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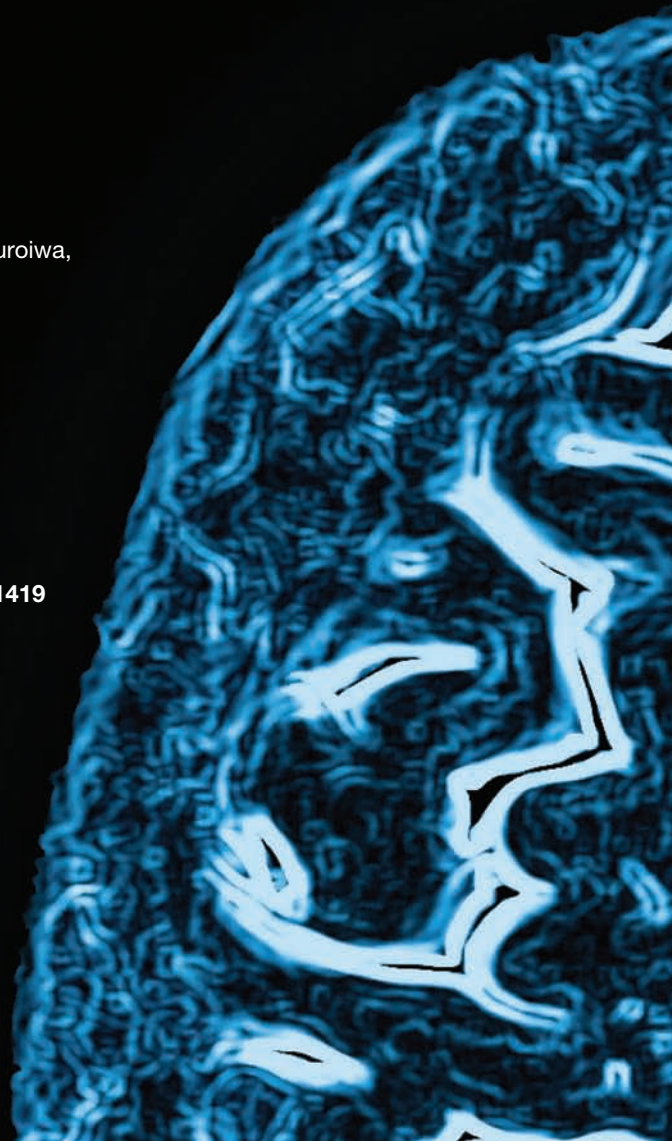

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Editorial WFNOS Magazine

Dear colleagues and friends in neuro-oncology,

It is a great pleasure to welcome you to the WFNO Meeting Year 2017. With great expectations, we are looking forward to a splendid world meeting in Zurich in early May.

Please allow a brief review of the EANO Meeting 2016 in Mannheim/ Heidelberg. We have experienced a couple of nice sunny late autumn days in the Rosengarten conference venue. The meeting has attracted colleagues from all over the world and despite a somewhat lower number of attendees has been specifically visited by our younger fellows. More than one quarter of all participants were PhD students, young PhDs, or residents, early in their careers. In addition, EANO was proud to have launched the Young EANO initiative at this meeting.

In the present magazine, you will find a fine selection of specialists' reviews on the current standard of practice in the use of bevacizumab. Further, biochemically targeted radiotherapy, namely boron neutron capture therapy, has been evaluated for use in practice by Dr. Miatake from Taktsuki. We would like to draw your special attention to a politically important topic that concerns all neuro-oncology societies, that is, inequality of access to treatment, social inequalities, and impact on outcome for cancer patients. The article by Roger Henriksson, board member of EANO and host of the EANO Meeting 2018 in Stockholm, provides a differential view on precision therapy. He lays out that precision medicine is not only about genes or drugs, but shows that patient care largely depends also on individual and societal social factors. We should all try to bridge gaps within our outreach areas and should certainly be prepared to draw our attention not only to the latest scientific developments, but also to improving care for all brain tumor patients.

With best regards and joyful reading,

Wolfgang Wick,
EANO President

Nino Chiocca,
SNO President

Boron Neutron Capture Therapy for Malignant Brain Tumors

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Abstract

Boron neutron capture therapy (BNCT) is a biochemically targeted radiotherapy based on the nuclear capture and fission reactions that occur when nonradioactive boron-10 (^{10}B), which is a constituent of natural elemental boron, is irradiated with low-energy thermal neutrons to yield high linear energy transfer alpha particles and recoiling lithium-7 nuclei. Therefore, BNCT enables the application of a high dose of particle radiation selectively to tumor cells in which ^{10}B has been accumulated. We applied BNCT using nuclear reactors for 167 cases of malignant brain tumors, including recurrent and newly diagnosed malignant gliomas and recurrent high-grade meningiomas, from January 2002 to May 2014. Here, we introduce the principle and the clinical results of our BNCT for the above-mentioned malignant brain tumors and describe a novel diagnostic tool: fluoride-labeled boronophenylalanine positron emission tomography.

Finally, we discuss the recent development of accelerators producing epithermal neutron beams. This development, reported here for the first time, could provide an alternative to the current use of nuclear reactors as a neutron source, and could allow BNCT to be performed in a hospital setting.

Keywords: boron neutron capture therapy, malignant glioma, glioblastoma, high-grade meningioma, positron emission tomography

Introduction and Principle of BNCT

In theory, boron neutron capture therapy (BNCT) provides a way to selectively destroy malignant cells while sparing normal cells. BNCT requires 2 components: a neutron and a boron-carrier. Sir James Chadwick discovered the neutron in 1932 and was awarded the 1935 Nobel Prize in Physics for his discovery.[1] A mere 4 years later, Locher introduced the concept of BNCT.[2] BNCT is based on the nuclear capture and fission reactions that occur when boron-10 (^{10}B), which is a nonradioactive constituent of natural elemental boron, is irradiated with low-energy thermal neutrons to yield high linear energy transfer (LET) alpha particles (^{4}He) and recoiling lithium-7 (^{7}Li) nuclei.

In order for BNCT to be successful, a sufficient amount of ^{10}B must be selectively delivered to the tumor cells ($\sim$20 μg/g weight or $\sim 10^9$ atoms/cell) with good contrast of accumulation to surrounding normal cells, and a sufficient number of thermal neutrons must be absorbed by the tumor cells to sustain lethal damage from the ^{10}B(n, α)^{7}Li capture reaction. Since the high LET particles have limited path lengths in tissue (5–9 μm), the destructive effects of high LET particles are limited to boron-containing cells.

The principle of BNCT is shown in **Figure 1**. In this figure, malignant gliomas in the brain are the presumed target. One characteristic of this type of tumor is that it infiltrates the surrounding normal brain, and thus care should be taken that the tumor cells selectively accumulate the ^{10}B atoms rather than the normal cells. This selective accumulation is achieved by the nature of the ^{10}B-containing compounds themselves, and is discussed in detail in the next section. After the ^{10}B-containing compounds are accumulated in the tumor cells, the tumor cells are irradiated with nonhazardous low-energy thermal neutrons. During this process, it is not necessary to aim the neutron irradiation exclusively at the tumor cells. High LET particles will destroy only ^{10}B-containing cells and preserve the normal surrounding cells, as shown in Figure 1.

Since BNCT is primarily a biochemically rather than a physically targeted type of radiation treatment, the potential exists to destroy tumor cells dispersed in normal brain tissue, if sufficient amounts of ^{10}B and thermal neutrons are delivered to the target volume, as described above. In this article, we will provide an update on BNCT, specifically as it relates to the treatment of recurrent gliomas, and recurrent high-grade meningiomas, based on our experiences. We will also introduce the concept of accelerator-based BNCT.

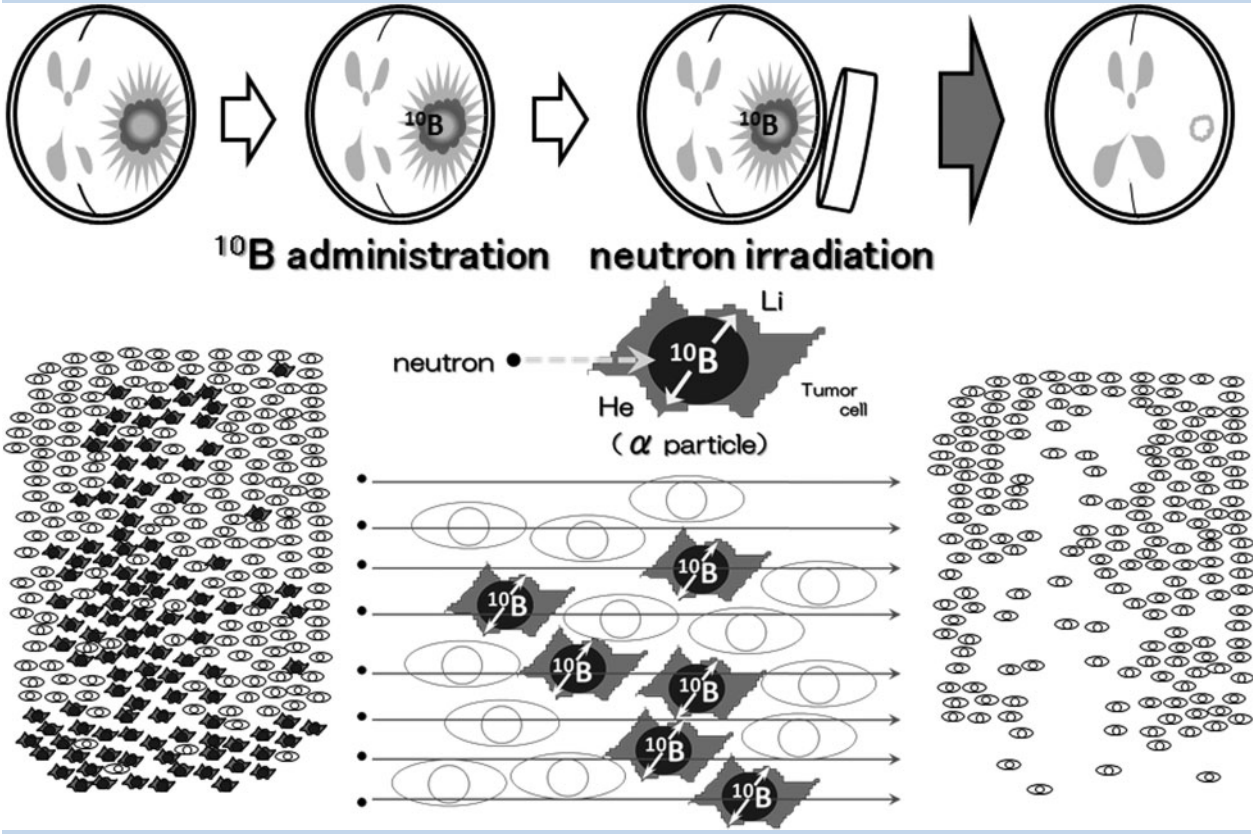

Figure 1. The principle of boron neutron capture therapy

BNCT is a binary approach: a boron-10 (^{10}B)–labeled compound is administered that delivers high concentrations of ^{10}B to the target tumor relative to surrounding normal tissues. This is followed by irradiation with thermal neutrons or epithermal neutrons that become thermalized at depth in tissues. The short range (5–9 μm) of high LET alpha and ^{7}Li particles released from the ^{10}B(n, α)^{7}Li neutron capture reaction realizes tumor-selective killing without damage to adjacent normal brain tissue.

Selective Accumulation of Boron Compounds and PET Imaging

There are only 2 boron delivery agents in clinical use: the polyhedral boron anion, sodium mercaptoundecahydro-closo-dodecaborate ($Na_2B_{12}H_{11}SH$), commonly known as sodium borocaptate (BSH)[3]; and the boron-containing amino acid (L)-4-dihydroxyborylphenylalanine, known as boronophenylalanine (BPA).[4]

Each of these compounds reaches or accumulates in different subpopulations of tumor cells in a different fashion.[5] BSH is not delivered into the normal brain through the blood–brain barrier, and thus the concentration of this compound in tumor tissue is related to both the tumor vasculature and its concentration in the blood. BPA accumulates preferentially in the actively proliferating subpopulation via the augmented expression of amino acid transporters on tumor cells. However, some of this compound inevitably accumulates in normal tissue.

The selective destruction of glioblastoma (GBM) cells in the presence of normal cells represents an even greater challenge than malignancies at other anatomic sites, since high-grade gliomas are highly infiltrative into the normal brain, histologically complex, and heterogeneous in their cellular composition.

