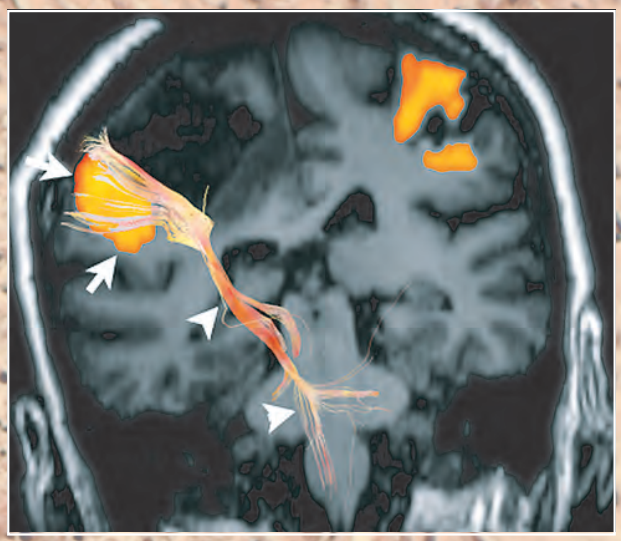
Volume 2 (2012) // Issue 3 // e-ISSN 2224-3453

European Association of NeuroOncology Magazine

Neurology · Neurosurgery · Medical Oncology · Radiotherapy · Paediatric Neuro-oncology · Neuropathology · Neuroradiology · Neuroimaging · Nursing · Patient Issues



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IMPRINT

European Association of NeuroOncology Magazine

ISSN-Online: e-ISSN 2224-3453

Official Organ of the European Association of Neurooncology

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Publisher's Office:
Krause & Pachernegg GmbH
Verlag für Medizin und Wirtschaft
3003 Gablitz, Mozartgasse 10, Austria
Tel. +43/2231/61258-0, Fax +43/2231/61258-10

Policy:
The *European Association of NeuroOncology Magazine* welcomes submission of clinically and original papers, reviews etc in the fields of neurology, neurosurgery, medical oncology, radiotherapy, pediatric neurooncology, neuropathology, neuroradiology, neuroimaging, nursing, patient issues, etc.

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The Present and the Vision of EANO's Future

Riccardo Soffietti, MD

In the last years, EANO has grown and improved significantly, and the number of members has grown to 670. The congress in Marseille (September 6–9, 2012) had 970 participants and 375 abstracts were submitted compared to 256 for the 2010 meeting in Maastricht. In particular, the field of basic and translational science was more extensively represented in the Educational Day, Scientific Workshops, and Free Communications. In Marseille, the Executive Board was partially renewed, and a plan of actions for the next 2 years (2013–2014) will be developed.

The vision of future developments of EANO involves many directions.

The EANO bylaws are being updated and by the end of this year the new draft, developed by the Executive Board, will circulate among EANO members for their definitive approval.

We are in the process of building a more structured World Federation of Neuro-Oncology, together with SNO (USA) and ASNO (Asia) in order to improve the organization of the Quadrennial Meeting (the next will take place in San Francisco in November 2013) and the cooperation in the initiatives toward the developing countries.

We will increase the relationships with the national multidisciplinary societies/groups of neuro-oncology: so far, almost all western countries have a multidisciplinary society of neuro-oncology, and a Committee of the National Chairmen has been created in Marseille. The first step will be to acquire and spread information on practice, organization, educational and scientific activities within each country. Information on existing guidelines, access to standard and advanced MRI and PET techniques, time to surgery, to adjuvant radiotherapy and to radiosurgery, availability and regulatory rules regarding antineoplastic agents (in particular new targeted agents) are examples of what we need to know to try to homogenize as much as possible the management of primary brain tumours and neurological complications of systemic cancers within Europe. In this regard, the development of European Guidelines will be further expanded.

Moreover, we need to work on the development of a post-residency "Core Curriculum in Neuro-Oncology" (as already established in USA) for both neurosurgical and medical neuro-oncology, and on to the definition of criteria for recognition of so-called centres of excellence or referral centres (especially for rare tumours) within the European countries.

Another future task of EANO should be to foster education in neuro-oncology and to promote the concept and practice of multidisciplinarity in Eastern Europe primarily, but also in North Africa and the Middle East by developing regional teaching courses and stimulating the access to EANO travel and exchange programmes.

In addition to EANO-EORTC-ESMO Educational Conferences, it could be important to set up conjoint scientific initiatives (ie, workshops, etc) with the scientific societies of neurosurgery, neurology, neuropathology/basic science, neuroradiology, radiation-oncology, and medical oncology on topics of common interest.

We are aware of the increasing financial limitations in the years to come, and we will pay particular attention to the balance between expected benefits and costs of old and new initiatives.

The *EANO Magazine* is going well and, ultimately, it will serve to improve communication among people from Europe and hopefully from other countries in the world.

I hope that all members will be increasingly involved in EANO initiatives, especially the younger people for an even better future of neuro-oncology in Europe.

Last, I would like to thank EANO's past-president, Wolfgang Grisold, and the members of EANO's Executive Board and Scientific Committee for their great commitment.

See you in Turin in October 2014 for the next EANO Congress!

Riccardo Soffietti, MD

EANO President (2012–2014)

Quality of Life of Brain Tumour Patients

Andrea Pace, Veronica Villani, Chiara Zucchella, Marta Maschio

Abstract: Health-related quality of life (HRQOL) has recently become an important outcome measure in neuro-oncology. At present, no single gold standard tool exists to measure HRQOL and there are no clear data on the role of different determinants of HRQOL and their changes during the course of disease in brain tumour (BT) patients. HRQOL measures may be helpful in evaluating cancer care outcomes and also have been recently evaluated as early independent predictors of survival. The negative influence of several clinical factors such as cognitive impairments, mood disorders, and epilepsy on HRQOL has been reported in several studies but needs to be better defined. Moreover, the HRQOL in advanced disease and during the end-of-life phase of brain tumour patients still remains a neglected issue. The objective of this review is to examine recent literature focusing on the most relevant HRQOL issues in neuro-oncology. **Eur Assoc NeuroOncol Mag 2012; 2 (3): 118–22.**

Key words: quality of life, brain tumor, cognitive impairment, outcome measure

Introduction

Primary malignant brain tumours (BT) have a low rate of incidence: in developed countries, the annual incidence is 5.8 males and 4.1 females, respectively, per 100,000. Despite aggressive multimodality treatment with surgery, radiotherapy, and chemotherapy, the prognosis of patients with primary brain tumours remains poor. Malignant gliomas have the worst outcome with the median survival ranging from 12–15 months for glioblastoma multiforme (GBM) and from 2–5 years for anaplastic gliomas [1].

Considering the limited survival of BT patients, in the last decades growing interest has been dedicated to the impact of treatment on health-related quality of life (HRQOL) [2–4].

HRQOL has become an important endpoint in cancer studies and has been included in several trials as an outcome measure supplementing other traditional survival end points (overall survival and progression-free survival) [5–7].

The concept of HRQOL involves the patient's subjective assessment or evaluation of important aspects of their well-being and is influenced by personal experience, beliefs, expectations, and perceptions. HRQOL measures should be patient-reported and are referred to as distinct areas exploring emotional, physical, cognitive, and social functioning as well as spiritual well-being [8, 9].

However, in brain tumour patients, HRQOL has long been a neglected issue. The objective of this review is to examine recent literature focusing on the most relevant HRQOL issues in neuro-oncology.

Received on July 14, 2012; accepted on August 14, 2012; Pre-Publishing Online on September 5, 2012

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Quality-of-Life Assessment

Quality of life (QoL) is a complex entity that originates from the interaction between a person's values and expectations and their actual experience [10]. Diseases and treatments constitute a new dimension that may change several domains of the pre-existing perception of QoL [11]. Several standard multidimensional HRQOL questionnaires have been utilized in BT patients. There is a general consensus that HRQOL evaluations should be patient-reported, given that they concern personal perceptions, but proxy-reported outcomes are still used to evaluate HRQOL as well [10, 11].

At present, no single gold standard tool exists to measure HRQOL. The most common tool in use was developed by the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life group: the EORTC QLQ-C30. The QLQ-C30 is a 30-item, self-reported questionnaire containing the following domains: physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), social functioning (2 items), global quality of life (2 items), fatigue (3 items), pain (2 items), and nausea and vomiting (2 items) as well as single items for dyspnoea, insomnia, anorexia, constipation, diarrhoea, and financial impact. The EORTC QLQ-BN20, specifically validated for patients with brain cancer, includes 20 items assessing visual disorder, motor dysfunction, various disease symptoms, treatment toxicity, and future uncertainty [12]. Multidimensional measurements are time-consuming and reliable serial measurement of HRQOL in BT patients is difficult. Many factors may affect the quality of the collected data, mainly poor patient compliance, dropout bias, or methodological problems. Patient-related issues may affect particularly HRQOL measurements at progressive stages of disease and at the end of life, given cognitive problems and inability to repeatedly complete complex forms. Simpler and more sensitive instruments (such as cognitive function) are therefore needed to detect HRQOL changes at advanced stages of disease.

However, there are no clear data on the role of different determinants of HRQOL and their changes during the course of disease in BT patients [13].

HRQOL as Outcome Measure and Survival Predictor

HRQOL measures have recently become a secondary outcome indicator in several phase-II and -III clinical trials. Evaluating cancer treatments, the pattern of HRQOL may be used as an easy and cost-effective measure of clinical benefit or treatment toxicity [14, 15].

Although clinical cancer trials are usually centred on traditional end points such as overall survival or progression-free survival, in the last years models of quality-of-life-adjusted survival have been proposed to explore the clinical benefit of cancer treatments. Originally developed for evaluating breast cancer treatments [16, 17], Q-TWiST ("quality-adjusted time without symptoms of disease or toxicity of treatment") analysis incorporates progression, survival, treatment toxicities and quality of life to better estimate the overall benefit for patients and evaluate both the quality and quantity of survival time.

HRQOL measures may not only be helpful in evaluating cancer care outcomes from the patients' or family carers' perspectives but have also been recently evaluated as early independent predictors of survival [18].

Only a few studies have addressed this issue in patients with primary brain tumours. Sehlen et al showed that HRQOL as measured by the FACT-G total score was independently predictive of survival in a patient population with primary and secondary brain tumours [19]. Different results were obtained in other studies showing that HRQOL scores did not predict survival but cognitive functioning was a significant predictor of survival [20]. Also Bosma et al [21] showed that baseline HRQOL evaluated by means of the Medical Outcomes Study Short Form 36 (SF-36) was not related to duration of survival. Mauer et al [22], in a large series of newly diagnosed glioblastoma patients, showed that HRQOL and tumour-related symptoms, as measured by means of the EORTC-QLQ-C30 and BCM-20 questionnaires, added relatively little to prognostic factors of clinical survival such as age, performance status, extent of surgery, corticosteroids at entry, cognitive status, and MGMT promoter methylation status.

At present, it is difficult to compare these contradictory findings, given the different measures that were used and different populations of BT patients evaluated. The prognostic role of HRQOL has to be confirmed in larger studies.

Neurocognitive Impairment and HRQOL

It is well recognized that impairment of neurocognitive functioning resulting in behavioural, emotional, and intellectual difficulties occurs in nearly all patients with brain tumours and eventually compromises their independence.

Cognitive impairment associated with primary or metastatic brain tumours occurs in a significant proportion of patients, with 10 % of patients developing progressive dementia and 50–90 % showing deficits when evaluated with sensitive neuropsychological tests [23]. Cognitive deficits, mostly affecting information-processing speed, frontal-lobe executive functions, memory, attention, and language, can vary from mild dysfunction with good information-processing and good performance to severe impairment [24, 25]; such impairment is related to a combination of various factors, including the tumour itself, tumour-related epilepsy, treatment, and patient-related factors [26].

Cognitive functioning has a major impact on HRQOL, being related to the patient's ability to perform activities of daily living, manage finances, recognize safe and unsafe behaviours, and comply with medication regimens. It has been suggested that neurocognitive impairment causes a decline in functional independence more often than physical disability; additionally, subtle cognitive deficits can prevent long-term brain tumour survivors from returning to premorbid autonomy, occupation, and social/familiar role [27–30]. Studies indicated that left-hemisphere localization and glioblastoma-multiforme-histological features represent principal predictors of neuropsychological deficits and reduced HRQOL in adults with newly diagnosed primary brain tumours [31].

Giovagnoli et al [13] studied patients with recurrent high-grade gliomas with the aim of evaluating different facets of HRQOL and concluded that psychosocial aspects were the strongest determinants; Gustafsson et al [24] reached the same conclusion in patients with low-grade gliomas, showing that HRQOL had a moderate relationship with emotional and cognitive functioning and a somewhat weaker relationship with physical performance. A recent study confirmed these findings, indicating that, in low-grade glioma patients, among factors significantly associated with the self-reported HRQOL, neurocognitive deficits were relatively prevalent [2].

Although information on neuropsychological performance and HRQOL in patients with primary central nervous system malignancies is becoming available, the relationship between the 2 in patients with brain metastases remains poorly studied [32]. In one study conducted in patients with brain metastases after whole-brain radiotherapy, deficits in neurocognitive functioning were evident before declines in patient ratings of HRQOL, with deterioration of performance on a memory test proving to be the strongest predictor of subsequent declines in patient-reported HRQOL [33].

Aware of the close relationship between cognitive functioning and HRQOL, researchers evaluated potential treatments for neuropsychological deficits. The first therapeutic agent used to reduce cognitive morbidity and improve HRQOL in irradiated brain tumour patients was the amphetamine methylphenidate [34, 35]. More recently, Shaw et al [36] conducted a prospective, open-label study, administering an AChE for 6 month to survivors of partial or whole-brain radiation therapy, showing a significant improvement in cognitive functioning, mood, and HRQOL. A potentially positive impact of a bevacizumab-based therapy on neurocognitive function, performance status, and/or QoL has also started to emerge from reports of clinical studies among GBM patients [37]. At present, however, there are no proven pharmacological treatments for cognitive impairment following brain cancer, nor are there any known effective preventive strategies. Another alternative approach is represented by cognitive rehabilitation. Gehring

et al [38] conducted a randomized, controlled trial to evaluate the effects of a multifaceted cognitive rehabilitation programme (CRP) on cognitive functioning and selected quality-of-life domains in patients with gliomas, showing a salutary effect on short-term cognitive complaints and on longer-term cognitive performance and mental fatigue.

In summary, neurocognitive and HRQOL assessments are important endpoints for patients with primary brain tumours, increasingly incorporated in clinical studies. Even if their evaluation may be regarded as time-consuming and burdensome for both the patient and the clinician [3, 39], relying solely on survival or performance status does not adequately evaluate the often subtle impairments that can only be identified through multidimensional assessments. Future directions for research include longitudinal assessment to better characterize HRQOL and neurocognitive issues, determination of predictors of poor functioning, and potential cognitive and psychopharmacological interventions.

Mood Disorders and QoL

The prevalence and impact of mood disorders is not fully delineated in BT patients. The prevalence of depression in patients with glioma ranges from 0–93 % [40]. In a recent review on depression and glioma, Rooney et al reported that clinically diagnosable depression occurred in roughly 15 % of glioma patients [41].

The majority of studies on depression in adults with glioma are small, cross-sectional, and retrospective. Also, the instruments used to screen for depression appear to inflate depression frequency compare with the clinical interview.

Depression results are associated with functional impairment, cognitive dysfunction, reduced quality of life, and reduced survival [15, 42]. The association of depression with lowered HRQOL has been reported by several authors but, unfortunately, only a few studies have investigated the contemporary assessment of depressive disorder and HRQOL by means of clinically valid tools. Furthermore, longitudinal studies with repeated measurements during the evolution of disease are lacking. Pelletier et al [43] showed that the presence of depression was the most notable single predictor of overall worse HRQOL among BT patients. Litofsky et al, in a large population of 598 glioma patients [40], reported an impressive incidence of depression (93 %) in patients enrolled in the glioma outcomes project. The incidence of mood disorders and the efficacy of investigative methods in cancer patients are controversial. In the literature on cancer and depression, the main issue is the difficulty in distinguishing major from mild depression. Standard screening tools often fail to distinguish between demoralization and major depression. Situational or reactive depression should be considered a normal psychological response to the changes associated with the diagnosis of cancer. This type of depression is essentially psychological in nature, rather than physiological, and is more responsive to supportive psychotherapy than medication [44].

