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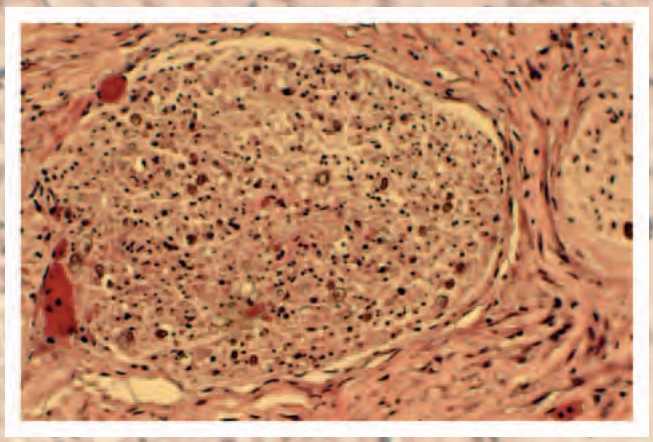

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Policy:
The *European Association of NeuroOncology Magazine* welcomes submission of clinically and original papers, reviews etc in the fields of neurology, neurosurgery, medical oncology, radiotherapy, pediatric neurooncology, neuropathology, neuroradiology,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

Inhalt

COLUMNS

Why Another Journal?

Wolfgang Grisold, MD

As the editor-in-chief and the president of EANO, it is my pleasure to write the editorial for the first issue. The *EANO Magazine* is an open access journal which will be available on our website. It aims at bringing education, news, and also European issues to persons interested in neuro-oncology. As the president, I am at the same time editor-in-chief, the managing editor is Riccardo Soffietti from Torino. The editorial board consists of Khê Hoang Xuan, Stefan Oberndorfer, Wolfgang Wick, Riccardo Soffietti, Michael Weller, Ufuk Abacioglu, Lorenzo Bello, Olivier Chinot, Johan M Kros, Giorgio Perilongo, Hanneke Zwinkels, and Kathy Oliver.

The new online magazine is financed entirely by the EANO and has no commercial bias – an important issue for such a project.

The format of an open access (OA) journal was chosen to meet timely needs of the growing neuro-oncology community in Europe. Easy and unlimited access is the advantage of OA publishing, meeting the needs of the web-based community.

What will be our future publishing policy for this magazine?

In addition to the website, which meets many educational and communicational needs, two additional features have been or will be implemented in 2011:

1. From 2011, the EANO has decided to make the joint journal of the SNO and EANO, *Neuro-Oncology*, available to our EANO members within the closed membership section. It is a highly scientific journal with an impact factor of about 5 and we are glad to be able to support our members with access to this journal – not only to make use of the scientific input but also increase the number of European scientific activities internationally and thus stimulate the scientific core of European neuro-oncology.
2. In contrast to the scientific journal, there is an additional need to disseminate knowledge and education on neuro-oncology. This has been done to some extent via the EANO website, which presents news from journalists, online case reports, and other pertinent information, and is to maintain this format. The EANO online magazine will be available on the website and contain educational articles and reviews on current topics intended as help and guidance for the practical issues of neuro-oncology. Thus, reviews on pertinent topics, guidelines, and information on current studies will be an important part. We will not aim at publishing cases and original scientific articles at this stage although the cases presented on the website will also be published in the journal.

The EANO is a multidisciplinary and multiprofessional society aiming to provide science, standards of care, education, and communication. We have equal space for related health groups, in particular nurses, and also have invited Kathy Oliver from the International Brain Tumour Association (IBTA) to grant us more insight into patient-related views and aspects. As EANO and SNO have decided to work together more closely in the near future on several issues such as meetings, education, and also the World Congresses of Neuro-Oncology, the SNO will contribute to our issues with its American point-of-view as well.

One key objective of the EANO is education. Over the past years, the EANO has increased the number of travel grants for EANO congress attendees and has in addition created two other programmes: department visits and fellowships. Both activities can be seen on the website in detail as well as the relevant application details.

Reports from successful grant recipients will be published to share experiences.

In addition, the EANO has sponsored attendance of 2 speakers for the 13th Joint ECCO-AACR-EORTC-ESMO Workshop on „Methods in Clinical Cancer Research" from June 18–24, 2011, in Waldhaus Flims, Switzerland, and one speaker for the Brain Tumor Epidemiology Consortium from June 5–7, 2011, in Cambridge, UK.

At present, an EU project with ECCO on onco-videos regarding common oncological matters is being developed, which will also be reported in the magazine.

To prepare and to achieve this goal, a publication committee has been founded, and care was taken to have representatives from all fields related to neuro-oncology. The editorial work is done by Riccardo Soffietti, who is very engaged in the plan to launch this journal. In Krause und Pachernegg, an Austrian publisher well-experienced in publishing print and open access journals, we have found an engaged and flexible partner to launch this journal and we have received the necessary technical and structural input.

I hope this will give you basic information on our open-access *EANO Magazine* and we hope that not only will you find it useful but that you will be part of it. One possibility is to submit letters and input for the comment section, and if you have news which you think would fit in the frame of our magazine do not hesitate to send it to us for consideration, as an OA journal is flexible and will develop through our input.

The journal will be a "pure" online journal and is presently not intended to be listed in PubMed. However, it will be listed in the Directory of Open Access Journals.

Wolfgang Grisold, MD
President of the EANO

Early Activities of Brain Tumour Research in Austria: A Historical Note

Kurt A Jellinger

Institute of Clinical Neurobiology, University of Vienna, Austria

The idea to organize a neurooncology research association was first proposed in 1990 by a group of brain tumour specialists and was realized in 1992, when Peter Krauseneck, then chairman of the "National Oncology Alliance" (NOA) organized a meeting of European neurooncologists in Pommersfelden (Germany). Ever since, the EANO has considerably progressed, with members from more than 30 countries, organizing biennial scientific congresses and successfully promoting research in neuro-oncology. As one of the first/initial members of this society, I was invited by Wolfgang Grisold, president of the EANO, an old friend and previous scholar, to write about the early development of neuro-oncology research in Austria, which antedated the establishment of EANO.

In 1967, Jellinger wrote a chapter on the pathology of brain tumours in infancy for a book on paediatric neurosurgery and, later, on connatal brain tumours and glioblastoma. In August 1974, together with H M Zimmerman, the famous neuropathologist from Montefiore Hospital, New York, he organized the first international symposium on malignant lymphomas of the nervous system, published as a supplement to *Acta Neuropathologica* in 1975. Several publications on primary malignant lymphomas of the CNS and involvement of the CNS by lymphomas and leukaemias followed between 1978 and 1984.

After 1975, the team of the Department of Neurology at the Lainz Hospital, Vienna (one of the staff members was W Grisold), was among the first to perform combined postoperative (adjuvant) radiation and chemotherapy (according to the COMP protocol) of malignant gliomas. The results were published at international meetings in Gardone, Italy (1979), Wiesbaden (1980), and London (1984). In 1986, the book "Therapy of Malignant Brain Tumors", edited by K Jellinger, was published by Springer, Vienna-New York, with chapters on pathology, neurosurgery, stereotactic biopsy, radiation and chemotherapy, and malignant brain tumours in children, written by a panel of international experts.

Early attempts to establish an internationally accepted systemic approach to brain tumour nomenclature began with the first AFIP book, "Tumors of the Central Nervous System", by J W Kernohan and G P Sayre in 1952, the AFIP fascicles under the auspices of the National Research Council published by L J Rubinstein in 1973, and the WHO "blue book", "Histologic Typing of Tumours of the Central Nervous System" in 1979 (edited by K J Zülch). International meetings of the WHO working group "Histological Typing of Tumors of the Central Nervous System" (one of the members K Jellinger, Vienna, Austria) in Houston, TX (March 1988), and Zurich (March 1990) followed. These resulted in the publication of the second edition of "Histological Typing of Tumours of the CNS" (P Kleihues et al, eds, Springer 2000), and the "Pathology and genetics of tumours of the nervous system" (edited by P Kleihues and W K Caveness, IARC Press, Lyon, 2000), which was followed by a revised edition in 2007. The historical perspective of the development of the WHO classification of tumours of the CNS was summarized by B W Scheithauer [1].

In the meantime, the classification, diagnosis, and treatment of tumours of the nervous system has made considerable progress, in particular through the activities of EANO that is also involved in the organization of the World Conference of Neurooncology (Washington 2002, Edinburgh 2005, Yokohama 2009, and Edinburgh 2011).

The author is proud to have been active in neuro-oncology research both as a neuropathologist and a clinician, trying to participate in early and current attempts to promote the diagnosis and treatment of nervous system neoplasms.

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WHO Guidelines for Diagnosis of Glial Tumours: What Is Old and What Is New?

Johan M Kros

Abstract: Histopathology remains crucial for basic classification and grading of CNS tumour entities. The usefulness of particular histological features has been proven while that of others appears not very reliable for classification, prognostication, or prediction. By now, integration of histopathology with molecular characteristics with prognostic or predictive value is at stake. Candidate histological and molecular parameters need to be tested for their relevance, reliability, and interdependency in prospective settings in order to optimize test batteries. For the relevant molecular changes, affordable tests which are practically applicable should be developed. The recent WHO editions have proven to be good guides in classification of CNS tumour entities and started to integrate molecular signatures into the definition of the entities. The gradual availability of evidence-based prognostic and predictive histological and molecular parameters will certainly affect the content of the editions in the near future. **Eur Assoc Neurooncol Mag 2011; 1 (1): 9–12.**

Key words: glioma, WHO classification, molecular marker, prognosis, predictive factors

The WHO Edition on Tumours of the Central Nervous System

The most recent version of the WHO classification for brain tumours dates from 2007 [1]. In 1997, the concept of this book was published by the IARC in Lyon, initiated and edited by Dr Kleihues [2]. The format appeared to be successful and soon a revised edition was published, now under recognition of the WHO [3]. The last edition (2007) was not only edited by 2 neuropathologists (Drs Louis and Wiestler) but also by 2 molecular biologists (Drs Ohgaki and Cavenee), reflecting the gradual shifts in modern pathology [1]. The chapters were written by various groups of authors while the final version of the text was centrally edited. The result is a compact catalogue on brain tumour prototypes based on the consensus of a large group of experts. The book is meant to present the most recent consensus view of diagnosing intracranial tumours in the context of their radiologic presentation and to provide an update on their genetic background. Although the information on the entities mentioned is helpful for differential diagnosis, the book first of all provides tumour prototypes and their diagnostic delineations. The definitions are crucial for protocols in clinical management and translational research.

Definitions

In the WHO edition, the gold standard used for the definition and diagnosis of brain tumours is the microscopic aspect of the tumour [1]. In addition, immunohistochemical profiles are provided, while in few tumours also the characteristic (or definitional) genotypes are included. For some tumours data from electron microscopy is also available. In only few centres, ultrastructural investigations for tracing lineage-specific cellular structures or extracellular components are still carried out on a daily basis. Because of advances in site-specific proteomics it may well be that in the future ultrastructural aspects of tumours will return to the diagnostic armamentarium. In the 1970s, immunohistochemistry was introduced into the diagnostic setting as an important addition for making diagnoses. In the WHO fascicle for each entity the complete immunohistochemical profile is summarized, irrespective of its discriminative value in differential diagnostics. For particular diagnoses, however, a specific immunoreactive profile is required. For instance, when diagnosing a central neurocytoma, a tumour type closely resembling oligodendroglioma, neuronal differentiation of the tumour cells should be proven by immunohistochemistry [4]. Immunohistochemical verification is also helpful in the differential diagnosis of certain glioblastomas with resemblance to metastatic tumours (or vice versa), lymphomas which should be delineated from non-tumour infiltrates and the differentiation of meningeal tumours from other primary brain tumours or metastatic tumours. Immunohistochemistry to the Ki-67 protein (Mib-1 antibody) is an important aid to estimate the proliferation of tumours, particularly in small specimens in which counting mitoses is not easily accomplished [5, 6].

In the WHO editions published in 2000 and 2007, respectively, and the IARC precursor edition of 1997, available data on molecular changes in the genome of tumours were carefully referenced and updated. Among the many genetic aberrations there are several associated with a particular histopathology or clinical/radiological presentation. In the 2007 edition, the WHO incorporated characteristic genotypical changes into the definition of some particular entities. For instance, in the definition of oligodendroglioma the phrase *"often harbouring deletions of chromosomal arms 1p and 19q"* was added, and for the entity of AT/RT *"associated with inactivation of the INI1/hSNF5 gene in virtually all cases"*. These additions herald the incorporation of molecular data in definitions of entities and reflect the need for prognostic and predictive parameters in clinical neuro-oncology.

Gliomas

The recent WHO fascicles conceptually divided glial tumours into those with diffuse infiltration in cerebral tissue and those that grow relatively circumscribed [1–3]. The diffusely infiltrating glioma group includes astrocytomas and oligodendrogliomas and their mixed forms as well as their various malignancy

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grades up to glioblastomas. The circumscribed glial neoplasms are mainly represented by pilocytic astrocytomas and gliomas with ganglion cells, with some rare tumours such as pleiomorphic xanthoastrocytomas belonging to this category as well.

In the WHO fascicle, the low-grade and anaplastic stages of diffusely infiltrating gliomas are presented in distinct chapters as if they represented different entities. However, a large part of diffusely infiltrating gliomas will invariably progress from low to high grade, eventually meeting the criteria of glioblastoma (so-called "secondary glioblastomas"). While these secondary glioblastomas have risen from a lower-grade (astrocytic) precursor, so-called "primary glioblastomas" appear to have followed another oncogenic pathway. A particular low-grade precursor lesion for this subset has not been identified [7, 8]. Within the group of glioblastomas, some more subtypes are distinguished. Giant-cell glioblastoma and gliosarcoma are microscopically recognizable entities, both deviating in clinical course from other glioblastomas: the former progressing more slowly and the latter faster. The morphological criteria for the delineation of mixed oligoastrocytomas are unclear and for most tumours with mixed morphology the genotypical characteristics of either oligodendroglioma or astrocytoma exist.

Attributing malignancy grades to the tumours of the diffusely infiltrating group has proven to be of clinical relevance. Based on the available literature, the WHO provides some provisionary criteria for grading gliomas into low and high grade (anaplastic) without issuing strict schemes for scoring. Data on prognostic histological parameters for oligodendrogliomas and astrocytomas is mostly based on retrospective studies [9]. The various histological parameters mentioned by the WHO are still being scrutinized in prospective settings [10]. Since the histopathological definition of mixed oligoastrocytomas is subject to large interindividual variability, it is obvious that grading criteria are not really available since one cannot grade a tumour type which has not been clearly defined. Since the main representatives of this ill-defined group are molecularly divided into either oligodendroglioma or astrocytoma, grading should be done according to the best schemes for these glioma subtypes.

The circumscribed tumours are generally associated with young age and also a characteristic location as well as scan appearance. The delineation between "diffuse" and "circumscribed" should not be taken too literally – diffuse gliomas may well have parts that are sharply demarcated from surrounding brain tissue while circumscribed tumours usually display invasive behaviour as well but progress more slowly. Circumscribed gliomas are usually rather stationary but in the long run some may show malignant behaviour. In gangliogliomas, the glial component may eventually undergo anaplastic change, as seen in diffusely infiltrating gliomas. The histological features of anaplastic change of pilocytic astrocytoma may be difficult to appreciate with the exception of the mitotic index (or Mib-1 labelling index) [11].

Guides for Clinical Management: Prognostic and Predictive Factors

Some tumour entities listed in the WHO fascicle occur far more frequently than others. Clearly, the reliability of data concerning clinical courses and effective therapies is larger for the more frequently occurring tumours. Only for the more common tumours data obtained in prospective studies are available. There are several ongoing trials on therapies for the commonly diffusely infiltrating gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed oligoastrocytoma, glioblastoma) and it is of paramount importance that pathologists take part in these studies in order to test their definitions and grading schemes of entities for consistency and validate their criteria for prognostication or prediction of therapy success [12]. It is difficult to gather evidence-based data for relatively uncommon tumours. International collaborations and trial initiatives are needed to identify prognostic and predictive factors for these tumour groups.

The molecular characteristics of tumours may be associated with particular morphological subtypes and therefore provide lineage specificity. An example is the loss of 1p and 19q for oligodendroglial lineage [13]. Molecular findings may also correlate roughly with the tumour grade. For instance, EGRF amplification/over-expression, LOH 10q, or mutation of PTEN are relatively late events in the development of diffusely infiltrating gliomas and thus associated with a higher malignancy grade [14–16]. Furthermore, molecular aberrations may carry prognostic information or may be predictive of the success of particular therapeutic interventions. The putative prognostic or predictive value of particular genetic changes has been tested in the context of clinical trials [17–26]. Loss of 1p/19q is mutually exclusive with EGFR amplification and appears not only to be predictive of the response to alkylating chemotherapy but also emerged as a prognostic factor [27, 28]. Since the location and extent of the losses on 1p correlate with the clinical aggressiveness of the tumour [24], relevant techniques are necessary to detail the 1p losses. Interestingly, loss of 1p/19q was found to correlate with immunoreactivity to α-internexin (INA) [29, 30]. The α-internexin gene encodes for a neurofilament-interacting protein which, just like 1p/19q loss, correlates with oligodendroglial morphology. Whether immunohistochemistry for INA would offer an alternative method to replace testing for 1p/19q should be assessed in a prospective setting.

Methylation of the promoter gene of O^6-methylguanine-DNA methyltransferase (MGMT) leads to loss of expression of MGMT and causes vulnerability to alkylating agents. Testing the methylation status of the CpG islands therefore would be a direct test predictive for the success of therapy. In a prospective setting, it was found that patients with glioblastomas with MGMT promoter methylation who received treatment with temozolomide survived longer [20]. In oligodendrogliomas the effect of MGMT promoter hypermethylation appeared to be prognostic rather than predictive [31]. However, thresholds for reading out methylation tests are still subject to debate [32, 33]. At this point, the status of methylation assays in the prognostication or therapy effect prediction requires additional study. Recently, heterozygous point mutations in codon 132 of the IDH1 gene coding for $NADP^+$-dependent isocitrate dehydrogenases were found in large numbers of diffusely infiltrating gliomas, among them astrocytomas but also oligodendrogliomas [34]. In the retro-

spective series studied, IDH1 mutation (more specifically, the R132H mutation) appeared to positively influence survival when controlled for tumour grade and this prognostic effect was confirmed in trials on anaplastic astrocytomas [35], oligodendrogliomas, and glioblastomas [36–38]. IDH1 immunohistochemistry may serve as a diagnostic tool in certain situations. Its contribution as prognosticator in the context of other prognostic parameters should be further explored. In retrospective surveys of large numbers of gliomas, characteristic tandem duplication leading to fusion of BRAF with KIAA1549 was found in > 70 % of pilocytic astrocytomas, particularly in those with cerebellar location [39]. Another recent finding is the presence of the specific BRAF V600E mutation occurring in 2/3 of pleomorphic xanthoastrocytomas and 18 % of gangiogliomas [40]. The mutation was also specifically observed in extra-cerebellar pilocytic astrocytomas [40]. Both the BRAF-KIAA tandem duplication and the V600E mutation are useful genetic signatures for making diagnoses. Importantly, the activating effect of BRAF mutations in the RAS/RAF/MEK/ERK kinase pathway opens possibilities for therapeutic intervention and candidate inhibitors should be explored in clinical trials. The strategies of incorporating testing for certain molecular markers in trials against the background of a limited repertoire of available drugs remain a matter of ongoing dispute [18, 41, 42]. The search for evidence-based prognostic and predictive parameters will continue and will gradually confine laboratory investigations meant to provide relevant information for therapeutic intervention. Future WHO editions will certainly be updated on the developments in improving diagnostic criteria as well as listing molecular parameters to be incorporated in a prognostic or predictive relevant diagnosis.

Over the past 10 years, high-throughput investigations on the expression of genes have been carried out in order to find genes and pathways which are important for tumour genesis or progression and thus would be candidate targets for therapy. The results of studies in gene expression arrays can be divided into those in which supervised analyses were carried out and those in which unsupervised clustering was performed. Supervised analyses included analyses in which the pathology diagnosis or particular prognostic categories were leading [43–45]. In general, for those lesions with better defined morphological characteristics (like low-grade astrocytomas) more specific and consistent expression profiles were obtained, while the entities with more variable morphologies (like glioblastomas) exhibit a much larger variation of expression patterns [43]. In some studies, unsupervised analyses of expression data showed intrinsic prognostic and predictive relevance of the molecular clusters without correlation with the histological diagnosis [45, 46]. Molecular classification within particular diagnostic categories like glioblastomas was shown to add prognostic information, and was therefore considered – to some degree – to be superior to conventional histology [47]. Classifying molecular signatures including proneural, proliferative, or mesenchymal profiles have been identified in expression array studies [43, 47]. The genes and their protein products underlying the clusters of tumours are rather variable, although specific genetic changes such as EGFR amplification, IDH1 mutation, and 1p/19q loss relate to particular tumour clusters.

It remains to be established what more genes are relevant for prognostication and which expressional patterns are important predictors for the success of therapies aiming at components of particular pathways. Issues like genetic or expressional heterogeneity of tumours, changing expression patterns as a result of the administration of certain therapies [17, 48], have as yet hardly been addressed. Molecular investigations searching for clinically relevant parameters can only be carried out successfully in the context of clinical trials. By now, there are still many difficulties to overcome in carrying out translational studies in trials. On the clinical side, there are many difficulties in accrual and passing ethical committees [49, 50]. Problems of property and transferring materials, especially in international studies, are the main barriers to be overcome by pathology and translational research. Nevertheless, significant steps are being made at a rather quick pace and it is to be expected that future WHO fascicles will require faster updates than ever before in order to keep up with developments.

Conflict of Interest

JMK has no conflict of interest to declare.

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In reminiscence of Dr Robert Charles Janzer, neopathologist and fine colleague in the EORTC Neuropathology Panel.

