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Riccardo Soffietti

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2014

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Dear colleagues,

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

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

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

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

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

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

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

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

Riccardo Soffietti, MD

EANO President (2012–2014)
Austrian Patients with Glioblastoma Multiforme and Their Families: Socioeconomic Aspects

Birgit Flechl, Christine Marosi

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

By analyzing quality of life (QOL), performance status, living and working situations, muscular strength of subsets of GBM patients, as well as satisfaction with the care and the end-of-life (EOL) situation of GBM patients of their primary caregivers, we tried to assess the impact of glioblastoma on patients and their families. We found that GBM long-term survivors (LTS) were mainly independent in their activities of daily living and mostly also in instrumental activities of daily living, but showed some moderate cognitive deficits and suffered from financial difficulties. Only a minority of GBM LTS was able to stay in their respective jobs. Even with adolescent and young adult (AYA) patients diagnosed with GBM before 40 years only 1/2 succeeded in staying employed after the diagnosis of GBM. Near half of the AYA patients returned to the household of their parents, which reflects their loss of independence. Moreover, we found that patients with GBM present a significant loss of strength in the proximal musculature of the legs, impairing their ability of climbing stairs and walking very early in the disease course. The complex patterns of physical, neurological, and cognitive impairments in GBM cause their needs for support starting very early in the disease.

Introduction

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

GBM Long-Term Survivors

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

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

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

Financial Aspects

After diagnosis of a malignant disease, when a person is unable to work for a prolonged time, the health care systems in Western Europe usually provide sick pay consisting of a high percentage of the last salary, but – at least in Austria – it is limi-
ated to the duration of one year. So patients with jobs where
tips or provisions are regular parts of their monthly income
suffer greater losses in their incomes than other professions.
Moreover, after the respective maximal duration of sick leave,
patients either have to return to work or apply for disability
benefit. In many European countries including Austria, dis-
ability benefit is calculated according to an algorithm based
on the last income and the number of working years, therefore
lower for younger patients. Opportunities for support from
social authorities are mostly available but application proce-
dures may be troubling and humiliating for GBM patients and
often beyond their cognitive and emotional capacities. Mainly
GBM patients dependent on disability pensions complained
about disease-related financial problems.

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

**Adult Young and Adolescent Patients with GBM**

Leibetseder et al recently published a study about 47 adoles-
cent and young adult GBM patients aged < 40 years [6]. Of
note, about half of these young patients with malignant brain
cancer were not able to manage and support their routine daily
life independently in their own home. They returned to the
households of their parents, mostly into their old nurseries.
This alarming number illustrates the high rate of loss of inde-
pendence in this group of patients. 57 % of AYA patients with
GBM lost their jobs within the first 2 months after diagnosis.
Only self-employed people or persons working in family
businesses or in large enterprises in administrative jobs or on
computers were able to stay employed. Patients from other
occupational groups, mainly craftsmen like butchers, car me-
chanics, photographers, shoemakers, clerks, fitters and, no-
ticeably, all health care workers, including physicians and
midwives, and all teachers lost their jobs due to their disease a
few weeks after diagnosis. None of the patients surviving in
good performance status for several years were able to return
to employment after GBM diagnosis.

**Loss of Muscular Strength**

It is well-known that glioblastoma leads to a decrease in mus-
cular strength due to neuromuscular dysfunction caused by
the tumour itself and due to corticoid treatment which is re-
quired to decrease intracranial pressure. Although steroids are
generally tapered off as soon as possible after neurosurgical
intervention, Keilani et al [7] recently described significant
deficits in muscular strength and general physical perform-
ance in Austrian GBM patients. The loss of strength of the proximal muscles of the legs needed for walking was mea-
sured before the start of radio/chemotherapy and did not im-
prove after 3 months.

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

**Family Caregivers**

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

**End-of-Life Phase**

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

Our study, performed at 2 centres in Vienna, supports this
conclusion. We evaluated retrospectively the perspective of family caregivers of patients with GBM on the EOL phase
defined as the last 3 months before death [10]. We used a questionnaire for the caregivers developed and validated by
the working group of Taphoorn et al (Medical University of
Amsterdam). Family caregivers of 52 patients with GBM, di-
agnosed from 2005–2009 and treated in Vienna, participated
in this study. As assumed, caregivers indicated that the GBM
patients suffered from fatigue, reduced consciousness, aphasia,
and various neurological deficits during the EOL phase,
which is different from the EOL phase of patients with other
cancers. Moreover, partners or family members who cared for
them went through a hard phase. Sadness, fear, and an alarm-
ingly high percentage of overstraining were reported by the
majority of caregivers, which reflects the excessive mental
and physical demands on them. Moreover, family caregivers
also mentioned financial difficulties due to the patients’ GBM. Caregivers who mentioned financial difficulties were also those who complained about insufficient information on the disease and about overstraining. However, Pace et al [11] showed in their impressive Italian study that a satisfying end-of-life period for both, patients and caregivers, is possible by supporting them at home with a mobile palliative team.

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

**Conclusion**

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

**Conflict of Interest**

Both authors declare that there is no conflict of interest.

**References:**


**Histopathology and Classification**

Of all primary tumours, brain tumours constitute approximately 2% and the global annual incidence reaches approximately 7 cases per 100,000 individuals [1–3]. There are > 100 types of brain tumours under the World Heath Organization (WHO) classification scheme. Among these, gliomas are the most prevalent of the primary intrinsic brain tumours. Astrocytic gliomas rank among the most lethal of solid cancers and account for > 30% of all primary brain and spinal malignancies. The World Health Organization (WHO) grades these tumours based on their histology to predict patient outcome. This classification system has been refined periodically, with the most recent changes published in 2007 [4]. WHO grade-I gliomas include several slow-growing tumours that are often located in specific anatomical locations, including juvenile pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma. These tumours are often managed primarily through surgical resection and display specific genetic profiles with rare malignant degeneration. Diffuse gliomas are highly infiltrative tumours without discrete borders divided into 3 grades (WHO II–IV). Grade-II gliomas infiltrate into normal brain parenchyma and exhibit increased cellularity and mitotic indices. Grade-III (anaplastic gliomas) and -IV (glioblastoma [GBM]) tumours are classified as high-grade gliomas with high cellular proliferative activity, mitoses, and cellular/nuclear atypia. The reported time to progression is approximately 2 and 5 years for WHO grade-II and -III gliomas, respectively. GBMs are distinguished by microvascular proliferation and necrosis. GBM comprises more than a half of all gliomas with a 5-year survival < 5%. Extremely low treatment efficacy against GBM has been observed despite decades of scientific efforts. Median life expectancy of newly diagnosed patients in clinical trials (ie, a selected patient population) has improved to 12–15 months, although outcome for elderly patients is much worse. Although GBMs are generally histologically indistinguishable from one another, increasing evidence supports subgroups of GBMs that are distinct in clinical course, genetic profiles, and epigenetic features. Primary GBMs arise rapidly de novo, representing the most common type of GBM (90–95%), and are seen predominantly in older patients. In contrast, secondary GBMs progress from pre-existing lesions with a lower degree of malignancy. Secondary GBMs are more frequent in younger patients and are seen in 5–10% of all cases.