Thus, symptoms of depression should be considered as a part of coping strategies, in a physiological process of adaptation to the disease, at least in those patients whose depressive symptoms do not meet criteria for major depression.

Several authors reported that depression is not only a psychological reaction to cancer but may be related also to biological factors. However, the absence of strong associations with other variables (including tumour location, histology, and extent of resection) implies that depression in glioma is primarily a psychologically mediated response to losses, including the loss of health.

At present, according to a recent comprehensive review on depression and glioma, the impact of tumour biology on the pathogenesis of depressive and the emotional response to glioma diagnosis remain largely unknown [41]. Antidepressant medications and psychotherapy (particularly cognitive behavioural therapy) have been shown to be of comparable effectiveness in the treatment of major depression [45]. Earlier studies among depressive cancer patients have reported that treatment of depression increased their survival [46, 47]. However, Litofsky et al [40] did not observe significant impact on survival among high-grade glioma patients treated for depression.

Current evidence shows that many tumour- and patient-related factors may influence depression in BTs. Larger studies are needed to identify patients whose depression can be treated, as well as to find out what is the appropriate treatment of choice for depression in BT patients.

Epilepsy and HRQOL

Patients with brain-tumour-related epilepsy (BTRE) present a complex therapeutic profile and require a unique and multidisciplinary approach. Epilepsy in BT patients may have a negative impact on both cognitive functions and HRQOL, particularly in low-grade glioma patients. The cognitive deficits could primarily be ascribed to the use of AEDs, whereas the low HRQOL scores were mainly related to poor seizure control [48].

The presence of epilepsy is considered the most important risk factor for long-term disability in BT patients [48, 49]. Good seizure control can significantly improve the patient's psychological and relational sphere (ie, social, personal, and professional) [50].

The evaluation of side effects (SE) of an AED is crucial in patients with BTRE due to the fact that SEs can affect the patient's perception of QoL more than seizure frequency [51, 52].

Epilepsy may affect the HRQOL of brain tumour patients, causing possible long-term disability either because of factors related to epilepsy itself or to the drugs utilized for controlling seizures. The choice of AED therapy must take into consideration not only the drug's efficacy for seizure control, but also possible effects of the drug on important aspects of the patient's daily life, for example cognitive function, sexuality, efficacy of systemic therapies, and intensity of side effects [53].

End of Life and HRQOL

The relationship between palliative care and HRQOL at advanced disease stages of BT patients has been poorly evaluated, however there is growing concern about the quality of care given at the end of life (EoL) in these patients. Palliative care is now understood as an approach to care concerned with caring for the entire person faced with a range of physical, psychological, and social needs. The WHO definition of palliative care is *"an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness"* [54].

Existing data in BT patients suggest that too many patients do not receive adequate palliative care at the final stage of disease [54, 55]. However, increasing attention is being given to palliative care and end-of-life (EoL) issues in neuro-oncology. From diagnosis to the EoL, the care needs of BT patients are high and sometimes underestimated. Clinical symptoms (such as motor, visual, and communication impairment) and low quality of life are typical features of BTs already present during early phases of disease [56]. There is a wide consensus about the need to improve our knowledge of end-of-life care and to improve the quality of palliative care for patients dying from BTs. Patients and their caregivers should be assisted in adequate settings by well-trained, multidisciplinary, palliative neuro-oncology teams dedicated to the management of the most frequent symptoms. Recently, some studies have focused on supportive care needs of BT patients at the last stage of disease, reporting that the lack of symptom control often leads to re-hospitalization with increasing costs for the health care system and worsening of the patient's quality of life [57]. Particularly, the occurrence of seizures at the end of life seems to influence quality of life of patients and their caregivers.

Recent studies reported that administrative data, and particularly hospital re-admission rates at the last stage of disease, may be considered a potential indicator of quality of EoL care [58].

In a recent paper of our group, we observed in a population of BT patients assisted until death with a neuro-oncologic palliative home care programme a high incidence of distressing symptoms influencing the quality of life during the course of disease and during the process of dying. We concluded that in order to allow the patient to experience a peaceful death, control of pain, confusion, agitation, delirium, or seizures by means of specific palliative interventions is needed [57].

The main goals of palliative care and end-of-life care in brain tumour patients are to offer adequate symptom control, relief of suffering, avoiding inappropriate prolongation of dying, and to support the psychological and spiritual needs of patients and families.

However, currently there is a lack of palliative-care provision for patients affected by advanced brain tumours with a negative impact on patient's quality of life at the end of life. Nevertheless, there is a great need for education in palliative care and end-of-life care for brain tumour patients. Wider availability of palliative programmes and home-care models of assistance may represent an alternative to in-hospital care for the management of patients dying from a brain tumour and may improve the quality of end-of-life care.

Conclusions

The assessment of patient-reported outcomes in clinical trials and in clinical practice is likely to become a standard part of clinical management of BT patients. HRQOL has been reported to have a positive relationship with survival duration but, at present, there is no definitive evidence that baseline HRQOL scores have additional value with respect to clinical factors for predicting survival. However, considering their limited survival, the HRQOL assessment in patients with BTs is particularly important. It is increasingly recognized that the choice of treatment should also involve careful consideration of its effects on the health-related quality of life (HRQOL) during the remaining survival time. As survival is limited, patients optimally should be informed of the impact of all treatment options on their quality of life at the time of diagnosis. Relatively little is known about HRQOL during the disease course of patients with high-grade gliomas. The pattern of HRQOL may serve as an easy and cost-effective tool to recognize early changes in the subjective clinical condition of BT patients, and the relationship with disease progression.

Moreover, regular use of HRQOL measures in neuro-oncology practice may improve quality of care by facilitating doctor-patient communication and patient participation in treatment decisions at every stage of the disease.

Conflict of Interest

None.

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Functional Magnetic Resonance Imaging (fMRI) in Brain Tumour Patients

Marion Smits

Abstract: Functional magnetic resonance imaging (fMRI) is increasingly used in the work-up of brain tumour patients preoperatively to assess the relationship between the functionally eloquent cortex and brain pathology. In cases of presumed tumour localisation in or near eloquent brain areas, such as the motor cortex or language areas, fMRI may be advantageous to guide the neurosurgical approach, shorten surgery duration, and obtain prognostic information prior to surgery. For the assessment of the primary motor cortex a good correlation between fMRI and intraoperative electrocortical mapping (ECM) has been reported, with sensitivities and specificities ranging from 88–100 %. For the localisation of language representation areas validation results are controversial with sensitivities from 22–100 % and specificities from 0–100 %, rendering fMRI less suitable as the sole technique for language cortex localisation. For the assessment of hemispheric language lateralisation, however, > 90 % agreement between fMRI and the invasive Wada test has led to fMRI now mostly having replaced the Wada test for this indication. There are several limitations of fMRI including issues that are inherent to the technique such as spatial and geometric uncertainty, tumour effects on the fMRI signal, inter- and intra-individual variability, lack of discrimination between essential and modulating brain regions, and lack of information on the underlying white matter. Such shortcomings need to explicitly be taken into account in every patient. The careful use of fMRI is justified to aid neurosurgical planning but intraoperative ECM remains the gold standard for localising the eloquent brain cortex. **Eur Assoc NeuroOncol Mag 2012; 2 (3): 123–8.**

Key words: brain neoplasms, magnetic resonance imaging, functional, glioma, brain mapping, motor cortex

Introduction

Functional magnetic resonance imaging (fMRI) is increasingly used in the work-up of patients at the preoperative stage to assess the relationship between the functionally eloquent cortex and brain pathology. Inter-individual normal variations of anatomy render such assessment unreliable based on structural imaging alone despite the definition of clear anatomical landmarks [1, 2]. This is even more of an issue when normal anatomy is obscured by a tumour mass effect or when functional anatomy is altered due to cortical plasticity.

fMRI has seen a rapid evolution from its first human application in 1991 [3] to an essential tool in the exploration of human brain function, most prominently in the scientific arena. In 2007, new Current Procedure Terminology (CPT) codes were developed for fMRI by the American Medical Association, signifying the transition of fMRI to a valuable tool in a clinical setting [4].

Recent major advances in clinical fMRI make its acquisition, image processing, and even integration of its findings for neuronavigational purposes relatively easy. However, the technique is not without limitations and validation issues which are easily forgotten when colour activation maps become readily available at the single click of a button. In this paper, the theoretical background, the validity in brain tumour patients, and several considerations of fMRI are addressed.

fMRI Background

Blood Oxygenation Level-Dependent (BOLD) fMRI is the most commonly used functional MR neuroimaging technique. BOLD fMRI takes advantage of the tight link between local neuronal activity and blood flow, called neurovascular coupling [5]. Due to neurovascular coupling, blood flow and volume increase locally with an increase of neuronal activity. This leads to an increase in oxygenated blood that is disproportionate to the increased need of oxygen for neuronal activity. As a result, there is a relative decrease of paramagnetic deoxygenated haemoglobin which in turn leads to an increase of MR signal in those areas of the brain that are active [6]. Such signal changes are small and relative, which means that many measurements need to be made, typically during an alternation of active and baseline conditions in a task that aims to activate the functional brain region of interest. Furthermore, the signal changes occur at a delay after and are more prolonged than the neuronal activity, defined by the hemodynamic response function. A statistical model is created to assess the correlation of the measured signal changes with the task, taking the hemodynamic response function into account. The resulting statistical map is thresholded at a certain p or T value and overlaid in colour on a high-resolution anatomical image which is acquired separately. This is the typical colour "activation" map produced by an fMRI image processing software, which is merely a combination of anatomical and statistical information very indirectly representing neuronal activation.

Task-Based fMRI

For clinical application, almost exclusively task-based fMRI is used. During the performance of a task by the subject in the scanner, rapid imaging of the brain is performed. Typically, the entire brain is scanned at intervals of 3–5 s for a duration of about 5 min so that > 100 measurements are made per task. The task consists of active and baseline conditions, which commonly alternate in blocks of 20–40 s. Such so-called blocked paradigms are statistically robust, since a lot of signal is acquired for each condition, but they are restrained because they do not leave much room for unexpected or short stimuli. In an event-related task design, individual stimuli, each representing a specific condition, are presented in random order and rapid succession. Such a task design offers the possibility to present unexpected stimuli as well as many different condi-

Received on May 15, 2012; accepted on August 14, 2012; Pre-Publishing Online on September 5, 2012

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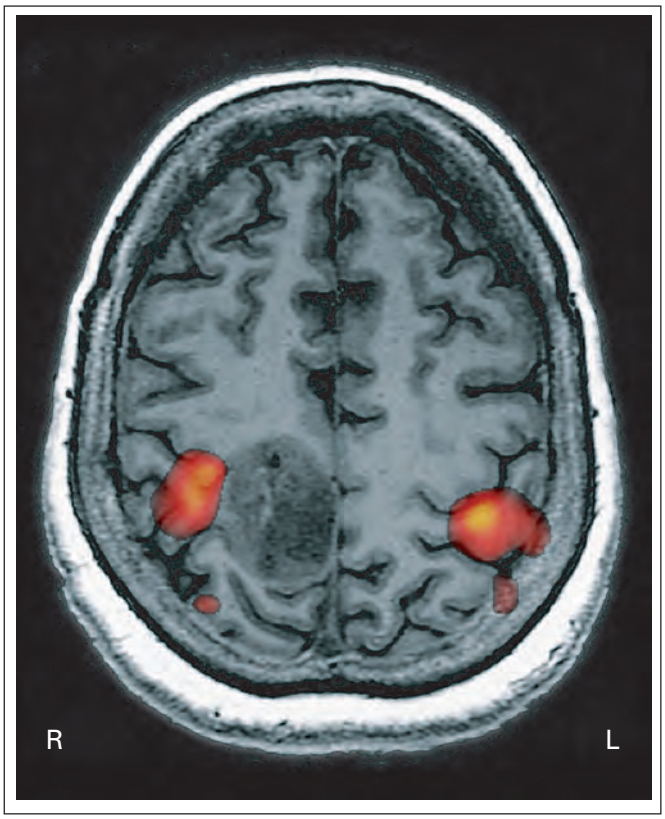

Figure 1. Brain tumour localised in the primary hand motor cortex as evidenced by fMRI activation of a bilateral finger tapping task adjacent to the tumour in the precentral and post-central cortex bilaterally.

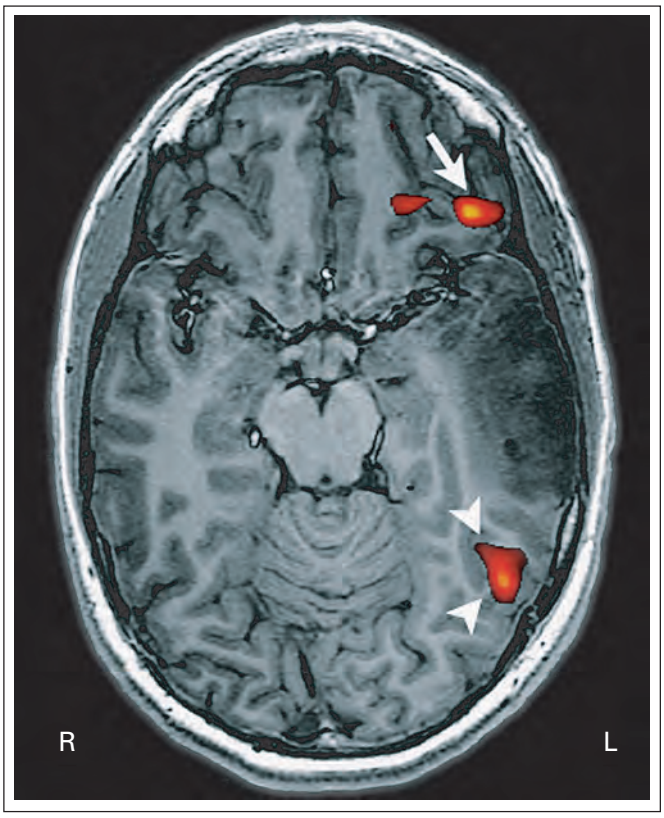

Figure 2. Brain tumour localised in the left temporal lobe of a left-handed patient. fMRI activation of a verb-to-noun generation is present in the expressive language area in the inferior frontal gyrus (arrow), as well as in the receptive language areas in the posterior temporo-parietal cortex (arrowheads). Activation is more pronounced in the left hemisphere, indicating a left-lateralised hemispheric language representation.

tions, rendering it very flexible, but statistically less robust since the signal acquired per condition is generally low. For clinical application, blocked designs are generally well-suited and preferable.

The choice of active and baseline conditions is driven by the brain function of interest. Typical tasks to induce motor activation are finger tapping (Figure 1), wrist flexion, foot tapping, and lip pouting, for somatotopic mapping along the motor cortex. Commonly used tasks to activate the language areas are verb-to-noun generation (Figure 2), passive listening, and picture naming [7]. The baseline condition can simply consist of no activity or stimulus presentation, but may also be used to exclude brain activation associated with the active condition that is not of interest. For instance, in an auditorily presented language task, the presentation of non-language auditory stimuli in the baseline condition will result in language-related activation without activation related to auditory processing in the comparison between active and baseline conditions.

Task-based fMRI is only as good as the patient's ability to perform the given task, since a task that is too difficult will result in underperformance or dropout, resulting in decreased or even absent activation. It is therefore crucial that task difficulty is adapted in patients with neurological and/or cognitive deficits. Training beforehand is also important to ensure adequate task performance; over-learning however should be avoided.

