

European Association of NeuroOncology Magazine

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

EDITORIAL

Riccardo Soffietti

REVIEW ARTICLES

Austrian Patients with Glioblastoma Multiforme and Their Families: Socioeconomic Aspects

Birgit Flechl, Christine Marosi

News and Views Basic Science: Glioblastoma Stem Cells

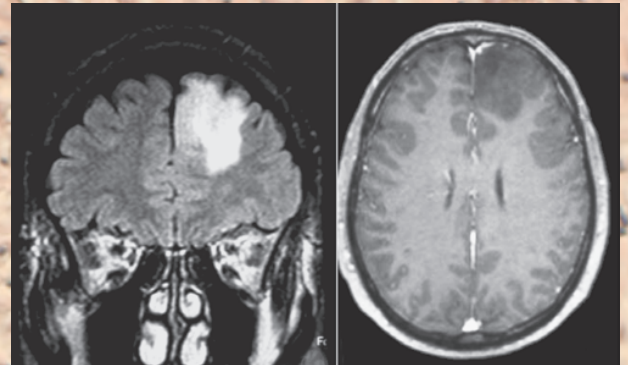
Petra Hamerlik, Jeremy N Rich, Justin D Lathia

Epidemiology and Brain Tumours: Practical Usefulness

Adelheid Wöhrer

Journey of Intraoperative Magnetic Resonance Imaging into Daily Use: A Review

Moritz Scherer, Christine Jungk, Andreas Unterberg



COLUMNS

Case Report

Nurses and Health-Related Groups

Patient Issues

Calendar of Events

Obituary

Congress Report

National Societies

Ongoing Trials

Hotspots in Neuro-Oncology

SNO News



THE EUROPEAN ASSOCIATION OF
NEUROONCOLOGY

Member of the



www.kup.at/journals/eano/index.html

Table of Content

EDITORIAL

Riccardo Soffietti	45
--------------------	----

REVIEW ARTICLES

Austrian Patients with Glioblastoma Multiforme and Their Families: Socioeconomic Aspects	46
Birgit Flechl, Christine Marosi	
News and Views Basic Science: Glioblastoma Stem Cells	49
Petra Hamerlik, Jeremy N Rich, Justin D Lathia	
Epidemiology and Brain Tumours: Practical Usefulness	56
Adelheid Wöhrer	
Journey of Intraoperative Magnetic Resonance Imaging into Daily Use: A Review	61
Moritz Scherer, Christine Jungk, Andreas Unterberg	

COLUMNS

Case Report	
Atypical Aggregation of Cancer	68
Emeline Tabouret	
Nurses and Health-Related Groups	
Grief, Bereavement, and Mourning	70
Hanneke Zwinkels	
Patient Issues	
When Personalised Medicine Meets HTA: Are We on Target?	72
Kathy Oliver	
Calendar of Events	74
Obituary	75
Congress Report	
17th Annual Scientific Meeting of the Society for Neuro-Oncology	76
Stefan Oberndorfer	

EANO MAGAZINE

Editor-in-Chief
Riccardo Soffietti

Managing Editor
Wolfgang Grisold



Editorial Board

Stefan Oberndorfer	J. M. Kros (neuropathology)
Khe Hoang Xuan	Giorgio Perilongo
Michael Weller	(pediatric neuro-oncology)
Wolfgang Wick	Marion Smits
Ufuk Abacioglu (radiotherapy)	(neuro-radiology)
Lorenzo Bello (neurosurgery)	Hanneke Zwinkels (nurses)
Olivier Chinot (medical oncology)	Kathy Oliver (patient issues)

Section Editors

Case reports:	Patient issues:
Stefan Oberndorfer	Kathy Oliver
Guidelines:	Ongoing trials:
Riccardo Soffietti	Ufuk Abacioglu
Nurses:	Hotspots in Neuro-Oncology:
Hanneke Zwinkels	Michael Weller

Table of Content

National Societies

- The Swedish Brain Tumour Study Group in the Framework of a New "Patient in the Focus of Cancer Care" in Sweden** 78

Roger Henriksson

- The Spanish Group of Research in Neuro-Oncology (Grupo Español de Investigación en Neuro-Oncología [GEINO]): History and Activities** 80

Miguel Gil-Gil

Ongoing Trials

- Interview with Dr Martin van den Bent (Rotterdam) About the EORTC TAVAREC Trial on Recurrent Grade-II and -III Gliomas** 82

Ufuk Abacioglu

- Hotspots in Neuro-Oncology** 84

Michael Weller

SNO News

- News from the Society for Neuro-Oncology** 86

J Charles Haynes

Front Page: Brain MRI of patient: Flair, T1 with gadolinium and spectrometry analysis, Fig. 1, from Emeline Tabouret: Atypical Aggregation of Cancer, p. 68.

IMPRINT

European Association of NeuroOncology Magazine



ISSN-Online: e-ISSN 2224-3453

Official Organ of the European Association of Neurooncology

Editor-in-Chief:

Riccardo Soffietti, MD
Division of Neuro-Oncology
Department of Neuroscience
University and San Giovanni Battista Hospital
10126 Turin, Via Cherasco 15, Italy
Tel. +39/(0)11/633-4904, Fax +39/011/696-3487
e-mail: riccardo.soffietti@unito.it

Managing Editor:

Wolfgang Grisold, MD
Department of Neurology
Sozialmedizinisches Zentrum Süd –
Kaiser-Franz-Josef-Spital
1100 Vienna, Kundratstraße 3, Austria
Tel. +43/1/60191-2001, Fax +43/1/60191-2009
e-mail: wolfgang.grisold@wienkav.at

Responsible for the content.

Please send queries to:

European Association of Neurooncology
c/o Vienna Medical Academy
Alser Straße 4, 1090 Vienna, Austria
Tel. +43/1/40 51 383-0, Fax +43/1/40 78 274
e-mail: office@eano.eu

Publisher's Office:

Krause & Pachernegg GmbH
Mag. Irene Schinnerl
e-mail: irene.schinnerl@kup.at
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, neuro-radiology, neuroimaging, nursing, patient issues, etc.

Disclaimer:

Authors, editors, and the publisher do not accept responsibility for any loss or damage arising from actions or decisions based on information contained in this publication: ultimate responsibility for the treatment of patients and interpretation of published material lies with the medical practitioner. Statements and opinions expressed in articles herein are those of the authors and not necessarily those of the editors or publisher. Great care is devoted to the compilation of the articles. Even so, however, errors in data processing cannot always be avoided. In view of this and because developments in medical science advance very quickly, it is recommended that the reader conducts his own independent inquiries and/or research as regards the stated diagnostic methods, measurements of medication etc. The editors and

publisher disclaim any responsibility or liability for the correctness of such material and do not guarantee, warrant or endorse any product or service advertised in this publication nor do they guarantee any claim made by the manufacturer of such product or service. The use of general descriptive names, trade names, trademarks etc in this publication even if not specifically identified, does not imply that these names are not protected by the relevant laws and regulations.

Conflict of interest, ethical approval:

A conflict-of-interest statement must be completed for each author of each submitted article. All original research involving human subjects must be accompanied by evidence of prior ethics committee approval. Authors must supply evidence of informed consent of research participants (patients).

Copyright:

© Krause und Pachernegg GmbH. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanic, including photocopy, recording, or any information storage and retrieval system, without written permission from Krause und Pachernegg.

Use of texts and files:

For personal, non-commercial use and information only. Not to be reproduced without permission of Krause & Pachernegg GmbH. The European Association of NeuroOncology Magazine is an open-access journal without commercial funding.

*The EUROPEAN
ASSOCIATION of
NEUROONCOLOGY*



11th MEETING

See you!

2014

October 9-12

TURIN, ITALY

Lingotto Convention & Exhibition Centre

www.eano.eu

Editorial

Dear colleagues,

as usual, this editorial is written to keep you informed about the ongoing and future initiatives of our society. The EANO Board met in Torino on May 10, 2013, and several decisions were taken. We updated and specified the rules for Travel and Educational Grants and Fellowships. On the website, we will have a unique call per year with July 1 as the deadline.

Following the recent suggestions of the EU Commission (EUCERD Directive), EANO will work, together with the national societies, on the definition of criteria for centres of expertise for rare brain tumours.

EANO guidelines for malignant gliomas and PCNSLs are ongoing: both will be ready by the end of 2013, then submitted to a scientific journal with IF and a shortened version will be available on the website and published in EANO Magazine.

A survey on patterns of palliative care has been launched in cooperation with SNO and ASNO and the results will be presented at the World Federation of Neuro-Oncology meeting in San Francisco in November 2013.

The EORTC/EANO/ESMO Educational Meeting in Prague in March 2013 was successful and resulted in 15 new EANO memberships. The European Cancer Congress (ECCO) will be held in Amsterdam from September 27 to October 1, 2013. EANO experts have been involved in the development of the programme that will include several educational sessions on brain tumours, and an EANO workshop will take place on September 29. By mid-June the final programme of the World Federation of Neuro-Oncology meeting in San Francisco from November 21–24 will be ready.

From November 1–2, 2013, a joint meeting of EANO and the Turkish Society of Neuro-Oncology will take place in Istanbul – this is in line with our strategy to increase the involvement in EANO activities of groups and/or people from non-Western European countries, North Africa, and the Middle East.

The preliminary programme of EANO 2014 in Torino will be ready by the end of the year.

Last but not least, we have left unchanged the membership fee and a discount will be available for people from low-income countries.

Riccardo Soffiatti, MD

EANO President (2012–2014)



Riccardo Soffiatti, MD



Austrian Patients with Glioblastoma Multiforme and Their Families: Socioeconomic Aspects

Birgit Flechl, Christine Marosi

Abstract: Patients with glioblastoma multiforme (GBM) are still confronted with an incurable cancer disease affecting not only their body but also their personality and cognition. We present recent Austrian studies performed at the Medical University of Vienna on GBM patients dealing with socio-economic outcomes.

By analyzing quality of life (QOL), performance status, living and working situations, muscular strength of subsets of GBM patients, as well as satisfaction with the care and the end-of-life (EOL) situation of GBM patients of their primary caregivers, we tried to assess the impact of glioblastoma on patients and their families. We found that GBM long-term survivors (LTS) were mainly independent in their activities of daily living and mostly also in instrumental activities of

daily living, but showed some moderate cognitive deficits and suffered from financial difficulties. Only a minority of GBM LTS was able to stay in their respective jobs. Even with adolescent and young adult (AYA) patients diagnosed with GBM before 40 years only $\frac{1}{3}$ succeeded in staying employed after the diagnosis of GBM. Near half of the AYA patients returned to the household of their parents, which reflects their loss of independence. Moreover, we found that patients with GBM present a significant loss of strength in the proximal musculature of the legs, impairing their ability of climbing stairs and walking very early in the disease course. The complex patterns of physical, neurological, and cognitive impairments in GBM cause their needs for support starting very early in the disease. Family

members become caregivers and are confronted with challenging life-changing situations. Thus, it is not surprising that family caregivers feel overstrained. We found that families with lower incomes and lower education levels showed higher distress levels as well as less satisfaction with the care of the patient, EOL care, and a worse bereavement adjustment. As a conclusion, in studies focusing on QOL and socio-economic impact of GBM we found an unmet need for support and information of patients and their caregivers. **Eur Assoc NeuroOncol Mag 2013; 3 (2): 46–8.**

Key words: glioblastoma, caregiver burden, socioeconomic aspects, financial difficulties, end-of-life phase, working situation

■ Introduction

As glioblastoma multiforme (GBM) is to date not curable despite resection, concomitant radio/chemotherapy, and adjuvant chemotherapy, patients are confronted with the scary outlook of a short remaining life span, aggravated by probable cognitive decline and loss of independence. The group of patients living ≥ 3 years after diagnosis is indeed small, but increases since the concomitant and adjuvant therapies with temozolomide have become standard of care and will hopefully further increase due to upcoming – probably personalized – therapeutic options.

■ GBM Long-Term Survivors

We recently published results of 17 GBM long-term survivors (LTS) treated at the Medical University of Vienna [1]. We investigated their cognition, sociodemographic characteristics, and quality of life. Their age ranged from 24–71 years with a median of 51 years. Seven GBM long-term survivors > 60 years were already retired at the time of diagnosis. The remaining 10 men and women had been employed in full-time jobs at the time of diagnosis. Noticeably, only 4 LTS were able to keep their jobs and thus maintain their income after diagnosis and therapy. They worked as actress, office clerks, and self-employed custodial worker. The remaining 6 pa-

tients, who were employed before being diagnosed with GBM, received disability benefits due to inability to continue working because of their disease.

Neurocognitive deficits in brain tumour patients have been shown to be associated with negative outcomes in a previous study and are unfortunately common [2]. We used the computer software NeuroCog FX for neurocognitive testing, a tool developed in Germany for patients with neurological deficits [3]. Analysis showed “conspicuous” results in 23 % of the patients, “borderline” results in 18 %, and “normal” summary values in 59 % of the patients. All patients who were still employed showed normal cognition. Interestingly, we measured a trend in cognitive functions, favouring the GBM patients with > 5 years survival after diagnosis. This is in contrast to older studies in which late toxicities of brain radiotherapy have been described [4] and supports the findings in the review of Armstrong et al [5] who reported that the late-delayed effects of radiation in cases of partial brain radiotherapy appear to be limited.

The quality-of-life analysis of GBM LTS showed no reduction in global health score compared to the reference values, but reduced scores in social and cognitive functioning. Unexpectedly, the highest difference between GBM LTS and the reference population was measured in the item “financial difficulties”. Seven patients (41 %) stated financial problems due to their cancer disease. Moreover, financial difficulties correlated significantly with uncertainty about the future.

■ Financial Aspects

After diagnosis of a malignant disease, when a person is unable to work for a prolonged time, the health care systems in Western Europe usually provide sick pay consisting of a high percentage of the last salary, but – at least in Austria – it is lim-

Received on January 17, 2013; accepted after revision on January 31, 2013; Pre-Publishing Online on February 18, 2013

From the Department of Medicine I, Medical University of Vienna, Austria Comprehensive Cancer Center – Central Nervous System Tumors Unit (CCC-CNS), Vienna, Austria

Correspondence to: Birgit Flechl, MD, Medicine I, Medical University of Vienna, Austria Comprehensive Cancer Center – Central Nervous System Tumors Unit (CCC-CNS), Währinger Gürtel 18–20, 1090 Vienna, Austria; e-mail: birgit.flechl@gmx.at

ited to the duration of one year. So patients with jobs where tips or provisions are regular parts of their monthly income suffer greater losses in their incomes than other professions. Moreover, after the respective maximal duration of sick leave, patients either have to return to work or apply for disability benefit. In many European countries including Austria, disability benefit is calculated according to an algorithm based on the last income and the number of working years, therefore lower for younger patients. Opportunities for support from social authorities are mostly available but application procedures may be troubling and humiliating for GBM patients and often beyond their cognitive and emotional capacities. Mainly GBM patients dependent on disability pensions complained about disease-related financial problems.

Finally, in “unprotected” working situations, it is unfortunately not surprising that most GBM patients lose their jobs. Frequent sick leaves during the first weeks of treatment, followed by fatigue and eventual neurocognitive deficits developing later in the disease course, as well as prejudices against patients with brain diseases by employers and workmates preclude their ability of remaining in their original employments. People with brain tumours are at risk of seizures and thus not allowed to drive professionally, to handle big machinery, or doing shift-work. Moreover, their need for breaks is also perceived as debilitating and thus not tolerable in many real-life working situations. In general, employers will prefer “healthy” applicants and patients with GBM get *a priori* the short end of the stick.

■ Adult Young and Adolescent Patients with GBM

Leibetseder et al recently published a study about 47 adolescent and young adult GBM patients aged < 40 years [6]. Of note, about half of these young patients with malignant brain cancer were not able to manage and support their routine daily life independently in their own home. They returned to the households of their parents, mostly into their old nurseries. This alarming number illustrates the high rate of loss of independence in this group of patients. 57 % of AYA patients with GBM lost their jobs within the first 2 months after diagnosis. Only self-employed people or persons working in family businesses or in large enterprises in administrative jobs or on computers were able to stay employed. Patients from other occupational groups, mainly craftsmen like butchers, car mechanics, photographers, shoemakers, clerks, fitters and, noticeably, all health care workers, including physicians and midwives, and all teachers lost their jobs due to their disease a few weeks after diagnosis. None of the patients surviving in good performance status for several years were able to return to employment after GBM diagnosis.

■ Loss of Muscular Strength

It is well-known that glioblastoma leads to a decrease in muscular strength due to neuromuscular dysfunction caused by the tumour itself and due to corticoid treatment which is required to decrease intracranial pressure. Although steroids are generally tapered off as soon as possible after neurosurgical intervention, Keilani et al [7] recently described significant

deficits in muscular strength and general physical performance in Austrian GBM patients. The loss of strength of the proximal muscles of the legs needed for walking was measured before the start of radio/chemotherapy and did not improve after 3 months.

Another adverse feature of brain tumours is that the resection scar and hair-loss resulting from radiotherapy are plainly visible. In addition, many patients gain weight and develop Cushingoid signs, which change their appearance – this might also unsettle persons in their working environment. It can be assumed that such cosmetic aspects are further disadvantages for patients with brain tumours looking for a job.

■ Family Caregivers

To compensate for the loss of income experienced by GBM patients, partners or other family members are forced to keep their jobs and incomes. As if this were not challenging enough, they experience a changing role. They become caregivers. This begins very early in the course of the disease. After a recovery phase *post* surgery, the logistic demands for daily transports to radio- and/or chemotherapy visits have to be organized. Kumthekar et al recently showed that the financial burden of families of GBM patients was much higher than in families with breast cancer or lymphoma patients [8]. Moreover, the patients’ work shares in household, garden, in the family as well as financial aspects have to be considered and managed. Family members are forced during this hard time not only to cope with the disease of their loved ones but also to keep their lives going. This is already hard in early stages of the patients’ disease but probably more challenging later, when patients develop dependencies due to neurological and neurocognitive deficits and require permanent assistance.

■ End-of-Life Phase

Sizoo et al [9] conducted a retrospective study in The Netherlands, evaluating a specially developed questionnaire for treating physicians and relatives of deceased high-grade glioma patients. They highlighted the importance of a timely discussion of end-of-life issues to reduce the patients’ and their caregivers’ burden.

Our study, performed at 2 centres in Vienna, supports this conclusion. We evaluated retrospectively the perspective of family caregivers of patients with GBM on the EOL phase defined as the last 3 months before death [10]. We used a questionnaire for the caregivers developed and validated by the working group of Taphoorn et al (Medical University of Amsterdam). Family caregivers of 52 patients with GBM, diagnosed from 2005–2009 and treated in Vienna, participated in this study. As assumed, caregivers indicated that the GBM patients suffered from fatigue, reduced consciousness, aphasia, and various neurological deficits during the EOL phase, which is different from the EOL phase of patients with other cancers. Moreover, partners or family members who cared for them went through a hard phase. Sadness, fear, and an alarmingly high percentage of overtraining were reported by the majority of caregivers, which reflects the excessive mental and physical demands on them. Moreover, family caregivers

also mentioned financial difficulties due to the patients' GBM. Caregivers who mentioned financial difficulties were also those who complained about insufficient information on the disease and about overstraining. However, Pace et al [11] showed in their impressive Italian study that a satisfying end-of-life period for both, patients and caregivers, is possible by supporting them at home with a mobile palliative team.

Gaiger recently presented a survey in 4000 cancer patients treated at the Medical University of Vienna [12]. Interestingly, patients with lower incomes showed significantly higher distress levels while patients with higher incomes more frequently underwent psychological counselling. Similar remarkable results were seen in their education levels. Patients with lower education levels showed higher distress levels but mentioned significantly less often the need for support.

Conclusion

Our results show that GBM patients and their caregivers have unmet needs regarding the socioeconomic impact of GBM on their lives. This starts with more practical information regarding the disease, different topics such as physical training, working situation, financial challenge, and social support possibilities. Particularly, GBM patients and families who are at risk of financial difficulties should be offered support to decrease their burden. Maybe early oncologic rehabilitation might help GBM patients to keep their jobs and lives running,

thereby maintaining the patients' and their family members' quality of life.

Conflict of Interest

Both authors declare that there is no conflict of interest.

References:

1. Flechl B, Ackerl M, Sax C, et al. Neuro-cognitive and sociodemographic functioning of glioblastoma long-term survivors. *J Neurooncol* 2012; 109: 331–9.
2. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol* 2004; 3: 159–68.
3. Hoppe C, Fliessbach K, Schlegel U, et al. NeuroCog FX: computerized screening of cognitive functions in patients with epilepsy. *Epilepsy Behav* 2009; 16: 298–310.
4. Crossen JR, Garwood D, Glatstein E, et al. Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. *J Clin Oncol* 1994; 12: 627–42.
5. Armstrong CL, Gyato K, Awadalla AW, et al. A critical review of the clinical effects of therapeutic irradiation damage to the brain: the roots of controversy. *Neuropsychol Rev* 2004; 14: 65–86.
6. Leibetseder A, Ackerl M, Flechl B, et al. Outcome and molecular characteristics of adolescent and young adult patients with newly diagnosed primary glioblastoma: a study of the Society of Austrian Neurooncology (SANO). *Neuro Oncol* 2013; 15: 112–21.
7. Keilani M, Krall C, Marosi C, et al. Strength of skeletal muscle and self-reported physical performance in Austrian glioblastoma-patients. *Wien Klin Wochenschr* 2012; 124: 377–83.
8. Kumthekar PU, Grimm S, Jacobs DI, et al. Financial burden experienced by patients undergoing treatment for malignant glioma: final data. Oral Presentation: 10th EANO Congress, Marseille, France, September 6–9, 2012.
9. Sizoo EM, Pasman HR, Buttolo J, et al. Decision-making in the end-of-life phase of high-grade glioma patients. *Eur J Cancer* 2012; 48: 226–32.
10. Flechl B, Ackerl M, Sax C, et al. The caregivers' perspective on the end-of-life phase of glioblastoma patients. Abstract: ESMO Congress 2012, Vienna, Austria.
11. Pace A, Lorenzo CD, Guariglia L, et al. End of life issues in brain tumour patients. *J Neurooncol* 2009; 91: 39–43.
12. Gaiger A, Acel A, Cenic O, et al. The Cancer Survival Index – a prognostic score integrating psychosocial and biological factors in patients diagnosed with cancer. *N Engl J Med* (submitted for publication).

