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It is our great pleasure to introduce to you an important, but also the last issue of the European Association for Neuro-Oncology (EANO) magazine.

2015 is a year of transition for this magazine with only a single issue—the present one. Meanwhile, EANO and SNO have engaged in a formal cooperation to issue a new magazine, the World Federation of Neuro-Oncology Societies (WFNOS) magazine as a joint publication from 2016 onwards. The WFNOS magazine shall build on the tradition of the EANO magazine and is a logical consequence of a closer interaction of EANO with our colleagues and friends from the Society for Neuro-Oncology (SNO) in the US and the Asian Society for Neuro-Oncology (ASNO). This WFNOS magazine shall serve as a forum for neuro-oncology activities worldwide.

The mission of this last EANO – as well as the new WFNOS – magazine is to promote education and to inform about recent developments in all areas of neuro-oncology. We invite contributions, perspectives, and viewpoints from all disciplines involved in the diagnosis, management, and care of our patients, and we particularly welcome reports on the state and development of neuro-oncology from various countries across the globe.

We confirm our invitation to all multidisciplinary national neuro-oncology societies worldwide to join WFNOS as outlined at: http://www.eano.eu/soc_wfnos.php

We are proud to stress that Austria, Belgium, China, Egypt, France, Germany, India, Italy, Japan, Korea, Netherlands, Spain, Switzerland, Turkey, and the United Kingdom have already joined WFNOS, and we believe that WFNOS will provide the best forum to promote the development of our field in all possible directions.

Special thanks go to Christine Marosi, Vienna, Austria, who assembled the last issue of the EANO magazine, and to the leadership of SNO, who have prepared the way for successful cooperation in the recent years, including joint ownership of the new journal Neuro-Oncology Practice as well as of this magazine as only two milestones within reach.

Kind regards,

Michael Weller,
on behalf of the EANO executive board
Recap of the 19th Annual Scientific Meeting and Education Day of the Society for Neuro-Oncology

Nicholas Butowski, MD
Associate Professor, UCSF Neurological Surgery, Division of Neuro-Oncology, San Francisco, California

The 19th Annual Scientific Meeting and Education Day of the Society for Neuro-Oncology was held on November 13–16, 2014, in Miami, Florida. The meeting enjoyed record attendance for a stand-alone SNO meeting, with close to 2000 registrants from 41 different countries in attendance.

We congratulate scientific meeting chairs, Drs. Patrick Wen and Gelareh Zadeh, for composing a comprehensive program that highlighted cutting-edge laboratory and clinical research. The meeting provided a fervent environment for the exchange of ideas among clinical and laboratory scientists involved in the research, diagnosis, care, and treatment of patients with central nervous system tumors. Special thanks are also extended to education day chairs Louis Burt Nabors, David Schiff, and Eudocia Quant Lee and to quality-of-life chairs Terri Armstrong and Alasdair Rooney.

This year’s education day was entitled “Metastasis to the CNS: Biology and Consequences” and included concurrent quality-of-life sessions focused on neurologic rehabilitation, pediatric survivorship, and caregiving.

The main scientific meeting built on the traditional SNO format and included top-scoring abstracts, plenary talks, mini-symposia, and early morning meet-the-professor session of an additional concurrent session each day, an increase in the number of sunrise sessions, the introduction of e-posters (which were viewable at kiosks located around the meeting space), more educational content during lunch breaks, and the introduction of discussed rapid reports, which allowed an increased number of oral presentations.

The scientific meeting began on Friday with sunrise sessions followed by the start of the first general session. The sunrise sessions included presentations entitled “Molecular Pathology for the Clinician,” “5-ALA-guided Surgery Update,” “ASNO session: CNS Germ Cell Tumor,” “Ependymoma,” and “Menigiomas.”

After the sunrise sessions, the first plenary session started with an official welcome by Drs. Zadeh and Wen followed by the top-scoring abstracts. The plenary session also included the EANO Travel Award for “The Role of Tumor-infiltrating Lymphocytes and PDL1 Expression in Glioblastoma and Brain Metastases” given by Anna Sophie Berghoff.

Next up was the Abhijit Guha Award Lecture, delivered by Kenneth Aldape and entitled “Neuropathologists: Who Needs Them?” This lecture was followed by the Victor Levin Award Lecture by Michael Prados entitled “Thoughts on the Meaning of Success or Significance (or both) in Translational Neuro-oncology.” David Reardon then delivered his presidential address. Lunch sessions were followed by afternoon concurrent sessions including clinical trials, preclinical models, and pediatric clinical and tumor biology. Friday evening, a special meeting reviewed emerging advances in immune-oncology in brain tumors, followed by a poster-viewing reception.

Saturday sunrise sessions featured the following topics: targeted therapies, focused ultrasound, pediatric gliomas, and epilepsy in brain tumor patients. There was also a special SNO/EANO session entitled “Controversies in the Management of Lymphoma,” chaired by Riccardo Soffietti, with contributions from Michael Weller on “Evidence-based Standards of Care,” Antonio Omuro on “How to Avoid Damage to Normal Brain,” and James Rubenstein on “Novel Therapies.” These sessions were followed by concurrent sessions on tumor biology, clinical trials, and a RANO town hall meeting on clinical trial endpoints. A young investigators luncheon provided trainees and early-phase independent investigators with grant-writing tips and instruction.

Then, there was the not-to-be-missed keynote speaker, Craig Thompson, President and Chief Executive Officer of Memorial Sloan Kettering Cancer Center, who discussed tumor metabolism. A poster session was organized after the oral sessions concluded for the day. That evening, the SNO gala dinner at the Perez Art Museum was the social highlight of the meeting and allowed us to recognize the important service of those who make the meeting possible.

The Sunday sunrise sessions included vaccine therapy, The Cancer Genome Atlas (TCGA), neuro-imaging, stem cell biology, and animal modeling. Concurrent meetings followed the sunrise sessions on several topics including bioinformatics, the WHO, and a forum on molecular classification Forum before the meeting’s adjournment.

Members of EANO are encouraged to join their North American colleagues at the 20th Annual SNO Scientific Meeting and Education Day, which will be held in San Antonio, Texas, on March 19–22, 2015.
Techniques in the Resection of Gliomas

Nader Sanai and Mitchel S. Berger

Associate Professor of Neurological Surgery, Division of Neurosurgical Oncology, Barrow Neurological Institute, Phoenix, Arizona (N.S.); Professor and Chairman, Department of Neurological Surgery, University of California at San Francisco, San Francisco, California (M.S.B.)

Corresponding authors:

Nader Sanai, MD,
Department of Neurological Surgery,
Barrow Neurological Institute,
(sanai@bnaneuro.net);

Mitchel S. Berger, MD,
Department of Neurological Surgery,
University of California at San Francisco
(berergm@neurosurg.ucsf.edu)
Microsurgical Management of Gliomas: an Overview

In the modern era of glioma management, maximal reduction of tumor burden is an essential first step in the multimodal treatment of low- and high-grade gliomas. Central paradigms in the multimodal treatment of these tumors include (i) tumor biopsy for the purpose of histological diagnosis, (ii) cytoreduction to the functional boundaries of the tumor, and (iii) judicious application of adjuvant therapy regimens tailored to the clinical circumstances. The choice of operative procedure depends on the tumor's location, size, histological characteristics, and radiographic features, as well as the preoperative neurological and medical condition of the patient. Contemporary neurosurgical techniques, including frameless navigational systems, intraoperative imaging, fluorescence-guided surgery, and functional mapping, enable neurosurgical oncologists to optimize tumor cytoreduction with the lowest neurological morbidity profile.

For adult supratentorial glioma patients, controversy persists regarding prognostic factors and treatment options for both low- and high-grade lesions. Among the various tumor- and treatment-related parameters, including tumor volume, neurological status, timing of surgical intervention, and the use of adjuvant therapy, the factors of age and tumor histology are consistently identified as primary predictors of patient prognosis. Importantly, despite significant advances in operative technique and preoperative planning, the clinical impact of glioma extent of resection remains unclear. While the value of glioma resection in obtaining tissue diagnosis and decompressing mass effect are unquestionable, a lack of Class I evidence prevents similar certainty in assessing the influence of extent of resection. Even though low- and high-grade gliomas are distinct in their biology, clinical behavior, and outcomes, understanding the effect of surgery remains equally important in both.

Nevertheless, in the modern neurosurgical era, a mounting progression of reports for both low- and high-grade adult supratentorial gliomas highlights the repeated association of extensive microsurgical resection with improved life expectancy. For glioblastoma patients, the level of evidence reaches Level 2b from retrospective analysis of randomized trial data, although most evidence is derived from retrospective case series (Level 3). Interestingly, in addition to providing greater overall survival (OS), more aggressive resections for low-grade gliomas (LGGs) may also impact the natural history of the disease, favorably altering its risk profile for malignant transformation. A prospective, randomized study using modern intraoperative techniques and standardized perioperative adjuncts remains the gold standard to settle the controversy, but such a trial may

Abstract

Neurosurgical intervention remains the first step in effective glioma management. Mounting evidence suggests that cytoreduction for low- and high-grade gliomas is associated with a survival benefit. Beyond conventional neurosurgical principles, an array of techniques has been refined in recent years to maximize the expertise of the neurosurgical oncologist and facilitate the impact of subsequent adjuvant therapy. With intraoperative mapping techniques, aggressive microsurgical resection can be safely pursued, even when tumors occupy essential functional pathways. Other adjunct techniques such as intraoperative magnetic resonance imaging, intraoperative ultrasonography, and fluorescence-guided surgery can be valuable tools to safely reduce the tumor burden of low- and high-grade gliomas. Taken together, this collection of surgical strategies has pushed glioma extent of resection toward the level of cellular resolution.

Keywords: extent of resection, fluorescence-guided surgery, glioma, intraoperative mapping, intraoperative MRI, intraoperative ultrasound, 5-aminolevulinic acid
never occur. For the time being, retrospective matched studies, retrospective reviews of randomized trials, and prospective observational trials remain the most practical solutions.

One of the largest studies to date reviewed 500 consecutive, newly diagnosed glioblastoma patients treated with standard adjuvant therapy regimens following image-guided microsurgical resection. Interestingly, both multivariate analysis and recursive partitioning analysis of the data revealed 78% as the minimum threshold of volumetric tumor resection associated with a survival benefit. Importantly, a stepwise improvement in OS was observed as the extent of resection increased beyond this threshold, even within the 95%–100% range. More recently, a comparable study of 170 first-recurrence glioblastoma patients who underwent standard surgical and adjuvant treatment at initial diagnosis also revealed a similar extent of resection threshold. It remains each practitioner’s responsibility to determine if the magnitude and quality of evidence are sufficient to influence their practice standards. In our practice, extent of resection is based on the functional nature of the tissue, not on its perceived biological aggressiveness.

Cortical and Subcortical Mapping Strategies for Gliomas

Language-mapping techniques were historically developed in the context of epilepsy surgery, where large craniotomies exposed the brain well beyond the region of surgical interest in order to localize multiple cortical regions containing stimulation-induced language and motor function (i.e., “positive” sites) prior to resection. Until recently, it has been thought that such positive site controls must be established during language mapping before any other cortical area could be safely resected. Traditionally, this tactic is used in awake craniotomies to identify positive language sites in 95%–100% of operative exposures. Brain tumor surgeons, however, have evolved toward a different standard of language mapping in which smaller, tailored craniotomies often expose no positive sites and tumor resection is therefore directed by the localization of cortical regions containing no stimulation-induced language or motor function (i.e., “negative” sites). This negative mapping strategy represents a paradigm shift in language-mapping technique by eliminating the neurosurgeon’s reliance on the positive site control in the operative exposure, thereby allowing for minimal cortical exposure overlying the tumor, less extensive intraoperative mapping, and a more time-efficient neurosurgical procedure.

Unreliability of Anatomical Localization

Prediction of cortical language sites through classic anatomical criteria is inadequate in light of the significant individual variability of cortical organization,2–10 the distortion of cerebral topography from tumor mass effect, and the possibility of functional reorganization through plasticity mechanisms.11–15 A consistent finding of language stimulation studies has been the identification of significant individual variability among patients.8,16,17 Speech arrest is variably located and can go well beyond the classic anatomical boundaries of Broca’s area for motor speech. It typically involves an area contiguous with the face-motor cortex and yet in some cases is seen several centimeters from the sylvian fissure. This variability has also been suggested by studies designed to preoperatively predict the location of speech arrest based upon the type of frontal opercular anatomy18 or functional neuroimaging.19–25 Furthermore, because functional tissue can be located within the tumor nidus,26 the standard surgical principle of debulking tumor from within to avoid neurological deficits is not always safe. Consequently, the use of intraoperative cortical and subcortical stimulation to accurately detect functional regions and pathways is essential for safely removing dominant hemisphere gliomas to the greatest extent possible.