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Technological Advances in Glioma Surgery

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Abstract: In the recent past, the impact of surgery has increased because of important technical advances which have significantly improved tumour resection for both high- and low-grade gliomas and at the same time patient quality of life. Today, surgery is asked not only to obtain tissue to reach a precise histological and molecular diagnosis but to influence many functional and oncological endpoints. To reach all these complex issues, surgery has significantly changed in the way it is performed. Surgeons have had the opportunity to incorporate many technical advances, particularly in imaging and intraoperative neurophysiology, which has significantly modified the way resection is conceived and technically performed. The surgeon should be able to critically integrate all these technologies, both at the time of surgical planning and also during surgery. Thanks to these improvements, surgery is today able to impact both survival and quality of life in patients with low- and high-grade gliomas. **Eur Assoc Neurooncol Mag 2011; 1 (1): 13–9.**

Key words: MRI, DTI-FT, fMRI, neuronavigation, brain mapping, glioma

Introduction

Surgery, along with radio- and chemotherapy, has for many years represented one of the main therapeutic tools for the treatment of intrinsic brain lesions. Traditionally, the role of surgery was to remove enough tissue to reach a histological diagnosis and, when considered to be feasible, to resect as much tumour as possible, to relieve symptoms and, particularly, to reduce intracranial pressure. The impact of surgical resection on patient survival was not established and in many cases also questionable. In the recent past, the impact of surgery has increased because of important technical advances which have significantly improved tumour resection for both high- and low-grade gliomas and at the same time patient quality of life. Nowadays, surgery is asked not only to obtain tissue to reach a precise histological and molecular diagnosis but to influence many functional and oncological endpoints. To reach all these complex issues, surgery has significantly changed in the way it is performed. Surgeons have had the opportunity to incorporate many technical advances, particularly in imaging and intraoperative neurophysiology, which has significantly modified the way resection is conceived and technically performed. Thanks to these improvements, surgery is today able to impact both survival and quality of life in patients with low- and high-grade gliomas. We thus aimed to explore and critically analyse the contributions of various technologies currently employed in the routine and upfront clinical practice at the pre- and intra-operative stage in the surgical management of gliomas.

Imaging

The major contribution to the recent improvement of surgical techniques regards imaging. Imaging technologies have been implemented in both the pre- and intraoperative settings, having a substantial impact on surgical planning and performance. Currently, imaging is asked to detect and delineate the tumour mass and its relationship with surrounding vascular or neural structures. Imaging is also asked to provide information on how functions and relevant functional structures at both the cortical and subcortical levels have been modified by the presence of the tumour, and to depict the relationship between the tumour and these structures. In addition, imaging is asked to provide metabolic information with regard to the tumour degree as well as to delineate the tumour's structural heterogeneity. Of course, the surgeon should carefully consider and integrate this huge amount of information in the surgical planning. In addition, selected information can also be incorporated intraoperatively by loading them into the neuronavigation system or similar guiding devices. Furthermore, the same technologies can be used post-operatively to study the effect of surgery and to monitor the tumour's biological behaviour during follow-up.

The Role of MRI

MRI represents the elective neuroradiological procedure for the study of gliomas. Several and different MRI sequences are applied according to the diagnostic query and clinical hints. T1-weighted imaging (T1WI) with and without use of gadolinium contrast, T2WI and fluid-attenuated inversion recovery (FLAIR) sequence are referred to as conventional MRI imaging. The first aim of conventional MRI is, in fact, to obtain an optimal depiction of the physiological and pathological anatomies, ie, the morphological features of the lesion of interest *per se* and its relationship with the surrounding structures [1, 2].

In addition, recent advances in MR techniques provide different types of data: the functional specialisation of an area of interest, with particular emphasis on the eloquent regions (fMRI); the normal and pathological anatomies along with the different degrees of involvement of selected subcortical white matter (WM) tracts (Diffusion-Tensor Imaging [DTI] and Fibre Tract [FT] reconstruction); the perfusion pattern described through the analysis of the Brownian motion of water molecules (Diffusion-WI, DWI, and Perfusion-WI, PWI); the metabolic changes detected non-invasively in vivo through biochemical tissue variations (Magnetic Resonance Spectroscopy [MRS]).

Both conventional and advanced MR applications have become a crucial step in the diagnosis of gliomas and a relevant means of support in the preoperative planning of their surgical

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removal. In fact, they represent a fundamental tool to tailor the mapping and monitoring techniques to the individual anatomo-pathological features of the patient and the lesion [3]. The same images can be loaded into the neuronavigation system and made available in an integrated manner during resection.

Conventional MR Imaging

Morphological T1, T2, and FLAIR images, as well as post-contrast T1 images, provide information on the site, location, and structural aspect of the tumour and of peritumoural abnormalities. They determine the relationship of the tumour with major vessels and quantify its volume. Macrocalcifications, cystic areas, intratumoural haemorrhages, and necrosis may orient towards the definition of its nature. These sequences, allowing a first typecasting of the lesion, are relevant in the initial differential diagnosis among a glioma and diverse mass lesions, such as lymphomas, brain metastases, abscesses, or haematomas, especially when combined with clinical and advanced imaging data. Post-contrast T1WI allows for a better definition of blood vessels and provides information on the condition of the blood-brain barrier (BBB), providing a first definition of the grade: low-grade gliomas (LGG) present a normal BBB and do not usually show enhancement in post-contrast images [1]. Furthermore, repetitive measurement on morphological MR images allows for the quantification of the tumour's growth rate, which is suggestive of the tendency towards aggressive biological behaviour [4, 5]: the growth of LGGs amounts to around 4 mm/year, while an increase in diameter > 8 mm/year is suggestive of a high tendency toward malignant transformation, even in the absence of contrast enhancement or modification of FLAIR images.

Advanced MR Imaging: fMRI, DTI-FT, MRS, PWI

Functional MRI and DTI-FT provide information on the site of cortical areas that are active in response to motor or language tasks and a depiction of the connectivity around and inside a tumour by identifying selected WM fiber tracts. Together, they provide information on how the tumour has modified the surrounding brain at both the cortical and subcortical levels and help define the level of plasticity that has been reached by the surrounding brain.

In particular, motor fMRI is employed clinically to depict the cortical motor sites and to understand their relationship with the tumour [6–8]. fMRI with different language tasks is used to build a map of the cortical areas mainly involved in object naming, naming of famous faces, verb generation, and verbal fluency [7–11].

DTI-FT provides anatomical information on the location of motor and several language tracts [12], such as the corticospinal tract (CST), and tracts involved either in the phonologic or semantic components of language, such as the superior longitudinalis fasciculus (SLF), which includes the fasciculus arcuatus and the inferior fronto-occipital (IFO) [7, 13]. The basic DTI-FT map includes the CST for the motor part as well as the SLF and the IFO for the language part [7, 13, 14]. Additional tracts can be reconstructed, such as the uncinatus (UNC) and the inferior longitudinalis (ILF) tracts and the subcallosum fasciculus, upon specific clues obtained by extensive pre-operative neuropsychological evaluation or for research purposes. DTI-FT depicts the relationship between the WM tracts and the tumour mass, describing these tracts as unchanged, dislocated, or infiltrated according to the degree of involvement [15]. Critical aspects for obtaining a reliable reconstruction are the quality of the raw data and an appropriate fraction-of-anisotropy (FA) threshold. Tumour characteristics, such as histology, oedema, and location, can influence tract depiction as well. Indeed, as obtained by intraoperative DTI-FT and DES correlation data, an FA of 0.1 should be used for an optimal visualization of tracts in LGGs [16]. DTI-FT is particularly useful and hence recommended in LGGs since these tumours more likely infiltrate WM fibres than high-grade gliomas (HGG), where DTI-FT can be performed in selected cases only [17].

MR spectroscopy (MRS) allows for the evaluation of intratumoural areas where the metabolism is more or less pronounced, according to the differential proton MR-spectral output of the analysed regions of interest (ROI) [18]. The differential representation in this spectra of choline, creatinine, and their ratio, n-acetyl-aspartate (NAA), lipids, lactic acid, and, occasionally, other metabolites, such as myo-inositol, can provide a presumptive diagnosis and grading of the lesion [19]. This is particularly crucial in case of tumour-mimicking masses [20], when a refinement of the differential diagnosis is required to choose an appropriate treatment protocol, for instance when a distinction between treatment-induced changes and recurrence or between a glioma and lymphoma is required. This is also of great help in guiding the tissue sampling at the time of surgery for histological and molecular diagnoses. Selected MRS images can be loaded into the neuronavigation system and integrated with conventional MR images for this purpose.

Perfusion-weighted imaging (PWI) studies the arterial and capillary vascular beds by analysing the paramagnetic effects of the contrast medium on the MR signal. Perfusion maps can be designed upon these data, providing information regarding the biological behaviour of the tumour. In fact, LGGs and HGGs display a different behaviour in this aspect [21], with hyperperfusion being suggestive of a more malignant nature. Areas of high perfusion in an LGG can be targeted to obtain a more precise histological and molecular diagnosis.

These different imaging modalities produce an impressive amount of information. These data constitute a complex map of the cortical and subcortical eloquent structures and of areas with different metabolic and perfusion assets, thus allowing for the establishment of anatomical and functional boundaries along with the metabolic and perfusion assets determined by the tumour. All these data are thus critical for pre-operative surgical planning and the evaluation of risks but become even more relevant when they are loaded into the neuronavigation system. These MR applications are a valuable intraoperative aid yielding a series of advantages: reduced operative time, more prompt and accurate choice of site of direct electrical stimulation (DES) with a resultant reduced number of stimulations needed for safe identification of eloquent structures and decreased likelihood of intraoperative seizure occurrence and, finally, decreased patient's fatigue [3, 17].

Multimodal Neuronavigation System: From the Pre-operative to the Intra-operative Stage

Morphologic volumetric T1WI, T2WI, or FLAIR images, along with motor and language fMRI and DTI-FT images are usually loaded into a frameless neuronavigation system. Neuronavigation is a set of computer-assisted technology enabling the integration of 3-dimensional anatomical and functional data and the match of the pre-operative imaging data with the intraoperative identification of a target. It thus represents an aid during surgery to localise the tumour and to find the relationship between the tumour and the surrounding functional and anatomic structures, both at cortical and subcortical levels [13].

Functional MRI and DTI-FT are usually loaded into the neuronavigation system and co-registered with anatomical MR images and reference points applied on the skull of the patient. For a reliable use of fMRI and DTI-FT data in this setting, 2 issues are critical: (1) data transfer to the neuronavigation system and (2) use of adjustments during surgery to maintain a global accuracy, as described elsewhere. The problem of brain shift has to be buffered, as will be addressed later.

The reliability of fMRI and DTI-FT images, thus their sensitivity and specificity in depicting the structures of interest, has been investigated by intraoperative brain DES studies correlating intraoperative findings with MRI data [7]. These investigations demonstrated that motor fMRI usually matches with data obtained with DES, although the extent of the functional activations is larger than the area defined with intraoperative mapping, and can guide in the choice of a safe cortical entry point. Being aware of a larger fMRI representation of a specific motor area, motor fMRI can be safely used for planning and performing surgery. In case of language tasks, results are instead variable and different with suboptimal correlation with intraoperative brain mapping results [11, 22, 23]. This is due to larger activation depicted by fMRI when compared with DES, which, conversely, demonstrates only essential language sites. Therefore, the use of exclusively language fMRI could not be recommended in critical decision-making without employing direct brain mapping in the awake surgery setting. On the contrary, language fMRI is reliable in establishing language laterality and can effectively replace the Wada test.

In the corresponding author's experience, the combined use of DTI-FT and DES is a feasible approach that can be effectively and safely applied in daily activity according to clinical and surgical requirements [7, 13, 17]. When loaded into the neuronavigation system, DTI-FT helps in decreasing the time of surgery, guiding the surgeon to the point of the tract where the stimulation can be started and, then, to proceed with a precise resection [3].

Remarks on Multimodal MRI Neuronavigation

The main limitation of the use of a neuronavigation system, particularly in case of large tumours or at the subcortical level, is the occurrence of brain shift. Brain shift is the displacement of the cerebrum from its normal position, especially in relation to its position at the time of the acquisition of the pre-operative MRI study loaded for intraoperative neuronavigation [6, 7, 24].

This event is due to intraoperative brain deformation, caused by mass removal, brain swelling, and cerebrospinal fluid leaks. The extent of brain shift of major WM tracts, for instance, can reach up to 8–10 mm [25, 26]. To reduce the effects of brain shift during resection, some countermeasures can be adopted [2].

Yet, other imaging techniques are also available to increase the accuracy of proper structure identification and thus of surgery, producing an ongoing depiction of resection at the intraoperative stage, such as ultrasound and intra-operative MRI.

Intra-operative Ultrasound

Ultrasound has been employed in a range of neurosurgical procedures [6, 26, 27]. It is also useful for intraoperative visualization of gliomas and employed for mapping. Advances in ultrasound technology have improved image quality [28]. Integrating the intraoperative ultrasound with neuronavigation represents an efficient, affordable, and flexible tool for intraoperative imaging and surgical guidance since it succeeds in outwitting the issue of brain shift, thus having direct consequences on intraoperative strategies and decisions [29]. Brain shift detected with intraoperative ultrasound could be used to update pre-operative image data such as fMRI and DTI-FT to increase the value of this information throughout the operation, especially at the subcortical level. Nevertheless, the ability of these methods to reveal tumour remnants is lower than that of intraoperative MR systems. Overall, initial studies demonstrated the clinical usefulness of the ultrasound technique in updating the neuronavigation system and leading towards a safer and wider resection [28, 30].

Intra-operative MRI (ioMRI)

Although all the above-mentioned methods enable the surgeon to correctly identify and spare eloquent structures and to complete the operation without tumour remnants, it is critical to meet one of the goals of surgery as well. Over the last 15 years, MRI has entered into the operating rooms to allow real-time imaging during surgery. Intraoperative MRI (ioMRI) has been used for surgical treatment of LGGs using both low (0.2 T or 0.5 T) or high (1.5 T, 3 T) magnetic fields [29]. High-field magnets have the potential for improved image quality and for the acquisition of advanced sequences [31], thus providing not only data on the EOR [29, 32] and on the localization of tumour remnants but also an updated depiction of metabolic changes, tumour invasion, and localization of functional eloquent cortical and deep-seated brain areas. The advantage of ioMRI is to have a precise judgment of surgical performance with the patient still in the operating room. In addition, ioMRI is a further worthy resource to overcome brain shift, since it enables us to acquire morphological images by performing repeated acquisition during surgery and then to load them into the neuronavigation system uploading its initial dataset [25]. IoMRI also enables the early detection of intraoperative complications.

The main limitation of the ioMRI system are its costs: of the machine itself, its equipment, and maintenance. Besides, especially with high-field magnets, titanium neurosurgical tools are mandatory. Given the gantry sizes, patient positioning can be altered to allow for a proper scan. In addition, the need to move the patient during surgery can increase operative time and compromise sterility. Finally, artefacts due to blood or air can disturb image reading.

Additional Imaging Techniques: PET and Intraoperative Tumour Fluorescence-based Technologies

Along with information provided by MRI, 2 other sets of imaging techniques have contributed to the substantial improvement of surgery: (1) PET and (2) intraoperative fluorescence techniques.

Nuclear medicine-based imaging techniques, particularly (11)C-MET PET and (18)F-FDG PET, have been widely used in brain tumours [33–35]. They are used to differentiate tumour recurrence from radiation necrosis. MET is useful in detecting and delineating the extent of the tumour, but not in evaluating the tumour grade and proliferative activity. The FDG uptake ratio correlates well with tumour grade and proliferative activity. Preoperative PET studies with FDG and MET play complementary roles in the planning of glioma surgery, and integrated information from both tracers helps us to plan the extent of tumour resection. In addition, they provide the surgeon with important metabolic information which can help in planning and performing targeted tumour biopsy, particularly in case of large and diffuse lesions. These have been proven to better define tumour structural characterization and, when loaded intraoperatively into the neuronavigation system, significantly help in performing tissue sampling and improving histological and molecular diagnoses.

Intraoperative tumour fluorescence provided by the chemical compound 5-aminolevulinic acid assists surgeons in identifying the true tumour margin during resection of glial neoplasms, consequently increasing the extent of resection [36]. 5-aminolevulinic-derived tumour fluorescence strongly correlates with anaplastic foci of anaplastic gliomas and glioblastomas seen on post-contrast MR or PET imaging. When used intraoperatively in high-grade gliomas, 5-aminolevulinic acid (5-ALA) has been shown to help visualize tumour tissue intraoperatively and significantly improve the possibility of achieving gross total resection of malignant brain tumours, strongly influencing patient survival. Unfortunately, the power in low-grade gliomas is limited.

Intraoperative Neurophysiology or So-called Brain Mapping Techniques

The term intraoperative mapping refers to a group of techniques which allow to safely and effectively remove lesions located in so-called eloquent or functional areas. Although the entire brain can be inferred as eloquent, eloquent areas usually and traditionally include those which are involved in motor, language, visual, or visuospatial control. Surgical removal of such a lesion aims at maximizing surgical removal while minimizing post-operative morbidity. This can be achieved by identification and preservation at the time of surgery of cortical and subcortical sites involved in specific functions [3, 37, 38]. The concept of detecting and preserving the essential functional cortical and subcortical sites has been recently defined as “surgery according to functional boundaries”, and it is performed using the so-called brain mapping technique. Brain mapping techniques are generally applied for the surgical resection of intrinsic lesions, in particularly low-grade gliomas [3, 13, 38–40]. Occasionally, they can also be utilized during removal of cavernoma or meningioma, whenever these lesions are located in or in close vicinity of functional areas of the brain.

To achieve the goal of satisfactory tumour resection associated with the full preservation of the patient’s abilities, a series of neuropsychological, neurophysiological, neuroradiological, and intraoperative investigations has to be performed [37]. Performing brain mapping requires a series of pre-operative evaluations and intra-operative facilities which involve different specialists. A complete neuropsychological evaluation is generally the first step of the process to select suitable patients and to individualize intraoperative testing. Then, sophisticated imaging techniques including fMRI and DTI-FT provide the opportunity to attentively plan surgical strategies. In addition, these images can be loaded into the neuronavigation system, thus becoming available peri- and intraoperatively for orientation (Figure 1). Intraoperative MR can be used as well, if available. Finally, and most importantly, a series of neurophysiological techniques are employed at the time of surgery to precisely guide the surgeon in the tumour removal. These include cortical and subcortical direct electrical stimulation, motor-evoked potentials (MEP), multichannel electromyography (EMG), electroencephalography (EEG) and electrocorticography (ECoG) recordings [3, 13, 37].

Neuropsychological evaluation comprises a large number of tests for the assessment of various neurological functions such as the cognitive, emotional, intelligence, and basic language functions. Such a broad spectrum evaluation provides information on how the tumour impacts the social, emotional, and cognitive life of the patient, which is frequently intact or only mildly impaired at the time of neurological examination. Testing must be done most extensively because the tumour, which grows along fibre tracts, may alter the connectivity between separate areas of the brain, resulting in the impairment of functions which might not be documented if the examination is limited to the testing of those functions strictly related to the area of the brain in which the tumour has grown. When this extensive testing is administered, some alterations in the aspects of the neuropsychological exams can be documented in > 90 % of the patients with low-grade gliomas, and in > 70 % with high-grade gliomas [37–39, 41, 42]. These data represent the baseline with which the effect of surgical and future treatments should be compared. Additionally, when the tumour involves language or visuospatial areas or pathways, a more extensive specific evaluation should also be added. Other than better defining the preoperative status of the patients, the neuropsychological assessment allows to build up a series of tests, composed of various items, which will be used

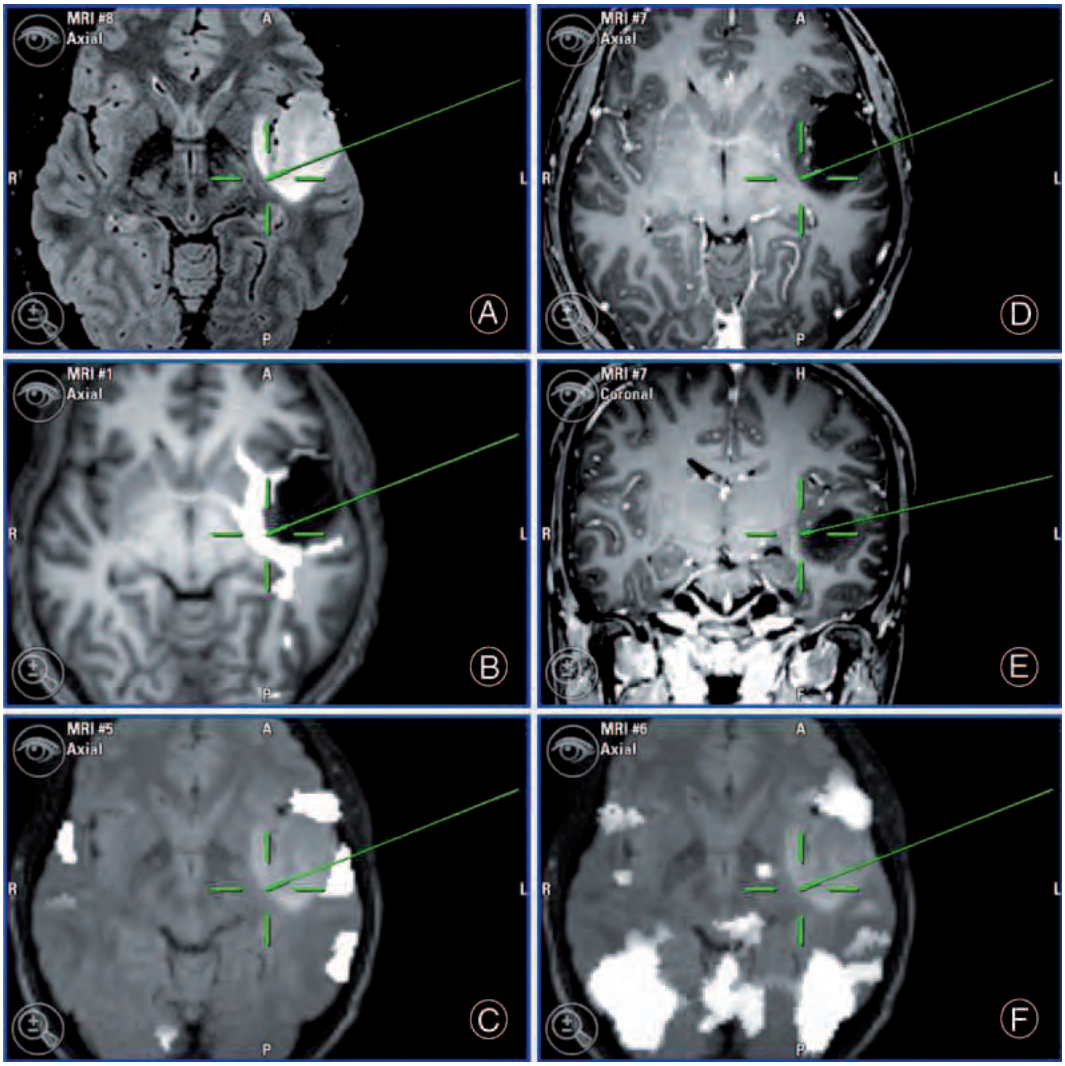

Figure 1. Example of integration in the operating theatre of various types of imaging in a case of left temporo-insular low-grade glioma: **(a)** volumetric FLAIR; **(b)** DTI FT reconstruction of IFO (white) superimposed onto a post-contrast T1-weighted MR image; **(c)** spots of activation for denomination (in white) obtained with fMRI, superimposed onto FLAIR images; **(d)** axial and **(e)** coronal post-contrast-T1 weighted images, and **(f)** spots of activation for verbal generation (in white) obtained with fMRI, superimposed onto FLAIR images. All these images were loaded into the neuronavigation system, co-registered, and fused together to be available during surgery. Surgery was performed in awake anaesthesia and the patient was continuously submitted to object-naming tests by the neuropsychologist during resection. The green cross indicates a subcortical site where semantic paraphrasia was induced by DES, at this site corresponded to the IFO as indicated in **(b)** and to the medial deep border of the tumour, as shown by FLAIR images **(a)**.

intraoperatively, and the brain mapping of various functions, among which memory, language in its various components, and visuospatial orientation are most important [3, 13, 37, 38].