News and Views Basic Science: Glioblastoma Stem Cells

Petra Hamerlik^{1,2,3}, Jeremy N Rich^{3,4}, Justin D Lathia^{4,5}

Abstract: Glioblastoma (GBM) are highly heterogeneous, infiltrative neoplasms with grave prognoses and five-year survival rates < 10 %. Particular challenges in GBM management include the striking therapeutic resistance of these tumours resulting in rapid and aggressive relapses, invasion of the tumour into normal brain preventing curative surgical resection, distinct intratumoural cellular heterogeneity, and limitations on delivery of therapeutics due to the blood-brain barrier. Surgical resection is beneficial but never curative and commonly followed by radiotherapy plus adjuvant chemotherapy via temozolomide, which offers

merely palliation with only modest effects on improving patient outcome. Targeted therapeutics have generally failed for glioblastomas with only modest activity from bevacizumab, an anti-VEGF antibody. Recent advances in GBM research have generated improved models, which better recapitulate the intra- and intertumoural heterogeneity found in patient tumours. These models attempt to address the complex genomic landscape as well as the presence of a cellular hierarchy with a self-renewing, tumourigenic cancer stem cell (CSC) population at the apex. These models also integrate the tumour microenvironment that

is composed of extracellular matrix components, stromal cells, vascular/hypoxic niches, and their heterotypic interactions. In this review, we provide a summary of GBM classification, their key features such as angiogenesis and therapeutic resistance, as well as the contribution of GBM CSCs and their microenvironment within the context of glioma biology and behaviour. **Eur Assoc NeuroOncol Mag 2013; 3 (2): 49–54.**

Key words: glioblastoma, cancer stem cell, angiogenesis, therapeutic resistance

■ Histopathology and Classification

Of all primary tumours, brain tumours constitute approximately 2 % and the global annual incidence reaches approximately 7 cases per 100,000 individuals [1–3]. There are > 100 types of brain tumours under the World Health Organization (WHO) classification scheme. Among these, gliomas are the most prevalent of the primary intrinsic brain tumours. Astrocytic gliomas rank among the most lethal of solid cancers and account for > 30 % of all primary brain and spinal malignancies. The World Health Organization (WHO) grades these tumours based on their histology to predict patient outcome. This classification system has been refined periodically, with the most recent changes published in 2007 [4]. WHO grade-I gliomas include several slow-growing tumours that are often located in specific anatomical locations, including juvenile pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma. These tumours are often managed primarily through surgical resection and display specific genetic profiles with rare malignant degeneration. Diffuse gliomas are highly infiltrative tumours without discrete borders divided into 3 grades (WHO II–IV). Grade-II gliomas infiltrate into normal brain parenchyma and exhibit increased cellularity and mitotic indices. Grade-III (anaplastic gliomas) and -IV (glioblastoma [GBM]) tumours are classified as high-grade gliomas with high cellular proliferative activity, mitoses, and cellular/nuclear atypia.

The reported time to progression is approximately 2 and 5 years for WHO grade-II and -III gliomas, respectively. GBMs are distinguished by microvascular proliferation and necrosis. GBM comprises more than a half of all gliomas with a 5-year survival < 5 %. Extremely low treatment efficacy against GBM has been observed despite decades of scientific efforts. Median life expectancy of newly diagnosed patients in clinical trials (ie, a selected patient population) has improved to 12–15 months, although outcome for elderly patients is much worse. Although GBMs are generally histologically indistinguishable from one another, increasing evidence supports subgroups of GBMs that are distinct in clinical course, genetic profiles, and epigenetic features. Primary GBMs arise rapidly *de novo*, representing the most common type of GBM (90–95 %), and are seen predominantly in older patients. In contrast, secondary GBMs progress from pre-existing lesions with a lower degree of malignancy. Secondary GBMs are more frequent in younger patients and are seen in 5–10 % of all cases.

■ Molecular Pathology and TCGA Classification

Despite the significant prognostic power of the WHO classification that is based largely on morphology, individual patients within each grade can have very different outcomes that are not otherwise accounted for by established prognostic factors, including age, Karnofsky Performance Status (KPS), and therapy [5]. Even though the incidence of gliomas is relatively low, the fatal outcome and poor prognosis associated with the diagnosis of GBM have prompted extensive large-scale molecular and phenotypic profiling informing several new classification schemes discussed below. To date, GBMs have been subjected to the most extensive genomic profiling of any cancer to show major chromosomal and expression alterations – possible drivers of pathogenesis and biology of this severe malignancy. Despite the extensive characterization of genomic alterations in GBM and clinical progress across many

Received on January 9, 2013; accepted on February 20, 2013; Pre-Publishing Online on March 19, 2013

From the ¹Danish Cancer Society Research Center, Copenhagen, Denmark; ²Institute of Molecular and Translational Medicine, Palacky University, Olomouc, Czech Republic; ³Department of Stem Cell Biology and Regenerative Medicine, Lerner Research Institute, Cleveland Clinic; ⁴Case Comprehensive Cancer Center; ⁵Department of Cellular and Molecular Medicine, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

Correspondence to: Justin D Lathia, PhD, Department of Cellular and Molecular Medicine, Lerner Research Institute, Cleveland Clinic, 9500 Euclid Avenue, NC10, Cleveland, OH 44195, USA; e-mail: lathiaj@ccf.org

cancer types, effective druggable tumour dependencies have yet to be exploited in glioma. Numerous small-scale studies with generally < 100 patients per diagnostic category have been published, identifying differentially expressed genes among morphologically defined gliomas [5]. These studies were deposited in publically available repositories (OncoPrint and Gene Expression Omnibus [GEO]) and provide a valuable “validation” tool for researchers [3]. A larger collective effort was undertaken in the National Cancer Institute’s REpository for Molecular BRAin Neoplasia DaTabase (REMBRANDT). Further, The Cancer Genome Atlas (TCGA) was established by the US National Cancer Institute and National Human Genome Research Institute in late 2005 with the mission of performing the first comprehensive cancer genome analyses applying multi-platform profiling to systematically and comprehensively analyze the gene copy number, mRNA expression, and the epigenetic state of approximately 200 tumours (today’s number has reached 600 patients), the majority being untreated primary GBMs [6]. This original study underwent accelerated publication to be published with a smaller-scale but deeper (whole exome) sequencing of a mix of patient tumours and xenografts that first identified mutations in isocitrate dehydrogenase (IDH1/2) [7], linking metabolism and tumour growth directly. A follow-on study demonstrated that IDH1 mutations occurred in low-grade tumours and secondary GBM [8]. IDH1 mutations serve a gain-of-function role to create an oncometabolite (2-hydroxygluturate) [9] and induce a methylation phenotype [10]. Other metabolic enzymes (eg, enolase) may be mutated as a passenger to cause sensitivity to specific inhibitors [11]. These studies have provided strong intellectual support for the identification for driving genetic lesions or other molecular sensitivities to inform therapeutic development.

Phenotypic gene expression profiling of glioblastomas has led to additional granularity of this disease. A seminal study by Phillips et al using unsupervised hierarchical clustering of expression profiles led to the characterization of 3 GBM tumour subgroups: proneural, proliferative, and mesenchymal [12]. A subsequent effort using the TCGA data delineated 4 subtypes: proneural, neural, classical, and mesenchymal on the basis of functional gene annotation and, prior to the Phillips study [12], linking the molecular signatures of gliomas with stages of neuroglial development. Moreover, TCGA effort utilized methylation profiling to identify a GBM CpG island methylator phenotype (G-CIMP) in a significant fraction of the proneural (29 %) subtype, secondary IDH1 mutation-positive GBM that progressed from lower-grade tumours in particular [13]. The 4 proposed subtypes were subsequently validated using previously published data and each of them was ultimately defined by a minimum list of 210 genes [14]. The proneural subtype was primarily enriched for amplifications of PDGFRA, OLIG2, CDK6, CDK4, and MET, where the first 2 represent markers highly relevant to oligodendrocyte development [15, 16]. The classical subtype can be characterized by more common epidermal growth factor receptor (EGFR) amplification/EGFRvIII mutation, PTEN and CDKN2A loss, whereas the mesenchymal subtype is enriched for mutations and/or loss of NF1, TP53, and CDKN2A. To evaluate whether these genomically identified subtypes predict biological or clinical heterogeneity in GBM, Brennan

et al [15] used a targeted proteomics approach to determine whether GBMs also segregate into the above-mentioned subtypes by activation of signalling pathways. 57 proteins or protein modifications were assessed in 20 GBM samples using unsupervised clustering and led to the identification of distinct tumour subgroups defined by EGFR-associated, PDGFR-associated signalling, or protein level changes associated with decreased NF1 expression [14]. In addition to previous studies, Sturm et al integrated paediatric GBMs to identify 6 epigenetic GBM subgroups displaying unique DNA methylation patterns, harbouring distinct hotspot mutations, DNA copy-number alterations, and transcriptomic patterns. Their findings correlate with molecular-genetic factors as well as key clinical variables such as patient age and tumour location of histologically indistinguishable GBMs [17]. Importantly, the established morphological classification system (WHO) and the evolving molecular subtyping should be considered complementary, not mutually exclusive, as the latter serves mainly as a diagnostic adjunct to more accurate classification of morphologically ambiguous tumours.

■ Angiogenesis

Robust neoangiogenesis and intratumoural heterogeneity are hallmark features of GBMs. Vascular endothelial growth factor (VEGF) expression strongly correlates with tumour aggressiveness, invasiveness, early relapse, and consequently commonly indicates poor prognosis and shorter survival of glioma patients [18, 19]. For many years, it was proposed that tumours beyond a diameter of 1 mm undergo so-called “angiogenic switch” resulting in the formation of tumour vasculature. This “switch” involves both activation of oncogenes [20] and inactivation of tumour suppressors to up-regulate pro-angiogenic pathways. To date, there are 6 principal cellular mechanisms described to take part in the process of neo-vascularization [19, 21]. These include

- vascular co-option involving formation of microvasculature surrounded by tumour cells
- vessel intussusception – formation of vessels by vascular invagination, intraluminal pillar formation, and splitting
- angiogenesis representing development of new vessels from pre-existing ones resulting in tortuous, abnormal vasculature with increased permeability
- vasculogenesis involving differentiation of circulating bone marrow-derived cells known as endothelial progenitors
- vascular mimicry – a controversial and insufficiently understood process defined as the ability of tumour cells to form functional vessel-like networks
- glioblastoma-endothelial cell transdifferentiation – the most recently reported mechanism, yet to be confirmed by further studies

VEGF is a key pro-angiogenic factor in both embryogenesis and tumour growth [18, 22]. Loss of VEGF or its 2 receptors VEGFR1 and VEGFR2 induces embryonic lethality in mouse models due to severe defects in the developing vascular system [23]. VEGF secreted by tumour cells acts through the VEGFR2 (VEGFR1 is believed to function as a “decoy” receptor to negatively regulate VEGF levels available for VEGFR2 activation) tyrosine kinase receptor, which is expressed pri-

marily in endothelial cells. Recent data, however, provide evidence of co-expression of VEGF/VEGFR2 in GBM cells – an indication of an autocrine control of VEGF signalling in gliomas in addition to the paracrine interplay of tumour and endothelial cells [24–26].

■ Therapeutic Resistance

Despite decades of concerted efforts for better understanding of the mechanisms that underlie the origin, development, and progression of GBM, currently available treatment modalities lack efficacy and these tumours remain among the most chemo- and radio-resistant solid cancers [27–29]. The current standard of care for GBM includes maximal surgical resection, followed by concurrent radio- and chemotherapy with adjuvant temozolomide (TMZ), a DNA-alkylating agent. The robust ability of GBM cells to invade normal brain parenchyma precludes surgical resection [14, 22, 30, 31]. The significant majority of GBMs (80–90 %) recur within 2–3 centimetres of the initial tumour location upon treatment with standard therapy [32, 33].

TMZ, an oral alkylating agent, has been investigated for use in primary and metastatic brain tumours for 2 decades [34]. Initially, it was approved for use in nitrosourea-resistant anaplastic astrocytomas but was extended to upfront use in glioblastoma after a seminal study in which it was administered concurrently with radiation [35]. The primary lethal adduct of TMZ involves methylation of guanine at the O6 position, a change that causes formation of DNA adducts, which if not repaired (by a mechanism known as base excision repair [BER]) results in failed replication. However, many tumours express MGMT, a suicide enzyme that can promote survival of tumour cells and hematopoietic stem cells. MGMT expression is often controlled by the methylation of the promoter and measuring MGMT expression by both promoter methylation and immunohistochemistry may identify patients likely to show limited benefit from TMZ treatment. Over the last decade, numerous phase-I and -II studies have investigated the efficacy and safety of TMZ in combination with other anti-GBM agents such as bevacizumab and interferon, as well as many other conventional chemotherapeutic agents (nitrosoureas) [36], such as irinotecan, pegylated doxorubicin, cisplatin, capecitabine, and sorafenib, for recurrent or progressive glioblastoma. MGMT promoter methylation status may serve as a prognostic factor but its use as a predictor of therapeutic response is more limited, as some patients with unmethylated MGMT promoters (thus, expected to express the gene product) do benefit from TMZ treatment [37].

EGFR amplification and EGFRvIII mutations were established as a key feature of the classical molecular GBM subtype and have long been known to be regulating intracellular signalling pathways that contribute to GBM pathogenesis including mTOR/PI3K/Akt and RAS/MAPK. The first generation of EGFR tyrosine kinase inhibitors (TKI) is represented by erlotinib and gefitinib, which were investigated in newly diagnosed and recurrent malignant gliomas, either as monotherapy or in combination with other cytotoxic agents [38]. Similarly to cetuximab, a monoclonal antibody directed at EGFR, and lapatinib that targets HER1 and HER2, these

agents were not associated with any significant treatment benefit [39–41].

Another recently evaluated inhibitor in gliomas is rapamycin and its intravenous and oral derivatives, temsirolimus and everolimus, the most widely tested mTOR inhibitors. These agents had minimal activity and no overall survival benefit in phase-II clinical trials with recurrent GBM either as monotherapy or in combination with EGFR TKIs in a smaller pilot study [38]. Additional promising strategies covering important RTK pathways in glioma development (PDGFR, VEGFR2) have only shown minimal activity in clinical trials [42–44].

The primary focus of current anti-angiogenic therapies is almost exclusively on tumour-derived endothelial cells as a constant element of tumour microenvironment and potential source of developing therapeutic resistance. Based on the response rate and presumed clinical benefit reported by 2 phase-II studies published by Vredenburgh et al [45] followed by Kreisl et al [46], bevacizumab (a humanized monoclonal antibody against VEGF; avastin, Genentech) was conditionally approved in 2009 by the US Food and Drug Administration (FDA) for the treatment of recurrent GBMs. Bevacizumab currently represents the most studied anti-angiogenic agent in the field of GBM. This agent specifically binds free VEGF ligands presumably in the systemic vasculature as a sink and so prevents its binding to putative receptors: VEGFR2 and VEGFR1, abrogating downstream signalling and resulting in decreased angiogenesis and tumour progression. Promising response rates but very limited median survival effects for recurrent GBM have been reported after bevacizumab treatment. Several concerns arose regarding the interpretation of the response rate, leading to denial of the bevacizumab registration by the European Medicines Agency because there was no inclusion of a bevacizumab-free control arm in any trial and consequently no proven effect on overall survival [36]. Ongoing phase-III trials may provide prospective data comparing bevacizumab-treated and -untreated cohorts, thereby facilitating the use of this drug in the therapy of GBM but preliminary reports suggest a modest increase in progression-free survival with significant toxicity. However, better understanding of angiogenesis on cellular as well as molecular levels is a necessity as well. It is known that anti-angiogenic agents decrease brain oedema and the requirement for corticosteroids by reducing vascular permeability [14, 47], thereby dramatically modifying the interpretation of GBM MRI scans [14, 44]. Whether these changes are a result of “vascular normalization” [48], actions on tumour cells, or effects on the blood-brain barrier remains unclear [49]. The phenomenon of so-called pseudo-response has been observed in bevacizumab-treated patients – an indication of treatment failure, development of resistance mechanisms promoting infiltrative spread of the tumour cells into healthy brain parenchyma [30, 31, 50], and/or switch in cellular metabolism and enhanced pro-survival signalling pathways.

■ Glioblastoma Stem Cells

Glioblastoma stem cells (GSC) are functionally defined by their capacity for (1) self-renewal, (2) recapitulation of a patient's phenotype when xenotransplanted into an immuno-

compromised host, and (3) multi-lineage differentiation, giving rise to a heterogeneous population of cells repopulating the tumour bulk [51–55]. These cells display severe resistance to current chemo- and radiation therapies, thus being considered one of the key determinants driving tumour recurrence [56–59]. Bao et al [56] reported elevated levels of the key components of the canonical DNA damage-response pathway in response to ionizing radiation (IR) and the ability of GSCs to escape the effect of IR by preferential activation of this pathway and lowered rates of apoptosis when compared to non-GSCs. GSCs also exhibit high levels of MGMT, thus making GSCs more sensitive to TMZ treatment [57]. However, TMZ did not affect propagation and maintenance of GSCs with “normal” levels of MGMT [60], which might be due to over-expression of certain ATP-binding cassette transporters (ABCT) such as ABCG2 responsible for active efflux of TMZ from the GSCs [58, 61].

Several prospective markers to identify and further isolate GSCs have been published so far, among those CD133 (prominin-1), CD15, Integrin α 6, CD44, EGFR, A2B5, L1CAM are surface antigens [62–67]: Sox2, Olig2, Oct4, Mushashi-1, BMI1, NANOG represent intracellular factors involved in GSC self-renewal and maintenance [68, 69]. Despite CD133 being the most frequently used marker to enrich GSCs from the tumour bulk, 2 independent studies suggested that CD133 is not a universal GSC marker, as tumours contain CD133-negative tumour cells that showed “stem cell” properties in stem-like conditioned media in vitro and initiated tumours when injected orthotopically in immunocompromised hosts [70, 71]. However, some studies use extensive cultures that may affect the hierarchy.

Recent research in this area has revealed that GSCs are localized into 2 specialized niches within the tumour, perivascular and hypoxic, where the hierarchy and their maintenance are regulated by a complex network of molecular signals and cell-to-cell/cell-to-extracellular matrix interactions (Figure 1). Normal neural stem cells also exist in vascular niches, into which endothelial cells secrete factors that regulate neural stem cell function [72–74]. Calabrese et al [75] provided evidence that the brain tumour microvasculature forms a niche that is critical for the maintenance of brain tumour stem cells,

where these cells physically interact with endothelial cells and tumour vasculature. A recent study by Zhu et al [76] took into consideration cell-to-cell contact between different cell types and proposed the endothelial Notch-ligand expression Dll4 (Delta-like ligand 4) as the juxtacrine mechanism driving stem cell maintenance. Interestingly, Notch is one of the crucial factors in GSC maintenance and also contributes to the radio-resistant phenotype as described by Wang et al [59]. Moreover, GSCs have been shown to secrete elevated levels of VEGF and SDF-1 [77, 78] and to operate the pro-angiogenic VEGF/VEGFR2 signalling in an autocrine manner [24, 26], being further potentiated by interaction with other pro-angiogenic factors such as NRP-1 and c-met. Integrating the recent findings on GBM-endothelial cell transdifferentiation and vascular mimicry, the mechanisms utilized by GSCs represent a putative source of resistance to current anti-angiogenic therapies [24, 25].

Hypoxia is a well-recognized tumour microenvironmental condition linked to poor patient outcome and resistance to therapies [79–81]. Evans et al [82] analyzed normal brain and glioma tissue oxygenation and showed that physiological oxygen concentrations in healthy brains range between 12.5 % and 2.5 %, whereas GBM tumours showed mild to moderate/severe hypoxia (oxygen concentrations ranging between 2.5 % and 0.5 % for mild hypoxia and 0.5–0.1 % for moderate/severe hypoxia). Li et al [83] showed that GSCs differentially respond to hypoxia with a distinct induction of HIF2 α , and moreover that expression of HIF2 α is significantly associated with poor patient survival. Pistollato et al [84] reported that hypoxia represses the differentiation responses to bone morphogenetic proteins (BMP).

The dependence of GSCs on hypoxic and perivascular niches offers potential therapeutic strategies based on vascular targeting, which may have a higher therapeutic index to GSCs as compared with normal neural cells. As anti-angiogenic therapies continue to be developed for many cancers, including GBM, efficacy can be improved by increasing our understanding of the molecular mechanisms by which these agents function. Further work correlating cell surface makers with phenotype as well as a deeper understanding of the key survival pathways driving their resistance are indispensable for a proper definition and clinical relevance of cancer stem cells to GBM and other advanced cancers.

Conclusions

The accumulation of knowledge over the past 2 decades has revealed many challenging questions and controversies. The attempts to decipher the complex inter- and intratumoural heterogeneity of GBM is beginning to provide important information regarding tumour behaviour, and is likely to drive future contribution to the development of therapeutic approaches with the primary focus not only on the tumour itself, but also interconnected components of its complex microenvironment. The way by which GSCs and their microenvironment contributes to glioma development, progression, and responses to therapies should remain the focus of future studies. Because the efficacy of current therapies is greatly affected by these factors, future therapies will most probably

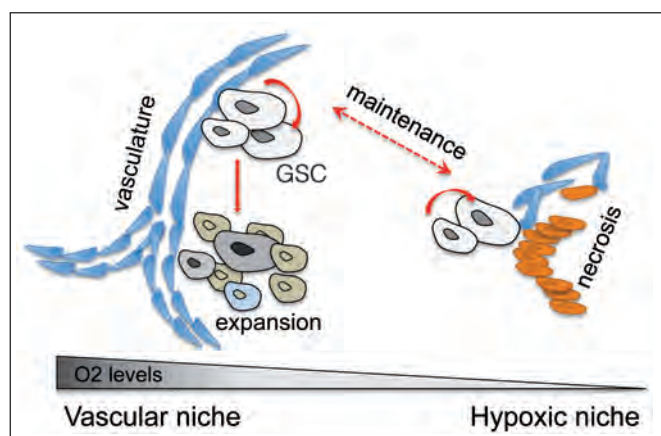


Figure 1. Glioblastoma stem cells (GSC) reside in vascular and hypoxic niches. Schematic representation of GSC residing in a vascular niche supported by blood vessels and hypoxic niche adjacent to necrotic regions. Each niche promotes the maintenance of the GSC population and supports the expansion of the tumour mass.

profit from combinational targeting of various survival mechanisms that involve niche components (such as hypoxia) that contribute to preferential selection and outgrowth of genetically unstable clones, thus being responsible for tumour recurrence and, consequently, patient death.