Resting-State fMRI (rsfMRI)

A recent development in the scientific field of fMRI is the measurement of spontaneous brain activity, present in multiple networks in the brain, called resting-state fMRI (rsfMRI) [8]. Spontaneous BOLD fluctuations are found to be highly correlated in distinct regions throughout the brain, and are presumed to indicate a functional connectivity within specific and highly organised neuroanatomical networks [9]. In healthy volunteers, such networks can reproducibly be found between the left and right sensorimotor cortices and between language areas, without any task being performed [8]. During an rsfMRI experiment, the subject is instructed to lie in the scanner and think of nothing in particular. Even when subjects are asleep or anaesthetised rsfMRI can be performed, with clear advantages in populations of small children or restless or cognitively impaired patients. The potential advantages for brain tumour patients are obvious: there is no dependency on patient cooperation, on task design or task performance. Several networks can be obtained from the same data set, which can typically be acquired within 10–15 min. A few small studies have recently indicated feasibility of assessing functional connectivity in brain tumour patients, demonstrating a considerable overlap between primary sensorimotor networks assessed with resting state and task-based fMRI [10–12].

In a recent study of 57 brain tumour patients using magnetic encephalography to assess functional connectivity, Martino et al reported a low positive predictive value (64 %) comparing functional connectivity with intraoperative electrocortical mapping (ECM), suggesting that no reliable distinction could be made between critical and less critical eloquent areas [13]. Negative predictive value, however, was high, meaning that in

areas of decreased functional connectivity no active sites were found on ECM and no increase of neurological deficit was found. This would indicate that areas of the brain with decreased functional connectivity are dysfunctional and may be resected without the increased risk of a postoperative neurological deficit. Similar findings were reported by Liu et al [10] and Kokkonen et al [11], demonstrating asymmetrical functional connectivity of the left- and right-hand motor areas in some patients. Task-based fMRI in those patients, however, indicated no hand motor area deficit. Such discrepancy may be explained by white matter infiltration, potentially even occurring at a distance of the primary motor cortex, disrupting inter-hemispheric functional connectivity between the 2 primary motor areas.

Promising as these findings may be, rsfMRI still requires validation in larger patient populations and against an adequate gold standard such as intraoperative electrophysiological cortical mapping (ECM) before its potential application as a clinical tool. Also, image processing tools, at present still largely available in a research environment only, need to be developed that are fast and user-friendly before rsfMRI can be introduced into clinical practice in the same way task-based fMRI was in the last decade. Such developments are certainly not far off, as demonstrated by the recent publication of a tool enabling the interactive assessment of functional connectivity in < 2 minutes for even inexperienced users [14].

Clinical Pre-Surgical fMRI Studies

The aim of neurosurgery in brain tumour patients is maximum tumour resection, while at the same time minimising the risk of new functional deficits post-operatively. For optimal results, the relationship between the tumour margins and eloquent brain regions needs to be established as accurately as possible. The gold standard for such assessment is intraoperative ECM, which has in fact been shown to significantly modify long-term survival in low-grade glioma patients [15]. However, intraoperative ECM is invasive, requires experience and expertise of the neurosurgical team, increases surgery duration, and requires awake and active participation, collaboration, and motivation of the patient. Additionally, only a limited number of tasks can be tested. Functional MRI may be used to make a risk assessment preoperatively, which is of particular value in young low-grade glioma patients, to plan and guide the neurosurgical approach, shorten surgery duration, and obtain prognostic information prior to surgery [16]. This was demonstrated in an elegant study of 39 brain tumour patients, in 19 of whom treatment plans were altered based on information obtained with fMRI [16]. Most notably, out of 9 patients considered inoperable based on information from conventional imaging, 7 were in fact operated after considering the fMRI results. Similar findings were reported for the pre-surgical assessment of 60 epilepsy patients, in the majority of whom further studies such as the invasive intracarotid amobarbital Wada test were avoided with fMRI and surgical planning was altered in > 40 % [17].

For fMRI to be used in such a setting, both high sensitivity and high specificity are required. High sensitivity for eloquent brain regions is needed to reduce the false negative rate so that no eloquent cortex is missed and no functional deficit is induced by surgery. At high specificity the false positive rate is low, which means that the visualised areas of activation relate to truly eloquent or critical brain regions. At low specificity non-critical brain regions are also visualised, inducing the risk that such areas are avoided at surgery and are subsequently exposed to a less extensive resection than would have been possible.

The validity of fMRI compared with intraoperative ECM as a gold standard has been studied for motor and to a lesser extent for language function representation in the brain.

Motor Function

Motor cortex assessment has been validated in a multitude of studies that generally report a good correlation between fMRI and intraoperative ECM. Reported sensitivities for localisation of the primary motor cortex range from 88–100 % [18–21]. Specificities are also high, ranging from 87–100 % [18–21]. Such high reliability may be contributed to by the robust activation that is seen with simple motor tasks that can be easily performed by the majority of patients. Also the functional anatomical stability of the sensorimotor area, at both the macroscopic and microscopic levels, probably contributes to the reliability of fMRI of motor function [22]. Spatial accuracy of fMRI motor cortex localisation is found to be within the range of 1–2 cm. Yetkin et al reported that all intraoperative ECM and fMRI sites of activation were within 2 cm, while 87 % were within 1 cm [23]. Importantly though, reliability seems to be decreased with high tumour grades, as demonstrated by Bizzi et al [19]. In their study of 17 patients with benign and malignant brain mass lesions in or near the primary motor cortex, overall sensitivity was 88 %, but only 65 % in grade-IV gliomas. This issue is further addressed in the next section on fMRI considerations.

Language Function

In contrast to the high validity shown for fMRI of motor function, results from language function validation studies are controversial, varying from 100 % sensitivity for fMRI to identify all critical language areas to as low as 22 % [24–27]. Reported specificity is even more variable, ranging from 0–100 %. Validation studies of fMRI of language function in brain tumour patients are relatively scarce, are generally performed in small patient populations, and suffer from differences in the validation methods used among the studies, disparities of brain lesions, and the variety of the language tasks performed preoperatively and during intraoperative ECM [22]. The mapping of language function is also more complex than that of the sensorimotor cortex due to the lack of consistent surface landmarks and substantial inter-individual variability. The language cortical network seems to consist of critical regions, essential for language processing, and participating but non-critical areas, which may be resected without inducing a permanent language deficit. These areas cannot be reliably distinguished with fMRI, resulting in low specificity of fMRI compared with intraoperative ECM. In one of only 2 studies in which a site-by-site correlation of fMRI language activation with a large number of tags of intraoperative ECM was performed, the verb generation task was found to be the most sensitive single task out of a language battery of 5 tasks, and is therefore a commonly used task for preoperative lan-

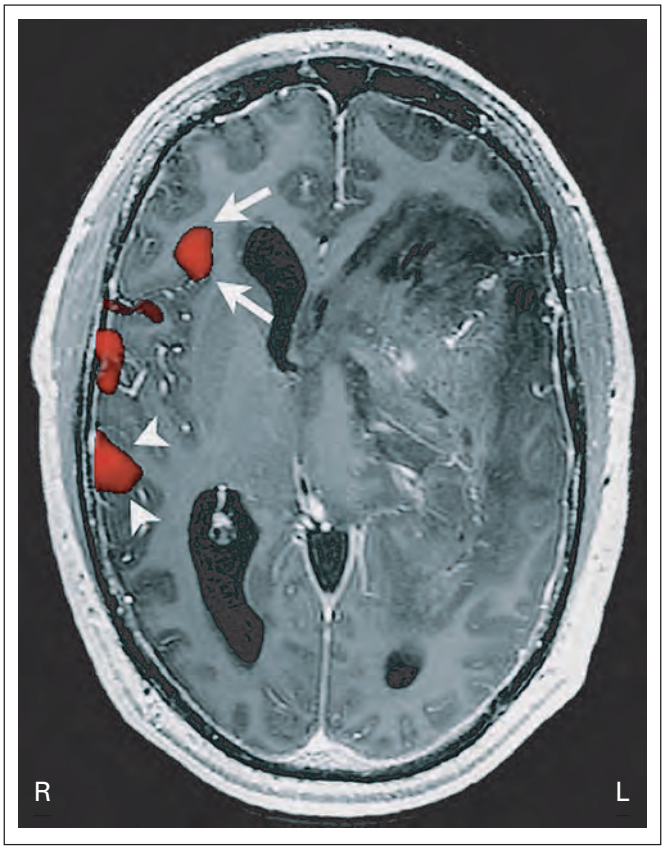

Figure 3. Large high-grade tumour in the left temporal lobe of a right-handed patient. fMRI activation of a verb generation task is present in the expressive-language area in the inferior frontal gyrus (arrows), as well as in the receptive-language areas in the posterior temporo-parietal cortex (arrowheads) in the right hemisphere. No activation is seen in the left hemisphere. Upon surgery, a left-lateralised hemispheric language representation was found with ECM, as would be expected in a right-handed patient. The atypical lateralisation towards the right hemisphere found with fMRI is most likely due to a tumour (mass) effect decreasing the BOLD signal in the affected left hemisphere.

guage fMRI [28]. Bizzi et al used the verb generation task for a site-by-site comparison between fMRI and intraoperative ECM, representing the only validation study in which the same task was used for fMRI and intraoperative ECM [19]. In their study of 17 patients with lesions in or near presumed language representation areas, sensitivity and specificity were found to be 80 % and 78 %, respectively.

Results from studies comparing preoperative fMRI with the Wada test to assess hemispheric language lateralisation, however, are much better [27, 29–32]. With reported agreements of > 90 % in a multitude of studies, fMRI has now mostly replaced the Wada test for the assessment of language lateralisation, given its obvious advantage of being non-invasive and, to a certain extent, giving additional spatial information on the language areas. Care still needs to be taken with large and/or high-grade tumours in or near the presumed language representation areas, since they may interfere with the cerebrovascular hemodynamic auto-regulation that the BOLD response in fMRI depends on (Figure 3) [33, 34]. Such considerations are discussed in more detail in the next section.

Taken together, the results of validation studies do not support the sole use of fMRI to localise language areas, but do show that fMRI can reliably replace the Wada test for the assessment of hemispheric language lateralisation. Atypical language lateralisation demonstrated with fMRI, however, should be considered as an indication for further assessment.

Other Functions

The visual cortex has been a frequent topic of study since the early days of fMRI, due to its relatively strong BOLD response and easy implementation of stimulus paradigms. Presurgical mapping of the primary visual cortex has been described [20] and may be indicated when the normal anatomy is severely distorted by the tumour and/or when the brain structure of interest is located deep inside the brain and cannot be assessed by ECM [35]. Commonly used stimulus paradigms are flashing lights presented with light-proof goggles and reversing black-and-white checkerboards [35].

Another function that may be assessed with fMRI is visuospatial attention, failure of which results in spatial neglect. This condition arises with damage of the temporoparietal or frontal cortex, the thalamus or the basal ganglia, generally of the right hemisphere [36]. It is an invalidating condition, in which patients behave as if the left part of the world does not exist. Functional localisation may be assessed with fMRI using a line bisection task [36], in which patients are asked to bisect 20-cm horizontal lines, which has been used successfully during ECM [37, 38].

Critical Issues

There are several limitations of fMRI that need to be considered when using the technique for pre-surgical assessment of brain tumour patients. These include issues that are inherent to the technique, such as spatial and geometric uncertainty, tumour effects on the BOLD signal, inter- and intra-individual variability, lack of discrimination between essential and modulating brain regions, and lack of information on the underlying white matter [39]. The imaging sequence used for BOLD fMRI is particularly sensitive to postoperative effects, such as metallic implants and surgical staples, air underneath the skull flap, and blood products, as well. This means that additional care needs to be taken in patients who have had previous surgery, biopsy, or haemorrhage. Small regions of haemosiderin deposition may not be visible on conventional imaging, but will show large artefacts in the BOLD fMRI data. Such artefacts are obscured on the fMRI activation colour maps, which would simply show decreased or no activation in the artefactual area. It is therefore crucial that the raw data are scrutinised for such artefacts in every patient [40]. Other issues with pre-surgical fMRI, that may be resolved in the future, are the lack of standardisation of tasks and image processing techniques.

Spatial and Geometric Uncertainty

Several papers advocate measuring the distance between the eloquent brain region as determined with fMRI and the tumour margin to assess the risk of postoperative neurological deficit. Mueller et al for instance reported that no motor deficit was caused when the distance exceeded 2 cm, but that this risk increased to 33 % when the distance was between 1 and 2 cm, and to 50 % when the distance was < 1 cm [41]. In a more recent study, Krishnan et al suggested that within a 1-cm range intraoperative ECM should be performed while com-

plete resection could be achieved safely when the distance between fMRI activation and tumour margin exceeds 1 cm [42]. The problem with such recommendations is that the measurement of the distance between fMRI activation and brain tumour margin highly depends on the statistical threshold that is applied to the fMRI data after image processing. With a more lenient threshold, the spatial extent of the fMRI activation cluster is increased compared with a more stringent threshold. Due to a large variation of fMRI activation among individuals, which is even more pronounced in brain tumour patients, there is no single optimum statistical threshold that can be used to assess fMRI data [15].

Instead, a centre-of-gravity approach should be used for activation clusters to localise the maximum activation to a certain gyrus. Even with this approach one should keep in mind that fMRI activation is an indirect visualisation of changes in the venous vascular bed near the site of neuronal activity. Small parenchymal venules are estimated to be up to 1.5 mm distant from the site of neuronal activity, while the larger draining veins are maximally 5 mm away [18]. Such spatial uncertainty is inherent to the BOLD fMRI technique, especially at the commonly used MRI scanner field strengths of 1.5T and to a lesser extent 3.0T.

Precise localisation of fMRI activation is further complicated by geometric distortions of the brain that are related to the imaging sequence used for BOLD fMRI, as well as the shift of the brain that occurs upon craniotomy, which may well be up to 2 cm. The latter issue may be resolved by applying intraoperative imaging techniques to update preoperatively acquired fMRI data to the intraoperative situation [43].

Tumour Interaction with the BOLD fMRI Signal

One of the major issues with the reliability of BOLD fMRI is the fact that the technique relies on the tight link between neuronal activity and hemodynamic changes. Neuronal activity is only measured indirectly as the BOLD signal, which relies on several assumptions of neurovascular coupling. While these assumptions may be valid in healthy volunteers, they may be utterly invalid in the presence of brain or even extra-cranial pathology affecting normal cerebrovascular hemodynamic auto-regulation [44]. Such processes lead to neurovascular uncoupling, which may occur both at the edge of brain tumours as well as in the normal vascular territories at some distance of the tumour. Several studies have shown that fMRI activation may be reduced adjacent to the brain tumour, while neurological function is still intact [33, 45].

At the edge of the tumour, astrocytes and macrophages release nitric oxide which increases local perfusion and may subsequently lead to a decrease of the BOLD signal [33]. Furthermore, high-grade gliomas induce the proliferation of abnormal vessels in the adjacent brain parenchyma that have been shown to lose auto-regulation and have shown a reduced response to physiological stimuli [45]. Both in high- and in low-grade gliomas, neurovascular coupling may be reduced by the tumour's infiltrative nature compromising the neuronal contacts with the capillary beds and astrocytes [33]. Finally, the mass effect of the tumour may have unpredictable effects on the BOLD signal. Moderate compression of the draining venules and larger veins may prevent pooling of blood and thus increase the outflow of deoxygenated blood from the area of activation, thereby reducing the BOLD signal [45]. Alternatively, compression of the draining venules may inhibit the outflow and cause pooling of deoxygenated blood in the tumour region, also reducing the BOLD signal [15].