As described, imaging gives the opportunity to carefully plan surgical strategies. In addition, images can be loaded into the neuronavigation system to be available peri- and intraoperatively for orientation. Imaging provides information based on probabilistic measurements, and although they may have a relatively high sensitivity or specificity, they still carry a certain amount of limitations. This is the reason why neuroradiological information loaded into the neuronavigation system always has to be supported during surgery by brain mapping results.

Once the preoperative work-up according to the site and the characteristics of the tumour, the results of the neuropsychological evaluation and of the functional and anatomic imaging are completed, each patient is offered an individualized surgical and monitoring strategy. The protocol includes mapping (DES) and monitoring (EEG, ECoG, MEP) procedures [3, 13, 37]. Intraoperative neurophysiology using DES allows to detect functions located at the cortical and subcortical levels. Detection of motor functions is generally performed in the asleep setting; identification of cortical and subcortical sites for language requires the patient to be awakened during the procedure and to be fully collaborative and actively interact with the in-house neuropsychologist and surgeon. Monitoring procedures allow to detect the intraoperative occurrence of seizures (EEG, ECoG) or of ischaemic events (MEP) (Figure 2).

Resection margins are usually kept very close to essential cortical sites and are usually coincident with subcortical sites. When this is achieved, motor or language deficits develop in the immediate postoperative period in 72.8 % and 65.4 % of cases, respectively. When we considered the results of the long-term postoperative neuropsychological evaluation, we found that 79.5 % of the patients had a long-term postoperative normal language, 18.6 % showed mild disturbances still compatible with normal daily life, and only 2.3 % incurred long-term impairment [13, 17, 37–39, 42]. Surgery performed with the aid of brain mapping techniques allows to reach several oncological endpoints, particularly in case of low-grade gliomas [9, 43–46]. It allows to obtain a large amount of material which helps the pathologist in the histological and molecular diagnosis. It increases the number of cases submitted to surgical treatment: in accordance with previous reports in the literature, this percentage in our series rose from 11 % of cases, when mapping was not available, to

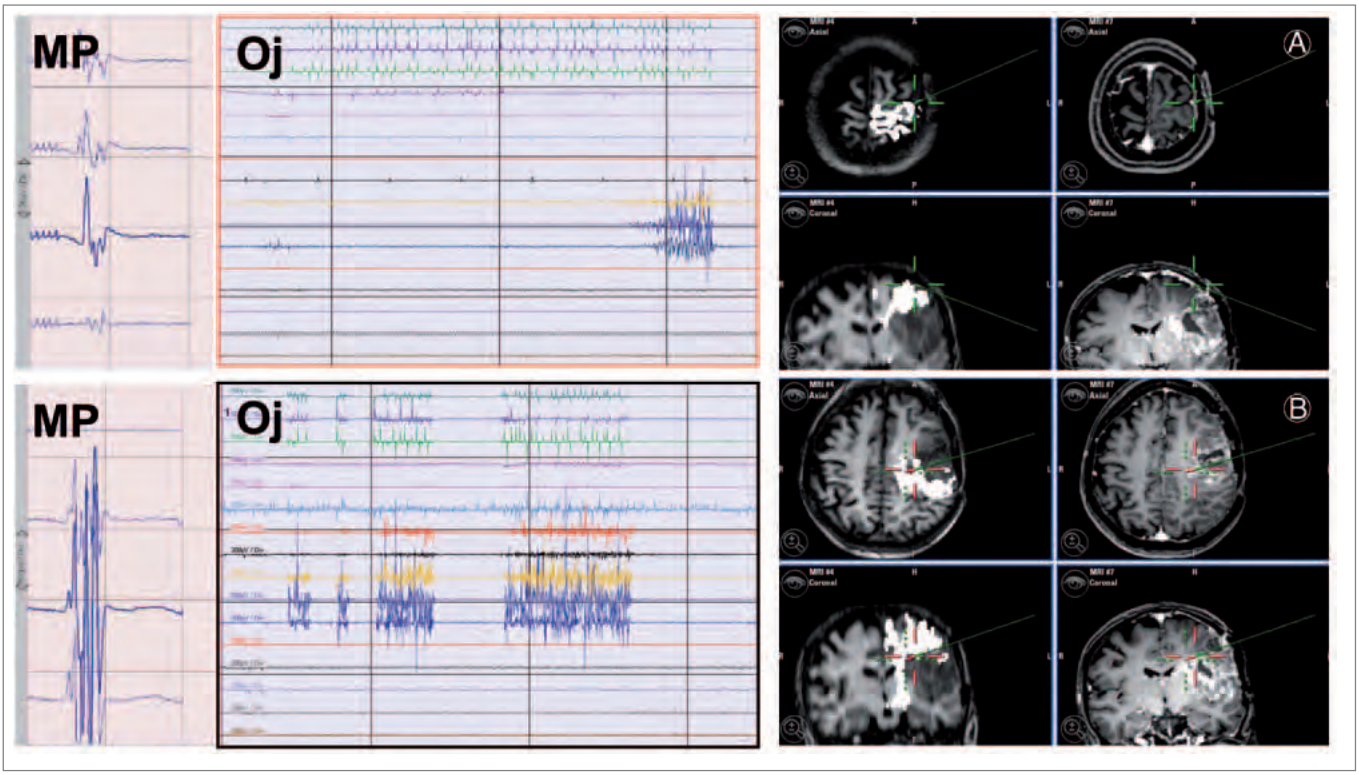

Figure 2. Example of integration of intraoperative neurophysiology with advanced MR imaging (DTI-FT) in a case of a left rolandic tumour. In this case, at the beginning of the resection the surgeon should integrate information coming from DES cortical mapping **(a)** (left and middle panel showing hand motor responses from the hand obtained by train of 5 techniques [left panel]) and 60 Hz probes [middle panel]), to those obtained by DTI-FT. The right panel shows the DTI-FT reconstruction for CST (in white) superimposed onto post-contrast T1-weighted images. The green cross indicates the position of the cortex where DES found hand motor responses. The site corresponded to the CST as indicated by DTI-FT images. The same type of integration is shown during resection at the subcortical level **(b)**. The green cross indicates the site where DES (with both train of 5 techniques and 60 Hz) located hand responses from the subcortical of the CST, which corresponded to the same position in the DTI-FT images.

81 % when mapping was applied, with a significant decrease in the number of cases submitted to biopsy only. Moreover, it decreases the percentage of permanent postoperative deficits, which fell from 33 % to 2.3 % either for language or motor functions [13, 17, 37, 38, 42]. Another important effect is the decrease in the incidence of seizures, particularly in low-grade glioma patients with a long epileptic history and affected by insular tumours. Seizure control is more likely to be achieved after gross-total resection than after subtotal resection/biopsy alone. Lastly, the use of brain mapping techniques increased the percentage of patients in whom a total and subtotal resection was achieved. This is particularly evident in low-grade gliomas. In our series of low-grade gliomas, the percentage of total and subtotal resections rose from 11 % in the pre-mapping period to 69,8 % in the time in which brain mapping techniques were applied [13, 17, 37, 38, 42].

An important observation that helps in planning surgery is the occurrence of the phenomenon of brain plasticity [37, 38]. Cerebral plasticity could be defined as the continuous processing allowing short-, middle-, and long-term remodelling of the neurono-synaptic organization. Plasticity may occur in the preoperative period in low-grade gliomas and in this case is the result of the progressive functional brain reshaping induced by these slowly growing lesions. The most important observation time for the occurrence of brain plasticity is the postoperative period. This has been shown by submitting patients recovered from postoperative deficit status to fMRI, demonstrating the activation of different areas of the brain, close or remote to those involved in the preoperative period. Plasticity may occur either at a cortical level, or, although less frequently, at a subcortical level, where it can be explained by the recruitment or unmasking of parallel and redundant subcortical circuits. The occurrence of plasticity allows for an extension of surgical indications: at the time of first surgery, by extending resection until functional boundaries are encountered, and by allowing the patient to recover in the postoperative period due to the activation of redundant functional areas; at the time of second surgery, when the functional reshaping induced by initial surgery can be used to perform second surgery with the aim to remove areas of the brain initially essential for function but losing their essentiality in terms of function after functional reshaping has been induced by initial surgery or to the continuous slow growth of the tumour. This phenomenon of functional reshaping can be observed up to a period of 6 months after initial surgery and allows to perform a more radical second surgery with an increase in the oncological benefit for the patient. In addition, plasticity can also be enhanced by means of chemotherapy when used in a preoperative setting [47].

Brain mapping techniques require the combined efforts of a multidisclipinary team of neurosurgeons, neuroradiologists, neuropsychologists, and neurophysiologists who contribute together in the definition of the location, extension, and extent of functional involvement that a specific lesion has induced in a particular patient. Each tumour induces particular and specific changes of the functional network that vary among patients. This requires that each treatment plan should be tailored to the tumour and to the patient. When this is achieved, surgery should be accomplished based on functional and anatomical boundaries with the aim of maximum resection with

maximum preservation of patient functionality. This can be reached at the time of initial surgery, depending on the functional organization of the brain, or may require additional surgeries, eventually intermingled with adjuvant treatments. The use of so-called brain mapping techniques extends surgical indications, improves the extent of resection with greater oncological impact, minimizes morbidity, and increases quality of life.

Conclusive Remarks

Surgery has significantly changed in the recent past, mostly due to the progress in imaging and intraoperative neurophysiology. Surgeons should have the ability to critically use different types of imaging, to integrate them in surgical planning and directly incorporate them into the operating theatre. In addition, the surgical procedure requires the active contribution of various professional groups, such as neurophysiologists and neuropsychologists, who all help the surgeon to safely and effectively perform the resection. By means of these developments, surgery is nowadays able to influence patient survival and at the same time to maintain a high level of functional integrity and quality of life.

Conflict of Interest

The authors have no conflict of interest to disclose.

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Tolerability of Chemotherapy in Elderly Patients

Martin Hohenegger

Abstract: In Western countries, prolonged life expectancies increase the importance of geriatric oncology. Consequently, the rationale for an aggressive procedure or best supportive care is a complex evaluation process which has to summarize the global situation of the old patient. While clinical cancer studies are designed on the basis of tumour type, staging, and other factors, factors such age, expected lifetime, performance status, and assessment of elderly patients are neglected. For instance, comorbidities > 75 years are found in almost 80 % for a single chronic disease, while ≥ 3 diagnoses are detectable in ⅓. Thus, it should be the primary aim to balance treatment, side effects, and potential benefits with reasonable therapeutic goals.

While conventional chemotherapy was limited in elderly people by serious life-threatening side effects, novel individualized drug regimens may support compliance and improve therapeutic success. The introduction of novel targeted therapies currently roughens up the field of oncology. However, consequences of the new possible drug combinations in the light of side effects are pending. Particularly in elderly patients, the tolerability of these new concepts requires more evidence-based data, nevertheless, first data on adverse event comparisons are encouraging.

The concept of a comprehensive geriatric assessment has been suggested to evaluate the multidimensional aspects of elderly cancer patients. Thus, profiling the personalized therapy may involve targeted anti-cancer therapy and adapted pharmacokinetics to ensure best clinical outcome. This review will summarize critical pharmacokinetic parameters which are important also in the general pharmacotherapy of elderly people. **Eur Assoc Neurooncol Mag 2011; 1 (1): 21–4.**

Key words: elderly, cancer, renal function, dose adjustment

Introduction

By definition, geriatricians assume now an age > 75 years as the landmark for old age. One can speculate that improvement of overall therapeutic concepts may elevate this threshold into the eighties. Nevertheless, the increase in length of life expectancy is accompanied by diseases and impaired mobility as monitored between 1998 and 2008 in the United States [1]. A central issue in clinical trials including elderly patients is given by the selection bias in favour of treatment. Inclusion criteria support selection of individuals who are considered fit enough to survive the study period. Thus, overall survival may not represent an appropriate endpoint in particular in the oldest age group. Nevertheless, age-stratified analyses in clinical trials may elucidate categories of benefit and harm in these age groups. Consequently, overall outcome and, even more importantly, quality of life aspects are important for elderly people, in particular in the presence of malignancies. Hence, adaption of chemotherapy to age-specific situations and disease parameters may reduce risk of adverse events and interactions from polypharmacy.

Pharmacological cancer therapy in elderly people has to account for pharmacokinetic and -dynamic aspects in view of age-related changes in organ function and disease-related alterations. Age-related changes in organ function might still be physiological and have to be discriminated from disease-related malfunction of organs.

Physiological Changes with Age

Age-related changes in organ functions generally do not result in reduced organ function at rest. However, adaption of organ function is reduced in response to physical activity, stress, or disease-related stress situations and correlates with age. Eg, while lung function in healthy old individuals is not impaired under rest, there is a delayed and diminished response to hypoxia and hypercapnia in the elderly [2, 3]. Similarly, the cardiovascular response to exercise progressively declines with age [4, 5].

Only a limited number of clinical studies are available monitoring the pharmacokinetics of anti-cancer therapeutics in the elderly. In general, a prolongation of the drug half-lives is observed and attributed to a reduction in renal function. This is an oversimplification which does not account for the multiple organic changes due to aging.

Age-related changes in the gastrointestinal tract involve reduction in splanchnic blood flow, motility, and secretory gland activity. This is accompanied by mucosal atrophy, which not only increases the risk for gastric and duodenal ulcerations but also reduces the intestinal surface for drug absorption [6]. To what extent drug absorption is affected solely by age-related alterations in the gastrointestinal tract remains to be elucidated.

Reduced liver mass, liver perfusion, and related metabolic changes have been reported [7, 8], but also raised the question of clinical relevance. Interestingly, reduced levels of cytochrome P450 have been found for CYP2E1, CYP3A, and NADPH cytochrome c reductase, while others have not (see [8]). However, age-related alterations in liver parameters seem to have less impact on drug metabolisation than individual polymorphisms of liver enzymes or drug-drug interactions on the level of hepatic metabolisation [9].

As ageing is associated with a ~1-% reduction in skeletal muscle mass per year, in old people serum creatinine is not predictive for glomerular filtration rates or renal function. Therefore, algorithms have been established to estimate the glomerular filtration rate from serum creatinine. The Cockroft-Gault formula has been used extensively but seems to

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underestimate the glomerular filtration rate [10, 11]. Alternative approaches have been evaluated and found serum concentrations of urea to be a sensitive indicator of renal function in the elderly. Thus, using serum urea levels the Levey algorithm provides an accurate estimation of renal clearance [11]. Nevertheless, the Cockroft-Gault formula has been recently confirmed to be accurate and safe to adopt pharmacotherapy to reduced renal function (CrCl < 50 ml/min) in lung cancer patients [12].

A considerable dose reduction has to be taken into account as soon as the creatinine clearance (CrCl) of patients is < 50 ml/min independent of age [13]. Secondly, drugs with an extrarenal elimination < 50 % require a considerable dose reduction. Which drugs are mostly affected and how is the extent of dose reduction calculated? The database provided by the Clinical Pharmacology and Pharmacoepidemiology Department of the Medical University Heidelberg is very helpful and summarizes the pharmacokinetics of the most commonly used drugs including chemotherapeutics (http://www.dosing.de). Using these instructions, dose adjustment can easily be calculated if necessary. Alternative databases exist and drugs with corresponding pharmacokinetic parameters have been listed in a recent review [13].

In contrast to the decline in total body water, skeletal muscle mass, and renal function, ageing is accompanied by an increase in body fat. Consequently, hydrophilic drugs have a smaller apparent volume of distribution and lipophilic drugs have an increased volume of distribution with a potentially prolonged half-life [13].

Finally, bone marrow mass is reduced in elderly individuals and shows a reduced ability for regeneration. There seems to be a reduction of hematopoietic stem cells which accounts for delayed response rates to treatments with filgrastim, pegfilgrastim, or erythropoietin [14]. Consequently, elderly cancer patients have a higher incidence of myelosuppression and hematotoxicity [15].

Given these various changes in organ and tissue function, the interindividual variability in drug disposition is considerable in elderly persons. In 2008, Hurria and Lichtman summarized chemotherapeutic studies that included elderly patients with reduced performance and found in only 5 out of 18 studies an age-related decrease in drug clearance [15]. Thus, interindividual differences (genetic polymorphisms), comorbidity, and polypharmacy represent higher risk factors than age alone. In conclusion, the complexity of interactions between individual genetic background, comorbidity, polypharmacy, and age-related changes in pharmacokinetics justifies the general rule “start low, go slow”.

Selected Chemotherapeutics in Elderly Patients

Alkylating Chemotherapeutics

This class of drugs includes cyclophosphamide, ifosfamide, melfalan, and temozolomide. Haematotoxicity is clearly the dose-limiting toxicity of these drugs. However, dose modification only due to age is not recommended and might preclude therapeutic success. Cyclophosphamide is metabolized by CYP3A and CYP2B families and adverse effects are expected from the toxic metabolite acrolein. However, a dose reduction by 20–30 % is only justified in case of impaired renal function, but not when it comes to the factor “age” [16]. Temozolomide has an excellent pharmacokinetic profile requiring no dose adjustment even under conditions of reduced renal function. Nevertheless, an age-related increase in the incidence of lymphopenia, neutropenia, and/or thrombocytopenia has been documented [17]. An association of the latter side effects with female gender has been observed as well.

Platinum Compounds

Platinum-containing chemotherapeutics, such as oxaliplatin, cisplatin, and carboplatin, are widely used and show severe side effects [18]. However, there is no evidence for dose adjustment based on age alone. Myelosuppression and peripheral neuropathy are commonly observed, severe side effects and in particular age-related hearing loss upon cisplatin administration have been reported [18].

Nephrotoxicity of cisplatin may lead to a salt-wasting syndrome which upon adequate treatment and hydration exerts an excellent prognosis with rapid recovery [19]. Thus, nephrotoxicity is not related to age, either [20]. Conversely, preexisting renal impairment requires dose adjustment or excludes cisplatin administration in particular in elderly [21].

Antimetabolites

The antimetabolite, 5-fluorouracil (5-FU), is commonly used in chemotherapeutic schemes [22, 23]. The pharmacokinetics of 5-FU are not altered in aged patients; however, an age-dependent increase in toxicity is observed with female preference. The latter is explained by a reduced dihydropyrimidine dehydrogenase activity, the crucial enzyme in 5-FU clearance [24]. Main toxicities involve diarrhoea, mucositis, and haematologic complications. In a retrospective comparison of efficacy and tolerability of 5-FU-based chemotherapies in colon cancer patients, older individuals performed similar and equivalent to younger patients [25]. Overall survival and response rates were not different between age groups. Thus, the authors conclude that palliative chemotherapy in colon cancer patients should not be withheld from elderly patients.

Capecitabine is a pro-drug of 5-FU with prolonged bioavailability and an improved spectrum of side effects. Due to metabolic activation, intact liver function is a prerequisite for the efficacy of capecitabine. Age does not affect the pharmacokinetics of capecitabine in the presence of intact renal function [23]. In patients with reduced CrCl (< 50 ml/min) dose adjustments are mandatory, while an administration < 30 ml/min is not recommended [26]. The spectrum of side effects (diarrhoea, nausea, vomiting, and stomatitis) is similar to 5-FU, but observed less often with capecitabine. The hand-foot syndrome has a higher incidence with capecitabine. Conversely, the incidence of myelosuppression is seen less often with capecitabine [27].

Anthracyclines

Anthracyclines have been widely established chemotherapeutics for a long time. With increasing age, they exert a progres-

sive increase in congestive heart failure. As a consequence, the use of anthracyclines in people > 70 years should be avoided or dosage considerably reduced. The cumulative doxorubicin dose is restricted to 400 mg/m^2 to prevent significant cardiac injury [28]. Besides, myelosuppression is often seen in aged people.

Camptothecins

The pharmacokinetics of the topoisomerase I inhibitor, topotecan, depend on the CrCl and age of the patient. Thus, dose adjustment is required to reduce the risk of myelosuppression in particular in elderly individuals with reduced renal function [15].

The prodrug irinotecan is extensively metabolized by cytochrome P450-3A4 (CYP3A4), which is of clinical relevance. Improved toxicity profile and reduced incidence of severe neutropenia were observed following individualized dosing of irinotecan on the basis of a midazolam clearance test, which is indicative for CYP3A4 activity [29]. Commonly observed side effects include diarrhoea, nausea, vomiting, and asthenia. Interestingly, genetic polymorphisms in the mannose-binding lectin are associated with a higher risk for irinotecan-induced febrile neutropenia corroborating individual stratification of chemotherapy [30].