Acknowledgements

PH is supported by the Danish Council for Independent Research/Medical Sciences ID4765/11-105457, Czech Ministry of Education (MSM6198959216), and Czech Ministry of Health (NT11065-5).

JNR is supported by the National Institutes of Health grants CA112958, CA116659, CA154130 and the James D McDonnell Foundation.

JDL is supported by a National Institutes of Health K99/R00 Pathway to Independence Award CA157948, Voices Against Brain Cancer, Ohio Cancer Research Associates, American Cancer Society, and by a V Scholar Award from the V Foundation for Cancer Research.

Conflict of Interest

The authors state no conflict of interest.

References

- Davis FG, Kupelian V, Freels S, et al. Prevalence estimates for primary brain tumors in the United States by behavior and major histology groups. *Neuro Oncol* 2001; 3: 152–8.
- Ohgaki H, Kleihues P. Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. *J Neuropathol Exp Neurol* 2005; 64: 479–89.
- Madhavan S, Zenklusen JC, Kotliarov Y, et al. Rembrandt: helping personalized medicine become a reality through integrative translational research. *Mol Cancer Res* 2009; 7: 157–67.
- Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007; 114: 97–109.
- Vitucci M, Hayes DN, Miller CR. Gene expression profiling of gliomas: merging genomic and histopathological classification for personalised therapy. *Br J Cancer* 2011; 104: 545–53.
- Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* 2008; 455: 1061–8.
- Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science* 2008; 321: 1807–12.
- Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med* 2009; 360: 765–73.
- Dang L, White DW, Gross S, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* 2009; 462: 739–44.
- Turcan S, Rohle D, Goenka A, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature* 2012; 483: 479–83.
- Muller FL, Colla S, Aquilanti E, et al. Passenger deletions generate therapeutic vulnerabilities in cancer. *Nature* 2012; 488: 337–42.
- Phillips HS, Kharbada S, Chen R, et al. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer Cell* 2006; 9: 157–73.
- Noushmehr H, Weisenberger DJ, Diefes K, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer Cell* 2010; 17: 510–22.
- Dunn GP, Rinne ML, Wykosky J, et al. Emerging insights into the molecular and cellular basis of glioblastoma. *Genes Dev* 2012; 26: 756–84.
- Brennan C, Momota H, Hambardzumyan D, et al. Glioblastoma subclasses can be defined by activity among signal transduction pathways and associated genomic alterations. *PLoS One* 2009; 4: e7752.
- Brennan C. Genomic profiles of glioma. *Curr Neurol Neurosci Rep* 2011; 11: 291–7.
- Sturm D, Witt H, Hovestadt V, et al. Hot-spot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. *Cancer Cell* 2012; 22: 425–37.
- Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. *Nat Rev Cancer* 2003; 3: 401–10.
- Hardee ME, Zagzag D. Mechanisms of glioma-associated neovascularization. *Am J Pathol* 2012; 181: 1126–41.
- Gatson NN, Chiochia EA, Kaur B. Anti-angiogenic gene therapy in the treatment of malignant gliomas. *Neurosci Lett* 2012; 527: 62–70.
- Hu YL, Jahangiri A, De Lay M, et al. Hypoxia-induced tumor cell autophagy mediates resistance to anti-angiogenic therapy. *Autophagy* 2012; 8: 979–81.
- Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med* 1971; 285: 1182–6.
- Shibuya M. Structure and function of VEGF/VEGF-receptor system involved in angiogenesis. *Cell Struct Funct* 2001; 26: 25–35.
- Hamerlik P, Lathia JD, Rasmussen R, et al. Autocrine VEGF-VEGFR2-Neuropilin-1 signaling promotes glioma stem-like cell viability and tumor growth. *J Exp Med* 2012; 209: 507–20.
- Lu KV, Chang JP, Parachoniak CA, et al. VEGF inhibits tumor cell invasion and mesenchymal transition through a MET/VEGFR2 complex. *Cancer Cell* 2012; 22: 21–35.
- Knizetova P, Ehrmann J, Hlobilkova A, et al. Autocrine regulation of glioblastoma cell cycle progression, viability and radioresistance through the VEGF-VEGFR2 (KDR) interplay. *Cell Cycle* 2008; 7: 2553–61.
- Lu C, Shervington A. Chemoresistance in gliomas. *Mol Cell Biochem* 2008; 312: 71–80.
- Polivka J Jr, Polivka J, Rohan V, et al. New molecularly targeted therapies for glioblastoma multiforme. *Anticancer Res* 2012; 32: 2935–46.
- Ziegler DS, Wright RD, Kesari S, et al. Resistance of human glioblastoma multiforme cells to growth factor inhibitors is overcome by blockade of inhibitor of apoptosis proteins. *J Clin Invest* 2008; 118: 3109–22.
- Narayana A, Kunnakkat SD, Medabalmi P, et al. Change in pattern of relapse after anti-angiogenic therapy in high-grade glioma. *Int J Radiat Oncol Biol Phys* 2012; 82: 77–82.
- Norden AD, Young GS, Setayesh K, et al. Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. *Neurology* 2008; 70: 779–87.
- Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. *Neurology* 1980; 30: 907–11.
- Chamberlain MC. Radiographic patterns of relapse in glioblastoma. *J Neurooncol* 2011; 101: 319–23.
- O'Reilly SM, Newlands ES, Glaser MG, et al. Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumours. *Eur J Cancer* 1993; 29A: 940–2.
- Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; 352: 987–96.
- Weller M, Cloughesy T, Perry JR, et al. Standards of care for treatment of recurrent glioblastoma – are we there yet? *Neuro Oncol* 2013; 15: 4–27.
- Suri V, Jha P, Sharma MC, et al. O6-methylguanine DNA methyltransferase gene promoter methylation in high-grade gliomas: a review of current status. *Neurol India* 2011; 59: 229–35.
- Tanaka S, Louis DN, Curry WT, et al. Diagnostic and therapeutic avenues for glioblastoma: no longer a dead end? *Nat Rev Clin Oncol* 2013; 10: 14–26.
- Brown PD, Krishnan S, Sarkaria JN, et al. Phase I/II trial of erlotinib and temozolomide with radiation therapy in the treatment of newly diagnosed glioblastoma multiforme: North Central Cancer Treatment Group Study N0177. *J Clin Oncol* 2008; 26: 5603–9.
- van den Bent MJ, Brandes AA, Rampling R, et al. Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034. *J Clin Oncol* 2009; 27: 1268–74.
- Lassman AB, Rossi MR, Raizer JJ, et al. Molecular study of malignant gliomas treated with epidermal growth factor receptor inhibitors: tissue analysis from North American Brain Tumor Consortium Trials 01-03 and 00-01. *Clin Cancer Res* 2005; 11: 7841–50.
- Dresemann G, Weller M, Rosenthal MA, et al. Imatinib in combination with hydroxyurea versus hydroxyurea alone as oral therapy in patients with progressive pretreated glioblastoma resistant to standard dose temozolomide. *J Neurooncol* 2010; 96: 393–402.
- Reardon DA, Desjardins A, Vredenburgh JJ, et al. Metronomic chemotherapy with daily oral etoposide plus bevacizumab for recurrent malignant glioma: a phase II study. *Br J Cancer* 2009; 101: 1986–94.
- Wen PY, Yung WK, Lamborn KR, et al. Phase I/II study of imatinib mesylate for recurrent malignant gliomas: North American Brain Tumor Consortium Study 99-08. *Clin Cancer Res* 2006; 12: 4899–907.
- Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. *Clin Cancer Res* 2007; 13: 1253–9.
- Kreis TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol* 2009; 27: 740–5.
- Gerstner ER, Sorensen AG, Jain RK, et al. Anti-vascular endothelial growth factor therapy for malignant glioma. *Curr Neurol Neurosci Rep* 2009; 9: 254–62.
- Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005; 307: 58–62.
- Seystahl K, Weller M. Is there a world beyond bevacizumab in targeting angiogenesis in glioblastoma? *Expert Opin Investig Drugs* 2012; 21: 605–17.
- Iwamoto FM, Abrey LE, Beal K, et al. Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. *Neurology* 2009; 73: 1200–6.
- Dirks PB. Brain tumor stem cells: the cancer stem cell hypothesis writ large. *Mol Oncol* 2010; 4: 420–30.
- Hemmati HD, Nakano I, Lazareff JA, et al. Cancerous stem cells can arise from pediatric brain tumors. *Proc Natl Acad Sci USA* 2003; 100: 15178–83.
- Ignatova TN, Kukekov VG, Laywell ED, et al. Human cortical glial tumors contain neural stem-like cells expressing astroglial and neuronal markers in vitro. *Glia* 2002; 39: 193–206.
- Singh SK, Clarke ID, Terasaki M, et al. Identification of a cancer stem cell in human brain tumors. *Cancer Res* 2003; 63: 5821–8.
- Singh SK, Hawkins C, Clarke ID, et al. Identification of human brain tumour initiating cells. *Nature* 2004; 432: 396–401.
- Bao S, Wu Q, McLendon RE, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature* 2006; 444: 756–60.
- Beier D, Rohrl S, Pillai DR, et al. Temozolomide preferentially depletes cancer stem cells in glioblastoma. *Cancer Res* 2008; 68: 5706–15.
- Chua C, Zaiden N, Chong KH, et al. Characterization of a side population of astrocytoma cells in response to temozolomide. *J Neurosurg* 2008; 109: 856–66.
- Wang J, Wakeman TP, Lathia JD, et al. Notch promotes radioresistance of glioma stem cells. *Stem Cells* 2010; 28: 17–28.
- Clement V, Sanchez P, de Tribolet N, et al. HEDGEHOG-GLI1 signaling regulates human glioma growth, cancer stem cell self-renewal, and tumorigenicity. *Curr Biol* 2007; 17: 165–72.
- Chen J, McKay RM, Parada LF. Malignant glioma: lessons from genomics, mouse models, and stem cells. *Cell* 2012; 149: 36–47.
- Bao S, Wu Q, Li Z, et al. Targeting cancer stem cells through L1CAM suppresses glioma growth. *Cancer Res* 2008; 68: 6043–8.
- Howard BM, Gursel DB, Bleau AM, et al. EGFR signaling is differentially activated in patient-derived glioblastoma stem cells. *J Exp Ther Oncol* 2010; 8: 247–60.
- Jijiwa M, Demir H, Gupta S, et al. CD44v6 regulates growth of brain tumor stem cells partially through the AKT-mediated pathway. *PLoS One* 2011; 6: e24217.

65. Lathia JD, Gallagher J, Heddleston JM, et al. Integrin alpha 6 regulates glioblastoma stem cells. *Cell Stem Cell* 2010; 6: 421–32.
66. Mao XG, Zhang X, Xue XY, et al. Brain tumor stem-like cells identified by neural stem cell marker CD15. *Transl Oncol* 2009; 2: 247–57.
67. Ogden AT, Waziri AE, Lochhead RA, et al. Identification of A2B5+CD133- tumor-initiating cells in adult human gliomas. *Neurosurgery* 2008; 62: 505–14.
68. Lathia JD, Heddleston JM, Venere M, et al. Deadly teamwork: neural cancer stem cells and the tumor microenvironment. *Cell Stem Cell* 2011; 8: 482–5.
69. Park DM, Rich JN. Biology of glioma cancer stem cells. *Mol Cells* 2009; 28: 7–12.
70. Beier CP, Beier D. CD133 negative cancer stem cells in glioblastoma. *Front Biosci (Elite Ed)* 2011; 3: 701–10.
71. Joo KM, Jin J, Kim E, et al. MET signaling regulates glioblastoma stem cells. *Cancer Res* 2012; 72: 3828–38.
72. Palmer TD, Willhoite AR, Gage FH. Vascular niche for adult hippocampal neurogenesis. *J Comp Neurol* 2000; 425: 479–94.
73. Ramirez-Castillejo C, Sanchez-Sanchez F, Andreu-Agullo C, et al. Pigment epithelium-derived factor is a niche signal for neural stem cell renewal. *Nat Neurosci* 2006; 9: 331–9.
74. Shen Q, Goderie SK, Jin L, et al. Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. *Science* 2004; 304: 1338–40.
75. Calabrese C, Poppleton H, Kocak M, et al. A perivascular niche for brain tumor stem cells. *Cancer Cell* 2007; 11: 69–82.
76. Zhu TS, Costello MA, Talsma CE, et al. Endothelial cells create a stem cell niche in glioblastoma by providing NOTCH ligands that nurture self-renewal of cancer stem-like cells. *Cancer Res* 2011; 71: 6061–72.
77. Bao S, Wu Q, Sathornsumetee S, et al. Stem cell-like glioma cells promote tumor angiogenesis through vascular endothelial growth factor. *Cancer Res* 2006; 66: 7843–8.
78. Folkins C, Shaked Y, Man S, et al. Glioma tumor stem-like cells promote tumor angiogenesis and vasculogenesis via vascular endothelial growth factor and stromal-derived factor 1. *Cancer Res* 2009; 69: 7243–51.
79. Chi JT, Wang Z, Nuyten DS, et al. Gene expression programs in response to hypoxia: cell type specificity and prognostic significance in human cancers. *PLoS Med* 2006; 3: e47.
80. Sathornsumetee S, Cao Y, Marcello JE, et al. Tumor angiogenic and hypoxic profiles predict radiographic response and survival in malignant astrocytoma patients treated with bevacizumab and irinotecan. *J Clin Oncol* 2008; 26: 271–8.
81. Vaupel P, Mayer A. Hypoxia in cancer: significance and impact on clinical outcome. *Cancer Metastasis Rev* 2007; 26: 225–39.
82. Evans SM, Jenkins KW, Jenkins WT, et al. Imaging and analytical methods as applied to the evaluation of vasculature and hypoxia in human brain tumors. *Radiat Res* 2008; 170: 677–90.
83. Li Z, Bao S, Wu Q, et al. Hypoxia-inducible factors regulate tumorigenic capacity of glioma stem cells. *Cancer Cell* 2009; 15: 501–13.
84. Pistollato F, Chen HL, Rood BR, et al. Hypoxia and HIF1alpha repress the differentiative effects of BMPs in high-grade glioma. *Stem Cells* 2009; 27: 7–17.



NEURO-ONCOLOGY - THE BEST OF TWO CONTINENTS
Adult • Pediatric • Spine • Peripheral Nerves



THE EUROPEAN ASSOCIATION
OF NEUROSURGICAL SOCIETIES

EANS Annual Meeting 2013



EANS Tumor Section
AANS/CNS Section on Tumors
Annual International Neuro-Oncology Updates

Tel Aviv, Israel, 11-14 November, 2013

www.kenes.com/eans2013



CONGRESS ORGANIZER

Kenes International, 1-3 Rue de Chantepoulet, PO Box 1726, CH-1211 Geneva 1, Switzerland
Tel: +41 22 908 0488; Fax: +41 22 906 9140; E-mail: eans2013@kenes.com

Epidemiology and Brain Tumours: Practical Usefulness

Adelheid Wöhrer

Abstract: Primary brain tumours are rare tumours which occur across all ages and comprise a large spectrum of different entities. This review compiles population-based information on age distribution, gender predilection, ethnical disparities, geographic variations, and time trends in the incidence of primary brain tumours. Unlike clinical trials, which are prone to selection bias, population-based incidence and mortality data provide a comprehensive picture of the real-life scenario and are thus of high relevance to the neuro-oncology community.

Descriptive epidemiology further constitutes the basis for all risk factor research. With re-

gard to primary brain tumours, only few risk factors including certain germ-line mutations and exposure to ionizing radiation are known to date. Latest results from epidemiological studies focusing on the exposure to radiofrequency electromagnetic fields from mobile phones and their implications are addressed. However, not only environmental risk factor research but also the incorporation of molecular techniques in epidemiological study designs has considerably contributed to our present-day knowledge. Herein, the latest findings on genetic risk loci and tumour-specific sub- and risk groups are highlighted. Hence, the translation of all those

findings into clinical applicability is now a major aim and largely depends on the development of practical, robust, and widely accepted biomarkers, which will pave the way for individualized patient treatment. **Eur Assoc Neuro-Oncol Mag 2013; 3 (2): 56–60.**

Key words: brain tumour epidemiology, descriptive epidemiology, risk factor research, susceptibility loci, risk groups, ionizing radiation, non-ionizing radiation

■ Background and Descriptive Epidemiology

Primary brain tumours are rare tumours which occur across all ages. In children, however, they are especially frequent; in this age cohort, they constitute the second most common tumours following leukaemias and are the most common cause of cancer-related death [1, 2]. Primary brain tumours comprise a large spectrum of different tumour entities, each being associated with a distinct biological background and disease course [3]. Thus, the prognosis of the individual patient varies considerably by tumour type, age at diagnosis, and neurological impairment. Based on their biological behaviour, brain tumours are categorized into benign, intermediate, and malignant tumours [4]. Cancer registration is most often restricted to malignant brain tumours (ie, cancer), whereas benign and intermediate lesions are not routinely reported. However, due to the localization within the central nervous system (often in close proximity to eloquent areas) and the potential for malignant transformation, non-malignant tumours (approximately 50 % of all brain tumours) considerably impact patient morbidity and mortality as well. Therefore, registration of all brain tumours – including non-malignant lesions – is of high relevance.

■ Incidence and Mortality

Reported overall incidence rates of primary brain tumours reach up to 20 per 100,000 person-years [5], the most common tumours in adults being meningiomas, glioblastomas, and pituitary adenomas [5, 6]. In children, however, the encountered spectrum of brain tumours differs substantially from that in adults due to a higher prevalence of embryonal

tumours, eg medulloblastomas, pilocytic astrocytomas, and ependymomas [6, 7].

The overall impact of brain tumour-related deaths on Western populations in terms of premature mortality has been quantified as an average of 21.3 years of a potential life lost [8]. This adds to a substantial loss of productivity due to the high occurrence of brain tumours in younger “working-age” individuals [9] and considerable costs for supportive care for daily living activities. Alternately, the diagnosis of a brain tumour renders the affected patients often in difficult financial situations due to frequent job losses and high treatment expenses [10]. On the other hand, survival times are increasing due to innovations in diagnosis and therapy. Hence, tumour- and/or therapy-associated effects on the social and cognitive functioning of long-term survivors’ “quality-of-life” are becoming increasingly relevant [11].

■ Gender Predilection, Regional Variation, and Ethnical Disparities

Overall, primary brain tumours are more frequent in females than males (female incidence rate [IR] 22.25 per 100,000 person-years, male 18.8 per 100,000 person-years) [5]. While meningiomas are twice as common in females, gliomas, embryonal tumours, lymphomas, and germ cell tumours show a slight male predilection (m/f ratio approximately 1.4).

Interestingly, CBTRUS data from the United States indicate ethnical disparities with a lower overall incidence of brain tumours in American Indian or Alaska Natives (AIAN; IR 13.15 per 100,000 person-years) as well as the Asian and Pacific Islander (API) population in the United States (IR 12.98 per 100,000 person-years) compared with whites (“Caucasians”; IR 20.61 per 100,000 person-years) and Afro-Americans (IR 20.12 per 100,000 person-years) [5]. However, the observed rates for the majority of brain tumour entities are significantly higher in whites of European ancestry when compared with Afro-Americans, AIAN, and API ethnicities. The only exceptions are meningiomas and tumours of the pitui-

Received on January 16, 2013; accepted after revision on January 29, 2013; Pre-Publishing Online on February 18, 2013

From the Institute of Neurology, Medical University of Vienna, Austria

Correspondence to: Adelheid Wöhrer, MD PhD, Institute of Neurology, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria; e-mail: adelheid.woehrer@meduniwien.ac.at

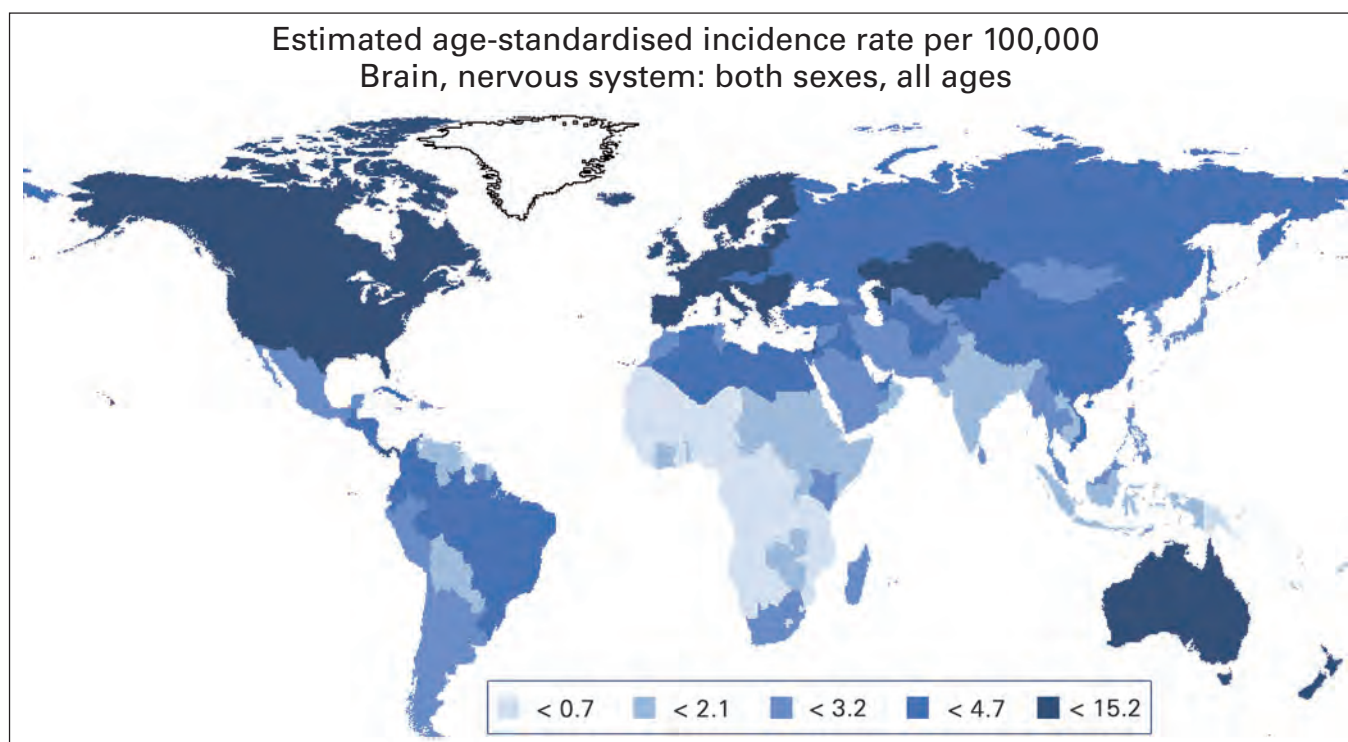


Figure 1. World-wide incidence of malignant brain tumour types. Source: [Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: <http://globocan.iarc.fr>, accessed on 29/01/2013]. The world-wide distribution of age-standardized incidence rates of malignant brain tumours shows higher rates of disease occurrence in developed countries.

tary, which are significantly more common in Afro-Americans [5]. These ethnic disparities might in fact account for the observed regional variation in the world-wide incidence of malignant brain tumours, with higher incidence rates being reported from developed countries (Figure 1) [12]. Still, differences in diagnostic and case ascertainment procedures between individual countries might obscure the picture. However, a higher incidence of germ cell tumours had been advocated for East Asia [13, 14] but this has not been confirmed in a recently conducted joint study between Japan and the United States [15].

