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Editorial
Riccardo Soffietti, Wolfgang Grisold

REVIEW ARTICLES
Role of PET Imaging in Patients with High-Grade Gliomas undergoing anti-angiogenic Therapy with Bevacizumab – Review of the Literature and Case Report
Irina Götz, Anca-Ligia Grosu, Timo S Spehl

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Oliver Schnell

Boron Neutron Capture Therapy for Glioblastoma: A Phase-I/II Clinical Trial at JRR-4
Kei Nakai, Tetsuya Yamamoto, Hiroaki Kumada, Akira Matsumura

COLUMNS
Case Report
Patient Issues
Nurses and Health-Related Groups
Ongoing Trials
Hotspots in Neuro-Oncology
National Societies

October 9-12

11th MEETING

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Turin, Italy
Lingotto Convention & Exhibition Centre

Abstract Deadline: March 23, 2014
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# Table of Content

**Editorial**

Riccardo Soffietti, Wolfgang Grisold

<table>
<thead>
<tr>
<th>REVIEW ARTICLES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Role of PET Imaging in Patients with High-Grade Gliomas undergoing anti-angiogenic Therapy with Bevacizumab – Review of the Literature and Case Report</strong></td>
</tr>
<tr>
<td>Irina Götz, Anca-Ligia Grosu, Timo S Spehl</td>
</tr>
<tr>
<td><strong>Impact of Molecular Markers on Personalised-Treatment Concepts in Gliomas</strong></td>
</tr>
<tr>
<td>Oliver Schnell</td>
</tr>
<tr>
<td><strong>Boron Neutron Capture Therapy for Glioblastoma: A Phase-I/II Clinical Trial at JRR-4</strong></td>
</tr>
<tr>
<td>Kei Nakai, Tetsuya Yamamoto, Hiroaki Kumada, Akira Matsumura</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COLUMNS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case Report</strong></td>
</tr>
<tr>
<td>Arnault Cazorla, Martine Fohlen, Sarah Ferrand-Sorbets, Marc Polivka</td>
</tr>
<tr>
<td><strong>Patient Issues</strong></td>
</tr>
<tr>
<td>Kathy Oliver</td>
</tr>
<tr>
<td><strong>Demystifying Palliative Care</strong></td>
</tr>
<tr>
<td><strong>Nurses and Health-Related Groups</strong></td>
</tr>
<tr>
<td>EANO Nursing session October 10th, 2014</td>
</tr>
<tr>
<td>Hanneke Zwinkels</td>
</tr>
<tr>
<td><strong>Ongoing Trials</strong></td>
</tr>
<tr>
<td>Interview with Dr. Antonio Omuro, MSKCC, about the RTOG 1114-Phase II randomized Study of Chemotherapy with and without Low-Dose WBRT for Primary Central Nervous Lymphoma</td>
</tr>
<tr>
<td>Ufuk Abacioglu</td>
</tr>
<tr>
<td><strong>Hotspots in Neuro-Oncology</strong></td>
</tr>
<tr>
<td>Riccardo Soffietti</td>
</tr>
<tr>
<td><strong>SNO News</strong></td>
</tr>
<tr>
<td>News from the Society for Neuro-Oncology</td>
</tr>
<tr>
<td>David A. Reardon</td>
</tr>
<tr>
<td><strong>National Societies</strong></td>
</tr>
<tr>
<td>The Swiss Working Group Brain Tumor of the Swiss Group for Clinical Cancer Research</td>
</tr>
<tr>
<td>Andreas F. Hottinger, Thomas Hundsberger</td>
</tr>
<tr>
<td><strong>Calender of Events</strong></td>
</tr>
<tr>
<td>Imprint</td>
</tr>
</tbody>
</table>
Dear EANO members, dear Colleagues,

Since my last Editorial in April 2014 several tasks have been completed. All financial matters are now managed at Vienna Medical Academy. In this regard, a call for donations to EANO is being set up on the Society website.

The two Task Forces on Guidelines on management of Malignant Gliomas and Primary CNS lymphomas respectively will present the final documents with recommendations in a special session at EANO 2014 in Turin. The paper related to Guidelines on Malignant Gliomas will soon appear in *Lancet Oncology*, while that on PCNSL will be sent to a major scientific journal by the end of the year. In the meantime two new Task Forces (on Brain Metastasis and on PET applications in Neuro-Oncology) are being activated.

By the end of 2014 / beginning of 2015 the EANO online magazine will be transformed into the EANO / World Federation of Neuro-Oncology magazine (together with SNO and ASNO), with a European Editor-in-Chief and two American and Asian Co-Editors. Thus, at the end, we will have three journals co-sponsored by EANO with different aims: *Neuro-Oncology* (IF 6.1) as the major scientific journal, *Neuro-Oncology Practice* as a more clinically oriented journal, and the *EANO/WFNO magazine* with educational and informative purposes.

The EANO 2014 meeting of October in Turin is quickly approaching, the educational and scientific programs have been defined, and 3 satellite-symposia (based on educational grants from the industry) are scheduled. The social program will include a Welcome Reception at Museo dell’Automobile and a dinner at Museo del Risorgimento.

Future meetings will be held in Heidelberg (2016) and Stockholm (2018).

Last point: In Turin I will leave my 2-year position as EANO President and I will be replaced by Michael Weller from Zurich for the period 2014–2016; he will work together with a partially renovated Executive Board and Scientific Committee. All these changes will be formalized during the General Assembly in Turin, and all of you are cordially invited to attend.

*See you in Torino!*

Best regards

Riccardo Soffietti
*EANO President 2012–2014*
Editorial

As the editor of the EANO Neurooncology Magazine I want to thank Kathy Oliver for raising the issue of palliative care so courageously.

Indeed as Mrs Oliver rightly points out the term of “palliative care” is used ambiguously, and is often confused with “end of life care” amongst others. And although all patients with neurooncological diseases are significantly affected in the course of the disease, and many people suffering from a brain tumor have a poor prognosis, the scientific research in palliative care and end of life setting is still taking only a minor part in neurooncologic scientific journals and congresses. This does not stop there, as we all note large differences in the practical, legal and ethical aspects of palliative care in different countries of the world. In addition there are also major cultural concepts in regard to treating patients and these aspects have an impact on facets of palliative care.

It is very useful that the WHO offers a definition, and it is also most useful, that large organizations such as the World Federation of Neurology (www.wfneurology.org) and the European Association of NeuroOncology (www.eano.eu) have established research groups to foster this topic and also guidelines on palliative care in neurological disease are being developed. It is a topic, which is all about human beings and involves patients, carers, and all persons concerned with the treatment of patients.

Frequently the question is asked if palliative care for patients with brain tumors is any different from general palliative care, and experience has taught us it is. Patients with brain tumors may have pain, weakness and ill-being in common with other cancer patients. But in all neurooncology patients the brain is affected and many tumors not only cause focal symptoms, seizures etc, but can influence our most precious functions which are cognition, language and often personality. We also know that these changes can be different in high-grade glioblastoma, in comparison to low-grade glioma and that the need for palliative care of any kind of tumors and neurooncologic malignancy arises at different points of the disease.

Even more complex, at least culturally, is the end-of-life phase which has been subject to many discussions and opinions. The end of life is not always clearly defined, and often hopes and sometime irrational wishes and needs appear. It is an important and unavoidable stage of the disease, and for physicians it is often not easy to comply with patient’s or family’s therapeutic wishes and concentrate on the best well-being of the patient under the given circumstances. Numerous experiences and studies have taught us that many symptoms in the end-of-life situation need special attention and treatment.

And this does not end here, as patients, relatives and carers may wish to increase all efforts for survival, even when death is, sadly, inevitable. Studies have shown, that in the last days of tumor diseases, helplessness is often reflected by unnecessary ancillary examinations.

And after the patient’s death, relatives and carers often feel left alone and deserted, as their focus of attention is not in need anymore. Carer counseling and debriefing is imperative after the patient’s death, and significantly helps to lift burden from their shoulders.

Palliative care, end-of-life care and awareness of the carers’ needs has to be taken seriously by all disciplines and professions, and we have to strive to implement these concepts into our daily practices and across all cultures.

Wolfgang Grisold, MD, Vienna
Managing Editor
Role of PET Imaging in Patients with High-Grade Gliomas Undergoing Anti-Angiogenic Therapy with Bevacizumab – Review of the Literature and Case Report

Irina Götz1, Anca-Ligia Grosu1, Timo S Spehl2

Abstract: Despite recent advantages in combination therapies, the prognosis of high-grade gliomas remains very poor. A new therapeutic concept in the treatment of brain tumours uses the anti-angiogenic drug bevacizumab to reduce tumour neovascularisation. However, due to a concomitant reduction of contrast agent enhancement in MRI, imaging modalities that do not depend on a disruption of the blood-brain barrier (BBB) would be desirable for therapy monitoring. Positron emission tomography (PET) imaging has emerged as a promising tool for better assessment of treatment response in patients undergoing anti-angiogenic therapy compared to MRI. The most important tracers are amino-acids like 11C-methionin and 18F-FET, but also 18F-FDG and 18F-FLT, a biomarker of cell proliferation. In this review, we provide an overview of current knowledge concerning the value of PET in patients with brain tumours undergoing anti-angiogenic therapy and present a clinical case that illustrates the utility of PET imaging.

Key words: PET, bevacizumab, therapy monitoring, 18F-FDG, 18F-FLT, 18F-FET

Introduction

High-grade gliomas (HGG) are highly aggressive brain tumours with limited treatment options. The most frequent primary brain tumour, accounting for 20 % of all intracranial tumours, is glioblastoma multiforme (WHO grade IV). Despite recent advances in combination therapy including surgery, radiation therapy, and chemotherapy, the prognosis remains very poor [1]. An important feature of tumour aggressiveness is increased tumour neovascularisation driven by the vascular endothelial growth factor (VEGF) pathway [2]. Tumour vessels are characterised by structural abnormalities that lead to an increase in the permeability of the blood-brain barrier (BBB), thus causing complications like tumour oedema and compression of adjacent structures. Under the premise of arresting tumour progression and local complications by inhibiting pro-angiogenic growth factors [3], the anti-angiogenic drug bevacizumab has been introduced into therapy of recurrent glioblastoma [4, 5] and has been approved by the FDA for this indication.

Under treatment with bevacizumab, high response rates based on morphological imaging using the conventional Macdonald criteria [6] have been reported, ranging from 30–60 % [7]. It must be borne in mind, however, that these response rates are based on a normalisation of the BBB that might not represent true tumour regression, and thus are described as “pseudosubtraction” [8]. There is growing evidence that bevacizumab may alter the recurrence pattern of malignant gliomas in MRI imaging by suppressing gadolinium-enhancing tumour recurrence more effectively than it suppresses non-enhancing, infiltrative tumour growth [9]. To enable a more precise response assessment, new criteria have been established for response assessment in neuro-oncology (RANO) that include T2-based fluid-attenuated inversion recovery (FLAIR) MRI sequences [10]. However, the morphological changes seen in these imaging sequences also include multiple non-specific changes like radiation-induced gliosis, peritumoural oedema, ischemia, and demyelination [11]. In this context, positron emission tomography (PET) with various tracers has been established to improve diagnostics, response assessment, and therapy planning.

We present an exemplary case of a patient with recurrent glioblastoma multiforme who was treated with bevacizumab. This case highlights the usefulness of PET imaging in response assessment compared to MRI. Furthermore, we give an overview of the current literature regarding PET imaging in patients treated with this promising new therapeutic agent.

Molecular Mechanisms of Bevacizumab

VEGF is a vascular endothelial growth factor correlated with pathological angiogenesis and plays an important role especially in highly vascularised tumours like glioblastoma. The extent of proliferation in this tumour entity has been shown to correlate with an increased recurrence and poor survival [12]. Moreover, a direct relationship between VEGF over-expression and poor prognosis has been reported [13]. Originating from the tumour bulk, glioblastoma cells migrate along normal vascular structures into adjacent brain regions [14], thus making VEGF a promising target for therapeutic agents. Preclinical studies accordingly showed that bevacizumab inhibits tumour growth as a single-agent therapy or in combination with cytotoxic agents [15]. Bevacizumab and other anti-angiogenic agents that bind and inactivate VEGF, including cedirab (AZD2171), aflibercept (VEGF Trap), XL184, and cilengitide (EMD 121974), are thus being evaluated as possible treatment option for use in recurrent and possibly also newly diagnosed glioblastoma.
Therapeutic Studies with Bevacizumab in Glioblastoma

The first phase-II study on bevacizumab and irinotecan (BEV/IR) in recurrent glioblastoma by Vredenburgh et al proved the feasibility of this regime and revealed an improvement in 6-months progression-free survival (PFS) of 46% compared with historical data [4]. The response rate was 57%, toxicity was moderate. Regarding side-effects, the authors reported thromboembolic complications in 4 patients and one CNS haemorrhage [4]. The response rate in the trial of Kreisl et al examining 56 patients was 35% based on the Macdonald criteria, 6-months PFS was 29% [16]. In addition to an increase in PFS, a clinical benefit was evident in terms of decreased cerebral oedema in 24 patients (50%). 15 patients were able to decrease corticosteroids and 25 patients (52%) had improved neurologic symptoms. Based on these 2 trials, the FDA granted accelerated approval of bevacizumab for the treatment of recurrent glioblastoma multiforme in May 2009.