Current Intraoperative Language and Motor Mapping Techniques

In general, a limited craniotomy should expose the tumor and up to 2 cm of surrounding brain. With the use of bipolar electrodes, cortical mapping is started at a low stimulus (1.0 mA) and increased to a maximum of 8 mA, if necessary. A constant-current generator delivers biphasic square wave pulses (each phase, 1.25 ms) in 4-second trains at 60 Hz across 1 mm bipolar electrodes separated by 5 mm. Stimulation sites (~5–20 per subject) can be marked with sterile numbered tickets. Throughout motor and language mapping, continuous electrocorticography can be used to monitor after-discharge potentials and therefore eliminate the chance that speech or naming errors could be caused by subclinical seizure activity.

Awake Cortical Stimulation for Language Mapping

Speech arrest is based upon blocking number-counting without simultaneous motor response in the mouth or pharynx. Dysarthria can be distinguished from speech arrest by the absence of perceived or visible involuntary
muscle contraction affecting speech. For naming or reading sites, cortical stimulation is applied for 3 seconds at sequential cortical sites during a slide presentation of line drawings or words, respectively. All tested language sites should be repeatedly stimulated at least 3 times. A positive essential site can be defined as an inability to name objects or read words in 66% or more of the testing per site. In all cases, a 1 cm margin of tissue should be measured and preserved around each positive language site in order to protect functional tissue from the resection.17 The extent of resection is directed by targeting contrast-enhancing regions for high-grade lesions and T2-hyperintense areas for low-grade lesions. Some groups advocate the use of language mapping along subcortical white matter pathways as well.28,29

Despite the considerable evidence supporting the use of intraoperative cortical-stimulation mapping of language function, the efficacy of this technique in preserving functional outcome following aggressive glioma resection remains poorly understood. Nevertheless, the long-term neurological effects after using this technique for large, dominant-hemisphere gliomas are important to define in order to accurately advocate its use.30

In a report of 250 consecutive dominant-hemisphere glioma patients (World Health Organization [WHO] grades II-IV), functional language outcomes following awake mapping were favorable, even in the setting of an aggressive resection.17 Overall, 159 of these 250 patients (63.6%) had intact speech preoperatively. At 1 week postoperatively, 194 (77.6%) remained at their baseline language function, while 21 (8.4%) worsened, and 35 (14.0%) had new speech deficits. However, by 6 months, 52 (92.9%) of 56 patients with new or worsened language deficits returned to baseline or better, and the remaining 4 (7.1%) were left with a permanent deficit. Interestingly, among these patients, any additional language deficit incurred as a result of the surgery improved by 3 months or not all. Thus, using language mapping, only 1.6% (4 of 243 surviving patients) of all glioma patients developed a permanent postoperative language deficit.

More recently, a meta-analysis of 90 intraoperative mapping reports, which were published between 1990 and 2010 and encompassed more than 8091 patients with infiltrative gliomas in eloquent areas, found that late-severe neurological deficits were observed in 3.4% of patients operated on with intraoperative mapping compared with 8.2% of patients who were operated on without brain mapping. Furthermore, gross total resection was achieved in 75% of patients undergoing intraoperative mapping compared with 58% of patients who did not undergo brain mapping.31 Taken together, these large-scale studies suggest that the associated risk of a highly eloquent glioma can be downgraded to a risk profile similar to that observed in the resection of noneloquent tumors with use of intraoperative mapping techniques.

Cortical and Subcortical Motor Mapping Techniques

For patients with gliomas that are located within or adjacent to the rolandic cortex and thus the descending motor tracts, stimulation mapping of cortical and subcortical motor pathways enables the surgeon to identify these descending motor pathways during tumor removal and achieve an acceptable rate of permanent morbidity in these high-risk functional areas.10,32,33 In a recent study, new immediate postoperative motor deficits were documented in 59.3% of patients in whom a subcortical motor tract was identified intraoperatively and in 10.9% of those in whom subcortical tracts were not observed. However, permanent deficits were observed in 6.5% and 3.5%, respectively.32 In another study of subcortical motor pathways in 294 patients who underwent surgery for hemispheric gliomas, 14 patients (4.8%) had a persistent motor deficit after 3 months. Interestingly, patients whose subcortical pathways were identified intraoperatively were more prone to developing an additional transient or permanent motor deficit (27.5% vs 13.1%).33 In another study with an 87% gross or subtotal resection rate, the overall neurological morbidity was 5% after using cortical motor mapping.16 Thus, collectively the recent literature suggests that intraoperative cortical and subcortical motor mapping can safely identify corridors for resection as well as define the limits of tumor resection. A supratotal resection using this strategy has been advocated and may represent a new approach to glioma resection.34

Negative Intraoperative Mapping

With tailored cortical exposures, <58% of patients have essential language sites localized within the operative field,17 suggesting that it is safe to employ minimal exposure of the tumor and to perform the resection based on a negative language map (Fig. 1). Importantly, such an approach to language mapping is generally more successful and safer at high-volume neurosurgical centers, where routine neuroanesthetic protocols are in place and intraoperative electrocorticography can validate the stimulation threshold for individual cases. Despite negative intraoperative brain maps, permanent postoperative neurological deficits have been reported.35 Other cases of unexpected postoperative deficits have also been attributed to progressive tumor infiltration into functional areas.36 Furthermore, both intraoperative stimulation and functional imaging techniques have provided evidence for redistribution of functional neural networks in cases of stroke,12,37,38 congenital malformations,39,40 brain injury,41 and brain tumors.12,13,42,43
Intraoperative Imaging Paradigms

In recent years, technologies such as intraoperative neuronavigation, intraoperative ultrasound, and intraoperative magnetic resonance imaging (MRI) have improved the likelihood of radiographically complete resection for gliomas. Stereotactic localization with frameless systems (i.e., intraoperative neuronavigation) has gained near-universal acceptance at major brain tumor centers for comparing intraoperative findings with preoperative imaging. However, while neuronavigation has emerged as a standard of care at most major brain tumor centers, intraoperative ultrasound and intraoperative MRI (iMRI) technologies are less commonly utilized, owing at least in part to issues of cost and technical expertise. Nevertheless, despite these technological advances, reported rates of LGG gross-total resection during the last decade have remained comparatively low, ranging from 14% to 46%. Disaggregation of the data sets from these LGG extent-of-resection reports indicates radiographic gross-total resection for 399 of 1462 LGGs—a 27.3% average rate of gross-total resection. A similar analysis of the literature for high-grade gliomas (HGGs), however, reveals a somewhat higher rate of 33%–76% gross-total resection, and disaggregation of these HGG data sets yields an average gross-total resection rate of 62.3% (1412 of 2266 HGGs).

Thus, for the neurosurgical oncologist, complete resection of both LGGs and HGGs remains a challenge.

Importantly, a recent Cochrane Database Review examined an array of intraoperative imaging tools (including iMRI, intraoperative ultrasound [iUS]), and fluorescence-guided surgery in the modern neurosurgical era. Four randomized controlled trials were identified, each using a different image-guided technique: (i) neuronavigation (n = 45 patients), (ii) diffusion tensor imaging (DTI)-neuronavigation (n = 238 patients), (iii) iMRI (n = 58 patients), and (iv) 5-aminolevulinic acid (5-ALA) (n = 322 patients). All studies included patients with HGG, with one study also including patients with LGG. Extent of resection was increased with iMRI (risk ratio [RR] incomplete resection: 0.13, 95% confidence interval [CI]: 0.02–0.96); 5-ALA (RR: 0.55, 95% CI: 0.42–0.71), and DTI-neuronavigation (RR: 0.35, 95% CI: 0.20–0.63). Insufficient data were available to evaluate the effects of conventional neuronavigation on extent of resection. There was no clear evidence of improvement in OS with 5-ALA (hazard ratio [HR]: 0.82, 95% CI: 0.62–1.07) or DTI-neuronavigation (HR: 0.57, 95% CI: 0.32–1.00) in patients with HGG, although the 5-ALA trial did demonstrate a progression-free survival benefit, as well as a survival benefit on a post hoc analysis. Overall, this analysis emphasized the need for additional high-quality data as well as the importance of balancing complex and expensive intraoperative adjuncts with realistic operative objectives.
Intraoperative MRI

Intraoperative low- and high-field MRI provide excellent tumor visualization and allow for interval updates of neuronavigation in real time. For large tumors or longer cases with accompanying brain shift, this technology provides instant feedback on extent of resection as well as minimizes the risk of inaccurate neuronavigation. The use of iMRI is of particular utility for LGGs, in which macroscopic tissue features are less useful for distinguishing normal from abnormal tissue. Use of IMR requires MR-compatible instruments (titanium or ceramic) to minimize artifact effects. Image distortion leading to inaccurate target registration may pose a problem with iMRI. Air-tissue interfaces may also result in artifact effects and are currently being studied with respect to image distortion. Extravasation of contrast agent may occur as a result of surgical insult to the blood-brain barrier and may be interpreted as residual tumor. Despite these challenges, iMRI has proven effective for facilitating extent of resection. In a recent study of 156 patients who underwent iMRI-guided resection of LGGs, an increase in gross total resection as well as 1-year, 2-year, and 5-year mortality rates of 1.9%, 3.6%, and 17.6%, respectively, were noted. A related subsequent study found that the sensitivity, specificity, positive-predictive value, and negative-predictive value of T2-weighted iMRI to identify residual LGG tumor were 85.7%, 100%, 100%, and 75%, respectively.

Intraoperative Ultrasound

The use of iUS provides a cost-effective and time-efficient alternative to iMRI, although with less anatomical detail. Decreased sensitivity and specificity during surgery, due to vulnerability to artifact, are recognized disadvantages of iUS. In particular, residual disease <1 cm in diameter can be particularly challenging to discern. Aberrant signals can be minimized if the transducer is placed directly upon the region of interest, although superficial cortical lesions directly below the transducer can be difficult to visualize because of its cone-shaped field of view. More recently, high-frequency linear probes have demonstrated extraordinarily high tissue resolution and are being integrated into the neurosurgical work flow with more promising results.

Fluorescence-guided Surgery

Intraoperative fluorescence-guided surgery using 5-ALA has emerged as the latest paradigm shift in neurosurgical oncology. 5-ALA is an orally administered prodrug that passes through the intact blood-brain barrier and is metabolized intracellularly to form the fluorescent molecule protoporphyrin IX. This heme synthesis pathway substrate accumulates preferentially in tumor cells and epithelial tissues and emits red-violet light (λ = 635–704 nm) when excited with blue light. Successful neurosurgical integration of 5-ALA-induced fluorescence for HGGs was demonstrated by a German randomized, controlled trial conducted by Stummer et al. in 2006. This phase 3A clinical trial was halted following an interim analysis of 270 patients that indicated a 65% versus 36% rate of gross-total resection and a 41% versus 21.1% rate of 6-month progression-free survival benefiting HGG patients who received 5-ALA. Importantly, 15% of enrolled patients received temozolomide, and none of the participating neurosurgeons used concomitant neuronavigation, which limited the generalizability of the study to current neuro-oncology principles. For LGGs, however, the standard intraoperative 5-ALA fluorescence-guided technique remains ineffective, as it does not produce visible fluorescence for more than 90% of WHO grade II gliomas. Interestingly, protoporphyrin IX fluorescence can be measured ex vivo in LGG tissue following 5-ALA administration. In these analyses, the resultant fluorescent intensity of the tumor tissue is significantly higher than that of similarly treated normal tissue and it increases proportionally with both tumor grade and MIB-1 proliferation index. Altogether, these reports indicate that 5-ALA tumor fluorescence can be microscopically localized to LGGs even when it is not macroscopically evident. Recently, the first combined effort using intraoperative confocal microscopy to visualize 5-ALA tumor fluorescence in LGGs during the course of microsurgical resection was reported. This initial experience detected 5-ALA fluorescence at a cellular level within WHO grade I and II LGGs and identified cellular LGG infiltration at the tumor margins (Fig. 2). These findings suggest that a combined approach may expand the utility of 5-ALA beyond glioblastomas. Specifically, intraoperative confocal microscopy can identify tumor fluorescence at a cellular level, and these findings correspond to tumor invasion on matched histological analysis. This combined strategy represents the first successful effort at real-time intraoperative detection of WHO grade I and II gliomas using 5-ALA and fluorescence-guided surgery. A Phase 3A randomized, placebo-controlled trial (BALANCE) is currently underway in the United States to definitively evaluate the clinical impact of 5-ALA for HGGs in conjunction with intraoperative neuronavigation and LGGs in combination with intraoperative confocal microscopy and intraoperative neuronavigation.