■ Time Trends

With the increasing availability of MR imaging, the overall incidence of brain tumours virtually increased during the 1980s but has remained relatively stable ever since. However, epidemiological data have shown a continuous rise in primary CNS lymphomas in the immunocompetent population over the last decades, whereas the incidence seems to be decreasing in patients with AIDS since the introduction of highly active anti-retroviral therapies [16, 17]. Conflicting data exist for acoustic neurinomas, with some reporting an increase in incidence rates [18], which has not been confirmed by others [19].

■ Analytical Epidemiology

Environmental Risk Factors

Ionizing Radiation

To date, exposure to moderate-to-high doses of ionizing radiation is the only established environmental risk factor for the development of brain tumours [20]. Especially the occur-

rence of secondary neoplasms such as meningiomas, gliomas, and sarcomas subsequent to therapeutic irradiation of a primary lesion represents a severe and potentially fatal complication. The ALL-Berlin-Frankfurt-Münster study, for instance, found a 19-fold increased risk for brain neoplasms in previously treated patients compared with the general population [21]. The cumulative risk for having developed a brain tumour at 15 years after treatment was 3.5 % (95-% confidence interval [CI]: 1.5–5.5 %) if therapy included cranial irradiation, but was substantially lower (1.2 %; 95-% CI: 0.2–2.3 %) if cranial irradiation was omitted [21]. Overall, the association between brain tumours and ionizing radiation seems stronger for meningioma than for glioma [20].

Radiation Exposure from X-Ray Investigations Including CT Scans

In addition to cranial irradiation, a large retrospective study found also a positive association for CT scans, which were performed in individuals under the age of 22 years (excess relative risk 0.023; 95-% CI: 0.010–0.049; $p < 0.0001$) [22]. The relative risk of brain tumours after a cumulative dose of 50–74 mGy was 2.82 (95-% CI: 1.33–6.03), thus almost tripled. The authors concluded that radiation doses from CT scans should be kept as low as possible and alternative procedures should be considered [22]. Of note, a major limitation of the study constitutes its retrospective design covering a large time period (1985–2002) without accounting for the various technical improvements that had meanwhile resulted in considerable dose reductions [23].

Likewise, dental X-rays, which were performed in the past, when radiation exposure was still greater, appear to be associated with a slightly to moderately increased risk for the devel-

Table 1. Genetic brain tumour syndromes [3].

Syndrome	Gene	Locus	Brain tumour
Cowden syndrome/Lhermitte-Duclos syndrome	PTEN	10q23	Dysplastic gangliocytoma of the cerebellum
Li-Fraumeni syndrome	TP53	17p13	Astrocytoma, PNET
Naevoid basal cell carcinoma syndrome/ Gorlin syndrome	PTCH	9q31	Medulloblastoma
Neurofibromatosis I	NF1	17q11	Neurofibroma, MPNST, optic and other gliomas
Neurofibromatosis II	NF2	22q12	Bilateral vestibular schwannoma, meningioma, ependymoma, and others
Rhabdoid tumour predisposition syndrome	SMARCB1/INI1	22q11.2	ATRT
Von-Hippel-Lindau syndrome	VHL	3p25	Hemangioblastoma
Tuberous sclerosis	TSC1 TSC2	9p34 16p13	SEGA, cortical tubers
Turcot syndrome	APC hMLH1 hPSM2	5q21 3p21 7p22	Medulloblastoma, glioblastoma
Familial meningioma	SUFU	10q24.32	Multiple meningiomas [31]

PNET: primitive neuroectodermal tumour; MPNST: malignant peripheral nerve sheath tumour; ATRT: atypical teratoid/rhabdoid tumour; SEGA: subependymal giant cell astrocytoma

Table 2. Molecular-genetic subtypes of common brain tumours as revealed by integrated genomic analysis

Brain tumour	Molecular subtypes	Prognostic impact	Source
Glioblastoma	IDH1 mutation/G-CIMP+ hypermethylation	Improved outcome	Sturm et al, 2012 [34]
	H3F3A G34 mutation	Poor outcome	
	H3F3A K27 mutation		
	Mesenchymal expression	Improved outcome	
	Proneural expression (PDGFRA amplification)		
	Classical expression EGFR amplification		
Medulloblastoma	WNT/wingless	Improved outcome	Northcott et al, 2011 [36]
	SHH	Poor outcome	
	Group 3		
	Group 4		
Posterior fossa ependymomas	Group A	Poor outcome	Witt et al, 2011 [37]
	Group B		
CNS PNET	Group 1 (primitive neural)	Poor outcome	Picard et al, 2012 [38]
	Group 2 (oligoneural)		
	Group 3 (mesenchymal lineage)		

PDGFRA: platelet-derived growth factor receptor- α ; EGFR: epidermal growth factor receptor; WNT: wingless int; SHH: sonig hedgehog; PNET: primitive neuroectodermal tumour

opment of meningiomas with odds ratios varying according to patient age and used technique from 1.4–1.9 [24].

Non-Ionizing Radiation

Over the last decade, exposure to low-frequency, non-ionizing electromagnetic fields via mobile phones has been critically discussed as a potential risk factor for brain tumours such as gliomas, meningiomas, and acoustic neurinomas [25]. The so far conducted case-control studies found inconsistent results, which were in part due to different study designs, small sample sizes, recall bias of mobile phone use, and lack of information on long-term use. The largest studies, so far,

include the Interphone and Hardell studies [26–29]. A meta-analysis on both studies found a significantly increased risk for temporal lobe gliomas (most exposed part of the brain) with an odds ratio of 1.71 (95%-CI: 1.04–2.81) in the > 10-year latency group. Ipsilateral mobile phone use > 1640 h in total gave an odds ratio of 2.29 (95%-CI: 1.56–3.37) [25]. With regard to acoustic neurinomas, ipsilateral mobile phone use in the latency group > 10 years resulted in an odds ratio of 1.81 (95%-CI: 0.73–4.45). For ipsilateral cumulative use > 1640 h an odds ratio of 2.55 (95%-CI: 1.50–4.40) was found [25].

Based on a comprehensive literature search with special

consideration given to the 2 studies mentioned above, the IARC has recently classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (press release No 208, 31-05-2011). However, whether the IARC carcinogenic classification has any impact on policy makers and results in concrete legislative acts to protect public health remains to be shown [25]. Furthermore, there are concerns that mobile phone use might differentially impact developing brains of children and adolescents. This is currently the topic of 2 large case-control studies: CEFALO and MOBI-KIDS (www.mbkds.net). First CEFALO results did not demonstrate an exposure-response relationship in children and adolescents [30].

Genetic Risk Factors

Genetic Tumour Syndromes

Genetic predisposition to primary brain tumours is well-known in the setting of rare tumour syndromes (Table 1). They involve tumour suppressor genes and are inherited in an autosomally dominant trait. However, the vast majority of brain tumours (> 90 %) occurs outside the setting of an established germ-line mutation [3].

Susceptibility Loci

Genome-wide association studies have recently identified 7 susceptibility variants for gliomas, which are associated with moderate increases or decreases in risk (odds ratios from 0.6–1.2) [32, 33]. While variants at 7p11.2 (EGFR both loci) affect all glioma subtypes, 20q13.33 (RTEL1), 5p15.33 (TERT), and 9p21.3 (CDKN2B) differentially impact the risk for glioblastoma, 8q24.21 (CCDC26) for oligodendroglioma, and 11q23.3 (PHLDB1) for low-grade glioma [32]. These data show that common low-penetrance susceptibility alleles are associated with the development of glioma and provide insights into disease causation [33]. Still, larger studies focusing on specific tumour subtypes or -groups are required to identify additional susceptibility loci and validate the proposed ones for glioma risk.

Molecular Epidemiology

Molecular epidemiology is a relatively new concept integrating the rapid advances in the fields of genomics, transcriptomics, proteomics, and metabonomics. With regard to brain tumour research, the integration of these high-throughput molecular techniques has significantly increased our understanding of the underlying genetic mechanisms of the most common brain tumours such as glioblastoma or medulloblastoma. Within traditional tumour entities further genetic subtypes have been identified, which differ not only in terms of cells of origin and involved genetic pathways, but also in their clinical outcomes and differential responses to therapy [34, 35]. Genetic brain tumour subtypes are listed in Table 2. Still, sophisticated molecular-genetic techniques are not widely available, cost-intensive, and not generally applicable to individual patients. Hence, the translation of such findings into clinical applicability now largely depends on the development of practical and robust subgroup-specific biomarkers and therapies [39].

Despite the huge number of proposed biomarkers for brain tumours, only single candidate biomarkers, which provide prognostic and/or predictive information, have translated into clinical use so far. The most prominent examples of tissue-based biomarkers include isocitrate dehydrogenase (IDH) 1 and 2 mutations in diffuse gliomas [40, 41], combined 1p19q loss in oligodendroglioma [42, 43], O6-methylguanine methyl-transferase (MGMT) promoter methylation status in glioblastoma [44], as well as MYCC/MYCN amplification and markers for WNT activation in medulloblastoma [45, 46]. While some of those markers are screened for in the setting of clinical trials (eg, MGMT, 1p19q, MYCC/MYCN amplification) serving as patient stratification factors, even less markers have already translated into routine clinical use, where they provide prognostic and/or predictive information on the individual patient (IDH1 mutational analysis and assessment

of combined 1p19q loss) [47]. With regard to the various biomarkers, clinical and analytical test performances remain an important issue [48] and there is a need for a widely accepted consensus among neuropathologists and neuro-oncologists on the levels of evidence and clinical utility of the various biomarkers.

Conclusion and Implications for Clinical Use

Brain tumour epidemiology provides basic information on the burden and force of the disease in the communities. It further allows for continuous monitoring of time trends in the incidence and survival at the population level. In contrast to clinical trials, which are prone to selection bias, population-based data provide a comprehensive picture of the real-life scenario, and are thus of high relevance to treating clinicians.

The majority of brain tumours are sporadic lesions. Rare genetic syndromes and prior exposure to ionizing radiation are the only established risk factors to date and account for < 10 % of all brain tumours. Latest risk factor research has focused on the exposure to radiofrequency electromagnetic fields from mobile phones. Despite conflicting study results the IARC has recently classified radiofrequency electromagnetic fields as possibly carcinogenic to humans, thereby indicating that additional studies focusing on long-term and heavy use are warranted. Whether this carcinogenic classification results in concrete legislative acts to protect public health remains to be shown. However, not only environmental risk factor research but also molecular epidemiology have considerably added knowledge. With the incorporation of molecular techniques into epidemiological study designs several low-penetrance susceptibility loci for glioma risk have been identified, which provide first insights into disease causation but await validation in larger cohorts focusing on specific glioma types. Likewise, rapid advances in genetic and transcriptome-based molecular research have provided information on the underlying biology of the most common malignant brain tumours and led to the identification of prognostically relevant sub- and risk groups. Hence, the translation of all those findings into clinical applicability now largely depends on the development of practical, robust, and widely accepted subgroup-specific biomarkers, which will pave the way for individualized patient treatment.

Conflict of Interest

None.

References:

1. Pritchard-Jones K, Kaatsch P, Steliarova-Foucher E, et al. Cancer in children and adolescents in Europe: developments over 20 years and future challenges. *Eur J Cancer* 2006; 42: 2183–90.
2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975–1995, National Cancer Institute. Bethesda, MD. SEER web site http://seer.cancer.gov/csr/1975_2009_pops09/, based on November 2011 SEER data submission.
3. Louis DN, Ohgaki H, Wiestler D, et al. (eds). WHO classification of tumours of the central nervous system. IARC Press, Lyon, 2007.
4. Fritz A, Percy C, Jack A, et al. (eds). International classification of diseases for oncology. 3rd ed. World Health Organization, Geneva, 2000.
5. Dolecek TA, Propp JM, Stroup NE, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009. *Neuro Oncol* 2012; 14 (Suppl 5): v1–v49.

6. Wöhrer A, Waldhör T, Heinzl H, et al. The Austrian Brain Tumour Registry: a cooperative way to establish a population-based brain tumour registry. *J Neurooncol* 2009; 95: 401–11.
7. Wöhrer A, Slavic I, Waldhör T, et al. Incidence of atypical teratoid/rhabdoid tumors in children: a population-based study by the Austrian Brain Tumor Registry, 1996–2006. *Cancer* 2010; 116: 5725–32.
8. Thuppal S, Propp JM, McCarthy BJ. Average years of potential life lost in those who have died from brain and CNS tumors in the USA. *Neuroepidemiology* 2006; 27: 22–7.
9. Bradley CJ, Yabroff KR, Dahman B, et al. Productivity costs of cancer mortality in the United States: 2000–2020. *J Natl Cancer Inst* 2008; 100: 1763–70.
10. Leibetseder A, Ackerl M, Flechl B, et al. Outcome and molecular characteristics of adolescent and young adult patients with newly diagnosed primary glioblastoma: a study of the Society of Austrian Neurooncology (SANO). *Neuro Oncol* 2013; 15: 112–21.
11. Brinkman TM, Palmer SL, Chen S, et al. Parent-reported social outcomes after treatment for pediatric embryonal tumors: a prospective longitudinal study. *J Clin Oncol* 2012; 30: 4134–40.
12. Curado MP, Edwards B, Shin HR, et al. (eds). *Cancer incidence in five continents*. IARC Scientific Publications, Lyon, 2007.
13. Kuratsu J, Ushio Y. Epidemiological study of primary intracranial tumors: a regional survey in Kumamoto Prefecture in the southern part of Japan. *J Neurosurg* 1996; 84: 946–50.
14. Kuratsu J, Takeshima H, Ushio Y. Trends in the incidence of primary intracranial tumors in Kumamoto, Japan. *Int J Clin Oncol* 2001; 6: 183–91.
15. McCarthy BJ, Shibui S, Kayama T, et al. Primary CNS germ cell tumors in Japan and the United States: an analysis of 4 tumor registries. *Neuro Oncol* 2012; 14: 1194–200.
16. Kadan-Lottick NS, Skluzacek MC, Gurney JG. Decreasing incidence rates of primary central nervous system lymphoma. *Cancer* 2002; 95: 193–202.
17. Olson JE, Janney CA, Rao RD, et al. The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. *Cancer* 2002; 95: 1504–10.
18. Propp JM, McCarthy BJ, Davis FG, et al. Descriptive epidemiology of vestibular schwannomas. *Neuro Oncol* 2006; 8: 1–11.
19. Aydin D, Feychting M, Schuz J, et al. Childhood brain tumours and use of mobile phones: comparison of a case-control study with incidence data. *Environ Health* 2012; 11: 35.
20. Braganza MZ, Kitahara CM, Berrington de Gonzalez A, et al. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. *Neuro Oncol* 2012; 14: 1316–24.
21. Loning L, Zimmermann M, Reiter A, et al. Secondary neoplasms subsequent to Berlin-Frankfurt-Münster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. *Blood* 2000; 95: 2770–5.
22. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* 2012; 380: 499–505.
23. Gardavaud F, Luciani A, Rahmouni A. CT scans in childhood and risk of leukaemia and brain tumours. *Lancet* 2012; 380: 1735.
24. Claus EB, Calvocoressi L, Bondy ML, et al. Dental X-rays and risk of meningioma. *Cancer* 2012; 118: 4530–7.
25. Hardell L, Carlberg M, Hansson Mild K. Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma. *Pathophysiology* 2013; 20: 85–110.
26. The Interphone Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol* 2010; 39: 675–94.
27. Hardell L, Carlberg M, Hansson Mild K. Mobile phone use and the risk for malignant brain tumors: a case-control study on deceased cases and controls. *Neuroepidemiology* 2010; 35: 109–14.
28. Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on the use of cellular and cordless telephones and the risk of benign brain tumours diagnosed during 1997–2003. *Int J Oncol* 2006; 28: 509–18.
29. Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997–2003. *Int Arch Occup Environ Health* 2006; 79: 630–9.
30. Aydin D, Feychting M, Schuz J, et al. Mobile phone use and brain tumors in children and adolescents: a multicenter case-control study. *J Natl Cancer Inst* 2011; 103: 1264–76.
31. Aavikko M, Li SP, Saarinen S, et al. Loss of SUFU function in familial multiple meningioma. *Am J Hum Genet* 2012; 91: 520–6.
32. Rajaraman P, Melin BS, Wang Z, et al. Genome-wide association study of glioma and meta-analysis. *Hum Genet* 2012; 131: 1877–88.
33. Shete S, Hosking FJ, Robertson LB, et al. Genome-wide association study identifies five susceptibility loci for glioma. *Nat Genet* 2009; 41: 899–904.
34. Sturm D, Witt H, Hovestadt V, et al. Hot-spot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. *Cancer Cell* 2012; 22: 425–37.
35. Kool M, Korshunov A, Remke M, et al. Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. *Acta Neuropathol* 2012; 123: 473–84.
36. Northcott PA, Korshunov A, Witt H, et al. Medulloblastoma comprises four distinct molecular variants. *J Clin Oncol* 2011; 29: 1408–14.
37. Witt H, Mack SC, Ryzhova M, et al. Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. *Cancer Cell* 2011; 20: 143–57.
38. Picard D, Miller S, Hawkins CE, et al. Markers of survival and metastatic potential in childhood CNS primitive neuro-ectodermal brain tumours: an integrative genomic analysis. *Lancet Oncol* 2012; 13: 838–48.
39. Northcott PA, Korshunov A, Pfister SM, et al. The clinical implications of medulloblastoma subgroups. *Nat Rev Neurol* 2012; 8: 340–51.
40. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med* 2009; 360: 765–73.
41. Hartmann C, Meyer J, Balss J, et al. Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. *Acta Neuropathol* 2009; 118: 469–74.
42. Reifenberger J, Reifenberger G, Liu L, et al. Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. *Am J Pathol* 1994; 145: 1175–90.
43. Cairncross JG, Ueki K, Zlatescu MC, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst* 1998; 90: 1473–9.
44. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005; 352: 997–1003.
45. Ellison DW, Kocak M, Dalton J, et al. Definition of disease-risk stratification groups in childhood medulloblastoma using combined clinical, pathologic, and molecular variables. *J Clin Oncol* 2011; 29: 1400–7.
46. Gajjar A, Hernan R, Kocak M, et al. Clinical, histopathologic, and molecular markers of prognosis: toward a new disease risk stratification system for medulloblastoma. *J Clin Oncol* 2004; 22: 984–93.
47. Zalattimo O, Zoccoli CM, Patel A, et al. Impact of genetic targets on primary brain tumor therapy: what's ready for prime time? *Adv Exp Med Biol* 2013; 779: 267–89.
48. Hainfellner JA, Heinzl H. Neuropathological biomarker candidates in brain tumors: key issues for translational efficiency. *Clin Neuropathol* 2010; 29: 41–54.

Journey of Intraoperative Magnetic Resonance Imaging into Daily Use: A Review

Moritz Scherer, Christine Jungk, Andreas Unterberg

Abstract: The introduction of intraoperative MRI (iMRI) for resection guidance was a milestone of technical innovation in neurosurgery more than a decade ago. Based on the general opinion that more radical and preferably complete tumour resection leads to significantly longer survival of glioma patients, advantages of

this method have become increasingly evident ever since. iMRI appears to be the most effective way to safely extend tumour resections and precisely delineate tumour boundaries in both high- and low-grade tumours. This review covers recent literature illustrating the contribution of iMRI to more radical tumour resections and un-

derscores why bringing this method into daily routine of glioma surgery was only a logical consequence. **EANO Mag 2013; 3 (2): 61–7.**

Key words: glioma surgery, extent of resection, patient survival, intraoperative magnetic resonance imaging, volumetric analysis

■ Introduction

Alongside adjuvant radio- and chemotherapy, surgery remains a mainstay in the treatment of patients with intracranial gliomas. Similar to recent advances in the field of neuro-oncology, resection techniques of intracranial gliomas have undergone many changes in the past decades. New technological developments range from microneurosurgery and multimodal neuro-navigation to routine implementation of high-field MRI scanners for intraoperative resection control in latest history. All these advances provide assistance to the operating surgeon, ensuring removal of as much tumour tissue as possible without causing any additional neurologic sequelae.

The contribution of intraoperative MRI imaging (iMRI) to maximized tumour resection, patient safety, and outcome has been subject of many studies since the first appearance of this method in the late 1990s. Following a controversial debate, maximum extended safe tumour resection has been proven to harbour significant survival benefits for glioma patients. The role of iMRI is to guide such maximum extended safe tumour resection and its unprecedented precision in delineating tumour borders has become evident in recent research. Regardless of its clinical benefits, high costs and manpower requirements still pose heavy limitations to widespread availability of iMRI which makes this method subject to economical and ethical considerations.