The BRAIN study [5] confirmed that bevacizumab, alone or in combination with irinotecan, was well-tolerated and effective in recurrent glioblastoma. This was a non-comparative trial. The randomised design was intended only to prevent bias in treatment assignment. Additionally, data of the BRAIN study were analysed by Vredenburgh et al to evaluate whether bevacizumab may have corticosteroid-sparing effects [17]. The results showed sustained reduction of corticosteroids in 30% of the bevacizumab-alone group and 20% of the bevacizumab-plus-irinotecan group, respectively. However, the data has to be interpreted cautiously due to the exploratory nature of the analysis.

Other studies reported bevacizumab as an effective treatment option in radionecrosis. In a series of 6 patients with biopsy-proven cerebral radiation necrosis treated with bevacizumab, MRI follow-up demonstrated radiographic response in all patients with an average reduction of 79% for the post-gadolinium studies and 49% for the FLAIR images and was noted for a mean follow-up time of up to 5.9 months [18].

First results of 2 phase-III trials were reported at the ASCO meeting in June 2013 and were published in the New England Journal of Medicine in February 2014 [19, 20]. The RTOG study 0825 [19] reported that addition of bevacizumab to the standard treatment regime with temozolomide for newly diagnosed GBM did not improve overall survival. A small effect was seen regarding prolonged PFS, but this did not reach the significance criterion. The patient group receiving bevacizumab even showed a decline of neurocognitive status. These results discourage the use of bevacizumab for patients with the best prognosis at the outset. The analysis did not identify a group of patients who experienced benefit from first-line bevacizumab.

AVAglio, a phase-III registration trial including > 920 patients worldwide, revealed similar findings for OS. The double-blind, randomised trial evaluates the benefit of an addition of bevacizumab to the standard of care in the first-line treatment of patients with glioblastoma. Median overall survival in each arm was 17 months. Median PFS was 10.6 months in the interventional arm with bevacizumab vs 6.2 months in the control arm (p < 0.001). In contrast to the RTOG trial, this difference was statistically significant. Even more, health-related quality of life was improved for patients receiving bevacizumab in the AVAglio trial [20] in contrast to the RTOG trial.

More encouraging results were reported for the GLARIUS study involving 182 MGMT unmethylated glioblastoma patients. Patients in the experimental arm received 4 cycles of bevacizumab over 6 weeks of radiation, then bevacizumab plus irinotecan were administered every 2 weeks until progression. At 6 months, PFS was significantly higher with BEV/IR: 9.74 vs 5.99 months (p < 0.0001). Overall survival was also significantly longer: 16.6 vs 14.8 months (p = 0.031). The experimental arm also required less corticosteroids [21].

Taken together, there is growing evidence for the usefulness of bevacizumab in the treatment of glioblastoma with regard to PFS. However, the expectations of the community regarding overall survival were not fulfilled by the 2 phase-III trials. Additionally, it is even not clear whether bevacizumab improves or impairs the neurological condition of the patients.

Due to high costs, severe side effects, and complicated image interpretation, reliable biomarkers for therapy monitoring are required. PET has emerged as a very promising tool in this field.

Role of PET Imaging in Response Assessment to Bevacizumab Therapy

PET imaging is increasingly used in HGG. It relies on the fact that it can visualise functional changes in tumour tissue rather than morphological details. Multiple different features of brain tumours can be addressed, eg, glucose metabolism, amino-acid uptake, or proliferation activity. These can serve as valuable biomarkers for diagnostics and response assessment.

Glucose Metabolism

The most widely used PET tracer in oncology is 18F-fluorodeoxyglucose (18FDG). The use of 18FDG-PET in brain tumours was reviewed by a National Comprehensive Cancer (NCCN) panel in 2009. Based on current evidence and consensus, a role for 18FDG-PET in the management of brain tumours was proposed for diagnosis, staging/restaging, prognosis, and possibly for treatment planning and response monitoring [22]. 18FDG-PET relies on an increased glycolytic metabolism of glial tumour cells mediated by increased hexokinase activity [23] and over-expression of glucose transporters [24] (Table 1). Furthermore, 18F-FDG uptake is strongly correlated with angiogenesis markers in gliomas [25]. Thus, it could serve as a biomarker for tumour neovascularisation. There is a study that investigates 18FDG-PET for treatment monitoring of high-grade gliomas under treatment with bevacizumab and irinotecan [26]. In this study, Colavolpe et al report that 18FDG-PET was the most powerful predictor of OS and PFS in a group of 25 patients in both uni- and multivariate analysis (p < 0.001). Interestingly, in multivariate analysis, 18FDG-PET performed better in predicting survival than histological grading, steroid...
intake, Karnofsky Performance Status, and number of previous treatments [26]. In another study, mean 18FDG uptake in anaplastic gliomas treated with bevacizumab turned out to be a significant prognostic factor at 4 weeks post-treatment [27]. These examples underline the clinical usefulness of glucose metabolism as an independent biomarker for therapy monitoring.

### Amino-Acid Uptake

Despite the usefulness of 18FDG-PET in general oncology, it is limited as a tracer in brain neoplasms due to its high physiological uptake of grey matter, where small tumours can be masked and low-grade tumours may not be discernible from white matter due to lower uptake. Therefore, multiple other biomarkers have been tested that have low uptake in normal brain tissue and thus allow for better contrast in PET imaging. Among the most promising PET tracers are radio-labelled amino-acids (AA), such as 18F-fluoroethyl-L-tyrosine (FET), whose half-life of 109 minutes makes it more readily available than the previously widely used 11C-methionine (MET), which is limited as a tracer in brain neoplasms due to its high physiological uptake of grey matter [32]. 18F-FET-PET is increasingly used in therapy monitoring of patients with rare indications like progressive brain-stem gliomas [40].

In addition to radiation therapy planning, 18F-FET PET could play a major role in the assessment of response in patients undergoing therapy with bevacizumab. Case reports hint that 18F-FET-PET may indicate therapy failure earlier than MRI [35, 36]. There are 2 studies that suggest that 18F-FET-PET could serve as a reliable biomarker to predict treatment failure and is superior to MRI based on RANO criteria for the detection of tumour progression [37, 38]. In the study of Galldiks et al [37], FET-PET predicted a significantly longer progression-free survival than MRI, while in 36.4 % of all cases, FET-PET and MRI were discordant and PET was able to detect treatment failure earlier than MRI (median time benefit 10.5 weeks). Similar results have been reported by Hutterer et al [38], where in 40 % of the patients, FET-PET was discordant with MRI and revealed treatment failure earlier than MRI (median time benefit 10.5 weeks).

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Radiopharmaceutical name</th>
<th>Isotope</th>
<th>Half-life</th>
<th>Molecular target (localisation)</th>
<th>Intracellular process</th>
<th>Molecular weight</th>
<th>Penetration through intact blood-brain barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>18F-FDG</td>
<td>2-deoxy-2-[18F]-fluoro-D-glucose</td>
<td>18F</td>
<td>109 min</td>
<td>Mainly GLUT-1 (transporter), substrate for hexokinase (HK-2, enzyme)</td>
<td>Intracellular storage, &quot;trapping&quot;</td>
<td>181.15 g/mol</td>
<td>Yes</td>
</tr>
<tr>
<td>11C-MET</td>
<td>[11C]methionine</td>
<td>11C</td>
<td>20 min</td>
<td>L-type amino-acid carriers (membrane)</td>
<td>Incorporated into proteins</td>
<td>149.21 g/mol</td>
<td>Yes</td>
</tr>
<tr>
<td>18F-FET</td>
<td>O-2-[18F]fluoroethyl-L-tyrosine</td>
<td>18F</td>
<td>109 min</td>
<td>L-type amino-acid carriers (membrane)</td>
<td>Not incorporated into proteins</td>
<td>22723 g/mol</td>
<td>Yes</td>
</tr>
<tr>
<td>18F-FLT</td>
<td>3'-deoxy-3'-[18F]fluorothymidine</td>
<td>18F</td>
<td>109 min</td>
<td>Thymidin-kinase (TK-1, enzyme)</td>
<td>DNA synthesis, proportional to proliferation</td>
<td>244.22 g/mol</td>
<td>Unclear (see text)</td>
</tr>
<tr>
<td>18F-DOPA</td>
<td>3,4-dihydroxy-6-[18F]fluoro-L-phenylalanine</td>
<td>18F</td>
<td>109 min</td>
<td>DOPA-decarboxylase (enzyme)</td>
<td>Intraneuronal storage in vesicles</td>
<td>215.18 g/mol</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Min: minutes. For details, see text.
PET-Imaging in Patients with high-grade Gliomas

### Table 2. Overview of studies examining PET as a biomarker for response assessment in HGG treated with bevacizumab

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Therapy</th>
<th>Tracer</th>
<th>PET response criteria</th>
<th>n</th>
<th>PD in MRI based on RANO criteria</th>
<th>Non-responders vs non-responders in PET</th>
<th>PFS responders vs non-responders (PET)</th>
<th>OS responders vs non-responders (PET)</th>
<th>Time benefit (PET vs MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutterer et al, 2011</td>
<td>BEV/IR</td>
<td>18F-FET</td>
<td>Reduction &gt; 45 % of tumour volume</td>
<td>11</td>
<td>18 %</td>
<td>54 %</td>
<td>10.24 vs 4.1 mo (p = 0.025)</td>
<td>11.0 vs 5.85 mo (p = 0.12)</td>
<td>9 wk (range: 4–14 wk)</td>
</tr>
<tr>
<td>Gallidoks et al, 2012</td>
<td>BEV/IR</td>
<td>18F-FET</td>
<td>Reduction &gt; 45 % of tumour volume</td>
<td>10</td>
<td>0 %</td>
<td>40 %</td>
<td>9 vs 3 mo (p = 0.001)</td>
<td>23.0 vs 3.5 mo (p = 0.001)</td>
<td>10.5 wk (range: 6–12 wk)</td>
</tr>
<tr>
<td>Chen et al, 2007</td>
<td>BEV/IR</td>
<td>18F-FLT</td>
<td>&gt; 25 % reduction of FLT uptake</td>
<td>21 (19 eligible)</td>
<td>33 %</td>
<td>53 %</td>
<td>“Tendency for prolonged PFS” (p = 0.061)</td>
<td>10.8 vs 3.4 mo (p = 0.003)</td>
<td>na</td>
</tr>
<tr>
<td>Schwarzenberg et al, 2012</td>
<td>BEV/IR or BEV alone</td>
<td>18F-FLT</td>
<td>&gt; 25 % reduction of FLT uptake</td>
<td>30</td>
<td>24 %</td>
<td>47 %</td>
<td>“PET predictive for PFS” (p &lt; 0.001)</td>
<td>12.5 vs 3.8 mo (p &lt; 0.001)</td>
<td>“PET earlier” (not specified)</td>
</tr>
<tr>
<td>Harris et al, 2012</td>
<td>BEV/IR or BEV alone</td>
<td>18F-FLT and/or 18F-DOPA</td>
<td>Voxel-wise changes in predefined regions</td>
<td>24</td>
<td>na</td>
<td>na</td>
<td>“18F-DOPA PET stratified short- and long-term PFS”</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Colavolpe et al, 2012</td>
<td>BEV/IR</td>
<td>18F-FDG</td>
<td>SUVmax and T/C ratio</td>
<td>25</td>
<td>40 %</td>
<td>Not specified</td>
<td>“FDG-PET most significant predictor of PFS” (p &lt; 0.001)</td>
<td>“FDG-PET most significant predictor of PFS” (p &lt; 0.001)</td>
<td>“FDG uptake may predict MRI response”</td>
</tr>
</tbody>
</table>

BEV: bevacizumab; IR: irinotecan; PD: progressive disease; PFS: progression-free survival; OS: overall survival; mo: months; wk: weeks; na: not available; RANO: response assessment in neuro-oncology; T/C: SUV ratio of tumour-to-contralateral hemisphere reference. Time benefit is time interval between diagnosis of progressive disease in PET vs MRI, when PET was able to detect progressive disease earlier. For details, see text.

### Proliferation Activity

In addition to radio-labelled amino-acids, 3'-deoxy-3'18F-fluorothymidine PET (18F-FLT) is increasingly used for therapy monitoring in brain tumours. 18F-FLT is a thymidine analogue that visualises tumour cell proliferation [41]. Uptake of FLT correlates with the activity of thymidine-1-kinase which is expressed during the DNA synthesis phase of tumour cells [42]. After phosphorylation, FLT is trapped inside the cell [43]. FLT uptake correlates with the Ki-67 proliferation index and FLT uptake has been shown to correlate with tumour grading and cell proliferation [44] (Table 1). It has been successfully investigated in brain malignancies [45, 46] and has been demonstrated to predict overall survival in HGG patients [47].

18F-FLT has also been investigated for its utility in treatment response assessment in HGG undergoing therapy with bevacizumab: in preclinical studies, 18F-FLT has been shown to be a sensitive marker of treatment efficacy in a rat model [48]. In this study, it was superior to 18F-FDG regarding evaluation of treatment efficacy. First clinical data were reported as early as 2007: in a pilot study with 21 HGG patients, Chen et al were able to demonstrate that 18F-FLT-PET is highly predictive of overall survival as early as 6 weeks after treatment initiation [49]. Response was defined as a > 25-% reduction of FLT uptake in the tumour mass compared to pre-treatment scans. In 2011, another study confirmed these results [50]. Using the same criteria, Schwarzenberg et al reported that changes in tumour 18F-FLT uptake were highly predictive of PFS and OS in patients with recurrent malignant glioma undergoing bevacizumab therapy and FLT-PET was more predictive than MRI for early treatment response [50]. In another study, 18F-FLT kinetics were analysed in recurrent HGG in 15 patients, and it reported that a persistently decreased 18F-FLT uptake (by means of measurements after 2 and 6 weeks) in the tumour was a predictor for longer survival [51].