**Molecular Pathology and TCGA Classification**

Despite the significant prognostic power of the WHO classification that is based largely on morphology, individual patients within each grade can have very different outcomes that are not otherwise accounted for by established prognostic factors, including age. Karnofsky Performance Status (KPS), and therapy [5]. Even though the incidence of gliomas is relatively low, the fatal outcome and poor prognosis associated with the diagnosis of GBM have prompted extensive large-scale molecular and phenotypic profiling informing several new classification schemes discussed below. To date, GBMs have been subjected to the most extensive genomic profiling of any cancer to show major chromosomal and expression alterations – possible drivers of pathogenesis and biology of this severe malignancy. Despite the extensive characterization of genomic alterations in GBM and clinical progress across many
cancer types, effective druggable tumour dependencies have yet to be exploited in glioma. Numerous small-scale studies with generally < 100 patients per diagnostic category have been published, identifying differentially expressed genes among morphologically defined gliomas [5]. These studies were deposited in publically available repositories (Oncomine and Gene Expression Omnibus (GEO)) and provide a valuable “validation” tool for researchers [3]. A larger collective effort was undertaken in the National Cancer Institute’s REpository for Molecular BRAin Neoplasia DaTabase (REMBRANDT). Further, The Cancer Genome Atlas (TCGA) was established by the US National Cancer Institute and National Human Genome Research Institute in late 2005 with the mission of performing the first comprehensive cancer genome analyses applying multi-platform profiling to systematically and comprehensively analyze the gene copy number, mRNA expression, and the epigenetic state of approximately 200 tumours (today’s number has reached 600 patients), the majority being untreated primary GBMs [6]. This original study underwent accelerated publication to be published with a smaller-scale but deeper (whole exome) sequencing of a mix of patient tumours and xenografts that first identified mutations in isocitrate dehydrogenase (IDH1/2) [7], linking metabolism and tumour growth directly. A follow-on study demonstrated that IDH1 mutations occurred in low-grade tumours and secondary GBM [8]. IDH1 mutations serve a gain-of-function role to create an oncometabolite (2-hydroxyglutarate) [9] and induce a methylation phenotype [10]. Other metabolic enzymes (eg, enolase) may be mutated as a passenger to cause sensitivity to specific inhibitors [11]. These studies have provided strong intellectual support for the identification for driving genetic lesions or other molecular sensitivities to inform therapeutic development.

Phenotypic gene expression profiling of glioblastomas has led to additional granularity of this disease. A seminal study by Phillips et al using unsupervised hierarchical clustering of expression profiles led to the characterization of 3 GBM tumour subtypes: proneural, proliferative, and mesenchymal [12]. A subsequent effort using the TCGA data delineated 4 subtypes: proneural, neural, classical, and mesenchymal on the basis of functional gene annotation and, prior to the Phillips study [12], linking the molecular signatures of gliomas with stages of neuroglial development. Moreover, TCGA effort utilized methylation profiling to identify a GBM CpG island methylator phenotype (G-CIMP) in a significant fraction of the proneural (29 %) subtype, secondary IDH1 mutation-positive GBM that progressed from lower-grade tumours in particular [13]. The 4 proposed subtypes were subsequently validated using previously published data and each of them was ultimately defined by a minimum list of 210 genes [14]. The proneural subtype was primarily enriched for amplifications of PDGFRα, OLIG2, CDK6, CDK4, and MET, where the first 2 represent markers highly relevant to oligodendrocyte development [15, 16]. The classical subtype can be characterized by more common epidermal growth factor receptor (EGFR) amplification/EGFRvIII mutation, PTEN and CDKN2A loss, whereas the mesenchymal subtype is enriched for mutations and/or loss of NF1, TP53, and CDKN2A. To evaluate whether these genically identified subtypes predict biological or clinical heterogeneity in GBM, Brennan et al [15] used a targeted proteomics approach to determine whether GBMs also segregate into the above-mentioned subtypes by activation of signalling pathways. 57 proteins or protein modifications were assessed in 20 GBM samples using unsupervised clustering and led to the identification of distinct tumour subgroups defined by EGFR-associated, PDGFR-associated signalling, or protein level changes associated with decreased NF1 expression [14]. In addition to previous studies, Sturm et al integrated paediatric GBMs to identify 6 epigenetic GBM subgroups displaying unique DNA methylation patterns, harbouring distinct hotspot mutations, DNA copy-number alterations, and transcriptomic patterns. Their findings correlate with molecular-genetic factors as well as key clinical variables such as patient age and tumour location of histologically indistinguishable GBMs [17]. Importantly, the established morphological classification system (WHO) and the evolving molecular subtyping should be considered complementary, not mutually exclusive, as the latter serves mainly as a diagnostic adjunct to more accurate classification of morphologically ambiguous tumours.