This review outlines the significance of maximum extended safe tumour resection in present-day multidisciplinary glioma treatment, explains how iMRI can provide substantial decision guidance to the operating surgeon, and demonstrates how such a sophisticated method can be implemented into the daily routine of neurosurgical procedures.

■ Benefit of Extended Tumour Resections for Patient Prognosis

Diagnosed with an intracranial mass lesion, patients need confirmation of histological diagnosis in order to receive adequate and specific therapy. Treatment guidelines for intracranial tumours explicitly recommend that tissue specimens be obtained before commencement of radio- or chemotherapy. In case of intracranial gliomas, the least surgery can offer is to provide the histological diagnosis required for further adjuvant therapies. Beyond that, maximum extensive safe surgery is increasingly accepted as an independent, positive, prognostic factor [1].

In recent years, routine acquisition of early post-resection MRI scans within 48–72 hrs after surgery has provided the opportunity to evaluate the correlation between the extent of resection (EOR) and different outcome measures. Among the many studies dedicated to this matter, heterogeneity of data and patient samples is huge. Up-to-date, large, randomized, controlled trials evaluating the value of maximized resection vs partial resections are lacking and ethically debatable. Many conclusions are drawn from subgroup analyses based on patient data acquired in another context. Additionally, retrospectively designed and single-centre reports are unfortunately subject to a biased patient sample regarding age, overall performance, imaging modalities, or adjuvant therapy regimens. Nevertheless, there is a growing body of evidence supporting the pursuit of maximized safe resection in the treatment of intracranial gliomas.

In case of high-grade gliomas (HGG), besides yielding a histological diagnosis surgery is also performed to relieve symptoms caused by the rapidly growing tumour mass and brain oedema. Due to the inevitable tumour invasion into healthy brain parenchyma, it is obviously never possible to remove all tumour cells but rather important to achieve substantial relief from tumour burden in terms of gross total resection (GTR, ie no residual contrast enhancement [CE] on post-resection scan). As opposed to subtotal or partial resection of the tumour (STR or PR, nodular or solid CE residual, respectively), GTR has been shown in various studies to have significant impact on patient survival. Besides known prognostic factors

Received on January 15, 2013; accepted on January 16, 2013; Pre-Publishing Online on February 12, 2013

From the Department of Neurosurgery, Heidelberg University Hospital, Germany

Correspondence to: Moritz Scherer, MD, Department of Neurosurgery, Heidelberg University Hospital, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany; e-mail: moritz.scherer@med.uni-heidelberg.de

Table 1. Increase of EOR in all cases where resection was continued after an intraoperative MRI scan.

Author, Year [Ref]	Cases (n)	WHO grade	iMRI EOR (%)	Final EOR (%)	± (%)	p
Nimsky et al, 2004 [20]	17	I–IV	88.6 ± 13.8	93.1 ± 10.3	+4.5	< 0.01
Schneider et al, 2005 [21]	31	IV	69.3	85	+15.7	NC
Hatiboglu et al, 2009 [19]	21	I–IV	76 (35–97)	96 (48–100)	+20	< 0.0001
Kuhnt et al, 2011 [22]	76	I–IV	66.55 ± 25.14	85.27 ± 23.26	+18.72	< 0.01
Scherer et al, 2012 (unpublished data)	101	I–IV	90.1 ± 15.6	99.8 ± 0.8	+9.7	NC

NC: not calculated

Table 2. Rates of successfully reached, predefined resection goals after a first iMRI scan, a postoperative scan, and the incidence of ongoing resections.

Author, Year [Ref]	Cases (n)	WHO grade	Predefined goal	Success after 1 st iMRI (%)	Success OP on post-MRI (%)	Ongoing resection (%)	p
Knauth et al, 1999 [24]	38	III–IV	GTR	37	76	39	0.0004
Nimsky et al, 2004 [20]	47	I–IV	GTR/IR	64	100	36	< 0.001 for IR
Hatiboglu et al, 2009 [19]	44	I–IV	GTR/IR	52	100	48	NC
Kuhnt et al, 2011 [22]	293	I–IV	GTR/IR	74	100	26	NC
Senft et al, 2011 [18]	24	(IV)	GTR	66	96	30	NC
Scherer et al, 2012 (unpublished data)	101	I–IV	GTR/IR	29.7	95.7	70.3	NC

GTR: gross total resection; IR: incomplete resection; HGG: high-grade glioma; NC: not calculated

such as age and Karnofsky performance status (KPS), GTR has been shown to be another independent positive prognostic factor in HGG [1–8]. To our knowledge, evidence of the highest available quality can be derived from a German multicentre, randomized, controlled trial by Stummer et al that compares 5-aminolevulinic acid (5-ALA) fluorescence-guided with conventional white-light HGG resections [9]. In a balanced re-stratification for resection extent, all patients who underwent GTR experienced prolongation of overall survival compared to incompletely resected patients (16.7 vs 11.8 months, respectively; $p < 0.0001$) [1, 7]. In addition, another high-volume series of McGirt et al evaluated 1250 patients harbouring a high-grade glioma and found a survival benefit up to 5 months when comparing GTR to PR (13 vs 8 months, respectively) [8]. These results were adjusted for factors with known association to survival such as age, KPS, or adjuvant therapies. Sanai et al present a thorough analysis of the current literature with a focus on precise calculation of EOR and clear statistical measures. They report a statistically significant beneficial effect from maximized EOR in 16/28 HGG studies [6]. Although prognosis in HGG remains poor, these recent results should be valued as encouraging. We see the impact of extended safe resection upon overall survival in glioblastoma alongside with the beneficial effects of concomitant radio-chemotherapy as reported by Stupp et al in 2005, formerly offering a median 2.5-month longer survival compared to previous standard treatment [10]. Even though this study did not include mandatory postoperative imaging and EOR was partly assessed by means of inaccurate estimation of the operating surgeon, in a *post-hoc* data analysis by Gorlia et al EOR was shown to have a significant impact on patient survival. Building on this and remembering that 5-

ALA data was acquired before the implementation of concomitant adjuvant radiochemotherapy, supplemental effects should be expected when both approaches are combined. Maximized safe resection followed by an individualized, targeted therapy is expected to further prolong overall survival for patients with HGG in the future [11].

Low-grade glioma (LGG) patients often show mild to *nil* clinical symptoms but eventual malignant tumour progression will aggravate symptoms and reduce life expectancy. As most of WHO °I and °II tumours are not easily amenable for radio- or chemotherapy due to their slow cell proliferation compared to their high-grade counterparts, watch-and-wait regimens are still applied after biopsy until a definite therapy is initiated [12]. To date, this approach should be questioned when surgery alternately can safely remove the tumour, diminishing the risk of malignant transformation or occurrence of neurologic symptoms or seizures. Besides, even small and deeply located lesions can be safely approached with today's techniques so that factors complicating surgery such as growth, malignant transformation, and tumour infiltration can be anticipated instead. The literature provides support for radical surgery in supratentorial LGG amenable for safe resection as the treatment of choice [13, 14]. Even though formal quality of evidence is weak, a systematic review of Sanai et al quotes 9/10 selected LGG studies as being in favour of extensive resection of LGG lesions. In uni- and multivariate analyses, EOR was revealed to be a significant positive prognosticator in 7 of these studies [6]. Even in case of tumour recurrence, Ahmadi et al could show a clearly beneficial effect of more radical surgery in terms of time to malignant progression and overall survival [15].

■ iMRI for Intraoperative Resection Control

Accurate delineation of tumour and normal brain parenchyma remains one of the major challenges in glioma surgery. In recent years, many technical advancements have been developed to assist the surgeon in locating and precisely confining brain tumours. Alongside with multimodal neuronavigation, intraoperative ultrasound, and 5-ALA in glioblastomas, intraoperative MRI acquisition is used in a growing number of centres for tumour resection control. Initial evaluation following the introduction of this method quickly showed beneficial effects of iMRI in glioma surgery. Reports of increased EOR and improved patient prognosis have accumulated over recent years and other advantages such as compensation for brain-shift phenomena through intraoperative update of neuro-navigation have been pointed out [16]. Moreover, surgeons have been exposed to commonly overestimate their own resection extent, which strengthens the call for routine intraoperative resection guidance based on the given correlation between resection radicality and patient prognosis [17].

In HGG, iMRI resection control is often compared to fluorescence-guided resection with 5-ALA, which has been shown to lead to more frequent GTR compared to white-light surgery. To corroborate the contribution of iMRI to a more radical EOR, a bundle of retrospective studies and cohort analyses have been published. Following the design of the 5-ALA study, Senft et al recently conducted a randomized controlled trial to further elucidate the use of iMRI. In their cohort of 49 HGG cases scheduled for total tumour resection, randomization assigned patients either to receive low-field iMRI-guided or conventional microneurosurgical extirpation of the tumour. In the iMRI resection group, this surgical goal was achieved in 96 % of cases compared to only 68 % in the conventional group (23 vs 17 of 49 patients, respectively) [18]. Adding up to other likeminded results, this study for the first time validated the gain of iMRI resection control in a randomized controlled fashion. For HGG resections, iMRI-guided surgery leads to a higher frequency of GTR at least comparable to results achieved using 5-ALA fluorescence.

In LGG, only intraoperative ultrasound (iUS) can help as an alternate imaging modality during surgery. High-field iMRI scanners are of special value in LGG surgery since they offer high anatomical resolution along with full-scale diagnostic capability. Sharp T2 and FLAIR sequences, MR-spectroscopy, and diffusion-weighted imaging (DWI) contribute greatly to a precise delineation of residual non-enhancing intracranial lesions. So far, there are only few retrospective studies available evaluating LGG outcomes after iMRI-guided resection. A group from the Brigham and Women's Hospital in Boston compared long-term results derived from their iMRI-guided LGG resections to results from a national registry. Their central finding was a significant reduction of 1-, 2-, and 5-year age- and histology-adjusted death rates compared to the national registry when iMRI was used for resection guidance (1.9 % [95-% CI: 0.3–4.2 %], 3.6 % [95-% CI: 0.4–6.7 %], and 17.6 % [95-% CI: 5.9–29.3 %], respectively). Stratifying for total and subtotal LGG tumour removal, a 1.4

times higher risk of recurrence (95-% CI: 0.7–3.1) and a 4.9 times higher risk of death (95-% CI: 0.61–40.0) was apparent when lesions were only removed subtotally [14]. These tendencies suggest a correlation between iMRI-guided extent of resection and longer patient survival also in low-grade tumours. But again formal evidence is weak, with the non-homogeneity of data and study groups impeding final conclusions until results are confirmed in larger, randomized, matched or other controlled populations.

Regarding EOR, volumetric analysis did also quantify the increased amount of tumour that could be removed by means of iMRI in some studies (Table 1). EOR could be increased from a median 76 % to 96 % in one series, and residual tumour fractions could be reduced from 21.4 ± 13.8 to 6.9 ± 10.3 % in another series across all WHO grades [19, 20]. Accordingly, Kuhnt et al and Schneider et al showed an increase in EOR from 66.55 % and 69.3 % at the point where MRI was performed intraoperatively to a final EOR of approximately 85 % on postoperative MRI scans [21, 23]. A preliminary analysis of our own prospective volumetric iMRI data has yielded similar results. In 101 analyzed patients operated under iMRI guidance in 2011, EOR was increased from $90.1 \% \pm 15.6$ % on intraoperative images to a final EOR of $99.8 \% \pm 0.8$ % (Scherer et al, unpublished data, 2012). In all of these studies, up to 20 % of the overall tumour resection was not performed until after an iMRI scan confirmed tumour remnants.

To deduct an increased extent of resection solely from the intraoperative use of iMRI would be much of a hasty reaction. Since surgeons were aware of the feasibility of iMRI right from the beginning of surgery, this possibility biased the decision of when to do the first intraoperative scan and led to a more defensive resection strategy in those studies. Accordingly, the absolute values of EOR increase after iMRI partly represent the surgeon's uncertainty in tumour delineation or the difficulty of surgery rather than the direct contribution of iMRI to more radical tumour surgery.

Rates of continued surgery after intraoperative resection control by means of iMRI are another interesting aspect when assessing the value of this intraoperative imaging modality. Among the iMRI studies presented here (Table 2), 21 out of 44 patients (47 %) [19] and 17 out of 47 patients (36 %) [20], respectively, underwent further tumour resection after iMRI resection control. Another report by Kuhnt et al states a 26-% incidence of additional resections after the first intraoperative scan. Referring to our own data analyzing the routine use of iMRI guidance for all glioma resections at our department, we observed high frequencies of ongoing resections beyond all WHO grades. In total, 71 of 101 (70.3 %) cases received additional tumour resection after iMRI with even higher rates for WHO °II and °III tumours (Scherer et al, unpublished data, 2012). In their randomized controlled cohort of WHO °IV tumours, Senft et al reported additional tumour resection in $\frac{1}{3}$ of cases of iMRI application, leading to successful accomplishment of GTR in all of these patients. In their conclusion, iMRI was accountable for the 30-% increase in complete resections and it was evident that without its use neither group would have differed significantly from the other [18, 23].

Table 3. Postoperative neurological deficits (visual, motor, language) after iMRI-guided surgery, permanent deficits at > 4 months after surgery.

Author, Year [Ref]	Postoperative Deficits		Permanent deficits (%)
	Further resections after iMRI (%)	No further resections after iMRI (%)	
Schneider et al, 2005 [21]	–	–	12.9
Hatiboglu et al, 2009 [19]	33	26	7
Kuhnt et al, 2011 [22]	14	26	6.8
Senft et al, 2011 [18]	0	13	–

Table 4. Outcome of patients operated under iMRI guidance with respect to the EOR. Data presented as difference in median survival times.

Author, Year [Ref]	Survival	Resection	± (months)	p
Wirtz et al, 2000 [25]	OS	GTR vs IR	+4.2	0.0035
Schneider et al, 2005 [21]	OS	GTR vs IR	+10	0.0004
Kuhnt et al, 2011 [22]	OS	GTR vs IR	+5	0.0001
Senft et al, 2011 [18]	PFS	GTR vs IR	+4.3	0.0003

GTR: gross total resection; IR: incomplete resection; OS: overall survival; PFS: progression-free survival

While these questions concern rather technical aspects of iMRI-guided surgery, it is important to focus on the true goal of surgery, which is to achieve maximized safe tumour resection in order to prolong patient survival. Among all iMRI studies that have documented their cases with respect to the pre-operatively defined resection goal it becomes evident that this surgical goal can be attained in a vast majority of cases where iMRI was used (Table 2). While the predefined goal was already reached in 37–74 % of cases when a first iMRI was performed, continued resections after iMRI led to eventual success in up to 100 % of cases. This implicates that independently from other available modalities for resection control iMRI is a convincingly precise and efficient way to push resection boundaries and achieve the goal of surgery in an overwhelming majority of tumour resections across all WHO grades.

Most importantly, iMRI-guided extended resection radicality was not achieved at the cost of any increased morbidity. Neither did the randomized study of Senft et al show a significant accumulation of deficits when comparing the iMRI with the white-light group (3 vs 2 permanent deficits; 13 % vs 8 %, respectively), nor did Kuhnt et al observe any aggravation of motor or speech deficits when comparing their cohort of additionally resected tumours with those resections terminated after an iMRI resection control (7.7 % vs 12.5 % accumulated morbidity at discharge, respectively; Table 3).

As mentioned earlier, prolonged survival after extended glioma surgery has been reported many times in general. Some studies have also directly addressed the contribution of iMRI-guided extended tumour resection upon patient overall survival [18, 21, 22, 25–27]. Among the HGG series, Kuhnt et al present a series including 135 glioblastoma patients operated using 1.5 T high-field iMRI guidance. EOR > 98 % and age < 65 were independent positive prognosticators leading to a 5-month longer overall survival when more radical surgery could be achieved (14 months [95-% CI: 11.7–16.2] vs 9 months [95-% CI: 7.4–10.5]) for EOR > 98 % and < 98 %, respectively ($p < 0.0001$) [22]. Results from other cohorts point in the same direction with a longer overall or progression-free survival after complete vs incomplete tumour resection (Table 4). Comparable to 5-ALA data, beneficial effects of extended surgical radicality have thus been observed independently of the technique used for resection guidance in HGG.

In their review, Kubben et al attempted not only to examine the benefit on survival but also to evaluate clinical performance and quality of life before and after iMRI-guided surgery. Focusing on precise EOR calculation, detailed reports of quality of life, and long-term documentation of patient survival, 12 non-randomized cohort studies out of 682 published studies from 1999 until 2010 were selected. Even though all included studies showed increased overall EORs, reliable data on the quality of life or prolonged survival was sparse. Only 3/12 studies included patient follow-up, each showing significantly longer median survival times. Another 3/12 studies evaluated clinical performance but failed to show a correlation to extended tumour resections. Data concerning quality of life after surgery was not provided by any study [28]. Performance scores are often documented before surgery in order to identify the calculated status as an outcome predictor; postoperative performance status, however, often remains elusive. Although a slight reduction in KPS within 2 weeks after surgery has been reported by Mehdorn et al, yet the value of this finding is unclear due to unbalanced and selected cohorts in this study [27]. So, apart from focal motor or speech deficits, the question of how patients are doing shortly after extended glioma surgery and during their assumedly longer survival has remained mostly unanswered.

Although not truly “online”, like intraoperative ultrasound (iUS) and 5-ALA, intraoperatively acquired MR imaging can reliably help the surgeon to delineate tumour tissue from healthy brain parenchyma. Especially in areas that are hard to explore with US or fluorescent light, iMRI might be superior in detecting residual tumour. Likewise, in LGG or anaplastic gliomas, where 5-ALA shows no or only weaker detection rates, iMRI has full distinction power leading to a greater EOR across all tumour entities without adding any specific neurologic morbidity. Spatial precision of tumour delineation of iMRI combined with multimodal neuronavigation is unprecedented. This offers the chance not only to enhance complete tumour resections but also to guide partial resections with borders close to eloquent areas, limiting resection extent precisely to only harmless tumour parts. Compared to any other intraoperative imaging modality iMRI enables the sur-

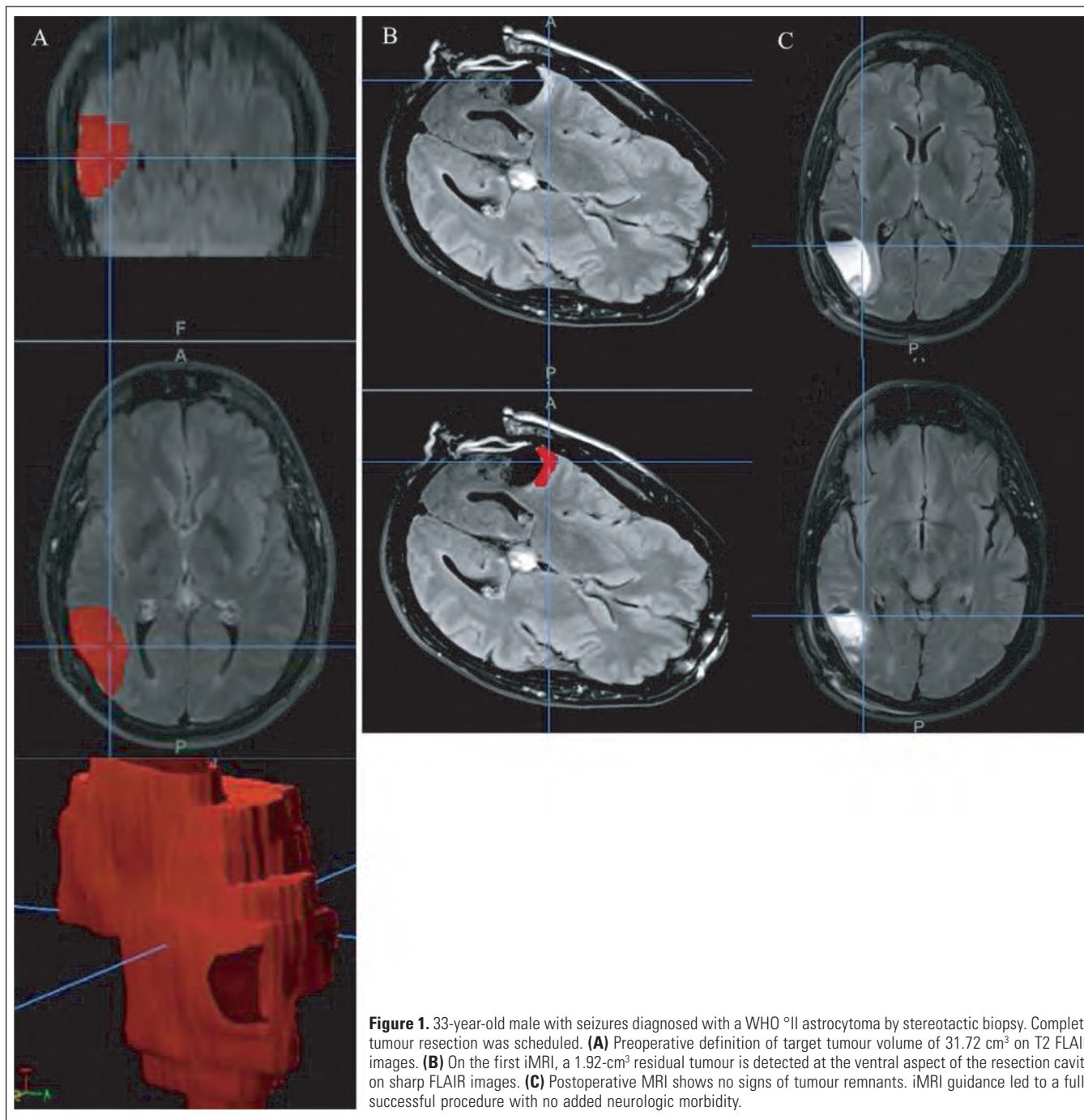


Figure 1. 33-year-old male with seizures diagnosed with a WHO grade II astrocytoma by stereotactic biopsy. Complete tumour resection was scheduled. **(A)** Preoperative definition of target tumour volume of 31.72 cm³ on T2 FLAIR images. **(B)** On the first iMRI, a 1.92-cm³ residual tumour is detected at the ventral aspect of the resection cavity on sharp FLAIR images. **(C)** Postoperative MRI shows no signs of tumour remnants. iMRI guidance led to a fully successful procedure with no added neurologic morbidity.

geon to achieve the seemingly contradictory goal of extending radicality while improving safety.