There is one study that combines the amino-acid 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (18F-DOPA) with 18F-FLT-PET [52]. Here, voxel-wise changes in tracer uptake were analysed in 24 patients with HGG. Harris et al reported that voxel-wise increase in PET uptake in areas of pre-treatment contrast enhancement defined by MRI stratified 3-month progression-free survival and 6-month overall survival (OS).
PET-Imaging in Patients with high-grade Gliomas

[52]. Log rank analyses, however, revealed that only the volume fraction of increased 18F-DOPA uptake between 2 post-treatment time points stratified long- and short-term OS, while 18F-FLT uptake did not. The authors state that 18F-DOPA might be slightly superior to 18F-FLT.

However, there is growing uncertainty about the mechanisms of transport of 18F-FLT into brain tumours. There is data suggesting that the uptake of 18F-FLT is highly dependent on BBB breakdown and much less on phosphorylation itself [53]. This hypothesis was confirmed in another study where uptake of 18F-FLT was largely related to leakage into extracellular space via a disrupted BBB, whereas the effect of nucleoside transporters was regarded to be much lower in comparison [54]. Taken together, these facts might limit the general use of 18F-FLT in patients undergoing therapy with bevacizumab. In addition, the presence of benign lesions showing BBB disruption cannot be distinguished from malignant tumours [55] in 18F-FLT-PET. Thus, 18F-FLT-PET needs to be carefully evaluated. Further investigations in this field will be necessary before 18F-FLT can be recommended for general use in brain tumours.

Outlook: Imaging of Angiogenesis and Hypoxia in Brain Tumours

In malignant gliomas, aβ3 integrin plays a key role in tumour angiogenesis and invasion [56]. To date, there is a single study reporting the use of 18F-labelled glycosylated Arg-Gly-Asp peptide (18F-Galacto-RGD) to successfully visualise aβ3 expression in patients with glioblastoma [57]. This tracer might be a promising tool not only for planning and monitoring integrin-targeted therapies but possibly also for bevacizumab therapy planning.

Another interesting biomarker in HGG undergoing therapy with bevacizumab might be hypoxia. 18F-misonidazole (18F-MISO) is the most intensively studied PET tracer for hypoxia detection, and baseline 18F-MISO uptake has been shown to correlate with tumour aggressiveness in glioblastoma [58]. Furthermore, regional hypoxia measured by 18F-MISO correlated with time to progression and survival [59]. In solid tumours, it has been proposed that drugs that induce vascular normalisation could alleviate hypoxia and increase the efficacy of conventional therapies if both are carefully scheduled. Thus, 18F-MISO was proposed as a potential tool for tracking the normalisation window in patients undergoing anti-angiogenic therapy, which is considered as the period of radiation and chemotherapy response enhancement due to improvement of oxygenation [60], but this has not been researched so far. In how far 18F-MISO is useful to evaluate anti-angiogenic therapy in glioblastoma is not clear, but currently under investigation, eg, in the HYPOONCO study (clinicaltrials.gov: NCT01200134).

To draw a reliable conclusion regarding the best imaging method under anti-angiogenic therapy we need more validation trials comparing MRI and PET, ideally performed on the same day. Contrast enhancement on MRI might not be accurate enough after anti-angiogenic-agent therapy like bevacizumab and leads to pseudo-response. Amino-acid PET has a high sensitivity and specificity in detecting tumour tissue and it is not influenced by the blood-brain barrier. These are good arguments for PET in such situations.

It is worthwhile to correlate both imaging techniques with histology. However, it is often hardly possible. So we have to decide about pseudo-progression or tumour progression from the clinical course and repeated imaging scans.

Conclusion

PET imaging is increasingly used in brain tumour imaging. Many different functional aspects of tumour growth and metabolism can be investigated and used for diagnosis, treatment planning, and response assessment. Use of novel therapeutic agents like bevacizumab that severely alter tumour appearance in conventional imaging requires reliable biomarkers for therapy monitoring, as demonstrated by the case presented in this paper. PET is a promising, possibly cost-efficient method to reliably assess tumour response to bevacizumab therapy and may thus be included in the clinical management of recurrent high-grade gliomas treated with anti-angiogenic drugs.

Conflict of Interest

The authors have no conflict of interest to disclose.

References

After radiation (Figure 1D), $^{18}$F-FET-PET presented a small decrease of uptake but still a visible tumour mass. In addition, progressive infiltration of the mesencephalon was seen, as compared to a small, focal enhancing lesion on MRI (Figure 2). In contrast, MRI showed only minimal contrast enhancement without relevant changes to the MRI prior to re-irradiation. The patient died 16 months after primary diagnosis. This case illustrates the often discordant results between contrast enhancement in MRI and amino-acid uptake in PET and demonstrates the clinical utility of PET for response assessment and therapy management.

We assume that the decrease of contrast enhancement was due to a reduction of the brain-blood barrier damage by bevacizumab and not due to a real tumour reduction. However, it was not possible to decide whether the MRI or the PET scan showed the real tumour dimension. An autopsy was not performed.
Abstract: Gliomas are rare brain-derived tumours classified according to mainly histopathological criteria by a 4-step grading system of the World Health Organisation (WHO grades I–IV). Differentiating between the underlying tumour cell components (eg, astrocytomas, oligodendrogliomas, ependymomas), grading intends to give clinicians a general estimation about their patients’ prognosis. Increasing knowledge about the molecular genetic profile now leads to a deeper insight into the predictive or prognostic value of several molecular markers with large impact on the treatment of glioma patients. Hypermethylation of the O-methylguanine-DNA methyltransferase (MGMT) promoter has turned out to be an important predictive marker for patients with glioblastoma multiforme (GBM, WHO grade IV) receiving radiochemotherapy with concurrent and adjuvant temozolomide chemotherapy and may be crucial for a treatment decision between (radio-) chemotherapy versus radiation only in older patients. Moreover, mutations of the isocitrate dehydrogenase (IDH) seem to have a strong prognostic impact in malignant gliomas since GBM patients with IDH mutation showed longer median survival compared to patients with anaplastic gliomas (WHO grade III) without IDH mutation. Additionally, genetic co-deletion on chromosomes 1p and 19q (LOH 1p/19q) has been demonstrated to be a favourable prognostic factor for patients with anaplastic gliomas receiving radiation, chemotherapy with alkylating agents, or both.

Hence, histological diagnosis will not be sufficient to render the best medical treatment to glioma patients in the future. Determination especially of MGMT promoter methylation status, IDH mutation, and LOH 1p/19q amongst others will have increasing influence on decision-making in order to meet the demand for more personalised treatment for glioma patients. Eur Assoc Neuro Oncol Mag 2014; 4 (3): 109–15.

Key words: glioblastoma multiforme (GBM), low-grade glioma (LGG), predictive and prognostic molecular markers, MGMT promoter methylation, IDH mutation, LOH 1p/19q, personalised therapy

Introduction

Numerous publications have underlined the importance of molecular genetic profiling in patients with gliomas [1–13]. Having been evaluated in several clinical studies as well as demonstrating predictive or prognostic value and the possibility to analyse them on a routine basis in a constantly increasing number of neuro-oncologic centres makes molecular markers now broadly available outside clinical trials. Nevertheless, there are also uncertainties about the predictive or prognostic impact of these markers in gliomas of different WHO grades and prediction for one special therapy may be difficult to follow in patients who receive several lines of therapy during the course of their disease on a regular basis. On the other hand, their relevance for decision-making is now constantly emerging with recent publications supporting the importance of MGMT promoter status especially in the elderly [9, 10, 14] or IDH mutation in malignant gliomas [6, 11] as well as LOH 1p/19q in patients with (anaplastic) oligodendroglial tumours [15, 16]. Therefore, this review focuses on these 3 markers and their impact on decision-making in the future.

Methylation of the O-Methylguanine-DNA Methyltransferase (MGMT) Promoter

MGMT is an enzyme which repairs DNA damage on the O-guanine position of the DNA caused by alkylating chemotherapeutic drugs like temozolomide (TMZ). Therefore, it has been concluded that epigenetic silencing of MGMT by hypermethylation of its promoter region on the DNA prevents MGMT synthesis, thereby giving the alkylating agent TMZ the opportunity to induce greater damage to tumour-cell DNA. An unmethylated MGMT promoter which does not interfere with MGMT synthesis would therefore act against chemotherapy (CT) by TMZ and combined treatment leading to worse response rates in these patients (Figure 1) [1, 17].

Methylation of the MGMT promoter stepped into the spotlight of neuro-oncology and glioma therapy when results of the landmark study of the European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC) were published in 2005.
[18], demonstrating that glioblastoma patients had significantly better median survival when treated with radiotherapy plus concomitant and adjuvant TMZ versus radiotherapy alone (14.6 vs 12.1 months). Even more interesting, patients with hypermethylation of the MGMT promoter were shown to have better survival rates with this combined treatment [1]. In the following years, these findings were verified several times and led to the conclusion that MGMT promoter methylation has to be considered as a predictive molecular marker for chemotherapy with alkylating agents like TMZ in patients with glioblastomas [1, 19]. On the other hand, in patients with anaplastic gliomas WHO grade III, methylation of the MGMT promoter was not predictive for CT with alkylating agents but had favourable prognostic impact independent of the applied treatment strategy [5, 20]. This somehow confusing fact may be in part explained by the different tumorigenic pathogeneses of anaplastic gliomas and primarily glioblastomas. Therefore, some authors have hypothesised that these differences might be responsible since anaplastic gliomas exhibit a higher rate of other favourable molecular markers like IDH mutation and its association with the cytosine-phosphatidyl-guanine (CpG) island methylator phenotype (CIMP) [21] or LOH 1p/19q [22]. Nevertheless, one has to keep in mind that patients > 65 or 70 years have often been excluded from many clinical trials in the past [23], which is also true for the EORTC/NCIC trial [18]. This is of importance since especially older patients often suffer from additional comorbidities and reduction of therapy-associated risks is mandatory. In elderly patients with diffuse GBM and methylated MGMT promoter, one might therefore consider giving TMZ without additional radiation therapy (RT) in order to avoid additional side effects. Different studies indeed provided evidence that elderly patients with GBM and methylated MGMT promoter have better prognoses when TMZ is applied, whereas patients with unmethylated MGMT promoter have better prognoses after RT [9, 24]. These data have now been confirmed by 2 large, randomised, controlled trials (NOA-08 and NORDIC) [10, 14]. While NOA-08 randomised patients > 65 years with malignant gliomas (anaplastic astrocytoma or glioblastoma) to either radiation therapy or dose-dense temozolomide (one week on, one week off), the NORDIC trial included only patients ≥ 60 years with newly diagnosed glioblastomas and randomised them to standard radiotherapy (60 Gy over 6 weeks), hypofractionated radiation (34 Gy over 2 weeks), or cyclic temozolomide (5/28 days, 200 mg/m²). In the NOA-08 trial, there was no statistical difference between both treatment groups and temozolomide was demonstrated not to be inferior to radiation therapy in this group of patients. Yet, it turned out that patients with methylated MGMT promoter status had longer overall survival (11.9 months) and showed longer event-free survival (EFS) when being treated with temozolomide (8.4 months) compared to radiation therapy (4.6 months). In comparison, patients with unmethylated MGMT promoter showed an overall survival of 8.2 months and EFS was longer if patients underwent radiotherapy (4.6 months) than with temozolomide (3.3 months). Consistent with these findings, the NORDIC trial demonstrated better prognosis for patients with methylated vs unmethylated MGMT promoter who were treated with temozolomide (9.7 vs 6.8 months) in contrast to treatment with radiotherapy (8.2 vs 7.0 months). Moreover, standard radiation was associated with worse overall survival compared to temozolomide or hypofractionated radiation therapy. Even if results from the comparison of combined radiochemotherapy to either treatment alone are still being analysed in an ongoing trial (NCT00482677), testing for MGMT promoter status has to be considered mandatory in elderly patients with malignant gliomas before deciding which therapy they should receive.