Conclusions

The exact value of glioma resection remains undefined, yet the available literature for both low-grade and high-grade hemispheric gliomas demonstrates mounting evidence that more extensive surgical resection and less residual disease are associated with a more favorable life expectancy for both LGG and HGG patients. For the neurosurgical oncologist, glioma resections using awake craniotomy and intraoperative stimulation-mapping...
Techniques in the resection of gliomas

Techniques are associated with fewer neurological deficits and more extensive resection. Unlike motor function, speech and language are variably distributed and widely represented, thus emphasizing the utility of language mapping in this particular patient population. Beyond functional stimulation techniques, emerging intraoperative adjuncts such as iMRI, iUS, fluorescence-guided surgery, and confocal microscopy may represent the next evolutionary step. As the neuro-oncology community develops better intra- and extraoperative techniques to visualize and track glioma infiltration, conventional metrics for glioma resection will likely migrate from macroscopic parameters based on neuro-imaging to microscopic indices based on cellular tumor burden.

Figure 2. Intraoperative confocal microscopy for fluorescence-guided surgery. (A) This 21-year-old male patient had a right frontal low-grade glioma detected incidentally following a motor vehicle accident. (B) The handheld confocal microscope was employed in the absence of macroscopic 5-aminolevulinic acid (5-ALA) tumor fluorescence. (C) Intraoperative neuronavigation confirmed localization of the confocal imaging within the tumor mass. (D) Multiple fluorescent cells were observed within this region, corresponding to 5-ALA metabolism. (E) Postoperative fluid-attenuated inversion recovery magnetic resonance imaging confirmed a 98% volumetric extent of resection. (Adapted from Sanai N, Snyder LA, Honea NJ et al.)
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References


Further Reading


Current Standards and Future Perspectives in Intraoperative Ultrasound

Dorothea Miller and Ulrich Sure

Corresponding authors:

Dorothea Miller, MD,
Department of Neurosurgery,
Essen University Hospital,
Hufelandstr. 55, 45147 Essen, Germany

Ulrich Sure, MD,
Department of Neurosurgery,
Essen University Hospital,
Essen, Germany.
Abstract

Intraoperative ultrasound (iUS) has been used during neurosurgical procedures for more than 3 decades. As ultrasound technology has improved enormously over the years, iUS has become an important diagnostic intraoperative tool. This article discusses technical aspects such as 2-dimensional, navigated, and 3-dimensional ultrasound, as well as their applications during surgery, and reviews the current literature concerning possible benefits during surgery for intracerebral tumors, hydrocephalus, epilepsy, and spinal tumors. Limitations and ongoing developments are highlighted. Moreover, this article gives an overview on possible future therapeutic aspects using ultrasound as a therapeutic tool.

Keywords: image-guided surgery, intraoperative ultrasound, 3-dimensional (3D) ultrasound

The beneficial potential of ultrasound (US) in neurosurgery was noted as early as 1950, when French et al. tried to localize brain tumors with pulsed echo signals in a postmortem study. Later, Leksell introduced A-mode echoencephalography. Intraoperative ultrasound (iUS) started to be used in neurosurgical procedures in the early 1980s with the introduction of B-mode imaging. Since then, technical developments such as improved image quality in B-mode, Doppler and duplex studies, navigated ultrasound (naviUS), and 3-dimensional applications (3D US) have increased its diagnostic value and led to more widespread use of the application. However, there are still shortcomings of the technology. The aim of this review is to describe current standards as well as future perspectives in intraoperative ultrasound.

Technical Aspects

2-dimensional Intraoperative Ultrasound

Numerous articles have described the use of intraoperative 2-dimensional (2D) B-mode images in various neurosurgical procedures. Earlier studies focused on describing pathomorphologies and comparing ultrasound images with those by preoperative MRI or CT. However, due to the rather low image quality in earlier studies, many surgeons felt that the utility of iUS during surgery was somewhat limited. Further developments in US technology have led to improvements in spatial and contrast resolution, thus leading to improved signal-to-noise-ratio. Today, multifrequency sector or curved array probes with a frequency range from 4 to 10 MHz are most commonly used for cranial applications. Linear array probes with higher frequencies can be useful for superficial lesions, whereas sector probes with smaller footprints are helpful in cases of small craniotomies. Several ultrasound providers have developed special burr hole probes for burr hole applications. Small linear probes with a frequency ranging between 10 and 15 MHz are used in spinal applications. During the examination, the area of interest should be scanned in 2 perpendicular planes by either sweeping or tilting the probe over the area to be scanned.

Recent articles have shown that simple 2D B-mode iUS still has its value in everyday neurosurgery. Mair et al. tried to establish a grading system for the visibility of intracerebral lesions on iUS. They concluded that ultrasound could be of benefit in allowing the surgeon to appraise the location, extent, and local environment of the target lesion as well as reduce the risk of preventable complications. According to the authors, iUS can be an inexpensive and ubiquitous alternative method to intraoperative MRI or fluorescence guidance. Moiyadi and Shetty performed another assessment concerning the utility of iUS for detecting and delineating the lesion, modifying the craniotomy or
laminotomy, guiding the durotomy and corticotomy, and showing the extent of resection as well as visualizing adjacent structures. In each of the 77 cases included in the study, iUS was deemed useful in at least 4 of these 7 parameters. The operating time was not significantly prolonged. Many surgeons, however, have expressed concern that the interpretation of iUS images depends on the experience of the examiner. The unusual and often oblique image plane of view makes orientation more difficult. Orientation can be improved by scanning the region of interest in 2 perpendicular planes that are close to the normal axial, coronal, or sagittal image planes. However, this might not always be possible. Moreover, only a small sector of the brain can be examined with iUS via craniotomy, thus leading to orientation difficulties.

Navigated 2D Intraoperative Ultrasound

These shortcomings mentioned above have led to the development of navigated 2D iUS (naviUS). An ultrasound device was connected to a navigation system in the mid 1990s in the first experimental studies on a limited number of patients. These early studies demonstrated the feasibility of naviUS and documented an intraoperative brain shift when comparing naviUS with preoperative MRI. Now, the integration of an external ultrasound device is supported by most neuronavigation systems. A tracking device has to be mounted on the ultrasound probe. Thereafter, a calibration process has to be performed using a calibration phantom. Then, the probe can be tracked with the navigation system, and naviUS images and preoperative images can be displayed side by side. This leads to improved orientation and easier interpretation of naviUS images by comparing them with MRI images in the same plane of view. The first studies, using commercial single-rack integrated ultrasound-navigation systems, were published in 2000 and 2006. The main advantages of these systems were precalibrated probes and improved theater ergonomics.

3D Intraoperative Ultrasound

Further technical developments have led to the introduction of 3D iUS. Usually, a series of navigated 2D iUS images or digital raw iUS data are reconstructed into a 3D volume. Then, multiplanar images can be reconstructed from the volume. Therefore, image quality depends on the quality of the original data, the way data are acquired, and the reconstruction algorithm used. In rare cases, either a mechanical 3D probe or matrix 3D array is used for 3D imaging without neuronavigation. In their preliminary study, Bozinov et al. compared 3D imaging using a navigated 2D probe with that using a non-navigated 3D probe. Even though the reconstruction process was more time-consuming, orientation was better using the navigated 2D probe since images could be displayed in familiar imaging planes and compared with preoperative MRI. Navigating a 3D probe is also possible and leads to higher-quality image reconstructions.

3D iUS has been shown to be advantageous in a variety of intraparenchymal pathologies. 3D iUS can help in solving the orientation problem by providing more user-friendly multiplanar images and therefore overcomes most of the limitations of conventional 2D iUS. Compared with other intraoperative imaging modalities, the flexibility of the 3D iUS technology is a main advantage of the system, allowing its use at any time during the operation. There is no need for special instruments and no need for radiologists or technicians; 3D iUS also adds very little extra time to the operation, and the investment costs are lower than those for MRI.

Color-coded Duplex Sonography and Power Doppler

By applying color-coded duplex mode, vascular flow direction, pattern, and velocity can be monitored in real time. Power Doppler displays the strength of a Doppler signal in color. It is therefore more sensitive for the detection of flow, particularly in small vessels or low-velocity flow. Both Doppler techniques can be useful adjuncts to B-mode imaging for displaying the vascular anatomy during various neurosurgical procedures. Power Doppler can be reconstructed into 3D images, which allow better understanding of the 3D anatomy.

Further Developments

Another technical development is the application of contrast-enhancing agents in iUS, leading to an improved signal-to-noise-ratio, thus facilitating tumor delineation and examining the vascular anatomy of tumors and vascular lesions. Even though results are encouraging, the use of contrast-enhancing agents is currently limited to ongoing studies. Transendoscopic ultrasound has been applied in single studies, however, its diagnostic value needs further evaluation.

Ultrasonic-elasticity imaging might be a new and promising method for differentiating subtle pathologic lesions or glial tumors from normal brain tissue. However, larger studies are needed to determine its diagnostic value.

Applications

Localization and Approach Planning

2D iUS is a useful tool for localizing pathological intraparenchymal lesions and guiding the approach to these lesions. Moiyady and Shetty showed, in their study of 77
procedures for various CNS tumors, that iUS was useful for identifying the lesion, delineating the lesion, modifying the craniotomy or laminotomy, planning the durotomy, and planning the corticotomy in 100%, 100%, 22%, 78%, and 85% of cases, respectively. Regelsberger et al. reported on ultrasound-guided resection of deep-seated lesions in 45 cases. They scanned the area of interest in 2 perpendicular planes, secured the surgical trajectory by catheter placement, and were able to locate all lesions easily. Additionally, reliable localization of the tumor margins (including gliomas and metastases) was reached in 23 of 28 (82%) cases. In another report, Woydt et al. could prove safe guidance by 2D iUS to deep-seated cavernous angiomomas in 35 cases. Other reports have shown the usefulness of naviUS or 3D iUS during the approach to deep-seated or eloquently located cavernomas. Both reports clearly show the ease of use and improved orientation with both techniques, thus allowing exact localization of the lesion and identification of the approach.

Visualization of Neighboring Structures

As described in numerous reports, neighboring structures can be displayed in real time by 2D iUS (Fig. 1), naviUS, and 3D iUS. By integrating the ultrasound device into the navigation system, real-time information on the progress of tumor resection can be combined with functional information such as DTI or fMRI (Fig. 2). This might help to avoid important structures and thus increase the safety of the operation.

Visualization of Vascular Anatomy and Vascular Lesions

A major advantage of iUS over iMRI is the ability to visualize not only the anatomy of cerebral vessels but also the flow direction, pattern, and velocity by color-coded duplex sonography. Power Doppler might be more sensitive for detecting smaller vessels. Both techniques can be helpful in tumor surgery as well as neurovascular surgery. NaviUS can be even more helpful than 2D iUS alone in understanding the vascular 3D anatomy. It can also be helpful for landmarking vessels detected on naviUS during an operation with the navigation system.

Rygh et al. have demonstrated the feasibility of 3D power Doppler in tumor surgery. They found it to be helpful for visualizing hidden vessels adjacent to tumors. Moiyadi et al. performed 3D power Doppler studies in one-third of all tumor cases. However, usually only power Doppler information can be imported into 3D reconstructions, which do not display any information about flow velocity or direction. Whether the 3D reconstruction adds any value compared with naviUS has yet to be determined.

In a prospective study of 20 patients with arteriovenous malformation (AVM), iUS could be helpful during surgery for detecting feeding arteries and draining veins as well as the nidus or associated hematomas. Moreover, it could document normalization of flow pattern in vascular lesions and thus monitor the progress of an operation. Residual nidus could be accurately detected. In a small study on 3D iUS for AVM surgery, US images corresponded well with intraoperative findings, and preoperative MRA. 3D iUS allowed confirmation of feeding vessels, identification of the perinidal dissection planes, and discrimination between perinidal neovascularization and true nidus. Moreover, a small residual AVM could be detected in 2 of 9 cases by 3D iUS.

Intraoperative Ultrasound in Tumor Surgery

iUS can be helpful during different steps of tumor resection. As outlined above, iUS can localize and delineate the lesion. The exact intradural approach can be planned using...
iUS. The progress of tumor resection can be monitored. It has been shown that iUS is less time-consuming than iMRI and thus does not interrupt the surgical workflow. According to the results of a meta-analysis of all major clinical publications on this topic since 1990, extensive surgical resection is associated with a longer life expectancy for patients with both low-grade gliomas and high-grade gliomas. Despite the preconception that iUS is of little use for resection control, several reports have shown that iUS can detect tumor remnants even though image quality might deteriorate at the end of resection due to artefact formation (see below). A case illustration on the use of 3D iUS for resection control in glioma surgery is shown in Fig. 3.