In summary, the literature shows clear benefits from improved iMRI-guided resection radicality such as lower risk of recurrence, longer progression-free survival, lower 1–5-year death rates (LGG), and longer overall survival (HGG). However, formal evidence for this knowledge is still lacking. Due to inconsistency of data acquisition and presentation, mixed patient populations, and other technical limitations such as different measurements of EOR or MRI field strengths it has so far been virtually impossible to elaborate a clear meta-analysis of existing studies dealing with this topic. As further randomized controlled trials evaluating the extent of resection and its effect on survival are ethically debatable from our current state of knowledge, well-designed, prospective, observa-

tional studies might be the only way to underscore the importance and benefit from more radical surgery for the treatment of intracranial gliomas in the future. Precise and prospectively addressed definitions of surgical goals (GTR, no residual contrast enhancement, vs PR, residual contrast enhancement), routine postoperative imaging 48–72 hrs after surgery and volumetric documentation of resection extent should be the least common ground for future data collections. This well-defined baseline data will help to merge knowledge in the field and to present high-volume multicentre series providing age- and histology-adjusted estimates of survival rates with respect to the achieved EOR. Beyond technical aspects, future studies also have to focus on clinical performance and quality of life along with survival benefits in order to give sustainable answers to the questions evolving around the use of iMRI in glioma surgery.

■ Feasibility of Routine iMRI: Implementation into Daily Surgery

Since acquisition and maintenance costs are still a substantial drag to a greater prevalence of iMRI units in hospitals today, it is important to take into account all therapeutic indications and their benefits for patients to justify their establishment.

High-field iMRI machines offer the full range of diagnostic sequences and high anatomical resolution. Accordingly, iMRI imaging can also assist in stereotactic biopsies, placement of catheters, or deep-brain stimulating electrodes and, lastly, transsphenoidal resections of pituitary tumours. From an economical point of view, frequent utilization of an iMRI promotes a faster return of initial investments while cutting maintenance costs at the same time. Hence, frequent and effective use of an iMRI unit will serve both medicine and management.

Routine implementation of an iMRI into daily surgical routine can only be accomplished under certain conditions. Patient safety has to be given top priority, which can easily be jeopardized by a strong magnetic field within an operating room (OR). Among different iMRI-suite set-ups, instead of placing the iMRI scanner in the OR itself, in our opinion a 2-room solution has obvious advantages for routine daily use. Our set-up in Heidelberg, where the patient is transported into the iMRI next door, allows us to perform regular surgery without any relevant limitations with regard to positioning or surgical instruments. Moreover, this set-up allows us to use the iMRI unit from 2 ORs, fostering efficient multiple daily use for various indications. Besides, separating the magnet from the OR is a relevant safety aspect, especially when the OR is used for cases where iMRI will not be used. Regardless of the iMRI set-up, dedicated standards of iMRI procedures and vigorous staff training are inevitable. On the one hand, standardized work-flows warrant patient safety while on the other hand, a straightforward iMRI procedure with reduced transfer times also contributes to efficient use of OR and labour time.

In Heidelberg, routine use of iMRI began when a new 1.5 T magnet was installed in June 2009. Since then, more than 670 surgical procedures have been performed using iMRI guidance. In our institution, all intracranial gliomas eligible for GTR are scheduled to undergo surgery with iMRI guidance. Whenever applicable, partial tumour resections are planned to be operated with iMRI resection control in order to safely increase radicality in these patients as well.

In 2011, we initiated a prospective collection of our iMRI-guided glioma resections in a volumetric database. Intended extent of tumour resection, iMRI residual tumour volumes, and postoperative tumour volumes are documented along with other patient parameters. An illustrative case demonstrating our routine procedures and volumetric documentation is shown in Figure 1 and some of our preliminary data, as mentioned above, is presented in Tables 1 and 2.

Implementing iMRI into routine glioma surgery certainly causes challenges and will most likely affect the strategic approach to a tumour as well as the manner of surgery itself. As

a consequence of routine iMRI use in glioma surgery one might expect the frequency of post-iMRI resections to increase over time, together with residual tumour volumes seen in a first intraoperative scan. This would resemble a more defensive surgical strategy in the first place. A preliminary analysis of our data seems to confirm this hypothesis with continued tumour resections performed after iMRI scans in almost $\frac{2}{3}$ of all patients. It might also be interesting to follow learning curves of young neurosurgeons over their time of training since iMRI provides immediate feedback on the resection progress. By means of this prospective single-institution database of unselected glioma cases, we hope to be able to address unanswered questions and confirm beneficial effects of iMRI surgery for glioma patients in the future. A newly formed German iMRI study group will further pursue this approach and try to derive a similar multi-centre database in order to merge data and produce solid evidence fostering the use and prevalence of iMRI in neurosurgery.

■ Conflict of Interest

The authors state that no conflict of interest exists.

References:

- Stummer W, van den Bent MJ, Westphal M. Cytoreductive surgery of glioblastoma as the key to successful adjuvant therapies: new arguments in an old discussion. *Acta Neurochir* 2011; 153: 1211–8.
- Ewelt C, Floeth FW, Felsberg J, et al. Finding the anaplastic focus in diffuse gliomas: the value of Gd-DTPA enhanced MRI, FET-PET, and intraoperative, ALA-derived tissue fluorescence. *Clin Neurol Neurosurg* 2011; 113: 541–7.
- Keles GE, Anderson B, Berger MS. The effect of extent of resection on time to tumor progression and survival in patients with glioblastoma multiforme of the cerebral hemisphere. *Surg Neurol* 1999; 52: 371–9.
- Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg* 2001; 95: 190–8.
- Laws ER, Parney IF, Huang W, et al. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. *J Neurosurg* 2003; 99: 467–73.
- Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. *Neurosurgery* 2008; 62: 753–6.
- Stummer W, Tonn JC, Mehdorn HM, et al. Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study. *Clinical article. J Neurosurg* 2011; 114: 613–23.
- McGirt MJ, Chaichana KL, Gathinji M, et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. *J Neurosurg* 2009; 110: 156–62.
- Stummer W, Pichlmeier U, Meinel T, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2006; 7: 392–401.
- Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; 352: 987–96.
- Gorlia T, van den Bent MJ, Hegi ME, et al. Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. *Lancet Oncol* 2008; 9: 29–38.
- Jakola AS, Myrmet KS, Kloster R, et al. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. *JAMA* 2012; 308: 1–8.
- Keles GE, Lamborn KR, Berger MS. Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome. *J Neurosurg* 2001; 95: 735–45.
- Claus EB, Horlacher A, Hsu L, et al. Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance. *Cancer* 2005; 103: 1227–33.
- Ahmadi R, Dictus C, Hartmann C, et al. Long-term outcome and survival of surgically treated supratentorial low-grade glioma in adult patients. *Acta Neurochir (Wien)* 2009; 151: 1359–65.
- Wirtz CR, Bonsanto MM, Knauth M, et al. Intraoperative magnetic resonance imaging to update interactive navigation in neurosurgery: method and preliminary experience. *Comput Aided Surg* 1997; 2: 172–9.
- Albert FK, Forsting M, Sartor K, et al. Early postoperative magnetic resonance imaging after resection of malignant glioma: objective evaluation of residual tumor and its influence on regrowth and prognosis. *Neurosurgery* 1994; 34: 41–5.
- Senft C, Bink A, Franz K, et al. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. *Lancet Oncol* 2011; 12: 997–1003.
- Hatiboglu MA, Weinberg JS, Suki D, et al. Impact of intraoperative high-field magnetic resonance imaging guidance on glioma surgery: a prospective volumetric analysis. *Neurosurgery* 2009; 64: 1073–81.
- Nimsky C, Fujita A, Ganslandt O, et al. Volumetric assessment of glioma removal

- by intraoperative high-field magnetic resonance imaging. *Neurosurgery* 2004; 55: 358–70.
21. Schneider JP, Trantakis C, Rubach M, et al. Intraoperative MRI to guide the resection of primary supratentorial glioblastoma multiforme – a quantitative radiological analysis. *Neuroradiology* 2005; 47: 489–500.
22. Kuhnt D, Becker A, Ganslandt O, et al. Correlation of the extent of tumor volume resection and patient survival in surgery of glioblastoma multiforme with high-field intraoperative MRI guidance. *Neuro Oncol* 2011; 13: 1339–48.
23. Kuhnt D, Ganslandt O, Schlaffer SM, et al. Quantification of glioma removal by intraoperative high-field magnetic resonance imaging – an update. *Neurosurgery* 2011; 69: 852–62.
24. Knauth M, Wirtz CR, Tronnier VM, et al. Intraoperative MR imaging increases the extent of tumor resection in patients with high-grade gliomas. *AJNR Am J Neuroradiol* 1999; 20: 1642–6.
25. Wirtz CR, Knauth M, Stauber A, et al. Clinical evaluation and follow-up results for intraoperative magnetic resonance imaging in neurosurgery. *Neurosurgery* 2000; 46: 1112–20.
26. Hirschberg H, Samset E, Hol PK, et al. Impact of intraoperative MRI on the surgical results for high-grade gliomas. *Minim Invasive Neurosurg* 2005; 48: 77–84.
27. Mehdorn HM, Schwartz F, Dawirs S, et al. High-field iMRI in glioblastoma surgery: improvement of resection radicality and survival for the patient? *Acta Neurochir Suppl* 2011; 109: 103–6.
28. Kubben PL, Ter Meulen KJ, Schijns OE, et al. Intraoperative MRI-guided resection of glioblastoma multiforme: a systematic review. *Lancet Oncol* 2011; 12: 1062–70.

Atypical Aggregation of Cancer

Emeline Tabouret

From the Department of Neuro-Oncology, AP-HM, Timone Hospital, Marseille, France

■ Case Report

A previously well 36-year-old man presented with moderately severe headache and a progressive, painful, subcutaneous right pectoral swelling. Clinical examination confirmed a pectoral mass, 6 cm of diameter. There were no other general or neurological symptoms or signs. An MRI scan was performed to evaluate the headache (Figure 1) and a CT scan of chest, abdomen, and pelvis to evaluate the chest mass. Brain MRI scan revealed an intrinsic, left frontal neoplasm. Surgical resection of the pectoral mass was performed and histological analysis concluded that the mass was a liposarcoma. A gross total resection of brain tumour demonstrated a WHO grade-II oligo-astrocytoma without 1p19q co-deletion. Methylguanine methyl-transferase (MGMT) promoter methylation status and IDH1 mutation analysis were both negative. The patient received no other treatment for the brain tumour. Two months after brain surgery, the patient was hospitalized unwell and with a fever. Blood count, electrolytes, renal and hepatic functions were all normal. C-reactive protein was elevated at 102 mg/l. Blood cultures were sterile. Viral serology was negative.

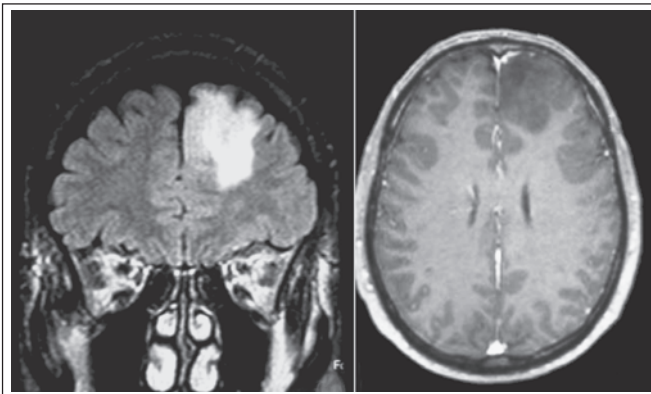


Figure 1. Brain MRI of patient: Flair, T1 with gadolinium and spectroscopy analysis.

Analyses of cerebrospinal fluid (CSF) showed an elevated protein at 0.98 g/l. CSF white-cell count was normal and there was no growth of organisms. The CT scan of chest, abdomen, and pelvis also demonstrated a heterogeneous right lung mass and a mass lesion in both adrenal glands (Figure 2).

■ Complete Diagnosis

Pectoral liposarcoma, left frontal low-grade glioma, lung carcinoma with bilateral adrenal metastases in the context of a Li-Fraumeni syndrome.

■ Discussion

Lung biopsy showed a poorly differentiated lung adenocarcinoma. First-line chemotherapy was initiated with cisplatin and vinorelbine. After 3 cycles, the CT-scan showed a progressive disease. Palliative care was initiated. The patient died 2 months later.

The Li-Fraumeni syndrome (LFS) is an autosomal dominant cancer predisposition syndrome associated with soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumours, adrenocortical carcinoma (ACC), and a variety of other neoplasms. More than 70 % of individuals diagnosed clinically have an identifiable disease-causing mutation in tumour suppressor gene p53 (TP53), the only gene known to be associated with LFS. Treatment of clinical manifestations involves routine management of cancers, except for those with breast cancer, where mastectomy is recommended rather than lumpectomy, in order to reduce the risks of a second primary tumour and to avoid radiation therapy. Prevention may include prophylactic mastectomy to reduce the risk of breast cancer in women with a germline TP53 mutation. Prevention of secondary complications includes the avoidance of radiation therapy in order to reduce the risk of radiation-induced

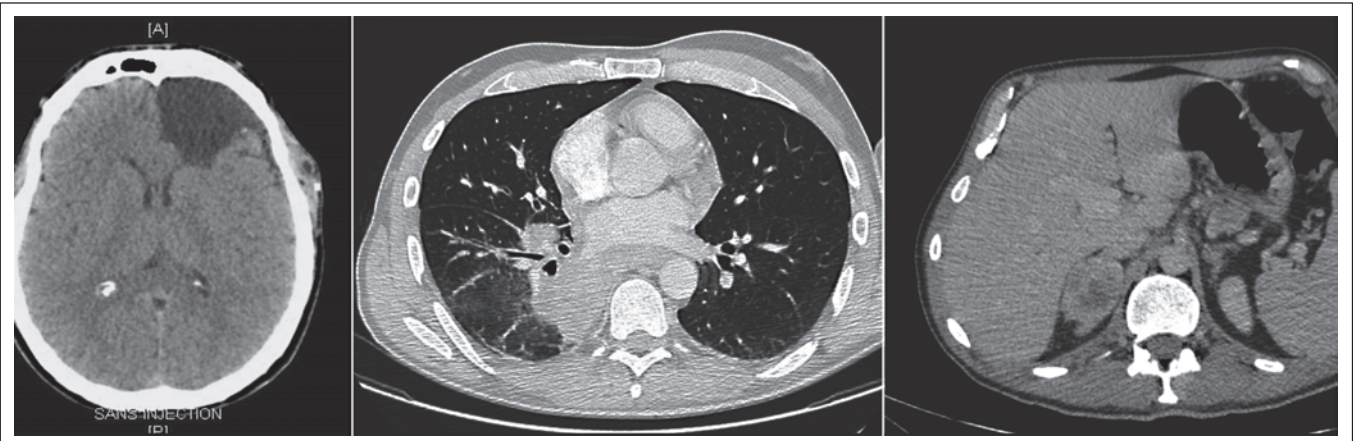


Figure 2. Brain, thoracic, and abdominal CT of the patient.

malignancies. Genetic counselling of relatives who are at risk is appropriate as well as to offer screening to all relatives who are at risk of having a familial TP53 mutation.

Further Reading:

GeneReviews: Li-Fraumeni Syndrome. <http://www.ncbi.nlm.nih.gov/books/NBK1311/> [accessed April 29, 2013].

Gonzalez K, Noltner K, Buzin C, et al. Beyond Li-Fraumeni syndrome: Clinical characteristics of families with p53 germline mutations. *J Clin Oncol* 2009; 27: 1250–6.

Olivier M, Goldgar DE, Sodha N, et al. Li-Fraumeni and related syndromes: correlation

between tumor type, family structure, and TP53 genotype. *Cancer Res* 2003; 63: 6643–50.

Reuss D, von Deimling A. Hereditary tumor syndromes and gliomas. *Recent Results Cancer Res* 2009; 171: 83–102.

Shen L, Sun X, Fu Z, et al. The fundamental role of the p53 pathway in tumor metabolism and its implication in tumor therapy. *Clin Cancer Res* 2012; 18: 1561–7.

Correspondence to:

Emeline Tabouret, MD

Department of Neuro-Oncology, Hôpital de la Timone

264 Rue Saint-Pierre

13385 Marseille Cedex 5

France

e-mail: emeline.tabouret@ gmail.com

Grief, Bereavement, and Mourning

Hanneke Zwinkels

In the years working as a nurse practitioner in neuro-oncology I have spoken with many patients and their carers about grief, bereavement, and mourning. In these conversations, they all talked about a period of grief after having heard the diagnosis, after recurrence of the tumour, after reaching the point when there are no treatment options left. Patients feel sorrow over the loss of future perspective, over their loss of ability to be independent, over the loss of functions. What touches me very often is grief over loss of communication ability.

During consultation hours I have been meeting Mrs M and her husband for 3 years now. When I first met her, we spoke about the operation the following day because of a suspected high-grade glioma in her left frontotemporal lobe. She had complained about loss of sense in her right hand and experienced an episode of speech arrest. She was full of hope of recovering after the operation and returning to everyday life, and at some point during our conversation she understood the seriousness of her illness. Several weeks later she told me she had been crying the whole evening before the operation, being aware of her changed future perspective.

During treatment with radiotherapy and chemotherapy according to the Stupp scheme, we got to know each other quite well and I was able to support Mrs M in her emotion-oriented coping. Because she participated in a clinical trial, we kept seeing each other on a regular basis. After every MRI, we discussed the results (after she and her husband had spoken the doctor) in relation to possible future treatment options and how she and her family – she has 2 teenage children – were doing.

She did quite well, with subtle speech disturbances when she was tired, as well as some lessened sensory feelings in her right hand.

“My life is of good quality, but when I am thinking of the fact it will not last long enough to see my children grow older, to see them go to university and graduate, start a relationship, marry, to see them become parents, to become a grandmother ... then I become very upset, very sad, very angry and I regret the fact this disease is my fate ... and the fact I am empty-handed ...”

By giving Mrs M and her husband the opportunity to talk about their loss of future perspective, by listening to their grief of lost health, their bereavement on powerlessness, about their mourning over the inescapable outcome, they were able to adjust to the situation and the results of that specific moment. Receiving reassurance and support was essential to Mrs M and her husband to help them to cope with the illness, and allowed them to hope for a next episode of stable disease. But the balance between realistic hope and their bereavement was fragile. Each time a new MRI was performed

and results had been discussed, they again asked for support in regaining this balance.

Mourning of a patient about loss of future perspective can be very comprehensive: loss of functions, loss of working satisfaction, loss of support by the partner, loss of communication with colleagues, loss of social interaction, loss of income, and by that an increasing social isolation, a feeling of uselessness, without the ability to perform daily tasks. During the disease progress psychological adjustment to the new situation is a dynamic process, in which the nurse practitioner can play an important role, in providing the supportive tools and guidance to facilitate adjustment. Patients faced with life-altering news and a loss of future perspective experience distress and need honest, personalized information to promote hope and adaptive coping. A discongruent coping style within a couple of which one is affected by a glioma could be an extra source of tension and distress, which could imply referral of the patient and his or her partner to the psychologist.

Mrs M was employed in her husband's company as a secretarial administrator but because of her language problems she was no longer able to work one year after her initial treatment. The children went to college and left the house, Mrs M and her husband regained a sort of balance but then the tumour recurred. It took a little while, but she realized she had no other choice than to participate in another trial. Every 6 weeks an MRI was performed, and every 6 weeks we spoke about the tension and fear of tumour recurrence, the MRI results, future treatment options, and her bereavement of future time. Every next step was a step closer to losing the ability of taking any step, as she said.

Several studies have investigated the supportive care needs of carers, focusing on the end-of-life phase. They concluded that information on end-of-life issues is of importance and state that when health care professionals are open and sensitive on these issues, they will be able to guide patients and carers and fine-tune communication. Psychosocial care and guidance aim at the patient being able to take control in the end-of-life phase, supported by his or her partner and relatives, regaining a balance in saying what has to be said, in experiencing coping on psychosocial and spiritual aspects of a completed life.

The last time I met Mr and Mrs M, she was wheelchair-bound because of a hemiparesis and not able to speak. We discussed the diagnosed tumour recurrence and the subsequent focal deficits, Mr M told me how he and his wife were doing at home. She needed help with daily activities, could speak a few words like yes and no, but most of the time could not find the right words, needed to rest more and more, was up for about 4 hours per day, but did not suffer from headache or nausea. A hospital bed had been arranged for, help from friends was available, the general practitioner was informed, and home care would soon be comming.

Mrs M tried to understand what we were talking about, but it was difficult for her to respond to questions. I asked them if they would agree to listen to what could be expected for the last phase, and Mrs M looked into the eyes of her husband with a question in her eyes. After some seconds, he told me, he would be glad to hear about that, she agreed by nodding her head and I carefully talked about what was expected to happen. Tears fell, not only from the eyes of Mr and Mrs M, and after ending our conversation we said goodbye. I wished her a valuable comfortable time, with a lot of love, care, understanding, and hope for a good and beautiful completion of her life.

Suggested Reading:

1. Cavers D, Hacking B, Erridge SE, et al. Social, psychological and existential well-being in patients with glioma and their caregivers: a qualitative study. *CMAJ* 2012; 184: E373–E382.
2. Sizoo EM, Braam L, Postma TJ, et al. Symptoms and problems in the end-of-life phase of high-grade glioma patients. *Neuro Oncol* 2010; 12: 1162–6.
3. Khalili Y. Ongoing transitions: the impact of a malignant brain tumour on patient and family. *Axone* 2007; 28: 5–13.

Correspondence to:

*Hanneke Zwinkels, RN, MA ANP
Medical Center Haaglanden
PO Box 432, NL-2501CK The Hague
e-mail: hannekezwinkels@eano.eu*

When Personalised Medicine Meets HTA: Are We on Target?

Kathy Oliver

One of the greatest American novels – *To Kill a Mockingbird* – is set in the Deep South of the United States and is a story of racial injustice and the destruction of innocence. The hero of the novel is a lawyer called Atticus Finch and at one point in the book he turns to his young daughter and offers her this crucial piece of moral advice.