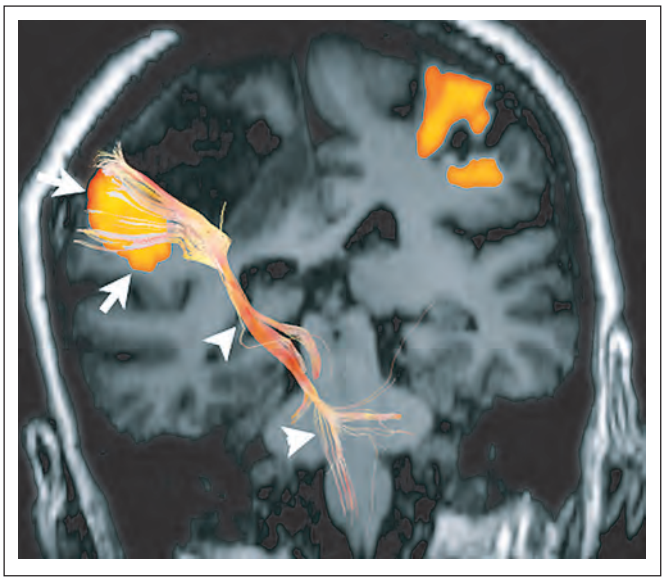

Figure 4. Combined fMRI and DTI tractography in a coronal view of a patient with a tumour near the primary motor cortex. Displacement of both the primary motor cortex (arrows) and the corticospinal tract (arrowheads) is seen.

White Matter Tracts

Functional MRI provides information on cortical representation of brain function, but not on the course of the subcortical and deep white matter tracts, such as the corticospinal tract (CST) and the arcuate fasciculus for motor and language function, respectively. Inadvertent transection may lead to equally devastating results as resection of the eloquent cortex. Visualisation of such tracts may be obtained with diffusion tensor imaging (DTI) and tractography. Diffusion-weighted imaging provides image contrast sensitive to the diffusion of water molecules [46], which is used in DTI to assess the favoured diffusion direction, such as parallel to highly structured white matter fibres. This information can then be translated into a vector field. When vectors that have the same orientation are combined, the course of white matter tracts may be visualised, which is known as tractography [47]. When fMRI and DTI are combined to perform tractography for specific white matter tracts, displacement and invasion by brain tumours can be visualised preoperatively (Figure 4) [48].

Conclusions

Functional MRI is a valuable tool in the pre-surgical assessment of brain tumour patients, but needs to be used with care. Interpretation of the results requires a lot of experience and may be difficult. Knowledge of functional brain anatomy is a first requirement for risk evaluation and to determine which fMRI tasks need to be performed. The shortcomings of fMRI in a clinical setting as described above need to explicitly be taken into account in every patient. In our institution, fMRI, combined with DTI tractography, is used to aid neurosurgical planning but intraoperative ECM is always used for confirma-

tion when activation is shown in the proximity of the brain tumour or if activation is atypical. Most importantly, the absence of fMRI activation does not exclude the presence of functional neuronal tissue, not even within infiltrative tumours.

Conflict of Interest

The author states that no conflict of interest exists.

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Gliadel Wafers in Clinical Practice: The Neurosurgical View

Maria Angela Samis Zella*, Marion Rapp*, Hans Jakob Steiger, Michael Sabel

Abstract: Gliadel wafers are the only local chemotherapeutic agent approved for the treatment of primary and recurrent malignant gliomas. Since the approval, considerable clinical experiences in multimodal regimens have been made and require a re-evaluation from a neurosurgical point of view.

We reviewed the database entries from Medline, EMBASE, and BIOSIS from 2005–2012. Search terms included: gliadel, carmustine, or BCNU wafer, implant and complications or adverse events (AE).

Endpoints of our analysis were efficacy and safety data of gliadel for primary and recurrent glioblastomas. AEs included intracranial infections, oedema, healing abnormalities, CSF fistulae, and hydrocephalus.

For primary glioblastomas (GBM), median progression-free survival (PFS) reached 12.3 months and overall survival (OAS) ranged from 19.2–20.7 months. For recurrences, the 6-month OAS was 82 %, 1- and 2-year OAS rates were 47 % and 10 %, respectively. Median OAS was 50.3 weeks. AE rates for primary GBMs ranged from 0.8–16.7 % for cerebral oedema, from 4.4–8.3 % for healing abnormalities, 5.5 % for liquor leaks, from 0.0–47.0 % for hydrocephalus, and 4.8 % for intracranial infection. AE rates for recurrent glioblastomas ranged from 0.0–7.2 % for cerebral oedema, from 4.8–55.6 % for healing abnormalities, from 4.8–33.3 % for CSF fistulae, from 0.6–22.2 % for hydrocephalus and 5.0 % for intracranial infection.

The use of gliadel wafers is determined by the individual decision of the responsible neurosurgeon due to the absence of general guidelines. The AE rates reported in current treatment strategies are relatively low. **EANO Mag 2012; 2 (3): 129–32.**

Key words: high-grade glioma, glioblastoma, gliadel wafer, adverse events

Introduction

Glioblastoma multiforme (GBM) is the most common and aggressive form of malignant glioma, with an annual incidence of approximately 2–3 cases per 100,000 persons (CBTRUS, http://www.cbtrus.org) [1].

Since 2005, standard treatment for GBM consists of the largest possible, functionality-preserving surgical resection, followed by radiotherapy with concomitant chemotherapy with temozolomide (TMZ), followed by 6 cycles of TMZ [2]. Despite these important improvements in surgical and adjuvant therapy, GBM remains an incurable tumour. Median time to progression is 7 months and survival remains limited with about half of patients succumbing to the disease within 1–2 years after diagnosis [2, 3].

Strategies to improve outcome are therefore needed. An obvious approach is to consider the combination of all available treatment options. The carmustine wafer (Gliadel®) is a nitrosourea oncolytic agent consisting of 192.3 mg of a biodegradable polyanhydride copolymer and 7.7 mg of carmustine (1,3-bis (2-chloroethyl) -1-nitrosurea [BCNU]). Following surgical resection, these wafers are applied directly into the tumour cavity. The carmustine release takes place in a controlled manner over a period of 20 days and reaches high concentrations in peritumoural regions by diffusion.

In 2 phase-III studies [4, 5], Gliadel® was shown to prolong survival of GBM patients, yet many neurosurgeons are reluctant to use this treatment modality mostly because of the expected post-operative complications. This review provides a summary (unfortunately without formal statistical analysis) of the current literature, suggesting potential benefit of Gliadel® with reasonable toxicity and side effects. Such an overview points out the potential benefit of Gliadel®, and may help establish Gliadel® as part of the standard of care for patients with HGG. Therefore, it might be useful to review the current data on the impact of Gliadel© wafer implantation from a neurosurgical point of view.

Material and Methods

We performed a review of the available database entries from Medline, EMBASE, and BIOSIS from 2005–2012. Search terms included: Gliadel®, carmustine, or BCNU wafer, implant and complications or adverse events (AE). Results were limited to human studies and the use of BCNU wafers in patients with high-grade gliomas (HGG).

Endpoints of our analysis were the efficacy and the safety data of Gliadel® by primary and recurrent GBMs. We specifically screened for AEs previously described in phase-III studies [5] including intracranial infections, oedema, healing abnormalities, CSF fistulae, and hydrocephalus.

To estimate the overall incidence of AEs, rates of AEs from singular studies were summarized as median rates. Due to the heterogeneity of the studies included, we did not conduct a formal statistical analysis to determine comparability among groups. To underline consistent similarities or differences between groups concerning overall incidence and the median rate, we performed a qualitative comparison.

Pivotal Trials

Brem et al [4] demonstrated in a double-blinded, randomized, placebo-controlled study a significant survival benefit for recurrent GBM patients after Gliadel® implantation (median overall survival [OAS] of 7.2 months for BCNU wafer-treated

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Received on August 14, 2012; accepted after revision on September 18, 2012; Pre-Publishing Online on October 18, 2012

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patients vs 5.4 months for placebo wafer-treated patients). This study led to the approval of Gliadel® in the treatment of recurrent GBM in 1995.

For primary GBMs, a meta-analysis combining the results of the randomized phase-III trial published by Westphal et al [5] and a randomized phase-III study by Valtonen et al [6] demonstrated a survival increase to 13.1 vs 10.9 months for placebo patients (p = 0.03). The combined results of these trials led to regulatory approval of BCNU wafers for the treatment of newly diagnosed malignant gliomas in March 2003.

In 2005, Stupp et al [2] demonstrated the efficacy of radiation therapy and concomitant TMZ in newly diagnosed GBMs in a phase-III trial. This protocol marked in a revealing way the therapeutic path of GBMs patients and became the standard treatment for newly diagnosed GBMs. Therefore, data on the efficacy and complication rate of Gliadel® wafer implantation in primary and recurrent GBM patients treated with the Stupp protocol are now of great interest.

Efficacy of Gliadel® Wafer Implantation in Primary GBM in Combination with the Stupp Protocol

Although the combination of Gliadel® wafer implantation and concomitant radiochemotherapy with temozolomide might combine successful treatment strategies for malignant gliomas, combined treatment with the Stupp protocol and Gliadel® wafer implantation has been evaluated only in few retrospective studies.

In a retrospective, non-randomized study, De Bonis [7] analysed 165 patients with newly diagnosed (n = 77) or recurrent (n = 88) GBM for safety and efficacy of Gliadel® wafers. Multivariate analysis showed that the only factor associated with longer survival for newly diagnosed GBM was the extent of resection. Patients with a higher number of wafers implanted were significantly at risk for AEs. He concluded that adding Gliadel® to standard treatment did not significantly improve outcome, with a significant higher risk for toxicity after Gliadel® use.

By contrast, Miglierini [8] concluded that the concomitant use of surgery with implantation of BCNU wafers followed by radiochemotherapy according to the Stupp protocol seems to be well-tolerated. From 2006–2010, this retrospective single-centre study enrolled 24 newly diagnosed GBM patients and revealed a median OAS of 19.2 months. Median progression-free survival was 12.3 months in this cohort. McGirt et al [9] demonstrated a median OAS of 20.7 months after treatment with a combination of Gliadel® wafers and the Stupp protocol with acceptable side effects.

Continuative studies of 111 GBM patients treated initially with Gliadel® wafers followed by the Stupp protocol demonstrated that MGMT promoter methylation status and low MGMT expression both were identified as positive prognosticators [10].

As becomes evident from the analysis proposed, a lot of authors assert that the combination of Gliadel® wafer implantation and Stupp protocol may be a good strategy against GBM, but data available do not permit to suggest it as standard treatment.

Efficacy of Gliadel® Wafer Implantation in Recurrent GBM

After failure of the first-line therapy, the application of Gliadel® wafers for the treatment of recurrent GBM is still controversial.

Quinn [11] conducted a phase-II, open-label, single-centre trial on patients with recurrent GBM. After gross total resection of the tumour, up to 8 Gliadel® wafers were implanted. Bolus infusion of 06-benzylguanine (06-BG) was administered at 120 mg/m^2 over 1 hour on days 1, 3, and 5, along with a continuous infusion at 30 mg/m^2/d. 52 patients were accrued. The 6-month OS was 82 % (95-% confidence interval [95-% CI]: 72–93 %). The 1- and 2-year OS rates were 47 % (95-% CI: 35–63 %) and 10 % (95-% CI: 3–32 %), respectively. Median OS was 50.3 weeks (95-% CI: 36.1–69.4 weeks). Treatment-related toxicity with this drug combination included grade-3 hydrocephalus (9.6 %), grade-3 cerebrospinal fluid (CSF) leak (19.2 %), and grade-3 CSF/brain infection (13.4 %). The author simply concluded that more trials are required to verify that Gliadel® wafer implantation results in increased survival benefits without added toxicity.

Menei [12] reports the results of a retrospective multicentre study including 80 patients with a recurrent glioma; 58 of them received Gliadel® wafers as a second-line therapy and 22 as a first-line therapy. In this group, 20 % received conventional radiotherapy, 32.5 % received systemic chemotherapy, and 16.3 % received concomitant radiochemotherapy with TMZ according to the Stupp protocol. Median survival in the recurrent glioma group was 7 months. Total or subtotal excision appeared to have an important impact on survival (243 vs 122 days, 62 % reduction for risk of death, 95-% CI: 27–80 %; p = 0.002), as did preoperative KPS (253 vs 183 days, 56 % reduction for risk of death, 95-% CI: 15–77 %; p = 0.012) on univariate analysis.

In this analysis, Menei concluded that the combination of Gliadel® and radiochemotherapy with TMZ was well-tolerated and appeared to increase survival without increasing AEs.

De Bonis [7] analysed in the previously mentioned retrospective, non-randomized study survival data for 88 patients with recurrent GBM. He demonstrated that the only factor associated with a longer survival was the extent of resection and he concluded that adding Gliadel® to standard treatment did not significantly improve the outcome and that toxicity after Gliadel® use is significantly higher, both for patients with newly diagnosed and patients with recurrent GBM.

Efficacy data concerning recurrences are affected by a variety of factors and are still too controversial to tread a path regarding the better therapeutic strategies.

Surgical Complications of Gliadel® Wafer Implantation in Primary and Recurrent GBMs (Table 1)

Intracranial Infections

In both trial groups involving patients with newly diagnosed and recurrent GBMs, rates of AEs were similar.

The overall incidence of serious intracranial infections (abscesses, meningitis) has been shown to be equal in the recurrent group (5.0 %) and in the newly diagnosed GBM group (4.8 %), although without statistical significance. Attenello [13] retrospectively reviewed 1013 patients undergoing craniotomy for resection of malignant brain astrocytoma (World Health Organization grade-III/IV disease); a total of 288 (28 %) received Gliadel® wafers (250 glioblastoma multiforme [GBM], 38 anaplastic astrocytoma/anaplastic oligodendroglioma [AA/AO], 166 primary resection, 122 revision resection). He reported a rate of perioperative surgical site infection of 2.8 % among the Gliadel® population vs 1.8 % among the non-Gliadel® population (p = 0.33), for meningitis of 0.3 % among the Gliadel® population vs 0.3 % among the non-Gliadel® population (p = 1.00).

This data is in line with the literature considering patients with brain tumour undergoing craniotomy (0.1–43 %) [14].

Hydrocephalus

Similar results were observed considering the incidence of hydrocephalus requiring a VPS; the range was 0.0–47.0 % of the patients with newly diagnosed GBMs versus 0.6%–22.2% of patients with recurrences. A recent study specifically designed to analyze the incidence of adverse events in first-line treatment of malignant glioma reported a postoperative hydrocephalus at an incidence of 7 % [15].

These studies confirmed the elevated risk of hydrocephalus associated with Gliadel® wafer implantation. Other studies indicate, however, that the risk of a hydrocephalus requiring an operative treatment does not appear to be increased with the use of Gliadel® wafers [15].

CSF Fistulae

According to the pivotal trials the incidence of CSF fistulae appears more common in the Gliadel® wafer group than in the placebo wafer group (5 vs 0.8 %), but this difference did not reach statistical significance.

Between the patients with newly diagnosed GBMs the risk of developing CSF fistulae reaches a median value of 5.5 % for newly diagnosed patients versus a risk ranging from 4.8–33.3 % for patients with recurrences (median value 9.1).

Attenello [13] reported a rate of CSF leak of 2.8 among the Gliadel® population versus 1.8 among the non-Gliadel® population (p = 0.33).

Gallego et al [16] reported 3 patients who had fatal hydrocephalus and CSF fistulae related to Gliadel® wafer implantation.

Healing Abnormalities

Pivotal trials showed a significant difference in the incidence of healing abnormalities: 14 % for the Gliadel® wafers group and 5 % for the placebo wafers group (p = 0.05). In non-phase-III trials, healing abnormalities appear to be one of the most common AEs [5] and appear to be higher in recurrent disease with a median value of 4.4 % than in newly diagnosed disease with a median value of 21.3 % [17–22].

According to the more recent literature, the rate of healing abnormalities is comprised in a range from 4.4–8.3 % of the patients with a newly diagnosed GBM and in a range from 4.8–55.6 % of the patients with recurrences [22]. Attenello [13] reported a rate of healing abnormalities of 0.7 among the Gliadel® population versus 0.4 among the non-Gliadel® population (p = 0.63).