Two reports including both high-grade and low-grade gliomas compared findings on 2D iUS at the end of resection with histopathology. Woydt et al. differentiated between hyperechoic areas and a small regular hyperechoic rim around the resection cavity on 2D iUS images. Samples taken from sonographically hyperechoic areas were proven to be residual solid tumor tissue in 89% of cases and infiltration zones in the remaining cases, whereas samples taken from the small hyperechoic rim revealed solid tumor (24%), infiltration zone (40%), or normal brain tissue (36%). Chacko et al. reported on a sensitivity of 97.1% and a specificity of 53.6% when using 2D iUS for resection control. When comparing 2D iUS with postoperative MRI in a prospective study of 70 patients with gliomas or metastases, 2D iUS accurately determined the extent of resection in all cases of primary operation but defined the extent of resection poorly in cases where histology showed radiation changes. In another study on a mixed series of tumors in 32 cases, 2D iUS and postoperative MRI showed fair-to-good intermethod agreement with a kappa value of 0.72. Gerganov et al. compared iMRI and naviUS for resection control in 26 patients with various tumor entities. The authors showed that small tumor remnants (<1 cm) were not detected by the examiner on naviUS in 2 of 21 patients but were identified on 1.5T iMRI. Suspicious signals on naviUS were misinterpreted as tumor remnants in another 2 cases. A statistical analysis was not performed in this study.

In another study with mixed tumor entities, 3D iUS led to further resection in 59% of cases in which 3D iUS was used with the intention of resection control. Rohde and Coenen evaluated the utility of 3D US for resection control in a small randomized, blinded prospective study on patients with gliomas and metastases by correlating 3D US results with postoperative MRI. 3D US correctly identified tumor remnants in 5 of 7 patients (71%) and correctly confirmed complete tumor removal in 3 of 5 patients (60%). Overall, the intraoperative situation was correctly visualized in 8 of 12 patients (67%).

Few studies look specifically at either high-grade or low-grade gliomas specifically. Rygh et al. reported that glioblastomas were delineated well by 3D US (sensitivity and specificity both 95%) prior to...
resection when comparing imaging results with histopathological samples. During resection, 3D US detected tumor remnants with a sensitivity of 87%; however, specificity decreased to 42% due to biopsies falsely classified as tumor by the surgeon. After resection, sensitivity was poor (26%) due to tumor or infiltrated tissue in several biopsies that were deemed normal by ultrasound, but the specificity was acceptable (88%).

Moiyadi et al. achieved gross total resection in 88% of resectable high-grade gliomas with the aid of 3D iUS. This rate is comparable to gross total resection rates achieved with other intraoperative methods such as fluorescence guidance or iMRI. 61,62

Even though prospective data showing a direct impact of iUS on survival rates of patients with glioblastomas are lacking, there is some weak evidence that routine use of iUS during glioblastoma resection has led to improved survival in a retrospective study with historical controls. 63 Claus et al. examined the association between the extent of low-grade glioma resection and survival in a series of 156 patients who underwent surgery with low-field iMRI control. Twenty-one patients with subtotal resection had a 1.4 times greater risk of disease recurrence, and a 4.9 times greater risk of death, relative to patients who underwent gross total resection. Despite its proven advantages, the wide application of iMRI is hindered by its high cost and specific requirements for operative setup. 64

In a direct comparative study of naviUS and iMRI in patients with low-grade gliomas, tumors were well defined on 10 of 11 iMRI studies and 9 of 11 iUS studies prior to resection. NaviUS was better in showing internal structures of the tumors as well as their vascular supply. The naviUS images provided reliable, almost real-time image control of the progress during surgery. The mean duration of image acquisition was less than 2 minutes and did not result in a major interruption of workflow. However, the authors reported a decrease in image quality during surgery due to artefact formation. A small superficial remnant was not identified, and an artefact was misinterpreted as tumor remnant on naviUS. 52

The small number of patients does not allow any conclusions on the superiority of one imaging modality or the other. Larger studies are needed to compare iUS and iMRI. In conclusion, there are no studies comparing the diagnostic value of 2D iUS, naviUS, and 3D iUS for resection control. The small numbers of patients limit the existing studies comparing iUS and iMRI. A prospective study showing the impact of iUS in glioma surgery on patient survival, as has been shown for fluorescence guidance and iMRI, 62,65 is still lacking.

**Approaches to Minimize Artefacts in Resection Controls**

Woydt describes a hyperechoic rim around the resection cavity, which can be tumor, infiltration zone, or normal tissue. It is usually <3 mm in diameter and is probably
caused by artefact formation at the border between saline and tissue.\textsuperscript{55}

One way of minimizing these artefacts could be the development of an ultrasound-coupling gel with similar sound attenuation properties as human brain.\textsuperscript{66}

Safety testing in an animal study has been performed by Jakola et al.\textsuperscript{87}

Another approach is the use of small intracavity probes at the end of resection.\textsuperscript{68} Coburger et al. compared a low frequency (2–7 MHz) 3D probe with a navigated high frequency (7–15 MHz) linear 2D probe. They showed that they could detect more tumor remnants with the linear probe than with the 3D probe. This is not surprising, as one would expect a lower resolution with a low-frequency probe. It might not always be possible to scan every wall of the resection cavity because the linear probe they used is rather large. Therefore, even smaller probes are necessary. Navigating a small intracavity probe seems unnecessary as one is only interested in the very near field that is directly under the probe. Steno et al. also described the use of a small intracavity 3D probe in a case report but do not precise the properties of the probe.\textsuperscript{89} Similar to Coburger et al., Steno et al. reported less artefact formation on postresection scans.

**Ultrasound-guided Biopsies**

Stereotactic biopsies show a high diagnostic yield leading to a diagnosis in 91%–94% of cases. Morbidity and mortality rates have been reported at 0.7%–6.9% and 0.7%–1.3%, respectively.\textsuperscript{70–72} However, the procedure requires special imaging for surgical planning. Real-time imaging through a single burr hole was first achieved by Tsutumi et al.\textsuperscript{73} Other special ultrasound transducers with small footprints had already been developed in the mid 1990s and have been improved since then.\textsuperscript{74,76} For ultrasound-guided biopsies, a diagnostic yield of 91%–98% has been reported in the literature.\textsuperscript{76–79} Permanent morbidity and mortality were 3% and 1%, respectively.\textsuperscript{76} These results are comparable to those of stereotactic biopsies. Moreover, ultrasound guidance is faster and more cost effective as compared with conventional stereotactic procedures. It also allows visualizing potential hemorrhage within the biopsied area during the procedure.\textsuperscript{76}

**Ultrasound-guided Ventricular Catheter Placement**

Although puncture of the ventricular system is one of the most frequently performed procedures in neurosurgery, ventricular catheter revision rates remain as high as 30%–40% at one year. Crowley et al.\textsuperscript{90} showed significantly reduced revision rates in US-guided shunt placements than with blind placements of the shunt in a retrospective study of 211 patients. Overall, revision rates were 21.7% and 29.3%, respectively. Ventricular catheter revisions and acute ventricular catheter revisions occurred in 9.8% and 2.2% of US-guided catheter placements and in 14% and 5.3% of catheter placements without US guidance. Pediatric revision rates were 30.6% with US versus 53.3% without, whereas adult revision rates were 16.1% and 23.3%, respectively.

In another retrospective study of 249 patients, stereotactic neuronavigation or US guidance reduced the rate of proximal shunt failure as compared with freehand catheter passage.\textsuperscript{81} A 3D US burr hole probe was developed and tested in a small number of cases by a Norwegian research group.\textsuperscript{82} A 3D US scan with a navigated burr hole probe was performed, then a navigated catheter was placed under neuronavigation guidance using the 3D US images for image guidance. The procedure was accurate in all cases.

**Epilepsy Surgery**

So far, very few studies exist on intraoperative imaging and neuronavigation in epilepsy surgery. Our group\textsuperscript{83,84} showed that iUS could detect malformations of cortical development. Similar to MR imaging results, lesions that were more pronounced on MRI were visualized more easily on iUS. NaviUS helped to enlarge resection and visualize brain shift. Furthermore, we could show that iUS depicted focal cortical dysplasia (FCD) IIB lesions and periventricular heterotopias clearly, while FCD type I lesions seemed to be more difficult to visualize. Recently, Chan et al. reported on a case of a MRI-negative lesion in focal symptomatic epilepsy that could be detected with intraoperative ShearWave elastography but not with B-mode imaging.\textsuperscript{79}

**Spinal Applications**

The spinal cord consists of a hypoechoic structure with a highly reflective dorsal and ventral surface and a central echo.\textsuperscript{86} As early as 1984, Quencer recommended the use of iUS in spinal surgery performed to resect or biopsy soft-tissue masses of the spinal canal or spinal cord.\textsuperscript{86} Since then, the improvements in image quality have led to more frequent use of iUS in spinal applications. Several authors considered iUS to be helpful during the approach. It has led to additional bony opening in 15%–22% of cases\textsuperscript{87,88} and allowed tailoring the durotomy\textsuperscript{87,88} and myelotomy.\textsuperscript{88} Moreover, iUS helped to distinguish between intra- and extramedullary tumors,\textsuperscript{88} showed the degree of displacement of the spinal cord, and was helpful in differentiating intradural tumor entities during the procedure.\textsuperscript{88} Toktas et al. reported a sensitivity of 92% for detecting tumor remnants.\textsuperscript{87} Figure 4 shows a variety of different pathologies on iUS in spinal surgery.
Future Aspects

Brain Shift Correction and Image Fusion

Deformations of the brain during surgery (brain shift) may be due to loss of cerebrospinal fluid, swelling, or retraction. These local deformations may reach more than 2 cm depending on the size, location, and type of tumor. Moreover, Hastreiter et al. showed that deformities of the brain surface and deeper brain structures are uncorrelated. Correct co-registration of preoperative MRI and iUS images or datasets is not always possible due to ongoing brain shift, and rigid co-registration accuracy will deteriorate with ongoing resection. Intraoperative imaging such as iUS can detect local brain shift. A true image fusion with preoperative images, however, depends on nonrigid image registration. In the last couple of years, a variety of different methods have been developed for image registration and modeling of brain shift. Regional deformities were displayed by detecting corresponding anatomical landmarks in different imaging modalities. Other methods included intensity-based nonrigid registration methods using similarity measures with or without additional contextual information. However, further studies are needed to make nonrigid registration methods faster and more robust. True image fusion using nonrigid registration methods of preoperative imaging data and iUS could be an interesting method for using information of both imaging modalities, including updated anatomical information, intraoperatively in the near future.

Intraoperative Ultrasound as a Therapeutic Tool

Ultrasound is evolving from a purely diagnostic tool to a promising therapeutic tool. Human and animal trials on thermal ablation or cavitation by focused ultrasound have shown that this might be a new noninvasive treatment option for movement disorders and hydrocephalus. Hematomas and ischemia could be treated by sonothrombolysis. Moreover, the blood-brain barrier could be disrupted to deliver nanoparticles or immune cells to tumor margins. Nano-scaled ultrasound contrast agents are currently being developed to incorporate drugs.

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References


Cell Phones and Glioma Risk: An Update

Milan Makale and Santosh Kesari

Translational Neuro-Oncology Laboratories, Moores Cancer Center, University of California San Diego, La Jolla, California (M.M., S.K.); Department of Neurosciences and Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, California (S.K.)

Corresponding authors:
Santosh Kesari, MD, PhD,
Chair, Department of Translational Neuro-Oncology and Neurotherapeutics,
Professor of Neurosciences,
John Wayne Cancer Institute,
2200 Santa Monica Blvd.,
Santa Monica, CA 90404
(Kesaris@jwci.org)

Milan Makale, PhD, MSEE,
Moores Cancer Center,
University of California San Diego,
3855 Health Sciences Drive,
MC#0819, La Jolla, CA 92093-0819
(mmakale@ucsd.edu).
The worldwide presence of cell phones has increased dramatically with an estimated 6 billion users at the end of 2011 and rapid growth in cell phone call frequency and duration. This imposing scenario has inevitably reignited questions about the possible health risks of cell phone radiofrequency electromagnetic radiation (RF-EMF). The primary health concern is that long-term RF-EMF exposure to the head may play a causal role in the development of brain tumors, a concern that is underscored by the rapidly growing use of cell phones by teens and children who typically are more susceptible to harmful carcinogens. Because of smaller cranial size and greater tissue water content, children and teens absorb more RF-EMF energy in key brain areas than do adults. This difference in absorption can be >1 order of magnitude, and up to 80% of teens aged ≥12 years sleep with a cell phone next to their head, often under the pillow. In view of rapidly expanding cell phone use by children and adolescents, some investigators contend that the potential public health problem is at a nascent stage and is analogous to the effects of other carcinogens with major societal impact such as tobacco, benzene, asbestos, and ionizing radiation that take decades to result in an increased incidence of tumor diagnosis. Considering the immense number of cell phone users, and the substantial clinical burden of brain cancer, even small elevations of risk could drive the future public health problem to significant proportions.