**Isocitrate Dehydrogenase (IDH) Mutations**

IDH is an enzyme of the Krebs cycle which leads to oxidative decarboxylation of isocitrate to α-ketoglutarate by generating NADPH from NADP⁺. While mutations of IDH1, which is present in the cytoplasm and peroxisomes, occur almost exclusively on the active binding site R132 (arginine), IDH2 is located in the mitochondria where it is involved in the Krebs cycle and shows mutations on the R172 arginine residue, which is the analogue to the R132 mutation of IDH1 [25, 26]. Genomic analyses recently demonstrated that mutations of IDH1 and IDH2 are almost exclusively present in WHO grade-II or -III astrocytomas and oligodendrogliomas or secondary GBM (ie, those that have emerged from low-grade astrocytomas), whereas ependymomas do not show IDH mutations and pilocytic astrocytomas only very rarely do [27–30]. Interestingly, the majority of low-grade astrocytomas with IDH mutation also display a mutation of the tumour suppressor gene TP53, whereas TP53 was only seldom found to be mutated unless IDH mutation was present. On the other hand, most oligodendrogliomas with IDH mutation also have a co-deletion of chromosomes 1p and 19q. Therefore, IDH mutation seems to be an early event in gliomagenesis which almost always precedes acquisition of TP53 in astrocytomas or LOH 1p/19q in oligodendrogliomas [31]. Moreover, patients with an IDH1 or IDH2 mutation have been shown to have a better prognosis and are substantially younger than those with the corresponding wild-type expression [4, 6, 32, 33]. For example, sequencing of the IDH1 gene at codon position 132 of 382 patients from the German Neuro-Oncology Group (NOA) 04 study and a prospective translational cohort of the German Glioma Network (GGN) revealed that 60 % of anaplastic astrocytomas and 7.2 % of glioblastomas carried an IDH1 mutation and that this was the most prominent single prognostic factor, even stronger than age, diagnosis, or MGMT methylation status [6]. This is remarkable since outcome analysis demonstrated that IDH mutation was significantly stronger than WHO grading and patients with anaplastic astrocytoma (AA) and IDH mutation had the most favourable prognosis, followed by GBM patients with IDH mutation who had an even more favourable prognosis than patients with AA and IDH wild type. Patients with GBM and IDH wild type experienced the worst prognosis. Furthermore, results from multivariate analysis indicated that most of the favourable prognostic effects of age may be due to the fact that IDH mutation was much more pronounced in younger patients [6]. Additionally, a recent report has demonstrated that GBM long-term survivors (> 36 months) have a significantly higher rate of IDH mutations (34 %) in contrast to patients with shorter survival (4.3 %). Again, these patients were younger and exhibited more often LOH 1p/19q or TP53 mutations.
than patients who had long-term survival but no IDH mutation [12]. Since these are typical genetic alterations found in WHO grade-II or -III astrocytomas or oligodendrogliomas as well as secondary GBM, there is now increasing evidence that this might define a special glioma subgroup with a particularly favourable prognosis.

The mechanism by which IDH mutations lead to a better prognosis has so far not been completely settled. It has been assumed that IDH-mutated enzymes might bind to IDH wild type which in turn reduces IDH activity and leads to higher amounts of isocitrate and lower amounts of α-ketoglutarate. Since α-ketoglutarate is a substrate for degradation of hypoxia-inducible factor (HIF), this might lead to larger amounts of HIF, which is known to have cancerogenic potential [34]. Newer data now indicate that the IDH mutation corresponds to a gain of function since α-ketoglutarate (αKG) can be transformed into 2-hydroxyglutarate (2HG) by mutated IDH. 2HG is a competitive inhibitor of αKG-dependent dioxygenases resulting in reduction of histone demethylases and TET hydroxylases, which in turn prevents histone demethylation and increases promoter methylation of certain genes including the MGMT promoter [12]. This explains why gliomas with IDH1/2 mutation exhibit the glioma-CpG island methylator phenotype (G-CIMP) [35]. However, it remains to be elucidated if reduction of α-ketoglutarate or elevation of 2-hydroxyglutarate is of more importance for the up-regulation of HIF-1α in glioma cells with IDH mutation [34, 36, 37].

Loss of Heterozygosity (LOH) on Chromosomes 1p and 19q

LOH 1p/19q is a chromosomal aberration which results from the co-deletion and unbalanced translocation of genetic material from chromosomes 1p and 19q and has been connected to oligodendroglial tumours [38, 39]. The tumourigenic mechanism with which LOH 1p/19q leads to tumour progression has not been elucidated so far. However, two tumour suppressor genes, CIC and FUBP-1, have been linked to this location but need to be further evaluated [21, 40]. Co-deletion of 1p and 19q is especially seen in WHO grade-II and -III oligodendrogliomas or oligoastrocytomas but rarely (approximately 5%) in GBM and a little more often (approximately 15%) in GBM with an oligodendroglial component [22, 41, 42], which has been defined as a separate entity in the current edition of the WHO classification of tumours [43].

Regarding clinical impact, co-deletion of 1p/19q has been connected to prolonged PFS and OS by several studies which has only recently presented long-term data. The Radiation Therapy Oncology Group (RTOG) 9402 study included patients with anaplastic oligodendrogliomas (AO) or mixed anaplastic oligoastrocytomas (AOA). Patients were randomised after surgery to either CT with procarbazine/lomustine/vincristine (PCV) followed by RT or to RT only. Long-term results showed that patients with AO or AOA and LOH 1p/19q had significantly longer OS if they received PCV + RT (14.7 years) or RT (7.3 years) than patients without 1p/19q co-deletion (2.6 and 2.7 years). Since survival was twice as high if patients with LOH 1p/19q received PCV + RT versus RT alone, combined therapy was assumed to be an effective treatment strategy for patients with AO or AOA, especially if they had additional LOH 1p/19q [15]. The EORTC 26951 trial included patients with newly diagnosed AO WHO grade III and randomised them either to RT or to RT plus adjuvant PCV chemotherapy [44]. Overall survival (OS) was prolonged for patients who received PCV in addition to RT (42.3 months) versus patients who had received RT alone (30.6 months). Patients with AO and additional co-deletion of 1p and 19q had better survival rates than patients without LOH 1p/19q and there was a trend towards combined chemoradiation (OS not

Table 1. Biological impact of the most important molecular markers in gliomas of different WHO grades. Co-deletion of chromosomes 1p/19q, IDH mutation as well as MGMT promoter methylation status have diverging (un-) favourable impact as well as prognostic or predictive value in gliomas of different WHO grades as demonstrated in this table.


<table>
<thead>
<tr>
<th>Glioma subtype</th>
<th>IDH mutation</th>
<th>LOH 1p/19q</th>
<th>MGMT promoter methylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological impact</td>
<td>Linked to DNA and histone methylation, energy metabolism, and pro-angiogenic pathways</td>
<td>Mode of action not elucidated yet; linked to oligodendroglial morphology</td>
<td>DNA repair enzyme</td>
</tr>
<tr>
<td>WHO grade II</td>
<td>Oligodendroglioma</td>
<td>Favourable</td>
<td>Significance unclear, probably favourable</td>
</tr>
<tr>
<td>Diffuse astrocytoma</td>
<td></td>
<td></td>
<td>Seldom present</td>
</tr>
<tr>
<td>WHO grade III</td>
<td>Anaplastic oligodendroglioma</td>
<td>Favourable in patients treated with either radiation and/or chemotherapy</td>
<td>Favourable in patients treated with radiation and/or chemotherapy; predictive for benefit from addition of PCV to radiation</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td></td>
<td></td>
<td>Seldom present</td>
</tr>
<tr>
<td>WHO grade IV</td>
<td>Primary glioblastoma</td>
<td>Rarely present, suggestive of sGBM</td>
<td>Rarely present, significance unclear</td>
</tr>
<tr>
<td>Secondary glioblastoma</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

sGBM: secondary glioblastoma multiforme; PCV: procarbazine/lomustine/vincristine
yet reached after 140 months median follow-up) compared to RT alone (112 months) in these patients [16, 45]. Additionally, the NOA-04 study also included patients with anaplastic gliomas (WHO grade III) and randomised them into 3 different treatment groups: (1) RT, (2) PCV chemotherapy, or (3) TMZ chemotherapy. In case of toxicity or progression, patients were transferred from RT to CT with either PCV or TMZ and from both CT regimens to RT in a cross-over study design. The present analysis once again resulted in better prognosis for patients with LOH 1p/19q in contrast to patients without this co-deletion but so far there is no difference between treatment groups regarding PFS and OS [5]. Yet, in light of both aforementioned studies, the current follow-up period is considered possibly too short for final evaluation of prediction to different treatment options (Table 1) [21].

**Interdependence of Molecular Markers**

MGMT promoter methylation, IDH mutation, and 1p/19q co-deletion have been demonstrated to have their own prognostic or predictive value in different glioma subtypes. Yet, there is growing evidence of an interrelation of these markers, even if the mechanisms responsible for it have not been completely elucidated so far.

IDH mutation is an early event in gliomagenesis and seems to occur before co-deletion of chromosomes 1p and 19q in oligodendrogliomas or TP53 mutation in astrocytomas (Figure 2) [46]. While LOH 1p/19q has been linked to better treatment response to chemotherapy in oligodendrogliomas, its prognostic relevance in WHO grade-II or -III oligodendrogliomas or glioblastomas with oligodendrogial components has not been clarified so far. On the other hand, IDH1 mutation has been associated with better prognosis in malignant gliomas WHO grades III and IV but not in diffuse low-grade gliomas WHO grade II; at least not until tumour progression and intervention with radiation or chemotherapy [11]. Moreover, after screen-
spond to neoadjuvant chemotherapy, allowing for a higher extent of surgical resection afterwards [53].

Since test validity is of great importance in order to provide the clinician with reliable information [54], this will also have large impact on the diagnostic routine of neuropathologists. Some additional markers have already been linked to prognostic relevance and may be helpful to discover which patients qualify for certain therapies. Unfavourable prognostic impact for PFS and OS has been demonstrated for low-grade astrocytomas and oligoastrocytomas grade II if TP53 mutation status is present [55]. Since mutations of TP53 and its pathway appear very early in the tumourigenesis of glial tumours [56] they are also present in approximately 65 % of secondary GBM but only in 30 % of primary GBM [57, 58]. Furthermore, almost 40 % of patients with primary GBM show amplification of the endothelial growth factor receptor (EGFR) but patients with secondary GBM only rarely do [57]. Apart from wild-type EGFR, there is a high expression of mutant EGFRvIII, which has been demonstrated to show high tumourigenic activity [59]. Signal transduction of EGFR and its mutant EGFRvIII include RAS, NF1, PTEN, PI3K as well as AKT and the mammalian target of rapamycin (mTOR) [58], some of which have already been identified as possible targets for new therapies [60, 61]. Apart from genetic alterations, there has also been an intention to deliver targeted therapies, eg, against vascular endothelial growth factor (VEGF), α, β, integrin, or the extracellular matrix protein tenascin, for selective antiangiogenic or radioimmunotherapy to GBM patients [62–65]. With emerging techniques for extensive genetic or protein profiling via microarray analysis, TP53, EGFR/EGFRvIII, and other signal transduction molecules may only be a small number of possible targets for novel treatment. Therefore, expression profiling for additional possible targets may become relevant in the future.

Definition of radiation volumes will have to be adjusted in light of all available information since recurrence pattern after radiochemotherapy in glioblastoma patients may be influenced by MGMT promoter status [66]. Therefore, requirements for neuroradiologists will increase in the future. The question of pseudo-progression in patients with methylated MGMT promoter [67] or imaging alteration after anti-angiogenic therapy [68] resulted in new criteria which have been recommended by the Response Assessment in Neurooncology Working Group (RANO) in order to deal with these problems [69–71].

Discrimination between treatment response and real tumour recurrence/progression may be achieved by positron emission tomography (PET) additionally to standard MRI [72]. New tracers in nuclear medicine might help to identify molecular marker profiles non-invasively in order to select patients most suitable for certain therapies (eg, integrins) [73] or analysis of proliferation or cellular turnover [72, 74].

At present, identification of MGMT promoter status in the elderly is important for all neuro-oncologists in order to include this information into decision-making since recent data from prospective and randomised trials clearly favour TMZ chemotherapy alone or in combination with radiotherapy in case of methylated MGMT promoter and radiotherapy only in patients with unmethylated MGMT promoter [10, 14]. In the future, LOH 1p/19q analysis might be crucial in order to select patients with anaplastic oligodendrogliomas or oligoastrocytomas who might profit from (PCV) chemotherapy [10, 15, 16, 75]. An increasing number of clinical trials already randomise patients depending on their MGMT promoter methylation status [76–78]. Therefore, at least stratification for molecular markers will be of increasing importance also in upcoming trials to get unbiased results. On the other hand, the issue will be which biomarkers have to be considered without reducing statistical power by subdividing treatment arms into too-small groups.

Conclusion

Histopathological diagnosis of gliomas based to the WHO criteria will not be sufficient in the future to allocate patients into the best available treatment group. Patient prognosis is also influenced by age, neurological performance status, imaging features, extent of resection, and the molecular genetic signature of these tumours.

MGMT promoter methylation has turned out to be an important predictive marker for chemotherapy in patients with glioblastomas and especially elderly patients profit from treatment adjustment according to the MGMT promoter status favouring chemotherapy in methylated and radiotherapy in unmethylated MGMT promoter cases. IDH mutation is an important prognostic factor, which groups prognostically favourable patients with malignant gliomas. Even if it is not predictive for a certain therapeutic scheme, its knowledge may be of importance in cases of doubt, where more aggressive treatment may be considered for patients with IDH wild type. Co-deletion of 1p/19q should be determined at least in patients with WHO grades II and III, where LOH 1p/19q will be necessary to identify which patients qualify for (additional) chemotherapy with PCV or other agents like TMZ.