Oedema

The trials considered did not underline any difference between the groups for brain oedema: the overall incidence in patients with newly diagnosed disease ranged from 0.8–16.7 % and from 0.0–7.2 % for recurrences. According to Attenello's retrospective study [13], a rate of oedema of 2.1 % among the Gliadel® population versus 2.3 % among the non-Gliadel® population (p = 1.00) was reached.

These data appear comparable to those registered by phase-III pivotal studies where patients who received Gliadel® wafers for recurrent HGGs reached a rate of 4 % of oedema [22].

In spite of the heterogeneity of the complication rates demonstrated in patients treated with Gliadel® wafers by the listed studies, one can infer that the complication rate is relatively low and, when present, these complications require minor treatment.

Conclusion and Future Aspects

Gliadel® wafers are approved for the treatment of patients with newly diagnosed GBMs as adjunct to surgery and radiation and are also indicated to treat recurrent GBMs. Their approval was based on clinical trial results showing the median survival of patients with high-grade malignant gliomas increased to 13.1 vs 10.9 months for placebo patients (p = 0.03) [5], and the median survival of patients with recurrent GBM increased from 5.4 months to 7.2 months [4].

Table 1. Rates of surgical complications following Gliadel® wafer implantation in primary and recurrent glioblastomas (GBM).

	Newly diagnosed GBM (%)	Recurrent GBM (%)
Hydrocephalus	0.0–47.0	0.6–22.2
CSF leak	5.5	4.8–33.3
CSF/Brain infections	4.8	5.0
Healing abnormalities	4.4–8.3	4.8–55.6
Oedema	0.8–16.7	0.0–7.2

Despite these results, the current data available on the use of Gliadel® wafers in primary or recurrent GBM are still controversial. First, since there are no prospective, randomized trials available on the efficacy and toxicity of Gliadel® wafer implantations after the introduction of the Stupp protocol, the use of Gliadel® wafers will be more determined by the individual decision of the responsible neurosurgeon than by general guidelines.

Second, since the complication rates for the implantation groups in most studies are consistent with the rates from historical BCNU wafer studies, the fear of complications should not preclude the use of BCNU wafers by recurrent GBMs after pre-treatment with the Stupp protocol. Survival data indicate a potential benefit, but formal, prospective studies are needed to more thoroughly assess toxicity risk and any potential survival benefit.

Both of these dichotomies need to be addressed for further studies, if possible, or for further progress to be realized.

Conflict of Interest

The authors state that no conflict of interest exists.

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Intractable Headache in a Glioblastoma Patient

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Case Study

A 37-year-old male patient was diagnosed with glioblastoma and received standard surgery and adjuvant radiochemotherapy with temozolomide. After 6 cycles of adjuvant chemotherapy he showed clinically and radiologically stable disease.

Five months after the end of adjuvant treatment he developed headache. The severity of headache gradually increased over days to weeks without response to initial steroids or conventional analgesic treatment. High dosages of opiates showed only little clinical efficacy. With respect to the primary tumour location, the glioblastoma was radiologically stable.

Besides the severe headache, the patient suffered from low-back pain, diffuse sensory deficits at the left upper as well as the left lower extremity, mild paresis at the lower limbs (left > right), and urinary dysfunction.

The reason for neurological deterioration as well as intractable headache needed to be resolved.

What Is Your Diagnosis?

The diagnosis of neoplastic meningitis was established by means of MRI of the neuroaxis showing typical enhancement of the meninges, as well as contrast-enhancing bulky lesions (Figures 1 and 2) together with neurological signs and symptoms. Due to a rapid clinical decline, only supportive management was applied. Palliative local radiotherapy to the cervical spine was initiated but had to be terminated due to the rapid clinical decline. The patient died shortly after the diagnosis of neoplastic meningitis.

Neoplastic meningitis in patients with malignant gliomas is a rare complication most frequently occurring at an advanced stage of the disease and represents a fatal complication. But it has also been reported as the initial presentation of malignant glioma [1]. Control of its neurological signs and symptoms is challenging.

Diagnosis of neoplastic meningitis can often be time-consuming and misleading. From the clinical point of view, patients with rapidly progressing intractable headache without clinical and radiological signs of increased intracranial pressure are highly suspicious for neoplastic meningitis. Mental changes and radicular sensorimotor signs can be predominant as well [2–4]. In accordance with neurological signs and symptoms, the diagnosis can be established by means of an MRI of the total neuroaxis. CSF analysis mostly indicates elevated protein levels but malignant cells are rarely found [1, 4].

Treatment is mainly supportive, although there are some case studies on intrathecal chemotherapy for example with liposomal ARA-C [5], or with temozolomide [6] reporting some benefit. Also local radiotherapy to symptomatic areas or bulky disease may be considered. With respect to headache, only high-dose opiates may show some clinical benefit.

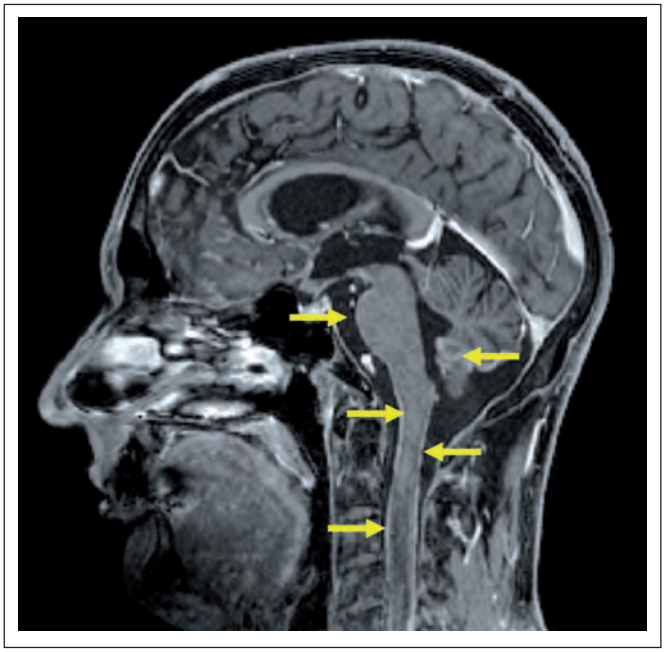

Figure 1. T1-weighted MRI (sagittal) with contrast media, showing enhancement of the meninges (arrows).

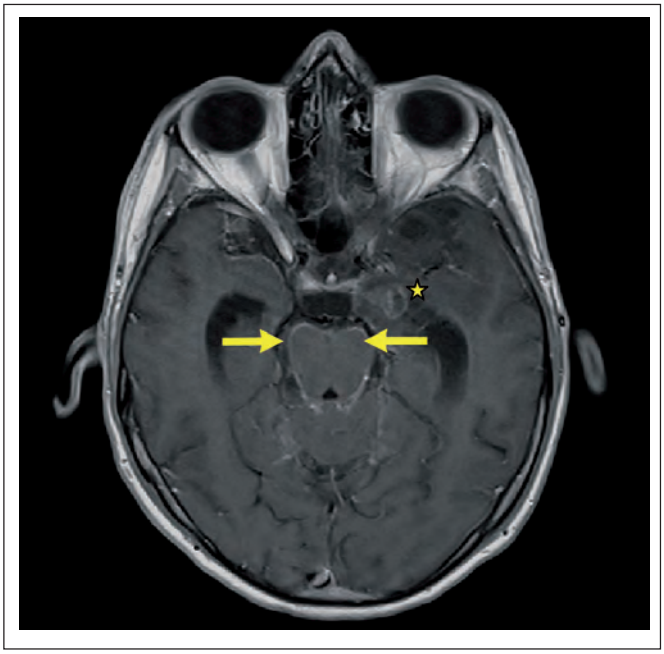

Figure 2. T1-weighted MRI (axial) with contrast media, showing enhancement of the meninges (arrows), and only little enhancement at the primary tumour location at the left temporobasal area (asterisk).

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An Exophytic Brainstem Lesion

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Case Study

A 45-year-old man was admitted to our hospital for progressive dysphagia and gait disturbance. The patient had no other medical history. Clinical examination showed IX-X-XI cranial nerve palsies and left pyramidal syndrome. MRI demonstrated an exophytic contrast-enhancing lesion in the medulla oblongata (Figure 1).

What Is Your Diagnosis?

Discussion

Partial surgical removal of the mass lesion was performed. The pathological diagnosis was a pilocytic astrocytoma (WHO grade I). Clinical symptoms progressively improved. Since the residual tumour progressed in the follow-up, carboplatine chemotherapy and focal radiotherapy were proposed. Four years later, the patient was still considered in remission.

Exophytic contrast-enhancing gliomas, which are well-known in children (up to 10 % of cases) and are associated with good prognoses, are extremely rare in adults, perhaps because most exophytic gliomas are pilocytic astrocytomas, which are rare tumour types in adults [1]. In adults, great caution is needed to attribute an exophytic contrast-enhancing brainstem mass to this type of benign lesion because malignant gliomas and other non-tumoural diseases may have a similar radiographic appearance, underlining the importance of histological confirmation [1, 2]. Surgical resection is recommended in some cases, including dorsal exophytic tumours protruding into the fourth ventricle. Improvement in neurosurgical techniques (particularly the use of intraoperative ultrasound, intraoperative neurophysiological mapping, and computer reconstruction techniques) has facilitated partial resection of tumours previously considered inoperable, or even gross total removal in some cases, without affecting the functional status.

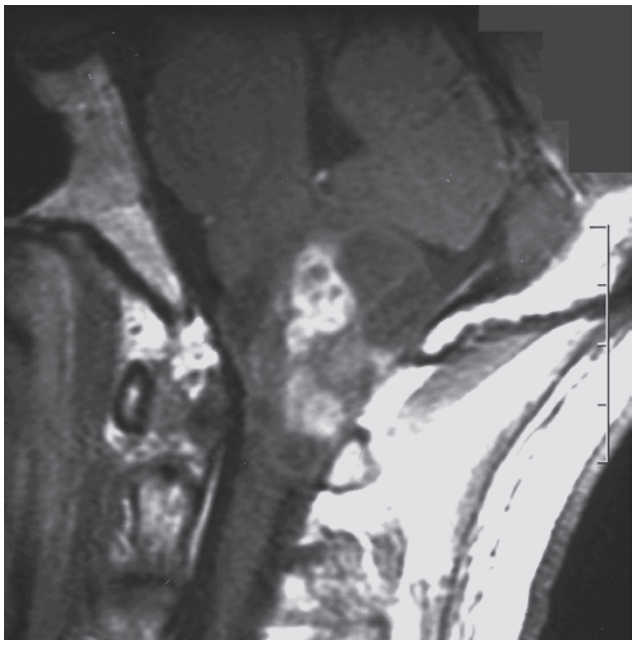

Figure 1. Brain MRI (T1-weighted/gadolinium) showing a contrast-enhanced lesion in the medulla oblongata. The tumour has dorsal exophytic and cystic components.

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Low-Grade Gliomas, Changes in Personality and Character, Maintaining Relations: A Case Study of a 49-Year-Old Male with an Oligodendroglioma

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Introduction

Patients with low-grade gliomas can be affected in several ways but all meet a disease with a limited life expectancy, with signs and symptoms like seizures and focal deficits. The treatment of a low-grade glioma and its symptoms may consist of neurosurgery, radiation therapy, chemotherapy, antiepileptic drugs, and corticosteroids. Symptoms like cognitive disorders and personal and character changes are described and are the subjects of investigation. These cognitive deficits can be caused by the tumour, by tumour-related epilepsy, by tumour treatment, and by psychological distress [1]. Health care professionals like clinical nurse specialists and nurse practitioners play an important role in the guidance of the patient and their partners through the disease by informing, educating, and supporting them [2]. Psychosocial support in behavioural and character changes could be part of the care, how nurses can pay attention to these possible, sometimes subtle changes in function and cognitive abilities is explored by a search in the literature with search terms such as personality and character changes and through the description of a case study of a patient with a low-grade oligodendroglioma.

Background

Patients with low-grade gliomas have a more favourable prognosis than patients with high-grade gliomas, they can undergo surgical resection, they may receive radiotherapy and chemotherapy at some point in the course of their disease but disease progression is inevitable, patients will eventually die because of their tumour. Median survival of low-grade oligodendrogliomas and mixed gliomas is 16.7 years. Despite this relatively favourable prognosis patients and their partners are being confronted with an incurable disease, cognitive deficits, and emotional decline. How patients and their partners deal with this knowledge and which difficulties they will meet has been subject of many studies.

Various studies have evaluated the effect of surgical and oncological treatments on cognitive status and quality of life (QoL) in low-grade gliomas. Klein et al [3] studied the impact of radiotherapy on QoL and cognitive functions in a group of mid-term to long-term survivors of low-grade gliomas and found neurological impairment to be rare, but serious disturbances in cognitive and affective status were frequently and equally found in both the control group and the group who received radiotherapy. Their conclusion was that disturbances in cognitive and affective status in these patients were likely to be tumour-related rather than radiotherapy-related. Douw et al [4] studied the impact of radiotherapy on cognitive functions of the same group of long-term survivors of low-grade gliomas at a mean of 12 years after first diagnosis. They found that patients who did not have radiotherapy had stable radiological and cognitive status, while patients with low-grade gliomas who received radiotherapy showed a progressive decline in attentional functioning. Because radiotherapy can delay progression but has no influence on overall survival, they suggested that the risk of long-term cognitive and radiological compromise that is associated with radiotherapy should be considered when treatment is planned.

Påhlson et al [5] demonstrated the usefulness of neuropsychological assessment as a complement to detect cognitive dysfunction in patients (n = 35) with low-grade gliomas, while this impairment was not detected by neurological examination and was only to some extent reported by the patients themselves. Gustafsson [6] evaluated the need of support by describing function, quality of life, and coping with illness-related problems in patients with low-grade gliomas. The study showed that difficulties in role, cognitive and emotional functioning had a great impact on quality of life, more than physical problems. This has an obvious social impact on family life.

Salander and Spetz [7] followed 25 patients and their spouses during the whole course of the disease and detected 4 different social processes influenced by different ways of coping and communication within their relationship. Awareness, recognition, and (in-) ability to communicate lead to sharing certain perceptions or drifting apart. These processes are (1) the patient does not seem to be aware, the spouse is aware but pretends not to be, (2) both are aware, but the patient does not want to share, they drift apart, (3) both are aware, they do/do not talk openly about the gravity of the situation; nevertheless there is a joint platform, and (4) neither patient nor spouse seems to be aware, they carry on living as before. This could imply a possible burden in maintaining a relationship, as has been described by Edvardsson and Ahlström [8] for low-grade gliomas. They concluded that being next of kin to a person with a low-grade glioma could lead to extremely stressful emotions, being invisible and neglected, changed relations and roles and problems enabling strength in everyday life. In their study, they made a distinction between male and female caregivers: most statements occurring in all 4 themes were by females next of kin. This probably has an impact on the relationship between patients and their spouses, it affects commitment and the ability to maintain the relationship. Glantz et al [9] investigated the meaning of gender in the rate of partner abandonment in patients with serious medical illness, 214 had a malignant primary brain tumour, 193 had a solid tumour with no nervous system involvement, and 108 had multiple

sclerosis. They found that there was a > 6-fold increase in risk for divorce or separation after diagnosis when the affected spouse was a woman. Marriage duration at the time of illness was also correlated with separation among brain tumour patients, there was also a trend toward an increased separation in patients with frontal lobe tumours that may reflect the concurrent neurobehavioral changes commonly observed in these patients.

Janda et al [10] identified 6 important themes to improve guidance through the disease process by interviewing patients and their carers and refined them into 5 important recommendations. To improve care, patients should be assigned a case manager, should receive proactive dissemination of information, education and psychosocial support, should have access to assessment of neuropsychological functioning, facilitation of easier access to welfare payments and services facilitating communication about difficult illness-related topics. In a cross-sectional survey among 75 patients and 70 partners Janda et al [11] scored unmet supportive care needs and found that both patients and their partners scored high on changes in mental or thinking ability, and for the partner in behavioural aspects and personality changes of the person with the brain tumour and adjustment to it. It has to be said that the response rate was low and that the investigators interpreted the group as patients and partners actively seeking support.