The question of whether cell phone use and brain cancer incidence are linked remains unresolved largely because the epidemiological studies have methodological limitations and have generated conflicting results and competing interpretations. Limitations include selection bias, recall issues, and the increasing paucity of subjects not exposed to cell phone RF-EMF. Brain tumors are relatively infrequent and may take decades to develop, so small changes in incidence are difficult to resolve. The reliance of long-term studies on subject recall, which is often inaccurate, may lead to bias. Moreover, younger age groups are now using cell phones, and individual usage intensity has risen dramatically such that even relatively recent studies may no longer mirror these developments. Incorporating a truly nonexposed cohort in future population studies may be challenging because cell phone penetration is now virtually 100% in many societies.

Despite shortcomings in the available evidence relating mobile phones and brain cancer risk, in May 2011 a working group of about 30 invited scientists from 15 different countries, under the aegis of the International Agency for Research on Cancer (IARC) of the World Health Organization, elected to characterize exposure to RF-EMF associated with mobile phone use as a Group 2B agent (i.e., possibly carcinogenic to humans). There are authors who go further and suggest that this is insufficient and that cell phone RF-EMF should be listed under Group 2A agents, which are probable carcinogens. A key deficiency is that neither recommendation concerning cell phone RF-EMF
Carcinogenic potential is unambiguously supported by in vitro or animal studies quantifying mobile phone RF-EMF exposure and endpoints based on genetic damage and tumorigenesis.\textsuperscript{4,15,19}

The salient scientific observations and obstacles influencing the determination of whether a link exists between cell phone use and brain cancer are summarized in Fig. 1. For the present review, a key premise is that population-based studies are limited by data reliability, study time frame, and paucity of control subjects not exposed to cell phone RF-EMF. Consequently, our approach here is focused around the perspective that cell-based and animal studies may assume added importance in terms of illuminating the potential of cell phone use to elicit brain tumors. Accordingly, a synopsis of in vitro and animal cell phone RF-EMF studies is provided, and in this context we suggest potential research strategies that could contribute to a more focused understanding of cell phones and brain cancer.

## Malignant Gliomas

**Overview** - Brain tumors are generally regarded as among the most difficult cancers to treat, and patient outcome in certain types of brain tumors is dismal despite costly and intensive therapy.\textsuperscript{20–22} Primary cancers of the central nervous system account for <2% of all new cases of cancer reported in the United States each year. The majority of these cancers are malignant gliomas, and high rates of mortality convert these cancers into a leading cause of cancer-related death among economically active age groups; malignant gliomas are the third-leading cause of cancer-related death in men aged 15–54 years and the

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**Figure 1.** The chart describes (1) the salient issues preventing the general acceptance of human studies purporting a linkage between cell phone usage and glioma risk, and (2) the inadequacies of preclinical models investigating whether there is a plausible mechanism for RF-EMF mediated DNA effects and incidence of brain tumors. Current cell based and animal data, and their limitations, relating cell phone RF-EMF exposure and glioma formation are depicted on the right side of the figure (light brown tabs).
forthcoming leading cause of cancer-related death for women aged 15–34 years.23 The primary focus of this review is the gliomas as they are the most common and the most dangerous malignant brain tumors, but other types of head tumors have been investigated in the context of cell phone use including vestibular schwannomas (acoustic neuroma), meningiomas (of which >80% are benign), and parotid gland tumors.24–30

**Causes and Incidence** - Unfortunately, the potential role of RF-EMF exposure in malignant gliomas is made more complex by the fact that little is known about how these tumors develop, although well-substantiated risk factors are exposure to ionizing radiation and rare genetic syndromes.12,21 Possible risk factors include head trauma, environmental toxins, and viral infections.32–37 There are >100 histological subtypes of brain cancers, and gliomas of astrocytic, oligodendrogial, and ependymal origin account for >70% of all these tumors.31,38,39 Data from the Central Brain Tumor Registry of the United States (CBTRUS) suggest a peak incidence of all primary brain tumors around age 50 years, although autopsy data indicate that incidence rises continuously with age and is highest in those aged 75–84 years.31,40 The 2007–2011 US annual incidence rate for primary brain and nervous system tumors in adults aged ≥20 years is 27.9 per 100 000 persons.41 Approximately one-third of tumors are malignant, and the rest are benign or borderline malignant, a certain percentage of which can progress to frank malignancy over time.41,42

**Glioblastoma Multiforme** - Grade IV gliomas constitute the most common and deadly brain malignancy in adults and are collectively referred to as glioblastoma multiforme (GBM). GBM is derived from transformed glial cells and rarely occurs before the age of 15 years but increases dramatically after the age of 45 years.35,43 Survival is dismal, with <5% of patients alive at 5 years and most patients dead within 2 years after diagnosis. It is concerning that a recent news release, based on the high-quality Danish Cancer Registry, stated that there has been an almost 2-fold increase in GBM over the past 10 years.44

**Pediatric Gliomas** - The incidence rate of primary brain tumors in children and adolescents (aged 0–9 years) is much lower (5.42 per 100 000) than in adults, although some tumors are the most common solid tumor in children.45 Moreover, a higher percentage of primary brain cancers are malignant in children compared with adults (65% vs 33%), and these tumors are the second-leading cause of childhood cancer death.40–42 Low-grade glial cell tumors, termed grade I and II glioma, are relatively common in children, and notably treatment-resistant variants include the pediatric brainstem gliomas that carry a dismal prognosis, with <10% of patients alive at 2 years after diagnosis.46–47 Low-grade gliomas can be difficult to manage, with poor long-term survival, and a significant proportion of patients progress to the more aggressive high-grade gliomas.48–50 Primary high-grade gliomas (grade IV - GBM) are relatively uncommon in children. Nonetheless 5-year survival is poor, even though children fare better than adults, and GBM contributes materially to childhood cancer death rates.45,51

**Epidemiological Studies Addressing Cell Phones and Brain Cancer**

**Meta-Analyses Supporting a Link Between Cell Phones and Brain Cancer** - Myung et al. (2009) performed a cross-sectional analysis on 22 relevant case-control cell phone risk studies to compare the results and derive an overall estimation of the risk of brain tumors from cell phone use.51 When the results were analyzed in greater detail, the pooled data from 8 studies showed a positive association between cell phones and brain tumors, 7 of which were from the Hardell group studies. These studies were considered by Myung et al. to have higher methodological quality because they used interviewer blinding as to whether the participant was a case or control.51 Fifteen other studies found an overall negative association between cell phone use and tumors. Nine of these studies were Interphone-related studies, which were criticized for lack of case versus control blinding.52 The authors determined that overall, there was a slight increase in the risk of brain tumors for regular cell phone users and that this risk is most pronounced for an induction period of ≥10 years.51 Khurana et al. (2009) analyzed data from multiple publications and concluded that the available evidence supports an association between cell phone use and brain tumor risk, especially for use periods of ≥10 years.53 The Khurana review took into consideration in vivo and in vitro studies as well as evolving evidence.54 Kundi (2009) conducted meta-analyses of the available literature and concluded that the overall evidence aligned with an increased risk for glioma and acoustic neuroma, but its magnitude could not be assessed because of insufficient information on long-term use.19

**Case-control Studies of Brain Cancer and Mobile Phone Use** - In this overview, the only studies reported had at least part of the recruitment period in the years after 2000 because earlier studies are uninformative due to the time periods of mobile phone use being too short (as has been pointed out by IARC).17 The 2 most comprehensive and intensively scrutinized databases concerning cell phone use and brain cancer risk are the often-cited studies of the Hardell group in Sweden and the multicenter Interphone studies coordinated by IARC.5,12,18,53,54 These 2 initiatives represent the largest-scale studies performed to date and collectively involved thousands of patients and controls over the period 1997–2009.55 Sweden was one of the first countries in the world to embrace mobile phones. In the early 1980s,
analog phones were available. Since then, several generations of wireless phone technology have been introduced in Sweden, where cell phones are used more than landline phones. Analog wireless phone use is associated with a 2-fold increased risk of brain cancer. The relatively large CERENAT study in France also identified a similarly increased risk in long-term heavy users of cell phones. Some analysts argue that these variously reported risk increases are modest at best, while others in fact view them as underestimates because delays in cancer registration of glioma cases could have caused recent incidence rates to underestimate the true rates.

Interpretations of the Hardell and Interphone studies vary. For example, Repacholi et al. (2012), Swerdlow et al. (2011), and Kundt et al. (2009) all conducted reviews of the available literature including the Hardell and Interphone studies. Both Repacholi and Swerdlow concluded there is no evidence for an association between cell phone use and brain cancer, and that there are insufficient data to make any determinations about long-term use (≥10 years), while Kundt concluded that the overall evidence aligned with an increased risk, but its magnitude could not be assessed because of insufficient information on long-term use.

**Hardell** - The Hardell studies include brain tumor patients diagnosed 1997–2003, and later Hardell studies included patients diagnosed 2007–2009. Hardell published a key paper in 2013 that incorporated data reported after the IARC determinations of cell phone risk, along with methodological changes stemming from external criticisms and a meta-analysis of Hardell's own recent research on > 1300 brain cancer patients as well as data from the Interphone study. The goal of the most recent study was to determine whether a link existed between long-term (>10 years) use of wireless phones and incidence of brain cancer. The authors pursued a case-control study of brain tumor patients aged 18–75 years who were diagnosed between 2007 and 2009. Each case was matched to one control. The authors concluded that the results confirmed an association between mobile phones and malignant brain tumors. Also noteworthy is the fact that the highest risk values are obtained in Hardell studies, in which the exposures began when the subjects were teenagers. Hardell et al. further claimed that the data revealed that GBM patients who began mobile phone use at younger ages had an elevated risk of shortened survival and that this points to a possible tumor-promotion effect of cell phone RF-EMF. In their publications, however, the authors do not cite definitive in vitro or in vivo data addressing mechanism(s) of genetic damage or malignant transformation caused by RF-EMF exposure. They do refer to a study by Liu et al. (2014) in which DNA-based damage in spermatozoa was caused by RF-EMF exposure. Other groups have reported RF-EMF-induced genetic damage in male sperm, but spermatozyte lines do not have DNA-repair enzymes and are subject to several causes of genetic instability that are hard to control, thus making interpretation problematic.

**Interphone** - The Interphone study was scientifically coordinated by IARC and funded by the European Union’s Fifth Framework Program, the Union for International Cancer Control (UICC), and by various additional sources in the participating countries. Interphone is an impressively large effort including 2765 glioma patients diagnosed between 2000 and 2004 with 7658 controls, and 614 glioma patients who used cell phones for 5–9 years and 252 patients who used cell phones for >10 years. Various groups have interpreted the results of the Interphone study differently; some have taken them to suggest that mobile phones cause tumors, while others contend that methodological limitations prevent a clear resolution. An Interphone study by Lakshol et al., which encompassed data from 5 northern European countries, found that nonregular cell phone users were 32% more likely to develop gliomas than subjects who used cell phones for 1–10 years (OR = 0.76 [95% CI]). When this association was further analyzed, a significant protective effect emerged for digital cell phones— but not for analog cell phones. Pooled analysis for other Interphone studies showed that cell phone usage for 1–114.9 hours, with a latency period (duration) of 1–4 years, was less likely to develop gliomas compared with nonregular users. Moreover, those subjects who used cell phones for 115–1639.9 hours for a latency period of 5–9 years were less likely to develop gliomas compared with subjects who...
used cell phones on an inconsistent basis.\textsuperscript{68} However, Vrijheid (2009) suggested that there is empirical evidence that the reduced risks were at least partly due to nonresponse bias. Patients and controls who initially declined to participate, but agreed to complete a short nonresponse questionnaire, had lower frequencies of regular mobile phone use than did those who participated fully.\textsuperscript{69}

The Interphone authors reported that a statistically significant increased risk for glioma was seen with 2–4 years of cell phone use, with 1–1.9 years used as reference category (OR = 1.68; 95\% CI = 1.16–2.41).\textsuperscript{18} The highest OR was found in the 10+ years category for regular use (OR = 2.18; 95\% CI = 1.43–3.31). Overall, cumulative use >1640 hours in the shortest latency group of 1–4 years resulted in an increased risk (OR = 3.77; 95\% CI = 1.25–11.4). The finding that this group had an OR of 3.77, which exceeded that of the ≥10 year group, is unexpected if the duration of cell phone use is associated with greater brain tumor risk.\textsuperscript{18} The Interphone study did not include subjects who were mobile phone users before 20 years of age and did not factor in exposure to other sources of RF-EMF.\textsuperscript{66}