Angiogenesis

Robust neoangiogenesis and intratumoural heterogeneity are hallmark features of GBMs. Vascular endothelial growth factor (VEGF) expression strongly correlates with tumour aggressiveness, invasiveness, early relapse, and consequently commonly indicates poor prognosis and shorter survival of glioma patients [18, 19]. For many years, it was proposed that tumours beyond a diameter of 1 mm undergo so-called “angiogenic switch” resulting in the formation of tumour vasculature. This “switch” involves both activation of oncogenes [20] and inactivation of tumour suppressors to up-regulate pro-angiogenic pathways. To date, there are 6 principal cellular mechanisms described to take part in the process of neoangiogenesis [19, 21]. These include – vascular co-option involving formation of microvasculature surrounded by tumours cells
– vessel intussusception – formation of vessels by vascular invagination, intraluminal pillar formation, and splitting
– angiogenesis representing development of new vessels from pre-existing ones resulting in tortuous, abnormal vasculature with increased permeability
– vasculogenesis involving differentiation of circulating bone marrow-derived cells known as endothelial progenitors
– vascular mimicry – a controversial and insufficiently understood process defined as the ability of tumour cells to form functional vessel-like networks
– glioblastoma-endothelial cell transdifferentiation – the most recently reported mechanism, yet to be confirmed by further studies

VEGF is a key pro-angiogenic factor in both embryogenesis and tumour growth [18, 22]. Loss of VEGF or its 2 receptors VEGFR1 and VEGFR2 induces embryonic lethality in mouse models due to severe defects in the developing vascular system [23]. VEGF secreted by tumour cells acts through the VEGFR2 (VEGFR1 is believed to function as a “decoy” receptor to negatively regulate VEGF levels available for VEGFR2 activation) tyrosine kinase receptor, which is expressed pri-
marily in endothelial cells. Recent data, however, provide evidence of co-expression of VEGF/VEGFR2 in GBM cells – an indication of an autocrine control of VEGF signalling in gliomas in addition to the paracrine interplay of tumour and endothelial cells [24–26].

### Therapeutic Resistance

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

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

EGFR amplification and EGFRvIII mutations were established as a key feature of the classical molecular GBM subtype and have long been known to be regulating intracellular signalling pathways that contribute to GBM pathogenesis including mTOR/Pi3K/Akt and RAS/MAPK. The first generation of EGFR tyrosine kinase inhibitors (TKI) is represented by erlotinib and gefitinib, which were investigated in newly diagnosed and recurrent malignant gliomas, either as monotherapy or in combination with other cytotoxic agents [38]. Similarly to cetuximab, a monoclonal antibody directed at EGFR, and lapatinib that targets HER1 and HER2, these agents were not associated with any significant treatment benefit [39–41].

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

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

### Glioblastoma Stem Cells

Glioblastoma stem cells (GSC) are functionally defined by their capacity for (1) self-renewal, (2) recapitulation of a patient’s phenotype when xenotransplanted into an immuno-
compromised host, and (3) multi-lineage differentiation, giving rise to a heterogeneous population of cells repopulating the tumour bulk [51–55]. These cells display severe resistance to current chemo- and radiation therapies, thus being considered one of the key determinants driving tumour recurrence [56–59]. Bao et al [56] reported elevated levels of the key components of the canonical DNA damage-response pathway in response to ionizing radiation (IR) and the ability of GSCs to escape the effect of IR by preferential activation of this pathway and lowered rates of apoptosis when compared to non-GSCs. GSCs also exhibit high levels of MGMT, thus making GSCs more sensitive to TMZ treatment [57]. However, TMZ did not affect propagation and maintenance of GSCs with “normal” levels of MGMT [60], which might be due to over-expression of certain ATP-binding cassette transporters (ABCT) such as ABCG2 responsible for active efflux of TMZ from the GSCs [58, 61].

Several prospective markers to identify and further isolate GSCs have been published so far, among those CD133 (prominin-1), CD15, Integrin α6, CD44, EGFR, A2B5, L1CAM are surface antigens [62–67]; Sox2, Olig2, Oct4, Mushashi-1, BMI1, NANOG represent intracellular factors involved in GSC self-renewal and maintenance [68, 69]. Despite CD133 being the most frequently used marker to enrich GSCs from the tumour bulk, 2 independent studies suggested that CD133 is not a universal GSC marker, as tumours contain CD133-negative tumour cells that showed “stem cell” properties in stem-like conditioned media in vitro and initiated tumours when injected orthotopically in immunocompromised hosts [70, 71]. However, some studies use extensive cultures that may affect the hierarchy.

Recent research in this area has revealed that GSCs are localized into 2 specialized niches within the tumour, perivascular and hypoxic, where the hierarchy and their maintenance are regulated by a complex network of molecular signals and cell-to-cell/cell-to-extracellular matrix interactions (Figure 1). Normal neural stem cells also exist in vascular niches, into which endothelial cells secrete factors that regulate neural stem cell function [72–74]. Calabrese et al [75] provided evidence that the brain tumour microvasculature forms a niche that is critical for the maintenance of brain tumour stem cells, where these cells physically interact with endothelial cells and tumour vasculature. A recent study by Zhu et al [76] took into consideration cell-to-cell contact between different cell types and proposed the endothelial Notch-ligand expression Dll4 (Delta-like ligand 4) as the juxtacrine mechanism driving stem cell maintenance. Interestingly, Notch is one of the crucial factors in GSC maintenance and also contributes to the radio-resistant phenotype as described by Wang et al [59]. Moreover, GSCs have been shown to secrete elevated levels of VEGF and SDF-1 [77, 78] and to operate the pro-angiogenic VEGF/VEGFR2 signalling in an autocrine manner [24, 26], being further potentiated by interaction with other pro-angiogenic factors such as NRP-1 and c-met. Integrating the recent findings on GBM-endothelial cell transdifferentiation and vascular mimicry, the mechanisms utilized by GSCs represent a putative source of resistance to current anti-angiogenic therapies [24, 25].

Hypoxia is a well-recognized tumour microenvironmental condition linked to poor patient outcome and resistance to therapies [79–81]. Evans et al [82] analyzed normal brain and glioma tissue oxygenation and showed that physiological oxygen concentrations in healthy brains range between 12.5 % and 2.5 %, whereas GBM tumours showed mild to moderate/severe hypoxia (oxygen concentrations ranging between 2.5 % and 0.5 % for mild hypoxia and 0.5–0.1 % for moderate/severe hypoxia. Li et al [83] showed that GSCs differentially respond to hypoxia with a distinct induction of HIF2α, and moreover that expression of HIF2α is significantly associated with poor patient survival. Pistollato et al [84] reported that hypoxia represses the differentiation responses to bone morphogenetic proteins (BMP).