Discussion

Age Per Se Is Not a Limiting Factor for Chemotherapy

There is accumulating evidence from retrospective studies and subset analyses that older cancer patients benefit from optimum chemotherapy comparable to younger individuals [31]. However, there is a lack of information from prospective studies. Thus, the occurrence of increased toxicity rates in older patients with multiple comorbidities and therefore the risk of drug-drug interactions have lead to a reluctance to treat older patients with biologicals [31]. Consequently, the inclusion of older patients into such clinical trials is urgently needed and adapted study designs have been suggested [32]. Additionally, usage of a geriatric assessment scoring system may facilitate identification of those patients who most likely benefit from optimum treatment (see [33]).

The parameters for decision of therapy have been recently evaluated in elderly patients with incurable non-small cell lung cancer [34, 35]. The driven force for conventional chemotherapy was the aggressive tumour species, while reluctance to receive chemotherapy led to gefitinib administration. Interestingly, the patient's age had no influence on therapeutic decisions.

General Considerations of Chemotherapy in the Elderly

Aged patients suffer from decreased symptom awareness. Therefore, physical activity is relevant in elderly patients and may improve their overall performance. Preliminary evidence from lung cancer patients before and after surgery corroborates that exercise therapy is safe and feasible. Thus, physical activity may be an important consideration in the multidisciplinary management of oncologic patients [36].

Moreover, diagnosis and treatment of complications are delayed, eg, skin alterations, febrile neutropenia, or thrombopenia-related bleedings [37, 38]. Consequently, there is already an attitude to manage side effects by proper observation and thereby to enhance the tolerability of chemotherapy in the elderly [39].

Comorbidity

In general, comorbidities in elderly cancer patients have a bad prognosis, which upon chemotherapy lead to inferior survival and outcomes. These patients are generally not included in clinical trials [35, 40]. Thus, limited information is available on comorbidities. In addition, comorbidity and polypharmacy are highly prevalent in the elderly.

Besides the aforementioned interactions in various organ systems, cardiovascular interactions, in particular ischemic complications, are often seen in high-dose chemotherapy [28, 41]. The spectrum of cardiac side effects of cancer chemotherapy has expanded with the development of combination, adjuvant, and targeted chemotherapies [41]. The cardiac toxicity of anthracyclines has been well-described for a long time and prevented by a dose limitation [28]. Similarly, high doses of cyclophosphamide or ifosfamide also have the potential to develop reversible heart failure and arrhythmias. More often, antibody-based targeted therapies and tyrosine kinase inhibitors are associated with heart failure, hypotension, or hypertension [41]. The molecular mechanisms are so far not clear in the latter cases. Thus, patients with pre-existing cardiovascular risks may substantially improve from referral to a cardiologist for close monitoring of their cardiovascular parameters.

Genetic Background and Polymorphisms

Targeted therapy does not only involve new therapeutics but also exact diagnosis of the individual tumour species and identification of genetic polymorphisms affecting drug pharmacokinetics [42, 43].

Very recently, genetic polymorphisms have been described in the ATP-binding cassette gene B1 (ABCB1, P-glycoprotein) of patients diagnosed with advanced gastric cancer and treated with second-line chemotherapy [44]. The AGCB1 transporter is in part responsible for resistance to several anticancer agents due to extrusion from tumour cells. This mechanism also alters the pharmacokinetics of these drugs with possible impact on therapeutic success. Interestingly, the 3435 CC polymorphism of ABCB1 was significantly associated with longer progression-free survival compared to the CT/TT type polymorphism. The cost-efficient availability of high-throughput techniques may allow for such an individualized genomic approach to identify biomarkers or susceptibility to new pharmacotherapies [42]. Moreover, pharmacogenetic studies are needed to identify genetic polymorphisms in distinct ethnic groups and gender to further optimize pharmacotherapies (see [43]). Finally, these findings will definitely improve individualized drug response and prevent inefficacies and toxicities of anticancer drugs particularly in the elderly.

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Conflict of Interest

The author states that no conflict of interest exists.

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Central Nervous System Toxicity of Chemotherapy

Uwe Schlegel

Abstract: Cytostatic drugs may exert toxic effects on the central nervous system by various mechanisms and may lead to reversible or irreversible neurologic dysfunction. The clinical symptoms are often self-limiting, but may be acute, dramatic, and sometimes even fatal. Since causative therapeutic and even preventive measures are limited, the knowledge of risk factors, characteristic clinical symptoms, symptomatic treatment, and monitoring of the affected patients is essential. **Eur Assoc Neurooncol Mag 2011; 1 (1): 25–9.**

Key words: chemotherapy, neurotoxicity, central nervous system, prevention, therapy

Introduction

Several cytostatic drugs may harm the central nervous system after systemic (intravenous, oral) administration or after topical, ie intrathecal, intraventricular, or intraarterial application. The brain is at particular risk and side effects may present as acute, subacute, or chronic encephalopathy. Seizures, focal symptoms like aphasia or hemiparesis, and cortical blindness may occur as isolated symptoms. These symptoms may present immediately after chemotherapy administration or with delay. Aseptic meningitis is a typical complication of intrathecal therapy; particular drugs can cause cerebellar ataxia, often after a certain cumulative dose has been exceeded. Toxicity to the spinal cord is rare but severe and most frequently it is the result of intrathecal drug administration. Certain antibodies used in oncology, such as rituximab, are associated with an increased risk of progressive multifocal leukoencephalopathy (PML), an opportunistic infection with the JC virus as a result of immunosuppression. However, these and other "indirect" CNS complications of chemotherapy will not be addressed here.

Neurotoxic complications of chemotherapy frequently present with characteristic symptoms and need to be separated from other morphologic (ie metastatic), infectious, or metabolic causes of CNS dysfunction in oncology. Complete or partial recovery may frequently be encountered, but irreversible damage and even death are possible as well. Since therapeutic measures are often limited, prevention is necessary and requires knowledge of neurotoxic side effects to ensure careful monitoring of patients at risk. Discontinuation of chemotherapy is often the only method to prevent further CNS toxicity. The frequency of CNS toxicity depends on the drug chosen, on its single and cumulative doses, on the duration of treatment, and on additional risk factors, such as coexisting neurological morbidity. Well-known factors to substantially increase this risk are dose escalation, combination versus monotherapy, high-dose chemotherapy with stem cell transplantation, and irradiation (RT) of the brain, with chemotherapy after RT probably being more harmful than the reverse sequence [1, 2]. Cytostatics most frequently associated with CNS toxicity are methotrexate (MTX), cytarabine (Ara-C), and ifosfamide. Table 1 shows chemotherapy-induced neurotoxic complications and the respective causative agents.

In the following, characteristic clinical pictures and cytostatics with well-known CNS toxicity will be described. Hypotheses with regard to pathogenesis and possible methods of prevention as well as therapy are discussed.

Acute Encephalopathy

Acute encephalopathy develops within a few hours to days after chemotherapy and presents with disorientation, confusion, agitation, and eventually coma. Myoclonic jerks, seizures, and hallucinatory symptoms may occur. The disorder has to be separated from non-convulsive epileptic state, (viral) encephalitis, metabolic disorders, paraneoplastic syndrome, such as limbic encephalitis, and others [2]. Protocols typically associated with acute encephalopathy include methotrexate (MTX), ifosfamide, and rarely others [3, 4] (Table 1).

Methotrexate

Acute encephalopathy is frequently self-limiting, but may be dramatic or even fatal: a life-threatening acute encephalopathy in a 32-year-old female came to our attention, who was treated for Burkitt lymphoma with 1.5 g/m^2 MTX intravenously (iv) over 24 hours and 15 mg intrathecally. She was found to be of homozygous allelic state of the G-allele of 5-methyltetrahydrofolate-homocysteine S-methyltransferase (MTR) c.2756A>G, which is observed in only approximately 4 % of the general population [5]. MTX-induced leukoencephaloapthy and demyelination have been linked to functional polymorphisms in enzymes influencing the methionine-homocysteine pathway so that S-adenosylmethionine (SAM), the only methyl-group donor in the CNS, is reduced [6, 7] and levels of (toxic) homocysteine [8, 9] may be increased. MTX therapy leads to a lack of the folate derivate used as MTR cofactor and thus to reduced MTR activity resulting in a reduction of SAM bioavailability. The G-allele of MTR c.2756A>G may therefore have pronounced the adverse effect of MTX on SAM synthesis and this rare homozygous allelic state might have contributed to the acute MTX-induced encephalopathy in the patient observed [5]. Since oral SAM substitution can revert CNS demyelination in patients with (inborn) SAM deficiency, SAM and folate-derivates may be interesting candidates for treatment of MTX-induced neurotoxicity [5].

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Table 1. Clinical syndromes of CNS toxicity caused by cytostatic drugs

Acute (reversible) encephalopathy	Methotrexate (MTX) Ifosfamide Paclitaxel 5-fluorouracil (5-FU) Cytosinarabinoside (Ara-C) Procarbazine Nitosoureas (high dose) Interferon-α Interleukin-2 Tamoxifen (high dose) Etoposide, VP16 (high dose) Steroids High dose with stem cell transplantation
Subacute encephalopathy	MTX Cis-platinum
Chronic encephalopathy	MTX iv/intrathecally Infrequently others High-dose polychemotherapies
Reversible posterior (leuko-) encephalopathy syndrome (PRES)	Cyclosporine Combination therapy including cyclophosphamide, Ara-C, cis-platinum, cyclophoshamide, ifosfamide, vincristine, gemcitabine, other immunosuppressants
Multifocal leukoencephalopathy	Capecitabine
Thrombotic microangiopathy	Mitomycine-C Gemcitabine Cyclosporine
Cerebral infarctions	MTX Cyclosporine Platinum derivates
Cortical blindness	Platinum derivates Fludarabine (high dose)
Cerebellar dysfunction	Ara-C 5-FU Infrequently vincristine, cyclosporine
Seizures	MTX, etoposide, VP-16 (high dose) Cis-platinum, vincristine, asparaginase BCNU, dacarbazine, amsacrin Busulfan (high dose), cyclosporine, misonidazol, paclitaxel
Aseptic meningitis	MTX, Ara-C (intrathecally)

Ifosfamide

Ifosfamide is another drug known to potentially induce acute encephalopathy, which may be severe and may even cause death: in 10–15 % of patients treated with dosages > 1 g/m^2 disorientation, lethargia, and coma may occur [4]. Non-convulsive epileptic states caused by ifosfamide have been reported [10]. The pathogenesis is not fully understood, however, ifosfamide and its metabolites may interfere with thiamine function and with that of its phosphorylated forms TPP and TTP, while vitamin B_1 levels themselves are not decreased. Thus, prophylaxis with thiamine, 100 mg iv every 4–6 hours, has been proposed for prevention of ifosfamide-induced encephalopathy [11, 12] as has been therapy/prevention with methylene-blue 50 mg 6× per day iv [13]. However, the therapeutic value of these measures was not confirmed by a recent retrospective analysis [14] and remains difficult to interpret since spontaneous recovery is frequent. A risk factor associated with the occurrence of ifosfamide-induced acute encephalopathy is reduced serum albumine [4, 15].

Subacute Encephalopathy

Subacute encephalopathy is rare and may develop days to weeks after administration of MTX (iv or intrathecally) or of cis-platinum, presenting as abrupt onset of confusion, seizures, focal signs, and symptoms such as hemiparesis and aphasia [4, 8, 16, 17]. Children are mainly affected [8, 16], but single cases in adults have been reported as well [17]. The mechanism of neurotoxicity is poorly understood: symmetrical hyperintense signals in diffusion-weighted imaging (DWI) and decreased apparent diffusion coefficient (ADC) on magnetic resonance imaging (MRI) paralleled the clinical symptoms in a patient reported and disappeared with their resolution. In the absence of vascular or perfusion changes, these MRI findings have been interpreted as cytotoxic oedema of the white matter but sparing the cerebral cortex [17]. Symptoms may resolve completely, however, lethal outcome has been observed [18]. In children suffering from subacute MTX-induced encephalopathy, dextrometorphane 1–2 mg/kg orally, a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, has been applied to 5 affected children, followed by complete resolution of symptoms [8], but has never been re-evaluated systematically since.

Chronic Encephalopathy

Chronic encephalopathy usually starts to develop with a latency of several months to years, is most frequently irreversible and sometimes even progressive. MTX-induced chronic encephalopathy is best known, however, other drugs or polychemotherapies such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) may also cause this complication, however, less frequently [1]. The main risk factor for the development of MTX-induced chronic encephalopathy is whole-brain irradiation [19]. The clinical spectra of chronic encephalopathy range from subtle memory disturbances, disorientation, lack of initiative and apathia to full-blown dementia. No efficient treatment is known. Cerebral imaging shows (often confluent) white matter disease, ie leukoencephalopathy, and progressive deep brain atrophy (Figure 1). It is of note, however, that even long-lasting extensive MTX-induced confluent white matter changes may be clinically asymptomatic [20]. High-dose chemotherapy with haematopoetic stem-cell support in patients with breast cancer was reportedly followed by memory disturbances in some of them [21], however, neuropsychometric findings from long-term follow-up are not available.

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is clinically characterised by headache, visual disturbances, such as visual field deficits and cortical blindness, confusion, seizures, and eventually coma [1]. It has been associated with severe hypertension, eclampsia, but also with administration of immunosuppressants, antibodies, and other substances. In several instances, PRES has been reported after chemotherapy with [22] or without accompanying electrolytic imbalance [23]: T2-weighted MRI shows characteristic hyperintense lesions parieto-occipitally involving the gray and white matters. These signal abnormalities are transient as

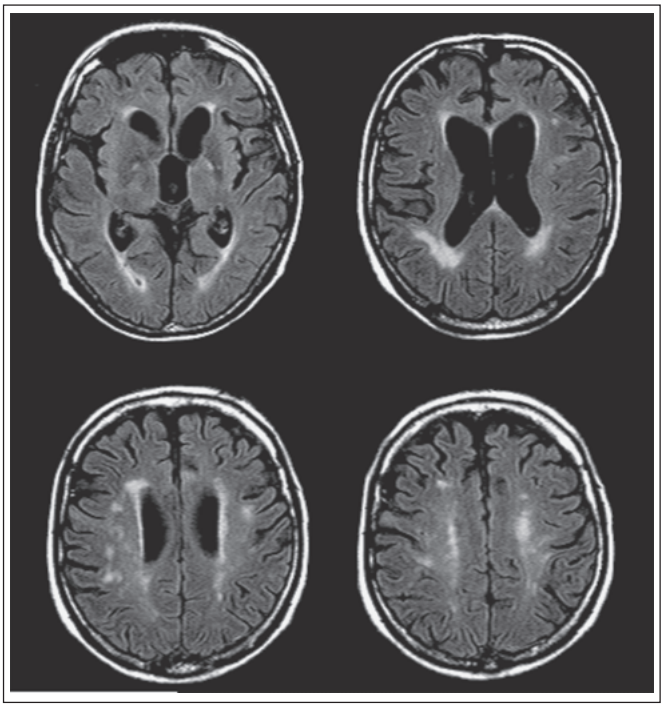

Figure 1. Cerebral MRI (FLAIR) of a 35-year-old male, treated with MTX-based chemotherapy and whole-brain irradiation at the age of 20: ongoing complete response of a high-grade malignant Non-Hodgkin's B-cell lymphoma. Cognitive dysfunction due to leukoencephalopathy and deep-brain atrophy.

is the clinical syndrome, which usually resolves within days after cessation of therapy and symptomatic treatment of seizures and electrolytic imbalance [22].

Cerebellar Dysfunction

Cerebellar dysfunction with dysarthria, nystagmus, and ataxia is a typical complication of cytarabine, usually at cumulative dosages > 36 g/m^2 [4], however, this complication has been encountered in single cases with lower dosages. Neuropathologic examination of patients coming to die with but not because of this complication showed widespread Purkinje cell loss [1]. Risk factors for the development of cerebellar dysfunction are older age, increased serum creatinine, and alkaline phosphatase [24]. The disorder is rarely accompanied by an acute encephalopathy, which is reversible after cessation of therapy. A similar cerebellar syndrome may be encountered after therapy with high-dose 5-fluorouracil, which is reversible after interruption of therapy, but may recur at drug re-exposure [1].

Cerebral Infarctions

Single cases of cerebral ischemia after MTX, platinum-derivates, and cyclosporine have been reported, primarily in children treated with MTX for acute leukaemia [16]. Patients receiving high doses may develop microangiopathy with calcifications in the vessel wall [16]. Thrombotic microangiopathy has been reported after exposure to mitomycine C, gemcitabine, and cyclosporine [1].

Myelopathy

Acute myelopathy with ascending para- or tetraparesis is a rare but devastating complication of intrathecal therapy with

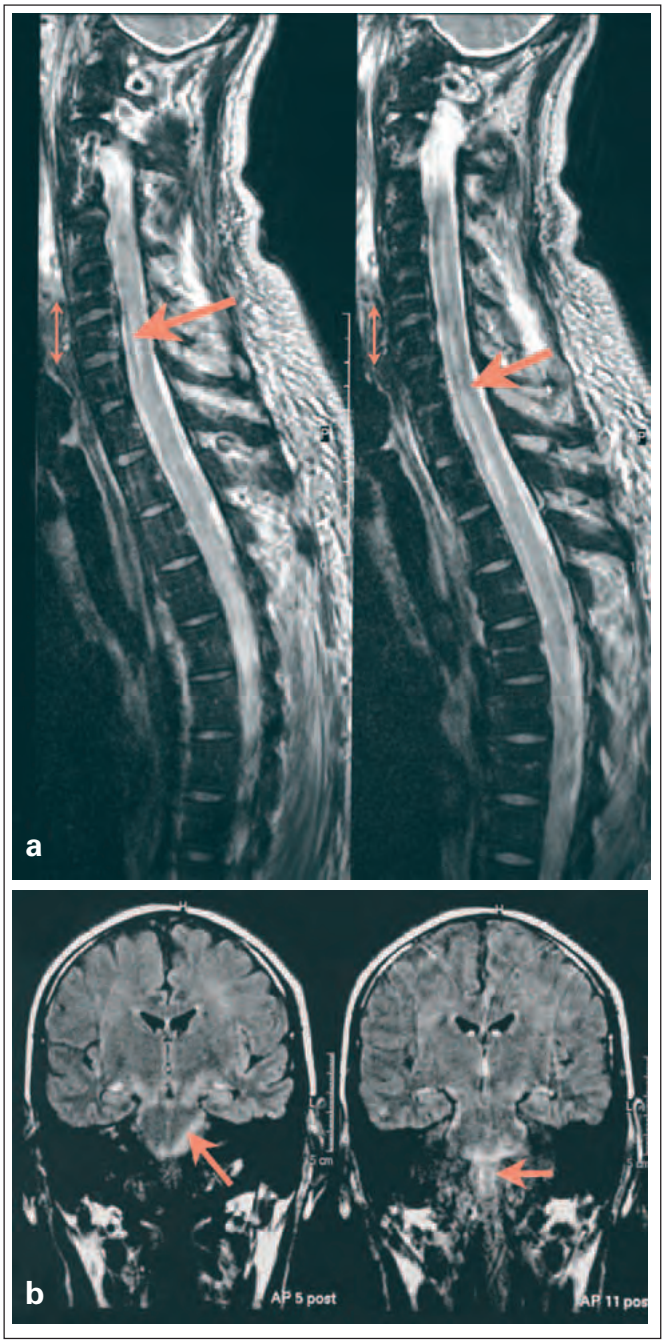

Figure 2. (a) MRI (T2-weighted) of the cervicothoracic spine showing extensive myelopathy (arrows) after intrathecal MTX 12 mg, Ara-C 30 mg + prednisolone 2.5 mg in a 31-year-old male treated for leukaemia ("triple therapy"): tetraplegia developing over 24 hours shortly after application. **(b)** Cerebral MRI of the same patient (FLAIR) showing affection of the pons (arrow) and medulla (arrow) resulting in coma and mechanic ventilation. Incomplete recovery with persistent paraparesis and severe bilateral hyakusis.

MTX [25], Ara-C [26] or with a combination of these („triple-therapy" with MTX, Ara-C, and steroids) [1, 25–27]. It can occur even after single-dose exposure, may involve the brainstem, as exemplified in Figure 2, may lead to a locked-in syndrome [1] or even death due to acute "encephalomyelitis" [28]. Possible risk factors are extensive meningeal disease, irradiation of the CNS, and childhood or old age [2]. The pathologic finding is that of a necrotizing myelopathy; efficient therapies have not been established. However, a recent case has been reported on a 54-year-old female with MTX-induced severe myelopathy who showed partial remission of symptoms beginning 3 days after continuous substitution of S-adenosymethionine (SAM) 3× 200 mg/die, folic acid 4×

Table 2. Therapy/prophylaxis of chemotherapy-induced CNS toxicity

Drug	Symptoms	Frequency	Threshold dosage	Risk factor	Therapy/prophylaxis
Methothrexate	Acute reversible encephalopathy	Rare	> 0.5 g/m² (?)	Whole-brain radiotherapy	Frequently self-limiting
	Subacute encephalopathy	Very rare	After 2nd or 3rd iv application	Homocysteine ↑	Dextrometorphan (?)
	Chronic encephalopathy	Infrequent after MTX alone	> 0.5 g/m² (?)	Whole-brain radiotherapy, intrathecal MTX	None
	Meningitis	< 10 %	Only after →	intrathecal application	Symptomatic
	Seizures	Infrequent	?	Seizures prior to application	Symptomatic
	Myelitis/ myelopathy	Very rare	?	Young/old age, aggressive leukaemia, radiotherapy	"CSF exchange"? Multiple folate metabolites
Ara-C	Cerebellar dysfunction + facultative acute encephalopathy	Frequent, if →	cumulative dose > 36 g/m²	Renal insufficiency, alkaline phosphatase ↑ age > 60, neurological comorbidity	Frequently self-limiting
	Meningitis	like →	MTX		
	Myelitis	like →	MTX		"CSF exchange"?
5-Fluorouracil	Acute encephalopathy	Rare	?	Dihydropyrimidine dehydrogenase ↓	None
	Cerebellar dysfunction + facultative additional CNS symptoms			+ Allopurinol + N-Phosphonoacetyl-L-aspartat (PALA) + thymidine	Often self-limiting
	Inflammatory multifocal leukencephalopathy			+ Levamisol	None
Ifosfamide	Acute encephalopathy	Up to 30 %	?	High dose, renal, hepatic insufficiency, albumine ↓	Frequently self-limiting; methylene-blue, thiamine?