He says: “If you can learn a simple trick, you’ll get along a lot better with all kinds of folks. You never understand a person until you consider things from his point of view, until you climb into his skin and walk around in it” [1].

It is important for all stakeholders in the brain tumour journey to symbolically climb into someone else’s skin, or put on another person’s shoes and walk around in them, so they can look at things from another point of view.

■ A Brave New World

These days, the patient’s point of view is often quite well informed based on a much more pro-active role in their treatment decisions. Many are fully aware that we are entering the brave new world of stratified medicine and targeted therapies.

As patients and their advocates, we should consider what the challenges of Health Technology Assessment (HTA) might be in relation to targeted therapies.

The National Cancer Institute’s definition of targeted cancer therapies is: “*Drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression*” [2].

With targeted therapies comes the necessity for companion diagnostic tests to determine if a particular therapy is relevant to an individual’s biomarkers.

Patients are beginning to recognise that marrying a diagnostic test to a treatment is a new and important approach for developing and implementing innovative neuro-oncology drugs.

Many patients are also acutely aware through popular media reports that the key health policy tool for managing the introduction and use of targeted therapies and companion diagnostics in the community is HTA.

So on the one hand we have the brave new world of targeted therapies but on the other hand the rather blunt tools that HTA currently uses to determine cost effectiveness.

■ What Levels of Evidence?

What levels of evidence will HTA use for targeted therapies? HTA likes traditional phase-III randomised controlled trials with thousands of patients providing masses of data on which to base not only clinical effectiveness but cost effectiveness as well.

How will HTA cope with targeted therapies that only produce trial evidence from much smaller patient cohorts? Will the same historic HTA principles and methodology still apply or will a new model of assessment be needed? As patients and their advocates, we believe that evidence developed through qualitative research – which might not have been considered previously – may now need to be incorporated into HTA, particularly for the much smaller brain tumour patient populations which will be the recipients of targeted therapies.

It will be more important than ever for HTA to not only worship more warily on the altar of the randomised controlled trial but to look at new ways of accepting different kinds of evidence.

■ Real-World Patient Data

For example, incorporating real-world brain tumour patient data into the HTA process will better reflect the patient’s lived experience and capture dynamic, extended data that is not available by any other means.

Real-world data can also inform pharmacovigilance. As brain tumour patients and caregivers, we are not only interested in whether a drug works or not, although of course it is crucial that a drug is effective. But we also need to know specifically how it impacts on people’s lives in terms of side effects for example.

Obviously, work needs to be done on ways of turning the experiential reports of the patient into the measurable, evidence-based assessments needed for good HTA.

The patient view on side effects, quality of life, and what really represents innovation and value for them should carry just as much weight in an HTA appraisal for a targeted therapy as the scientific data. And there should be tools created to fairly and accurately measure these aspects. Educating patients about how these tools work is also crucial so they better understand how their real-world data is captured and interpreted by HTA.

Speaking of value, any value-based pricing assessment mechanism must fully incorporate the patient perspective.

■ What Is Really Valued?

These days, we seem to know the cost of everything but not always the value of everything. We need to change that and think about what really matters to patients and caregivers.

My husband and I cared for our son for seven-and-a-half years after he was diagnosed with a brain tumour, and the notion of healthcare delivering value was something which constantly impacted his life and ours.

We highly valued a chemotherapy which could be easily and conveniently taken at home as a capsule.

We put high value on a therapy which allowed our son to return to work for a while and be a contributing member of society rather than a consumer of expensive healthcare resources.

We welcomed the value of a newer epilepsy medication for our son which did not cause him to break out in spots, making him self-conscious in front of his friends, as the older medication he was originally taking did.

■ What About Companion Diagnostics and HTA?

Will results from companion diagnostics for targeted therapies be reliably replicated and consistently and accurately interpreted from country to country, lab to lab, so that not a single patient who is appropriate to that treatment will mistakenly be denied access?

Even for one targeted therapy there may be different diagnostic tests or varying methods of conducting these tests. Tests may be given in different sequences or have different cut-off points between labs A, B, and C.

What about the supply of a new molecular drug when diagnostics are subject to such variables, or if a diagnostic is not 100 % accurate?

With this in mind, how will diagnostics be subject to HTA scrutiny?

How does HTA view stratification? Will there be criteria in place to evaluate the credibility of subgroup analyses? And how will the move towards a more value-based healthcare system affect, and be affected by, stratification?

One of our fears as patient advocates is this: that *personalised* medicine will become *exclusive* medicine where, based on genetic profiling, targeted therapies and companion diagnostics create “haves” and “have-nots” in the patient population.

How can we all ensure that academic institutions and industry are incentivised to develop innovative medicines to treat the “have-nots” as well as the “haves”? Does HTA have a role to play in this scenario?

What about patients who defy their genetic profiling and despite scientific belief, do well on a targeted therapy that officially was not meant to work for them? There are always exceptions to the rule. How will HTA grapple with this possibility?

And while HTA is working out the complex methodological issues required to jointly assess a diagnostic and a targeted treatment, what do we do about patient access to therapy in the meantime? We must ensure that any shift in methodology happens as swiftly as possible because there are always patients waiting for treatment.

■ Patients Are Willing to Share Their Medical Data

Finally, it is important to dispel one of the myths that may be holding back innovative development of new targeted therapies.

Despite belief to the contrary, patients are actually quite willing to share their personal medical data for the advancement of science.

This fact was highlighted by a 6-country survey of patients and the general public carried out by pharmaceutical company Eli Lilly as part of their new global initiative called “Patient Access to Cancer care Excellence” (PACE) [3].

The “PACE Cancer Perceptions Index” found that 89 % of the total general population surveyed (nearly 4500 people) would be willing to allow their medical records and test results to be shared with clinicians and scientists who are doing cancer research. However, the survey also highlights the importance of keeping these records secure. Forty-four per cent of those surveyed said security is a worry.

With very small patient subgroups using targeted therapies, the sharing of patient data will be absolutely critical across not only countries but continents. Digitalisation of information will make this easier.

■ Walking Around in Someone Else’s Shoes

Clearly, we need new HTA processes to meet the challenges of innovative targeted therapies, companion diagnostics, digitalisation, and what constitutes value. We need new relationships, new partnerships, and new understanding.

And maybe what we also all need is someone else’s shoes in which to walk around for a while, and understand other peoples’ perspectives.

■ Disclosure

KO serves as a patient advocate on the Global Council for the PACE initiative.

References:

1. Lee H. To Kill a Mockingbird. William Heinemann Ltd, London, 1960.
2. National Cancer Institute (NCI). National Cancer Institute FactSheet: Targeted cancer therapies. <http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted> [accessed March 15, 2013].
3. Patient Access to Cancer Care Excellence (PACE). <http://pacenetwork.com/> [accessed March 14, 2013].

Correspondence to:

Kathy Oliver

International Brain Tumour Alliance

PO Box 244, Tadworth, Surrey KT20 5WQ, United Kingdom

e-mail: kathy@theibta.org

Calendar of Events

2013

June 7	The Brain Tumor Biotech Summit	New York, NY, USA	http://www.braintumorbiotechsummit.org/
June 8–14	North American Association of Central Cancer Registries (NAACCR) 2013 Annual Conference	Austin, TX, USA	
June 22–28	Methods in Clinical Cancer Research	Flims, Switzerland	http://www.ecco-org.eu/Education/Clinical-trials-workshop/Flims-workshops/FLIMS-15.aspx
June 24–25	Cancer and Metabolism 2013	Amsterdam, The Netherlands	http://www.ecco-org.eu/Global/Events/Other-Events/Cancer-and-Metabolism-2013.aspx
July 5–6	Immunotherapy: current knowledge and controversies	Valencia, Spain	oncology.seronosymposia.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 8–13	XV WFNS World Congress of Neurosurgery	Seoul, South Korea	http://www.wfns2013.org/
September 21–26	XXI World Congress of Neurology	Vienna, Austria	http://www.wcn-neurology.com
September 27–29	Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology 2013 International Cancer Care Symposium	Berlin, Germany	http://www2.kenes.com/mascc2013/Pages/Home.aspx
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
October 10–11	V InterAmerican Oncology Conference Current Status and Future of Anti Cancer Targeted Therapies	Buenos Aires, Argentina	http://www.ecco-org.eu/Global/Events/Other-Events/V-InterAmerican-Oncology-Conference-Current-Status-and-Future-of-Anti-Cancer-Targeted-Therapies.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	
November 21–24	African Organisation for Research and Training in Cancer 9th International Conference on Cancer in Africa	Durban, South Africa	http://www.ecco-org.eu/Global/Events/Other-Events/AORTIC-2013-Conference.aspx

2014

April 5–9	American Association for Cancer Research Annual Meeting 2014	San Diego, USA	http://www.aacr.org/
May 30–June 3	2014 ASCO Annual Meeting	Chicago, IL, USA	http://www.asco.org
July 3–6	20. Jahrestagung der Deutschen Gesellschaft für Radioonkologie	Düsseldorf, Germany	
July 26–30	5th World Congress – IFHNOS and Annual Meeting AHNS	New York, 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	www.eano.eu
November 13–16	Society for Neuro-Oncology Meeting	Miami, FL, USA	
November 18–21	EORTC – NCI – AACR International Symposium on Molecular Targets and Cancer Therapeutics	Barcelona, Spain	

2015

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

In Memoriam Jerzy Hildebrand, MD, PhD

Jerzy Hildebrand, MD, PhD, died on February 11, 2013. Jerzy was born in Warsaw in April 1936. Soon after the invasion of Poland by Russia, his father was executed in 1940 in Katyń with many other Polish officers. Jerzy and his mother were then sent to Siberia where they spent 5 years in very difficult conditions. He described this episode of his life in a recently published beautiful book entitled “Wanda”.

After World War II, Jerzy and his mother were eventually granted visa for Belgium – an opportunity for which Jerzy was always grateful. He attended medical school in Brussels and became professor of neurology and chairman of the Department of Neurology at the Erasmus university hospital. In this position, Jerzy was a pioneer in European neuro-oncology and among the first to engage in clinical trials in gliomas. He founded the Brain Tumour Group of the EORTC (European Organization on Research and Treatment of Cancer) in 1972, and was its chairman for more than 10 years. He also played a key role in the creation of the European Association of Neuro-Oncology and was its chairman from 1995–1996. Jerzy retired in 2001 but remained very active as a consultant at the Institut Jules Bordet in Brussels and at the Salpêtrière hospital in Paris where he volunteered for 10 years. He was made Chevalier de la Legion d’Honneur in 2006 for his remarkable dedication.

On a humane and professional point of view, Jerzy Hildebrand was an outstanding man. We will miss him greatly. We express our deepest sympathy to his wife Michele and to his three children.



Reprinted with kind permission
of Marc Sanson, MD

Jean-Yves Delattre and Charles Vecht

17th Annual Scientific Meeting of the Society for Neuro-Oncology

Stefan Oberndorfer

Department of Neurology, Landeskrankenhaus St. Pölten-Lilienfeld, Austria

The 17th Annual Scientific Meeting of the Society for Neuro-Oncology (SNO) was held in Washington, DC, from November 15–18, 2012. The programme started with an education day followed by 3 days of scientific programme including more than 400 abstracts and 80 oral presentations covering the whole spectrum of neuro-oncological diseases from laboratory to clinical research. Interaction of multiple disciplines involved in neuro-oncology makes these meetings especially stimulating. This article provides a focused personal overview covering some of the presented data.

One of the highlights of SNO 2012 was the presentation of the AVAGLIO trial by Olivier Chinot. This randomized placebo-controlled phase-III trial in newly diagnosed glioblastoma compared concomitant standard treatment (radiotherapy and temozolomide [TMZ]) versus standard treatment with bevacizumab. Almost 900 patients were included. The trial was positive with respect to the primary endpoint (mPFS). One-year survival exhibited no difference between the 2 arms, and mOS is not available so far. Investigator-assessed mPFS was 6.2 months in the standard arm, 10.6 months in the bevacizumab arm, and 4.3 months in the standard arm versus 8.4 months in the bevacizumab arm rated by an independent radiological facility. Secondary endpoints, such as HRQoL measures, showed prolonged maintenance in multiple domains of HRQoL (motor function, social function etc) from 4 to approximately 7–8 months, a significant reduction of steroids, and longer conservation of better KPS with bevacizumab (BEV). It is also worthwhile to mention the low rate of intracranial bleedings in the bevacizumab arm (1.5 vs 0.7 % in the standard treatment arm) – a complication which could have been a major obstacle in the treatment with BEV.

Concerning glioblastoma treatment at recurrence, a retrospective study (n = 390) by Selfridge et al, University of California, Los Angeles, investigated whether treatment with bevacizumab at first, second, or third recurrence has any influence on outcome. Survival as well as mPFS after progression was similar in all 3 groups. These results suggest that deferred use of bevacizumab has no effect on its antitumour efficacy.

In another retrospective study from the UCLA, Nghiemphu et al confirmed earlier observations that re-challenge with temozolomide can be effective in a subgroup of patients with malignant glioma. They included 14 patients with glioblastoma receiving 12 cycles of adjuvant temozolomide. Patients had stable disease without tumour progression for a median of 23.2 months according to the RANO criteria. PFS(6) after re-challenge was 43 % and mOS 13.5 months, which is impres-

sive data as compared to other glioblastoma studies at first relapse. As prior data indicated, this study confirms that the benefit from re-challenge with temozolomide increases the longer-the-stable disease interval is. These confirmatory findings are helpful for a small subgroup of patients.

Also of great interest were the follow-up results of the 2 anaplastic oligodendroglial tumour trials EORTC 26951 and RTOG9402. Both studies showed a 2-fold increase in mOS survival in co-deleted (1p/19q) tumours treated initially with radiotherapy and adjuvant PCV chemotherapy versus radiotherapy alone followed by chemotherapy at recurrence. These data are generally commented on as practice-changing in the treatment of co-deleted anaplastic oligodendrogliomas. Further molecular analyses including IDH-1 mutation and gene expression profiling are under way in both studies in order to detect chemotherapy- or radiotherapy-sensitive subtypes.

An update on PFS and OS was provided for the RTOG 0131 phase-II trial investigating pre-irradiation and concurrent temozolomide therapy in newly diagnosed anaplastic oligodendrogliomas and mixed gliomas. Median follow-up was 7.4 years, and mPFS 5.9 years. Median OS has not been reached yet. 1p/19q co-deletion was detected in 23 patients, but mPFS and OS have not been reached so far in these patients. From PFS data at 3 and 6 years (82 % and 77 %, respectively), the authors concluded that results indicate comparable activity to RTOG 9402.

Several interesting immunological treatment approaches (20 abstracts from lab immunology research and 29 abstracts from clinical immunotherapy) were presented at the 2012 meeting. In a phase-II study from Spain (Valle RD et al), 31 patients received immunotherapy with autologous tumour lysate-pulsed dendritic cells for newly diagnosed GBM following ALA-guided resection. Vaccination was started prior to standard radiochemotherapy. They reported a significant survival benefit in the vaccination arm with a mOS of 27.4 months as compared to 14.7 months in the standard arm. Importantly, only patients with complete resection or a tumour load < 1 m² after resection were included in the study. Another phase-I/II trial by Duane Mitchell (Duke University) investigated whether targeting the CMV integument protein pp65 with pp65-RNA-transfected dendritic cells has any immunological effect or provides estimates on efficacy. There was a strong correlation of migration of dendritic cells to the vaccine site-draining lymph nodes with PFS and OS. This observation suggests that migration of dendritic cells might be an important biomarker for increasing efficacy of CMV vaccination strategies.

Preliminary data on the ERC-1671 Gliovac study (vaccination with autologous tumour cell lysate combined with heterologous components of different glioblastoma donors) in recurrent glioblastoma showed that mPFS (9.5 weeks) and mOS (17 weeks) might be superior as compared to other treatment after failure with bevacizumab. However, only 8 patients have been enrolled so far in this study.

Correspondence to:

Stefan Oberndorfer, MD
Department of Neurology
Landeskrankenhaus St. Pölten-Lilienfeld
Propst-Führer-Straße 4, 3100 St. Pölten
Austria
e-mail: stefan.oberndorfer@stpoelten.lknoe.at

The Swedish Brain Tumour Study Group in the Framework of a New “Patient in the Focus of Cancer Care” in Sweden

R. Henriksson

Regional Cancer Center Stockholm Gotland, Karolinska University Hospital, Stockholm and Department of Radiation Sciences, University Hospital, Umeå, Sweden

In Sweden, approximately 57,000 people are diagnosed with a cancer disease and among them are 1,300 new primary brain tumours every year. The number of new patients suffering from brain metastases is estimated annually to be approximately up to 10,000.

The Swedish Brain Tumour Group, a non-profit organisation, was founded in 1993 with 2 main goals – to create public awareness of a neglected patient group in society and to improve health care standards for patients suffering from brain tumours. This national group was supported from the beginning by the national Cancer Foundation and by the departments responsible for the care of brain tumour patients, ie, in Sweden departments of neurosurgery, neurology, and oncology. The departments involved are mainly located at university hospitals but some patients are also given non-surgical treatment at oncology departments outside universities. The National Group holds formal meetings 4 times per year.

■ Science and Research

An important activity has been to promote science and neuro-oncological research. The group has initiated and finalised several important clinical studies, such as the elderly study recently published in *Lancet Oncology* [1]. The whole group, or part of it, has taken part in many national and international clinical studies in different clinical settings. In addition, members of the group have important roles in various molecular and genomic studies of brain tumours, published in highly ranking journals. Neuropathologists and neuroradiologists are also active participants in this neuro-oncological network. In addition, the group closely collaborates with the national association of nurses in neuro-oncology and also neuro-psychologists. Several scientific publications have stemmed from these collaborations.

■ Cancer Registry

Sweden has > 20 national clinical databases related to cancer, including the cancer registry to which all patients diagnosed with cancer have been reported since 1958. The National Quality Registry for primary brain tumours, a subgroup of the Swedish Brain Tumour Study Group, was initiated in 1999 for primary registration and extended to follow-up registration in 2006. The aim was to ensure good treatment for all brain tumour patients with a high international standard and without regional differences. Registration is regionally based. Every year, all data is aggregated on a national level and reported. This registration covers > 90 % of all patients with primary brain tumours although further improvements in the registra-

tion are needed for some regions. The national brain tumour registration covers aspects not included in the legally decided cancer registry, such as treatments, time for management, complications, and follow-up parameters like survival.

■ Patient Advocacy Group

Members of the national group have supported the foundation of a specific patient advocacy group for brain tumour patients, and for the past 8 years the 2 separate organisations have been arranging annual brain tumour public meetings for patients and caregivers.

■ Scandinavian Neuro-Oncology Group

The Swedish Brain Tumour Study Group also takes part in the Scandinavian Neuro-oncology Group in the framework of collaboration between the Nordic countries in conducting clinical trials and arranging common scientific meetings every second/third year.

■ New Cancer Strategy and Cancer Plan

In Sweden, cancer care has been integrated without any specific cancer centres. Survival rates of cancer patients are high for most tumour types when compared internationally, however, we do also have problems. We see weak coordination in prevention, long and variable waiting times, lack of patient focus, lack of pathologists and radiologists, and, most noteworthy, treatment opportunities are unequally distributed among the population. Therefore, the Swedish government and authorities have decided on a new national and regional cancer strategy, which includes establishment of 6 regional cancer centres with an overall responsibility for the cancer care in their respective regions. The national aspects are especially emphasized. All centres have to lead and coordinate well-aligned patient-focused care processes in cancer, including for patients diagnosed with brain tumours, design a plan for psychosocial support, rehabilitation, and palliative care of good quality, develop support for relatives, introduce a written, individual care plan for each cancer patient, and every patient should have the support of a contact nurse. Patient-related outcomes should be used in the cancer process work and caregivers must have knowledge about a patient's right to a second opinion. The regional cancer centres have an obligation to develop national guidelines/clinical practice guidelines and, most importantly, to implement these guidelines as well. A national clinical practice guideline for malignant brain tumours was finalized in 2012. The centres also have to strengthen clinical cancer research and to optimize the quality and use of national quality registries and biobanks in this research.

This exciting work has just begun and the expectations are high also in the field of neuro-oncology. Members of the Swedish Brain Tumour Study Group are highly involved in this important work for all patients regardless of their position in society or residence.

The Swedish Brain Tumour Study Group will continue its work with a patient perspective for equal and fair cancer care for all patients. There is much more to be done. Therefore, it is important to further improve our cooperation with other national and international organisations as well as to support interdisciplinary collaboration. The new organisation for cancer care gives us a truly good opportunity to continue our work.

Reference:

1. Malmström A, Grønberg BH, Marosi C, et al.; Nordic Clinical Brain Tumour Study Group (NCBTSG). Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol* 2012; 13: 916–26.

Correspondence to:

Roger Henriksson, MD, PhD
Regional Cancer Center Stockholm Gotland
S3:00
Karolinska University Hospital
171 76 Stockholm
Sweden
e-mail: roger.henriksson@sll.se

The Spanish Group of Research in Neuro-Oncology (Grupo Español de Investigación en Neuro-Oncología [GEINO]): History and Activities

Juan Miguel Gil-Gil

Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain

The group was established on November 26, 1998, fruit of the awareness and enthusiasm of a group of 17 professionals interested in the treatment of the central nervous system tumours. Shortly afterwards, the first clinical trial was set up [1]. In February 2002, it was awarded official recognition as a non-profit scientific association [2]. The group was initially developed within the field of medical oncology (GENOM), but later on other specialties, essential part of the management of brain tumour patients such as neurosurgery, neurology, pathology, radiology, and radiotherapy, were subsequently included.

In October 2010, the group changed its name to the present Spanish Group of Research in Neuro-Oncology (GEINO) to become a multidisciplinary group with the aim of establishing valuable research activity and contributing to neuro-oncology development in our country.

GEINO comprises more than 134 members from different specialties related to 72 hospitals in Spain. The association's official head office is at the Spanish Medical Oncology Society, located at C/ Velázquez, 7–3ª planta, 28001 Madrid, but its independent technical secretariat can be found at C/ Secretari Coloma, 64–68, esc. B, entlo. 5ª, 08024 Barcelona (secretaria@geino.es). The association's management structure is formed by a chairman, a deputy chairman, a secretary, and 8 members of the board of directors from different specialties. All management structure members hold unpaid positions and are appointed by the general assembly every 2 years.