Besides the determination of the MGMT gene promoter methylation status, IDH mutation, and LOH 1p/19q, there might be other factors to analyse in the future and the question will be, which markers are most likely to achieve clinical relevance next. For example, several trials have already tried to determine the impact of EGFRvIII inhibition in glioblastoma patients. Despite controversial results, a large international trial is currently ongoing, using vaccination against EGFRvIII as a novel strategy in these patients (ACT IV). Furthermore, as already mentioned, the interdependence of already known as well as possible upcoming markers will have to be elucidated in more detail in the future. Modern personalised treatment concepts in neuro-oncology will have to take these into account in order to provide the best possible care for patients. The primary target in the treatment of gliomas will therefore not be to define one overall standard for each WHO grade which has to be rendered to every patient, but to expand our toolbox of possible therapies to choose the particular therapy that suits the individual patient best. Hence, our current and future knowledge of molecular markers will help to develop more personalised treatment concepts for our patients.
Conflict of Interest
None.

References:
Impact of Molecular Markers On Personalised-Treatment Concepts in Gliomas

Patients with glioblastoma is influenced by MGMT methylation status. Radiother Oncol 2012; 104: 78–82.
**Introduction**

The first clinical trial of boron neutron capture therapy (BNCT) for brain tumours was performed in the 1950s using a research reactor in the United States [1–3]. Although glioblastoma (malignant glioma WHO grade 4; GBM) has been a candidate for BNCT for more than 60 years [4–12], BNCT for GBM has not become widely accepted for complex and diverse reasons. Over 900 patients have undergone BNCT worldwide and the radiobiological effects of BNCT on malignant tumours and normal surrounding tissue seemed to be established. However, all previous trials of BNCT for brain tumours had small patient series (Table 1) and used different treatment systems (ie, the neutron source and boron agents).

In addition, at present, the only neutron source suitable for BNCT is a nuclear research reactor. In Japan, to maintain safety standards at each nuclear reactor, the reactor must be shut down for several months each year and thus cannot be used for BNCT during that period. Research reactors require costly maintenance and adequate manpower, and the issue of nuclear fuel recycling is a worldwide problem. Moreover, the boron agents required for clinical trials are reagent products that require their own clinical trials to be certified as medical drugs.

We focused on clinical trials for glioblastoma and provide an overview of BNCT based on our BNCT experiences at the Japan Research Reactor No 4 (JRR-4) with a discussion of our new protocol and thoughts about the future of BNCT.

**Principles of BNCT**

BNCT ideally damages only boron-accumulating cells. Preloaded $^{10}$B, which is a non-radioactive isotope of boron, and low-energy thermal neutrons make the nuclear reaction notation $^{10}$B(n, α) $^7$Li, which releases the high linear energy transfer of α particles and $^7$Li particles with a short path-length as cell diameter (Figure 1). Therefore, the cell-killing effect would be distributed only around the boron atoms. The effectiveness of BNCT depends on the boron distribution and the concentration ratio between normal tissue and tumour tissue, and on the neutron-beam permeability.

**Materials and Methods**

**Neutron Source:** Japan Research Reactor No 4 JRR-4 is a light-water-moderated and -cooled enriched-uranium swimming pool-style reactor that uses ETR-type fuel. Modification of JRR-4 for core conversion began in 1996, and a medical irradiation facility was installed for BNCT and the reactor was adopted to generate epithermal as well as thermal beams. The BNCT facilities are a neutron beam system, which can be used with thermal and epithermal neutrons and their mix-beam, a wide irradiation room, an irradiation monitoring system, and a fully equipped operation room for craniotomies and setting simulations. The neutron beam spectrum can be changed by D$_2$O thickness in a heavy-water tank with a cadmium shutter [4].

We started clinical BNCT trials in 1998 at JRR-4 with the thermal neutron beam [5]. In this trial (protocol II), each patient receives general anaesthesia and intraoperative neutron irradiation is performed. At the later stage of intraoperative BNCT (since 1999), we used the epithermal beam mode. The epithelial neutron beam penetrates to deeper lesions compared to the thermal beam, and it thermalises in the tissue; the use of the epithelial beam thus improved neutron distribution at deep lesions.
Using a pre-treatment simulation, we started a new protocol of non-craniotomy BNCT. However, in December 2007, a crack in a graphite reflector of the reactor core was found on a weld of the aluminium cladding. JRR-4 was stopped until February 2010 for replacement of the graphite reflector. After restarting BNCT in 2010, we treated 3 patients (with newly diagnosed GBM, recurrent GBM, and malignant meningioma, respectively) under the new protocol. Because of the March 2011 East Japan earthquake and tsunami, JRR-4 was stopped again with no prospect of restarting.

**Design of Our Clinical Trial**

The BNCT protocols were approved by the Medical Ethics Committee of the University of Tsukuba, and all participating patients were fully informed and provided their written informed consent. Table 2 summarises the changes in protocol. The later stages of this trial (protocols III and IV) were registered with the Japanese authority on clinical trial registration (ie, the University Hospital Medical Information Network Clinical Trial Registry: UMIN-CTR; trial IDs: C000000298, UMIN000003984, and UMIN000003692). The concept of our clinical trial was a phase-I/II study for newly diagnosed GBM. The primary endpoints were safety and dose distribution to the tumour evaluated in GBM patients who were treated with BNCT, secondary endpoint was the survival benefit. Yamamoto et al described the details of clinical trials IIs and III in 2009 [6]. After the restart of JRR-4 in 2010, we started up new protocols (protocols IV and IVr) and 3 patients were treated.
Table 2. BNCT protocols for malignant glioma by the University of Tsukuba.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Period</th>
<th>Tumour grade (WHO)</th>
<th>Beam</th>
<th>Operation</th>
<th>Dose estimation</th>
<th>Boron agents</th>
<th>Additional external radiotherapy</th>
<th>n (WHO IV/total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>1999–2002</td>
<td>III, IV</td>
<td>Epithermal</td>
<td>+</td>
<td>JCDS</td>
<td>BSH 5 g/body</td>
<td>–</td>
<td>2/3</td>
</tr>
<tr>
<td>III</td>
<td>2003–2004</td>
<td>IV</td>
<td>Epithermal</td>
<td>–</td>
<td>JCDS</td>
<td>BSH 5 g/body + BPA 250 mg/kg</td>
<td>30 Gy/15 fr</td>
<td>8/8</td>
</tr>
<tr>
<td>IIIr</td>
<td>2005–2007</td>
<td>IV rec</td>
<td>Epithermal</td>
<td>–</td>
<td>JCDS</td>
<td>BSH 5 g/body</td>
<td>–</td>
<td>3/3</td>
</tr>
<tr>
<td>IV</td>
<td>2010</td>
<td>IV</td>
<td>Epithermal</td>
<td>–</td>
<td>JCDS</td>
<td>BPA 250 mg/kg</td>
<td>40 Gy/20 fr</td>
<td>1/1</td>
</tr>
<tr>
<td>IVr</td>
<td>2010</td>
<td>IV rec</td>
<td>Epithermal</td>
<td>–</td>
<td>JCDS</td>
<td>BPA 250 mg/kg</td>
<td>–</td>
<td>1/1</td>
</tr>
</tbody>
</table>

JCDS: JAERI-computed dosimetry system; IV rec: Patients of grade-IV recurrence or malignant transformation pathologically proven by surgical specimens; BPA: boronophenylalanine; BSH: sodium mercaptoundecahydro-closo-dodecaborate; fr: fraction

Inclusion criteria for newly diagnosed GBM were met by patients who had supratentorial unilateral tumours, located no deeper than 7 cm from the brain surface, with a Karnofsky Performance Status (KPS) ≥ 50, who had undergone neither previous chemotherapy or radiotherapy nor previous therapy for any other cancers, and who had no allergy to sodium borocaptate (BSH) or p-dihydroxyboryl-phenylalanine (BPA), and no previous malignancy. Patients with tumour dissemination were excluded. For recurrent cases, almost the same criteria were adopted, but a history of radiotherapy or chemotherapy was accepted. 17 GBM patients were enrolled in the clinical trial.

From the start of protocol III, newly diagnosed patients were treated with additional conventional radiotherapy. Radiotherapy was started within 2 weeks after BNCT and consisted of fractionated focal irradiation at a dose of 30 Gy delivered in 15 fractions of 2 Gy over a 3-week term. The most recently used protocol, IV, permits additional conventional radiotherapy at a dose of 40 Gy delivered in 20 fractions of 2 Gy and the concomitant use of temozolomide (TMZ) while not using BSH infusions. Protocols IIIr and IVr were treatments for recurrent or regrowing GBM patients. These are corresponding to protocols III and IV, respectively, except for previous radiochemotherapy in the inclusion criteria. Additional post-BNCT X-ray radiotherapy was abbreviated in protocols IIIr and IVr.

Boron Compounds

Two boron compounds are used clinically in BNCT. Their chemical structures are shown in Figure 1C. First, we use sodium mercaptoundecahydro-closo-dodecaborate Na₂B₁₂H₁₁SH (BSH). BSH distributes only through the fragile tumour vessels and cannot pass the normal blood-brain barrier. Twelve hours prior to neutron irradiation, 5 g of BSH is dissolved in 500 ml normal saline and given to the patient in a 1-h intravenous infusion. The tumour/blood boron concentration ratio was not high in our patient series (n = 15), but no adverse event related to BSH infusion was reported.

Next we tried the combined use of 2 drugs in protocol III, BSH and BPA, to improve the boron concentration of the target lesion. 90 minutes prior to neutron irradiation, dissolved BPA-fructose complex was given. Active tumour cells accumulate the BPA for protein synthesis as an amino-acid analogue. The most recent protocol IV used BPA only because we add X-ray external irradiation after the BNCT, and this protocol may have an effect equal to that of the non-selective boron dose.

BSH was purchased from Katchem spol. (Prague, Czech Republic), and BPA was purchased from Interpharma Praha (Prague, Czech Republic) or Stella Pharma Corp (Osaka, Japan).

Treatment-Planning System

We calculated the photon-equivalent BNCT dose by multiplying the weighting factors. We detected the thermal neutron dose by radio-activation methods with gold wire or foil placed into the operative field during craniotomy for neutron radiation. The gold wire measured radioactivity and was pulled out during or after radiation. It reflected thermal neutron fluence at the lesion. Once epithermal neutrons were introduced, BNCT was performed without craniotomy. Therefore, we cannot directly measure the neutron dose at the tumour site by gold-wire activation. To evaluate the normal and target doses a treatment planning system for BNCT was required. Previously, several systems were used for BNCT treatment planning [7, 8]. Kumada et al released the JAERI computational dosimetry system (JCDS) for clinical epithermal beam BNCT [9, 10]. The most useful point of the JCDS system was that it was manufactured by the researchers and a new version can be created for development [11, 12].

The JCDS generates a 3-D volume of data for each patient; based on the CT scan, the tissue is automatically divided into soft tissue, bone, and air. The material data of each composition have been defined by the International Commission on Radiation Units (ICRU).

The medical team defines the region of interest (ROI) of the lesions and surrounding critical organs as well as the ideal incident direction of the neutron beam. After defining the boron-related parameters including the predictive average tumour and normal boron concentrations, the relative biological effectiveness, and the limiting dose of normal surrounding tissue, the JCDS calculates the dose with a particle transport simulation – for example, using the MCNP code with the Monte-Carlo method.

The output from the JCDS can display the dose-volume histogram, the isodose contour image, which contains the boron-
related dose, and the boron-unrelated dose. The boron-unrelated dose includes the “nitrogen dose” from the interaction with nitrogen in the tissue, the “gamma-ray dose” consisting of the primary gamma-ray dose transported from the reactor core, and the secondary gamma-ray dose induced by the reaction in the tissue. The fast neutrons induce the “fast-neutron dose” by the proton recoil reaction with hydrogen nuclei.

The BNCT dose was calculated by multiplying the weighted factors to account for the radiobiological effect of the high-LET dose. There are still unsolved problems regarding the estimation of the true radiation effect because the tumour tissue is heterogeneous, and different microdistributions of boron around and in the tumour cells influence the effectiveness. The prediction of tumour boron concentration from the blood boron concentration and PET images could not reflect this heterogeneity on boron microdistributions. Hence, the tumour dose calculated here may be overestimated since there is a part of the tumour with lower boron concentration.

Estimation of Boron Concentration and Patient Position During and After Neutron Irradiation
The JCDS can compensate for the patient’s position with 3-D geometry position data. In our protocols, blood sampling was conducted right before and after irradiation; boron concentration of the whole blood was analysed by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) and confirmed by prompt gamma ray analysis (PGA). We confirmed the patient’s final maximum normal brain dose after confirmation of the blood boron concentration and geometrical data. Later protocols permitted the performance of 18F-labelled BPA positron emission tomography (PET) [40, 41] to determine the lesion-to-normal ratio of BPA-mediated 10B for estimating the BPA-mediated tumour dose.

Irradiation Set-Up (of Protocols III and IV)
JRR-4 is located approximately 60 km from the University of Tsukuba Hospital. At the hospital, the patient is administered intravenous BSH 24 h prior to the predicted irradiation start time. An ambulance with the medical team takes the patient to JRR-4. At JRR-4, to reduce exposure, the patient position setting is done at a radiation port model, and intravenous BPA administration is initiated 1.5 h before the start of neutron irradiation. A blood sample is taken, and an electrocardiogram monitor, blood oxygen saturation monitor, and drip infusion unit are implemented. After the patient enters the irradiation room, the 3-dimensional coordinates of the patient’s head are set and recorded. By monitoring the output of the reactor and the blood
BNCT for Glioblastoma: A Phase-I/II Clinical Trial at JRR-4

Figure 2. (a) Serial MRI image of the GBM patient treated with protocol IV. The scalp was unremarkable. Hair loss continued for more than 1 year. (b) Recurrent GBM patient who underwent BNCT after 60-Gy irradiation. The tumour was stable for more than 3 years.

boron concentration just before irradiation, we decide on the radiation time so that the normal surrounding-brain dose is less than 12 Gy-Eq.