20 mg/die, cyanocobalamine 100 µg/die and methionine 5 g/die (iv for one week, then orally) [29]. For lack of other established treatments, substitution of these derivates of the folic acid and methionine/homocysteine metabolic pathway may be tried as well as complete CSF "exchange".

Others

Other neurotoxic complications of chemotherapy are listed in table 2. Five patients with capecitabine-induced multifocal leukoencephalopathy have been described with clinically and radiologically (nearly) complete resolution of signs and symptoms after discontinuation of the drug [30]. Cortical blindness may occur as an isolated symptom after cis-platinum or fludarabine administration [1]. Seizures may follow the administration of many drugs, in particular the systemic or intrathecal application of MTX [31]. Aseptic meningitis and headache affect about 10 % of patients receiving intrathecal chemotherapy [2].

Differential Diagnosis

The diagnosis of chemotherapy-related neurotoxicity can only be established if other possible causes of neurologic dysfunction are excluded: Parenchymatous and/or leptomeningeal metastatic disease has to be ruled out by MRI and CSF analysis. Epileptic seizures may present as non-convulsive status epilepticus, which can only be diagnosed by EEG recording. This is in particular necessary if ifosfamide-induced acute encephalopathy is suspected, since ifosfamide may cause a non-convulsive status [10] which needs to be treated accordingly. Routine clinical chemistry including electrolytes and metabolic measures are essential since in patients treated for malignant tumours, infectious complications, electrolytic imbalances, disturbances of osmolarity, renal and hepatic failures, thiamine deficiency, endocrine disturbances, and tumour lysis syndrome need to be considered. The diagnosis of a paraneoplastic neurological syndrome can be confirmed by detection of specific antibodies.

Conflict of Interest

The author has received honoraria from Essex-Pharma, Mundipharma, Amgen, and Sigma-Tau.

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Management of Brain Metastases: A Case Study

Anna Berghoff[1], Julia Furtner[2], Adelheid Wöhrer[3], Brigitte Gatterbauer[4], Karin Dieckmann[5], Matthias Preusser[1]

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Introduction

A 53-year-old male patient presented with headache, right-sided motor dysfunction, impaired vision, and intermittent confusion since one week. The medical history included former alcoholism, chronic pancreatitis with insulin-dependent diabetes, and nicotine abuse.

Computed cranial tomography (CCT) showed an 8-cm, partially cystic lesion with marked contrast agent uptake and perifocal edema in the left temporoparietal lobes (Fig 1A) and an additional small lesion in the right parietal lobes (Fig 1B). Due to the cerebrospinal fluid circulation impairment, acute craniotomy and neurosurgical resection of the left parieto-occipital lesion was performed.

What Is Your Diagnosis?

The histopathological examination revealed metastases of a solid carcinoma, most likely a non-small-cell carcinoma of the lung (Fig 2). Immunohistochemically, the tumor tissue was positive for cytokeratin 7 (CK-7) and thyroid transcription factor 1 (TTF1) and negative for synaptophysin, neuron-specific enolase (NSE), and chromogranin A. Indeed, a whole-body CT showed a 5-cm and several smaller tumourous lesions with inhomogeneous contrast medium enhancement in both lungs (Fig 3). In addition, there were a 4-cm metastasis in the right adrenal gland and abdominal lymph node metastases.

Clinical Course

We treated the patient with whole-brain radiotherapy (WBRT) at 30 Gray (Gy) in 10 fractions, stereotactic radiosurgery of the right parietal metastasis, and 8 cycles of intravenous chemotherapy with cisplatin and etoposide. The therapy was well-tolerated. Periodic re-staging CTs showed a stable systemic disease according to the RECIST criteria and initially there was complete response of the cerebral metastases. However, 11 months after first diagnosis, a follow-up MRI showed 2 new intracerebral metastases, one in the cerebellum and one in the parietal lobe. At this time, there was stable systemic disease as documented by CT and the patient was in good clinical condition (Karnofsky Performance Status 80 %). We treated both new brain metastases with radiosurgery. Two months later, a follow-up MRI showed no neoplastic lesions but

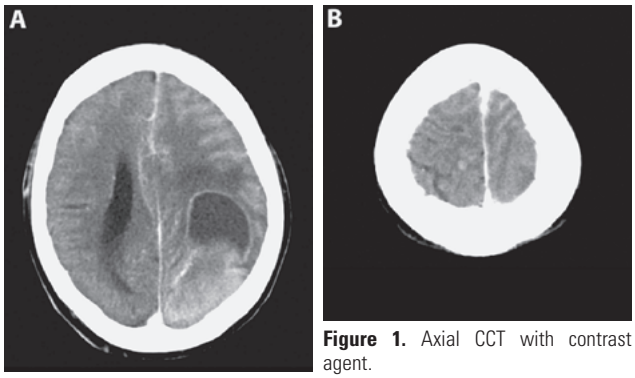

Figure 1. Axial CCT with contrast agent.

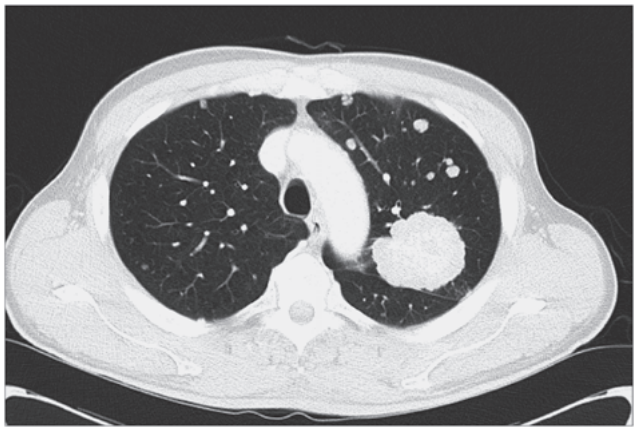

Figure 3. Thoracic CT with contrast agent.

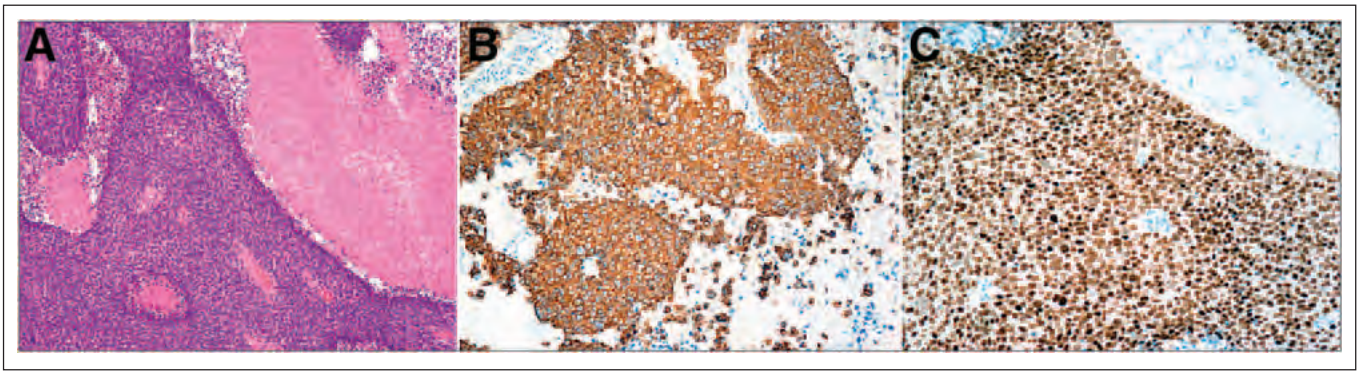

Figure 2. Histopathology and immunohistochemistry. **(A)** Hematoxylin and eosin, **(B)** anti-cytokeratin (Lu-5), **(C)** anti-thyroid transcription factor (TTF) 1-alpha.

marked leukoencephalopathy (Fig 4). There was progressive decline with episodes of confusion, repeated seizures, and somnolence despite intensive symptomatic therapy. A home palliative care unit was involved and the patient died 14 months after initial diagnosis.

Comments

Brain metastases are the most common malignancy of the central nervous system. The most common primary carcinomas are lung cancer, breast cancer, melanoma, colorectal cancer, renal-cell carcinoma, and cancer of unknown primary origin [1]. Prognosis of patients with brain metastases is generally poor (median survival 2.3–7.1 months) and therapy aims to provide optimum quality of life while reducing tumour relapses [2]. Appropriate treatment is based on prognostic indices which consider the patient's age, Karnofsky Performance Status, number of brain metastases, and the activity of extracranial disease [3]. The modern multidisciplinary management of brain metastases includes neurosurgical resection, stereotactic radiosurgery, WBRT as well as systemic therapies [4]. Surgery of a single metastasis may be considered in patients with controlled systemic disease and good performance status with the aim to relieve symptoms associated with a large tumor or impairment of CSF flow, achieve local control, or establish a histopathological diagnosis [2]. Stereotactic radiosurgery permits the treatment of few metastases of 3–3.5 cm maximum diameter. [2] Adjuvant WBRT after surgery or radiosurgery significantly reduces intracranial relapses and neurologic deaths, but does not improve functional independence or overall survival [5]. The true risk of cognitive deficits in long-term survivors is not well-known. The limiting factors for systemic therapy like chemotherapy, radiosensitizers, and biologic agents are the blood-brain-barrier penetration and the efficacy in specific tumour histologies [2]. In conclusion, the ideal combination of treatments remains a matter of research. Further prospective series are needed to optimize and individualize care of patients with brain metastases.

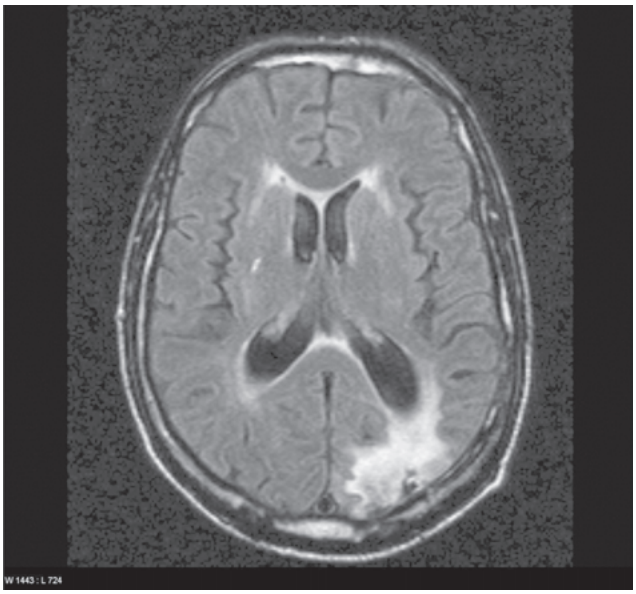

Figure 4. Axial FLAIR-MRI.

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A 39-Year-Old Patient with Double Vision and Rapidly Progressing Bulbar Palsy

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Case Report

A 39-year-old male patient with a history of an upper respiratory tract infection 4 weeks before admission presented with headache, vertigo, and abdominal pain persisting for 2 weeks.

Neurologic examination, laboratory findings, gastroscopy, and an abdominal ultrasound remained negative except for leukocytosis (18,100 WBC/µl) and gastrooesophageal reflux disease. Three days after admission to the local hospital the patient developed double vision, dysphagia, blurred speech, and an unsteady gait. Neurologic examination revealed palsy of the sixth nerve, dysarthria, areflexia, and ataxia. Contrast-enhanced cerebral CT showed no abnormalities.

Lumbar puncture (LP) revealed a CSF pleocytosis (90 cells/µl) with protein and glucose within normal limits. A differential diagnosis of encephalitis versus Miller-Fisher syndrome was made. In favour of a viral aetiology the patient received aciclovir 1 g 3×/day and was transferred to the neurology department of our clinic.

Nerve conduction velocity studies and anti-ganglioside antibodies were within normal limits. Cerebral MRI showed diffuse leptomeningeal enhancement (Figure 1). A second LP revealed an elevated CSF protein (61 mg/dl) and pleocytosis (80 cells/µl). Treatment with aciclovir (750 mg 3×/day) was continued and intravenous antibiotics covering listeria spp and legionella spp were added.

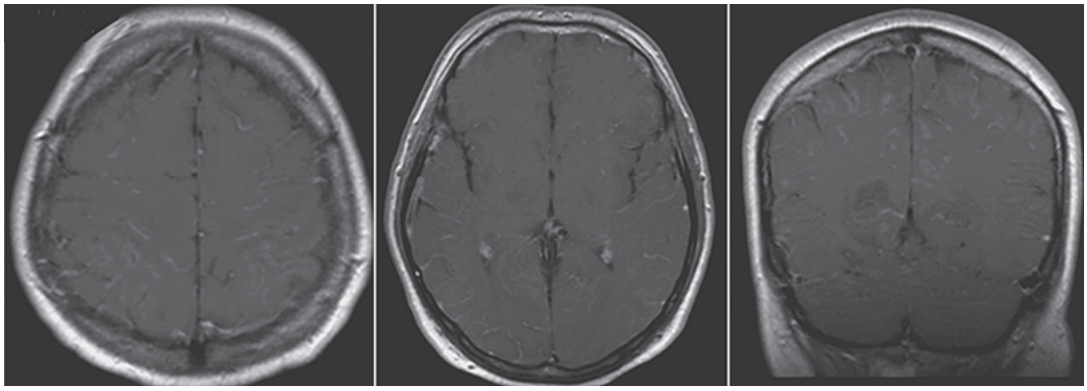
Unfortunately, the patient rapidly deteriorated and required artificial ventilation 2 days after admission.

What Is Your Diagnosis?

Meanwhile, the results of the extended CSF diagnostics were available yielding malignant cells in the CSF (Figure 2a) indicating neoplastic meningitis.

In search of the primary tumour, elevated serum CEA (carcinoembryonal antigen 170 µg/l [upper limit 5 µg/l]) and CA 19-9 (carbohydrate 34,815 kU/l [upper limit 37 kU/l]) were detected. A whole-body CT revealed metastases in the

Figure 1. Cerebral MRI (T1 with gadolinium enhancement) showing diffuse leptomeningeal enhancement.



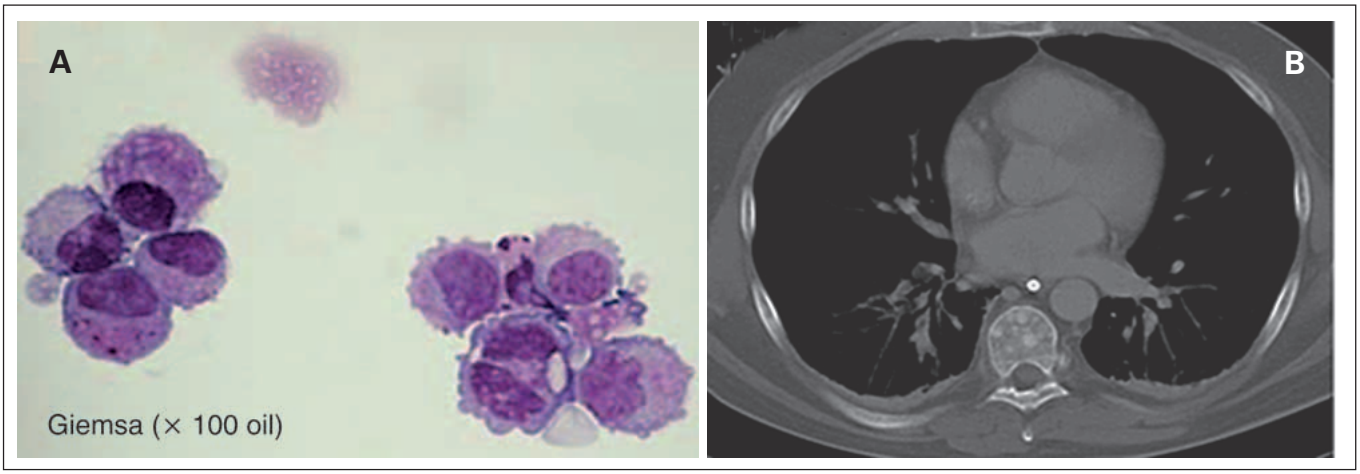


Figure 2. (a) CSF-cytology with clusters of carcinoma cells and **(b)** CT showing bone metastases in the thoracic spine.

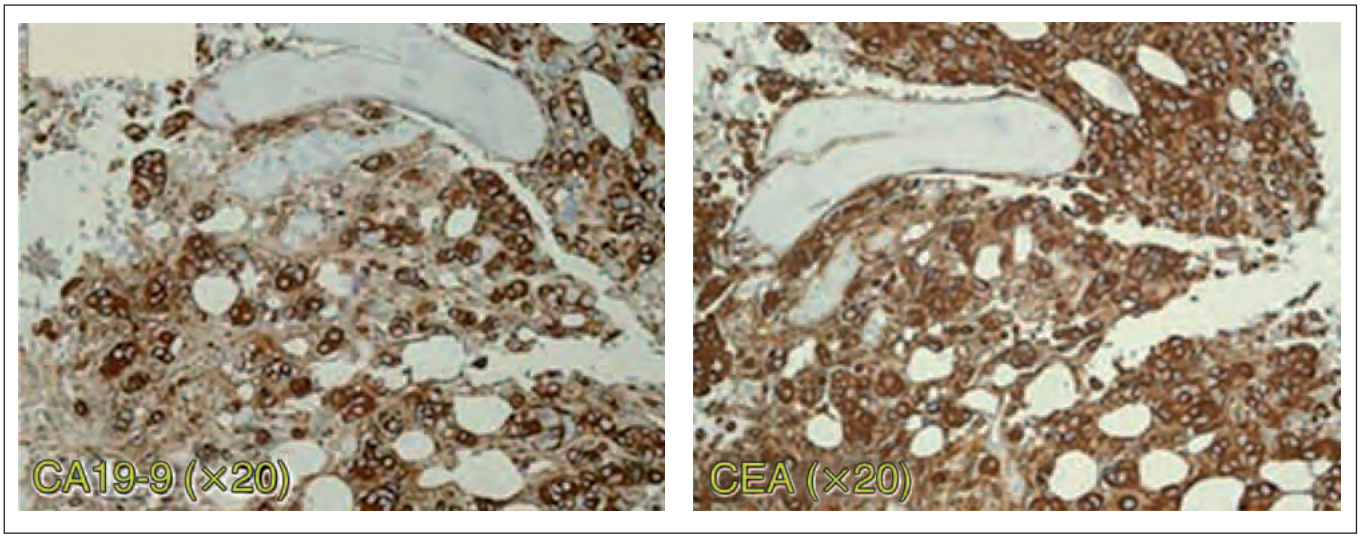


Figure 3. Immunohistochemistry of bone marrow biopsy stained for CA 19-9 and CEA.

thoracic spine (Figure 2b). A bone marrow biopsy showed tumour formations of an anaplastic adenocarcinoma with signet cells and immunohistochemical expression of CEA and CA19-9 indicative of a gastrointestinal malignancy (Figure 3). The clinical course was characterized by a fulminant brain oedema refractory to steroids and other antioedematous therapies and the patient died 5 days after admission to the intensive care unit.

Autopsy confirmed a poorly differentiated gastric adenocarcinoma (Lauren diffuse type, linitis plastica) with peritoneal carcinomatosis, bone metastases, and carcinomatous meningitis (CM) without brain parenchymal metastases.

Comments

This case of CM as the presenting manifestation of gastric cancer is instructional in several respects and deserves some annotation.

CM, which complicates systemic cancers in 3–8 %, represents the primary symptomatic site in up to 5 % of cases with confirmed CM [1]. Although CM was first reported in a patient with gastric cancer, only a few cases have been published in the literature [2]. The largest series of CM complicating gastric cancer has been reported from Korea, where gastric cancer represents the most common malignant solid tumour. In a systematic analysis of 54 cases with CM complicating gastric cancer, CM represented the initial clinical manifestation in 5 of these patients [3].

The patient presented with an unusually fulminant course of CM and gastric cancer was not detected by gastroscopy performed only 2 weeks before the patient's death. Interestingly, a subtype of a poorly differentiated adenocarcinoma called linitis plastica (LP) has been reported to mainly affect young adults and to be particularly aggressive in nature and tricky to diagnose locally [4]. This subtype originates in the submucosa and infiltrates all segments of the gastric wall, resulting in a typically segmental rigidity rather than luminal stenosis [4]. Out of several different possible routes by which cancer cells can reach the CSF space, direct infiltration into the paravertebral venous plexus (Batson's venous plexus) or spinal bone metastases may favour development of CM in this particular type of malignancy.

In conclusion, CM as the initial manifestation of gastric cancer is unusual with 11 patients reported in the literature including our case [5]. Gastric linitis adenocarcinoma represents a particularly aggressive subtype and CM may develop early in the course of the metastatic disease.

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Guidelines on the Management of Low-grade Gliomas: EANO Task Force Report

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Abstract: In adults, diffuse infiltrative low-grade gliomas of the cerebral hemispheres are a group of tumours with distinct clinical, histological, and molecular characteristics whose management is still controversial. Scientific evidence from the literature was evaluated and graded according to the EFNS guidelines and recommendations were given accordingly. The WHO classification recognizes grade-II astrocytomas, oligodendrogliomas, and oligoastrocytomas. MRI is used for differential diagnosis, guiding surgery, planning radiotherapy, and monitoring treatment response. Advanced imaging techniques can increase the diagnostic accuracy. Younger age, normal neurological examination, oligodendroglial histology, and 1p loss are favourable prognostic factors. Prophylactic administration of antiepileptic drugs is not useful whilst there is no evidence that one drug is superior to others. Total/near total resection can improve seizure control as well as progression-free and overall survivals while reducing the risk of malignant transformation. Early post-operative radiotherapy improves progression-free but not overall survival. Low doses of radiation are as effective as high doses and better tolerated. Modern radiotherapy techniques reduce the risk of late cognitive deficits. Chemotherapy can be useful both at recurrence after radiotherapy and as an initial treatment after surgery to delay the risk of late neurotoxicity from large-field radiotherapy and improve seizure control. Neurocognitive deficits are frequent and can be caused by the tumour itself, tumour-related epilepsy, treatments, and psychological distress. **Eur Assoc Neurooncol Mag 2011; 1 (1): 37–44.**

Key words: low-grade glioma, guideline, diagnosis, treatment

Introduction

Low-grade gliomas (LGGs) are a group of tumours with distinct clinical, histological, and molecular characteristics. These guidelines will focus on diffuse infiltrative WHO grade-II tumours of the cerebral hemispheres in adults. Brain stem or cerebellar tumours, which are rare and present specific problems of management, will not be discussed. LGGs represent up to 30 % of gliomas and affect patients at a younger age than high-grade gliomas. LGGs are commonly located in or close to eloquent areas, ie, those areas of the brain involved in motor, language, visuospatial, and memory function [1]. The 5-year overall (OS) and progression-free survival (PFS) rates in randomized studies range from 58–72 % and 37–55 %, respectively. Patients with LGGs may survive for up to 20 years [2], but these tumours grow continuously [3, 4] and tend to progress to a higher grade, leading to neurological disability and ultimately to death. The optimal treatment of patients with LGG is still controversial [5].