To ensure the selective accumulation of BPA and to make a dose simulation prior to neutron irradiation, we used ^{18}F-BPA–positron emission tomography (PET). This readily provided us with accurate information on the BPA accumulation and distribution before neutron irradiation (ie, without craniotomy).[6–8] A representative ^{18}F-BPA-PET image is depicted in **Figure 2**. The lesion-to-normal brain (L/N) ratio of the enhanced tumor was 7.8 in this case. Note that even the periphery of the main mass—that is, the infiltrative portion of the tumor without contrast enhancement—showed BPA uptake. These results were used to estimate the L/N ratio of BPA uptake, which in turn was used for the dose planning. The PET image

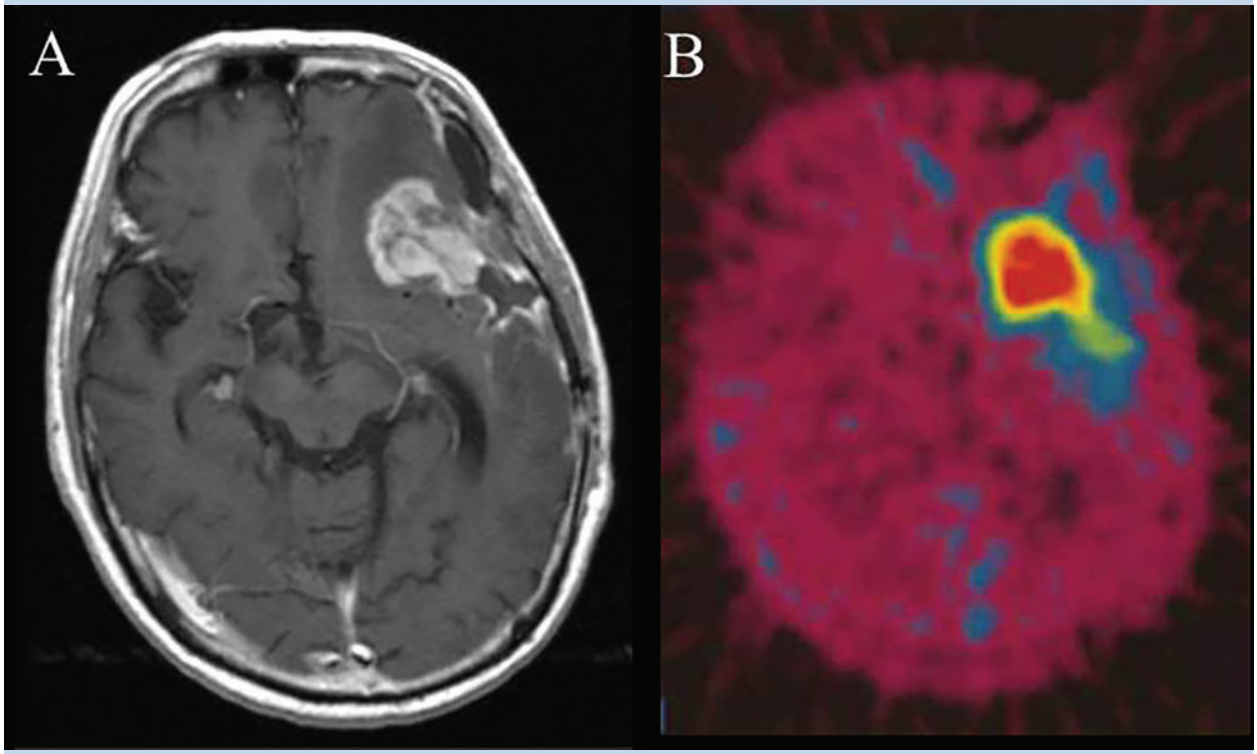

Figure 2. Contrast-enhanced T1-weighted MRI of a representative glioblastoma patient and ^{18}F-labeled BPA-PET image after initial debulking surgery

The patients received ^{18}F-BPA-PET to assess the distribution of BPA and to estimate the boron concentration in tumors before BNCT without direct determination of boron concentration in the tumor. (A) Gadolinium-enhanced T1-weighted MRI. (B) F-BPA-PET image. All images were obtained after initial debulking surgery and prior to BNCT. The lesion-to-normal brain (L/N) ratio of the enhanced tumor was 7.8 in this case. Note that even the periphery of the main mass, that is, the infiltrative portion of the tumor and non-enhanced area, showed BPA uptake. The L/N ratio of BPA uptake was estimated from this study and was then used for the dose planning. ^{18}F-BPA-PET provided an accurate estimate of the accumulation and distribution of BPA as previously reported.[36,37]

provides clear evidence of tumor cell–selective destruction by BNCT using BPA.

BNCT for Recurrent Malignant Gliomas

Initially we applied BNCT for recurrent malignant gliomas. In the clinical setting, either BPA alone or in combination with BSH has generally been used for BNCT of recurrent malignant gliomas. On neuroimages, marked early shrinkage of the enhanced lesions or perifocal edema was evident in these initial studies.[9,10] More than 50% of the contrast-enhanced volumes disappeared in 8 of the initial 12 patients during the follow-up period.[10] To overcome the weak points of BNCT as performed in the 1950s and to improve the clinical results, we used an epithermal neutron beam instead of a thermal neutron beam, since the neutron flux by the latter was often insufficient, especially in the deeper parts of the brain. In addition, we used BSH and BPA simultaneously, a method reported elsewhere as modified BNCT.[10]

Figure 3 shows representative MRI changes in a case of recurrent malignant glioma treated by BNCT using BPA as the sole boron compound. The original histological diagnosis was anaplastic oligoastrocytoma, and the mass recurred after chemo-irradiation using standard chemoradiotherapy consisting of X-ray treatment (XRT) and temozolomide (TMZ). BNCT was applied for this patient according to our recent protocol for recurrent malignant gliomas and meningiomas.[11] Briefly, only BPA was administered over a 2-h period (200 mg/kg/h) just prior to and during the neutron irradiation (100 mg/kg/h). Based on the PET-based simulation described above, we chose a neutron irradiation time that would keep the peak brain dose below 12.0 Gy-Eq (Gray-equivalent). Here, Gy-Eq corresponds to the biologically equivalent X-ray dose that would have equivalent effects on tumors and on the normal brain. Figure 3 shows the marked shrinkage of the mass; this patient survived more than 4 years after BNCT.

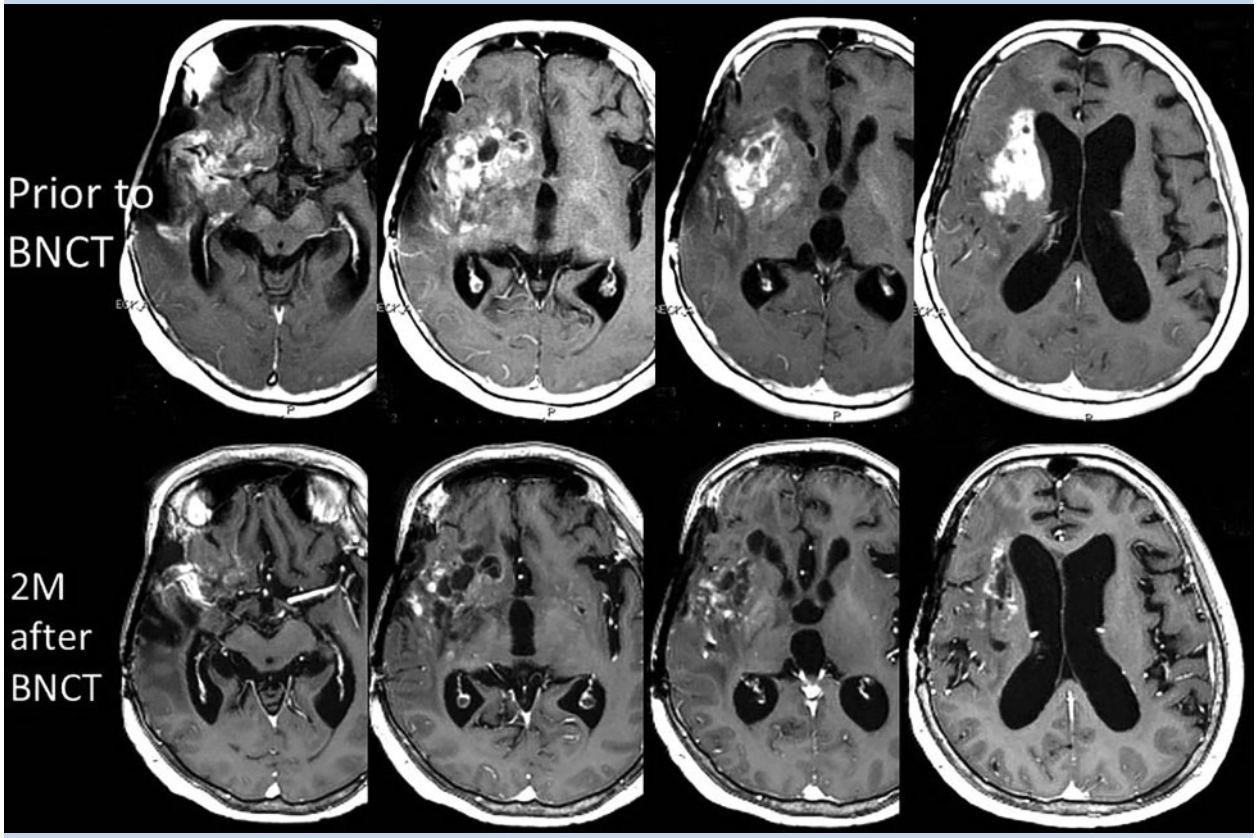

Figure 3. Representative MRI changes in a case of recurrent malignant glioma treated by BNCT.

The patient underwent a craniotomy and the histological analysis indicated anaplastic oligoastrocytoma. She received chemo-irradiation with several chemotherapeutic regimens, including procarbazine/lomustine/vincristine and TMZ. Unfortunately, the mass recurred with aggravation of the left hemiparesis. RPA classification for recurrent malignant gliomas was judged as class 3, and therefore the estimated median survival time at recurrence was 3.8 months. The MRI prior to BNCT showed irregularly enhanced mass infiltrates from the right frontal and temporal lobes into the basal ganglia. Two months after BNCT, the mass shrunk rapidly. She survived more than 4 years after BNCT.

Next we assessed the survival benefit of treating recurrent malignant gliomas by BNCT.12 Unfortunately, however, no standard treatment has yet been established for recurrent malignant gliomas. Therefore it was difficult to evaluate the survival benefit of BNCT for recurrent malignant gliomas. To address this problem, we evaluated the survival benefit in patients classified into 2 groups, low- and high-risk recurrent malignant gliomas, by adopting the recursive partitioning analysis (RPA) classification for recurrent malignant glioma advocated by Carson et al. This classification system, which was presented in a 2007 article in the *Journal of Clinical Oncology*, was based on the results of 10 recent protocols of phase I and II trials applied by the New Approaches to Brain Tumor Therapy CNS Consortium for recurrent malignant glioma.[13] When we published our initial results of BNCT for recurrent malignant glioma, the survival data were analyzed using 22 consecutive cases of recurrent malignant gliomas treated by BNCT from 2002 to 2007. Here, cases without GBM based on initial histology and with KPS $\leq$70% were assigned to RPA class 3, while those with GBM based on initial histology, age $\geq$50, and steroid use were classified as RPA class 7. The median survival times (MSTs) after BNCT for all patients and for glioblastoma as on-study histology at recurrence were 10.8 months ($n = 22$; 95% CI, 7.3–12.8 mo) and 9.6 months ($n = 19$; 95% CI, 6.9–11.4 mo) in our series, respectively. The MST for high-risk RPA classes (class 3 + 7) was 9.1 months ($n = 11$; 95% CI, 4.4–11.0 mo). By contrast, the original data of Carson et al showed that the MST of the same RPA classes was only 4.4 months ($n = 129$; 95% CI, 3.6–5.4 mo). BNCT showed a marked survival benefit for recurrent malignant glioma, especially in the high-risk group.[12] Moreover, the median target volume on contrast MRI in our series was 42 mL, which is too large for treatment by stereotactic radiosurgery. In the *Journal of Neuro-Oncology* in 2009, we published data on 22 cases of recurrent malignant glioma treated by BNCT[20]; among

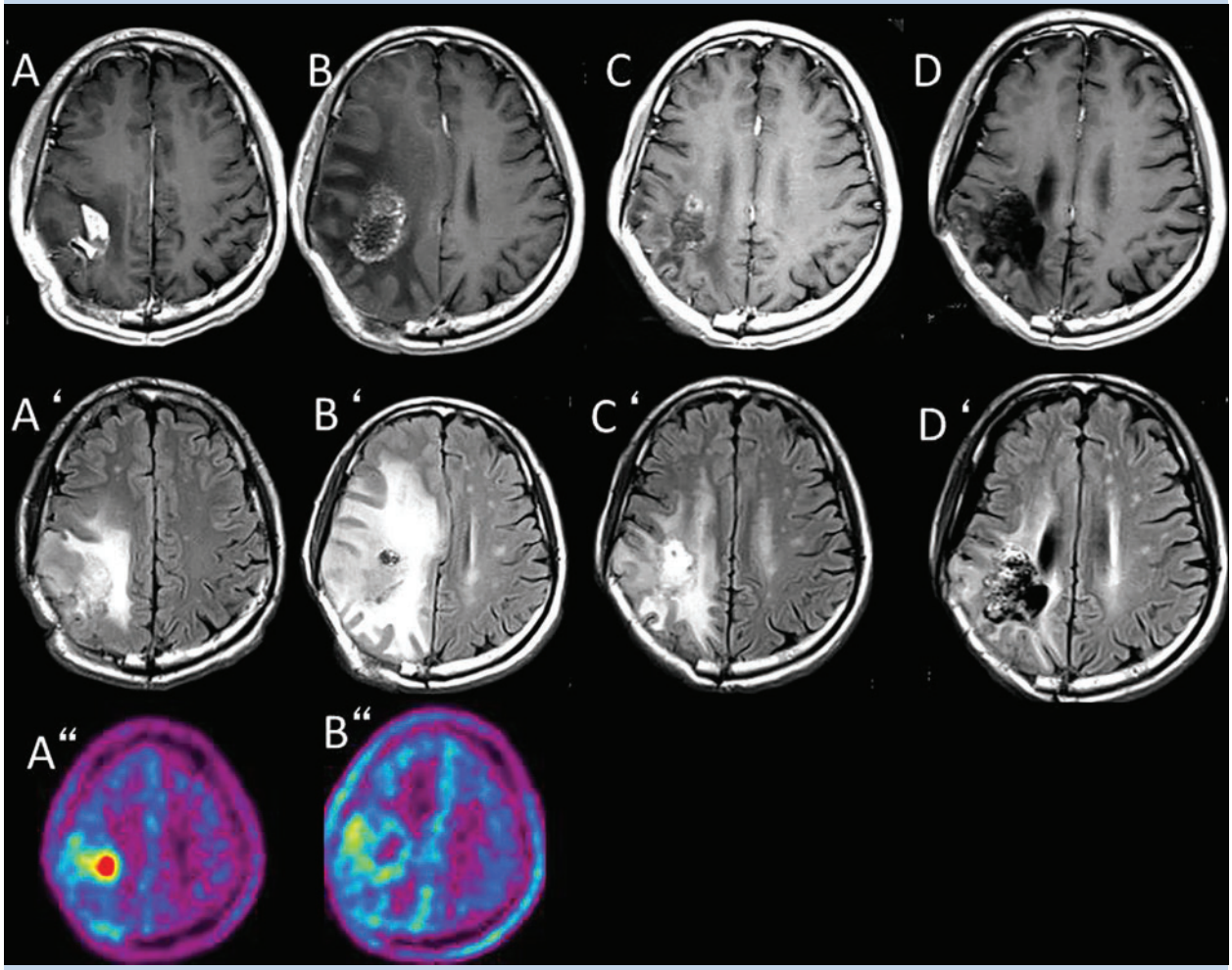

Figure 4. A representative case of brain radiation necrosis caused by BNCT and treated with bevacizumab successfully

