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Editorial

First of all on behalf of EANO I would like to congratulate the SNO leadership for an amazing conference in San Francisco. In addition to the insights from invited lectures and educational activities in part supported by the US Moonshot program, the EANO highlight for sure was the award-winning clinical abstract on the CeTeG-trial, in which Ulrich Herrlinger from Bonn presented the NOA-09 trial demonstrating an overall survival benefit in a small, but controlled randomized study for the combination of cyclic CCNU and temozolomide in patients with newly diagnosed glioblastoma harboring a hypermethylated MGMT promoter.

In this issue of the magazine we will have opinion papers on the value of brain tumor epigenetics, as well as on the role of radiation therapy in combined modality therapies with a focus not only on the classical approaches but also radiosensitization and immunotherapies. In addition to the large body of literature on precision medicine approaches, three colleagues from the US share their vision on the present, but more important also on the potential future use of next-generation sequencing and other high-throughput technologies in neuro-oncology. We have the periodic updates on Nurses Activities, featured articles from Neuro Oncology and Neuro Oncology Practice as well as a view from the EANO youngsters on mentoring.

Two of our national organizations (the British and the Indian societies) present their views on the WFNOS and the national Indian Neuro Oncology conference, respectively.

On behalf of my colleagues from the EANO board, I would like to wish all readers a successful completion of 2017 and a great start into the year 2018 with one highlight, our EANO conference in Stockholm in October, already determined.

W. Wick

President EANO

Editorial

This year from November 15 to 19 SNO held its 22nd annual meeting in San Francisco. Each meeting has a theme and this year's overall theme focused on the "Cancer Moonshot" program that was proposed by former president Obama in 2016 and was initially led by former vice-president Biden, whose son perished from a GBM. The meeting was attended by over 2500 participants from all over the world with a record number of submitted abstracts (over 1800). The meeting was preceded by two successful former meetings: the Neuro-oncology Review Course and the SNO/SCIDOT course on interstitial CNS delivery, both held on Nov. 15. Our Education Day was held on Nov. 16; it focused on the subject of GBM resistance and was organized by Sue Bell, Robert Cavaliere, Khalid Shah, and Albert Kim. The main meeting was organized by Manish Aghi, Vinay Puduvalli, and Frank Furnari and was highlighted by keynote talks by Jennifer Doudna on

CrispR/Cas9 and Carlo Croce on microRNAs. There were multiple SNO educational events from a sunrise session to lunchtime tutorials and dinner events, such as very well attended poster and e-talk sessions. There were also multiple events dedicated to stress relief as well, including opening receptions, gala dinners, and burnout relief events. We are looking forward to the 23rd meeting in New Orleans, which will be led by our new officers (President: Patrick Wen; Vice-President: Gelared Zadeh, and Secretary/Treasurer: Tracy Batchelor).

E.A. (Nino) Chiocca

President SNO

Brain Tumor Epigenetics: From Research to Clinical Practice

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Introduction

Epigenetics is defined as the study of heritable changes in gene expression that are not caused by alterations in DNA sequences.[1] The phenotypic difference between a caterpillar and a butterfly, for example, is due to epigenetic regulation of gene expression in the same animal with the same DNA. I particularly like this example to explain the meaning of the term epigenetics, as it impressively demonstrates how powerful these mechanisms are in controlling phenotypic changes. Epigenetic changes are reversible and include the key processes of DNA methylation, histone modifications, and noncoding RNA-associated gene silencing (recently reviewed[2]), known to play an essential role during the embryonic and postnatal development of an organism and in tissue homeostasis.[2] Disruptions of epigenetic processes can induce changes in gene function, which together with genetic changes can lead to the neoplastic transformation of a normal cell (recently reviewed).[3]

Recent technological advances have significantly contributed to the tremendous progress in understanding how these epigenetic modifications are regulated in normal cells and deregulated in cancer cells. For example, this knowledge has enabled the translation into better diagnostic algorithms for tumor classification, prognostication, and risk assessment. Importantly, we are now entering a time when novel therapies targeting these deregulated epigenetic mechanisms are being developed, with some of them showing very promising effects in preclinical models.

It is beyond the scope of this article to comprehensively review mechanisms of epigenetic regulation of gene expression and their deregulation in brain tumors; excellent recent reviews are available to the readers on these subjects.[2–5] Here, I will discuss a few examples of recent epigenetic discoveries which have informed the development of novel diagnostic and prognostic tools or led to successful preclinical testing of new epigenetic drugs in experimental models.