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

**Conclusions**

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

---

**Figure 1.** Glioblastoma stem cells (GSC) reside in vascular and hypoxic niches. Schematic representation of GSC residing in a vascular niche supported by blood vessels and hypoxic niche adjacent to necrotic regions. Each niche promotes the maintenance of the GSC population and supports the expansion of the tumour mass.
profit from combinatorial targeting of various survival mechanisms that involve niche components (such as hypoxia) that contribute to preferential selection and outgrowth of genetically unstable clones, thus being responsible for tumour recurrence and, consequently, patient death.

Acknowledgements

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Conflict of Interest

The authors state no conflict of interest.

References:


Glioblastoma Stem Cells

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Epidemiology and Brain Tumours: Practical Usefulness

Adelheid Wöhrer

Abstract: Primary brain tumours are rare tumours which occur across all ages. This review compiles population-based information on tumour type, age at diagnosis, and neurologically relevant location within the central nervous system. It provides an overview of incidence, mortality, and survival rates for primary brain tumours, focusing on malignant and non-malignant tumours, including glioblastomas, medulloblastomas, and ependymomas. The overall impact of brain tumour-related deaths on Western populations in terms of premature mortality has been quantified as an average of 21.3 years of a potential life lost. This adds to a substantial loss of productivity due to the high occurrence of brain tumours in younger “working-age” individuals and considerable costs for supportive care for daily living activities. The diagnosis of a brain tumour renders affected patients often in difficult financial situations due to frequent job losses and high treatment expenses. On the other hand, survival times are increasing due to innovations in diagnosis and therapy. Hence, tumour- and therapy-associated effects on the social and cognitive functioning of long-term survivors “quality-of-life” are becoming increasingly relevant.

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

Background and Descriptive Epidemiology

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

Incidence and Mortality

Reported overall incidence rates of primary brain tumours reach up to 20 per 100,000 person-years [5], the most common tumours in adults being meningiomas, glioblastomas, and pituitary adenomas [5, 6]. In children, however, the encountered spectrum of brain tumours differs substantially from that in adults due to a higher prevalence of embryonal tumours, e.g., medulloblastomas, pilocytic astrocytomas, and ependymomas [6, 7]. The overall impact of brain tumour-related deaths on Western populations in terms of premature mortality has been quantified as an average of 21.3 years of a potential life lost [8]. This adds to a substantial loss of productivity due to the high occurrence of brain tumours in younger “working-age” individuals [9] and considerable costs for supportive care for daily living activities. Alternately, the diagnosis of a brain tumour renders affected patients often in difficult financial situations due to frequent job losses and high treatment expenses [10]. On the other hand, survival times are increasing due to innovations in diagnosis and therapy. Hence, tumour- and therapy-associated effects on the social and cognitive functioning of long-term survivors’ “quality-of-life” are becoming increasingly relevant [11].

Gender Predilection, Regional Variation, and Ethnical Disparities

Overall, primary brain tumours are more frequent in females than males (female incidence rate [IR] 22.25 per 100,000 person-years, male 18.8 per 100,000 person-years) [5]. While meningiomas are twice as common in females, gliomas, embryonal tumours, lymphomas, and germ cell tumours show a slight male predilection (m/f ratio approximately 1.4). Interestingly, CBTRUS data from the United States indicate ethnical disparities with a lower overall incidence of brain tumours in American Indian or Alaska Natives (AIAN; IR 13.15 per 100,000 person-years) as well as the Asian and Pacific Islander (API) population in the United States (IR 12.98 per 100,000 person-years) compared with whites (“Caucasians”: IR 20.61 per 100,000 person-years) and Afro-Americans (IR 20.12 per 100,000 person-years) [5]. However, the observed rates for the majority of brain tumour entities are significantly higher in whites of European ancestry when compared with Afro-Americans, AIAN, and API ethnicities. The only exceptions are meningiomas and tumours of the pitui-
Clinical Implications of Brain Tumour Epidemiology

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

- Time Trends

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

- Analytical Epidemiology

Environmental Risk Factors

Ionizing Radiation

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

Radiation Exposure from X-Ray Investigations Including CT Scans

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

Likewise, dental X-rays, which were performed in the past, when radiation exposure was still greater, appear to be associated with a slightly to moderately increased risk for the develop-
Clinical Implications of Brain Tumour Epidemiology

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

Non-Ionizing Radiation
Over the last decade, exposure to low-frequency, non-ionizing electromagnetic fields via mobile phones has been critically discussed as a potential risk factor for brain tumours such as gliomas, meningiomas, and acoustic neuromas [25]. The so far conducted case-control studies found inconsistent results, which were in part due to different study designs, small sample sizes, recall bias of mobile phone use, and lack of information on long-term use. The largest studies, so far, include the Interphone and Hardell studies [26–29]. A meta-analysis on both studies found a significantly increased risk for temporal lobe gliomas (most exposed part of the brain) with an odds ratio of 1.71 (95-% CI: 1.04–2.81) in the > 10-year latency group. Ipsilateral mobile phone use > 1640 h in total gave an odds ratio of 2.29 (95-% CI: 1.56–3.37) [25]. With regard to acoustic neuromas, ipsilateral mobile phone use in the latency group > 10 years resulted in an odds ratio of 1.81 (95-% CI: 0.73–4.45). For ipsilateral cumulative use > 1640 h an odds ratio of 2.55 (95-% CI: 1.50–4.40) was found [25]. Based on a comprehensive literature search with special consideration given to the 2 studies mentioned above, the IARC has recently classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (press release No 208, 31-05-2011). However, whether the IARC carcinogenic classification has any impact on policy makers and results in concrete legislative acts to protect public health remains to be shown [25]. Furthermore, there are concerns that mobile phone use might differentially impact developing brains of children and adolescents. This is currently the topic of 2 large case-control studies: CEFALO and MOBI-KIDS (www.mbkids.net). First CEFALO results did not demonstrate an exposure-response relationship in children and adolescents [30].

Table 1. Genetic brain tumour syndromes [3].

