuroprosthetics. This new field involves the use of a brain computer interface (BCI) with which electrical impulses from the brain parenchyma are transformed into usable data to overcome, for example, an acquired or congenital neurological deficit. The idea of a paraplegic patient simply using their thoughts to control a mechanical wheelchair, or better yet, to walk with robotic leg braces, is very appealing. The possibilities for such a technology are seemingly limitless. However, in its current state, there are some issues that must be dealt with. The authors point out many of the hurdles that must be overcome. For example, implanted depth electrodes develop surrounding gliosis, which essentially renders them useless after a period of time. While research into new biomaterials may provide answers to inflammatory reactions of the brain, one must also consider plasticity reactions of the brain. BCI systems must be made to adapt as existing neural connections are used in novel ways. The authors also mention the idea of feedback. This can be accomplished by combining both input and output BCIs. This could be used, for example, to input proprioceptive information to the sensory cortex, while outputting commands to a robotic appendage from the motor cortex. Regardless of the current technological issues, this article gives neurosurgeons an introduction to a field in which we will undoubtedly see a rapid expansion of in the not too distant future.

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The idea of the expansion of brain functions and their interaction with the world outside the body is always considered in the human being history. Plato, in *The Republic*, used, for the first time, the word cybernetic to signify the interface between each man and the governance of people. In 1834, André-Marie Ampère included "cybernètique" in his classification of human knowledge.

The study of the communication and control of regulatory feedback between human and machines was born around the Second World War and the intersection between neurology and electronic network theory became a powerful vogue idea between 1948 and the 1970s. The organic life form interfaced with technological devices strongly stimulates many cultural fields, generates a great debate in the philosophy of mind, telecommunication engineering, and many cult movies performed in the past 20 years (*Terminal Man*, *Blade Runner*, *Minority Report*, *Matrix*) always considered the interface brain-machine under control of the machine.

The development of neuroprosthetics includes deep brain stimulation to improve movement disorders or psychiatric disease, but neuroprosthetics based on the BCI go beyond the imagination of the most writers. Interface with visual cortex could build up visual prosthesis, but the interaction with the retina, hippocampus, and cochlea are just a few examples of possible implants.

There is the awareness that clinical application of BCI has only started, and I am quite sure that improvement of computer technology and knowledge of brain activity will make feasible the clinical application of BCI on severely impaired patients. So far the electroencephalography-based systems represent a promising way to develop an interface to provide a better quality of life. Actually, we don't know which patient affected by acute lateral sclerosis or spinal cord injury will benefit from BCI, and, to select the ideal patient, a first attempt using scalp electroencephalography could be a promising suggestion. Another issue consists of the brain structure to be used for BCI; if the scalp electroencephalogram is one term of the system, it should be stressed that the Ì activity is not constant and rarely recorded (the 8-12 Hz activity is the · rhythm typical of the occipital region). Even when a motor response of a robotic arm is requested, the BCI does not necessarily have to be linked to a pericentral activity. For instance, a Ï activity should be used. The use of the single unit-based system is very attractive, but, unfortunately, is still theoretical and poses heavy limitations. The problems of a long-term function of such a method is real and the single unit approach should be considered after the resolution of the electrode encapsulation phenomenon. From this point of view, the placement on the cortex of strip or grids seems to be the ideal solution. The activity recorded is clear, has fewer artifacts, and its possible application should included on a demanding system to control seizures. Also, the subcutaneous placement of the cable connected to the grid and a subclavicular teleme-

try device allows safe and easy daily use of the BCI.

Electrocochleography seems to be very attractive, but the corticocortical evoked potential is a challenging alternative. Researchers have to realize that the high definition of the language, visual, and motor areas by this technique allows broad neuronal network detection.

The greatest advantage of the clinical application of BCI justifies accepting the risk faced from more invasive procedures. It must be remembered that, in epilepsy surgery, the preoperative evaluation by the placement of grids on the brain surface has proven to be a very low-risk methodology.

In my opinion, it must be remembered that BCI is not the only solution: the research on restorative neurosurgery focused on stem cells, gene therapy, and neurotrophic factors supporting brain structures, are reporting promising results.

In conclusion, the present report is particularly interesting because of the clinical perspective of the possibility of translating a neural input by an effect independent of any peripheral systems and the prospect to the neurosurgical audience what may be the future of behavioral science. The authors have provided us with a new perspective in the field of neurosurgery, particularly in restorative neurosurgery.

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Leuthardt et al. present us with a review of the current state-of-the-art in man-machine interfaces. Focusing on output BCIs intended to restore motor control, they paint an optimistic picture of how these devices may restore function to our patients incapacitated by permanent neurological injuries. Although this technology is still in its infancy, it is certainly likely that useful neuroprosthesis will become available long before neurorestorative strategies, such as stem cell therapies, and neurosurgeons will likely be playing a significant role in the development and implementation of such technology.

Nevertheless, many hurdles remain in this area. The authors are correct in stating that the fidelity and quality of electrical signals would be highest with implantable BCIs, such as cortical or single-unit systems. For these implantable devices, local tissue reactions and scarring can significantly dampen the extraction of electrophysiologic data, and, as the authors point out, the ability to revise such operations needs to be considered. Next-generation devices will have to be composed of truly inert biomaterials or use biological strategies to prevent these phenomena. Other problems relate to the need for BCIs to reliably translate complex electrophysiological data sets into a variety of meaningful signals to reproduce normal human motor function. Ultimately, technological advancements will likely overcome these and other hurdles. The authors have provided a commendable introduction to this exciting and important emerging field.

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