Epigenetic Profiles in the Molecular Classification of Brain Tumors

Glioma: One of the first examples of an epigenetic change informing the design of an assay for diagnostic screening to corroborate a therapeutic decision is the assessment of methylation of the MGMT promoter in malignant gliomas.[6] MGMT (O^6-methylguanine DNA methyltransferase) is a key enzyme in the DNA repair network, which removes the mutagenic and cytotoxic adducts from O^6 guanine in DNA, the preferred point of attack of alkylating chemotherapeutic agents (ie, BCNU, temozolomide, etc). Hypermethylation of cytosine-phosphate-guanine (CpG) islands located in the promoter region of MGMT is primarily responsible for the loss of MGMT function in many tumor types, hence leading to an increased sensitivity to the killing effects of alkylating drugs used in chemotherapy.[6] This test is widely used in clinical practice to predict response to temozolomide, the alkylating drug of choice in high-grade gliomas, although it should be stressed that there is still no consensus as to which test method to use, which CpG sites to assess, and what the methylation cutoff should be.

Ependymoma: Until very recently, these tumors have been subclassified and graded on the basis of histological features into low and high grade. In 2015 a molecular classification, based on DNA methylation profiling, has been proposed, which defines 9 molecular subgroups, 3 for each anatomical location of these tumors (supratentorial, posterior fossa, and spinal cord).[7] In the supratentorial location, ependymomas with the fusion gene *C11ORF95/RELA* (ST-EPN-RELA) have a poor prognosis and in the posterior fossa it is the ependymoma group EPN-A that is characterized by a poor prognosis.[7] All other ependymomas show a comparatively good prognosis.[7] Although not yet included in the World Health Organization (WHO) 2016 classification, a recent consensus paper has recommended that this classification be used for enrollment in prospective clinical trials,[8] and it is expected to contribute to informing decisions on molecular-based treatments as they become available.

Medulloblastoma (MB): International consensus recognizes 4 medulloblastoma molecular subgroups: WNT (MBWNT), SHH (MBSHH), Group 3 (MBGrp3), and Group 4 (MBGrp4), each defined by their characteristic DNA methylation and genome-wide transcriptomic profiles.[9] Recently, the heterogeneity within these subgroups has been reduced by 2 independent studies which have defined additional subtypes. Schwalbe and colleagues[10] have suggested to split MB^{SHH} into 2 age-dependent subtypes corresponding to "infant" ($<$4.3 y) and "childhood" patients ($\geq$4.3 y), and MB^{Grp3} and MB^{Grp4} into further high-risk and low-risk subtypes, while the MB^{WNT} group remains unchanged.[10] Interestingly, the low-risk subtypes were defined primarily by hypermethylation in comparison to normal cerebellum, whereas the high-risk subtypes were defined by relative hypomethylation.[10] Cavalli and coauthors[11] used integrative clustering of DNA methylation and gene expression datasets from 763 patients to split the original 4 subgroups into 12 subtypes: MB^{SHH} is split into 4 subtypes (α,β,γ, δ); MB^{WNT} into 2 subtypes (α,β) MB^{Grp3} and MB^{Grp4}into 3 subtypes each (α,β,γ).[11] The subtypes identified in these 2 studies overlap considerably, and the main differences seem to be related to the inclusion of adult MB patients in the Cavalli study. Importantly, MB subgroups and their subtypes, identified by their

epigenetic and related transcriptional profiles,[10,11] have distinct genetic and clinicopathological features[10,11] and their implementation for patient stratification for better prognostication and enrollment into subgroup/subtype-directed therapies in the context of clinical trials will be a step change in the treatment of MB patients.

All CNS tumors: A classification tool for brain tumors, based on genome-wide DNA methylation patterns and a random forest-based machine learning approach, has been developed and extensively tested by the German Cancer Research Center (www.molecularneuropathology.org). This resource is available online and has proven to be a valuable tool to improve brain tumor diagnostics. This approach has facilitated the identification of common druggable molecular pathway alterations across various histological tumor entities, thus allowing patients to enter the most appropriate clinical trials and in some cases be offered molecularly matched therapies. As an example, DNA methylation profiles allow precise identification of cases with mitogen-activated protein kinase (MAPK) activation, which is a feature of tumors with BRAF V600E mutation,[12,13] which can span various traditional histological entities such as pilocytic astrocytomas, pleomorphic xanthoastrocytomas, ganglioglioma, and subependymal giant cell astrocytomas, to predict response to specific inhibitors interrupting the BRAF/MEK component of the MAP kinase pathway.[14]

Novel Therapeutic Approaches Targeting Epigenetic Deregulation

Diffuse intrinsic pontine glioma (DIPG) is a highly aggressive pediatric tumor located in the brainstem and characterized by a rapid and diffusely infiltrative pattern of growth. These tumors cannot be treated surgically because of their location and infiltrative nature.[15] Radiation therapy is the standard treatment, although it provides only temporary symptom relief, with no overall survival benefits, and conventional chemotherapy drugs are ineffective.[15]