The right parietal GBM recurred after standard chemoradiotherapy. The F-BPA-PET image showed marked tracer uptake in the right parietal region with a 3.8 L/N ratio of the tracer, indicating that the lesion was a recurrent GBM. The patient was treated with BNCT. Periodic MRIs showed gradual enlargement of both the enhanced lesion and perifocal edema, whereas F-BPA-PET showed a gradual decrease of the tracer uptake. The final L/N ratio, 13 months after BNCT, was 2.3. This L/N ratio and the simultaneous MRI suggested that the lesion was brain radiation necrosis. The patient was not able to continue his work as a cook, and we decided to begin intravenous bevacizumab treatment biweekly (5 mg/kg). After 4 treatments, MRI showed marked improvement in the perifocal edema and left hemiparesis. The patient is now doing well and has resumed his work as a cook, 57 months after the BNCT, without tumor progression or recurrence of the radiation necrosis.

A, A′, and A″: gadolinium (Gd)-enhanced T1-weighted and fluid attenuated inversion recovery (FLAIR) MRI and F-BPA-PET imaging taken just prior to BNCT. B, B′, and B″: Gd-enhanced T1-weighted and FLAIR MRI and F-BPA-PET imaging taken 13 months after BNCT. From B″, we judged that this worsening on MRI represented brain radiation necrosis. C, C′: Gd-enhanced T1-weighted and FLAIR MRI taken 15 months after BNCT and 2 months after the initiation of bevacizumab treatment. D, D′: Gd-enhanced T1-weighted and FLAIR MRI taken 57 months after BNCT with bevacizumab treatments.

these 22 cases, we lost 5, 10, 1, and 3 cases due to local tumor progression, CSF dissemination, a combination of both, and uncontrollable brain radiation necrosis (BRN), respectively.

The biggest drawback of BNCT for recurrent malignant gliomas is the occurrence of BRN and symptomatic pseudoprogression (PsPD). Recurrent malignant glioma cases generally receive nearly 60 Gy XRT prior to reirradiation by BNCT. Even with tumor-selective particle radiation BNCT, BRN and symptomatic PsPD may develop, because nonselective gamma-ray and nitrogen-neutron reaction and BPA uptake in normal tissue are inevitable. Occasionally BRN causes severe neurological deficits and sometimes endangers the patient's life. The key molecule in this pathology is vascular endothelial growth factor (VEGF). Bevacizumab, an anti-VEGF antibody, has been used recently for the treatment of symptomatic BRN.[14,15] We have used bevacizumab in an

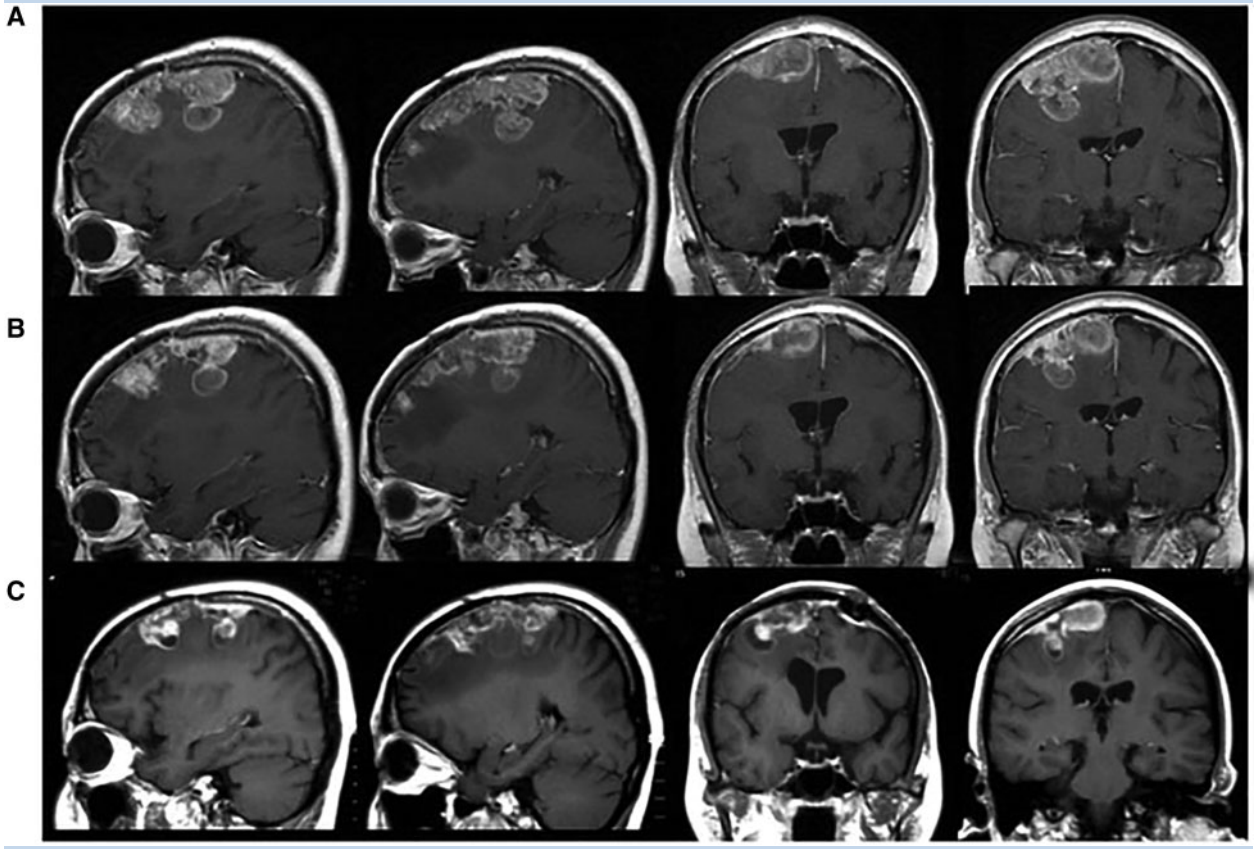

Figure 5. Representative treatment effects of BNCT on high-grade meningioma

A 25-year-old woman who had a history of repetitive recurrence of rhabdoid meningioma (World Health Organization grade III) even after several surgeries and stereotactic radiosurgeries. Serial contrast-enhanced axial, coronal, and sagittal MR images demonstrated that a right frontal tumor, which had rapidly regrown after the last Gamma Knife surgery, was reduced gradually in the 4 months after BNCT. Prior to BNCT, she manifested left hemiparesis and could mobilize only with a wheelchair, whereas she began to walk a week after BNCT.

Row A: 1 week prior to BNCT; row B: 2 weeks after BNCT; row C: 4 months after BNCT.

attempt to control the symptomatic BRN and the symptomatic PsPD encountered after BNCT for recurrent malignant gliomas with promising results.[16–18] Therefore, BNCT with the combination of bevacizumab should improve the quality of life and prolong the survival of recurrent malignant glioma patients. In **Figure 4,** we introduce a representative case of BRN caused by BNCT and successfully treated with bevacizumab.

BNCT for Newly Diagnosed Malignant Gliomas

Hatanaka and his colleagues reported a good result of BNCT for newly diagnosed malignant gliomas between 1987 and 1994.[19] However, Laramore et al[20] analyzed the survival data of a subset of 12 patients who had been treated by Hatanaka et al and concluded that there were no differences in their survival times compared with the Radiation Therapy Oncology Group RPA classifications.[21]

Several clinical studies of BNCT for newly diagnosed malignant gliomas[22–25] were reported in the first decade of the 2000s in Europe and the USA. In each of these studies, the MST was approximately 13 months. Although these survival times were similar to those obtained with surgery followed by XRT, no firm conclusions can be made as to whether the clinical results of BNCT are equivalent or superior to those of XRT.

On the other hand, after confirming the effectiveness of BNCT for recurrent malignant glioma, we applied BNCT for newly diagnosed malignant gliomas, most of which were GBM. We have carried out several clinical studies in

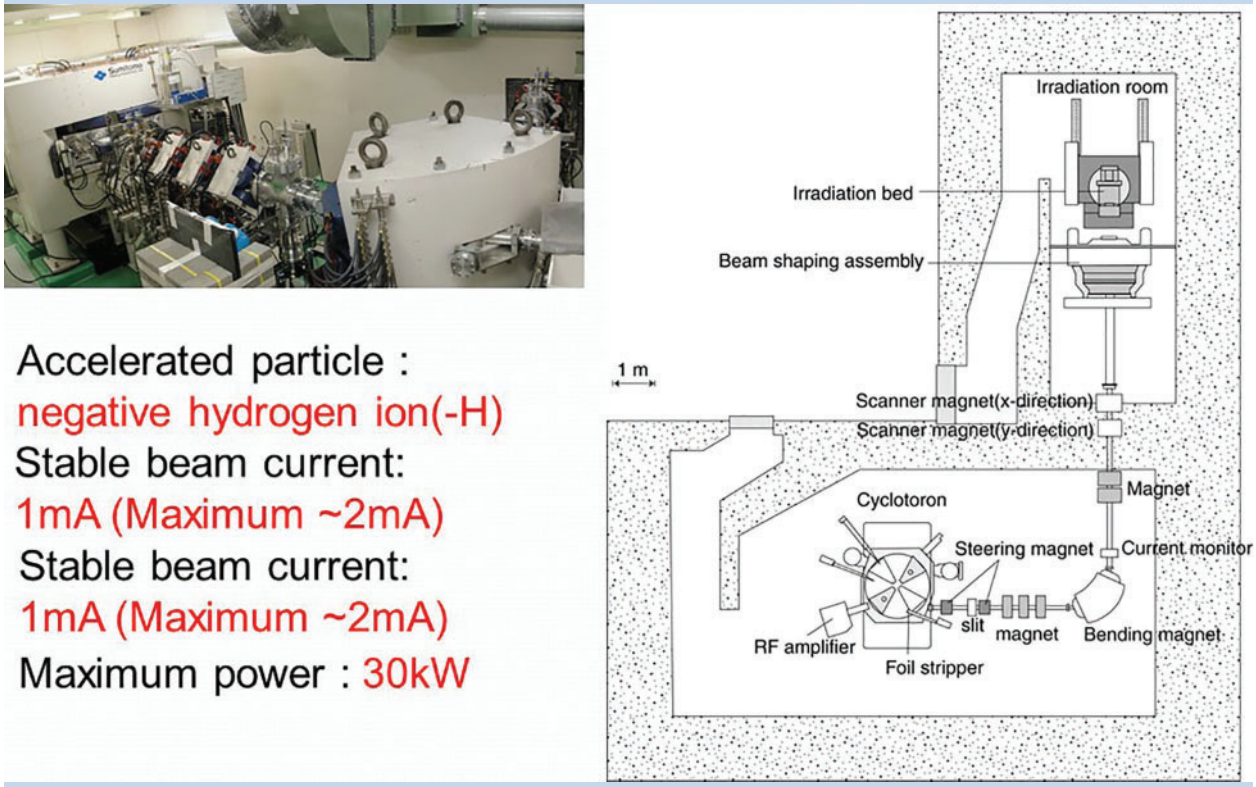

Figure 6. A cyclotron-based accelerator for neutron generation and a schematic drawing of an irradiation room including a beryllium target, collimator, and irradiation bed or chair

Courtesy of Sumitomo Heavy Industries, Ltd. The size of the cyclotron itself is very compact at 3.030 × 1.724 × 1.620 meters.

which BPA alone or in combination with BSH was administered for treatment of patients with primary, surgically resected malignant glioma.[26] In patients with newly diagnosed GBMs, favorable responses were seen using BNCT with BPA and BSH either with or without an XRT boost, especially in high-risk groups. The MST of patients treated with this regimen (BNCT with an X-ray boost) was 23.5 months compared with 15.6 months (95% CI, 12.2–23.9 mo) after diagnosis for patients who had surgery followed by BNCT alone. This was significantly longer than the MST of 10.3 months for the historical controls ($n = 27$) at Osaka Medical College who had undergone surgical resection followed by XRT and chemotherapy with nitrosourea (mainly ACNU).[27] Note that for these cases TMZ was not used.