Joseph et al. (2010) found that mobile phone use accounted for one-third of total exposures to RF-EMF, while the balance was generated by routers and base stations.\textsuperscript{70} Repacholi et al. (2012) conducted meta-analyses of the available literature including the Hardell and Interphone studies\textsuperscript{66}, and essentially rejected the conclusions of these two studies and stated that there is no evidence for an association between cell phone use and brain cancers. Moreover Repacholi et al indicated that Hardell and Interphone contained insufficient data to make any determinations about longer-term use (≥10 years).\textsuperscript{66}

**CERENAT** - The CERENAT study reported by Coureau et al. (2014) is a multicenter case-control study carried out in 4 areas in France in 2004–2006 that reported on 253 gliomas, 192 meningiomas, and 892 controls.\textsuperscript{1} Data about mobile phone use were collected through a detailed interview. Conditional logistic regression for matched sets was used to estimate adjusted odds ratios\textsuperscript{71} and 95\% confidence intervals. No association between cell phone use and brain tumors was observed when comparing mobile phone users with nonusers.\textsuperscript{1} However, there was a statistically significant link for the heaviest users when life-long cumulative duration was factored in (≥896 hours; OR = 2.89, 95\% CI:1.41–5.93 for gliomas; OR = 2.57, 95\% CI: 1.02–6.44 for meningiomas) and number of calls for gliomas (≥18 360 calls, OR = 2.10, 95\% CI:1.03–4.31). Risks were higher for gliomas, temporal tumors, and for subjects engaged in occupational and urban mobile phone use.\textsuperscript{1}

**Studies Reporting no Significant Effect of Cell Phones on the Incidence of Brain Cancer** - Ahlborn et al. (2009) reviewing the field stated that the available evidence does not suggest an association between cell phone use and brain cancer within approximately 10 years of use.\textsuperscript{70,30,72}

Data from the Nordic countries for 1974–2003 (Deltour et al., 2009) and the pediatric Nordic population for 1985–2006 (Schmidt et al., 2011) and from Switzerland for 1969–2002 (Roosli et al., 2007), England for 1998–2007 (de Vocht et al., 2011), and the United States for 1992–2006 (Inskip et al., 2010) and for 1987–2007 (Kohler et al., 2011) did not reveal any increases in brain tumor incidence with the use of mobile phones up to 20 years after their introduction and 10 years after their use became widespread.\textsuperscript{41,73–77} However most of these studies were based on low numbers and may be of questionable use in assessing the relationship between cell phone use and glioma risk.

Aydin et al. (2011) performed a case-control study (CEFALO) and analyzed data for all children and adolescents aged 7–19 years who were diagnosed with a brain tumor between 2004 and 2008 in Denmark, Norway, Switzerland, and Sweden.\textsuperscript{4} Overall mobile phone use was associated with an increased OR of 1.36 that was not statistically significant. Subjects with a self-reported onset of mobile phone use >5 years before diagnosis were not at increased risk compared with those who had never used mobile phones regularly. There was no statistically significant relationship to the reported amount of use; however, in a subset of 56\% of participants for whom operator-recorded data were available, a statistically significant increase in brain tumor risk was seen with the length of time subjects had acquired a mobile phone subscription.\textsuperscript{4} A significantly increased risk was developed after ≥2 years of subscription. This is considerably shorter than the >10 years observed in studies including adults only.\textsuperscript{1,12,68}

Recently, Barchana et al. (2013) analyzed data from the Israeli National Cancer Registry (1980–2009) for 5,300 brain tumor cases and related this to cell phone usage rates for Israel which the authors characterize as a ‘semi-ecological’ or population based approach.\textsuperscript{15} They reported that high-grade glioma incidence increased significantly from 1980–2009, but a lower, non-significant, rate of increase was observed in males and a lower one (significant) in females in the period after cell phones were introduced, 1994–2009. They also claim that a change in tumor laterality occurred the time period over which cell phones went into widespread use. Based on their data the authors concluded that the assumption that mobile phone use is a causative factor for brain gliomas was not supported. Hsu et al. (2013) analyzed the incidence of brain neoplasms in 23 million cell phone users in Taiwan over the period 2000 to 2009.\textsuperscript{78} The overall conclusion was that ten years of observational data showed no significant connection between intensive cell phone use and the incidence rate or mortality of malignant brain tumors in Taiwan. There are concerns with this paper however, for example the abstract indicates that there were only 4 deaths due to malignancies out of 23 million users during the period 2000–2009. When reviewing these data, it must be noted that many of the aforementioned studies were conducted when cell phone penetration was much lower in the pediatric population than it is now, and cell phone use on an individual basis was below the levels that have emerged over the past 10 years.\textsuperscript{1} This is significant because, for
most known carcinogens, decades elapse between exposure and the clearly identifiable appearance of solid tumors. This very long latency period was the case with the atomic bombs that were dropped on Hiroshima and Nagasaki in August 1945. Increased risk of solid tumors was reported in survivors only in the 1960s, and elevated risk of brain tumors was only evident 50 years later.

Cell-based and in Vivo Studies on the Genetic and Tumorigenic Effects of Exposure to Mobile Phone Levels of RF-EMF

Tissue-heating Effects - An important limitation in the understanding of human epidemiological data related to cell phone RF-EMF is that there is no mechanism that has been unambiguously shown to be linked to how cell phone emissions could trigger the development of cancer. RF-EMF can raise tissue temperature, and elevated temperature can induce DNA synthesis in cultured cells and play a role in carcinogenesis. By law in the United States, cell phones are restricted to a specific absorption rate (SAR) at or below 1.6 W/kg over 1 gram of tissue, and the European Union limits SAR to 2 W/kg in 10 g of tissue. This level of RF-EMF exposure can cause mild heating. The maximum temperature rise in the human brain attributable to exposure to RF-EMF from cellular phones was calculated in 1999 by Van Leeuwen et al. to be 0.1°C. Christ et al. (2007) modeled tissues in humans exposed to cell phone levels of RF-EMF and reported that temperature might rise as much as 3.5°C at depths of ~15 mm assuming the worst case scenario with no physiological cooling effects, (i.e. blood circulation). Inner organs at greater depths were predicted to experience a maximum rise of only 0.7°C. It is not clear how the predictions of Christ et al. would translate to the skull and brain since these authors did not model RF-EMF exposure and temperature for the head. Another key question is whether increases in brain temperature would lead to inflammation and/or other changes that could promote tumorigenesis over long periods of time. Cell phones deposit energy mainly in the outermost layers of the brain, and Huber et al. (2008) reported that 900 MHz EMF applied via cellular phones to the heads of human volunteers significantly increased cerebral blood flow in the ipsilateral (same) side of the brain, indicating a biological effect of RF-EMF. A study by Volkow et al. (2011) revealed clear evidence of increased glucose metabolism on the side of the brain exposed to 50 minutes of cell phone RF-EMF. While the data provided by the Huber and Volkov groups suggest that exposure of brain regions to cell phone RF-EMF can elicit a local biological response, the clinical significance of such effects over the long term (≥10–15 years) is not known.

DNA Mutations in Glioblastoma - DNA is a key target in carcinogenesis because of its critical and driving role in overall cellular function, proliferation, viability, mutation, and cancer. In human primary GBM (grade IV gliomas), several DNA mutations are present including the gene for phosphatase and tensin homolog (PTEN), phosphoinositide-3'-kinase (PI3K), and plekstrin-homology-domain serine- and threonine kinase (Akt). The signaling pathway represented by these molecules harbors mutations in up to 70% of GBMs. PTEN is a tumor suppressor and is mutated in > 40% of GBM, and ~15% of GBMs exhibit gain of function mutations of PI3K (Class Iα subunit; PIK3CA). The p53 tumor suppressor gene is mutated in 35%–65% of GBMs, while retinoblastoma gene mutations have been found in up to 25% of high-grade astrocytomas, and the INK4A gene is deleted in the majority of GBMs. Collectively, these findings clearly show that DNA alterations in a variety of critical genes play an important role in the genesis of GBM.

DNA Damage in General Associated with Cell Phone RF-EMF - The literature in terms of RF-EMF exposure and effects on DNA is contradictory, and Phillips et al. (2009) noted that cell phone emissions are complex, variable, and difficult to compare between studies. They referenced their own studies, which indicated that different cell phone signals can cause variable and opposite effects on DNA. Cell phone RF-EMF levels are classified as belonging in the low range of potential energy levels and are too low to cause DNA damage directly. One possible mechanism of RF-EMF-induced DNA damage is the enhancement of free radical (ROS) formation within cells via a metabolic cascade that partly depends on intracellular iron levels. Brain cells may have enhanced free radical formation because they contain relatively high levels of iron, and they may be susceptible to genotoxic effects because they are slow to repair DNA. Yakymenko et al. (2014) in their analysis found that 76 of 80 peer-reviewed papers (92.5%) reported the detection of significant RF-EMF-related cellular oxidative stress including overproduction of ROS, lipid peroxidation/increased concentrations of malondialdehyde, protein peroxidation, increased concentrations of nitric oxide, and changes in the activity of antioxidant enzymes. Phillips et al. found that exposure of Molt-4 human lymphoblastoid cells to 2.4–24 W/Kg for 2–21 hours was able to cause DNA damage detectable by the comet assay under some conditions. The authors further reported that differences in RF-EMF frequency, modulation, and exposure time led to variable effects on cell DNA. However, the results of that report were contradicted by Hook et al. (2004), who found no statistically significant difference in the level of DNA damage or apoptosis between sham-treated Molt4 cells and cells exposed to RF radiation at any frequency, modulation, or exposure time.

Lagroye et al. found no significant change in DNA strand breaks, protein–DNA crosslinks, and DNA–DNA crosslinks in RF-EMF-exposed mouse mesenchymal (C3H 10T1/2)
In Vitro/Vivo Studies of RF-EMF Triggered Brain Cell DNA Damage and Tumorigenesis

DNA Damage - Table 1 summarizes in vitro and in vivo exposure data of brain cells in the context of the salient publications described in the present review. Sarkar et al. (1994) conducted a whole animal RF-EMF exposure study in mice and found that the observed increased tumor incidence and increased tumor frequency of lymphoma was largely responsive to RF-EMF exposure.) Takahashi et al. (2002) explored whether RF-EMF caused DNA damage in mouse brain glial cells when mice were head-exposed to a 1.5 GHz TDMA (mobile telephone time division multiple access pulsing pattern) signal with a SAR of 2.0 W/kg for 90 minutes per day, 5 days per week for 2 or 4 weeks. Deletion mutations were slightly increased in both the 2- and 4-week exposure groups compared with sham controls, but the differences were not statistically significant. A significant point articulated by Takahashi et al. is that their study encompassed 4 weeks while cellular phones are often used for much longer periods. The scientific rationale for their experimental design was to determine whether RF-EMF could physiologically elicit potential tumor-initiating mutations in mouse brain DNA. In order to further support their study design, Takahashi et al. cited a report concluding that a sampling time of 4 weeks is adequate for detecting genotoxic effects in slow/nonproliferating tissues such as brain. Increased single- and double-strand DNA breaks were reported by Lai et al. in several publications using rat brain cells exposed to RF-EMF between 0.6 and 1.2 W/kg for 2 hours. Importantly, this effect was abolished by antioxidants, suggesting a free radical mechanism of DNA damage. However, Malyapa et al. (1998) exposed Sprague-Dawley rats to 1.2 W/kg RF-EMF and found no evidence of DNA damage via the comet assay but with a different protocol. Verschaeve et al. (2006) exposed female rats to RF-EMF and the drinking water carcinogen 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) for 2 years. The RF-EMF was applied 2 hours per day for 2 or 4 weeks. The alkaline comet assay failed to disclose any enhanced genotoxic effects of RF-EMF exposure in brain and other tissues.

Tumorigenesis

Lymphoma - The first in vivo studies of RF-EMF exposure on tumor incidence reported an increased frequency of lymphomas. Repacholi et al. (1997) indicated that lymphoma incidence was increased 2-fold after whole-body 900 MHz EMF far-field exposure in E-Pim1 transgenic mice for 30 minutes twice a day for 18 months. The authors observed that follicular lymphomas were largely responsible for the increased tumor incidence and concluded that long-term RF-EMF exposure may increase the probability of lymphoma in mice bearing a lymphomagenic oncogene.
They further suggested that, in general, cancer risk with RF-EMF exposure should be assessed using genetically cancer-prone mice as a model system. However Utteridge et al. (2002) in a very comprehensive approach attempted to precisely reproduce the Repacholi study and address its methodological shortcomings (e.g. using several dosage levels rather than one and taking steps to minimize variation in RF-EMF dose.) Utteridge et al. found no increase in lymphoma incidence in E-Pim1 mice exposed to RF-EMF. Oberto et al. (2007) also failed to uncover any increase in lymphoma associated with RF-EMF in E-Pim1 mice, while Sommer et al. (2004) observed no increase in lymphoma after RF-EMF exposing AKR/J mice. Lee et al. (2011) exposed 6 week-old AKR/J mice to RF-EMF at a total SAR of 4 W/kg for 45 minutes per day, 5 days per week over 42 weeks. There was no increase in lymphoma detected between the exposed mice and sham controls.