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Locus</th>
<th>Brain tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowden syndrome/Lhermitte-Duclos syndrome</td>
<td>PTEN</td>
<td>10q23</td>
<td>Dysplastic gangliocytoma of the cerebellum</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
<td>17p13</td>
<td>Astrocytoma, PNET</td>
</tr>
<tr>
<td>Neurofibromatosis I</td>
<td>NF1</td>
<td>17q11</td>
<td>Neurofibroma, MPNST, optic and other gliomas</td>
</tr>
<tr>
<td>Neurofibromatosis II</td>
<td>NF2</td>
<td>22q12</td>
<td>Bilateral vestibular schwannoma, meningioma, ependymoma, and others</td>
</tr>
<tr>
<td>Rhabdoid tumour predisposition syndrome</td>
<td>SMARCB1/INI1</td>
<td>22q11.2</td>
<td>ATRT</td>
</tr>
<tr>
<td>Von-Hippel-Lindau syndrome</td>
<td>VHL</td>
<td>3p25</td>
<td>Hemangioblastoma</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1</td>
<td>9p34</td>
<td>SEGA, cortical tubers</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC2</td>
<td>16p13</td>
<td></td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>APC</td>
<td>5q21</td>
<td>Medulloblastoma, glioblastoma</td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>hMLH1</td>
<td>3p21</td>
<td></td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>HPSM2</td>
<td>7p22</td>
<td></td>
</tr>
<tr>
<td>Familial meningioma</td>
<td>SUFU</td>
<td>10q24.32</td>
<td>Multiple meningiomas [31]</td>
</tr>
</tbody>
</table>

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

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

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

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

Genetic Tumour Syndromes

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

Susceptibility Loci

Genome-wide association studies have recently identified 7 susceptibility variants for gliomas, which are associated with moderate increases or decreases in risk (odds ratios from 0.6–1.2) [32, 33]. While variants at 7p11.2 (EGFR both loci) affect all glioma subtypes, 20q13.33 (RTIL1), 5p15.33 (TERT), and 9p21.3 (CDKN2B) differentially impact the risk for glioblastoma, 8q24.21 (CCDC26) for oligodendroglioma, and 11q23.3 (PHLDB1) for low-grade glioma [32]. These data show that common low-penetration susceptibility alleles are associated with the development of glioma and provide insights into disease causation [33]. Still, larger studies focusing on specific tumour subtypes or -groups are required to identify additional susceptibility loci and validate the proposed ones for glioma risk.

Molecular Epidemiology

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

Despite the huge number of proposed biomarkers for brain tumours, only single candidate biomarkers, which provide prognostic and/or predictive information, have translated into clinical use so far. The most prominent examples of tissue-based biomarkers include isocitrate dehydrogenase (IDH) 1 and 2 mutations in diffuse gliomas [40, 41], combined 1p19q loss in oligodendroglioma [42, 43], O6-methylguanine methyltransferase (MGMT) promoter methylation status in glioblastoma [44], as well as MYCC/MYCN amplification and markers for WNT activation in medulloblastoma [45, 46]. While some of those markers are screened for in the setting of clinical trials (eg, MGMT, 1p19q, MYCC/MYCN amplification) serving as patient stratification factors, even less markers have already translated into routine clinical use, where they provide prognostic and/or predictive information on the individual patient (IDH1 mutational analysis and assessment of combined 1p19q loss) [47]. With regard to the various biomarkers, clinical and analytical test performances remain an important issue [48] and there is a need for a widely accepted consensus among neuropathologists and neuro-oncologists on the levels of evidence and clinical utility of the various biomarkers.

Conclusion and Implications for Clinical Use

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

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

Conflict of Interest

None.

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Introduction

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

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

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

Benefit of Extended Tumour Resections for Patient Prognosis

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

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

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

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such as age and Karnofsky performance status (KPS), GTR has been shown to be another independent positive prognostic factor in HGG [1–8]. To our knowledge, evidence of the highest available quality can be derived from a German multicentre, randomized, controlled trial by Stummer et al that compares 5-aminolevulinic acid (5-ALA) fluorescence-guided with conventional white-light HGG resections [9]. In a balanced re-stratification for resection extent, all patients who underwent GTR experienced prolongation of overall survival compared to incompletely resected patients (16.7 vs 11.8 months, respectively; p < 0.0001) [1, 7]. In addition, another high-volume series of McGirt et al evaluated 1250 patients harbouring a high-grade glioma and found a survival benefit up to 5 months when comparing GTR to PR (13 vs 8 months, respectively) [8]. These results were adjusted for factors with known association to survival such as age, KPS, or adjuvant therapies. Sanai et al present a thorough analysis of the current literature with a focus on precise calculation of EOR and clear statistical measures. They report a statistically significant beneficial effect from maximized EOR in 16/28 HGG studies [6]. Although prognosis in HGG remains poor, these recent results should be valued as encouraging. We see the impact of extended safe resection upon overall survival in glioblastoma alongside with the beneficial effects of concomitant radio-chemotherapy as reported by Stupp et al in 2005, formerly offering a median 2.5-month longer survival compared to previous standard treatment [10]. Even though this study did not include mandatory postoperative imaging and EOR was partly assessed by means of inaccurate estimation of the operating surgeon, in a post-hoc data analysis by Gorlia et al EOR was shown to have a significant impact on patient survival. Building on this and remembering that 5-ALA data was acquired before the implementation of concomitant adjuvant radiochemotherapy, supplemental effects should be expected when both approaches are combined. Maximized safe resection followed by an individualized, targeted therapy is expected to further prolong overall survival for patients with HGG in the future [11].