Similarly, Yamamoto et al reported improved survival by combining BNCT with a photon boost.[28] Based on these experiences, we recently completed a multicenter phase II Japanese clinical trial to evaluate BNCT in combination with TMZ and an XRT boost (Osaka-TRIBRAIN 0902, NCT00974987) for newly diagnosed GBM. We are currently opening the results of this clinical trial and hope to report on our findings in the near future.

BNCT for High-grade Meningiomas

The management of high-grade meningioma, especially malignant meningioma, is very difficult. In a large series of patients with this disease, the 5-year recurrence rate of high-grade meningioma was reported as 78%–84%.[29] The MST of patients has been reported as 6.89 years; late mortality due to recurrence after the initial surgery has been reported at 69%.[30] Although some treatments for recurrent high-grade meningioma have been reported, including chemotherapeutic regimens, no standard treatment has yet been established.[31]

Since 2005, we have applied BNCT for cases of high-grade meningioma recurrent after or refractory to any intensive treatment modality.[32,33] To date, we have treated 32 consecutive cases of high-grade meningiomas with BNCT. Twenty cases were followed up for more than 4 years, and the MSTs after BNCT and diagnosis were 14.1 (95% CI, 8.6–40.4) and 45.7 months (95% CI, 32.4–70.7), respectively.[11] A representative case is shown in **Figure 5**. Like the case shown in this figure, all cases responded

well to BNCT and showed good shrinkage of the mass after BNCT.

However, many cases were lost even after BNCT. Out of 20 cases of high-grade meningioma treated by BNCT, we lost 13 cases: 2 from local tumor progression with radiation necrosis, 1 from simple local tumor progression, 4 from systemic metastasis, 1 from intracranial distant recurrence outside the irradiation field, 3 from CSF dissemination, and 2 from other diseases.[11] These problems must be overcome.

From Reactor to Accelerator

Before 2012, all BNCT clinical irradiations were carried out at nuclear reactor neutron sources. As described above, BNCT is very effective for malignant gliomas and high-grade meningiomas. The biggest restriction of BNCT for universal and standard use as radiation therapy not only for malignant brain tumors but also for malignancies at other organs is the use of nuclear reactors. More than 8 such facilities have been constructed for clinical use in the USA, Argentina, Europe, and Asia. However, nuclear reactors require a vast amount of land and very large structures. In addition, they run the risk of contamination by radioactivity. In the disastrous 2011 Tohoku earthquake and tsunami in northern Japan, one of the 2 nuclear reactors that could be used for BNCT was lost. In addition, as this manuscript is being prepared, another Kyoto University Research Reactor has been ordered closed since the beginning of June 2014 for a thorough check and maintenance.

Another potential source of neutrons are the accelerator-based neutron generators currently being developed in hospital settings. Accelerator sources are expected to be much easier to license in a hospital setting than nuclear reactors. Proponents of accelerator-based neutron sources also believe that they could be more compact and less expensive than comparable reactor sources.

For practical use, a small accelerator-based neutron source has been produced in Japan by Sumitomo Heavy Industries, in which a cyclotron is used to generate the protons (cyclotron-based epithermal neutron source).[34,35] **Figure 6** presents a photograph and a schematic drawing of this cyclotron-based epithermal neutron source system. We have finished a phase I clinical trial for patients with recurrent malignant gliomas that was the first in the world to use a cyclotron-based epithermal neutron source system. This was followed by a trial in patients with recurrent head and neck cancers. We are now starting a phase II clinical trial for recurrent GBM using a cyclotron-based epithermal neutron source. Hopefully all nuclear reactors currently in use for clinical BNCT will be replaced with accelerator-based neutron sources in the next decade.

Differences Between BNCT and Other Particle Radiation Modalities

Finally, we should consider the differences between BNCT and other particles such as protons and carbon. As we have discussed, BNCT is cell-selective, high LET particle radiation. Thus, it is especially efficacious for tumors with an infiltrative nature, irrespective of X-ray sensitivity. However, the real absorbed dose is still uncertain because the compound biological effectiveness is only a putative value. In addition, the neutron penetration is limited in depth. Finally, BPA uptake depends on the biological activity of the target tumor. Therefore, we do not recommend that BNCT be used for skull base chordomas and so on. In contrast, protons and carbon have the merit of achieving a very precise irradiation field by referencing the Bragg peak. However, they are not appropriate for tumors with an infiltrative nature. In the future, we should apply these highly sophisticated radiation modalities in a case-specific manner depending on the target tumor characteristics and location.

Conflicts of Interest Disclosure

There is no conflict of interest to disclose for any of the authors.

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Viral Induction of Gliomas

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Infectious diseases are frequently linked with human cancer

Cancer is diagnosed in ~13 million people annually worldwide. Infections with bacteria, fungi, viruses, and parasites account for ~16% of all new cases of cancer every year. The microbes most commonly associated with human neoplasm are *Helicobacter pylori*, human papilloma viruses, hepatitis B and C viruses, Epstein-Barr virus, and Kaposi sarcoma herpes virus, with a relative contribution to all cases of 32%, 30%, 30%, 5%, and 2%, respectively. The importance of infectious diseases for the occurrence of human cancer varies considerably among geographic regions and socioeconomic groups. The institution of large screening programs for cervical cancer in Western countries, for example, greatly reduced the rates of this papilloma virus–associated cancer long before the development of effective vaccines for the prevention of the infection. Similarly, treatment and particularly prevention of hepatitis B virus infection with use of effective vaccines and stringent hygiene measures reduced dramatically the rates of liver cancer in Western countries. In contrast, these infectious diseases are still very common causes for human cancer in developing countries. Current knowledge on the association between microbes and cancer very likely reflects only the tip of an iceberg. Multiple new microbes, and particularly viruses, are discovered every year with the progress in detection methods, and some of these novel microbes have been associated with human cancer such as Merkel cell polyomavirus (MCPyV), which was named after an aggressive skin cancer.

Gliomas are common brain tumors

Primary brain tumors are cancers that originate in the brain and develop from glial cells. Glial cells provide the structural backbone of the brain and support the function of the neurons (nerve cells), which are responsible for thought, sensation, muscle control, and coordination. The term “glioma” sums this large and diverse group of common brain tumors, which in their microscopic appearance are similar to healthy brain cells (ie, astrocytes, oligodendrocytes, and ependymal cells). For each of these different types of gliomas, there are cancer types that span a broad spectrum of biological aggressiveness. Accordingly, these brain tumors also differ significantly in their biological properties, prognoses, and treatment approaches. Patients diagnosed with malignant gliomas have to face an aggressive cancer accompanied by increasing neurological deficits, which also impact their quality of life, including particularly epileptic seizures, the side effects of high-dose corticosteroids, and thromboembolic complications.

The role of viruses in the evolution of gliomas

The origin of these brain tumors, however, is not clear. The role of infectious pathogens in the evolution of gliomas has been discussed for decades, particularly in view of the development of effective antimicrobial treatments and vaccines against a diversity of bacteria and viruses. Identification of a causal link between microbe and brain tumor would potentially open whole new avenues to the prevention and treatment of this disease. One of the most commonly implicated microbes is human cytomegalovirus (CMV), which is a herpes virus that chronically infects 40%–100% of the general population. Following primary infection, CMV remains latently and is dormant for the lifetime of its host in a diversity of human cells. The symptoms may be significant during primary infection (subsumed as infectious mononucleosis) but resolve permanently thereafter. Infected individuals may only experience symptoms in the course of reactivations in the presence of significant immunocompromise, such as in solid-organ transplantation.

Association of cytomegalovirus with gliomas

CMV was linked to gliomas for the first time in 2002 in a study by Cobbs and colleagues, who demonstrated the presence of CMV in tumor cells but not adjacent tissues. Detection of viral particles was possible in several different types of gliomas and with different virus detection methods, but not in the brains of patients without neurological disease. Several follow-up studies further confirmed this finding by testing glioma samples of patients from other geographic regions and glioma cells after isolation from other tissue by culture and with the use of other detection methods. Recent studies could even show that the CMV particles detected were from different strains of viruses, which made it further unlikely that a contamination of samples with CMV during collection or in the laboratory may have caused these positive results. The presence of CMV in tissue samples could be correlated with a poorer outcome of the glioma. Finally, treatment of glioma cells and animals with gliomas with the antiviral drug cidofovir resulted in an improved survival. Hence, antiviral treatment of patients with gliomas

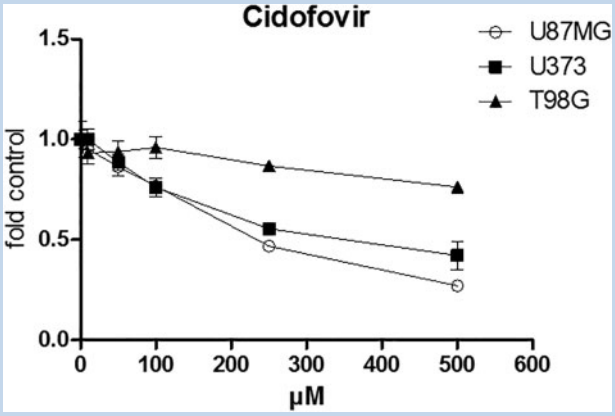

Figure 1 Effect of cidofovir on glioblastoma cells in vitro. Dose-response curves after 72 hours of drug exposure with the indicated concentrations of cidofovir were evaluated by MTT assay. Assay was performed in triplicate in the indicated glioblastoma cell lines (Lötsch D., Steininger C., Berger W. unpublished data). MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

appeared to be a whole new and highly effective therapeutic option.

Nevertheless, several other studies raised questions with regard to these positive findings. Our group could reproduce the antitumor effect of cidofovir on glioma cells but only at concentrations of the antiviral drug that may not be achieved in humans because of toxic side effects (**Figure 1**). Re-analysis of a successful clinical study on the effectiveness of another antiviral drug (valganciclovir) in the treatment of gliomas suggested a significant statistical miscalculation of results (immortality bias). Screening of glioma tissues for the presence of CMV with the same methods yielded uniformly negative results in the hands of other research groups. Testing of glioma samples with use of modern, metagenomic methods that allow the detection of all viral nucleic acids also yielded negative results.

In summary, the jury on a causal link of CMV infection with the evolution of gliomas is still out. Multiple lines of evidence suggest involvement of CMV infection, but study results could not be confirmed by many other research groups. Accordingly, antiviral treatment of patients with gliomas appears to be premature given the incomplete evidence for a significant benefit and the considerable potential side effect associated with these compounds.

Bevacizumab in Glioblastoma

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Introduction

The use of bevacizumab in glioblastoma (GBM) is a narrative filled with promise and disappointment, which reveals the remarkable challenges confronting advancement in this disease. Despite decades of research, GBM remains a baleful diagnosis with a dismal prognosis. After maximal surgical resection, treatment with radiotherapy plus concomitant and adjuvant temozolomide chemotherapy is the standard of care; median overall survival (OS) for those treated with this standard therapy is no more than 20 months.[1] Optune, or tumor treating field therapy, a novel antimitotic device that works through the generation of alternating electric fields, recently gained approval based on a large randomized trial that concluded it was a safe and effective adjunct therapy, conferring an added survival benefit of 4.8 months over current standard of care.[1,2]

Regardless of treatment, GBM invariably recurs, causing progressive neurologic decline and death for most within 1–2 years, with less than 10% of patients surviving beyond 3 years.[3] Patients with disease recurrence face a meager landscape of known effective therapeutic options. For some patients with surgically resectable recurrent tumor, reoperation prior to systemic treatment is undertaken with the logic that ensuing treatments may be more effective with reduction in bulky disease. However, in many patients, reoperation is precluded by risk of injury to eloquent areas of the brain or rendered impractical when only a small portion of the tumor can be removed, limiting any potential benefit. Systemic therapy with other alkylating agents, such as nitrosoureas, has only modest benefit when used at recurrence. Also, in the recurrent setting, tumor treating field therapy may be as efficacious as the other commonly used therapies.[4]

Bevacizumab, a humanized monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A) and has demonstrated clinical antitumor activity in other human tumors, is also approved for use in recurrent GBM[6]; bevacizumab's use is based on the fact that VEGF-A is a key regulator of tumor-associated angiogenesis in GBM, that GBMs are highly vascularized tumors, and that angiogenesis is a histological hallmark of its diagnosis. In fact, the sprouting of serpiginous and abnormal new vessels lays out an important mechanism for tumor proliferation and maintenance, as well as potential spread along perivascular spaces.[5] This article briefly reviews the history of bevacizumab use in glioblastoma and potential future directions.