**Brain** - Adey et al. (2000) performed a detailed study exposing Fisher F344 rats to analog RF-EMF with a brain SAR of 1–1.2 W/kg for 2 hours per day, 4 days per week for 2 years. A cohort of rats in addition to RF-EMF exposure also received the neurocarcinogen ethylnitrosourea (ENU) in utero, which alone would be expected to yield a lifetime increase in CNS neoplasms of 10%–15%. No FM field-mediated changes were observed in the number, incidence, or histological type of either spontaneous or ENU-induced brain tumors. Interestingly the authors’ earlier study (Adey et al. 1999) used standard digital phone fields pulsed on and off, in which RF-EMF appeared to reduce the incidence of both spontaneous and ENU-induced CNS tumors Shirai et al. (2007) administered ENU to Fisher F-344 rats on gestational day 18 and subsequently exposed them to 2 W/kg of RF-EMF starting from 5 weeks of age, 90 minutes per day, 5 days per week for 104 weeks and found no increase in CNS tumors with RF-EMF. Juutilainen et al. (2011) published a comprehensive review of 44 animal studies on carcinogenicity of RF electromagnetic fields for various tissues and organs including the brain. They concluded that the reported studies were consistent overall and showed no RF-EMF carcinogenic effects at cell phone levels of exposure.

### Table 1. Effects of radiofrequency electromagnetic radiation on preclinical brain models

<table>
<thead>
<tr>
<th>Study</th>
<th>Cell type</th>
<th>Animal Model</th>
<th>Exposure W/kg</th>
<th>Timing/Duration</th>
<th>RF-EMF Effects – Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakurai et al. (2011)</td>
<td>Normal human glial</td>
<td>–</td>
<td>10 W/kg</td>
<td>24 h</td>
<td>No change in gene expression</td>
</tr>
<tr>
<td>Lai and Singh (1996)</td>
<td>Rat brain</td>
<td>–</td>
<td>1.2 W/kg</td>
<td>2 h</td>
<td>Double/ single DNA strand breaks in brain</td>
</tr>
<tr>
<td>Sarkar et al. (1994)</td>
<td>Mouse: Swiss Albino</td>
<td>–</td>
<td>1.18 W/kg</td>
<td>2 h/d</td>
<td>DNA disrupted in brain and testes</td>
</tr>
<tr>
<td>Takahashi et al. (2002)</td>
<td>Mouse: Big Blue (BBM)</td>
<td>–</td>
<td>2 W/kg</td>
<td>90 min/d, 5 d/wk</td>
<td>DNA deletions but not statistically significant</td>
</tr>
<tr>
<td>Malyapa et al. (1998)</td>
<td>Rat: Sprague Dawley</td>
<td>–</td>
<td>1.2 W/kg</td>
<td>2 h</td>
<td>No brain DNA damage</td>
</tr>
<tr>
<td>Verschaeve et al. (2006)</td>
<td>Rat: Wistar</td>
<td>–</td>
<td>0.9 W/kg &amp; carcinogen(^b) drinking water</td>
<td>2 h/d, 5 d/wk</td>
<td>No genotoxic effects seen</td>
</tr>
<tr>
<td>Adey et al. (1999)</td>
<td>Rat: F344</td>
<td>–</td>
<td>1.2 W/kg &amp; ENU(^a) in utero</td>
<td>2 h/d, 4 d/wk</td>
<td>Brain tumor frequency reduced</td>
</tr>
<tr>
<td>Adey et al. (2000)</td>
<td>Rat: F344</td>
<td>–</td>
<td>1.2 W/kg &amp; ENU(^a) in utero</td>
<td>2 h/d, 4 d/wk</td>
<td>No increased frequency of brain tumors</td>
</tr>
<tr>
<td>Shirai et al. (2007)</td>
<td>Rat: F344</td>
<td>–</td>
<td>2 W/kg &amp; ENU(^a) in utero</td>
<td>90 min/d, 5 d/wk</td>
<td>No increased frequency of brain tumors</td>
</tr>
</tbody>
</table>

**Abbreviations:** d, day; h, hour; RF-EMF, radiofrequency electromagnetic radiation; wk, week.

\(^a\)ENU = ethylnitrosourea (carcinogen).

\(^b\)carcinogen 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) at 19 microg/mL.

### Summary and Conclusions

Human studies on the association between cell phones and brain cancer risk are constrained by unavoidable methodological limitations. In addition, a mechanism for
cell phone RF-EMF-induced cellular damage has not been identified, and the question of how environmental and genetic factors may conspire to instigate an increase in the incidence of brain tumors is not understood. Hence, it is not feasible to identify and account for those individuals who might be inherently more susceptible to possible tumorigenic effects of cell phone RF-EMF. Nonetheless, concern about cell phone use in the pediatric population has motivated recent large-scale studies such as MOBIKIDS to assess the potential link between the risk of brain tumors and environmental risk factors, including use of communication devices in subjects aged 10–24 years. MOBIKIDS involves 1000 brain tumor patients and 2000 controls and is currently ongoing in 14 countries.\textsuperscript{18}

Given the difficulties associated with human population analyses and in order to provide a plausible mechanistic basis for cell phone RF-EMF exposure and brain cancer, cell-based and animal studies have been pursued. Contradictory information for all types of studies has been generated by a multitude of reports that differ widely in terms of the type of RF-EMF used, the conditions of exposure (e.g. controlling for background EMF fields), and the overall level of scientific rigor. Despite the lack of a demonstrated RF-EMF–based mechanism for genetic damage, we suggest that long-term experiments combining conditions simultaneously are warranted. A potential experimental framework may include (i) brain cell lines and mice genetically prone to brain tumors such as p53 deficient-INKARF modified cells, (ii) exposure of sub-cohorts of genetically cancer-prone cells and animals to neurocarcinogens, and (iii) exposure of genetically vulnerable cells and animals to cell phone levels of RF-EMF both with and without known carcinogens. In this general context, an interesting epidemiological study conducted by Navas-Acien et al. in Sweden indicated that persons with long-term exposure to solvents, lead, and pesticides/herbicides only exhibited increased glioma incidence when they were also exposed to moderate or high levels of low-frequency magnetic fields.\textsuperscript{19}

Experimental studies of RF-EMF should be performed on genetically vulnerable models to more faithfully emulate what may be occurring in human populations. Moreover, genetic profiling, RNA microarray studies, and protein expression arrays of transformation-prone cells upon exposure to RF-EMF may identify alterations in specific signaling pathways and genes governing cell behavior. Such data could help in narrowing the focus on possible key cellular targets of RF-EMF and set the stage for more precisely defined mechanistic studies.

Notwithstanding epidemiological study limitations and conflicting data that have been published, both the Hardell and Interphone studies as well as the French CERENAT study, which represent large human population-based investigations, are in agreement that there is an increased incidence of brain tumors with long-term extensive cell phone use. Given these apparent results combined with the fact that the human studies do have qualifying weaknesses, it may be premature at the present stage to abandon further explorations and deliberations addressing brain tumor risk associated with extensive exposure to cell phone RF-EMF. A missing yet essential validation is a definitive demonstration in cell and animal models of a cell phone RF-EMF based mechanism that can cause genotoxic damage and enhance tumorigenesis.

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Interview with Prof. Dr. Michael Kundi, Professor of Environmental Health at the Medical University of Vienna and member of the task force of the World Health Organization on the research agenda for high-frequency electromagnetic fields (EMF). The interview was conducted by a.o. Prof. Dr. Christine Marosi, Deputy Director of the Division of Oncology, Department of Medicine I, at the University Hospital in Vienna.

Prof. Marosi: Prof. Kundi, the International Agency for Research on Cancer (IARC) has classified EMF as possibly related to cancer development, and you have stated that there is a potential risk but that this risk cannot yet be quantified. What is your opinion now?

Prof. Kundi: Never before has a technological device emitting microwaves reached comparable universal prevalence as mobile phone use has in the last decades. There was virtually no exposure in 1990, and in 2010 more than 5 billion persons worldwide were using cell phones daily. There has been debate since the 1930s that tissue heating may not be the only relevant effect considering the safety of high frequency EMF; but data on exposure have been scarce, and previous sources of EMF were not used at such close distance to the body and for comparable long time periods. The exponential growth of cell phone use came as a surprise to industry and to scientists involved in EMF risk assessment, when other EMF sources such as broadcasting were outdated phones (see table). I would also recommend choosing a phone with a specific absorption rate (SAR) value as low as possible, especially for children, and to remember that the level of exposure to EMF decreases by the square of the distance from the antenna.

Prof. Kundi: I agree that the evidence from animal experiments and in vitro studies is still weak. There are main 2 mechanisms discussed about how EMF can cause DNA damage.

The first hypothesis states that EMF from technical devices is usually polarized and may modify the functionality of calcium channels in the cell membrane, thus modifying selective cell membrane permeability, which thereby influences intracellular signaling and results in DNA damage. The second hypothesis involves NADH oxidase at the cell membrane that is modified and leads to increased formation of reactive oxygen species, which activates a matrix metalloproteinase that results in DNA damage. The third hypothesis involves NADH oxidase at the cell membrane that is modified and leads to increased formation of reactive oxygen species, which activates a matrix metalloproteinase that results in DNA damage.

Prof. Marosi: How can non-ionizing radiation cause DNA damage? Isn't the laboratory evidence for the association of cell phones and tumor development very weak?

Prof. Kundi: I agree that the evidence from animal experiments and in vitro studies is still weak. There are mainly 2 mechanisms discussed about how EMF can cause DNA damage.

An intriguing fact is that more and more animal experiments show tumor induction with EMF acting as a co-carcinogen at low levels, which are absolutely comparable with human exposure. I want to cite the experiment done by Prof. Alexander Lerchl. Lerchl in the womb of a known chemical carcinogen developed significantly more tumors when they were also exposed to cell phone signals (UMTS) at low levels. This experiment was designed to repeat (and contest) previous findings from Tillmann et al—and the results are even more decisive. These findings will be discussed extensively at the next bioelectromagnetics meetings.

Prof. Marosi: What kind of recommendations would you give for cell phone use?

Prof. Kundi: I would suggest following the recommendations by the Highest Health Council of the Ministry of Health of Austria (see table). I would also recommend choosing a phone with a specific absorption rate (SAR) value as low as possible, especially for children, and to remember that the level of exposure to EMF decreases by the square of the distance from the antenna.

Recommendations for safer cell phone use

1: If possible, do not use your cell phone in areas with bad reception.
2: Keep calls short.
3: In situations where a choice between cell phone and landline presents itself, use the landline.
4: Limit cell phone use in the car to a minimum.
5: With GSM cell phones, wait a moment after dialing before moving the phone towards the head.
6: Use headsets or a free-speaking system.
7: When buying a new cell phone, look out for low SAR values (Specific Absorptions Rate).
8: Do not carry the cell phone directly on your body.
Maximizing the Extent of Resection in Gliomas: Intraoperative Awake Mapping Versus Intraoperative Imaging

C. F. Freyschlag, J. Kerschbaumer, and C. Thomé

Department of Neurosurgery, Innsbruck Medical University, Innsbruck, Austria

Corresponding author:
Christian F. Freyschlag, MD, Department of Neurosurgery, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria (christian.freyschlag@tirol-kliniken.at).
After the introduction of cortical mapping by Penfield in the early 20th century and the consequent advances by Ojemann in the 1970s, brain mapping became the gold standard for surgery in eloquent areas of the human brain. More recently, mapping techniques and testing routines have become more elaborate, leading to intraoperative assessment of higher cortical functions such as judgment and mathematical problem solving. The outcome of state-of-the-art brain tumor surgery is not only benchmarked by survival parameters but also by neuropsychological assessments and quality of life. With modern mapping techniques, surgeons can prevent permanent neurological deficits without limiting the extent of resection. With iMRI, neurosurgeons can visualize tumor remnants intraoperatively while performing the resection. Nonetheless, intraoperative imaging does not provide information on the functional status of the patient. This review critically appraises both techniques in order to achieve the goals in modern neuro-oncological surgery: maximizing the resection and preserving function and quality of life.

Keywords: awake craniotomy, brain mapping, extent of resection, intraoperative MRI (iMRI), low-grade glioma, quality of life
Awake Brain Mapping

The surgeon’s goal when using direct cortical stimulation in awake brain surgery is to prevent damage to eloquent structures by identifying them reliably, thus resulting in a low risk of postoperative neurological sequelae. The concept of functional neuro-oncology, aims to maximize the extent of resection by removing brain tumors within functional boundaries unrelated to any imaging technique. Supramaximal resection is achieved safely if the visible tumor (by MRI and intraoperative ultrasound) and surrounding tissue are of no eloquence and are therefore removable. To achieve these aims it is necessary to take advantage of: (i) preoperative neuroradiological imaging and (ii) extensive preoperative neuropsychological examinations combined with intraoperative direct cortical mapping in the awake condition; (iii) after discharge, it is crucial that patients undergo postsurgical rehabilitation.