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Search Strategy

We searched the following databases: the Cochrane Library to date, Medline-Ovid (January 1966 to date), Medline-ProQuest, Medline-EIFL, Embase-Ovid (January 1990 to date), Cancer Net, and Science Citation Index. We used specific and sensitive key words as well as combinations of key words, and publications in any language from countries represented in the Task Force. The search was completed in June 2011.

Methods for Reaching Consensus

The panel covered all fields of expertise in neuro-oncology, ie, neurosurgeons, neurologists, neuropathologists, radiation and medical oncologists, and a clinical trials expert.

The scientific evidence of papers collected from the literature was evaluated and graded according to the EFNS guidelines and recommendations were given accordingly [6]. Class-I evidence was derived from prospective, randomized, well-controlled clinical trials; class-II evidence was derived from prospective studies, including observational studies, cohort studies and case-control studies; class-III evidence was derived from retrospective studies; class-IV evidence was derived from uncontrolled case series, case reports, and expert opinion. As for recommendations, level A required at least one class-I study or 2 consistent class-II studies, level B at least one class-II study or overwhelming class-III evidence and level C at least 2 consistent class-III studies. Regarding pathology and genetics, the classification of evidence was limited to the strongest aspects in terms of prognosis, whilst clinical features and conventional MRI were simply reviewed but not graded. When sufficient evidence for recommendations A–C was not available, we gave a recommendation as a Good Practice Point if all Task Force members agreed. When analyzing results and drawing recommendations, at any stage, the differences were resolved by discussion.

Review of the Evidence

Pathology and Genetics

The World Health Organization (WHO) classification [7] recognizes grade-II astrocytomas, oligodendrogliomas, and oligoastrocytomas (class I). Morphological features distinguish astrocytomas from oligodendrogliomas. However, application of the same diagnostic criteria poses difficulties for the separation of oligoastrocytomas from both astrocytomas and oligodendrogliomas because the diagnostic features present as a continuum from one end of the histological spectrum to the other and modern surgical approaches and scientific interest in fresh tumour tissue reduce the amount of material seen by neuropathologists. This aggravates the inherent sampling problem and prevents the WHO from providing a recommendation on the proportion of tissues with astrocytic or oligodendroglial differentiation required for the diagnosis of oligoastrocytomas.

Diffuse astrocytomas include fibrillary, gemistocytic, and protoplasmic variants. The most common is the fibrillary astrocytoma. It is important to separate gemistocytic astrocytomas because they are more prone to malignant progression. The fibrillary astrocytoma is composed of a uniform cell population with only moderate nuclear atypia in a fine fibrillary tumour matrix. The hallmark of the gemistocytic variant are cells with ballooned eosinophilic cytoplasm and eccentric nuclei making up > 20 % of the tumour cells. The mitotic activity in astrocytomas WHO grade II is very low; single mitosis should not result in the diagnosis of an anaplastic astrocytoma, while single mitosis in stereotactic biopsy should raise the suspicion of anaplasia.

The single most frequent molecular alteration in astrocytomas is the IDH1 mutation reported in 75 % of astrocytomas [8]. However, this alteration is seen with comparable frequency in oligodendroglial tumours and thus represents a marker unifying astrocytomas, oligoastrocytomas, and oligodendrogliomas of WHO grades II and III.

Development of an IDH1-R132H mutation-specific antibody (H09) greatly assists in the diagnosis of astrocytomas as well as oligodendrogliomas and oligoastrocytomas [8]. H09 covers > 90 % of all IDH1 mutations in diffuse gliomas and separates these tumours from other lower-grade gliomas [9]. The Ki-67/MIB-1 labelling index in diffuse astrocytomas usually is < 4 %. Tumour necrosis, vascular proliferation, vascular thrombosis, and high mitotic activity are not compatible with diffuse astrocytomas WHO grade II. The best immunohistochemical marker is glial fibrillary acidic protein, which is expressed in both tumour cells and astrocytic processes. Molecular findings typical for diffuse astrocytoma are TP53 mutations in 50 % of cases; gemistocytic astrocytomas carry TP53 mutations in > 80 % whilst combined 1p/19q deletion is rare [10]. Oligodendrogliomas are moderately cellular and typically exhibit perinuclear halos termed “fried egg” or “honey comb pattern”. Occasionally, tumour cells with a small, strongly eosinophilic cytoplasm are encountered and termed mini-gemistocytes. Oligodendrogliomas have a dense network of capillaries and frequently contain calcifications. Occasional mitoses and a Ki-67/MIB-1 labelling index up to 5 % are compatible with oligodendrogliomas WHO grade II. There is no immunohistochemical marker specific for oligodendrogliomas.

The molecular hallmark of oligodendrogliomas is combined loss of 1p/19q occurring in 80 % of these tumours [11] (class II), whilst TP53 mutations are encountered in only 5 %. Somatic IDH1 mutations are present in 80 % of oligodendrogliomas [12, 13]. Oligoastrocytomas should be diagnosed upon detection of convincing astrocytic and oligodendroglial components, but the interobserver difference for the diagnosis of oligoastrocytomas remains high [14]. Most oligoastrocytomas carry either 1p/19q loss or TP53 mutations and there is a tendency for these aberrations to be present in both tumour compartments [15]. Up to 80 % of oligoastrocytomas carry somatic mutations in IDH1 [12, 13].

Clinical Features

Seizures are the most common presentation and may be partial or generalized. They occur in > 90 % of patients and are intractable in 50 %. Seizures are more frequently associated with cortically based tumours, particularly in frontal, temporal, and insular/parainsular location and with oligodendroglial tumours [16].

There is no clear association between severity of epilepsy and behaviour of the tumour. Focal neurological deficits are unusual, developing over many years. Raised intracranial pressure is rare in patients with supratentorial tumours and is typically seen in posterior fossa and intraventricular tumours. Intratumoural haemorrhage can occur.

Conventional and Advanced Neuroimaging

Standard MRI sequences are useful for differential diagnosis, guiding biopsy or resection, planning radiotherapy (RT), and monitoring treatment response [17]. LGGs appear as low-signal mass lesions on T1-weighted MRI and high signal on T2-weighted and FLAIR sequences. Contrast enhancement is usually absent; when present, it may indicate a focal area of high-grade transformation, although some tumours, particularly oligodendrogliomas, have patchy enhancement, which remains stable over time.

The use of advanced imaging techniques can increase diagnostic accuracy [18, 19] (class II–III). Proton Magnetic Resonance Spectroscopy (MRS) measures major metabolites in tumour tissue. The typical spectrum of an LGG shows elevated choline, reflecting increased membrane turnover and decreased N-acetyl-aspartate (reflecting neuronal loss), but similar abnormal spectra may be seen in non-neoplastic lesions. Grading of gliomas is not possible by spectroscopy alone as there is a considerable overlap between low- and high-grade lesions. The presence of lactate and lipids is associated with higher proliferative activity and more aggressive behaviour [20]. MRS is helpful in guiding a biopsy to an area of high-grade activity but not in longitudinal monitoring [21]. Dynamic susceptibility contrast MRI (DSC-MRI) allows for the measurement of relative cerebral blood volume (rCBV) that correlates with vascularity at the histological level. Increase in rCBV in LGGs predicts high-grade transformation before gadolinium enhancement occurs [22]; however, these

observations are limited to astrocytomas since oligodendrogliomas have significantly higher rCBV [23]. Dynamic Contrast-Enhanced Imaging (DCE-MRI) measures the permeability of the blood-brain barrier by means of the transfer coefficient, Ktrans, which is related to the tumour grade although the correlation is not as strong as for rCBV [24]. Regarding diffusion-weighted imaging, apparent diffusion coefficient (ADC) values are lower and more variable in oligodendrogliomas compared with astrocytomas [25]. There is no correlation between ADC and choline [26]. Quantitative MRI in oligodendrogliomas with loss of heterozygosity of chromosome 1p/19q shows more heterogeneous T1- and T2-dependent signals, less distinct margins, and higher rCBV than in tumours with intact chromosomes [27, 28].

PET Imaging

PET with [18F]-fluorodeoxyglucose (FDG) is of limited value since LGGs show a low FDG uptake compared to the normal cortex. The usefulness of FDG-PET is limited to the detection of anaplastic transformation in astrocytomas [29] (class III) and to the differentiation of radiation necrosis from tumour recurrence [30] (class II). PET with 11C-methionine (MET) is most frequently used and the uptake of MET correlates with the proliferative activity of tumour cells. The background uptake with MET-PET in normal brain tissue is lower than with FDG-PET, providing good contrast with tumour uptake and delineation of LGG [31].

LGGs with an oligodendroglial component show a higher MET uptake. PET with MET is useful in differentiating LGGs from non-tumoural lesions [32] (class II), guiding stereotactic biopsies [33] (class II), defining pre-operative tumour volume [31] (class II), and monitoring response to treatment [34] (class III).

18F-fluoro-L-thymidine is a proliferation marker but does not enter the brain unless there is a blood-brain-barrier defect, therefore its usefulness seems limited [35].

More recently, the amino acid tracer 18F-fluoro-ethyl-L-tyrosine (FET) has been used for biopsy guidance and treatment planning in gliomas [36]. FET has the advantage of a longer half-life than MET, enabling tracer production in a central cyclotron and transport to other units. The experience of FET-PET is somewhat limited compared to MET-PET, but the tracer shows a very similar uptake intensity and distribution in brain tumours.

Prognostic Factors

Age > 40 years and presence of pre-operative neurological deficits are adverse prognostic factors [37–39] (class I).

Regarding conventional neuroimaging, larger tumours and tumours crossing the midline correlate with a short OS and PFS [37] (class II). Growth rates are inversely correlated with survival [4] (class III). There are conflicting reports as to whether contrast enhancement is associated with a worse prognosis [40, 41]. A low CBV [42] and low uptake of 11C-MET [43] correlate with longer PFS and OS (class III). Overall, measurement of rCBV correlates with time to progression or death and can be replicated across different institutions [44].

Oligodendrogliomas have a better prognosis than astrocytomas, whereas oligoastrocytomas have an intermediate outcome (class I). 1p loss (with or without 19q loss) is a favourable prognostic factor [45–47] (class II). MGMT promoter methylation could predict a shorter time to progression in untreated patients [48], while predicting longer PFS and OS in patients receiving chemotherapy with temozolomide (TMZ) [49] (class III).

IDH1 codon 132 mutations are of major prognostic importance for glioblastomas and anaplastic gliomas (WHO grade III) [50, 51], and are also prognostic for overall survival in diffuse gliomas of WHO grade II (class III) [52].

Antiepileptic Treatment

There are no trials dealing with antiepileptic drugs (AED) in patients with LGG and seizures. The level of evidence is strong for treatment of seizures in general.

Patients with no history of seizures have no benefit from prophylactic treatment [53–55] (class I).

In patients with single seizures, immediate treatment with antiepileptic drugs increases time to second seizure and first tonic-clonic seizure compared to delayed treatment, without differences with respect to quality of life or serious complications [56] (class I).

Older anticonvulsant agents, eg, carbamazepine, phenytoin, and valproate, have class-I evidence for efficacy and effectiveness in placebo-controlled trials in adults [57]. Regulatory requirements to demonstrate efficacy of newer AEDs as monotherapy differ between Europe and the United States. European regulators require a comparison with an established, optimally dosed AED, typically using a non-inferiority design, whereas in the US superiority is required to be demonstrated versus a comparator. Superiority monotherapy trials in the US have traditionally relied on inclusion of controls with a suboptimal (low-dose) comparator [58]. Newer anticonvulsants, including lamotrigine, gabapentin, oxcarbazepine, and topiramate, have shown equivalence but generally not superiority to carabamazepine, phenytoin, and valproate [59, 60]. A randomised controlled trial (RCT) of carbamazepine versus newer anticonvulsants (gabapentin, lamotrigine, oxcarbazepine, or topiramate) demonstrated longer time to treatment failure with lamotrigine [61]. Comparator studies of lamotrigine versus slow-release carbamazepine also show a slightly better cognitive profile for lamotrigine. Levetiracetam has a license for monotherapy usage in partial symptomatic epilepsy and has also demonstrated equivalence to carbamazepine in a short-duration 28-week RCT [62]. Levetiracetam can be introduced and built up quickly which may be seen as an advantage in comparison to other drugs, such as lamotrigine. Levetiracetam is also available for intravenous use, as is valproate. Studies suggest that newer anticonvulsants are as effective as the older ones and may have a better side effect profile in some areas (rash), but evidence is lacking; moreover, drug withdrawals in comparison studies are generally similar [60].

Valproate may potentiate the haematotoxicity of chemotherapy. Enzyme-inducing antiepileptic drugs (EIAED) interact with some chemotherapy agents (nitrosoureas, paclitaxel, cyclophosphamide, topotecan, irinotecan, thiotepa, and molecular agents), being associated with lower plasma levels and lower bone marrow toxicity [53] (class II).

The decision to withdraw treatment should be individualised, taking into account lifestyle issues and withdrawal should be gradual and take place over approximately 6 months [63].

Status epilepticus is a medical emergency and 2–5 % of all cases of status epilepticus in most studies and 12 % in one study were due to an underlying tumour [64]. The mortality from a tumour-associated status epilepticus is up to 20 %. In patients without a tumour, a recent meta-analysis of 11 RCTs of > 2000 people demonstrated that intravenous lorazepam was superior to diazepam [65]. For benzodiazepine-refractory status epilepticus, phenytoin infusion is standard practice. For a tonic-clonic status resistant to lorazepam and phenytoin, anaesthetic doses of propofol, midazolam, or barbiturates are employed. In partial status epilepticus, the European Federation of Neurological Sciences guidelines in adults support the role of intravenous levetiracetam or intravenous valproate prior to using anaesthetics [66].

Surgery

Surgery is necessary to provide tissue for distinguishing between the histologic types, grading the malignancy, and assessing the molecular status of tumours. Moreover, there are scenarios that pose problems of differential diagnosis between LGGs and non-neoplastic lesions (demyelination, inflammation, or infection), thus histological verification is mandatory. Total resection improves seizure control, particularly in patients with a long epileptic history and insular tumours [16] (class II). The use of brain mapping techniques increases the percentage of patients in whom a total and subtotal resection is achieved and has decreased the percentage of post-operative permanent deficits [67–69] (class II). Awake surgery is a well-tolerated procedure which could enable us (1) to increase the indications of resection in eloquent areas, (2) to identify the structures crucial for brain functions, especially language, both at the cortical and subcortical levels, and (3) to optimize the extent of resection with glioma removal being performed according to functional boundaries [69] (class III). Awake surgery has increased the safety of re-operation owing to mechanisms of brain plasticity. The effect of the extent of surgery on OS and PFS is still uncertain. There are no randomized trials specifically addressing this question. There is a general trend for most of the recently published articles [70, 71] to support extensive resections based on the surgeon's intraoperative impression (class II).

A critical point is a precise definition of total resection that for non-enhancing LGGs implies removal of all the hyperintense regions on T2 or FLAIR images and thus can only be determined by comparing pre- and post-operative tumour volumes on MRI. This has been performed in a few studies only and all have shown that total/near-total resection decreases the incidence of recurrence and the risk of malignant transformation and improves PFS and OS [68, 72] (class III).

Recent studies demonstrated that delineation of truly functional areas by intraoperative mapping in high-risk patients to maximize tumour resection can dramatically improve long-term OS [73] and that awake mapping in non-eloquent areas can allow to achieve "supratotal" resection (ie, to take a margin around the tumour visible on MRI) with a significant impact on anaplastic transformation [74] (class III).

Nonetheless, even with intraoperative MRI-guided surgery, total resection is achieved in no more than 36 % of patients [75].

When complete resection is not possible for functional reasons, reoperation(s) can be considered, with an impact on OS while preserving brain functions [76, 77] (class III).

The initial report of RTOG 9802 [78], which performed observation after surgery in patients aged ≤ 40 years and complete resection, reported a 5-year survival rate of 93 %, but 52 % of patients progressed within 5 years and received salvage RT (class II).

The timing of surgery is controversial in young patients who present with an isolated seizure (medically well-controlled) and with small tumours. Potential surgical morbidity may compromise the otherwise intact functional status and some authors have advocated deferring surgery in lieu of radiographic control ("watch-and-wait policy") [79, 80], especially in oligodendroglial tumours [81]. The risk of deferring surgery includes managing a larger tumour at a later point in time which may have undergone anaplastic transformation.

Radiotherapy

Four phase-III randomized trials have been performed so far (Table 1). EORTC 22845 [71, 82] investigated the role of RT timing: although improved PFS was demonstrated for patients treated with immediate RT, this did not translate into improved OS (class I). Besides prolonging the time to tumour progression, RT has several other potential benefits, such as symptom control, particularly of epileptic seizures [83]. Two randomized trials investigated different radiation doses: the EORTC 22844 and NCCTG studies showed no advantage for higher versus lower doses [84, 85] (class I). If higher doses are used, increased toxicity is observed with a 2-year incidence of radiation necrosis of 2.5 % [84] or lower levels of functioning concerning quality of life, especially for fatigue,

Table 1. Phase-III trials on radio- and chemotherapy for low-grade gliomas.

Study	Treatment arms	n	5-year PFS		5-year OS	
			%	p	%	p
EORTC 22845	S	157	37	= 0.02	66	ns
	S + RT	154	44	= 0.02	63	ns
EORTC 22844	S + RT 45 Gy	171	47	ns	58	ns
	S + RT 59.4 Gy	172	50	ns	59	ns
NCCTG	S + RT 50.4 Gy	na	55	ns	72	ns
	S + RT 64.8 Gy	na	52	ns	64	ns
RTOG 94.02	S + RT	125	46	= 0.005	63	ns
	S + RT + PCV	126	63	= 0.005	72	ns

PFS: progression-free survival; OS: overall survival; S: surgery; RT: radiotherapy; PCV: chemotherapy (procarbazine, ccvu + vincristine); na: not available; ns: not significant

insomnia, and emotional functioning [86]. RTOG 9802 compared RT alone vs RT plus PCV [87]. As $^{2}/_{3}$ of patients in the RT arm who progressed received chemotherapy at progression, this trial might be considered a trial of early chemotherapy vs chemotherapy at progression. PFS but not OS was improved (class I). However, beyond 2 years, the addition of PCV to RT conferred a significant OS and PFS advantage and reduced the risk of death by 48 % and progression by 55 %, suggesting a delayed benefit for chemotherapy. Grade-3–4 toxicity was higher among patients receiving RT + PCV (67 % vs 9 %; class I). Patients treated with whole-brain RT had a higher incidence of leucoencephalopathy and cognitive deficits in comparison with patients treated with focal RT [88] (class II). In studies using modern standards of RT, less negative impact on cognition is observed [89–91] (class II), although recent data related to patients who had a neuropsychological follow-up at a mean of 12 years and were free of tumour progression suggest that those without RT maintain their cognitive status whereas patients receiving RT do worsen with regard to their attentional and executive functionings as well as information processing speed [92].

Chemotherapy

The usefulness of chemotherapy for patients progressing after surgery and RT is well-established (class II), with more data available for oligodendroglial tumours. PCV (procarbazine, CCNU, and vincristine) and TMZ yield similar objective response rates on CT/MRI (45–62 %) and duration of response (10–24 months), with a toxicity profile favouring TMZ in terms of better tolerability (reduced myelotoxicity) [93–97]. The response rate of enhancing tumours, possibly reflecting high-grade pathology, is higher than that of non-enhancing tumours. A clinical benefit (ie, reduction of seizure frequency and improvement of neurological deficits) is commonly seen in patients responding radiologically and in some patients with stable disease. Chemotherapy (PCV or TMZ), as initial treatment after surgery, has been investigated in high-risk patients (ie, those with incomplete resection, persisting seizures, and progression on CT/MRI). All studies have a level-of-evidence class II [98–101]. Complete responses are generally lacking with a prevalence of minor over partial responses (overall, 53 %), and tumour volume decrease can be delayed as long as 24–30 months and persist once chemotherapy is terminated [102]. Patients more likely to respond have symptomatic/enlarging oligodendroglial tumours but mixed or astrocytic tumours may respond as well. Most patients with seizures have a clinical benefit, even in the absence of a radiological change [103, 104]. Evaluation of response on conventional MRI (T2-weighted and/or FLAIR images) is difficult in non-enhancing tumours: new criteria, proposed by the RANO International Group, have been recently proposed (June 2011) [105], and require validation in future studies. Chemotherapy with nitrosoureas can be an effective initial treatment for unresectable astrocytomas [106] (class IV). The response rate after chemotherapy is higher and duration of response is longer in patients with 1p/19q loss than in those with 1p/19q intact [101] (class III). Protracted low doses of TMZ could offer potential advantages over standard doses, especially in unmethylated tumours [107] (class III), but toxicity could be increased [108]. Preoperative chemotherapy could reduce tumour infiltration/extension and thus improve surgical resectability [109] (class IV).

Overall, quality of life does not seem to change over time while patients are receiving temozolomide [110] (class II).

Neurocognitive Deficits

Neurocognitive deficits in LGGs can be caused by the tumour itself, tumour-related epilepsy, treatments, and psychological distress. The cognitive decline that might ultimately lead to dementia negatively affects quality of life and well-being. Consequently, neurocognitive function is increasingly incorporated as secondary outcome measure in clinical trials in patients with LGG. In the literature, neurocognitive outcome has been assessed systematically in a limited number of studies with a relatively small number of patients (class II).