Case Study

A male patient was diagnosed at the age of 34 with a suspect low-grade glioma in the left frontal lobe in 1995 after a tonic clonic secondary generalized seizure, after which he had a second seizure in February 1996. Epileptic activity was controlled by diphantoine until September 2001 when he experienced again a tonic clonic seizure. Because of the pregnancy of his spouse the intended biopsy was postponed until December 2001. After the biopsy and the diagnosis anaplastic oligodendroglioma (with deletion of 1p and 19q) radiation therapy was applied. Because of the impact of the illness in this phase on this young couple, they were referred to a psychologist for psychosocial support. Neuropsychological investigation to determine ability to work revealed inability for resumption, because of less attention and concentration, less initiative, and fatigue. In February 2004, the activity of the epilepsy and focal deficits on the right part of his body increased and he was operated in March 2004, the tumour was resected. Treatment afterwards existed of oral chemotherapy with temozolomide, after recurrence of the tumour treatment consisted of procarbazine, lomustine, and vincristine and currently bevacizumab with irinotecan. In guiding the patient and his wife the nurse practitioner spoke with them about the impact of the changes in behaviour and cognition on their relation and in the spring of 2009 the spouse decided to make an important step. She could no longer take care of her partner, her children and herself without being afraid of losing herself and becoming very unhappy. Her husband now lives in an institution for patients with non-congenital brain damage. *"I don't want to relieve myself from the responsibility to take care of my husband, I want to be loyal to my commitment but it is not that much fun anymore … My love is still there but my feeling of loneliness is prevailing.*"

Cognition

After a third seizure in 2001, the patient became less aware of his situation, where he was, who he was speaking to, for example his wife was pregnant and he forgot that they had agreed the name of the unborn child was to be kept a secret. In this period, priority was given to the birth of their firstborn and he was admitted to the hospital a week thereafter to undergo biopsy. After surgery, he was unable to accomplish concrete daily activities and assist his wife in the care for their child, he for instance did not take initiative to hold his son. He was afraid of having a seizure while holding the baby, he thought of him as a puppy which needed to be fed and did not take any initiative to cuddle his son. He also was afraid to be home alone. Taking initiative, planning, and organizing things, accomplishing concrete daily activities are aspects of the disease which were gone from this moment. The patient's parents took over and he became a child again depending on them, while his wife was at work and his son was in day care. *"He more and more became child of his parents than man of his wife…"*. Shared responsibility in financial matters was over, the spouse imitated his signature in important matters. Initiative later in this process to look for help and psychosocial support came from the spouse, the patient relied on his wife in these matters as well.

Emotions and Behaviour

The couple had been married for several years when the patient had his first seizure, they had a good relation and were both happy with their work and social status. After the first seizure in 1995, the patient experienced fear of the dark, fear of water – he had been very fond of all kind of water sports before his illness –, and fear of driving the car alone. Because he related the occurrence of seizures to the unexpected ringing of bells, he developed a fear for doorbells, alarm bells, and phones ringing suddenly.

In the first period after the diagnosis he was quiet, feeling discouraged, and cried for about a week after which he recovered from this feelings and continued his life. In 2002, after the diagnosis of the tumour – *"'it' got a name and a life expectancy"*, he was feeling sad and was able to share that in a certain way with his spouse by telling her of being afraid to leave her behind and not being able to see his child grow older. After radiation therapy, he became more tired, there was more need to sleep, resulting in staying in bed during the morning while his wife was working, his son was in day care, and his parents were caring. He now and then went back to his work, but after 2 years' sick leave after his diagnosis and treatment he was discharged and stayed at home. He was a person with low interest in being able to work, it was necessary but did not have his heart.

He became more directed to himself, had less social contacts, the days his wife was at home, he went back to bed just before lunch and his wife was not able to get him out of his bed when she wanted to. *"It became a silent battle, he did not do anything*". After recurrence of the tumour in 2004 with an increase in epileptic activity he was at some point more emotional about his treatment options and future. The second operation in March 2004 resulted in a subtle damage, a slight hemiparesis of his right leg and arm and some speech distur-

bances, because of this the expression of feelings became more difficult, he became even more introvert. He later on became more easily irritated, the reason for this irritation could be frustration because of the fact his children were overruling him in their play and he was slower due to his physical restrictions. *"He is not aggressive in any way, he doesn't hit his children or is verbally aggressive, he just struggles with his words"*.

The patient kept having unreal expectations towards his treatment and his options. He still wants to prolong his driving license and thinks he is still able to drive his scooter.

Maintaining the Relationship

In 2001, after the third seizure and admittance to the hospital, the birth of his child and the biopsy, the patient was no longer able to experience empathy for his wife or child. Before these events he was concerned about his pregnant wife, went shopping, took care of preparing dinner, cleaned the house, but afterwards these aspects of taking care within their relation disappeared. *"Loneliness entered …"* Retrospectively, this symptom was also present in 1995 but it disappeared after a short period.

Between the partners there was no longer a normal sexual relationship after the birth of the first son. When his wife decided for a second child she spoke about this with her parents, they supported her in her wish and understood the meaning of a second child for their daughter and grandchild. The second pregnancy soon was realized with more or less mechanic intercourse.

In 2009, the spouse stated that her husband's empathy was gone, he experiences his wife and sons in his thinking but not in his feeling and compassion. He asks about them but there is no longer any real interest, he does not anticipate on their needs. He does not realize the severity of his limitations and the effect of it on his relation with his wife and he does not have the power to restore it. Also comprehension has been lost for quite some time, he relies on his wife for decisions concerning their relation, family issues, and his well being. He relies on his physicians for his tumour treatment and on health care personnel in the institution he is in *"because my wife wants that"* for his daily activities. The structure in this unit contributes to his wellbeing and he participates in several activities in his tempo.

Conclusion

Several qualitative studies describe the existence of cognitive dysfunction and experienced changes in personality and character, influencing the QoL of patients and their partners. Besides, they also could have an impact on their relationship. Psychosocial support for the patient and the partner should be available during the treatment of disease and its symptoms, but the question of how to guide and inform patients and their partners about possible personality and character changes is not addressed.

In guiding the patient and his spouse for several years, the nurse practitioner was easily accessible to discuss such changes. Because of the slow growth of a low-grade glioma with a successive neurocognitive, physical, and psychosocial worsening of symptoms, it is not always easy to recognize the severe impact behavioural changes can have on QoL. Retrospectively, these changes appeared to be present for a longer time than assumed.

In supporting the patient, health care professionals should approach not only the patient but also the spouse on the possible strains in everyday life, from diagnosis to death, including dealing with limitations of deficits such as possible emotional, cognitive, and behavioural changes. In low-grade glioma patients with a favourable prognosis but with possible cognitive deficits and emotional decline, health care professionals such as clinical nurse specialists are in a position to pay attention to cognitive and behavioural changes, which can best be addressed by open and honest conversation with both the patient and the spouse.

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Patient Advocates and Guideline Development: Token Involvement or Meaningful Input?

Kathy Oliver

Clinical practice guideline (CPG) development is thriving across Europe.

We are moving toward consensus on the treatment of all kinds of cancer – from the very common to the very rare – reflecting the fact that treating cancer patients today requires a complex multidisciplinary approach.

At a recent "Forum on Multidisciplinary Clinical Guidelines in Oncology" hosted by the European CanCer Organisation (ECCO), over a dozen major medical societies – who among them have created more than 175 sets of clinical practice guidelines – met to debate the possibilities of greater cooperation and harmonisation in the development of European guidelines. The aim is to increase their quality and use.

But international harmonization of CPGs is a substantial challenge. A 2011 editorial in the *Annals of Oncology* explained that homogeneity among the developmental processes relating to internationally available guidelines does not exist [1].

Furthermore: *"In a recent report, nine well-known CPGs (ASCO, ESMO, NICE, SIGH, START, NHMRC, NCI, NCCN and CCO) and three representative tumors (advanced breast, lung and colon cancer) were selected and scrutinized. Results have shown that a diverse heterogeneity in development, structure, target user and endpoints were prominent among them"* [1, 2].

Of course, the creation of any CPG does not necessarily guarantee its full implementation across all treatment centres even in any one country. Compliance is a thorny issue and the tough economic times in which we now live, among other reasons, may preclude full adherence by cash-strapped health authorities.

An example of non-uniform compliance is the "Improving Outcomes Guidance for Brain and other CNS Tumours" published by the UK's National Institute for Health and Clinical Excellence (NICE) in June 2006 [3].

This crucial document sets out 11 key recommendations for delivering a high standard of care and support to this group of patients in England and Wales within the overall context of the UK National Cancer Action Plan.

But 6 years later, these multidisciplinary guidelines are still not uniformly in place across all English and Welsh treatment centres.

Another barrier to compliance is the challenge of dissemination. Guidelines are sometimes slow to pass into standard practice simply because they are not efficiently distributed and publicised.

The same *Annals of Oncology* editorial mentioned above describes the European Society of Medical Oncology's (ESMO) long-standing and successful association with the development and dissemination of clinical guidelines [1].

ESMO's dissemination of its CPGs relies on a variety of different methodological tools such as *"the translation of ESMO's CPGs into various languages"*; *"the organization of the ESMO interactive sessions during the ESMO Congresses"*; and the *"publication of editorials or articles [about CPGs] in oncology journals"*. Future ESMO plans for increasing implementation and dissemination of CPGs include pocket-sized booklets, slide sets, and mobile apps.

It is important for clinical guideline developers to utilise patient advocates who can play an important role in contributing to the success of CPGs, from their very inception to their successful dissemination and implementation. Currently, input into guidelines from patient advocates seems to range from involvement at the outset to simply reading the finished product and commenting.

As NICE itself states: *"Patients and carers can help those responsible for developing a clinical guideline to understand what it is like to live with a medical condition ... and what different forms of treatment and care mean to them ... This can include information about what patients want from their treatment and care, the acceptability of different treatments and their preferences for different treatment options"* [4].

In the brain tumour community, patient advocates are a relatively numerous, outspoken group, considering that CNS tumours are a rare disease.

Brain tumour patient advocates can help with scoping the objectives of a set of CNS CPGs. They can assist with defining key research questions. They can write and review recommendations. They are crucial in developing patient versions of CPGs, too.

Brain tumour patient advocates were involved in the creation of clinical practice guidelines with the British Neuro Oncology Society (BNOS) in collaboration with the UK National Cancer Action Team (NCAT) who developed CPGs for 4 very rare brain tumours: adult PNET, primary CNS lymphoma, pineal and optic pathway glioma [5].

In recognition of the important role that brain tumour support, advocacy, and information groups play, these 4 sets of guidelines also included an appendix listing the major brain tumour patient groups in the UK. We believe that this inclusion gave added value to the guidelines.

According to the ECCO Patient Advisory Committee (PAC) Chair, Ian Banks: *"An added benefit of patient involvement in the design of clinical practice guidelines is that the relationship between medical teams and their patients can improve as a result of this collaboration. Patients' involvement in guidelines may also increase concordance with therapy requirements.*"

Brain tumour patient advocates can also assist CPG developers with dissemination of guidelines throughout the brain tumour community. In the UK alone, nearly 50 brain tumour charities represent thousands of patients and their caregivers. These groups are potential conduits for spreading the word about clinical practice guidelines.

The IBTA has identified an additional 20 brain tumour patient organisations across Europe that could help with the dissemination of CPGs. There are also various online forums for European brain tumour patients plus a number of major brain tumour e-newsletters which provide substantial communication channels. The IBTA's mailing list for its monthly e-newsletter includes nearly 2000 European subscribers plus another 5000 people outside Europe.

Involvement of brain tumour patient advocates in the creation of CPGs does require, however, a commitment to appropriately train those advocates and provide clear guidance as to exactly what is expected of them.

Finally, it is important that brain tumour clinical practice guidelines fully reflect the collaboration and multidisciplinarity that is so crucial to successful treatment. To achieve truly patient-centric clinical guidelines, patient advocates should be involved in their creation, compliance, and dissemination. This involvement should not simply be tokenistic but should embrace real and meaningful input from the relevant patient community.

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EANO 10th Meeting 2012 – Summary Statistics

Stuart Bell

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The 10th EANO Meeting was held at the Parc Chanot Convention and Exhibition Centre, Marseille, France, from September 6–9, 2012. This meeting continued the trend of increasing delegate numbers at the EANO meetings, attracting some 970 delegates (+9.5 %) from 67 countries around the world (Table 1). This is the largest number of countries ever represented at an EANO meeting, and reflects the growing international stature of this conference and the successful efforts of the EANO Board to make EANO the leading voice of neuro-oncology in Europe.

Over 4 days of concurrent sessions, the meeting showcased 375 abstracts (+48 % compared to 2010), covering all aspects of relevance to neuro-oncology. Plenary sessions on topics such as immunotherapy, tumour angiogenesis, and tumour microenvironment were included along with meet-the-expert sessions, keynote lectures, and poster discussions. The meeting, for the first time, included a day-long Nursing Research and Care programme, highlighting the growing importance of neuro-oncology-specific nursing. In the same line, the Quality of Life / supportive care plenary session was very well-attended and generated rich discussion.

A breakdown of delegate numbers by specialty reveals that the meeting attracts delegates from a range of specialisms, with a good balance between neurosurgeons, neurologists, and medical oncologists, who are most strongly represented, accounting for almost three-quarters of delegates (Table 2).

In addition to the world-class research data presented at the meeting, the delegates also got to enjoy the beautiful setting of a late-summer Marseille, with the social highlight being the conference reception at the stunning 19th-century Palais de la Bourse in the Old Port area of the city, housing the Chamber of Commerce of Marseille as well as the Museum of the Marine Economy.