Bevacizumab for recurrent glioblastoma

In 2008, 2 phase II open-label trials were published examining the use of bevacizumab in recurrent glioblastoma both alone and in combination with irinotecan chemotherapy. The National Cancer Institute study by Kreisl et al[6] evaluated single-agent bevacizumab at a dose of 10 mg/kg every 2 weeks in recurrent GBM. The trial met its primary endpoint with a 6-month progression-free survival (PFS) of 29%, which compared favorably with historical controls. As a secondary endpoint, the trial showed that 35% or 71% of patients had an objective radiographic response (by modified Macdonald or World Health Organization [WHO] radiographic criteria, respectively). Approximately half of patients had reduction of cerebral edema with improvement of neurological symptoms, and more than half were able to significantly reduce their corticosteroid dose as a result of therapy. The authors thus concluded that single-agent bevacizumab has significant clinical activity in recurrent glioblastoma. Similarly, in the BRAIN study by Friedman et al,[7] single-agent use of bevacizumab at the same dose and schedule was associated with a favorable 6-month PFS of 42.6% compared with historical controls, with an objective radiographic response rate of 28.2% (by WHO radiographic criteria), and a trend in decreasing steroid doses, though this was not rigorously studied. As a result of the promise of these phase II studies, neither of which showed a survival benefit, the FDA granted accelerated approval to bevacizumab for the treatment of recurrent glioblastoma, anticipating confirmation of efficacy in phase III randomized controlled trials.

However, clinical efficacy of bevacizumab in these initial trials was largely based on dramatic radiographic reduction in contrast enhancement and the ability of bevacizumab to keep gadolinium extravasation low as a measure of prolonged PFS. Although the BRAIN study did take into account new areas of non-enhancing T2/fluid attenuated inversion recovery (FLAIR) lesions to indicate progressive disease, until the advent of the Response Assessment for Neuro-Oncology (RANO) criteria in 2010, prior radiographic assessment in clinical trials did not uniformly evaluate T2/FLAIR quantitatively and qualitatively, or stipulate durability of responses to be sustained for greater than 4 weeks. Given the vascular mechanism of VEGF inhibition, the dramatic, notably rapid reduction of contrast enhancement in a large proportion of patients raised questions of a likely "pseudo-response," where transient reduction of gadolinium extravasation and alteration of vessel permeability mediated by VEGF inhibition could produce a false impression of tumor reduction.

Given the accelerated approval by the FDA based on largely uncontrolled trials, many later trials also failed to incorporate a control arm to compare bevacizumab treatment versus therapy without bevacizumab. In 2014, the BELOB trial[8] was published and cast doubt upon the biological activity of bevacizumab in gliomas. This phase II open-label randomized study was initially designed with 2 treatment arms: bevacizumab alone and bevacizumab plus lomustine. However, a third arm for control with lomustine alone was added after the European Regulatory Agency rejected the use of bevacizumab for recurrent glioblastoma. To overcome confounding effects of potential pseudoresponse, the authors avoided

focusing on PFS, which was generally seen as altered by the gadolinium-restricting effects of anti-angiogenic agents acting to modify vascular permeability. Instead, they measured OS at a time point of 9 months as the study's primary end point. Furthermore, this was one of the first trials to employ the new RANO criteria to assess progression, which among other stipulations requires that any response (whether partial or complete) be sustained for at least 4 weeks, and counts any significant increase in non-enhancing T2/FLAIR lesions that cannot be attributed to any cause other than tumor as indicative of progression. These modifications became crucial in the era of bevacizumab, where researchers were concerned about the steroid-like effects of pseudoresponse being misrepresented as stable or treatment-responsive disease while tumors progressed undetected.

In BELOB, the groups were noncomparative, and thus not powered to assess differences in survival between the groups. Rather, each group's performance was measured against predetermined criteria to determine whether that therapy or combination was worthy of further study in a phase III trial. Of the treatment groups, only the combination treatment with bevacizumab and lomustine met the criteria with 63% (combining both treatment doses of lomustine) OS at 9 months to warrant further study, whereas single-agent bevacizumab was decidedly inactive clinically with an OS of only 38% at 9 months. Single-agent lomustine was not much better, with 43% OS at 9 months, though possibly affected by a very limited number of doses received. The same story was seen with regard to median OS, as well as OS at 12 months. Interestingly, bevacizumab alone had a moderate objective response rate (ORR) of 38%, whereas lomustine had a low ORR of 5%, though single-agent treatment with either resulted in very similar PFS and OS. This speaks to the ability of RANO to filter out pseudoresponse rather than a meaningful difference in PFS.

After the results of BELOB showed that bevacizumab, used alone, likely has little if any clinical activity against recurrent glioblastoma, the window remained open for the possibility of combining bevacizumab with other agents, such as traditional cytotoxic agents. Despite the hope for possible efficacy of combined lomustine and bevacizumab in BELOB, the follow-up randomized phase III trial by the European Organisation for Research and Treatment of Cancer, EORTC 26101,[9] showed that the addition of bevacizumab produced no additional OS benefit to lomustine alone. Thus, the promise of bevacizumab in recurrent glioblastoma, which gained accelerated approval, has been unfulfilled.

Bevacizumab for newly diagnosed glioblastoma

The question of whether bevacizumab has efficacy in newly diagnosed patients with glioblastoma was answered by 2 large phase III, double-blind, randomized studies with a combined total of 1500 patients[10,11] who were randomized to maintenance therapy with either bevacizumab or placebo in addition to standard of care radiation plus temozolomide. In both the AVAglio and Radiation Therapy Oncology Group (RTOG)-0825 studies, bevacizumab did not confer an OS benefit compared with the standard of care, although crossover in the trials was not negligible. PFS and radiographic response rate were increased with bevacizumab treatment, although the PFS advantage only reached prespecified statistical significance in the AVAglio study. Furthermore, there was divergence between the 2 studies of a possible impact on quality of life (QoL), with AVAglio suggesting a prolonged stable health-related QoL, whereas RTOG-0825 observed some reduction in particular domains of overall QoL while other domains remained stable. Although post-hoc analysis of AVAglio did identify a potential survival benefit in the proneural *IDH1* wild-type subgroup of GBM, the lack of standardized testing for genetic subtypes in the study and the ad hoc nature of this finding leave the community less than convinced. The clear conclusion was that bevacizumab does not improve OS in patients with glioblastomas, whether new or recurrent. Although use of the drug may hold some benefit for PFS in the "right" patients, consistent with a steroid-like improvement in vasogenic edema, it is unclear whether this translates to a significant clinical benefit with a reliable preservation of QoL.

What happens at tumor progression after bevacizumab treatment?

The dramatic and relatively immediate reduction in radiographic enhancement typically seen in GBM patients treated with bevacizumab has long suggested that the impact of the drug on tumor was more related to changes in vessel permeability rather than cytoreduction. However, the actual reasons why bevacizumab and anti-angiogenic treatments have failed to improve OS in glioblastomas remains an area of investigation. Correlative studies[12] among clinical, radiographic, and histopathological cases have shown that tumor progression after prolonged bevacizumab use alters tumor biology and produces a distinctive phenotype that is invasive in the absence of angiogenesis. In such studies, researchers identified cases of clinical progression with increase in mass-like T2/FLAIR hyperintensity in high-grade glioma tumors undergoing bevacizumab treatment without concomitant increase in enhancement, and found recurrent tumor on pathology. However, despite highly cellular histology, microvascular proliferation had reduced with bevacizumab treatment compared with profuse vascular

proliferation noted upon prior diagnostic pathology. In GBM, areas of necrosis, caused by rampant tumor proliferation and consequent hypoxia, are intimately linked to and characteristically appear in proximity to vascular proliferation as tumor neo-angiogenesis brings forth aberrant vessels to satisfy the great need for oxygen and nutrients to sustain an ambitious rate of growth. Yet after bevacizumab-induced "normalization" of the vasculature, studies note new areas of necrosis in the recurrent or progressive tumor devoid of any vascular proliferation. In xenograft models similarly treated with bevacizumab, this atypical infiltrative non-enhancing FLAIR pattern of progression appeared with invasion along the perivascular spaces of normally existing vessels associated with elevated insulin-like growth factor binding protein 2 and matrix metalloproteinase 2, potential mediators of tumor evasion of VEGF inhibition,[12] a pattern not similarly appreciated in the controls.

Prolonged anti-angiogenic therapy to infiltrative tumor progression may create selective pressures from hypoxia and nutrient deprivation that may induce the mechanisms of escape from anti-VEGF therapy: (1) hypoxia generated from prolonged inhibition of angiogenesis in this recalcitrant tumor could enable an alternate pathway of angiogenesis separate from the VEGF pathway, including activation of fibroblast growth factor (FGF), platelet derived growth factor (PDGF), and other endothelial growth factors to partially reconstitute needed vasculature to sustain tumor growth; (2) the added metabolic stress on the tumor induces alternate nonvascular mechanisms of proliferation and spread via neuropil invasion, as suggested by the pathological findings in the above study; (3) the tumor invades along the perivascular spaces of otherwise normal microvessels, which it adapts as a scaffold for diffuse invasion. This latter phenomenon, dubbed "autovascularization," has been widely discussed in recent years and is now well supported in preclinical models as well as clinical samples from human GBM patients. In work by Baker et al,[13] the co-immunolabeling of antibodies to vimentin and von Willebrand factor in human GBM biopsied tissues proves the existence of neoplastic cells in the perivascular space and "substantiates perivascular tissue invasion as a clinically relevant mechanism of human malignant brain tumor growth." The authors argue that the perivascular space of normal microvessels can be an ideal scaffold for invasion by virtue of the fact that it is the place of entry for oxygen and nutrients, and the basement membrane is rich in highly glycosylated matrix proteins that can support cell adhesion and migration as well as stimulate pro-survival pathways—and for these reasons the perivascular space is also often co-opted in the invasive progression of other peripheral cancers.

The search for combinatorial therapies

Trials of numerous other anti-angiogenic therapies in GBM have been thoroughly reviewed in the literature[14] and found to be unsuccessful, including trials of aflibercept and cedirinib, as well as other tyrosine kinase inhibitors such as sunitinib and pazopanib, among others. Strategies that involve angiogenic pathways outside of VEGF, including thalidomide (which inhibits FGF as well as VEGF) and celingitide (an inhibitor of integrins implicated in activated endothelial cells of gliomas), also have resulted in disappointment. Due to these failures and that of single-agent bevacizumab to improve OS in GBM, there has been interest in combination strategies with bevacizumab. Despite the disappointing clinical findings, many still hold to the fact that vascular proliferation remains the rate limiting step to cancer growth and invasion. Thus, one of the most promising combinatorial approaches involves pairing bevacizumab with a pathway-independent anti-angiogenic attack on tumor co-opted microvasculature. VB-111 is a novel viral gene therapy that specifically targets endothelial cells within the tumor angiogenic microenvironment for apoptotic cell death. It does so via a nonreplicable adenovirus vector to infectively transfer an episomal element in vascular cells that is preferentially expressed in the right environment. Only in the angiogenic and hypoxic proliferative climate of tumor-related microvasculature is the signal activated by recognition of a modified murine promoter of precursor protein of endothelin-1, which then expresses a human pro-apoptotic transgene that is a chimera of Fas and tumor necrosis factor–receptor 1 (TNF-R1) into the cell membrane. Apoptosis is induced by activation of Fas only in the setting of TNF-R1 binding by TNF-alpha (which is upregulated in tumor and downregulated in normal tissues), leading to selective apoptosis of angiogenic blood vessels.[15] Preclinical studies have found that VB-111 successfully reduced tumor-related capillary density and extended survival in several GBM xenograft lines.[16] A multicenter phase II trial of VB-111 added to bevacizumab in recurrent GBM found a strong signal of preliminary efficacy, whereby the median OS was nearly doubled (to 15 mo) compared with historical controls receiving bevacizumab alone (8 mo in the BELOB bevacizumab arm).[17] A subsequent phase III randomized controlled trial is hoping to confirm efficacy of combined VB-111 with bevacizumab over bevacizumab alone (NCT 02511405).

Outside anti-angiogenic therapies, other therapies have been investigated in combination with bevacizumab in GBM. Combination treatment with cytotoxic chemotherapies such as irinotecan, lomustine, and temozolomide have been rigorously explored in trials,[7,9–11] with the rationale being that they represent an important but different mechanism of action and because vascular normalization by bevacizumab may allow for improved delivery of these agents to areas of tumor. Thus far, there have been no efficacious regimens identified. Other combination therapies are continuing to be explored. Vorinostat is a small-molecule histone deacetylase inhibitor that crosses the blood–brain barrier and has preclinical antitumor activity, but also promotes anti-angiogenic

effects,[18] including downregulation of VEGF, FGF, and hypoxia inducible factor 1a, and therefore may have utility in combination with bevacizumab. [19]

The Src family of kinases (SFKs) are implicated in the generation of increased tumor invasiveness after bevacizumab treatment and activate epidermal growth factor receptor, PDGF receptor, and integrins, key pathways of glioma migration and proliferation. Future clinical studies are supported by preclinical work with xenograft GBM models which demonstrate that SFKs are activated after bevacizumab treatment; dasatinib, a broad spectrum potent inhibitor of all SFKs effectively blocked the increased tumor invasiveness associated with bevacizumab resistance[20] and may be used in trials. Ongoing clinical trials are also poised to test the combination of bevacizumab with tumor-treating field therapy, one of the few other FDA-approved therapies for patients with GBM in the recurrent[4] as well as the newly diagnosed[1,2] setting[21, 22]. It utilizes a novel mechanism of alternating electric fields to disrupt tumor microtubule polymerization during mitosis and cause aneuploidy and apoptosis. It remains to be seen whether the addition of bevacizumab could enhance efficacy of this novel therapy (NCT01894061).