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

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

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

NC: not calculated

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

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

GTR: gross total resection; IR: incomplete resection; HGG: high-grade glioma; NC: not calculated
iMRI for Intraoperative Resection Control

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

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

In LGG, only intraoperative ultrasound (iUS) can help as an alternate imaging modality during surgery. High-field iMRI scanners are of special value in LGG surgery since they offer high anatomical resolution along with full-scale diagnostic capability. Sharp T2 and FLAIR sequences, MR-spectroscopy, and diffusion-weighted imaging (DWI) contribute greatly to a precise delineation of residual non-enhancing intracranial lesions. So far, there are only few retrospective studies available evaluating LGG outcomes after iMRI-guided resection. A group from the Brigham and Women’s Hospital in Boston compared long-term results derived from their iMRI-guided LGG resections to results from a national registry. Their central finding was a significant reduction of 1-, 2-, and 5-year age- and histology-adjusted death rates compared to the national registry when iMRI was used for resection guidance (1.9 % [95-% CI: 0.3–4.2 %], 3.6 % [95-% CI: 0.4–6.7 %], and 17.6 % [95-% CI: 5.9–29.3 %], respectively). Stratifying for total and subtotal LGG tumour removal, a 1.4 times higher risk of recurrence (95-% CI: 0.7–3.1) and a 4.9 times higher risk of death (95-% CI: 0.61–40.0) was apparent when lesions were only removed subtotally [14]. These tendencies suggest a correlation between iMRI-guided extent of resection and longer patient survival also in low-grade tumours. But again formal evidence is weak, with the non-homogeneity of data and study groups impeding final conclusions until results are confirmed in larger, randomized, matched or other controlled populations.

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

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

Rates of continued surgery after intraoperative resection control by means of iMRI are another interesting aspect when assessing the value of this intraoperative imaging modality. Among the iMRI studies presented here (Table 2), 21 out of 44 patients (47 %) [19] and 17 out of 47 patients (36 %) [20], respectively, underwent further tumour resection after iMRI resection control. Another report by Kuhnt et al states a 26-% incidence of additional resections after the first intraoperative scan. Referring to our own data analyzing the routine use of iMRI guidance for all glioma resections at our department, we observed high frequencies of ongoing resections beyond all WHO grades. In total, 71 of 101 (70.3 %) cases received additional tumour resection after iMRI with even higher rates for WHO °II and °III tumours (Scherer et al, unpublished data, 2012). In their randomized controlled cohort of WHO °IV tumours, Senft et al reported additional tumour resection in 63 % of cases of iMRI application, leading to successful accomplishment of GTR in all of these patients. In their conclusion, iMRI was accountable for the 30-% increase in complete resections and it was evident that without its use neither group would have differed significantly from the other [18, 23].
Journey of iMRI into Daily Use

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>Author, Year [Ref]</th>
<th>Postoperative Deficits</th>
<th>Permanent deficits (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Further resections after iMRI (%)</td>
<td>No further resections after iMRI (%)</td>
</tr>
<tr>
<td>Schneider et al, 2005 [21]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kuhnt et al, 2011 [22]</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>Senft et al, 2011 [18]</td>
<td>0</td>
<td>13</td>
</tr>
</tbody>
</table>

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

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

GTR: gross total resection; IR: incomplete resection; OS: overall survival; PFS: progression-free survival
geon to achieve the seemingly contradictory goal of extending radicality while improving safety.

In summary, the literature shows clear benefits from improved iMRI-guided resection radicality such as lower risk of recurrence, longer progression-free survival, lower 1–5-year death rates (LGG), and longer overall survival (HGG). However, formal evidence for this knowledge is still lacking. Due to inconsistency of data acquisition and presentation, mixed patient populations, and other technical limitations such as different measurements of EOR or MRI field strengths it has so far been virtually impossible to elaborate a clear meta-analysis of existing studies dealing with this topic. As further randomized controlled trials evaluating the extent of resection and its effect on survival are ethically debatable from our current state of knowledge, well-designed, prospective, observational studies might be the only way to underscore the importance and benefit from more radical surgery for the treatment of intracranial gliomas in the future. Precise and prospectively addressed definitions of surgical goals (GTR, no residual contrast enhancement, vs PR, residual contrast enhancement), routine postoperative imaging 48–72 hrs after surgery and volumetric documentation of resection extent should be the least common ground for future data collections. This well-defined baseline data will help to merge knowledge in the field and to present high-volume multicentre series providing age- and histology-adjusted estimates of survival rates with respect to the achieved EOR. Beyond technical aspects, future studies also have to focus on clinical performance and quality of life along with survival benefits in order to give sustainable answers to the questions evolving around the use of iMRI in glioma surgery.

**Figure 1.** 33-year-old male with seizures diagnosed with a WHO II astrocytoma by stereotactic biopsy. Complete tumour resection was scheduled. (A) Preoperative definition of target tumour volume of 31.72 cm$^3$ on T2 FLAIR images. (B) On the first iMRI, a 1.92-cm$^3$ residual tumour is detected at the ventral aspect of the resection cavity on sharp FLAIR images. (C) Postoperative MRI shows no signs of tumour remnants. iMRI guidance led to a fully successful procedure with no added neurologic morbidity.
Feasibility of Routine iMRI: Implementation into Daily Surgery

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

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

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

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

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

Implementing iMRI into routine glioma surgery certainly causes challenges and will most likely affect the strategic approach to a tumour as well as the manner of surgery itself. As a consequence of routine iMRI use in glioma surgery one might expect the frequency of post-iMRI resections to increase over time, together with residual tumour volumes seen in a first intraoperative scan. This would resemble a more defensive surgical strategy in the first place. A preliminary analysis of our data seems to confirm this hypothesis with continued tumour resections performed after iMRI scans in almost ¾ of all patients. It might also be interesting to follow learning curves of young neurosurgeons over their time of training since iMRI provides immediate feedback on the resection progress. By means of this prospective single-institution database of unselected glioma cases, we hope to be able to address unanswerd questions and confirm beneficial effects of iMRI surgery for glioma patients in the future. A newly formed German iMRI study group will further pursue this approach and try to derive a similar multi-centre database in order to merge data and produce solid evidence fostering the use and prevalence of iMRI in neurosurgery.

Conflict of Interest

The authors state that no conflict of interest exists.