Its main purpose consists of promoting clinical and basic research in the area of neuro-oncology. GEINO's leading role includes the design and implementation of clinical trials within the multidisciplinary cooperation work frame, translational research, diffusion of research results at medical conferences and scientific publications, as well as organization of training activities, promoting the exchange of knowledge among its members, and it aims to improve the quality of healthcare for this neuro-oncology patients.

Up to February 2013, GEINO has promoted 11 clinical trials, mainly phase-II trials (phases I–IV are covered), recruiting > 600 patients in total. The group has presented > 30 scientific reports at the ASCO, EANO, ESMO, and SEOM conferences and has published 4 articles in international journals [1, 3–5].

The GEINO statutes also provide for the collaboration with other public or private, national or international organizations, in activities aimed at research and training in the neuro-

oncology field. In this area, GEINO has collaborated in clinical research protocols led by other European research groups such as EORTC as well as pharmaceutical industry-sponsored trials.

GEINO has produced clinical guidelines on the topics glioblastoma, anaplastic glioma, low-grade glioma, and medulloblastoma in adults [6]. It timely collects and publishes information on patients treated within these clinical protocols [5].

Since 2012, GEINO has awarded 2 yearly grants of € 15,000 each, designed to finance research projects in neuro-oncology.

To spread scientific knowledge, GEINO organizes an international symposium every year. Its fifth edition will take place in Barcelona on November 29–30, 2013. Since 2006, the group has also carried out a yearly face-to-face training course in neuro-oncology addressed at trainee doctors and young consultants as well as various on-line courses in neuro-oncology, whose fourth edition is currently taking place, and in 2012, GEINO organized a preceptorship programme providing hospital rotations at the ICO L'Hospitalet and ICO Badalona, in which 4 young consultants took part.

Moreover, GEINO collaborates and gives advice to ASATE, the Spanish Brain Tumour Association.

As a channel of information and intercommunication among its members, GEINO publishes the journal *Actualidad en Neuro-oncología* twice a year (www.geino.es). The group has collaborated in the publication of 3 books in Spanish:

- Balañá C, Roussos I (eds). Manual Práctico de Tumores cerebrales. Manual Práctico. (Practical handbook of Brain Tumours. Practical handbook). Publicaciones Permanyer ediciones de 2006, 2008 y 2010.
- Colección de monografías: Tratamiento Farmacológico y de Soporte de los Tumores cerebrales (4 números). (Monograph series: Pharmacological and supportive treatment of Brain Tumours – 4 numbers).
- Benavides M, Arraez MÁ, Herruzo I, et al (eds). Tumores del SNC en el adulto y en la infancia. Enfoque multidisciplinar neuro-oncológico (Central Nervous System tumours in adults and children. Neuro-oncological multidisciplinary approach) in its 2 editions. Grupo aulamédica, 2012.

We hope that together we can enable GEINO to maintain its research activity and that within EANO it will significantly contribute to the development of neuro-oncology in Spain.

Acknowledgements to all GEINO board members: Pedro Pérez-Segura, Hospital Clínico San Carlos, Madrid; Manuel Benavides, Hospital Carlos Haya, Málaga; Ángel Rodríguez-Sánchez, Hospital Universitario de León; M^a Ángeles Vaz, Hospital Universitario Ramón y Cajal, Madrid; Alfonso Berrocal, Hospital Universitario General de Valencia; Carmen Balañá, Institut Català d'Oncologia Badalona, Barcelona; Jordi Bruna, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona; Cristina Carrato, Hospital Germans Trias i Pujol, Badalona, Barcelona; María Martínez-García, Hospital del Mar, Barcelona; Juan Manuel Sepúlveda, Hospital 12 de Octubre, Madrid; Jose Luis Garcia, Hospital Universitario Ramón y Cajal, Madrid; Javier Pardo, Fundación Jimenez Diaz, Madrid; Gaspar Reynés, Hospital la Fe, Valencia; and Oscar Gallego, Hospital Sant Pau, Barcelona.

References:

1. Balañá C, López-Pousa A, Berrocal A, et al. Phase II study of temozolomide and cisplatin as primary treatment prior to radiotherapy in newly diagnosed glioblastoma multiforme patients

with measurable disease. A study of the Spanish Medical Neuro-Oncology Group (GENOM). J Neurooncol 2004; 70: 359–69.

2. Balañá Quintero C, Reynes G, Gil-Gil M, et al.; Comité Ejecutivo del Grupo Español de Neuro-oncología Médica. Constitución del Grupo Español de Neuro-Oncología Médica (GENOM). Clin Transl Oncol 2002; 4: 344.

3. Berrocal A, Perez-Segura P, Gil M, et al. Extended-schedule dose-dense temozolomide in refractory gliomas. J Neurooncol 2010; 96: 417–22.

4. Pérez-Segura P, Gil M, Balañá C, et al. Phase II trial of temozolomide for leptomeningeal metastases in patients with solid tumors. J Neurooncol 2012; 109: 137–42.

5. Gil MJ, de las Peñas R, Reynes G, et al. Bevacizumab plus irinotecan in recurrent malignant glioma shows high overall survival in a multicenter retrospective pooled series of the Spanish Neuro-Oncology Research Group (GEINO). Anticancer Drugs 2012; 23: 659–65.

6. Berrocal A, Gil M, Gallego O, et al. SEOM guideline for the treatment of malignant glioma. Clin Transl Oncol 2012; 14: 545–50.

Correspondence to:

Juan Miguel Gil-Gil, MD
Institut Català d'Oncologia
L'Hospitalet de Llobregat
Gran Via s/n Km 2,7
08907 Barcelona
Spain
e-mail: mgilgil@iconcologia.net

Interview with Dr Martin van den Bent (Rotterdam) About the EORTC TAVAREC Trial on Recurrent Grade-II and -III Gliomas

Ufuk Abacioglu

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

Q: *Dr van den Bent, what can you tell us about the ongoing TAVAREC trial on grade-II and -III gliomas? What is its background and objective?*

A: The background of the trial are the reports on the activity of bevacizumab in recurrent glioblastoma and a few reports on bevacizumab in recurrent grade-III glioma. None of those trials were controlled and the reported activity in recurrent grade-III glioma was similar compared to glioblastoma trials. The obvious question is whether bevacizumab given to grade-III tumours treated at recurrence with temozolomide improves outcome. The principle investigators of this EORTC study are Ahmed Idbaih, a neurologist at the La Salpêtrière Institute in Paris and myself.

Q: *How is the trial designed? Which patients are eligible for this trial?*

A: The trial has been set up as a randomized phase-II trial investigating temozolomide as a single agent in the control arm, and the combination temozolomide/bevacizumab in the other arm. Because progression-free survival is less reliable in trials on anti-VEGF agents, overall survival at 12 months is the primary endpoint. To explore the clinical significance of any difference in PFS – should that be observed –, quality of life and cognitive functioning are also assessed. The hypothesis is that bevacizumab may help to maintain good quality of functioning, alternatively, the development of unenhancing gliomatosis cerebri as observed during treatment with anti-VEGF agents may induce deterioration even in the absence of progression as assessed on contrast-enhanced T1 MR images. Eligible for this study are patients with a recurrent and dedifferentiated grade-II or -III glioma, without combined 1p/19q loss, showing either measurable disease or having a confirmed (secondary) glioblastoma at surgery for the recurrence.

Q: *What are the schemes and durations of treatment in both arms?*

A: The patients of arm A (the control arm) are receiving temozolomide day 1–5 every 4 weeks for 12 months, in the

other arm (the investigational arm) they receive the same temozolomide regimen but in combination with iv bevacizumab 10 mg/kg every 2 weeks, with bevacizumab given until progression.

Q: *What are the stratification factors?*

A: The stratification factors are the treating institution, initial histology (grade II versus III), WHO PS: 0 + 1 versus 2, and prior treatment (RT alone, TMZ or PCV alone, vs TMZ/RT).

Q: *Why did you choose overall survival at 1 year as the primary endpoint, while 6-month progression-free survival is preferred in most recurrent high-grade glioma trials?*

A: Well, PFS 6 is actually only an established endpoint for trials on recurrent glioblastoma. But, more importantly, bevacizumab is likely to obscure the diagnosis of radiological progression by the normalization of the increased leakiness of tumour vessels that is inherent to anti-VEGF agents. Therefore, in general, neuro-oncology trials with bevacizumab in recurrent glioma should have OS as the primary endpoint.

Q: *Do you have any planned translational studies for investigating the molecular subtypes?*

A: We are in particular interested in IDH status and MGMT promoter status and we will assess markers of the VEGF pathway in tumour tissues.

Q: *How is response assessed in this trial? Do you use the RANO criteria?*

A: Indeed, we will be using the RANO criteria. One of the reasons to develop the RANO criteria were the issues observed in patients treated with bevacizumab: in particular the diagnosis of unenhancing progression and even the development of frank gliomatosis. Also, the RANO criteria allow to continue treatment in case of unclear progression, and call progression with hindsight if the further clinical developments show that progression was indeed present.



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

A: Accrual is going steadily although somewhat slowly, we have now 47 patients randomized and we need to enrol 144 patients altogether. We hope to complete enrolment in the next 2 years. It will take another year to get the results.

Thank you very much!

Dr Martin van den Bent is the study coordinator (along with Dr Ahmed Ibdaih) of the EORTC Brain Tumor Group trial entitled, “A randomized trial assessing the significance of Bevacizumab in recurrent grade II and grade III gliomas. The TAVAREC trial”.

EORTC protocol number is 26091 and EudraCT number 2009-017422-39.

Contact Details:

Martin van den Bent, MD
Erasmus University Medical Center
Postbus 5201 NL 3008 AE
Rotterdam, The Netherlands
e-mail: m.vandenbent@erasmusmc.nl

Ahmed Ibdaih, MD
CHU Pitié-Salpêtrière (AP-HP)
Service de neurologie Mazarin
47–83, boulevard de l’Hôpital
75651 Paris Cedex 13, France
e-mail: ahmed.idbaih@gmail.com

Correspondence to:

Ufuk Abacioglu, MD
Department of Radiation Oncology, Neolife Medical Center
Yucel Sok # 6, 1. Levent, Besiktas
34340 Istanbul, Turkey
e-mail: ufuk@abacioglu.com

Hotspots in Neuro-Oncology

Michael Weller

From the Department of Neurology, University Hospital Zurich, Switzerland

■ Management of Treatment-Associated Toxicities of Anti-Angiogenic Therapy in Patients with Brain Tumors

Armstrong TS, et al. Neuro Oncol 2012; 14: 1203–14.

Antiangiogenic therapies have become the most intense area of clinical research in the treatment of malignant gliomas. Introduction of such agents has altered the risks and side effects of overall glioma treatment, and it is unclear in what way the addition of antiangiogenic compounds modifies the safety and tolerability of additional treatment such as radiation or chemotherapy. In the light of these novel developments, it is appropriate to review the management of such treatment-associated toxicities in glioma patients as done in an authoritative review by Armstrong et al, published in the October issue. Specifically, the authors address how to deal with hypotension and proteinuria, wound healing, and the presumably increased risk of thromboembolic events in patients treated with antiangiogenic compounds. The authors also provide recommendations for the diagnosis, monitoring, and management of such complications. Since antiangiogenic compounds will stay with us in neuro-oncology for some time, this review is worthwhile to read to be up to date in a field that is gaining increasing importance in clinical neuro-oncology.

■ Glioblastoma Resistance to Anti-VEGF Therapy Is Associated with Myeloid Cell Infiltration, Stem Cell Accumulation and a Mesenchymal Phenotype

Piao Y, et al. Neuro Oncol 2012; 14: 1379–92.

According to a press release by Roche (Basel, Switzerland), the registration trial for bevacizumab in the treatment of newly diagnosed glioblastoma, AVAGlio, has reached the primary endpoint of improving progression-free survival whereas no mature results for the overall survival endpoint have been made available yet. These preliminary observations underscore the urgent need to understand pathways of constitutive or acquired resistance to anti-vascular endothelial growth factor (VEGF) treatments. In the November issue of *Neuro-Oncology*, Piao et al from the MD Anderson Cancer Center analysed the evolution of resistance to anti-VEGF therapy, using either the VEGF antibody, bevacizumab, or the tyrosine kinase inhibitor, sunitinib, in the U87MG orthotopic human glioma model. Bevacizumab doubled survival whereas sunitinib did not. Sunitinib plus bevacizumab, was superior to bevacizumab alone. Both agents reduced tumour vascularity, but bevacizumab was more effective in inhibiting vascularity in the periphery of the tumours, and revascularization occurred earlier in sunitinib-treated tumours, associated with tumour progression. Increased numbers of CD11b⁺/F4/80⁺

cells were observed earlier in control and sunitinib-treated animals than in bevacizumab-treated animals and were associated with treatment failure. Although only one cell line model was studied, the study supports the view that a better understanding of tumour/host cell interactions might help to improve on the results obtained with angiogenesis inhibition in the clinic so far.

■ EORTC 26083 Phase I/II Trial of Dasatinib in Combination with CCNU in Patients with Recurrent Glioblastoma

Franceschi E, et al. Neuro Oncol 2012; 14: 1503–10.

Novel approaches to the treatment of recurrent glioblastoma are urgently needed. In the December issue, the results of EORTC trial 26083 were reported. This trial examined the combination of the Src kinase inhibitor dasatinib and CCNU in 26 patients with recurrent glioblastoma as the phase-I part of a planned multicentre, randomized phase-II trial. However, the randomized part of the trial was not initiated because of the results of this trial. Five dose levels were explored. Ten patients experienced dose-limiting toxicity which was mostly myelosuppression, with rates of grade-3-of-4 neutropenia in 26.9 % and thrombocytopenia in 42.3 %. Median progression-free survival was only 1.35 months, and only 7.7 % of the patients were free from progression at 6 months. These results are inferior compared with historical controls with CCNU alone; accordingly, EORTC 26083 did not provide any rationale to move this combination forward in the treatment of recurrent glioblastoma.

■ Survival and Secondary Tumors in Children with Medulloblastoma Receiving Radiotherapy and Adjuvant Chemotherapy: Results of Children's Oncology Group Trial A9961

Packer RJ, et al. Neuro Oncol 2013; 15: 97–103.

In the January issue, Packer et al reported very interesting results from Children's Oncology Group trial A9961 which compared radiotherapy combined with vincristine plus adjuvant chemotherapy with platinum, vincristine, and either CCNU or cyclophosphamide. Patients were enrolled between December 1996 and December 2000. 379 eligible patients were analyzed. Five- and 10-year event-free survival rates were 81 % and 76 %, corresponding results for overall survival were 87 % and 81 %. The primary site of relapse of the primary tumour was local. Importantly, 15 patients suffered secondary neoplasms in the absence of medulloblastoma relapse after a median time of 5.8 years from diagnosis. All secondary tumours occurred in body regions exposed to radia-

tion. The high risk of secondary tumours, many of which are malignant gliomas, is of concern especially with the recent great advances in the molecular subclassification and more targeted therapy options for patients with these tumours. It is of utmost importance to revisit the current standards of care once novel, more effective agents to treat medulloblastoma, which impact survival, are introduced into clinical practice.

■ **Survival Meta-Analyses for >1800 Malignant Peripheral Nerve Sheath Tumor Patients with and without Neurofibromatosis Type 1**

Kolberg M, et al. Neuro Oncol 2013; 15: 135–47.

Malignant peripheral nerve sheath tumours (MPNST) are malignant tumours derived from the peripheral nervous system that are notoriously difficult to treat. Surgery and radiotherapy remain the mainstay of therapy whereas chemotherapy is often ineffective. These tumours are strongly associated with neurofibromatosis type 1 (NF1). In the February issue, Kolberg et al performed a metaanalysis of > 1800 pa-

tients with MPNST and reviewed characteristics of 179 patients from 3 European sarcoma centres in Norway, Sweden, and Italy. Over time, they found that the traditionally assumed poorer outcome for MPNST in association with NF1 was not observed anymore in the last 2 decades possibly because of more aggressive treatment approaches to MPNST in NF1. Altogether these observations suggest that MPNST with or without NF1 may not be intrinsically different tumours and should be diagnosed, managed, and monitored accordingly. Of note, the similar outcome with or without NF1 was calculated for disease-specific survival whereas, overall, there may still be increased mortality for NF1 patients from other NF1-associated conditions. This data compilation provides a valuable basis for the planning and design of future interventional studies in NF1 and MPNST.

Correspondence to:

Michael Weller, MD

Department of Neurology, University Hospital Zurich

Frauenklinikstrasse 26

8091 Zurich, Switzerland

e-mail: michael.weller@usz.ch

News from the Society for Neuro-Oncology

J Charles Haynes

Society for Neuro-Oncology, Bellaire, TX, USA

The Society for Neuro-Oncology is hard at work organizing the 4th Quadrennial Meeting of the World Federation of Neuro-Oncology which will be held in conjunction with SNO's 2013 Scientific Meeting and Education Day. The meeting will take place on November 21–24, 2013, in San Francisco, California, at the Marriott Marquis Hotel.

Meeting chairman Dr Mitchel Berger extends a warm welcome to members of all neuro-oncology societies to share in this unique educational event. The meeting is being organized by a committee comprised of representatives of each of the Charter WFNO societies, including Susan Chang and Russell Pieper (SNO), Riccardo Soffietti and Michael Weller (EANO), and Ryo Nishikawa and Koichi Ichimura (ASNO).

The meeting will build on the traditional SNO format of presenting top-scoring abstracts and invited meet-the-expert sessions. The regular deadline for abstract submission is May 22, 2013. New this year, the Society for Neuro-Oncology will allow authors to submit their "Late-Breaking" research for consideration for the 2013 scientific meeting programme. SNO recognizes that some rapidly advancing investigations may include results that will not be available at the time of the abstract submission deadline of May 22, 2013. However, authors should note that this category is not intended to offer a second deadline for regular abstract submissions. Complete details on abstract submission can be found on the SNO website, www.soc-neuro-onc.org

The meeting will feature an education day entitled "From Drug Discovery to Clinic" which will address the various aspects of clinical development of agents that range from pre-clinical testing, pharmacokinetic and pharmacodynamic considerations, first-in-man studies, and the challenges of phase-0–III clinical trials. Concurrent sessions will address

the specific challenges of clinical design and specific pathways that are being evaluated in the preclinical area.

Running concurrently on education day will be a quality-of-life session with modules focused on palliative care, symptom management, and caregiver challenges.

On Friday evening, a special "Townhall Meeting" is planned that will review the results of the recent international randomized phase-III trials evaluating the use of antiangiogenic strategies for newly diagnosed and recurrent glioblastoma. This special session will provide a forum for open and interactive discussion about how these results may impact clinical care and efforts for further research.

During the meeting, each WFNO Charter Society will present a keynote speaker as follows: Frank McCormick (SNO), Do-Hyun Nam (ASNO), and Stefan Pfister (EANO).

The social highlight of the meeting will be a gala dinner at the magnificent San Francisco City Hall. Please note that registrants who want to attend the gala dinner must buy a separate ticket. Seats are limited, and it is highly recommended to purchase the ticket during on-line registration process as it is likely the gala will be sold out.

A full programme will be posted to the SNO website www.soc-neuro-onc.org in the coming months.

Correspondence to:

J Charles Haynes, JD

Society for Neuro-Oncology

4617 Birch Street, Bellaire, TX 77401-5509, USA

e-mail: chas@soc-neuro-onc.org

European Association of NeuroOncology Magazine

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

WHY SUBMIT A PAPER TO THE EANO MAGAZINE?

- Official journal of the European Association of NeuroOncology (www.eano.eu)
- Independent
- Peer-review
- Free of charge
- Open access
- Educational
- Editorial support
- Pre-Publishing Online
- No advertisements



THE EUROPEAN ASSOCIATION OF
NEUROONCOLOGY

www.eano.eu

EANO MAGAZINE

Editor-in-Chief

Riccardo Soffietti

Managing Editor

Wolfgang Grisold

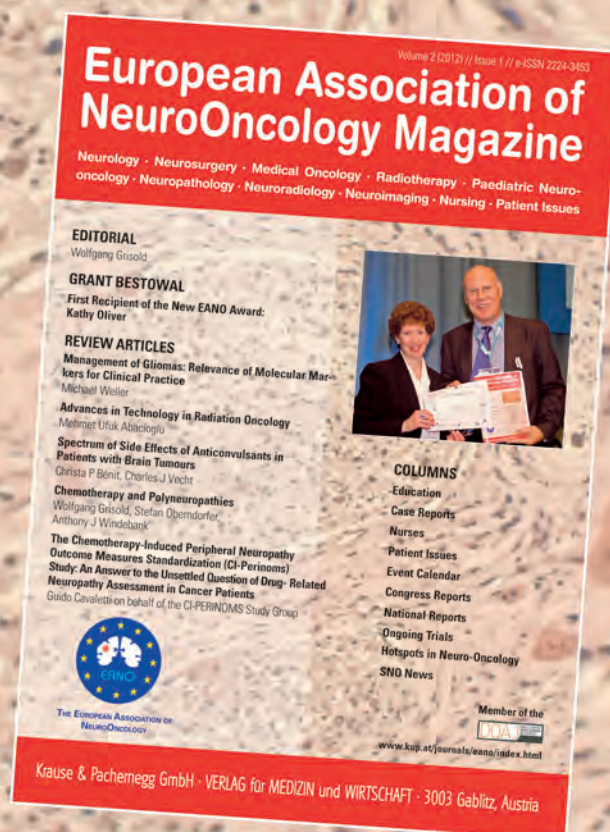


Editorial Board

Stefan Oberndorfer
Khe Hoang Xuan
Michael Weller
Wolfgang Wick
Ufuk Abacioglu (radiotherapy)
Lorenzo Bello (neurosurgery)
Olivier Chinot (medical oncology)
J. M. Kros (neuropathology)
Giorgio Perilongo (pediatric neuro-oncology)
Marion Smits (neuro-radiology)
Hanneke Zwinkels (nurses)
Kathy Oliver (patient issues)

Section Editors

Case reports:
Stefan Oberndorfer
Guidelines:
Riccardo Soffietti
Nurses:
Hanneke Zwinkels
Patient issues:
Kathy Oliver
Ongoing trials:
Ufuk Abacioglu
Hotspots in Neuro-Oncology:
Michael Weller



Online journal: www.kup.at/eano