We now know that angiogenesis can facilitate tumor immune evasion, and anti-VEGF therapies have also been shown in preclinical studies to increase tumor permeability to activated T cells, rendering the tumor more vulnerable to immune attack.[14] Rindopepimut, a targeted vaccine for the GBM epitope epidermal growth factor receptor variant III conjugated with keyhole limpet hemocyanin, has shown promise in a phase II double-blind, randomized controlled trial in combination with bevacizumab. In this ReACT study[23] of 73 bevacizumab-naïve patients with recurrent GBM, both PFS and OS were favorably prolonged in the dual therapy arm versus bevacizumab plus no-vaccine without significant toxicity. On the last update, 25% of patients treated with rindopepimut plus bevacizumab were still alive at 2 years compared with none in the control group. Unfortunately, in a large phase III trial[24] involving patients newly diagnosed with GBM, the use of single-agent rindopepimut added to standard of care maintenance temozolomide offered no survival benefit compared with vaccine-free controls. In this case, the control group had matched median OS of ~20 months, which was surprisingly better than prior matched historical controls. Notably, compared with the earlier ReACT, bevacizumab combination therapy was not evaluated in this study and the treatment group was newly diagnosed rather than recurrent GBM. Thus, there has been no subsequent work to confirm or refute the preliminary efficacy of combining rindopepimut with bevacizumab in recurrent GBM as previously seen with further studies. Given the disappointment of the phase III trial, enthusiasm for future trials using rindopepimut has waned. However, other vaccine trials are under way to explore the ability of bevacizumab to enhance immunogenicity in GBM, such as the ongoing phase II study of the heat shock protein vaccine HSPP-96 (NCT01814813).

Lastly, there has been interest in injection of bevacizumab intra-arterially after blood–brain barrier disruption to concentrate the dose to the tumor compared with intravenous infusion, which has been studied in small phase II studies,[25,26] although larger phase II or phase III confirmatory studies are needed to clarify efficacy (NCT02285959).

Toward imaging prediction of treatment response or failure

To date, there have been no established biomarkers to predict response to bevacizumab. However, bevacizumab investigations in GBM have not only stimulated development of standardized imaging criteria to better evaluate treatment response, but also prompted investigations of novel imaging modalities in hopes of finding a predictive model for true prolonged response (efficacy) or early detection of treatment failure in subsets of patients. For example, an exploratory analysis using PET imaging with a MET tracer (^{11}C-methyl-L-methionine), an amino acid metabolite that rapidly accumulates in tumor cells despite an intact blood–brain barrier (unlike the false harbinger of reduced enhancement with vascular normalization by bevacizumab), has shown a greater potential to rule out false positives and identify true responders at 8 weeks from the starting bevacizumab therapy when paired with traditional MRI than MRI alone.[27] Others have tried to leverage other innate properties of MRI to detect recurrence sooner than traditional methods. One study used quantitative maps of increased T1 prolongation times to detect slight increases in permeability of water (which is a smaller and more penetrable molecule than standard contrast agents) and hence detect subtle blood–brain barrier disruption associated with tumor recurrence before it becomes visible on conventional imaging.[28] Similarly promising investigations include MRI-PET imaging[29] and radiomic profiling[30] of numerous quantifiable imaging features, in an attempt to isolate an imaging biomarker indicative of bevacizumab efficacy.

The promise reduced but hope remains

The failure of bevacizumab to improve OS in newly diagnosed or recurrent GBM is a disappointment for patients and physicians who battle this implacable disease; to some, the benefit in PFS and QoL remains controversial. However, a core tenet of GBM biology is that a rate limiting step of tumor growth and spread must involve

angiogenesis, and the field of neuro-oncology continues the search for an effective anti-angiogenic strategy to halt the relentless growth and rampant recurrence of disease. At this juncture, the promise of bevacizumab, although substantially reduced, is not extinguished; follow-up examination of imaging prediction of responders and combinatorial therapies, including a burgeoning pipeline in conjunction with vaccines, still offers reason for hope.

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It is Not Just About Biology and Drugs . . .

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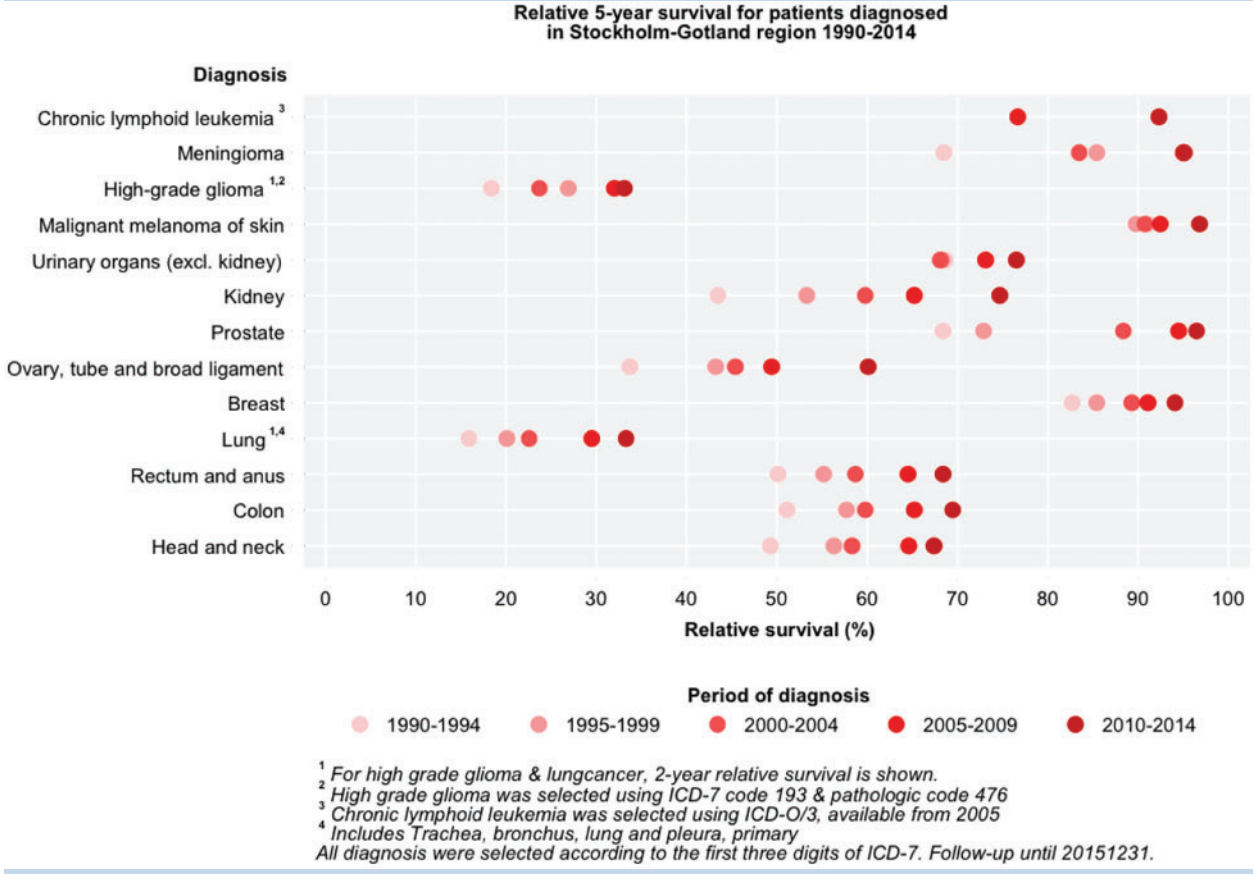
The survival in cancer has been gradually improving during the last decades. The proportion of patients surviving beyond 5 years has increased for all cancer diseases, including even those tumors that still have a dismal prognosis, exemplified in the figure below by the situation in Stockholm county, Sweden.

Furthermore, the quality of life aspects, even in the context of short life, such as when treating high-grade glioma, have attracted an increased awareness. The overall pattern is therefore positive, but at the same time there are unacceptable variations among different tumor types, countries, regions, and not least various socioeconomic groups.

Place of Residence and Socioeconomics

Associations among place of residence, level of education, socioeconomic factors, and cancer incidence and mortality are well documented and supported by scientific evidence. Population-based data from, for example, the Swedish Board of Health and health boards in the USA and UK show differences in attending cancer screening, cancer incidence, and survival. There is evidence of inequalities at all stages of the patient pathway, from information provision and treatment through to palliative care. It is estimated that at least 10% of all deaths from cancer can be attributed to inequalities. It is obvious that some groups who do not have access to information, optimal resources, and services required do not take full advantage of these improvements in health. Even in the management of brain tumors, variations related to inequality have been reported. Some of these studies demonstrate a strong association between higher socioeconomic status and higher risk of glioma. On the other hand, in spite of improvement in the overall survival of patients with high-grade glioma, this improvement has been reported to be confined to younger patients and has been most prominent among patients living in high-income districts. Similar results are seen in Sweden. However, it has to be emphasized that the knowledge in these aspects about brain tumors, especially for outcome, are extremely limited, and therefore the ultimate



[1] *For high grade glioma & lungcancer, 2-year relative survival is shown.*
[2] *High grade glioma was selected using ICD-7 code 193 & pathologic code 476*
[3] *Chronic lymphoid leukemia was selected using ICD-O/3, available from 2005*
[4] *Includes Trachea, bronchus, lung and pleura, primary*
All diagnosis were selected according to the first three digits of ICD-7. Follow-up until 20151231.

challenge with inequalities must also be more of a focus in neuro-oncology.

Lifestyle factors have been found to have an impact upon cancer incidence and mortality and show evidence of differential levels between socioeconomic populations. The Swedish authorities and Cancer Research UK are among those who estimate that around one third to half of all cancers could be prevented by changes in lifestyle. Differential levels of exposure or engagement in risky health behaviors are the most significant cause of inequalities in the likelihood of developing cancer. Associations between lifestyle factors and the incidence and outcome in the treatment of brain tumors, including glioma, are still controversial.

Tobacco causes ~9 out of 10 cases of lung cancer as well as many other cancers. Smoking is one of the main causes of variations in illness and death between the poor and the wealthy. Inequalities in smoking rates therefore impact cancer rates in different countries and patient population communities. No conclusive studies have shown a correlation between brain tumors and smoking.

Almost a third of all cancer deaths have been linked to **diet**, including the risk of cancers in the gastrointestinal tract, but an association has also been shown for other cancer types. The variations in food consumption between more and less affluent groups are linked to the availability and cost of food and knowledge of healthy eating. The result is that higher-income families tend to consume healthier versions of most foods compared with lower-income families. Moreover, people with lower incomes and lower education levels are less likely to meet government guidelines for healthy eating. The link of diet to brain tumors needs to be studied further.

A lack of **physical activity** increases the risk of a number of cancers, and inactive lifestyle is estimated to account for around 5% of all cancer deaths. Low levels of physical activity combined with a poor diet can also lead to **obesity,** which is thought to increase cancer risk. Adult obesity is strongly related to social class. Men involved in manual employment tend to be more active than those in nonmanual jobs, mainly due to the physical nature of their occupations. At the same time, participation in physical activity outside of work is strongly related to household income, with those in higher-income households more likely to participate. The beneficial effects of physical activity have also been proposed for patients suffering from brain tumors. Exercise behavior was shown to be a strong independent predictor of survival that provides incremental prognostic value to performance status as well as traditional markers of prognosis in malignant recurrent glioma. It has also been shown that there is a decreased risk of brain tumor mortality from running and walking. The recommendations of physical activity above are still rather generic, and additional research is of importance to develop optimal tools for promoting physical rehabilitation in patients suffering from brain tumors. Nevertheless, there is a strong belief that the importance of exercise for cancer patients in general must also be valid for brain tumor survivors.

A lot of data support that patients with the same cancer, at the same stage of development, on many occasions do not receive the same type of **cancer treatment.** This seems also true for brain tumors. However, inequalities in cancer treatment are difficult to identify given the options available to people according to the type of cancer diagnosed in them, the stage of disease at diagnosis, the way the disease develops, and not least the increased presence of comorbidities among those living in deprived areas and the extent to which other health and lifestyle factors (eg, poor diet, tobacco use) render people less physically able to face or survive cancer treatment. This could at least partially explain why there are mixed findings regarding correlation between socioeconomic or sociodemographic factors and cancer treatment. Furthermore, access to services is often worse for those living in rural areas, due to a lack of infrastructure, which can lead to poorer outcomes for these communities. These factors could pose particular problems for older or disabled individuals, who as a result have been found to be diagnosed at a later cancer stage.

Perceptions of Cancer Risk and Treatment Possibilities

Wealthier populations seem more likely to have knowledge of cancer risk factors (smoking, sunlight, etc) compared with those at the other end of the socioeconomic scale. Early diagnosis of cancer is a critical factor which determines the types of treatment available to an individual and his or her chances of survival. Awareness of cancer symptoms is a crucial factor in early diagnosis, as people who recognize that their symptoms may be serious are more likely to visit a health care provider. For all the main risk factors, the wealthier an individual, the more likely he or she is to be aware of their link to cancer, compared with people from the most deprived groups and communities. People from disadvantaged groups can face difficulties in communicating with health professionals. Among disadvantaged groups there is evidence of misunderstanding and more or less fear about cancer. This could result in people being reluctant to seek health care. People from deprived groups are the most likely to delay seeking medical advice and are therefore more likely to present at health services (and be diagnosed) when their cancer is at a more advanced stage. For those with mental health problems, the assumptions made by health professionals may make it more difficult to get possible cancer symptoms recognized. At the same time, communication difficulties make incorrect diagnosis or unmet needs for this group more likely.