References:

Atypical Aggregation of Cancer
Emeline Tabouret
From the Department of Neuro-Oncology, AP-HM, Timone Hospital, Marseille, France

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

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

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

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

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

Further Reading:

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Grief, Bereavement, and Mourning

Hanneke Zwinkels

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

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

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

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

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

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

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

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

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

The last time I met Mr and Mrs M, she was wheelchair-bound because of a hemiparesis and not able to speak. We discussed the diagnosed tumour recurrence and the subsequent focal deficits. Mr M told me how he and his wife were doing at home. She needed help with daily activities, could speak a few words like yes and no, but most of the time could not find the right words, needed to rest more and more, was up for about 4 hours per day, but did not suffer from headache or nausea. A hospital bed had been arranged for, help from friends was available, the general practitioner was informed, and home care would soon be coming.
Mrs M tried to understand what we were talking about, but it was difficult for her to respond to questions. I asked them if they would agree to listen to what could be expected for the last phase, and Mrs M looked into the eyes of her husband with a question in her eyes. After some seconds, he told me, he would be glad to hear about that, she agreed by nodding her head and I carefully talked about what was expected to happen. Tears fell, not only from the eyes of Mr and Mrs M, and after ending our conversation we said goodbye. I wished her a valuable comfortable time, with a lot of love, care, understanding, and hope for a good and beautiful completion of her life.

Suggested Reading:

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

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

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

### A Brave New World

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

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

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

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

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

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

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

### What Levels of Evidence?

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

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

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

### Real-World Patient Data

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

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

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

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

Speaking of value, any value-based pricing assessment mechanism must fully incorporate the patient perspective.
What Is Really valued?
These days, we seem to know the cost of everything but not always the value of everything. We need to change that and think about what really matters to patients and caregivers.

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

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

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

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

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

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

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

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

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

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

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

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

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

Patients Are Willing to Share Their Medical Data
Finally, it is important to dispel one of the myths that may be holding back innovative development of new targeted therapies.

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

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

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

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

Walking Around in Someone Else’s Shoes
Clearly, we need new HTA processes to meet the challenges of innovative targeted therapies, companion diagnostics, digitalisation, and what constitutes value. We need new relationships, new partnerships, and new understanding.

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

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

References:

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### 2013

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<td>Cancer and Metabolism 2013</td>
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<td>July 5–6</td>
<td>Immunotherapy: current knowledge and controversies</td>
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### 2014

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<td>EORTC – NCI – AACR International Symposium on Molecular Targets and Cancer Therapeutics</td>
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### 2015

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In Memoriam Jerzy Hildebrand, MD, PhD

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

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

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

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

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

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

In another retrospective study from the UCLA, Nghiemphu et al confirmed earlier observations that re-challenge with temozolomide can be effective in a subgroup of patients with malignant glioma. They included 14 patients with glioblastoma receiving 12 cycles of adjuvant temozolomide. Patients had stable disease without tumour progression for a median of 23.2 months according to the RANO criteria. PFS(6) after re-challenge was 43 % and mOS 13.5 months, which is impressive data as compared to other glioblastoma studies at first relapse. As prior data indicated, this study confirms that the benefit from re-challenge with temozolomide increases the longer-the-stable disease interval is. These confirmatory findings are helpful for a small subgroup of patients.

Also of great interest were the follow-up results of the 2 anaplastic oligodendroglioma tumour trials EORTC 26951 and RTOG 9402. Both studies showed a 2-fold increase in mOS survival in co-deleted (1p/19q) tumours treated initially with radiotherapy and adjuvant PCV chemotherapy versus radiotherapy alone followed by chemotherapy at recurrence. These data are generally commented on as practice-changing in the treatment of co-deleted anaplastic oligodendrogliomas. Further molecular analyses including IDH-1 mutation and gene expression profiling are under way in both studies in order to detect chemotherapy- or radiotherapy-sensitive subtypes.

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

Several interesting immunological treatment approaches (20 abstracts from lab immunology research and 29 abstracts from clinical immunotherapy) were presented at the 2012 meeting. In a phase-II study from Spain (Valle RD et al), 31 patients received immunotherapy with autologous tumour lysate-pulsed dendritic cells for newly diagnosed GBM following ALA-guided resection. Vaccination was started prior to standard radiotherapy and adjuvant PCV chemotherapy versus radiotherapy alone. They reported a significant survival benefit in the vaccination arm with a mOS of 27.4 months as compared to 14.7 months in the standard arm. Importantly, only patients with complete resection or a tumour load < 1 m2 after resection were included in the study. Further analyses including IDH-1 mutation and gene expression profiling are under way in both studies in order to detect chemotherapy- or radiotherapy-sensitive subtypes.
Preliminary data on the ERC-1671 Gliovac study (vaccination with autologous tumour cell lysate combined with heterologous components of different glioblastoma donors) in recurrent glioblastoma showed that mPFS (9.5 weeks) and mOS (17 weeks) might be superior as compared to other treatment after failure with bevacizumab. However, only 8 patients have been enrolled so far in this study.

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

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

■ Science and Research

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

■ Cancer Registry

Sweden has > 20 national clinical databases related to cancer, including the cancer registry to which all patients diagnosed with cancer have been reported since 1958. The National Quality Registry for primary brain tumours, a subgroup of the Swedish Brain Tumour Study Group, was initiated in 1999 for primary registration and extended to follow-up registration in 2006. The aim was to ensure good treatment for all brain tumour patients with a high international standard and without regional differences. Registration is regionally based. Every year, all data is aggregated on a national level and reported. This registration covers > 90 % of all patients with primary brain tumours although further improvements in the registration are needed for some regions. The national brain tumour registration covers aspects not included in the legally decided cancer registry, such as treatments, time for management, complications, and follow-up parameters like survival.

■ Patient Advocacy Group

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

■ Scandinavian Neuro-Oncology Group

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

■ New Cancer Strategy and Cancer Plan

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

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

Reference:

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

Juan Miguel Gil-Gil
Institut Català d’Oncologia, L’Hospitalet de Llobregat, Barcelona, Spain

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

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

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

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

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

The GEINO statutes also provide for the collaboration with other public or private, national or international organizations, in activities aimed at research and training in the neuro-oncology field. In this area, GEINO has collaborated in clinical research protocols led by other European research groups such as EORTC as well as pharmaceutical industry-sponsored trials.

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

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

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

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

As a channel of information and intercommunication among its members, GEINO publishes the journal Actualidad en Neuro-oncología twice a year (www.geino.es). The group has collaborated in the publication of 3 books in Spanish:
– Colección de monografías: Tratamiento Farmacológico y de Soporte de los Tumores cerebrales (4 números). (Monograph series: Pharmacological and supportive treatment of Brain Tumours – 4 numbers).