Regarding the effects of the tumour, Tucha et al [111] found neurocognitive deficits, such as impairment of executive functions and memory attention, in 91 % of patients before surgery. Similar findings corroborate the notion that neurocognitive impairments in these patients mainly originate from the tumour itself and/or confrontation with the diagnosis [112].

Patients with gliomas are prone to have more global neurocognitive deficits, unlike patients with stroke who tend to have site-specific deficits. Patients with a tumour in the dominant hemisphere have more memory problems and poorer attention, verbal fluency, and verbal learning than those with non-dominant tumours [113] and have a smaller chance to normalize following surgery [114]. Due to the reduction of tumour mass, surgery is beneficial for neurocognitive functioning (class II). Long-term improvement of verbal memory compared to preoperative assessment has been reported after low-grade glioma resections in frontal premotor and anterior temporal areas [115], usually after transient focal neurocognitive deficits [116].

The severity of neurocognitive deficits after RT ranges from mild attention or memory disturbances to dementia (class II). A follow-up of the Klein et al 2003 study [92] demonstrated that there is a relation between neurocognitive status and cerebral atrophy and leukoencephalopathy, and radiological abnormalities increase only in the irradiated group. Neurocognitive side effects of AEDs can add to previous damage by surgery or RT (class II). Older AEDs (phenobarbitone, phenytoin, carbamazepine, and valproic acid) can decrease neurocognitive functioning by impairing attention and memory [117]. Among newer AEDs, gabapentin, lamotrigine, and levetiracetam have fewer adverse neurocognitive effects while topiramate is associated with the greatest risk for neurocognitive impairment [118]. A randomized trial showed that cognitive rehabilitation has a salutary effect on both short- and long-term cognitive complaints and mental fatigue [119] (class II).

Recommendations

– Astrocytomas, oligodendrogliomas, and oligoastrocytomas are diagnosed using morphological criteria according to the WHO classification (level A).

– Immunohistochemical analysis with IDH1-R132H mutation-specific antibody H09 distinctly separates the vast majority of astrocytomas, oligodendrogliomas, and oligoastrocytomas from other lower-grade glioma variants and greatly assists in the diagnosis of these tumours in samples deriving from the tumour periphery.
– Combined loss of 1p/19q is a marker in favour of the diagnosis of oligodendrogliomas or oligoastrocytomas (level B).
– MRI with contrast enhancement is the gold standard to monitor LGG after surgery: an MRI examination every 6 months might be enough unless physicians decide differently (good practice point).
– MRS is useful for the differentiation of LGG from non-tumoural lesions, pre-operative definition of extent, and guiding stereotactic biopsies (level C).
– DSC-MRI can be employed during follow-up to predict malignant transformation (level C).
– PET with FDG is useful for detecting malignant transformation in astrocytomas (level C) and for differentiation between radiation necrosis and tumour recurrence (level B).
– PET with MET is useful for the differentiation of LGG from non-tumoural lesions (level B), guiding stereotactic biopsies (level B), pre-treatment evaluation (level B), and monitoring treatment (level C).
– Prophylactic AEDs must not be used before any epileptic seizures have occurred (level A).
– AEDs should be started after the first seizure (level A).
– AEDs should be individualized according to seizure type, co-medication, comorbidity, and patient preferences (good practice point).
– In patients requiring treatment with chemotherapeutics, non-EIAEDs are to be preferred (level B).
– Surgical resection represents the first treatment option, with the goal to maximally resect the tumour mass whenever possible while minimizing post-operative morbidity (level B).
– Identification of the eloquent cerebral areas, which have to be preserved during surgery, is performed by means of pre-operative neuroimaging modalities (functional MRI, fibre tracking), and intraoperative brain mapping techniques (level B).
– Awake surgery could improve the results by delaying the risk of anaplastic transformation and by increasing long-term survival (level C).
– Reoperation could improve survival while preserving brain function and might be more frequently considered (level C).
– When surgery is not feasible (because of tumour location, extension, or comorbidities), a biopsy (either stereotactic or open) should be performed to obtain a histological diagnosis (good practice point).
– For patients with unfavourable prognostic factors (older age, incomplete or no resection, existing neurological symptoms), an adjuvant treatment is indicated at any time (level B), and this is more commonly RT (good practice point).
– A total RT dose of 50.4–54 Gy in fractions of 1.8 Gy represents the current standard of care (level A). Modern RT techniques (conformal dose delivery or intensity-modulated techniques) should be preferred (level B).
– Younger patients (< 40 years of age) with (nearly) complete resection and tumours with an oligodendroglial component have a more favourable prognosis and can be observed after surgery (level B), but close follow-up is mandatory (good practice point).
– Chemotherapy is an option for patients with recurrence after surgery and radiation therapy (level B).
– Chemotherapy is an option as initial treatment for patients with large residual tumours after surgery or unresectable tumours to delay the risk of late neurotoxicity from large-field RT (especially when 1p/19q loss is present) and to improve seizure control (level B).
– Neuropsychological tests at diagnosis and during follow-up can be useful, being selected according to the needs of the clinical setting (good practice point). They must have standardized materials and administration procedures, published normative data, moderate-to-high test-retest reliability, brief administration time (30–40 min), and be suitable to monitor changes over time (good practice point).
– Cognitive rehabilitation can be helpful (level B).

Conflict of Interest

RS, BGB, LB, HD, MF, WG, RG, FG, KHX, MK, BM, JR, TS, AS, and WW have no conflict of interest to declare.

AvD: Under a licensing agreement between DIANOVA GmbH, Hamburg, Germany, and the German Cancer Research Center, Andreas von Deimling is entitled to a share of royalties received by the German Cancer Research Center on the sales of H09 antibody. The terms of this arrangement are being managed by the German Cancer Research Center in accordance with its conflict of interest policies.

RSt: Scientific advisory boards for Roche, MSD/Merck & Co, Merck KGaA, MDxHealth; principle investigtor for research including Merck Serono and MSD/Merck & Co.

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The Growing Role of Neuro-Oncology Nurses

Hanneke Zwinkels

In June 2001, I started at the neuro-oncological outpatient clinic within a multidisciplinary care team consisting of neurosurgeons, neuro-oncologists, neuroradiologists and radiotherapists. As a trained oncology nurse, I started seeing patients and their families in consulting hours, learning from them what they needed in the course of their disease. Realizing that the chance of dying from a tumour was bigger than to recover from it, I found the challenge in wanting to be involved in the "voyage of the patient and his family". Consequently, I searched for literature and articles about primary brain tumours to gain knowledge for what was my main task: supportive care and coordination of care for this patient group. What have I learned during the past 10 years?

A Specialty?

Neuro-oncology patients are different from oncology patients as well as from neurology patients because they do not only have a limited life expectancy due to the malignancy, but they also encounter neurological signs and symptoms like epilepsy and focal deficits such as hemi-paresis and aphasia, and on top of that they may be affected by cognitive deficits. To perform neuro-oncology nursing with a focus on clinical care and anti-tumour therapy, symptomaticcare and research activities all within a multidisciplinary team, special skills, and knowledge are required. In my opinion, neuro-oncology nursing is a specialty in nursing and in oncology care and cure. In the United Kingdom and in the Netherlands, national focus groups of neuro-oncology nurses have been established that share and exchange knowledge.

Growing Awareness

Over the past 10 years, a growing awareness has occurred within neuro-oncology care and cure. This means awareness of the needs of patients and their families in guidance throughout their disease concerning possible problems in coping, anxiety, fear, and depression, in finding their way in special resources in their home environment, in obtaining access to care and cure with a low threshold in case of emergencies or sudden questions and in shared responsibility in treatment and end-of-life decision-making.

In several European countries, specialized neuro-oncology nurses are included in a care team to act as the most direct contact for patients, their caregivers, and all the healthcare professionals involved in the clinical management of the patient with a brain tumour. The nurse deals with clinic scheduling, symptom management, medication/steroids, psychological support, and referral to other agencies, as part of the process of advancing patient care. Neuro-oncology nurses therefore function as the "spider in the web'' and by coordination and continuation of care improve the quality of neuro-oncology care.

Literature

Neuro-oncology nursing research has resulted in several publications, mainly from the USA, the UK, and some Scandinavian countries, probably due to the development of more extended roles and education of nurses in these countries. Most publications investigated specialist nurse functions and the type of relationships a specialized nurse in neuro-oncology can fulfill. Moreover, articles about symptom clustering for patients with brain tumours are found and their effect on the functional status and quality of life, which can give direction to symptom assessment and necessary nursing interventions. Psychosocial and cognitive aspects of neuro-oncology patients are described in various articles by doctors and (neuro-) psychologists: these publications grant insight into the supportive care that neuro-oncology patients require.

Supportive Care

Problem areas that can be identified during counselling by neuro-oncology nurses include fear and anxiety related to seizures or focal and cognitive deficits, fatigue, uncertainty, work-related problems, housing, children, changes in behaviour, partner issues, as well as problems with coping and dying. Supportive care consists of informing and educating patients and their families about the disease and its signs and symptoms, treatments, side effects, medication, listening to their needs and problems and trying to find the best way in support and guidance through the disease process or referral to other health care personnel.

Task Reallocation

Task reallocation is the process by which certain duties and responsibilities, which previously fell exclusively to medical staff care, are reassigned to other healthcare professionals such as the nurse practitioner and the physician assistant. My role as a specialist nurse has been extended over the years and has developed to the role of nurse practitioner. Through training, education, and experience I gained responsibility for treating patients with temozolomide (TMZ) using a protocol. This role includes prescription of chemotherapy, anti-emetics and other necessary co-medication, while the neuro-oncologist acts as supervisor. In evaluating toxicity of TMZ, the nurse practitioner decides on dose-delay and dose-adjustment by protocol. She can also perform neurological exams to evaluate a patient's condition and discuss her findings with the attending physician. Research into TMZ toxicity has

optimized guidance and treatment of patients receiving TMZ using evidence-based practice guidelines.

Survey

The European Association of Neuro-Oncology – of which I am the nurse board member – would like to address all medical disciplines concerning neuro-oncology, but EANO also has an interest in creating awareness with nurses and other health care professionals dedicated to the neuro-oncology patient. Not only nurses but also social workers, physiotherapists, speech therapists and (neuro-) psychologists are responsible for supportive care of the neuro-oncology patient. We would like to know which possibilities exist for the neuro-oncology patient in Europe and want to try to increase knowledge of European colleagues. To which professional does the responsible physician refer his neuro-oncology patient? For that reason a survey will be performed to gain insight in European neuro-oncology supportive care.

Summary

Specialized neuro-oncology nurses can play a key role in the care and cure of patients with brain tumours by monitoring and managing symptoms of the disease and side effects of treatments, they can be easily accessible for patients and their family carers: they are in a position to communicate occurring problems with responsible physicians. Neuro-oncology nursing to me is a fascinating field within oncology nursing which has a focus on the guidance of patients and their family carers from diagnosis until death, in order to improve the quality of life of neuro-oncology patients. To optimize quality of multidisciplinary care, I would like to endorse that specialist nurses in neuro-oncology should participate and contribute to a good future perspective!

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Why Do We Need Brain Tumour Patient Advocates?

Kathy Oliver

Patient advocacy may be more of an art than a science, but without it brain tumour patients may find themselves consigned to the shadows on the cancer map.

Each year, there are 200,000 people in the world who develop a primary malignant brain tumour [1]. Even in the most powerful countries on earth, these people and the many, many thousands of others who develop low-grade, benign, and metastatic brain tumours can be lost in a maze of uneven and inequitable care. In the poorer, less-developed countries, even the most basic of brain tumour therapies and elements of palliative care are still not available.

Additionally, many governments and major cancer control organisations have prioritised prevention, screening, and healthy lifestyle campaigns in the fight against cancer. These are all excellent initiatives, of course. But unfortunately brain tumours cannot be helped by this approach as there is no realistic screening for them and their causes are, as yet, generally unknown.

Brain tumour advocacy groups – whether local, regional, national, or international – have an important role to play in ensuring that patients' views are listened to and acted upon so patients are not marginalized, discriminated against, or excluded in any way from obtaining optimal care.

Brain tumours are the only cancer to directly attack a person's physical, behavioural, and cognitive abilities and this, combined with their dire prognosis, means that most patients, their families, and caregivers are often too debilitated and mentally and physically exhausted by the disease to have the energy to fight for better therapies, care, and support themselves.

The lack of durable therapeutic options, the fact that brain tumours are responsible for the highest cancer burden with an average of over 20 years of life lost per patient [2] and the significant economic strain that these rare tumours inflict – because cutting-edge brain tumour therapies certainly do not come cheap – all add up to a tremendously daunting challenge.

This is clearly a patient population in desperate need of highly focused advocacy efforts in order to ensure that (1) there is much more research funding available for the development of new therapies; (2) there is adequate support and information available for patients and carers, and (3) there are safety nets in place for patients facing an assault on their economic stability.

In the last decade or so, a number of very determined brain tumour advocacy groups have, despite the enormous odds, arisen – many of them from the grass roots. Some of these have been established by carers or former carers of brain tumour patients. It often falls to this group of people to advocate for their loved ones who may not be able to do so themselves. And, in some cases, brain tumour patients have become involved in advocacy groups because, even in the brain tumour arena, there is a small cohort of patients who confound the statistics and survive for an extended period.

The International Brain Tumour Alliance has encouraged brain tumour advocacy organisations in Lithuania, Cyprus, Belgium, Spain, Denmark, South Africa, Zimbabwe, and Australia. These organisations augment those advocacy groups which have already been firmly established in places such as the United States, Canada, some countries in mainland Europe, and the United Kingdom.

So, how can brain tumour patient advocacy organisations help keep brain tumours out of the shadows on the cancer map?

Advocates can vigorously lobby governments for more recognition of the very specific and unique challenges which brain tumours present. They can campaign for increased levels of government spending on brain tumour research. They can communicate with regulators and health technology assessment (HTA) bodies to highlight the patient's perspective.

Brain tumour advocacy groups can provide input into the design of clinical trials, even at the early stages, to help ensure that such studies are more efficient, effective, and more widely acceptable to patients. Indeed, a 3-year European-Union-funded project called "PatientPartner" suggests that the vast range of experiential knowledge which patient advocates can bring to the research arena results in better recruitment strategies, more patient-relevant research findings, wider dissemination of those findings, and improved information leaflets [3]. Brain tumour advocacy groups can also bridge any gaps in understanding between the scientific and medical community on the one hand and patients and carers on the other.

The collective voice of brain tumour patient advocacy groups around the world is growing in intensity. International cooperation between such organisations benefits patients and their carers by providing greater knowledge, greater collaboration, and greater hope.

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Calendar of Events

2011

September 16–17	**Brain Metastasis: Emerging Therapeutic Strategies and Opportunities in Basic & Translational Research**	Marseille, France	http://www.brain-mets.com
September 23–27	**ECCO-ESMO Congress**	Stockholm, Sweden	http://www.esmo.org/events/stockholm-2011-congress.html
September 20–22	**Oncologic Imaging: A Multidisciplinary Approach**	Shanghai, China	http://www.mdanderson.org/education-and-research/education-and-training/schools-and-programs/cme-conference-management/conferences/final-china-brochure-v22.pdf
October 2–6	**ASTRO Annual Meeting**	Miami Beach, FL, USA	http://www.astro.org/Meetings/AnnualMeetings/index.aspx
October 6–7	**IVth InterAmerican Oncology Conference: Current Status and Future of Anti-Cancer Targeted Therapies**	Buenos Aires, Argentina	http://www.oncologyconferences.com.ar/
October 7–8	**Annual Meeting Austrian Society of Neurosurgery**	Vienna, Austria	http://www.mediaplan.co.at/kongress/dokumente/NEUROCHIR11_ Ankuendigungen.pdf
October 13–15	**ISNCC Conference**	Warsaw, Poland	http://www.isncc.org
October 20–22	**North American NeuroEndocrine Tumor Society Symposium**	Minneapolis, Minnesota	http://www.nanets.net/education/articles/neuroendocrine-tumor-symposium
October 20–23	**Cancer Survivorship – Leadership Training Institute: Helping Cancer Survivors to Live Well Beyond Cancer**	Boston, MA, USA	
October 27–29	**EORTC-NCI-ASCO Annual Meeting on Molecular Markers in Cancer**	Brussels, Belgium	http://www.eortc.be/Seminar/ENASCO2011/default.htm
November 2–4	**Pediatric Palliative Care Retreat**	Houston, TX, USA	
November 2–8	**Program in Palliative Care Education and Practice – Part II**	Cambridge, MA, USA	http://www.hms.harvard.edu/pallcare/Documents/PCEP_2011.pdf
November 10–11	**ESMO Symposium Metastases**	Zurich, Switzerland	http://www.esmo.org/fileadmin/media/pdf/2011/events/metastases/ESM_Programma_Metastases_FINAL.pdf
November 16–17	**Nursing Clinical Review for Hospice and Palliative Care**	Houston, TX, USA	
November 17–20	**The 2011 SNO Scientific Meeting and Education Day**	Garden Grove, CA, USA	http://www.soc-neuro-onc.org/index.cfm
November 18–19	**15th Annual Interdisciplinary Approach to Symptom Control, Palliative and Hospice Care Conference**	Houston, TX, USA	

2012

January 27	**Brain Tumours: Now is the Future … !**	The Hague, The Netherlands	http://www.boerhaavenet.nl/agenda/agenda2.php?id=1700&PHPSESSID=4928b8de18862e383a1cd716fefb926c
February 9–11	**15th Biennial Canadian Neuro-Oncology Meeting**	Vancouver, BC, Canada	www.cbtc.ca
March 8–10	**International Congress on Targeted Anticancer Therapies**	Amsterdam, The Netherlands	http://www.tatcongress.org/tat12-home.html
March 21–24	**EBCC 8**	Vienna, Austria	http://www.ecco-org.eu
June 1–5	**2012 ASCO Annual Meeting**	Chicago, IL, USA	http://www.asco.org
June 7–10	**18. Jahreskongress der Deutschen Gesellschaft für Radioonkologie**	Wiesbaden, Germany	www.degro.org/degro2012
June 24–27	**15th International Symposium on Pediatric Neuro-Oncology**	Toronto, ON, Canada	http://www.soc-neuro-onc.org/en/cev/66/
July 7–10	**EACR 22**	Barcelona, Spain	http://www.eacr.org
September 6–9	**10th EANO Congress**	Marseille, France	http://www.eano.eu
September 19–21	**ESSO 2012**	Valencia, Spain	http://www.ecco-org.eu
September 28–October 2	**37th ESMO Congress**	Vienna, Austria	http://www.esmo.org/events/vienna-2012-congress.html
November 6–9	**Molecular Targets and Cancer Therapeutics**	Dublin, Ireland	http://www.ecco-org.eu

Congress Report: Trends in Central Nervous System Malignancies

Susan Short

From the Department of Oncology, University College Hospital, London, UK

This was the second of the so far very successful neuro-oncology meetings organised as a collaboration between EORTC and EANO. These meetings are deservedly popular as update meetings since delegates can expect to gain a thorough overview of new data and an insight into what is happening in the field in the space of 2 days of focused talks in neuro-oncology. The venue this year was **Bucharest**, perhaps not a city that is so familiar to many delegates, although the view of the immense palace constructed by Ceausescu during his years in power in Romania and within site of the conference venue certainly made it memorable.

It is very clear from the programme that the field of neuro-oncology is moving fast and that much of this progress is driven by basic science, particularly in the area of molecular pathology. It is amazing just how quickly new information has been taken up by the clinical community and **Prof Reifenberger's** talk on IDH1 was a reminder of the recent emergence of this extraordinary story in glioma. Although we still do not understand why mutations in the isocitrate pathway should be such powerful drivers of oncogenesis this talk introduced the idea of mutant proteins producing increased concentrations of moieties such as 2-hydroxyglutarate which may function as an 'onco-metabolite'. It is obvious that this will lead to much greater understanding of the biology of oncogenesis in CNS and IDH1 is already accepted as probably the most powerful biomarker for prognosis in astrocytic tumours and also an extremely useful diagnostic aid in identifying infiltrating tumour cells. A similarly arresting view of the power of molecular pathology in identifying tumour sub-groups was also given by **Prof Taylor**, reviewing recent data in medulloblastoma in which it is clear that tumours can be grouped into very distinct prognostic groups using gene expression data.

There has been huge interest in the field of angiogenesis in brain tumours in the last few years and it was extremely valuable to be able to hear updates on the clinical and regulatory status of anti-angiogenic agents along with some exciting new laboratory data. It is becoming clear that the success or not of these agents in the clinic may rely on a better understanding of the relationship between neo-angiogenesis and other tumour characteristics, such as invasion, and **Prof Bjerkvig** demonstrated that in pre-clinical models these may be quite distinct phenomena. He also drew our attention to the fact that phenotypic flexibility and adaptation to specific niches may be a marker for tumour stem cells which may allow them to either migrate through brain tissue or promote neoangiogenesis so that these processes may effectively become competing. While angiogenesis remains a fascinating target it is clear that other targets, particularly proteins involved in DNA repair, may also be effective in enhancing response of gliomas to treatment. **Prof Wen** overviewed several of these targets which are the subject of ongoing research and early clinical studies including PARP, checkpoint signaling, and IDH1 targeting. It is clear that we need to be able to predict rational combinations of agents as well as to identify which pathways are relevant in glioma. In brain metastases there is an obvious need to identify whether molecular targeting agents that are active at the primary site are also effective in CNS disease.

We are all aware of the limitations of non-invasive imaging in assessing response to treatment in CNS and **Dr Bendszus** reviewed the approaches that are available and which may be most relevant in brain tumour monitoring. A major issue, which several research groups, including the EORTC, are addressing, is the need to standardize imaging parameters across study sites. There was a timely reminder of the limitations of conventional imaging applied to new agent studies, particularly those that alter blood brain barrier function as in for example review of the REGAL study of cediranib in relapsed gliomas, which failed to reach the primary end point and could have been limited by interpretation of MRI data.

Turning our attention away from glioma, **Prof Weller** gave an informative account of the state of the art in treatment of PCNSL. We were reminded that this has proven a remarkably difficult disease to treat which has not yet benefited from the advances that have been made in the treatment of lymphoma elsewhere. There are few large randomized studies in this area, but this will be remedied in the next few years with ongoing and proposed studies addressing the role of retuximab, intrathecal treatment and radiotherapy in patients with PCNSL in different age groups.