Clinical Follow-Up
All 17 patients were carefully followed up every 1–3 months by means of neurological examinations and MRI imaging. The time to progression and overall survival (OS) were determined. Adverse events were recorded with grading by the National Cancer Institute Common Toxicity Criteria Versions 2 and 3. The patients were treated with nimustine- (ACNU-) based chemotherapy as a general rule during the follow-up period. No patient had been treated with TMZ before tumour regrowth, except for one treated under protocol IV.

Results
The patients’ characteristics and average boron concentrations, calculated tumour and normal brain doses are shown in Table 3. The data of 15 patients with newly diagnosed GBM were retrospectively analysed [6].

Adverse Events
Only 2 of the newly diagnosed GBM patients suffered an acute adverse event beyond grade 2. One protocol-III patient suffered transient orbital swelling accompanied by double vision (grade 2); one of the protocol-I patients suffered post-epileptic brain swelling (grade 4) requiring surgical intervention. We had some grade-1 adverse events of redness, fever, and itching in protocols I and II.

Boron Concentration
Patients provided as many as 7–10 blood samples before and after irradiation. Both concentrations (boron from BSH and boron from BPA) were predicted from the time course of the boron concentration curve. Average blood boron concentra-

tion from the predicted BSH and BPA concentrations was 34.6 ± 9.6 μg/g for BSH and 17.4 ± 2.4 μg/g for BPA (protocol III, n = 8).

Dose Estimation
In protocol I, the neutron dose was analysed with a gold radio-activation method using fine gold wires. We placed the gold wire on the surface of the brain and in the surgical cavity during craniotomy, but the spatial resolution of the measurement point was > 5 mm. The peak dose of the treatment field is described in Table 3. The maximum normal brain dose of protocols I and II was 29.4 ± 6.0 Gy-Eq (n = 7, range 20.1–36.0).

In protocols II–IV, as described in the treatment planning system, the boron dose and the non-boron dose were summed and converted to the equivalent dose of 2-Gy-fraction conventional radiotherapy. The maximum normal brain and skin doses were 11.4 ± 1.5 Gy-Eq. The minimum tumour dose of the clinical target volume (CTV –2 cm) was 15.1 ± 5.4 Gy-Eq.

A Protocol-IV Case
The 40-year old male patient had suffered from severe headaches due to increased intracranial pressure. Emergency left-temporal tumour removal was performed and the pathological specimen revealed a GBM. Two months after surgery, BNCT was performed. The average blood boron concentration was 12.6 μg/ml, the maximum skin dose was 9.8 Gy, and the normal brain dose was 11.7 Gy. The minimum target (GTV + 2 cm) dose was 11.2 Gy. After BNCT, he received 40 Gy of 20 fractionated external photon irradiations instead of a BSH-induced boron dose. The serial MRI scan is shown in Figure 2. The tumour was controlled for 1 year, but outfield tumour growth resulted in his death 19.9 months after BNCT. Normal brain tissue tolerated this protocol. The effect of the protocol on the patient’s scalp was unremarkable, but loss of hair remained for more than 1 year.

Protocol-IVr Case
The 53-year old male patient had a tumour in the left-temporal lobe removed with the pathological diagnosis being GBM. At a deep part of the surgical defect, there was a residual tumour growing during postoperative radiation and concomitant temozolomide treatment. He was referred to our hospital for additional BNCT, which was performed 4 months after initial surgery, using BPA only. Average blood boron concentration was 13.7 μg/ml, maximum skin dose was 8.4 Gy, and normal brain dose was 10.5 Gy. Minimum target (GTV + 2 cm) dose was 15.9 Gy. The serial MRI image is shown in Figure 2B. The patient underwent skin and muscle transplantation due to infection and necrosis, but more than 3 years after BNCT, the MRI image of the tumour and his performance status were stable.

OS of Newly Diagnosed GBM
Median overall survival (mOS) of GBM patients has already been reported [34]. In our series, mOS was 22.3 months for grade-4 patients (protocols I, II, III, and IV; n = 16). The Kaplan-Meyer curve is given in Figure 3. The longest mOS was that obtained in protocol III (n = 8) alone, which was 27.1 months.
Discussion

In our case series, we selected patients with shallow glioblastoma and KPS > 50%. During the protocol-III period, about ¼ of the GBM patients underwent BNCT, and another ¼ underwent proton radiotherapy. The remaining half were treated by conventional radiotherapy. We have reported that the positive effect of BNCT and proton treatment is unlikely to reflect patient selection alone in our serial case series [6], and overall survival of a particle therapy group was 24.4 months (95%-CI: 18.2–30.5 months) compared with 14.2 months (95%-CI: 10.0–18.3 months) for those treated with conventional radiotherapy. This survival difference between the conventional treatment group and the high-dose particle radiation group suggests that our case selection was appropriate.

Among the 15 selected GBM cases, we observed one long-term survivor who did not develop a recurrence over a period of > 5 years. She has shown no symptoms and takes no medication. Even if a statistically significant difference is not revealed in the entire series, curing GBM is possible by choosing the cases appropriately.

GBM is the most common and invasive form of malignant glioma. The Japanese tumour registry indicates that the 1-year survival rate for GBM is 55.1%, and the 5-year survival rate is 6.9%. This data was collected before the approval of temozolomide, and recent data would be pre-analytical. Randomised clinical trials for GBM patients have been initiated; for example, a search of clinicaltrials.gov revealed 829 trials for glioblastoma but only 45 trials with results. This illustrates that the difficulty in completing a clinical trial for GBM patients is due to the onset frequency and the limited number of patients.

Randomised controlled trials for GBM indicate that at least several hundred cases would be necessary to statistically prove the effectiveness of new chemoradiotherapy. Because reactor-based BNCT can be conducted only at a few sites around the world, it is challenging to enroll the necessary hundreds of GBM cases in order to perform randomised controlled trials and test the effectiveness of BCNT for this disease. Moreover, primary brain tumours are an “orphan disease” as the Japanese brain tumour registry revealed an annual incidence of primary brain tumours of approximately 12–15 cases per 100,000 persons and a 9.1% rate of primal brain tumours for GBM [42].

Other BNCT Trials for Glioblastoma

Previous BNCT clinical trials for glioma are summarised in Table 1. Kyoto University and Osaka Medical School carried out clinical trials with modern BNCT techniques. They used 100 mg/kg BSH and 700 mg/kg BPA with a 6-h infusion, and the patients also received an X-ray boost. MOS was 23.5 months following diagnosis [29, 43, 44].

Kankaanranta et al at the Helsinki University Central Hospital and the VTT Technical Research Center of Finland performed BNCT for GBM and recurrent GBM, using 290 mg/kg BPA or 450 mg/kg; the reported survival was 13.4 months and 21.9 months, respectively [27]. The European Organization for Research and Treatment of Cancer carried out a phase-I study of BSH-based BNCT (protocol #11961). They reported the toxicity of BSH-based BNCT, cerebral atrophy, and white-matter abnormalities [25, 45, 46]. A group in Sweden used 900 mg/kg BPA for a 6-h infusion. MOS for their 29 patients was 14.2 months [36, 37]. All of these clinical trials were carried out with very small numbers of patients and the patients were selected cases. It is thus difficult to compare these results with historical or standard therapy data.

Developing Accelerator-Based BNCT

If there are many target patients, treatment throughput is very inefficient with reactor-based BNCT because of difficulties in enrolling the treatment. It is difficult to market medical equipment using a nuclear reactor in Japan, but the development of the accelerator neutron source is of greater concern. Although the accelerator neutron source presents the issues of the heat-treatment of the target and radio-activation of the facilities, a clinical treatment facility was built by Kyoto University, and a phase-I clinical trial is ongoing at the facility.
We are also developing a new neutron source. The conceptual design of the neutron generator of this Linac-based BNCT facility at the University of Tsukuba is as follows:

1. Proton energy is 8 MeV, and the average proton current is set to 10 mA.
2. A RFQ and DTL-type Linac is used as the proton accelerator of the BNCT device. Figure 4 shows a schematic drawing of the Linac-based BNCT device and photographs of the RFQ, DLT, and Klystron.
3. The design uses 0.5-mm beryllium as the neutron target material and a copper plate is located on the back-side of the thin beryllium plate as a heat sink.
4. The neutron transport device consists of a fast neutron filter; the moderator, collimator, and radiation shield were determined. In addition, a simulation calculated that the neutron generator can emit high-flux neutrons (> 2.0 n/cm²/s) at the beam port.

After the entire system is installed, the intensity allows the performance of BNCT irradiation within 15 min. The entire treatment system is small enough to build in-hospital. According to the current schedule, the first clinical trial using the Linac-based BNCT facility will be performed in 2015.

There is a possibility for medical-equipment marketing with a treatment system for in-hospital facilities such as proton-beam.

**Development of Boron Agents**

BPA and BSH may not be the best drugs for use in BNCT and the compound itself showed no treatment effect. Previous clinical trials revealed some adverse events such as urine crystallisation and acute renal dysfunction with BPA at a dose of 700–900 mg/kg. Safer and more effective new boron compounds are eagerly awaited but the dose remains a question; several grams of boron compounds with a one-shot intravenous administration were a stringent condition in previous trials. The most important requirement for the clinical dose is safety.

BNCT must achieve clinical usefulness in order to develop and establish effective small molecular boron compounds [47] or boronated nanoparticles using drug delivery system technology [48, 49]. We must first confirm the effectiveness of the pre-existing compounds and begin high-throughput clinical trials or approved treatment.

BNCT has the potential to be a standard treatment modality for GBM patients, but first BNCT’s superiority over conventional radiotherapy must be investigated. Radiotherapy for GBM is effective at a dose of ≥ 45 Gy. High-dose treatment such as that provided by a 3-dimensional conformal beam [50], intensity-modulated radiation therapy (IMRT), or gamma knife can send a high dose to a localised lesion, but healing is not ensured [51, 52]. To assess the efficacy of cell-selective treatment for GBM, it must be determined whether boron is taken in the forefront of the invading tumour nest. Randomised control studies comparing BNCT with conventional radiation treatment are required. However, it is also necessary to lead and to develop a practical treatment system that includes a boron compound supply, an easily manageable neutron source in the brain, and a treatment-planning system that is easy for radiation oncologists to use.

**Conclusions**

Our clinical trial for BNCT for glioblastoma patients showed promising survival benefits. BNCT presents a difficulty as a high-throughput treatment, and thus the studies of BNCT clinical treatment have all used small case series. To overcome these difficulties we look forward to the development of accelerator-based BNCT.

**Conflict of Interest**

The authors have no conflicts of interest to report.


Case Report

An 11-year-old girl visited the Department of Neurology, complaining of increased frequency of complex partial seizures. She had an 8-years history of partial epilepsy.

Neurological examination showed no focal or false-localizing signs. Examination of other systems was unremarkable. A magnetic resonance imaging (MRI) revealed a well-circumscribed right-sided frontal lesion. The lesion was diffusely hyperintense on T1- and T2-weighted images and did not exhibit significant enhancement after Gadolinium administration (Fig. 1A and C). Electroencephalography (EEG) was characteristic with focal epileptic changes in the right frontal region. The index of epileptic discharges was approximately unchanged. Brain 18FDG-positron emission tomography (PET) showed a diffuse hypometabolism of the lesion as it is observed in low-grade tumors (Fig. 1B). Hypometabolism may also show the epileptic focus because PET scan is a good interictal method to localized epileptic foci. **En-bloc** resection of the right superior frontal gyrus was performed. The resection included the tumor and the surrounding cortex.

The patient remained free from seizures with antiepileptic medications and showed no evidence of tumor recurrence 6 months later.

**Diagnosis**

Angiocentric glioma.

Histopathological examination revealed a tumoral proliferation compound of spindle-shaped cells with palisade arrangements (Fig. 2A) and formation of perivascular rosettes (Fig. 2B). Tumor cells have small, round and regular nuclei with fine chromatin without atypia or mitosis.

On immunohistochemistry, the neoplastic cells strongly expressed GFAP (Fig. 2C) and characterized by cytoplasmic dot-
like staining of EMA (epithelial membrane antigen). The Ki-67 labeling index was less than 1% throughout the specimen.

**Comments**

The last revised WHO Classification of Tumors of Nervous System (WHO 2007) has introduced this new tumor type and is now included under the category “Other Neuroepithelial Tumors”.

Angiocentric glioma is a rare and slow-growing cerebral hemispheric tumor arising preferably in children and young adults. Approximately 65 cases have been reported in the literature. Presenting symptom is seizure and patients are all intractable to antiepileptic medications. The second most common symptom is headache.

Radiologically, this tumor is solid and well-circumscribed and is generally localized in the cortex of frontal lobe. On MRI, angiocentric glioma appears hypointense on T2-weighted images and FLAIR-hyperintense. This lesion lacks enhancement following contrast administration. Calcifications are rare.

Histologically, they are characterized by monomorphous, bipolar glial tumor cells oriented along vascular structures. The nuclei of tumor cells are slender with stippled granular chromatin. This lesion does not present high-grade features such as elevated mitotic activity, necrosis and endothelial proliferation.