Table 1. Delegate breakdown by country

Country	No.	Country	No.
France	90	Poland	4
Netherlands	88	South Korea	4
Germany	80	Brasil	3
China	73	Greece	3
United Kingdom	65	Hungary	3
Sweden	51	Libya	3
Belgium	50	Tunisia	3
USA	36	Turkey	3
Austria	36	Bosnia-Herzegovina	2
Switzerland	35	Latvia	2
Russian Federation	33	Philippines	2
Italy	31	Portugal	2
Japan	29	Slovakia	2
Denmark	24	Slovenia	2
Spain	22	Albania	1
Canada	17	Algeria	1
Argentina	16	Chile	1
Iran	14	Cyprus	1
Bulgaria	12	Estonia	1
Colombia	12	French Polynesia	1
Ireland	12	India	1
Romania	12	Indonesia	1
Australia	10	Iraq	1
Israel	8	Jordan	1
Taiwan	8	Korea	1
Croatia	7	Lithuania	1
Syria	7	Morocco	1
Azerbaijan	6	New Zealand	1
Finland	6	Panama	1
Ukraine	6	Saudi Arabia	1
Norway	5	Singapore	1
Czech Republic	4	Thailand	1
Egypt	4	Uruguay	1
Luxembourg	4		

Table 2. Delegate breakdown by specialty

Specialty	%	Specialty	%
Neurosurgery	28	Neuroscience	5
Neurology	22	Industry	3
Medical oncology	20	Neuropathology	1
Radiation oncology	13	Paediatric oncology	1
Other	6	Neuroradiology	1

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To access the online survey, please click here

Calendar of Events

2012

November 11–15	**Joint Meeting of IPOS, 14th World Congress and COSA's 39th Annual Scientific Meeting**	Brisbane, Australia	http://www.ipos-society.org/ipos2012/
November 15–18	**17th Annual Scientific Meeting and Education of the Society for Neuro-Oncology**	Washington, DC, USA	http://www.soc-neuro-onc.org/2012/
November 21	**First International Course of Neuro-Oncology**	Montevideo, Uruguay	http://oncologia2012.com/
November 22–24	**22. Jahrestagung Deutsche Gesellschaft für Neurorehabilitation**	Fürth, Germany	http://www.conventus.de/dgnr2012/

2013

March 25–26	**EORTC EANO ESMO 2013: Trends in Central Nervous System Malignancies**	Prague, Czech Republic	http://www.ecco-org.eu/Conferences/Conferences/EORTC_EANO_ESMO.aspx
April 6–10	**American Association for Cancer Research Annual Meeting**	Washington, DC, USA	http://www.aacr.org/
April 10–11	**AHNS 2013 Annual Meeting during the Combined Otolaryngology Society Meetings**	Orlando, FL, USA	
April 12–13	**3. ASORS-Jahreskongress Supportive Therapie und Rehabilitation bei Krebs**	Berlin, Germany	http://www.kongresseonline.de/ASORS_2013/html/impressum.html
May 9–12	**19. Jahreskongress der Deutschen Gesellschaft für Radioonkologie**	Berlin, Germany	
May 30–June 2	**13th World Congress of the European Association for Palliative Care**	Prague, Czech Republic	http://www.eapc-2013.org/
May 31–June 4	**2013 ASCO Annual Meeting**	Chicago, IL, USA	http://www.asco.org
September 4–7	**XXIV Brazilian Congress of Neurophysiology**	Rio de Janeiro, Brazil	http://www.kenes-group.com/Events/xxiv-brazilian-congress-of-neurophysiology
September 21–26	**XXI World Congress of Neurology**	Vienna, Austria	http://www.wcn-neurology.com
September 27–October 1	**17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Congress**	Amsterdam, The Netherlands	http://www.ecco-org.eu/Conferences/Conferences/ECCO-17.aspx
November 11–14	**EANS Annual Meeting**	Tel Aviv, Israel	http://www2.kenes.com/eans2013/Pages/Home.aspx
November 21–24	**World Federation for Neuro-Oncology Meeting**	San Francisco, CA, USA	

2014

April 5–9	**American Association for Cancer Research Annual Meeting**	San Diego, CA, USA	http://www.aacr.org/
May 30–June 3	**2014 ASCO Annual Meeting**	Chicago, IL, USA	http://www.asco.org
June 3–6	**20. Jahrestagung der Deutschen Gesellschaft für Radioonkologie**	Düsseldorf, Germany	
July 26–30	**5th World Congress – IFHNOS and Annual Meeting AHNS**	New York, NY, USA	
September 26–30	**39th ESMO Congress**	Madrid, Spain	http://www.esmo.org/events/madrid-2014-esmo-congress.html
October 9–12	**11th EANO Congress**	Turin, Italy	http://www.eano.eu
November 13–16	**Society for Neuro-Oncology Meeting**	Miami, FL, USA	

2015

April 18–22	**American Association for Cancer Research Annual Meeting**	Philadelphia, PA, USA	http://www.aacr.org/
May 29–June 2	**2015 ASCO Annual Meeting**	Chicago, IL, USA	http://www.asco.org

News from the British Neuro-Oncology Society (BNOS): Where Have We Come Since 1980?

Geoffrey Pilkington

School of Pharmacy & Biomedical Sciences, University of Portsmouth, UK

In 1980, David G T Thomas, a consultant neurosurgeon at The Institute of Neurology, Queen Square, London and John Darling from David's research team expressed a strong interest in bringing together UK-based laboratory researchers and clinicians involved in the diagnosis and treatment of glioma and to instigate a fairly informal "club" to meet, present, and discuss research and clinical practice. Through his vision, inspiration, and enthusiasm, as well as a substantial input from John, the "British Glioma Group" was born. In 1981, the first of what would become a series of annual conferences was held at Queen Square and, along with a variety of UK speakers, we were joined by Darell Bigner from Duke University, USA. The group gained impetus and these conferences, which were largely research-based, continued to be held at different centres across the UK until 1989 when it was decided to change the name to "British Neuro-Oncology Group" in order to encompass nervous system tumours other than glioma. Through most of these early years John Darling and Geoff Pilkington acted as joint treasurer/secretary/organisers until Robin Grant and Tracy Warr took over the responsibilities. It is, perhaps, gratifying that this format was the first of its kind and more national groups were formed throughout Europe, North America, and further afield. Finally, in 2004, the group became the "British Neuro-Oncology Society" (BNOS), with more structure and purpose. It has continued to grow and prosper rapidly over the ensuing years. We have now met at over 20 different centres and 2013 sees the 32nd annual conference, which will be held at yet another centre, the University of Durham, from July 10–12 (see BNOS website www.BNOS.org.uk for further information). Over the last 32 years we have entertained some of the key international figures in neuro-oncology including Lucien Rubinstein, Darell Bigner, Paul Kleihues, Victor Levin, and many significant others. In addition to the ever-changing spectrum of research and clinical practice being presented, the formulation of conferences underwent changes. In 1997, a series of education days was introduced which resulted in an extension of the meeting to 3 days. These sessions have been a huge success over the years and we have now set up a postgraduate forum in which our younger members can present their work and contribute in a very real way to the society's activities and aims. A young investigator award was established in 2010; prizes for best poster and best oral presentations had already been in place since 1998. Other activities within the conference programmes have included open debates on "hot topics", commercial symposia, "Association of Neuro-Oncology Nurses" (ANON) nurse symposia and, over the past 4 meetings, a neuropathology symposium or international speakers have been sponsored by the "British Neuropathological Society" (BNS), notably evidenced by Dr Ken Aldape's excellent talk at the 2012 BNOS conference in Manchester. We now regularly see 250–300 delegates at conferences as the scope and quality continually increases. Abstracts are now published in *Neuro-Oncology* which reaches a highly appropriate audience of readers. On becoming a society BNOS no longer simply functions as an organisation with a remit of convening annual conferences. Our membership comes from neurosurgeons, neuroscientists, neurologists, neuropathologists, neuroradiologists, neuropsychologists, neuropsychiatrists, clinical nurse specialists, oncologists, radiotherapists, members of charities and many more disciplines. In this context the society is central to promoting all branches of medicine related to neuro-oncology and leads the way in enhancing both clinical practice and research through interaction with appropriate national and international bodies. The current BNOS officers are Dr Geoff Pilkington (President), Dr David Walker (Vice-President), Mr David Jellinek (Hon Secretary), and Dr Jeremy Rees (Hon Treasurer). In addition, BNOS council is now composed of some additional 13 members, who represent many sub-disciplines and geographic locations. We have also been extremely fortunate to retain the services of Jenny Loughlin (administrator@bnos.org.uk) as administrator to the society. Jenny has been an all-important lynch-pin in our activities over the past few years and has not only kept us in focus but has instigated several new, more professional systems which have enhanced the effectiveness of council. In addition, Jenny has now been joined by our new communications officer, Elizabeth Tudball (communications@bnos.org.uk), who is actively advancing awareness of BNOS and developing relationships with other professional societies as well as with the media.

There has been a massive growth in membership, scope, interest, and activities of BNOS in recent years which catalysed significant changes to the society constitution which were implemented following the 2012 annual general meeting. This constitutional change aims to increase democratic policy and mediate involvement of a greater proportion of the membership in the activities and administration of the society. Where possible council membership reflects the diversity of disciplines involved in neuro-oncology as well as different geographical locations within Britain but essentially such membership infers a considerable level of dynamic input to the society by our council members.

In addition, provision of sub-committees of experts in various areas who report directly to council now serve to reduce the need for long, expensive council meetings and speed up decision-making processes in order to efficiently meet the aims of the society. The new constitution aims to give clarity to the way the society carries out its business and gives greater and fairer access to members wishing to become council members

as well as the introduction of rotation of officer's posts. In addition, it addresses of provision of different types of membership to attract both charity and commercial sectors. A number of our new sub-committees are now fully active and pushing ahead with a broad range of developments which will underpin the continued plan of BNOS development. The sub-committee structure seeks to involve those who are not council members or are not able to spend as much time as council members in the society's activities by virtue of their specialist knowledge in some aspect of BNOS business. It is particularly pleasing to report that members of the junior section of the society (the postgraduate sub-committee) have already been active in providing reports for the website and newsletter as well as being central to formulating a postgraduate/trainee session for the BNOS conferences. To help our younger members in their careers we have also recently introduced a bursary scheme for meeting attendances. We are also striving to find a means to integrate the neuro-oncology nurse sector more effectively into society activities and better satisfy their requirements. From 2013 partnership membership will be available to organisations, including registered charities and commercial companies, involved in medical or scientific activities associated with or relevant to neuro-oncology. Each charity or commercial organisation will be offered this grade of membership which will permit persons within their organisations to enjoy all the benefits of membership with the exception of voting rights.

We also wish to forge closer relationships with the brain tumour charities which constitute a significant force in furthering the discipline to the benefit of patients and professionals alike and will aim to engage increasingly with the UK government's All Party Parliamentary Group on Brain Tumours in bringing our clinical and research endeavours to the fore. Brain tumours remain very much the Cinderella of the oncology world; the discipline is under-reported, under-researched, and under-funded, but, through BNOS and the united forces of the charity sector we will strive to change that situation.

Having already forged a fruitful interaction with the "British Neuropathological Society", we are now seeking to develop good working relationships and hold joint meetings with additional neuroscience-based bodies. As a first step in this direction, we are organising a neuro-oncology symposium as part of the British Neuroscience Association's "Festival of Neuroscience" (https://meeting.tfigroup.com) which is scheduled for April 7–10, 2013, at the Barbican Centre, London. This will provide both a showcase of British neuro-oncology and address the issues of public engagement in science (in our case CNS tumours). In addition, a second symposium at the festival organized by Dr Anne Leaver and Dr Geoff Pilkington on scientific aspects of brain tumours is being supported by the "British Pharmacological Society". We are also committed to engaging more with mainstream oncology and, to these ends, we are already organising neuro-oncology symposia jointly with NCRI groups to both educate general oncologists about brain tumours and, perhaps more importantly for us, to learn from those with experience in other branches of oncology and cancer research.

We are also pleased to report that during the NCRI annual cancer conference in Liverpool (http://www.ncri.org.uk/ncriconference/) there will be – on Tuesday, November 6, 2012 – a morning NCRI Brain Day Satellite Symposium and an afternoon NCRI Brain Day Workshop aimed at oncologists, surgeons, nurses, and pathologists involved in the management of patients with cerebral metastases on improving the management of cerebral metastatic disease. In this context, it is hoped to investigate whether we can develop a national stratified approach to the management of cerebral metastatic cancer with a greater involvement of neuro-oncologists. Further information on this can be found on the BNOS website events page (http://www.bnos.org.uk/events.html).

With regard to current UK representation within EANO, Anthony Chalmers has joined Peter Collins on the scientific board while Geoff Pilkington has joined the executive board. Dr Robin Grant continues as a council member of BNOS and we will look to him for advice and continuity of EANO issues.

The last few years of progress have given some sense of how the "British Neuro-Oncology Society" is growing and undergoing metamorphosis into a strong and meaningful organisation which not only represents the interests of its members from all disciplines involved with diagnosis and treatment of, and research into, tumours affecting the nervous system, but also plays a major role in the co-ordination of, and advice on, every area of neuro-oncology and brings us ever nearer to providing some realistic expectations of improved outcomes for patients.

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German Brain Tumour Association – Commitment to Brain Tumour Patients

Melanie Thomas

Deutsche Hirntumorhilfe e. V., Leipzig, Germany

In Germany, approximately 8000 people are diagnosed with a primary brain tumour every year. The number of patients with brain metastases developing as a result of lung cancer, breast cancer, or other cancerous diseases is even higher. Both brain metastases and malignant gliomas, the most frequent primary brain tumours in adults, confront patients, relatives, and doctors with a challenging situation. For more than one decade the "Deutsche Hirntumorhilfe" has been dedicated to all people concerned.

With the intention to promote science and neuro-oncological research as well as to improve health care standards for brain tumour patients, the "Deutsche Hirntumorhilfe" was founded in Leipzig on August 1, 1998. The independent non-profit organisation is an important contact point for everyone confronted with a brain tumour diagnosis. Supporting especially the issues of patients with brain tumours and brain metastases, the "Deutsche Hirntumorhilfe" is unique in the German-speaking countries and strives for further cooperation with other international organisations. All projects are financed exclusively by donations, membership fees, and project-related subsidies.

Knowledge Creates Future

More than 700 members and 7000 supporters from all over the world are pursuing one common goal: to find a cure for brain tumours and to find it as quickly as possible. True to the motto that knowledge creates future, the "Deutsche Hirntumorhilfe" provides health care professionals and patients with detailed information on standards and innovations in the treatment of brain tumours. The organisation stands up for the promotion of science and research in the field of neuro-oncology and supports interdisciplinary collaboration of all involved areas.

Brain Tumour Information Service and Patient Helpline

One important project for improving patient care is the brain tumour information service. Annually, it provides more than 3000 affected people with quality-assured information on performance data, therapy options, and clinical diagnosis. Besides inquires from German-speaking countries, patients from all over Europe direct their questions and concerns to the "Deutsche Hirntumorhilfe" as well. In addition to scientific information, a psycho-oncological helpline is offered, which gives advice on all non-medical issues and helps handle anxiety and psychological distress.

Communication and Information

Informative literature supplements the information and awareness activities of the "Deutsche Hirntumorhilfe". The periodically published magazine *Brainstorm* accosts patients as well as physicians. It provides important current information about neuro-oncology. Twice a year, the "Deutsche Hirntumorhilfe" organizes national symposia with leading experts informing about standards and innovations in brain tumour treatment. Certified by the medical association, these events with more than 500 participants are often attended by physicians for further medical education.

An international clinical trial registry and an internet platform as well as workshops and tutorials for brain tumour patients are further projects funded by the "Deutsche Hirntumorhilfe". Moreover, the organisation represents the interests of patients in various political committees, medical societies, and boards of health care providers.

Thanks to the support of volunteers and sponsors, numerous brain tumour patients and their families have been helped so far. Moving on, the "Deutsche Hirntumorhilfe" will demonstrate that it is possible to achieve much more. What began more than a decade ago is a challenge and an obligation at the same time. There is still much to do to improve the situation of patients and to promote neuro-oncological research.

Please help us to make our idea of a pan-European advocacy of brain tumour patients become real.

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Interview with Dr Brigitta Baumert about the EORTC Low-Grade Glioma Trial

Ufuk Abacioglu

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

Q: *Dear Dr Baumert, can you tell us about the ongoing EORTC "Low-Grade Glioma" trial? What is the rationale and background for this trial?*

A: The optimal management of cerebral low-grade glioma (LGG) has not yet been defined. Many patients are treated only when needed. A "need for treatment" is based on several studies, which could clearly identify patient groups based on prognostic factors. Survival seems to be more dependent on specific factors such as age, tumour grade, histological diagnosis, and neurological function. Based on the data of 2 earlier EORTC trials on low-grade glioma, a group of patients with the poorest outcome (= high-risk disease) can be identified and thus needs treatment. This trial has been specifically set up to investigate the optimal treatment paradigm for this patient group with a high-risk disease.

It is a multi-institutional randomized phase-III clinical trial (EORTC 22033-26033) to compare the progression-free survival (PFS) of patients with a low-grade glioma treated with radiotherapy alone versus treatment with temozolomide only. In addition, the impact of genetic deletions of 1p and 19q in low-grade gliomas (LGG) is investigated at the same time: the prognostic effect of tumours with deletion on progression-free survival – overall and by treatment group – and the interaction between treatment and cytogenetic features.

Q: *What are the design and the inclusion criteria?*

A: Inclusion criteria are histologically confirmed low-grade glioma (LGG) WHO grade II, supratentorial tumour location only, RTOG neurological function 0–3, and not being a candidate for surgical treatment alone as well as presence of high-risk disease or progressive tumours. High-risk disease is determined by the presence of at least one of the following criteria: age ≥ 40 years and/or radiologically proven progressive lesion and/or new or worsening neurological symptoms other than seizures only (eg, focal deficits, signs of increased intracranial pressure, or mental deficits).