The improving outcome in treating glioma and the changing demographic of age at child birth has meant that most practitioners in neuro-oncology have had to face difficult questions involving young women who become pregnant with a diagnosis of brain tumour. Data on the risks of tumour progression during pregnancy are sparse, but **Dr Taillandier** presented some recently collated data which suggest that, at least in women who are referred for MRI during pregnancy, progression occurs in a significant proportion and may be a direct result of the physiological changes that are associated.

The final session of the conference included a session on the rather vexed question of appropriate treatment for elderly patients with gliomas. It is obviously a problem that we cannot define biological age with any certainty. It is more of a problem that recent studies have failed to reach consensus on appropriate management. These were reviewed and discussed by **Dr Malmstrom** and **Prof Stupp**. Although it seems clear that 6 weeks of radiotherapy is not usually an appropriate treatment for patients over 70, whether short-course radio-

therapy, temozolomide or the combination is the way forward is not yet clear, although this should be answered by the ongoing EORTC/RTOG study.

Brain metastases is another area in which treatment approaches have been slow to change. This may have been altered by the recent EORTC study data, confirming that WBRT improves progression in CNS but not overall survival in patients with oligometastases. These data and their implications were discussed by **Prof Soffietti** and considered in the context of modern radiotherapy approaches. It is clear that while radiotherapy can be used to deliver complex dose distributions to CNS, we do not yet have the knowledge that will allow us to recommend particular treatment approaches to improve local control and/or reduce toxicity, for example by hippocampal sparing. It should also be remembered that a significant proportion of patients with brain metastases have a very poor prognosis and **Prof Taphoorn** delivered a thought-provoking talk on end-of-life issues in brain tumour patients. This is an area where much research still needs to be done and one which is still limited to some extent by differences in cultural attitudes towards end-of-life care.

It was appropriate that the meeting ended with a lively discussion on management issues in patient groups that provoke difficult questions. Overall, this meeting lived up to the expectation, the 403 attendees should have come away feeling that they have had a thorough update on the field with the opportunity to ask questions of experts from around the world.

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Congress Report: ASCO 2011 – The Neurooncology Perspective

Wolfgang Wick, Michael Platten

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RTOG-0S25: The Standard Remains!

We expected another brain tumour focus for the ASCO 2011 meeting, following the remarkable success of the EORTC 26981/22981/NCIC CE.3 trial in 2004. RTOG-0525/EORTC 26052 (http://clinicaltrials.gov, NCT00304031), the largest brain tumour trial ever performed (abstract 2006) aimed at demonstrating that the intensification of temozolomide maintenance treatment of glioblastoma is superior to the standard of care. The data were presented by the principal investigator, **Mark Gilbert, MD**, from the MD Anderson Cancer Center in Houston on behalf of the RTOG, the leading cooperative group, in the oral abstract session on June 5, 2011.

The rationale of this trial was based on several studies that had shown a prolonged exposure to temozolomide to deplete O6-methyl-guanyl-methyl-transferase (MGMT) activity in blood cells. It was believed that this process could potentially increase the antitumour activity of the drug in patients with putatively MGMT-active (unmethylated) tumours. Additionally, patients with formal sensitivity to the drug (methylated promoter) should benefit from the about 2.1-fold exposure of temozolomide. In brief, both ideas were proven to be wrong. Overall survival for arm 1 (standard temozolomide) was 16.6 months and 14.9 months for the dose-dense temozolomide arm. Those patients with a methylated MGMT promoter (30 %) had a significantly better progression-free (PFS) and overall survival (OS). In fact, the known depletion of MGMT activity in blood cells may just have led to the increased toxicity of the dose-dense therapy arm.

MGMT and Beyond: Steps Towards Personalised Medicine

Although this trial clearly failed the primary endpoint, it is important and will guide future research and trial development. First, the neurooncology community has proven to manage the successful conduct of a large trial with prospective tissue collection and central molecular testing of MGMT. Second, there is a clear answer to a relevant clinical hypothesis. Third, due to the large amount of fresh-frozen tissue in addition to the paraffin-embedded samples, **Ken Aldape, MD,** could present first data on a new molecular risk classification with 4 groups spanning a median survival from 12–26 months. The biomarkers evaluated were isocitrate dehydrogenase 1 mutations, the glioma-CpG island methylator phenotype, a microarray-based mRNA panel with 17 candidates, and a novel MGMT promoter methylation assay (abstract LBA 2000).

Two other interesting abstracts on the topic of MGMT were presented by the German Glioma Network and the group in Los Angeles. **Michael Weller, MD,** presented a high frequency of > 50 % MGMT-methylated tumours in a cohort of patients > 70 years of age. This high frequency contrasts with the poor prognosis in this age group. Interestingly, the study indicated a predictive role of the MGMT methylation status for the PFS to chemo- and/or radiotherapy (abstract 2001). Lai et al used a combined immunohistochemical (IHC) and promoter methylation assessment approach and found the best prognostic values for the combination of IHC (with a cut-off at 30 % staining) and methylation assessment, which preferentially should be done with bisulfite sequencing, as compared to either marker alone (abstract 2003).

Glioblastoma: No Promising New Agent Ahead

The Eli Lilly trial S039 in patients with newly diagnosed glioblastoma without methylation of the MGMT promoter presented by the Heidelberg group (abstract 2007) looked at the radiosensitizing properties of the protein kinase C beta inhibitor, enzastaurin. Despite some encouraging results in the PFS rate at 6 months (PFS-6) the trial did not reach its primary endpoint of a PFS-6 of 55 % with the observed rate of 51.8 % (confidence interval: 38.1–63.9). Here, the question emerges how much mono-compound activity is necessary to dare performing a trial even if the main rationale is to demonstrate a radiosensitizing effect. **Dr Eisenstat** presented trial data of yet another approach to target EGFR in recurrent malignant glioma (abstract 2010). Afatinib (BIBW 2992), an irreversible erbB family blocker, was studied alone or in combination with a dose-dense temozolomide regimen for 21/28 days. The control was 21/28 days temozolomide only. Interestingly, the dose-dense temozolomide regimen was quite active with a progression-free survival rate at 6 months (PFS-6) of 22 % in the mono-compound arm and 17 % in the combination with afatinib. Afatinib alone with 3 % did not produce a meaningful PFS-6. Hence, the major outcome of this trial and other activities in recurrent glioma may be that dose-dense temozolomide does not have a role in the first-line but potentially second-line treatment.

Debate over PCNSL

The Berlin group aimed at presenting prognostic factors for the PCNSL-SG1 trial (abstracts 2004 and 2005). Although of interest, their approach to leave out the impact of therapy as potential prognosticator raised considerable concern and led

to helpful suggestions by **Lisa de Angelis** on how to improve the analysis.

Conclusions

In summary, the talks but also other presentations at this year's ASCO demonstrated considerable activity in the field. Compared to earlier years, the slots for neurooncology-related topics and presentations are getting wider. The relevance of biomarker assessment and new drug development specifically for brain tumours and conducted by brain tumour specialists is largely recognized. Despite some negative trials and specifically the disappointment with the RTOG0525 trial the community is optimistic that we will have another "Brain Tumour ASCO" in the near future.

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National Societies: Austria

Stefan Oberndorfer

In Austria, neurooncology at present is represented by various subspecialties such as neurology (ARGE Neurooncology of the Austrian Society for Neurology), neurosurgery (ARGE for Neurosurgical Oncology [ANCO]), experts from clinical oncology, radiooncology, neuropathology, and basic science, as well as multiple centres with interdisciplinary tumour-boards with neurooncological expertise in brain tumour and spinal tumour management, neurological complications of cancer, neurotoxicities of anticancer treatments, paraneoplastic neurological syndromes, as well as palliative care and quality-of-life issues.

On July 1, 2011, Austrian neurooncologists officially founded a joint Austrian Society for Neurooncology (SANO), which, for the first time, invites Austrian members from all medical subspecialties involved in the neurooncological field to facilitate and enhance cooperation. This accommodates the international trend towards national, interdisciplinary neuro-oncological societies, which are already established in many other European countries.

One of the main goals of the SANO will be to concentrate information on neurooncological studies and centres as well as contact persons throughout Austria. We will also elaborate on specifically Austrian diagnostic and therapeutic guidelines on different neurooncological topics in cooperation with other European neurooncological societies. We also plan to develop an annual Austrian neurooncological meeting for education and training. A platform for patients and carers will also be provided.

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The homepage, www.sano.co.at, has been online since July 2011.

To contact the society please mail to sano@medacad.org

Interview with Dr Martin van den Bent (Rotterdam) about the EORTC CATNON Trial on Grade-3 Gliomas

Ufuk Abacioglu

From the Department of Radiation Oncology, Marmara University Medical School Hospital, Istanbul, Turkey

Q: *Dr van den Bent, what can you tell us about the ongoing CATNON trial on grade-3 gliomas? What is its background?*

A: The background of this trial is the fact that both the North American and the European trials on adjuvant PCV chemotherapy failed to improve outcome in anaplastic oligodendroglial tumors, whereas the EORTC trial on chemo-irradiation with temozolomide improved survival in glioblastoma – a much less chemotherapy-sensitive disease compared to anaplastic oligodendroglial tumours. And although many people have intuitively felt that grade-2 and grade-3 tumours were simply less aggressive compared to glioblastoma, the current developments in the IDH1 arena clearly show that these are different diseases. Thus, the question is on the table whether combined chemo-irradiation improves outcome in anaplastic glioma. Just the fact that it occurs in the same organ does not justify a similar treatment – the best treatment needs to be investigated. After all, we are not treating ovarian cancer in the same way as breast cancer, simply because they occur both in females.

Q: *How is the trial designed?*

A: It is a randomized phase-III study requiring 740 patients, using a 2 × 2 design. Patients are randomized to radiotherapy alone, radiotherapy followed by adjuvant temozolomide, radiotherapy with concomitant temozolomide, and radiotherapy with both concomitant and adjuvant temozolomide. That design will also allow us to investigate whether the outcome is improved with early temozolomide treatment, and whether both adjuvant and concomitant temozolomide are contributing to the improved outcome.

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

A: This is truly an intergroup effort with contributions from 3 continents. In Europe, EORTC, MRC, and NOA are contributing, in the United States the effort is led by the RTOG with active participation of NCIC and NCCTG. On top, our colleagues in Australia and New Zealand are very active and have entered more than 20 patients.

Q: *Why did you choose to do a 4-arm trial?*

A: It is not really a 4-arm trial, but the 2 × 2 design allows us to make a more meaningful analysis than a 2-arm study. A true 4-arm study would lead to a huge study, which would not be feasible in this disease.

Q: *What are the stratification factors?*

A: In this trial, the stratification factors are institution, performance status, age, loss of 1p, the presence of oligodendroglial elements, and the MGMT promoter methylation status. This implies that, prior to randomization, patients are both tested for 1p/19q status and MGMT promoter methylation. This trial really marks the transition from inclusion based on histology to inclusion based on molecular features.

Q: *There is a central pathology review. How do you do that and what kind of difficulties do you have about it? Do you have any preliminary MGMT data for anaplastic tumours? Do you plan to implement IDH-1 mutation analysis in the trial?*

A: It is at present well understood that the diagnosis of grade-2 and grade-3 gliomas is subject to a considerable interobserver variation. To be eligible a confirmation of the grade-3 diagnosis and absence of a combined 1p/19q co-deletion is required. Patients can be entered for central review once a local diagnosis of a grade-3 tumour has been made. It was expected that we would experience a high interobserver variation, and to make the central reviewer process less subjective we included 2 central reviewers. The rule for this trial is that a patient becomes eligible if both central reviewers make the diagnosis of a grade-3 tumour. Indeed, so far, our experience in this trial confirms the experience of other projects, with a high interobserver variation. However, I would like to stress the importance of submitting sufficient and representative material. As an example, from a recent patient, we only received a fragment of tissue with some dural membrane in it. Another important element is to submit tissue blocks. This is of particular relevance for future research. This type of research has been pivotal for many of the important discoveries that were made in the recent EORTC trials.

Currently, a trial amendment is in preparation that will include testing for IDH mutations as part of the obligatory testing within the study. A pre-specified study analysis based on the IDH1 mutational status will also be part of this amendment.

Q: *In recent clinical trials, we observe more quality assurance issues. How is that issue taken care of in CATNON?*

A: Apart from more regular monitoring of sites, there is quality control of radiotherapy. This means that the site is asked to fill in a questionnaire and an RT dosimetry study prior to local trial activation. After study activation and patient entry, the radiotherapy planning of a certain number of patients will be

reviewed. For this, the actual radiotherapy plan has to be submitted.

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

A: Currently, all groups have activated the study and this is truly a multi-continental study with participation of European groups (EORTC, MRC, NOA), North-American groups (RTOG, NCCTG, NCIC) and Australian/New Zealand sites (through the TROG). With all these groups being activated, accrual has gone up steeply, in the last month [ie, April 2011] 15 patients were entered. A total of more than 200 patients have now been entered into this study that requires 740 patients. The accrual will take another 3–4 years, and it is expected that after completion of the accrual another 3–4 years are needed to get the first results.

Thank you very much!

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Hotspots in Neuro-Oncology

Michael Weller

From the Department of Neurology, University Hospital Zurich, Switzerland

Bogdahn U, Hau P, Stockhammer G, et al.; Trabedersen Glioma Study Group. Targeted therapy for high-grade glioma with the TGF-β2 inhibitor Trabedersen: results of a randomized and controlled phase IIb study. Neuro Oncol 2011; 13: 132–42.

In the January issue, the results of the randomized phase-IIb study on an antisense oligonucleotide against transforming growth factor (TGF) β_2, Trabedersen, were presented. This study was the first randomized study to assess the safety and efficacy of a TGFβ-antagonistic approach in glioblastoma. Although the trial was negative for the primary endpoint, the investigators provided extensive subgroup analyses to support the claim that Trabedersen was active in patients with recurrent anaplastic astrocytoma and subgroups of patients with glioblastoma. These interpretations raised concerns as summarized in the correspondence section of the May issue of the journal.

→ *Chamberlain MC. Convection-enhanced delivery of a transforming growth factor-{beta}2 inhibitor Trabedersen for recurrent high-grade gliomas: efficacy real or imagined?, in reference to Bogdahn et al. (Neuro-Oncology 2011; 13: 132–42). Neuro Oncol 2011; 13: 558–9.*

→ *Wick W, Weller M. Trabedersen to target transforming growth factor-{beta}: when the journey is not the reward, in reference to Bogdahn et al. (Neuro-Oncology 2011; 13: 132–42). Neuro Oncol 2011; 13: 559–60.*

→ *Bogdahn U. Response to MC Chamberlain: Convection-enhanced delivery of transforming growth factor-{beta}2 inhibitor Trabedersen for recurrent high-grade gliomas: efficacy real or imagined?, in reference to W Wick and M Weller: Trabedersen to target transforming growth factor-{beta}: when the journey is not the reward, in reference to Bogdahn et al. (Neuro-Oncology 2011; 13: 132–42). Neuro Oncol 2011; 13: 561–2.*

Reardon DA, Galanis E, DeGroot JF, et al. Clinical trial end points for high-grade glioma: the evolving landscape. Neuro Oncol 2011; 13: 353–61.

In the March issue, the Response Assessment in Neuro-Oncology (RANO) Working Group published a position paper on the currently used clinical trial endpoints in the field of malignant glioma, including a critical reappraisal of radiographic endpoints, the associated limitations of progression-free survival as an endpoint, as well as the ultimate need for demonstrating survival benefits in this disease. This article provides an up-to-date summary that should be valued by neurooncologists embarking on the design of clinical trials in the future.

Scott JG, Suh JH, Elson P, et al. Aggressive treatment is appropriate for glioblastoma multiforme patients 70 years old or older: a retrospective review of 206 cases. Neuro Oncol 2011; 13: 428–36.

In the April issue, a retrospective review of 206 patients with glioblastoma aged 70 or more was presented. Although the authors concluded that aggressive treatment may be appropriate in this patient population, this publication, like many others in that area, suffers from the fact that treatment allocation was probably heavily influenced by patient characteristics and that less fit patients were less likely to receive what is nowadays considered aggressive treatment. Accordingly, only the results from large randomized trials will eventually clarify the role of intensifying treatment in elderly patients with glioblastoma.

→ *Weller M, Wick W. Are we ready to demystify age in glioblastoma? Or does older age matter in glioblastoma? Neuro Oncol 2011; 13: 365–6.*

Johnson DR, Kimmel DW, Burch PA, et al. Phase II study of subcutaneous octreotide in adults with recurrent or progressive meningioma and meningeal hemangiopericytoma. Neuro Oncol 2011; 13: 530–5.

In the May issue, results from a phase-II study of subcutaneous octreotide in patients with recurrent progressive meningioma and haemangiopericytoma were reported. Treatment with somatostatin agonists is currently among the most promising options for patients with meningioma who may not have further surgical or radiotherapeutic options. Somewhat unexpectedly, no neuroradiographic responses were observed in this group of 12 patients, with only 2 patients experiencing prolonged progression-free survival. The search for more effective medical treatments for meningioma must go on.

Wefel JS, Cloughesy T, Zazzali JL, et al. Neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab. Neuro Oncol 2011; 13: 660–8.

In the June issue, Wefel et al described the neurocognitive function in patients treated with bevacizumab in the BRAIN trial for recurrent glioblastoma. Apparently, patients considered stable by radiographic analysis had improved or stable neurocognitive function, indicating that the radiographic responses translated into a clinical benefit. This publication adds to the increasing awareness that neurocognitive function should be seriously considered at least as a surrogate endpoint of neurooncological trials with poor-prognosis patient populations like patients with recurrent glioblastoma.

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News from the Society for Neuro-Oncology

Frederick F Lang, Charles Haynes

From the Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

First and foremost, the leadership and members of the Society for Neuro-Oncology (SNO), the North American sister society to the European Association for Neuro-Oncology (EANO), congratulate EANO for publishing this inaugural edition of *European Association of Neuro-Oncology Magazine*, which will offer exciting reading to all those interested in the discipline of neuro-oncology. SNO leaders look forward to contributing regularly to this magazine and hope that through this medium we will be able to keep our EANO colleagues up-to-date on SNO initiatives that may be of interest to them.

SNO Celebrates 15 Years

In this spirit, 2010 marked the 15th anniversary of the founding of SNO. To commemorate this milestone, the SNO leadership commissioned the development of a brochure to chronicle the history of SNO and to celebrate the vision and efforts of the founders and members who have steered SNO to its current place. The brochure highlights the events surrounding the formation of SNO and outlines milestones and achievements of the first 15 years of the society. It also acknowledges the members who actively contributed, and continue to contribute, to the success of the Society. Members of EANO are encouraged to download an electronic copy of the brochure from the SNO website at the address below.

SNO Conferences and Annual Meeting

SNO's first boutique meeting, the Paediatric Neuro-Oncology Basic and Translational Science Conference, was held May 19–20, 2011, in New Orleans, Louisiana. The meeting enjoyed attendance of over 200 paediatric basic and translational scientists from 12 countries. The conference encouraged the sharing of ideas and results, new collaborations, and provided attendees with a state-of-the-art update in the field of paediatric brain tumour research. The Scientific Program Committee created a highly informative and educational program from over 130 accepted abstracts. The program featured informative plenary sessions and informal poster sessions, as well as "Meet the Expert Sunrise Sessions", at which attendees were able to catch up with late breaking areas of research and controversies in the field. Based on the success of the meeting, SNO has decided to make this meeting a regular biennial event and is already planning for the next conference in 2013.

Looking ahead, SNO is actively planning for its 16th Annual Scientific Meeting and Education Day, which will take place November 17–20, 2011, at the Hyatt Regency Hotel, in Orange County, California. SNO is pleased to announce that this year the meeting will be held in conjunction with the AANS/CNS Section on Tumours. This added neurosurgical component will further enhance this already highly educational meeting. Over 650 abstracts were received this year, an increase of over 10 % from 2010. In addition to the plenary, concurrent and poster sessions, the meeting will feature an Education Day which this year will focus on Radiosurgery and Radiobiology. Concurrent Quality of Life sessions will also be offered. In addition, a young investigators' workshop on Thursday afternoon will explore current challenges associated with neuro-oncology clinical trials design, conduct, and evaluation. Members of the Section on Tumours and SNO who have served as a principal investigator of clinical trials will review trial endpoints, response assessments, evaluation of treatment toxicities as well as statistical considerations. Regulatory requirements for applications to the Federal Drug Administration and institutional review boards will also be reviewed during the course. If the response to the course is favourable, SNO hopes to work with our colleagues from EANO and other sister societies to develop a 2-day workshop addressing clinical trial issues to be held during the next World Federation of Neuro-Oncology Quadrennial Meeting that will take place in San Francisco, California, in 2013.

As part of SNO's international outreach efforts to developing regions, SNO is now accepting applications for travel scholarships to our annual meeting. A total of 8 US$ 1500.– scholarships will be awarded to recipients from each of the following geographical regions (one per region): Central America & the Caribbean, Central and Southern Africa, China & associated countries, Eastern Europe, Far East and Australasia, Indian Sub-Continent, North Africa & the Middle East, and South America.

Neuro-Oncology Journal

As many EANO members of already know, the impact factor for our official journal, *Neuro-Oncology*, has increased by 10 % to reach 5.483 in the most recent Journal Citation Reports (up from 4.98). This means that *Neuro-Oncology* has maintained its position as the premier journal in the field and is now ranked 15th out of 185 titles in the clinical neurology category, and 24th out of 184 titles in oncology. Thanks to a historic agreement between SNO, EANO, and Oxford University Press, EANO members now have electronic access to the journal via the EANO website.

SNO and EANO Collaborations

In an effort to foster improved relations between the leading neuro-oncology societies, SNO leadership met with EANO leadership during the recent American Society of Clinical Oncology Annual Meeting. It was agreed that a new inter-organizational committee should be established and that outreach to other international sister organizations should be undertaken and formalized. It is hoped that this committee will allow for regular communication between the various international organizations, addressing issues such as the Quadrennial World Federation of Neuro-Oncology, educational exchange, administrative issues, and other multilateral collaborative opportunities.

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EANO Neuro-Oncology Online Magazine

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

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

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

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