We hope that together we can enable GEINO to maintain its research activity and that within EANO it will significantly contribute to the development of neuro-oncology in Spain.
Acknowledgements to all GEINO board members: Pedro Pérez-Segura, Hospital Clínico San Carlos, Madrid; Manuel Benavides, Hospital Carlos Haya, Málaga; Ángel Rodríguez-Sánchez, Hospital Universitario de León; Mª Ángeles Vaz, Hospital Universitario Ramón y Cajal, Madrid; Alfonso Berrocal, Hospital Universitario General de Valencia; Carmen Balañá, Institut Català d’Oncologia Badalona, Barcelona; Jordi Bruna, Hospital Universitario de Bellvitge, L’Hospitalet de Llobregat, Barcelona; Cristina Carrato, Hospital Germans Trias i Pujol, Badalona, Barcelona; María Martínez-García, Hospital del Mar, Barcelona; Juan Manuel Sepúlveda, Hospital 12 de Octubre, Madrid; Jose Luis García, Hospital Universitario Ramón y Cajal, Madrid; Javier Pardo, Fundación Jimenez Diaz, Madrid; Gaspar Reynés, Hospital la Fe, Valencia; and Oscar Gallego, Hospital Sant Pau, Barcelona.

References:

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

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

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

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

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

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

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

A: The patients of arm A (the control arm) are receiving temozolomide day 1–5 every 4 weeks for 12 months, in the other arm (the investigational arm) they receive the same temozolomide regimen but in combination with iv bevacizumab 10 mg/kg every 2 weeks, with bevacizumab given until progression.

Q: What are the stratification factors?

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

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

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

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

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

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

A: Indeed, we will be using the RANO criteria. One of the reasons to develop the RANO criteria were the issues observed in patients treated with bevacizumab: in particular the diagnosis of unenhancing progression and even the development of frank gliomatosis. Also, the RANO criteria allow to continue treatment in case of unclear progression, and call progression with hindsight if the further clinical developments show that progression was indeed present.
Q: How is the accrual and when do you expect to reach the accrual goal? When can we get the first results?

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

Thank you very much!

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

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

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


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

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


According to a press release by Roche (Basel, Switzerland), the registration trial for bevacizumab in the treatment of newly diagnosed glioblastoma, AVAGlio, has reached the primary endpoint of improving progression-free survival whereas no mature results for the overall survival endpoint have been made available yet. These preliminary observations underscore the urgent need to understand pathways of constitutive or acquired resistance to anti-vascular endothelial growth factor (VEGF) treatments. In the November issue of Neuro-Oncology, Piao et al from the MD Anderson Cancer Center analysed the evolution of resistance to anti-VEGF therapy, using either the VEGF antibody, bevacizumab, or the tyrosine kinase inhibitor, sunitinib, in the U87MG orthotopic human glioma model. Bevacizumab doubled survival whereas sunitinib did not. Sunitinib plus bevacizumab, was superior to bevacizumab alone. Both agents reduced tumour vascularity, but bevacizumab was more effective in inhibiting vascularity in the periphery of the tumours, and revascularization occurred earlier in sunitinib-treated tumours, associated with tumour progression. Increased numbers of CD11b+/F4/80+ cells were observed earlier in control and sunitinib-treated animals than in bevacizumab-treated animals and were associated with treatment failure. Although only one cell line model was studied, the study supports the view that a better understanding of tumour/host cell interactions might help to improve on the results obtained with angiogenesis inhibition in the clinic so far.

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


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

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


In the January issue, Packer et al reported very interesting results from Children’s Oncology Group trial A9961 which compared radiotherapy combined with vincristine plus adjuvant chemotherapy with platinum, vincristine, and either CCNU or cyclophosphamide. Patients were enrolled between December 1996 and December 2000. 379 eligible patients were analyzed. Five- and 10-year event-free survival rates were 81 % and 76 %, corresponding results for overall survival were 87 % and 81 %. The primary site of relapse of the primary tumour was local. Importantly, 15 patients suffered secondary neoplasms in the absence of medulloblastoma relapse after a median time of 5.8 years from diagnosis. All secondary tumours occurred in body regions exposed to radia-
tion. The high risk of secondary tumours, many of which are malignant gliomas, is of concern especially with the recent great advances in the molecular subclassification and more targeted therapy options for patients with these tumours. It is of utmost importance to revisit the current standards of care once novel, more effective agents to treat medulloblastoma, which impact survival, are introduced into clinical practice.

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


Malignant peripheral nerve sheath tumours (MPNST) are malignant tumours derived from the peripheral nervous system that are notoriously difficult to treat. Surgery and radiotherapy remain the mainstay of therapy whereas chemotherapy is often ineffective. These tumours are strongly associated with neurofibromatosis type 1 (NF1). In the February issue, Kolberg et al performed a metaanalysis of > 1800 patients with MPNST and reviewed characteristics of 179 patients from 3 European sarcoma centres in Norway, Sweden, and Italy. Over time, they found that the traditionally assumed poorer outcome for MPNST in association with NF1 was not observed anymore in the last 2 decades possibly because of more aggressive treatment approaches to MPNST in NF1. Altogether these observations suggest that MPNST with or without NF1 may not be intrinsically different tumours and should be diagnosed, managed, and monitored accordingly.

Of note, the similar outcome with or without NF1 was calculated for disease-specific survival whereas, overall, there may still be increased mortality for NF1 patients from other NF1-associated conditions. This data compilation provides a valuable basis for the planning and design of future interventional studies in NF1 and MPNST.

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News from the Society for Neuro-Oncology

J Charles Haynes

Society for Neuro-Oncology, Bellaire, TX, USA

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

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

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

The meeting will feature an education day entitled “From Drug Discovery to Clinic” which will address the various aspects of clinical development of agents that range from preclinical testing, pharmacokinetic and pharmacodynamic considerations, first-in-man studies, and the challenges of phase-0–III clinical trials. Concurrent sessions will address the specific challenges of clinical design and specific pathways that are being evaluated in the preclinical area.

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

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

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

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

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

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