Mutations in histone H3 variants occur in more than 80% of DIPG and result in a lysine-to-methionine substitution (H3K27M).[16, 17] H3K27M has been shown to inhibit polycomb repressive complex 2 (PRC2) by binding to its catalytic subunit EZH2 and reducing the methylation of H3 at lysine 27 (H3K27me) at selected target loci.[18] The residual PRC2 activity is required to maintain DIPG proliferative potential, by repressing neuronal differentiation in patient-derived cell lines and in a genetically engineered mouse model.[19,20] Importantly, small-molecule EZH2 inhibitors abolish tumor cell growth in these models, raising the possibility that inhibition of EZH2 could be a novel therapeutic strategy for these tumors.[19]

An independent study showed that H3K27M associates with increased H3K27 acetylation (H3K27ac) and that the majority of the heterotypic H3K27M-K27ac nucleosomes co-localize with bromodomain proteins at the loci of actively transcribed genes.[20] The authors have shown that blocking the recruitment of bromodomain proteins by heterotypic H3K27M-K27ac nucleosomes in DIPG with bromodomain and extraterminal domain family inhibitors efficiently inhibited tumor progression, thus identifying this class of compounds as potential therapeutics in DIPG.[20]

These important advances in understanding the underlying biology of DIPG have led to the identification of novel epigenetic therapeutic approaches, which are very effective at the preclinical level and, if confirmed in translational studies, could change the way we treat these tumors in the near future.

Conclusion and outlook

These are exciting and challenging times for the neuro-oncology community. Exciting because there is growing expectation in the field that new discoveries, such as those discussed in this article, can soon translate into new and more effective therapeutic approaches. Challenging because it is clear that new skill sets are required to effectively apply them to benefit patients.

The clinical training in many neuro-oncology specialties will have to take into account the additional knowledge and skills needed in the field and offer education in complementary disciplines, such as next-generation sequencing technologies integrated with interpretative data analysis as well as molecular biology for the design of biologically informed assays and tools. The requirement for these new, highly specialized skills also needs to be reflected in the composition of the clinical teams, where bioinformatics expertise will play an increasingly important role for the integration of multimodal data in patient care.

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The Value of Surgical Resection for Malignant Gliomas in the Modern Era: Beyond Extent of Resection

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Malignant gliomas are among the most difficult oncological entities to treat. Despite aggressive treatment, prognosis remains poor, and recurrence and treatment failures seem inevitable. The current standard-of-care therapy includes maximal safe surgical resection, followed by concurrent and adjuvant chemoradiotherapy. Historically, surgical resection has conferred greater survival benefit to these patients than adjuvant therapies, presumably through the cornerstone principle of cytoreduction. However, the extent of surgical resection is frequently limited by nearby eloquent tissue and risks to key neurological functions. In addition, the value of such aggressive approaches has been questioned in light of the widespread infiltration of glioma cells. Meanwhile, our understanding of glioma biology continues to advance rapidly, fueled in large part by the acquisition of tumor tissue during surgery. Thus, the exact role and value of surgery, particularly in comparing the clinical benefits of maximal extent of resection (EOR) with the biomedical benefits of tissue provision, has been a topic of great interest and debate in both the neuro-oncological and neurosurgical communities.

EOR, patient age, tumor histology, performance status, and molecular markers have been widely accepted as significant predictors of patient outcomes in malignant glioma.[9] In the past 2 decades, many large retrospective cohort studies have demonstrated improvements in survival with increasing EOR.[5,9,17] Due to ethical considerations, evidence from a randomized prospective study supporting the clinical benefit of aggressive resections does not exist, and likely never will. Instead, the closest thing to such evidence in malignant glioma comes from the randomized phase III trial comparing surgical resections with or without the use of 5-aminolevulinic acid (5-ALA). The use of 5-ALA, serving as a means to and a proxy for greater EOR, resulted in extended overall survival for patients with newly diagnosed glioblastoma.[19] A recent meta-analysis of 41 117 unique patients by Brown et al, adherent to the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), also demonstrated a clear survival benefit for gross total resection over subtotal resection or biopsy at upfront surgery for glioblastoma.[1] The body of literature as a whole clearly favored aggressive resections, and there seemed to be little disagreement for a strategy toward maximal resection when clinically feasible. However, the challenge still remains when such strategies come at the risk of neurological morbidity. A recent report by Rahman et al illustrates that the survival benefits from aggressive resection are lost if the patient develops a new postoperative neurologic deficit as a result.[15]