The relationship between inequalities and cancer is complex and multifaceted. Certain types of cancer—such as lung, mouth, and esophagus—are more likely to be diagnosed in the most deprived groups. For other types of cancer—such as breast and prostate—death rates are higher among the most deprived despite the fact that incidence rates are lower. There is a substantial amount of evidence relating to the impact that a range of socioeconomic and sociodemographic factors have upon uptake of cancer services (from screening through to palliative care), which ultimately lead to decreased survival.

A Local Initiative

In view of the above, the Regional Cancer Center Stockholm Gotland has initiated a project in a multicultural and multilingual county of Stockholm. The goal is to increase knowledge about cancer and prevention in this community, focusing on lifestyle and self-care. A main part of this project is to arrange and conduct public information activities to raise awareness about cancer and cancer prevention. Many of these activities are arranged in collaboration with multicultural organizations that are active in the community. Our experience so far is that these information activities bring us closer to populations we usually do not reach with other health campaigns. Challenges encountered in the project include issues related to language barriers, health literacy, and different cultural and/or religious attitudes about cancer. We have addressed the issue of language barriers by having local interpreters at our meetings and translating the printed information materials into 8 different languages. Besides an excellent collaboration between local and regional stakeholders, the active participation of non–health care professionals and patient representatives at all levels has been a driving factor for the success of the project. The peer advisors are in a unique position to reach populations who may be unfamiliar with the Swedish health care system and may have a low level of health literacy. The fact that the project manager is a cancer survivor has also been important for the project's legitimacy.

It is Not Just About Biology

The knowledge and awareness of inequalities is in general low. Therefore, it is important also in neuro-oncology to consider whom we reach with our diagnostic and treatment efforts. Even the most promising cancer treatment advances are only as good as our ability to deliver them to patients.

Interview

Christine Marosi

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Driving provides us with individual mobility and a sensation of liberty, despite all the reservations one could have on environment, the lack of parking space, and traffic jams. For most patients with brain tumors, losing the authorization to drive a car is a major impact on their self-esteem and quality of life. We asked the members of our editorial board to answer a question that everyone involved in the care of brain tumor patients has been asked many times:

"Am I allowed to drive?"

The depth of the regulations greatly differs from country to country.

Editorial Board Member	Q1: Does the justice system of your country provide explicit laws regulating the authorization of driving a car after the diagnosis of a brain tumor, or is this topic included in laws regulating driving for patients with epileptic seizures?	Q2: Are patients with recurrent brain tumors and without seizures allowed to drive?	Q3: Do you think that patients drive after you have told them that they should not?
 Roberta Rudà, Neurologist, Torino, Italy	In Italy the laws regulating authorization of a driving license after a diagnosis of brain tumor are included in the laws regarding patients with epileptic seizures in general. In this regard the law differentiates between "first or unique unprovoked seizure" and "epilepsy," defined by "two or more seizures in a time interval of less than 5 years." In the first case, the patient is declared fit to drive after a time interval of 6 months seizure free. In case of epilepsy, the patient is authorized to drive after a period of one year without seizures. In either case, patients are monitored by a medical committee until they have at least 5 years without seizures in the absence of antiepileptic drugs.	In Italy there is no difference between newly diagnosed and recurrent brain tumors; patients with recurrent disease without seizures are allowed to drive in the absence of significant functional disabilities.	Yes: this could be true in particular for young, "fit" patients or when driving is important for keeping a job.

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 Andreas Hottinger, Neurologist, Switzerland	In Switzerland the situation of driving and seizure is currently hotly debated as a commission of the Swiss League against Epilepsy released new guidelines about "the authorization of driving following a seizure" in 2015. These guidelines call for a very strict limitation of a 6-month ban on driving for any person who suffered a first unprovoked seizure and 12 months in case of epilepsy (Commission de la circulation routière de la LscE, Directives actualisées de la Commission de la circulation routière de la Ligue Suisse contre l'Epilepsie (LScE) Epilepsie et capacité à conduire un véhicule, *Bull Med Sui*, 2006;87: 6, 219–221). These periods can be shortened in certain situations (including in case of focal seizures) but can also be extended, notably in case of the "presence of progressive lesions." Although not specifically mentioned, brain tumors must probably be included in the latter situation. Moreover, this panel recommends that patients at high risk (defined as $>$ 40% of risk of seizure in the coming year) should also be prohibited from driving, even in the absence of seizure.These guidelines have been discussed intensely and prompted several reactions from both epileptologists and neuro-oncologists as it is felt that they are much too restrictive compared with the global risks involved. A comparative analysis of accidents in the USA suggested that the risks are well below this limit of 40% (Winston GP, Jaiser SR. Western driving regulations for unprovoked first	No specific guidelines are provided for this situation in Switzerland. In my opinion it is important to evaluate the global situation of the patient, not only regarding risk of seizure but also the neuropsychological situation and potential limitations linked to visual field defects.	Yes, probably.

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	seizures and epilepsy. *Seizure*. 2012;21(5):371–376). Moreover, the risk of a recurrent seizure is maximal in the first 3 months (Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D. Medical Research Council MESS Study Group. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet*. 2005;365(9476): 2007–2013).		
 Sebastian Brandner, United Kingdom	You must tell the Driver and Vehicle Licensing Agency [DVLA] if you have a brain tumor. You must also speak to your doctor, who might tell you to surrender your license.You can be fined up to £1000 if you don't tell DVLA about a medical condition that affects your driving. You may be prosecuted if you're involved in an accident as a result. **Car or motorcycle license** Fill in form B1 and send it to DVLA. The address is on the form. **Bus, coach, or lorry license** Fill in form B1V and send it to DVLA. The address is on the form. • https://www.gov.uk/brain-tumour-and-driving • https://www.gov.uk/government/publications/b1-online-confidential-medical-information It appears that it is regulated specifically for brain tumors.	Patients whose licenses were suspended can reapply for the reinstatement of the license. https://www.gov.uk/reapply-driving-licence-medical-condition	I cannot comment on this, as I do not see patients. I am a neuropathologist.

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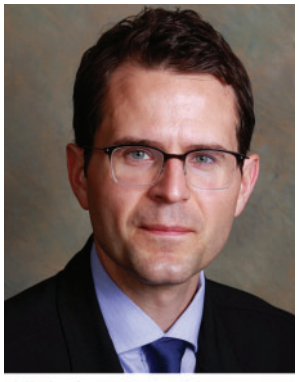
 Philip de Vos, Medical Oncologist, Utrecht, the Netherlands	In the Netherlands according to statutory provision 111, section 4, 130 –132 and 134 of the Road Traffic Bill of 1994, people with brain tumors (including brain metastasis) are not qualified automatically to drive a vehicle. In the case of people with brain tumors, the prognosis and any functional impairments are the criteria for fitness to drive. In contrast to people with cerebrovascular disease, the Fitness Criteria Regulation 2001 is based on the risk of recurrence and the risk of other disorders, as well as any functional impairments. The proposal is likely to result in more patients with tumors or cerebrovascular disease being assessed as fit to drive on group 1 driving licenses (cars and motorcycles); in the case of group 2 licenses (heavy goods vehicles) it is generally somewhat more "stringent" than the current rules. Driving license holders should be obliged to notify the authorities if they contract a disorder that could affect their fitness to drive. The maximum age up to which driving licenses remain valid without a further medical checkup should be reduced from 70 to 60.	Judged on their fitness to drive, patients with brain tumors are allowed to drive after the Central Bureau for Distribution of Driving Licenses has been sent a specialized report. In case of visual disturbance, extra conditions need to be met. If motor or cognitive disturbance is mentioned in this specialized report, a yearly driving test is necessary to evaluate the fitness to drive. If a stable clinical condition exists in the absence of functional disabilities, a driving license for the maximal duration of 5 years can be issued.	Yes, but in limited cases such as fit patients without clear disabilities and with a limited social network. Although at time of diagnosis we stress the importance not to drive without renewal of the driving license, we tend to believe there is some level of noncompliance due to the limiting effect in personal freedom and movement.
 Nicholas Butowski, USA	The laws in the US differ per state—though all center on seizure rather than tumor.	Yes	Yes

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 Chae-Yong Kim, South Korea	There is no specific law or regulations for patients with brain tumors. And more, for epilepsy patients, there is also no specific regulations. However, a few months ago, there was a traffic accident caused by a driver who was an epilepsy patient, so we are now discussing making a law regarding driving a car by a brain tumor patient or epilepsy patient.	Yes. If the patient has no deficit (motor weakness or decreased cognitive function) as well as no seizure, he or she is allowed to drive. Actually there is no rule or regulation for them.	Yes, I do. They may do that.
 François Ducray, France	The topic is included in laws regulating driving for patients with different medical conditions that can affect driving (sensorimotor deficit, visual deficit, visual field deficit, and epileptic seizures); no specific law for brain tumor patients. In my experience, in France, brain tumor patients who are seizure free for 6 months are in most cases allowed to drive again by the medical experts who decide this point.	Yes, if the neurological status is ok.	Probably yes, but I would not say that this is the majority.
 Marcos Maldaun, Brazil	The justice system allows the patient's physician to decide it. He should write a certificate of condition to drive to the drive department physician allowing or not driving and for how long. Regulations for brain tumor patients are the same for those with epileptic seizures.	Yes, if they have no other clinical condition that prohibits it.	Absolutely and unfortunately. They used to say that was a neighborhood of easy driving . . . and families complain but allow it.

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 Samy El Badawy, Egypt	Unfortunately our justice system does not specify brain tumors. It requires a general health certificate, but not a detailed one.	Again it is not specified in the law, but it always comes from the treating physician.	I think some will do.
 Xia Yunfei, Guangzhou, China	I don't know.	The patients with recurrent brain tumor and without seizures are allowed to drive.	Yes, I think that patients still drive.
 Gupta Tejpal, India	In India, there is no explicit law regulating the authorization of driving after being diagnosed with a brain tumor. However, all driving license applicants have to fill in a form which specifically asks, "Do you have epilepsy?" If a person answers in the affirmative, he or she is denied a driving license. Unfortunately, most people do not necessarily reveal their medical history of seizures and/or use of anticonvulsant medication when applying for such a license.	There are no laws regulating authorization of driving by patients with brain tumors (either newly diagnosed or recurrent). Given the existing laws in India (as clarified above), if the patient has not had a seizure, he would be allowed to drive.	Yes, but this varies from individual to individual. Many of our patients from the lower socioeconomic strata of society do not drive simply because they do not have access to a vehicle (car or bike). Among the middle-income and higher income strata, a proportion of patients do continue to drive even after they have been specifically asked to stop driving. However, a large majority do not drive after understanding the

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	The Indian Epilepsy Association has been campaigning for amendment to the Motor Vehicles Act such that epileptics can obtain driving licenses as in other countries (seizure free for some periods of time, generally 1–2 years).		implications (endangering their lives as well as negatively impacting public safety in case of a seizure episode while driving).
 Florence Lefranc, Neurosurgeon, Belgium	This topic is included in laws regulating driving after epilepsy. A treated patient without crises can drive. However, a patient with secondary epilepsy has to wait 1 year without any crisis before obtaining the green light to drive.	Yes	Yes

Determinants of long-term survival in glioblastoma—EORTC 1419

Study chair:

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Glioblastomas represent almost 50% of malignant brain tumors in adults and belong to the most lethal cancer types, due to their highly infiltrative nature, with approximately half of all affected patients dying within the first year of diagnosis despite a multimodal therapeutic approach including surgery, radiotherapy, and chemotherapy. However, a small percentage of 5% of all glioblastoma patients survive for 5 years and more, and are referred to as long-term survivors. Still, the group of long-term survivors is heterogeneous, and the determinants of this survival benefit are not fully understood so far.

Identifying and understanding potential clinical, biological, and lifestyle-related factors of this long-term survival is the aim of a large comprehensive multicenter study that will be conducted in more than 30 sites worldwide, with the support of the Brain Tumor Funders' Collaborative and under the lead of the Brain Tumor Group of the European Organisation for Research and Treatment of Cancer (EORTC) and the Brain Tumor Center at the University Hospital Zurich. Over a period of 2 years, extensive clinical data of more than 400 confirmed glioblastoma patients with a survival of more than 5 years from first diagnosis are recorded in a central database. Moreover, quality-of-life–related data, including extensive neurocognitive assessments, are collected to allow for a better understanding of the implications of the disease as well as the therapies in affected patients. For molecular analyses, tumor tissue and blood samples are collected centrally in a large biobank to study genetic features of glioblastoma in long-term survivors, and the results will be compared with a preexisting dataset of glioblastoma patients with shorter survival. Immunological studies are performed in parallel to potentially establish a specific immunological long-term survivor profile. Moreover, tumor growth patterns and development of the tumors will be investigated by analysis of all neuroimaging studies available from the selected patients with different imaging tools.

Considering the rareness of long-term survival in this disease, only a multicenter approach involving as many clinical neuro-oncological sites as possible allows for a sufficient number of collected patients to gather meaningful results. Additional associated sites have therefore been authorized for patient registration and contribute to the increasing number of enrolled long-term survivors.