First, it is important that preoperative DTI visualize existing anatomical fiber bundles. fMRI techniques show regions of activity while patients are addressing given tasks that do not necessarily identify an area involved in speech or language.

Second, meticulous preoperative neuropsychological assessment is necessary to identify concealed deficits that may not be discovered in a regular neurologic assessment and provide a baseline examination for further follow-up. Moreover, the surgical and intraoperative testing methodology must be adapted for each patient individually (eg, testing mathematical functions in physicists). Finally, postsurgical rehabilitation has to be planned in advance to immediately challenge any transient worsening.

It is strongly recommended that mapping of either cortex or subcortical pathways be performed under local anesthesia; although motor functions can be monitored in patients under general anesthesia, their complexity of movement cannot be addressed. In practice, a bipolar electrode with 5 mm spaced tips is used to deliver a biphasic current (pulse frequency of 60 Hz, single pulse duration 1 ms) and applied to the brain surface. The threshold of intensity is adapted to each patient by starting at a 2-mA baseline and increasing the amplitude progressively in steps of 1 mA. While the upper limit for awake procedures is 6 mA, the upper limit for mapping under general anesthesia is 16 mA (in order to prevent seizures). In case of seizure activity, direct application of cold irrigation is recommended. Furthermore, it is absolutely necessary that patients never be informed if or when the brain is being stimulated and that no site should be stimulated twice in succession (in order to avoid seizures). Achieving a single positive stimulation response is highly recommended. Some authors, however, emphasize that it might be beneficial to approach lesions by smaller exposure and that negative-mapping is satisfactory for resecting language-involving tumors.

There is absolutely no cortical function that cannot be addressed by awake intraoperative mapping. Standard procedures (eg, language, movement, and counting) can be easily performed in any operating theater. Furthermore, somatosensory functions and visual functions can be tested. Sophisticated functions (eg, calculation, spatial recognition, memory, and cross-modal judgment) can also be examined. It is crucial to discriminate the symptomatology of stimulated disorders accurately; do not count only the number of speech disturbances. It is necessary to interpret the different symptoms (eg, speech arrest, anarthria, speech apraxia, semantic paraphasia, perseveration, anomia, syntactic errors, and phonological disturbances) accurately to discriminate between their anatomical and functional origins.

Cortical brain mapping has to be combined with subcortical mapping to achieve a maximized extent of resection within functional boundaries. Whereas the anatomical description of the dominant frontal operculum (the so-called “Broca’s area”) is meant to be the area of speech, Benzagmout et al. reported a complete resection of this area of diffuse low-grade gliomas without sequelae.

To achieve reliable subcortical mapping, concise knowledge of white matter anatomy is very important, and several major pathways are described in the literature. We describe only 2 bundles as showcases for subcortical mapping of language pathways.

The inferior fronto-occipital fasciculus (IFOF) is a combination of optic radiation (OR) and the inferior longitudinate fascicle (ILF). It connects the frontal lobe with the occipital lobe and establishes connection with the parietal and the temporal lobes, including the insular region. It is the longest associative bundle connecting occipital cortex, temporoparietal areas, and superior parietal lobule to the frontal lobe. An anatomical study of 11 cadaveric hemispheres demonstrated that there are 2 components of the IFOF (superficial and deep) as previously described and that they can be visible at the fronto-temporal junction and within the frontal lobe. On the basis of their findings, Sarubbo et al. hypothesized that the IFOF might be a multifunction bundle connecting distant and more distributed brain areas and the dependent subserving language and non-language functions.

As a combination of fascicles, the sagittal stratum (SS) is a large structure located laterally to the atrium of the lateral ventricle and takes a sheet-like course in an anteroposterior direction. The SS includes the IFOF and the ILF; therefore, it is a major subcortical pathway in the human brain whose function is poorly understood. In a study by Chan-Seng et al., the SS was addressed specifically in 8 patients undergoing awake brain tumor surgery for dLGG. Their findings showed that mapping detected functional fibers in all patients by generating semantic paraphasia in the upper part of the resection cavity corresponding to the functional connectivity of the IFOF. Alexia occurred in 3 patients during stimulation of the basal area corresponding...
to the ILF, whereas visual disorders (OR) in between were induced by stimulating 5 patients of the tested cohort.

As a compendium of the complex cortical and subcortical connectivity, DeBenedictis and Duffau\textsuperscript{3} proposed their concept of brain hodotopy, meaning that functional deficits can arise from both a cortical level with hypofunction and hyperfunction (or both) and from the underlying connecting network resulting in disconnection or hyperconnection (or both) if structurally damaged.

### Intraoperative Imaging

Since the introduction of intraoperative MRI (iMRI) scanners in 1995, this technique has been increasingly used with promising results. Most notably, the extent of resection in glioma surgery could be increased significantly because tumor remnants can be identified in up to 57\% of patients undergoing surgery within an iMRI.\textsuperscript{29,30} Senft et al. produced evidence in a randomized controlled trial that patients who underwent surgery using IMRI, were at a lower risk for developing local tumor progression and showed significantly increased overall survival. In that trial, a more radical attempt was not associated with an elevated rate of postoperative neurologic deficits.\textsuperscript{31}

Introducing high-field MRI into neurosurgical operating theaters allows conductance of MR spectroscopy and fMRI intraoperatively, thus providing additional metabolic and functional information.\textsuperscript{32} Even DTI is possible during surgery, allowing visualization of fiber tracts. Evidence of better visualization of tumor remnants (compared with low-field MRI) is still lacking.

Two major disadvantages have to be considered when implementing iMRI in all neurosurgical routines: (i) most of the available literature compares the typical outcome parameters (overall survival and progression-free survival) after glioma surgery with a gross total resection (meaning that contrast-enhancing tumor is visible in conventional MRI studies,\textsuperscript{5,33,34} at least in malignant gliomas). This fact seems controversial since the infiltrative nature of contrast-enhancing tumors within the hemisphere or even bilaterally is well known and described.\textsuperscript{35} Additionally, most investigators differentiate LGG between well circumscribed versus diffuse lesions and postulate that more than 30\% of these tumors grow in an infiltrative pattern, which is impossible to delineate with MR imaging.\textsuperscript{36} Therefore, the major limits of intraoperative imaging relate to gross total resection and do not involve infiltrative border zones around conventionally visible tumors.

A recent Cochrane Review from 2014,\textsuperscript{37} which focused on different modalities of intraoperative imaging, noted that only one prospective randomized study has assessed the potential benefits and risks when using iMRI.\textsuperscript{31} By acknowledging the prolongation of survival due to more radical resection, facilitated by IMRI, criticism was raised on the interpretation of the extent of resection focused on contrast-enhancing residuals. The authors noted that MRI alone is not sufficient for discerning human glioma since techniques such as amino acid PET have clearly shown tumor extension outside the region of contrast enhancement.\textsuperscript{38} Senft et al.\textsuperscript{31} compared iMRI with 5-ALA-guided resection described by Stummer et al.\textsuperscript{39} and reported no increased rate of neurological deterioration. Even in the control group without IMRI, the rate of neurological deterioration is quite low, indicating a high proportion of favorably located tumors.

In summary, iMRI is an indispensable, useful tool in modern neuro-oncological surgery, but the physician has to be aware of its limitations.

### Discussion

Planning brain tumor surgery is usually based on preoperative standard imaging and sometimes on functional considerations as well. It is therefore reasonable to use intraoperative imaging to visualize the intraoperative conditions and plan the resection up to that point. Because we are already accustomed to planning surgery based on preoperative images, intraoperative imaging adds new and valuable information.

Mapping techniques rely on intraoperative testing and online information about the brain’s conditions and functions. When a surgeon relies on mapping, he or she can resect more tumor tissue safely because of the information communicated by the awake patient. The resection would stop before any impact on the patient’s functioning since it is not linked to imaging data. Supramaximal resection and preservation of function with good quality of life are now achievable goals in modern brain tumor surgery.\textsuperscript{10}

When comparing both techniques, the biggest difference between surgery with iMRI and surgery with awake brain mapping is the planned extent of resection. Numerous studies have shown that the extent of resection is delineated clearly with MRI, and the volume of gross total resection is increased in the MRI group of the trials,\textsuperscript{37,39,40} but the goal of image-guided surgery is resection of signal abnormalities and contrast enhancements despite the diffuse character of glioma infiltration.\textsuperscript{41} Nonetheless, preoperative functional diagnostics (as well as iMRI) cannot detect eloquent sites reliably in the course of the resection.\textsuperscript{42} Biomathematical models are used for neuroimaging, calculations, which explains their lack of reliability at the individual level (particularly with higher cognitive functions such as language).\textsuperscript{43} Above all, imaging is not capable of differentiating crucial areas from regions in which loss could be compensated. Thus, there would be concerns about even taking a patient into surgery or performing only biopsy or incomplete resection because of the IMRI data suggesting functional areas near the tumor tissue. In fact, it might be possible to remove all tumor tissue with no permanent neurological deficit under awake conditions. Fig. 1 shows a case in which partial resection of a dLGG was performed under general...
anesthesia in an iMRI suite. The same patient underwent a second surgical intervention under awake conditions, which resulted in more extensive resection without permanent deficits.

It is widely accepted that resection of brain tumors in the nondominant frontal lobe should be done under general anesthesia because of the absence of eloquent areas, as described by Broca, Wernicke, and Geschwind. Recent studies have indicated that the nondominant hemisphere is a component in several language tasks (eg, semantic processing and figurative meaning of verbal material) and that crossed aphasia can be induced by stimulating the right frontal cortex in a right-handed patient. In conclusion, even extensive preoperative testing is not providing reliable information about dominance in language processing. Moreover, there is no prospective trial comparing intraoperative imaging and integration of functional data in navigation with intraoperative brain mapping.

Integration of direct functional testing via mapping with direct cortical stimulation provides fine tuning for the raw data from imaging modalities and leads to the best result in both main outcome parameters in neuro-oncology, overall survival, and functional independence—therefore quality of life.

Conflict of interest statement. The authors declare no conflict of interest.

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Trabectedin for Recurrent Grade II or III Meningioma: A Randomized Phase 2 Study of the EORTC Brain Tumor Group

Study chair:
Matthias Preusser, MD
Department of Medicine I and Comprehensive Cancer Center Vienna, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria (matthias.preusser@meduniwien.ac.at).

Synopsis
Recurrent meningiomas are relatively rare but pose a significant unmet clinical need. Up to now, there has been no known effective therapy for atypical (WHO grade II) or malignant (WHO grade III) meningiomas recurring after exhaustion of all available neurosurgical and radiotherapeutic treatment options. A number of drugs, including hydroxyurea, temozolomide, irinotecan, interferon-alpha, miltefosine, octreotide analogues, megestrol acetate, bevacizumab, sunitinib, vatalanib, imatinib, erlotinib, and gefitinib, have been investigated in small and uncontrolled studies. Bevacizumab, vatalanib, and sunitinib showed some evidence for clinically relevant activity; however, these data need to be confirmed in randomized studies.

Trabectedin is a tetra-hydroisoquinoline alkaloid that is approved for treatment of ovarian cancer and soft-tissue sarcoma and for which in vitro and single-patient activity has been shown in high-grade meningioma. Based on these findings, the European Organisation for Research and Treatment of Cancer (EORTC) is conducting an international, multicenter prospective randomized phase 2 trial (EORTC trial 1320, NCT02234050) to investigate whether trabectedin demonstrates sufficient antitumor activity against recurrent grade II or III meningioma to justify further evaluation. The trial will randomize, in a 2:1 ratio, 86 participants with radiologically documented progression of atypical or anaplastic meningiomas without surgical or radiotherapeutic options to receive either local standard of care (LOC) or trabectedin. Trabectedin will be given every 3 weeks as a 24-hour infusion via a central venous catheter at a starting dose of 1.5 mg/m² until progression, occurrence of unacceptable toxicity, or withdrawal of participant consent. The primary endpoint will be progression-free survival, and secondary endpoints will include response rate, overall survival, safety, and health-related quality of life. The study will be conducted in close to 50 study sites within the EORTC network, and patient accrual has started in October 2015. The planned accrual period is 28 months. EORTC trial 1320 will be the first randomized trial to evaluate a novel and innovative therapy in recurrent high-grade meningioma and will hopefully be able to generate new information to improve patient outcomes in this rare but devastating cancer type.

Reference