Cortical dysplasia, associated with other epileptogenic tumors, such as ganglioglioma and dysembryoplastic neuroepithelial tumor, has not been reported in angiocentric glioma.

Immunohistochemically, tumor cells express GFAP, S-100 protein, vimentin and EMA with a dot-like pattern but do not express neuronal markers. Ki-67 labeling index is less than 5%.

Prior to other epilepsy-associated tumors such as ganglioglioma and pleomorphic xanthoastrocytoma, there is no mutation of BRAF gene in angiocentric glioma. Indeed, one recent study failed to reveal any BRAF mutation in three cases and another did not evidence any expression of BRAF V600E on immunohistochemistry in nine tested cases.

Their precise histogenesis remains unclear. Based on the cytology, morphology and immunohistochemistry, ependymal derivation has been postulated.

The treatment of choice is total resection. The prognosis of this tumor is favorable if totally resected. Gross total resection
leads to children becoming seizure free in all documented cases of the literature. Nevertheless, postoperative seizure freedom is not achieved in most of cases with subtotal resection. No recurrence and progression has been reported after gross total or subtotal removal of tumor, except for one patient who died of tumor progression. There are no reported cases of malignant transformation.

References:


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Demystifying Palliative Care

Kathy Oliver

According to the New England Journal of Medicine, palliative care has “an identity problem” [1]. If you ask the man in the street about palliative care, he will most likely say: “It means you’re dying.” An article in the US National Pain Report (sponsored by the National Pain Foundation) talks about palliative care as part of a “conspiracy of silence” [2]. A 2011 national survey of 800 adults in the United States found that 70% were “not at all knowledgeable” about palliative care [3]. And when palliative care is mentioned to them, the first reaction of many people with a life-threatening illness is often one of fear, because it is associated in their minds with the end of life.

Palliative care: perceptions are confused

Public awareness of palliative care – what it is and where and when it should be optimally provided – is, at best, confused. The WHO definition explains that palliative care “… is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.” [4]

In the survey mentioned above, palliative care is further defined as “… specialized medical care for people with serious illnesses. This type of care is focused on providing patients with relief from the symptoms, pain and stress of a serious illness – whatever the diagnosis … Palliative care is appropriate at any age and at any stage in a serious illness, and can be provided together with curative treatment.” [5]

Yet the popular belief is often that palliative care is singularly associated with death and dying. While palliative care certainly plays a critically important role at the end of life, good palliative care is also very relevant to many earlier stages of a disease trajectory, often a considerable time before death is approaching.

The understanding of palliative care amongst healthcare professionals also seems confused. Some physicians asked about the definition of palliative care in connection with the US survey responded: “[Palliative care is] comfort care during one’s last few weeks of life to allow patients to pass in comfort and dignity.” “Palliative care is helping families to give them comfort and options for what to do at their loved one’s end of life.”

Palliative care for the whole brain tumour journey

In reality, palliative care is not just for people who are dying. Effective anti-epilepsy medication for brain tumour patients with seizures, for example, is palliative care. Help in coping with fatigue is palliative care. Psychological support to combat anxiety and depression is palliative care. Spiritual and existential counseling are facets of palliative care.

For people diagnosed with brain tumours, high-quality early palliative care is essential. High-grade brain tumours, in particular, can cause significant morbidity. Patients can experience severe headache, nausea, vomiting, intense fatigue and seizure activity. Additionally, patients may suffer from aphasia, impaired vision and hearing, hemiparesis, and mood/personality and cognitive deficits. The needs of patients with brain tumours (particularly glioblastomas – GBMs) are complex and require a multi-disciplinary approach. Yet, as identified by Lin et al in their paper on “Neuro Oncology and palliative care: a challenging interface”, few multidisciplinary teams routinely include in their core group palliative care members [6].

The paper goes on to argue that “Palliative care teams bring complementary expertise in symptom management, communication skills and practical physical and psychosocial support, both within and outside the hospital environment. With the known consequences of GBM diagnosis, it follows that palliative care should and must become an integrated standard part of best practice neuro-oncologic care…Given the demonstrated benefits of early palliative care integration with anticancer therapies in other cancer diagnoses, the time for robust investigation into palliative care for patients with GBM is now.”

Indeed, several randomized studies very much support the notion that the sooner palliative care is provided to cancer patients, the better this difficult journey becomes for them. Early palliative care intervention can have a very positive impact, resulting in better symptom control and thus significantly improved quality of life.

One study involved 151 metastatic non-small-cell lung cancer patients randomized to receive early palliative care with standard oncological care or standard oncological care alone. The study found that the patients who received early palliative care reported a better quality of life and survived more than two months longer on average than the patients in the standard oncological care only-arm of the study (11.6 months versus 8.9 months), even though the patients in the early palliative care arm received less aggressive end-of-life care [7].

Debunking myths and misperceptions

But what about the need to demystify palliative care, to make it more understandable to patients and their families so that the mention of it doesn’t instill confusion and fear? And how can we dispel the popularly-held myth that palliative care only means end-of-life care?

Good, clear communication is paramount. It is important that the professional palliative care community ensures that their messages to patients and caregivers about this crucial aspect
of the cancer journey are not disparate but rather that they are consistent across the field.

A good example of promoting clarity and consistency in the way palliative care is described is the online glossary of palliative care terms produced by the Palliative Care Programme Working Group of the Irish Health Service Executive (HSE) [8].

Additionally, palliative care specialists should be given every opportunity to have a much more open and frank dialogue with stakeholders – from patients, families, caregivers and healthcare providers to the media, general public and politicians.

Pragmatic suggestions as to how this can be achieved include easy-to-understand, general purpose leaflets on how palliative care is practiced; specific instructions on how patients can make contact with palliative care specialists and discuss their needs; and media campaigns in the national press. It’s also vital that the added value aspects of early intervention palliative care are brought to the attention of key opinion leaders and politicians so that they can support better understanding of the service and promote its importance in terms of prioritizing healthcare expenditure.

Auditing the effects of palliative care is also important. Systems to obtain feedback from patients about the palliative care they are receiving, and its outcomes, as well as seeking the opinions of family, friends and caregivers would be useful.

Of course, pro-active steps like these require both human and financial resources and lack of these is recognized as a barrier which also needs to be addressed.

**An important role for brain tumour patient organisations**

Brain tumour patient organisations and charities can play a key role in changing attitudes towards palliative care. An important strategy for improving public awareness about palliative care is providing education and publicity – two areas in which many patient organisations have much experience and know-how which they can use to help achieve a better understanding of what palliative care means and the advantages which early intervention can bring.

Brain tumour patient organisations also have extensive networks through which to spread information about the benefits of early palliative care. The palliative care team might even involve representatives from patient organisations who can provide support and information about, for example, social workers and counsellors or religious and spiritual care workers.

Finally, in order to demystify palliative care so it is better understood and better integrated into standard oncological practice, do we need to take radical steps? There seems to be increasing confusion about the use of palliative care terminology. It is important to be consistent and clear.

Should we accept the suggestions from some that the descriptor “palliative care” should be jettisoned and replaced with a term like “supportive care” or “comfort care” or “quality of life care” thus moving away from the widespread belief that palliative care equates only to hospice and end of life care? Whatever you call it, we need to be much more open in our discussions about palliative care.

People need to understand that palliative care is not an approach only associated with dying – nor that the timing of its implementation for individual patients means that all hope has been abandoned.

References:


5. Center to Advance Palliative Care, op cit.


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Exchange of knowledge

As an EANO nurse board member I am responsible for the development of the Nursing Research and care program at EANO conferences. This motivated me, for the second time – in 2012 the first full day nursing programme was held in Marseille – to look for health care professionals who could contribute to a good level of exchange of knowledge in the field of neuro-oncology. Besides, in collaboration with the presenting experts, I wanted to choose topics of interest that could address the demand of education for more or less trained neuro-oncology nurses and other health care professionals (HCPs), themes that could be worthwhile to get attention and add important skills, competences and understanding of neuro-oncology care.

Knowledge enriches!

To increase access to education, EANO offers oncology nurses a parallel session during the biannual European neuro-oncology conference, which will be held in Torino from October 9–12, 2014. This will take place on October 10th in Centro Congressi Lingotto. During this parallel nursing session Italian translation will be available and accreditation by the European Oncology Nursing Society has been approved of. Besides, the website of EANO contains a special subsection for nurses – and other HCPs – to be found at the homepage with interesting educational material to advance and apply knowledge of neuro-oncology.

There is much knowledge to be obtained and spread for oncology nurses concerning neuro-oncology, despite the fact that in the past decades a growing awareness occurred within neuro-oncology care and cure. In this respect, awareness of the needs of patients and their families in guidance throughout their disease concerning possible problems in coping, cognitive functions, anxiety and depression, in obtaining access to care and cure with a low threshold and in shared responsibility in treatment and end of life decision making is very important. Besides, it is interesting to learn more about the meaning (from a patient’s view) and the point (from a professional view) of rehabilitation, about end of life care, about cognitive disturbances in relation to psychosocial disorders, clinical trials and new effective cancer therapies. To address all these topics, we have created a program with a multidisciplinary character; clinical specialist and research nurses, a physiotherapist, psychologists and physicians are presenting enabling the attending health care professionals to gain and share their knowledge and experience with each other.

Nursing session

W. Sterckx performed an interesting study in Leuven, in which she studied the experiences and needs of patients with a high grade glioma and their family caregivers and she found that both patient as well as their carers describe the need for hope, support and information. C. Nijboer will tell us about implementation difficulties and pitfalls of an electronic pathway on neuro-oncological care and F. Salassa will speak about how to organize a regional network in which neuro-oncology nurses can communicate neuro-oncology care. Nowadays, new therapies bring new side effects and adverse events, and S. Panizolo will speak on how to manage antiangiogenic therapies and clinical trials. Later that day E. Gortmaker discusses the do’s and don’ts in clinical research for nurses from a research nurse perspective.

P. Salander will reflect on the relationship between patients and their spouses and their different views on the world, after which the privacy – solidarity conflict with regards to the communication between doctor, patient and their caregiver will be discussed by C. Y. Finocchiaro. After these two interesting topics, F. Malabaila will bring us new insights in coping strategies in patients and their caregivers for cognitive changes.

In the afternoon, K. Pii will share her findings on needs and preferences for supportive and rehabilitative interventions among patients with high-grade gliomas and their relatives. H. Radford will speak about the role of physiotherapy for patients with high-grade gliomas in the clinical setting, which could mean that the physiotherapist guides the patient in how to adjust to handicaps and disability and in that way aims to prevent and address secondary complications. Topics such as long-term survivorship by M. Lovely and awake craniotomy by F. Kloet will help us guide and inform our patients even better.

During palliative and end of life care, communication and support with the patient, his caregivers, and communication within the multidisciplinary team, can bring on an emotional toll on HCPs, so partnership is very important. Finally lessons on management of epilepsy and other events in the end of life phase by J. Koekoek and last but not least a presentation on how to share the decision process at the end of life – involving patients, caregivers and HCPs – by L. Guariglia will contribute to a better understanding of the problems we all encounter in our daily practice.

Finally, I hope to meet all the participants after the session and discuss what we have learned by networking with a drink and a toast on future neuro-oncology nursing sessions.

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Interview with Dr. Antonio Omuro, MSKCC, about the RTOG 1114-Phase II Randomized Study of Chemotherapy with and without Low-Dose WBRT for Primary Central Nervous Lymphoma

Ufuk Abacioglu

From the Department of Radiation Oncology, Neolife Medical Center, Istanbul, Turkey

Q: Dr. Antonio Omuro, can you tell us about the ongoing RTOG 1114 Randomized Study of Rituximab, Methotrexate, Procarbazine, Vincristine and Cytarabine with and without Low-Dose Whole-Brain Radiotherapy (WBRT) for Primary Central Nervous System Lymphoma? What is the rationale and background for this trial?

A: This trial is a follow-up to a single-arm phase II study conducted in the US that used R-MPV (rituximab, methotrexate, procarbazine, vincristine) chemotherapy followed by reduced doses of radiotherapy in patients who achieve a CR, and which found an intent-to-treat median PFS of 3.3 years and OS of 6.6 years; the group that received reduced WBRT achieved a median PFS of 7.7 years, with the median OS not reached after median follow-up of 6 years [1]. Neuropsychological evaluation suggested that these doses of radiotherapy are much safer and less toxic than full doses of radiotherapy. The intent is to confirm the excellent results in a community environment and also to determine whether the efficacy could actually be a result of the improved chemotherapy regimen, which is different from previous studies because of the addition of rituximab, and has never been tested without radiotherapy.

Q: Can you tell us the background to choose this chemotherapy scheme?

A: The MPV chemotherapy has been successfully used for a long time in studies conducted at MSKCC, with favorable results that have been attributed to institutional bias. Other critics of this regimen believe it is highly toxic and uses drugs that do not penetrate well into the brain. However, increasingly, it appears that this regimen is indeed very effective, as suggested by preliminary results of the ANOCEF/GOELAMS trial conducted in France that showed more favorable results of MPV as compared to methotrexate and temozolomide [2]. We felt MPV would be the optimal backbone to test the low-dose radiotherapy hypothesis, as this radiotherapy will work best in the setting of minimal residual disease after chemotherapy. Rituximab has been added, and nobody knows if it made a difference, but given the favorable results, we decided to keep it as not to change too many variables.

Q: What are the objectives of this trial?