The information gained with this study may contribute and benefit for improved survival in all glioblastoma patients in the future, and may help develop better treatment strategies in general as well as improve quality of life.

EORTC 1419 is open to patient registration.

Questions concerning the protocol or participation can be addressed to: Caroline Happold (Caroline.Happold@usz.ch), Emilie Le Rhun (emilie.lerhun@chru-lille.fr), Tina Verschuere (tina.verschuere@eortc.be) or Michael Weller (Michael.Weller@usz.ch)

Hotspots in Neuro-Oncology

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1. Novel MET/TIE2/VEGFR2 inhibitor altiratinib inhibits tumor growth and invasiveness in bevacizumab-resistant glioblastoma mouse models

Piao Y et al, Neuro Oncol. 2016 Sep;18(9):1230–1241

Glioblastoma highly expresses the proto-oncogene MET in the setting of resistance to bevacizumab. MET engagement by hepatocyte growth factor (HGF) results in receptor dimerization and autophosphorylation mediating tumor growth, invasion, and metastasis. Evasive revascularization and the recruitment of macrophages expressing tunica interna endothelial cell kinase 2 (TIE2) are also triggered by anti–vascular endothelial growth factor (VEGF) therapy.

The authors investigated the activity of altiratinib (a novel inhibitor of MET/TIE2/VEGF receptor 2) against human glioblastoma stem cell lines in vitro and in vivo using xenograft mouse models. The biological activity of altiratinib was assessed in vitro by testing the expression of HGF-stimulated MET phosphorylation as well as cell viability after altiratinib treatment. Tumor volume, stem cell and mesenchymal marker levels, microvessel density, and TIE2-expressing monocyte infiltration were evaluated in vivo following treatment with a comparison with control, bevacizumab alone, bevacizumab combined with altiratinib, or altiratinib alone.

In vitro, HGF-stimulated MET phosphorylation was completely suppressed by altiratinib, and altiratinib markedly inhibited cell viability in several glioblastoma stem cell lines. More importantly, in multiple xenograft mouse models, altiratinib combined with bevacizumab dramatically reduced tumor volume, invasiveness, mesenchymal marker expression, microvessel density, and TIE2-expressing monocyte infiltration compared with bevacizumab alone. Furthermore, in the xenograft model, altiratinib combined with bevacizumab significantly prolonged survival compared with bevacizumab alone. Together, these data suggest that altiratinib may suppress tumor growth, invasiveness, angiogenesis, and myeloid cell infiltration in glioblastoma. Thus, altiratinib administered alone or in combination with bevacizumab may overcome resistance to bevacizumab and prolong survival in patients with glioblastoma.

2. Primary CNS lymphoma at first relapse/progression: characteristics, management, and outcome of 256 patients from the French LOC network

Langner-Lemercier S et al, Neuro Oncol. 2016 Sep;18(9):1297–1303

The treatment of relapsed/refractory (R/R) primary CNS lymphoma (PCNSL) is poorly defined, because randomized trials and large studies are lacking. The aim of this study was to analyze the characteristics, management, and outcome of R/R PCNSL patients after first-line therapy in a nationwide cohort. The authors analyzed R/R PCNSL patients following first-line treatment who had been prospectively registered in the database of the French network for oculocerebral lymphoma (LOC) between 2011 and 2014.

Among 563 PCNSL patients treated with first-line therapy, 256 patients with relapsed ($n = 93$, 16.5%) or refractory ($n = 163$, 29.0%) disease were found. Patients who were asymptomatic at relapse/progression (25.5%), mostly diagnosed on routine follow-up neuroimaging, tended to have a better outcome. Patients who received salvage therapy followed by consolidation (mostly intensive chemotherapy plus autologous hematopoietic stem cell transplantation [ICT + AHSCT]) experienced prolonged survival compared with those who did not receive salvage or consolidation therapy. Independent prognostic factors at first relapse/progression were: KPS $\geq$70 versus KPS $<$70, sensitivity to first-line therapy (relapsed vs refractory disease), duration of first remission (progression-free survival [PFS] $\geq$1 y vs $<$ 1 y), and management at relapse/progression (palliative care vs salvage therapy).

In conclusion, patients who relapsed early after first-line therapy (ie, PFS $<$1 y) had a poor outcome, comparable to that of refractory patients. Conversely, patients experiencing late relapses (PFS $\geq$1 y) and/or undergoing consolidation with ICT + AHSCT experienced prolonged survival.

3. Upfront bevacizumab may extend survival for glioblastoma patients who do not receive second-line therapy: an exploratory analysis of AVAglio

Chinot OL et al, Neuro Oncol. 2016 Sep;18(9):1313–1318

In this post-hoc, exploratory analysis, the authors examined outcomes for patients enrolled in the AVAglio trial of front-line bevacizumab or placebo plus radiotherapy/temozolomide who received only a single line of therapy. Patients with newly diagnosed glioblastoma received protocol-defined treatment until progressive disease (PD). Co-primary endpoints were investigator-assessed progression-free survival (PFS) and overall survival (OS). After confirmed PD, patients were treated at the investigators' discretion. PFS/OS were assessed in patients with a PFS event who did not receive post-PD therapy (Group 1) and patients with a PFS event who received post-PD therapy plus patients who did not have a PFS event at the final data cutoff (Group 2). Kaplan–Meier methodology was used. A multivariate Cox proportional hazards model for known prognostic variables was generated.

Baseline characteristics were balanced. In patients with a PFS event who did not receive post-PD therapy (Group 1; $n = 225$ [24.4% of the intent-to-treat population]), the addition of bevacizumab to radiotherapy/temozolomide resulted in a 3.6-month extension in both median PFS (hazard ratio [HR]: 0.62, $P = .0016$) and median OS (HR: 0.67, $P = .0102$). Multivariate analyses supported this OS benefit (HR: 0.66). In the remaining patients (Group 2; $n = 696$), a 5.2-month PFS extension was observed in

bevacizumab-treated patients (HR: 0.61, $P < .0001$), while OS was comparable between the treatment arms (HR: 0.88, $P = .1502$). No significant differences in safety were observed between the 2 groups.

In conclusion, this exploratory analysis suggests that the addition of bevacizumab to standard glioblastoma treatment prolongs PFS and OS for patients with PD who receive only one line of therapy. Unfortunately, these results will not affect the indications of bevacizumab (patients relapsed after the Stupp protocol).

4. Long-term analysis of the NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide

Wick W et al, Neuro Oncol. 2016 Nov;18(11):1529–1537

Optimal treatment and precise classification for anaplastic glioma are needed. The objective for long-term follow-up of German NOA-04 was to optimize the treatment sequence for patients with anaplastic gliomas. Patients were randomized 2:1:1 to receive the standard radiotherapy (RT) (arm A); procarbazine, lomustine, and vincristine (PCV) (arm B1); or temozolomide (TMZ) (arm B2). Results showed that primary endpoint was time-to-treatment-failure (TTF), defined as progression after 2 lines of therapy or any time before if no further therapy was administered. Exploratory analyses examined associations of molecular marker status with TTF, progression-free survival (PFS), and overall survival (OS).

At 9.5 years (95% CI: 8.6–10.2), no difference between arms A versus B1/B2 was observed in median TTF (4.6 y [3.4–5.1] vs 4.4 y [3.3–5.3]), PFS (2.5 y [1.3–3.5] vs 2.7 y [1.9–3.2]), and OS (8 y [5.5–10.3] vs 6.5 y [5.4–8.3]). Oligodendroglial versus astrocytic histology—but more so the subgroups according to cytosine-phosphate-guanine island methylator phenotype (CIMP) and 1p/19q codeletion status—revealed a strong prognostic value of CIMP(pos) with (CIMP(codel)) versus without 1p/19q codeletion (CIMP(non-codel)) versus CIMP(neg)), but no differential efficacy of RT versus chemotherapy for any of the endpoints. PFS was better for PCV- than for TMZ-treated patients with CIMP(codel) tumors (HR B1 vs B2 0.39 [0.17–0.92], $P = .031$). In CIMP(neg) tumors, hypermethylation of the O^6-DNA methylguanine-methyltransferase promoter provided a risk reduction for PFS with chemotherapy.

In conclusion, there is no differential activity of primary chemotherapy versus RT in any subgroup of anaplastic glioma. Molecular diagnosis for prediction of outcome seems superior to conventional histology.

5. Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection

Wefel JS et al, Neuro Oncol. 2016 Dec;18(12):1656–1663

Patients with malignant gliomas present with variation in neurocognitive function (NCF) not attributable to lesion size or location alone. A potential contributor is the rate at which tumors grow, or "lesion momentum." Isocitrate dehydrogenase 1 wild type (IDH1-WT) tumors are more proliferative and aggressive than IDH1 mutant (IDH1-M) tumors. The authors hypothesized that patients with IDH1-WT would exhibit worse NCF than patients with IDH1-M tumors. Comprehensive NCF testing was completed in 119 patients with malignant glioma prior to surgical resection. IDH1 status was determined with immunohistochemistry and sequencing. Rates of impairment and mean test performances were compared by IDH1.

NCF impairment was significantly more frequent in patients with IDH1-WT tumors in terms of memory, processing speed, visuoconstruction, language, executive functioning, and manual dexterity. Mean performances of patients with IDH1-WT were also significantly lower than those with IDH1-M tumors on measures of learning and memory, processing speed, language, executive functioning, and dexterity. Lesion volume was not statistically different between IDH1-WT and IDH1-M tumors. Tumor and lesion volumes on T1-weighted and fluid attenuated inversion recovery MRI were significantly associated with most NCF tests in patients with IDH1-WT, but only significantly associated with a single measure in patients with IDH1-M tumors.

In conclusion, patients with IDH1-WT show reduced NCF compared with those with IDH1-M malignant gliomas. Lesion volume is inversely associated with NCF for patients with IDH1-WT, but not IDH1-M tumors. These findings are consistent with the hypothesis that patients with IDH1-WT tumors present with more severe NCF impairment due to greater lesion momentum, which may impede compensatory neuroplasticity and cerebral reorganization.

6. Clinical parameters outweigh diffusion- and perfusion-derived MRI parameters in predicting survival in newly diagnosed glioblastoma

Burth S et al, Neuro Oncol. 2016 Dec;18(12):1673–1679

The purpose of this study was to determine the relevance of clinical data, apparent diffusion coefficient (ADC), and relative cerebral blood volume (rCBV) from dynamic susceptibility contrast (DSC) perfusion and the volume transfer constant from dynamic contrast-enhanced (DCE) perfusion for predicting overall survival (OS) and progression-free survival (PFS) in newly diagnosed treatment-naïve glioblastoma patients. Preoperative MR scans including standardized contrast-enhanced T1 (cT1), T2 fluid attenuated inversion recovery (FLAIR), ADC, DSC, and DCE of 125 patients with subsequent histopathologically confirmed glioblastoma were performed on a 3 Tesla MRI scanner. ADC, DSC, and DCE parameters were analyzed in semiautomatically segmented tumor volumes on cT1 and hyperintense signal changes on T2 FLAIR. Univariate and multivariate Cox regression analyses including age, sex, extent of resection

(EOR), and KPS were performed to assess the influence of each parameter on OS and PFS.

Univariate Cox regression analysis demonstrated a significant association of age, KPS, and EOR with PFS and of age, KPS, EOR, lower ADC, and higher rCBV with OS. Multivariate analysis showed independent significance of male sex, KPS, EOR, and increased rCBV contrast enhancement for PFS and of age, sex, KPS, and EOR for OS. The conclusion was that MRI parameters help to predict OS in a univariate Cox regression analysis, and increased rCBV contrast enhancement is associated with shorter PFS in the multivariable model.

In summary, these findings suggest that the relevance of MRI parameters is outperformed by clinical parameters in a multivariable analysis, which limits their prognostic value for survival prediction at the time of initial diagnosis.

Greetings

We all have high hopes that 2017 will bring good news of promising therapeutic advances in the treatment of brain and CNS tumors. A number of recent developments have been encouraging. In 2016 these included an update by the World Health Organization of its classification system for brain tumors which now focuses on molecular profiles together with traditional histopathology to reclassify tumor entities. This will lead, in 2017 and beyond, to more accurate diagnoses and better stratification in clinical trials as well as more appropriate, personalized treatments for brain tumor patients. Some of the examples that signify reasons to be optimistic for the future include: immunotherapeutic approaches; further study into biomarkers and liquid biopsies; the use of innovative devices; efforts to improve drug delivery; and a more prominent focus on quality of life issues for brain tumor patients. Brain tumor patient advocacy is also making great strides as we forge new and exciting collaborations with the scientific community and are becoming much more actively involved in providing the patient voice in the research and development of new treatments and supportive care. Patient advocates are also playing an increasingly important role in policy and regulatory work. We hope that with all of these developments, and others, we will see some significant advances in brain tumor treatment in the near future.

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Erratum

In the article “Introduction of the Korean Society for Neuro-Oncology (KSNO)”, in volume 1, issue 3 of *World Federation of Neuro-Oncology Societies Magazine* the editors would like to correct the author name credited to this article as follows:

Yun, Hwan Jung, M.D., Ph.D.

President, Korean Society for Neuro-Oncology

Professor, Department of Internal Medicine

Chungnam National University Medical Center

Jeong Hoon Kim and Chul-Kee Park are chair and secretary of Scientific Committee of KSNO respectively. The editors apologize for the oversight.