In addition to clinical factors, patients are stratified according to a molecular analysis of the 1p/19q status. The central collection of tissue will also allow to subsequently identify additional molecular markers in order to predict individual outcome and response to therapy, therefore the availability of tumour material is an inclusion criterion. Patients with high-risk disease or with progressive tumours are randomized between primary radiotherapy (28× 1.8 Gy, 50.4 Gy, control arm) or primary chemotherapy with low-dose TMZ for up to 1 year (12 cycles) (Figure 1). Trial endpoints are progression-free survival, overall survival, but also acute and delayed toxicity, quality of life, and cognitive function.

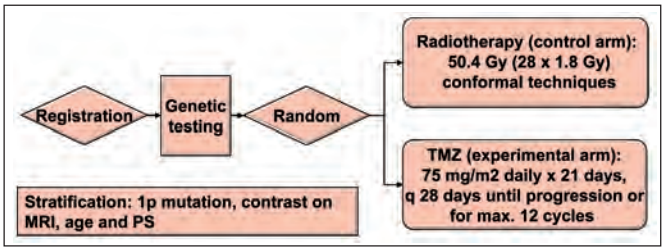

Figure 1. Trial design of the EORTC 22033-26033 intergroup trial with NCI Canada, TROG Australia, and the MRC UK including patients with a low-grade glioma and high-risk disease.

Q: *Which groups, countries and how many centres participate in the trial?*

A: This is an international intergroup study conducted by the European Organisation for Research and Treatment of Cancer (EORTC) together with the National Cancer Institute of Canada (NCIC) Clinical Trials Group, the Tasmanian Radiation Oncology Group (TROG) from Australia, and the Medical Research Council (MRC) from the United Kingdom. Overall, there are 78 participating institutions from Europe, Canada, Australia/New Zealand and one from Singapore. Within Europe, there are about 13 participating countries including Great Britain.

Q: *Do you have any translational or biological investigation in this trial?*

A: Indeed, there is an accompanying translational research package to this trial. Beside the fact that this study is the first to use a stratification based on molecular markers (changes in genes 1p/19q) to identify patients that benefit most from either radio- or chemotherapy we will conduct additional translational research based on this tissue material. We are searching for biomarkers, cancer-relevant molecular pathways, and new targets, as well as diagnostic, prognostic, and predictive biomarkers. The programme is set up to understand underlying molecular mechanisms for successful treatment of LGG. The tumour tissue will be characterized for genome-wide aberrant DNA methylation and respective associations with clinical parameters including response to therapy.

The generated molecular data will also identify tumours that should not be treated as low-grade gliomas despite favourable characteristics. Identifying new treatment strategies: because of the limited treatment options for LGG, new treatment options should be identified. Tumours depend on their acquired genetic changes for growth and a rational way to identify novel treatments is to use these changes to target the tumour. A growing number of drugs that target such changes have shown significant clinical benefit. We will therefore analyze

and screen for frequently mutated genes like IDH1 and others in order to identify potential new treatment strategies. The aim is to identify potential therapeutic drugs that act on the identified affected pathways and can be entered into future clinical trials and, thus, new treatment options.

Q: *Do you have quality of life and neurocognitive evaluation along with the study?*

A: Indeed, this study features both quality-of-life and neurocognitive evaluations. Quality of life (QoL) is included as a secondary endpoint. The hypothesis is that the use of primary temozolomide may have better QoL outcomes because of deferring radiotherapy and thus late radiation-induced toxicity. QoL is measured by a standardised questionnaire in a longitudinal setting.

Late radiation-induced toxicity consists for a larger part of the development of neurocognitive side effects as, for example, a decrease in short-term memory. The assessment of neurocognitive functioning is conducted as a side study. Patients are tested at baseline, before treatment, and repeatedly thereafter every 6 months to detect potential changes over time.

Like the stratification based on genetic tumour characteristics, this is the first study to have a prospectively conducted neuropsychological evaluation based on a standardized test battery specifically designed for this study purpose.

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

A: We have reached the recruitment target with an inclusion of 707 patients and about 470 patients randomized. However, it is important to note that the second study step, the randomisation, is still open to allow further registered patients to be randomised. Therefore, a registered patient can still be randomized and treated as per protocol after the study has been closed for patient registration (Figure 1). We may expect first preliminary results within the next 2 years.

Also, recently, first results of the accompanying quality assurance programme for radiotherapy have been published [1]. This study had an accompanying detailed quality assurance programme reviewing the irradiation technique of the centres involved with regard to compliance of the protocol guidelines and radiation treatment technique. We observed that strict evaluation by digital review of radiotherapy resulted in overall grades of larger protocol deviations of about 30 %.

Thank you very much!

Brigitta Baumert is the study coordinator (along with study co-chair Roger Stupp) for the EORTC 22033-26033 trial entitled, “Primary chemotherapy with temozolomide vs radiotherapy in patients with low-grade gliomas after stratification for genetic 1p loss: a phase III study”.

Reference:

1. Fairchild A, Weber DC, Bar-Deroma R, et al. Quality assurance in the EORTC 22033-26033/CE5 phase III randomized trial for low grade glioma: the digital individual case reviews. Radiother Oncol 2012; 103: 287–92.

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Hotspots in Neuro-Oncology

Michael Weller

From the Department of Neurology, University Hospital Zurich, Switzerland

Induction of Brain Tumor Stem Cell Apoptosis by FTY720: A Potential Therapeutic Agent for Glioblastoma

Estrada-Bernal A, Palanichamy K, Chaudhury AR, et al. Neuro Oncol 2012; 14: 405–15.

Although their existence has remained somewhat enigmatic, the identification and selective therapeutic elimination of glioma stem cells or initiating cells remains a focus of current research in neuro-oncology. In the April issue, another pharmacological approach to target specifically the stem cell compartment in glioblastoma was proposed. FTY720 is a sphingosine analogue that decreases the levels of G protein-coupled sphingosine-1-phosphate receptors. This drug was approved for the treatment of multiple sclerosis in 2010. It shows high blood-brain barrier permeation and should therefore in principle be capable of targeting glioma cells shielded by the blood-brain barrier. Estrada-Bernal et al report that FTY720 inactivates the ERK/MAP kinase pathway, induces the BH3-only protein Bim and, in terms of cell death induction, does so in synergy with temozolomide. These effects were demonstrated specifically in "brain tumour stem cells". Furthermore, FTY720 inhibited the growth of intracranial xenograft tumours transplanted in nude mice, too. Admittedly, as in multiple sclerosis, it remains somehow unclear how precisely FTY720 is inducing its therapeutic effect. This will probably be the subject of further studies. Yet, given that the drug is already available and tolerated by human patients, it may represent a valid option for clinical evaluation in patients with refractory glioblastoma.

Soluble Factors Secreted by Glioblastoma Cell Lines Facilitate Recruitment, Survival and Expansion of Regulatory T Cells: Implications for Immunotherapy

Crane CA, Ahn BJ, Seunggu J, et al. Neuro Oncol 2012; 14: 584–95.

Immunotherapeutic approaches to glioblastoma experience a revival at present, with multiple smaller vaccination trials ongoing and the epidermal growth factor receptor vIII peptide vaccination entering randomized phase-II and -III trials. Yet, the immune privilege of glioblastoma conferred by an immunosuppressive microenvironment created by these tumours represents a major obstacle for immunotherapy. In the May issue of *Neuro-Oncology*, Crane et al readdress the role of soluble mediators released by glioblastoma cells and specifically examine their effects on regulatory T cells, a major immunosuppressive T cell population. There was an increase in the frequency of regulatory T cells in the tumour tissue as opposed to the periphery in glioblastoma patients. The chemokine CCL22 induced the migration of regulatory T cells more effectively than that of conventional T cells. Yet, interfering with CCL22 signalling at the receptor level did not completely block T cell migration, suggesting that factors other than CCL22 are involved in this process. The authors also found a correlation between tumour burden and regulatory T cell populations in the peripheral blood, reinforcing the idea (that has never been proven) that immunotherapy will work better in glioblastoma patients with minimal residual disease. This study illustrates once more how glioblastomas maintain their micromilieu in an immunosuppressed state and shows that the balance between immunosuppressive and immunostimulatory signals must be altered to facilitate tumour cell recognition and attack by the immune system.

Treatment-Related Myelodysplasia in Patients with Primary Brain Tumors

Baehring JM, Marks PW. Neuro Oncol 2012; 14: 529–40.

The life expectancy of many glioma patients, notably suffering from non-glioblastoma gliomas, is probably increasing, due to improved techniques in neurosurgery and radiotherapy as well as an increasing repertoire of medical treatments, and also improved post-treatment surveillance and symptomatic treatment. At the same time, more patients are treated with alkylating-agent chemotherapy up-front whereas radiotherapy is delayed. Therefore, as outlined in a comprehensive overview by Baehring and Marks in the May issue, treatment-related myelodysplastic syndrome (t-MDS) and treatment-related acute myelogenous leukemia (t-AML) require attention during long-term follow-up. In that regard, the EORTC study 22033, which compares radiotherapy with protracted dose-dense temozolomide in patients with low-grade gliomas, will be particularly helpful for estimating the risk of such complications. So far, the risk for t-MDS and t-AML remains low among glioma patients, but the occasional practice of maintaining patients on alkylating-agent chemotherapy for more than a year or even until progression should be discouraged until appropriate data indicate a survival benefit from such prolonged chemotherapy regimens.

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News from the Society for Neuro-Oncology

J Charles Haynes

Society for Neuro-Oncology, Bellaire, TX, USA

The Society for Neuro-Oncology (SNO) is now putting the finishing touches on our 17th Annual Scientific Meeting and Education Day which will be held November 15–18, 2012, in Washington, DC. Congratulations are due to meeting chair Antonio Chiocca for his outstanding effort in assembling a comprehensive programme highlighting cutting-edge laboratory and clinical research in the field of neuro-oncology. The meeting promises to be a unique environment for the multidisciplinary exchange of ideas among clinician and laboratory scientists in the fields of neuro-oncology, medical oncology, neurosurgery, neuropathology, radiation oncology, neuroradiology, paediatrics, nursing, and other specialties involved in the research, diagnosis, care, and treatment of patients with central nervous system tumours.

On Thursday, November 15, the pre-meeting will begin with a timely and relevant programme for Education Day, with a morning session focused on Targeted Therapies organized by Balveen Kaur and Vinay Puduvalli, and a concurrent session on Quality of Life/Symptom Management organized by Michael Glantz. That afternoon, Susan Chang and Ken Aldape will lead a course on the Basics of Biomarkers.

The main scientific meeting officially commences on Friday, November 16. The meeting starts with Sunrise Sessions on NF2, Energetics and Metabolism, Re-engineered T Cells and Bone Marrow Cells, as well as a special EANO/SNO joint session entitled "From Guidelines to New Trials in Low-Grade Gliomas: The American and European Views". After the Official Meeting Welcome by Dr Chiocca, the Top-Scoring Basic Science Abstracts will be presented. This session will be followed by the inaugural presentation of the Abhijit Guha Award and Lecture given by James Rutka of the University of Toronto. To conclude the morning, SNO is especially pleased to welcome Bert Vogelstein of Johns Hopkins, who will offer the meeting's Keynote Address.

Building on the success of previous events, we look forward to a Young Investigators Roundtable Luncheon at noon on Friday. Senior trainees and early-phase independent investigators will participate in informal discussions with senior investigators at roundtables organized in several different topic areas including Neurosurgery, Adult Neuro-Oncology, Paediatric Neuro-Oncology, Basic Science, Translational Science, and Radiation Oncology.

This will be followed by afternoon concurrent sessions on Medical, Neuro- and Radiation Oncology, Basic Sciences, Quality of Life, Molecular Epidemiology, "-Omics", and Prognostic Markers. The evening will feature an informative session entitled "Management of 1p/19q codeleted anaplastic gliomas" which will discuss the updated results of the available phase-II and -III trials, how patients should now be managed, what role biomarkers have in patient selection, the choice of chemotherapy regimen, and the design of the ongoing trials (including CODEL and CATNON).

Saturday, November 17, Sunrise Sessions feature Pituitary Tumours: Biology and Treatment, Mechanisms of Glioblastoma Immuno-evasion, the CMV and Glioma Connection, as well as a special session organized by the Asian Society for Neuro-Oncology. These are followed by a Paediatric Mini-symposium and a plenary session presenting the Top Scoring Clinical Abstracts. Before lunch, the Victor Levin Award and Lecture will be given by joint-recipients, Gregory Cairncross and Robert Jenkins. The afternoon concurrent sessions will feature Cell Biology and Signalling, Epidemiology, Angiogenesis and Invasion, and Surgery and Immunology. The second poster session will take place after the oral sessions conclude for the day. That evening, the SNO Banquet promises to be a social highlight of the meeting.

Sunday, November 20, begins with Sunrise Sessions on Oncolytic Viruses, Radiobiology, the Biology of Brain Metastases, and MicroRNA Biology. These will be followed by a plenary session featuring more Top Scoring Clinical Abstracts. The final scientific session of the meeting will be devoted to a discussion of RANO: recommendations and ongoing efforts.

Upon the conclusion of the scientific sessions, Young Investigators are invited to attend a special Career Development event. Attendees will take part in an organized networking and mentoring session and each participant will have the opportunity to interact with many potential collaborators and mentors for brief, high-value exchanges that will form the basis of mutually beneficial professional relationships. This will be followed by an informal reception to allow for more extensive follow-up conversations.

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EANO Neuro-Oncology Online Magazine

Instructions for Authors

Policy:

Published quarterly since September 2011, the EANO Neuro-Oncology Online Magazine is the official open-access online journal of the European Association of Neuro-Oncology (EANO).

Dedicated to providing superior and rapid publication of information in all areas of neuro-oncology, this education-oriented journal contains peer-reviewed articles and reviews, case reports, congress reports, letters, society news and announcements from around the world with a special focus on Europe and the EANO member states.

The goal of the EANO Neuro-Oncology Online Magazine is to provide the European neuro-oncology community, in particular of the EANO member states, with high-quality rapid publication of information in all fields of neuro-oncology via open online access.

Areas covered include, but are not limited to, neurology, neurosurgery, medical oncology, radiotherapy, pediatric neurooncology, neuropathology, neuroradiology, neuroimaging, nursing, and patient issues.

Submitted manuscripts should not contain previously published material or be under consideration for publication elsewhere. Manuscripts should conform to the „Uniform Requirements for Manuscripts Submitted to Biomedical Journals“ (http://www.icmje.org/urm_main.html).

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Author's Checklist

1. What and where to submit

- Copyright transfer agreement hand-signed by all authors (to be mailed or faxed to the editorial office).
- Authors who submit manuscripts to the journal must
  - provide signatures from all persons acknowledged, stating that they have seen and approved mention of their names in the article;
  - cite all sources of support for research. If authors have potential conflicts of interest that relate to the manuscript, these must be stated;
  - indicate in a statement of submission that all authors have read and approved submission of the manuscript, and that the manuscript has not been published and is not being considered for publication elsewhere in whole or in part in any language except as an abstract.
- If an author's prior work is in preparation, has been previously submitted or published, or is currently in press, and is potentially overlapping or provides information essential to the referee's understanding of a submitted manuscript, submit one copy of that work with the manuscript.
- Electronic submission of the manuscript at all review stages is mandatory. The submission package must comprise the latest version of the complete manuscript (including tables and figures), author information, acknowledgements, and references.
- Send manuscript and related parts to the editorial office. Manuscripts cannot be submitted by fax.

2. General instructions

- Type manuscripts double-spaced, including references, figure legends, and tables, on one side of the page only. Original contributions generally should not exceed seven pages when typeset. As a reference for manuscript length, there should be no more than l figure or 1 table for every 750 words. The manuscript should not exceed 35,000 keystrokes including title page, abstract, key words, references, legends, and tables. Authors should eliminate redundancy, emphasise the central message, and provide only the data necessary to convey their message. Manuscripts may exceed seven pages when exigencies of design or complexities of research require it and length is approved by editors.
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- Do not cite references in the abstract.
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