A: The primary objective is to determine the PFS in both arms, on an intent-to-treat basis. We will also evaluate quality of life and perform neuropsychological evaluation, and of course look at overall survival and response rates.

Q: How is the trial designed? What are the eligibility criteria?

A: This is a randomized phase II study, with a total of 89 patients randomized on a 1:1 basis to receive either R-MPV with versus without low-dose RT. Patients are stratified by the MSKCC RPA class, prior to the chemotherapy. After chemotherapy which includes 8 methotrexate doses, patients either receive low-dose RT followed by cytarabine or cytarabine alone, regardless of their response status.

Q: What do you mean by Low-Dose Radiotherapy, and can you compare the dose within the previous trials?

A: Our regimen consists of WBRT given at a total dose of 23.4 Gy in 13 fractions. Previous work on MPV has used doses of 45 Gy, but very high neurotoxicity rates were seen. In the literature, WBRT doses are all over the place, ranging from 36–60 Gy, but characterization of neurotoxicity is difficult because each study defines and reports it in one way.

Q: Which groups and how many centers participate in the trial?

A: This is a study being conducted by the NRG (former RTOG), which is a cooperative group sponsored by the NCI. There are currently 81 activated sites across the USA.

Q: Do you have any translational research, quality of life and cognitive function assessments in the study?

A: Yes, all patients are followed with neuropsychological evaluation and quality of life for 5 years, regardless of tumor progression. If we have more relapses in the chemotherapy arm and similar survival, we will be able to find out in the aggregate results if it is best to have reduced dose RT up front, or let the disease relapse and use salvage treatments, which can also cause cognitive deterioration. We are also collecting tumor specimens with the intent of performing DASL-based gene expression studies for molecular characterization of PCNSL, as well as radiographic images and blood to look for polymorphisms predicting toxicity to methotrexate and radiotherapy.

Q: How is the recruitment and when do you expect to reach the accrual goal? When can we get the first results?

A: We have already accrued 51 patients, and we expect to complete enrollment in 12–18 months. We are hoping to present the first results by 2016.

Thank you very much!


Ongoing Trials

Dr. Antonio Omuro is the study coordinator for the trial entitled "RTOG 1114 Phase II Randomized Study of Rituximab, Methotrexate, Procarbazine, Vincristine and Cytarabine with and without Low-Dose Whole-Brain Radiotherapy for Primary Central Nervous System Lymphoma".

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Ongoing Trials
Association between DNA repair gene polymorphisms and risk of glioma. A systematic review and meta-analysis


Association studies of germline DNA repair single nucleotide polymorphisms (SNPs) and glioma risk have yielded inconclusive results. In the June issue, Fahsmideh et al have performed a systematic review and metanalysis of studies investigating this association: 27 eligible studies investigating 105 SNPs in 42 DNA repair genes were identified. The authors found that SNPs rs3212986, rs13181, and rs25487 in DNA repair genes ERCC1, ERCC2 and XRCC1 may increase the risk of glioma, while SNPs rs1136410 and rs12917 in PARP1 (ADPRT) and MGMT are associated with decreased susceptibility to glioma. These data must be further confirmed in robust statistical analyses.

Deferred use of bevacizumab for recurrent glioblastoma is not associated with diminished efficacy


The optimal timing to initiate bevacizumab (BV) for recurrent glioblastoma (GBM) is still unclear. In the June issue Piccioni et al investigated progression-free survival (PFS) and survival time (ST) in a retrospective cohort of 468 patients with GBM patients treated with BV at different recurrences. They found that PFS and ST did not differ between 1st, 2nd, and 3rd recurrences; therefore they concluded that deferred use of BV is not associated with diminished efficacy. However, patients with age more than 60 years and low extent of resection were unable to tolerate BV delay. Overall, these data are in line with the well known strong antiedema mechanism of action of BV.

Evaluation of amifostine for protection against cisplatin-induced serious hearing loss in children treated for average-risk or high-risk medulloblastoma


Currently, no established treatments or procedures exist to prevent platinum-induced hearing loss in children or adults. In the June issue Gurney et al investigated amifostine for protection from cisplatin-induced serious hearing loss in patients with both average-risk and high-risk medulloblastoma who received cisplatin in 2 sequential clinical trials at St. Jude Hospital. Amifostine was not randomly administered at a dose of 600 mg/m² immediately before and 3 hours into each cisplatin infusion. They found a protective effect of amifostine in average-risk patients but not in those that were high-risk. These data need to be confirmed in a randomized trial.

Integrating diffusion kurtosis, dynamic susceptibility-weighted contrast-enhanced MRI and short echo time chemical shift imaging for grading gliomas


Several studies of advanced MRI techniques to grade gliomas have been published with different set-ups and mixed results. In the July issue Van Cauter and colleagues have evaluated the diagnostic accuracy of diffusion kurtosis imaging (DKI), dynamic susceptibility-weighted contrast-enhanced (DSC) MRI and short echo time chemical shift imaging (CSI) for grading gliomas. Statistically significant differences among tumor grades were shown for MK, MD, mean rrCBV, mean rrCBF, rDR, lipids over total choline, lipids over creatine, sum of myo-inositol, and sum of creatine. DSC-MRI proved to be the modality with the best performance when comparing modalities individually, while the multimodal decision tree proved to be most accurate in predicting tumor grade, with a performance of 86%. All these results must be validated in larger prospective cohort of patients.

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The Society for Neuro-Oncology (SNO) is in the final planning stages of the 2014 Annual SNO Meeting (November 13–16, 2014) which will be held at the Loews Hotel in South Beach, Miami, Florida. SNO is grateful to meeting co-chairs Patrick Wen and Gelareh Zadeh for their energy and commitment to make the agenda for the 2014 meeting exceptional. SNO received 885 abstract submissions for this year’s meeting which represents a 30% increase compared to 2012 and is a new record for a non-WFNO year.

The main scientific meeting will build on the traditional SNO format presenting top-scoring abstracts, plenary talks, minisymposia and early morning meet-the-expert sessions. This year the meeting will also incorporate several important new features, including the addition of a concurrent session each day (for a total of three per day); an increase in the number of sunrise sessions; the introduction of e-posters viewable via kiosks located around the meeting space; more educational content during lunch breaks; and the introduction of discussed rapid reports allowing for an increased number of oral presentations. This year’s Keynote Speaker is Craig Thompson, President and Chief Executive Officer, Memorial Sloan Kettering Cancer Center, who will discuss tumor metabolism.

SNO also recognizes Burt Nabors, David Schiff, and Eudocia Quant Lee for their efforts to organize the 2014 Education Day program entitled “Metastasis to the CNS: Biology and Consequences”. Terri Armstrong and Alasdair Rooney served as co-chairs for the Quality of Life sessions, which this year are more formally integrated into the overall Education Day program.

Members of EANO may also be interested to note that two additional programs will occur immediately prior to the SNO Annual Meeting. The first, developed by Marcej Mrugala, is a half-day “Neuro-Oncology Review Course” which will take place on November 12, 2014. This course is intended as an update on basics related to our field and is ideally suited for those less experienced in neuro-oncology looking for a good overall review.

The second program is a very exciting offering developed by Victor Levin entitled “The CNS Anticancer Drug Discovery and Development Conference”. This program will run November 12–13, 2014, and will provide a state-of-the art discussion of drug development for neuro-oncology by bringing together top academia and pharmaceutical researchers focused on drug delivery into the CNS.

We hope that both of these programs will be of value to SNO members and members of our sister societies. If successful, they could be repeated and/or expanded in future years. Information on registration for these meetings can be found on the SNO website, www.soc-neuro-onc.org.

In addition to the Annual Meeting, another major focus has been on the journals published in partnership with Oxford University Press. Patrick Wen has succeeded WK Alfred Yung as the Editor-in-Chief of Neuro-Oncology and is working to build on Dr. Yung’s productive tenure. In addition, a new journal, Neuro-Oncology Practice, has been successfully launched thanks in major part to Susan Chang’s leadership and energy. SNO is extremely grateful to the efforts of Drs. Wen and Chang and their respective editorial boards.

Another important effort that is nearing completion is the redevelopment of the SNO website. Erik Sulman, Nicholas Butowski and Chas Haynes are working to create a revised website that will be of significant benefit to our membership. More than simply a redesign, the new website will feature an integrated communications platform that will enable the creation of secure online communities, driving collaboration and engagement across neuro-oncology subspecialties.

Finally, SNO is pleased to announce a new International Symposium Award designed to support a Neuro-Oncology Symposium or Educational Course in the developing world. This initiative is supported by Dr. Mark Bernstein, the Greg Wilkins-Barrick Chair at the University Health Network, University of Toronto, with additional matching support from the SNO Foundation. A $10,000 award will be given based on the budget presented in the proposal. Additional information and application documents have been posted to the SNO website. The deadline for the receipt of applications is November 1, 2014, and awards will be announced at the SNO Meeting in Miami. Members of EANO are asked to kindly share this information with colleagues they may have in developing regions.

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In Switzerland, like in any other country, cancer remains one of the most important risks for patient mortality. The development of a better understanding of cancer and the research for new, improved treatments remains key. Recognizing these challenges, the Swiss Group for Clinical Cancer Research (SAKK) was created in 1965 as a non-profit organization to address those issues and to promote clinical trials in oncology all over Switzerland. The Working Group on Brain Tumors has been developed as a branch of the SAKK to specifically address the issues related to brain tumors.

Over the years, thanks to the work of its previous presidents, including Roger Stupp and Silvia Hofer, this working group has become the center-point for Swiss Neurooncology. The biannual meetings organized by the SAKK have served as a meeting point where not only oncologists, but also neurosurgeons, radiation oncologists, neuroradiologists and neuropathologists can convene, share ideas, and develop new projects. The missions of the Brain Tumor Groups centers on providing an exchange platform for specialists involved in the management of patients with primary and secondary brain tumors, on providing regular postgraduate education in neurooncology to ensure the highest possible level of care for patients and to foster clinical and translational research.

Science and Research

In recent years, a number of projects have been completed by the Swiss Neurooncology community. For instance, Dr Th. Hundsberger aimed to assess the clinical and radiological parameters of patients with brainstem tumors treated in Switzerland and to evaluate their outcome. This work, published recently, demonstrated that histological verification of adult BSGs is feasible and has an impact on postoperative treatment. We further demonstrated that low-grade gliomas can simply be followed or treated with radiotherapy alone. Radiochemotherapy with temozolomide can safely be prescribed for high-grade gliomas without additional CNS toxicities.

One specific project has been key to strengthen the links between Swiss Neurooncology Centers and has allowed us to demonstrate the feasibility of an “all Swiss” clinical trial: The ARTE trial, launched by Dr G. Tabatabai and Prof M. Weller, has included, to date, over 50 of the 60 planned patients. This randomized phase II trial aims to evaluate the role of bevacizumab (Avastin®) in addition to hypofractionated radiation therapy in elderly patients. Elderly patients with GBM represent a specific challenge, as one must carefully balance the risk of additional toxicity linked to the treatment in this population of fragile patients. This trial will not only provide preliminary information about the efficacy of this treatment combination, but also provides a unique platform for translational and imaging research with both MRI and FET-PET. The value of this project has been recognized internationally and the follow-up study will be implemented as a phase III trial by the EORTC.

The SAKK Brain Tumor Group is also working in close collaboration with an initiative led by Prof A. Raabe from the Inselspital University Hospital Bern to establish the Swiss Glioma Network. This prospective database will include clinical and imaging data as well as a virtual tumor biobank, and aims to realize scientific projects in the field of neurooncology in Switzerland. A number of specific projects have already been linked to this platform including an evaluation of the prognostic role of neurosurgical resection in recurrent GBM. This project is being led by Dr Ph. Schucht. This database will also allow for comparisons in the management of patients and provide opportunities to harmonize treatment strategies. Indirectly related to this project, our colleagues from the Cantonal Hospital of Sankt Gallen, under the lead of Dr Putora, have developed a method to analyze and compare the decision trees for the management of recurrent GBMs. This project has allowed identifying over 100 parameters that are being taken into account by the different institutions for the management of these patients, and also allows to identify widespread consensus and/or discrepancies between institutions.

The Brain Tumor Working Group is also participating in the successful national and international implementation of a database that collects clinical and histological information on gastric cancers that have spread to the CNS (www.gastriccancerregistry.org). This venture is led by Dr S. Hofer and J. Feilchenfeld.

Annual Swiss Neurooncology Meeting

Postgraduate education also represents a key aspect to ensure the highest possible quality of care for patients with brain tumors. The Annual Swiss Neurooncology Meetings have been implemented to provide an up-to-date and optimal teaching environment to review both the basic aspects in brain tumors and to provide a platform to present the latest developments. In 2013, the meeting has been held in Lugano (organized by Dr Pesce) jointly with our colleagues from Northern Italy, and this year we had the pleasure to welcome our
French colleagues from the Association des Neurooncologues d’Expression Française (ANOCEF) in Lausanne. Given the wide success of these 2 previous editions, the next meeting will be held jointly with our colleagues from Austria in Sankt Gallen on September 18–19, 2015. You are all more than welcome to join this meeting. For information please contact www.neurologie.kssg.ch.

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**Calendar of Events**

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<thead>
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<th>Event</th>
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<tbody>
<tr>
<td></td>
<td>50. Jahrestagung der Österreichischen Gesellschaft für Neurochirurgie</td>
<td>Vienna, Austria</td>
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