All the while, our understanding of glioma genetics, molecular biology, and mechanisms of resistance has continued to deepen and evolve, borne of thoughtful and systematic studies using patient-acquired tumor samples. Molecular profiles and tumor genetics have proven themselves to be the best predictors of clinical behavior and now represent crucial components of the diagnostic classification scheme of infiltrating gliomas.[12] With tumor tissue at the molecular and genetic level being able to robustly predict patient outcomes, accurate tissue diagnosis has become paramount in the management of gliomas. The role and value of open surgical resection toward this end have become clearer, as concerns of sampling error with biopsy alone led to a number of studies evaluating the "accuracy" of stereotactic biopsy procedures. Jackson et al reported a series of 81 patients who underwent stereotactic biopsy followed by open surgical resection. The tissue diagnosis was concordant between biopsy and open resection samples in only 51% of patients.[6] Other studies have also demonstrated diagnostic concordance between stereotactic biopsy and surgical resection samples in only 57% to 79% of cases.[13,14,28] The major limitation of stereotactic biopsy for infiltrating gliomas likely stems from the significant intratumoral heterogeneity, and collectively these studies highlight the value of open surgical resection in providing a more global representation and understanding of the tumor tissue.

The value of extensive resection is perhaps even more profound when considering the therapeutic implications of such heterogeneity. Multiple-site and serial-sampling analyses have revealed a high degree of both spatial and temporal heterogeneity within these tumors, a consequence of serial evolutionary events during tumor growth and progression.[23] These studies have also led to the concept of therapy-driven clonal selection and preferential regrowth of resistant cell populations as a potential mechanism of treatment failure. Efforts to expand our understanding of the tremendously complex network of mutations and biological consequences of chronological hierarchy would be greatly facilitated by carefully planned, thoughtful acquisition of tumor samples during surgery.

Despite the recent paradigm shift in glioma diagnostic classification, little gains have been made in improving the overall prognosis for patients with malignant gliomas since the introduction of concurrent and adjuvant temozolomide in 2005.[21] The strategies more recently tested in large randomized phase III trials by and large have yielded disappointing results, while the reasons and mechanisms of treatment failures remain unclear. Even so, encouraging responses have occasionally been seen in various subsets of patients, and studies exploring the presence of potential biomarkers have generated intriguing and promising results in these populations. The development of the anti–vascular endothelial growth factor monoclonal antibody bevacizumab is one such example. Two initial phase II trials showed prolonged progression-free survival in recurrent glioblastoma relative to historical controls, prompting the US Food and Drug Administration to grant accelerated approval to bevacizumab for recurrent glioblastoma in 2009.[8,25] However, 2 large randomized trials evaluating the addition of bevacizumab to radiation and temozolomide in the newly diagnosed setting failed to show a benefit in overall survival,[2,4] and its utility in the

recurrent setting is now a topic of debate in light of subsequent phase III trial results. However, a post hoc analysis of patients enrolled in the AVAglio trial recently demonstrated that bevacizumab improved overall survival for those with a proneural subtype tumor.[18] Just as O^6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation does for temozolomide, the genetic profile of the tumor could serve as a potential biomarker of clinical response for bevacizumab as well, and validation studies are currently ongoing. Such analyses, although performed post hoc, require targeted, prospective collection of tumor tissue at initial surgery. In addition, genetic profiling of newly diagnosed malignant gliomas will need to become routine if this approach is to be utilized widely. Similarly, cilengitide, an inhibitor of aVb3 and aVb5 integrins with anti-angiogenic properties, showed initial promise in recurrent glioblastoma studies but failed to show any additional benefit in the newly diagnosed setting.[20] A subsequent post hoc analysis of the phase II trial revealed improved progression-free and overall survival in patients with high aVb3 levels in the tumor cells.[26] However, tumor tissues were not systematically collected and less than half of the patients' tumor tissues were available for analysis from the phase III trial. Unfortunately, this drug will most likely not undergo further development, and one cannot help wonder if the outcome would have been different if the enrollment in the phase III trial had been enriched for or restricted to tumors with high expression of the aVb3 integrin. The only true "success story" since the adaptation of radiation and temozolomide has come from the novel approach of tumor treating fields (TTFields), a transcutaneous delivery of low-intensity intermediate frequency alternating electric fields. The multicenter phase III trial EF-14 randomized patients with supratentorial glioblastoma without evidence of tumor progression following standard chemoradiation to receive maintenance treatment with TTFields plus temozolomide or temozolomide alone.[22] The study was terminated early based on results of a planned interim analysis demonstrating benefit in progression-free survival; overall survival, a secondary endpoint, was also significantly enhanced at this time. Despite the trial's success, TTFields has not been universally adopted by the neuro-oncology community, and enthusiasm among clinicians and patients remains low.[27] Experts have raised concerns regarding the study design, such as its open-label design lacking a sham-treatment control arm as well as the generalizability of the results based on the unique randomization point occurring after concurrent chemoradiation.[16] Perhaps most significantly, a lack of widely understood mechanism of action has also been raised as a factor; with comparison to other treatments, the preclinical data for TTFields is relatively lacking, particularly when applied in conjunction with chemoradiation.[27] Even during the early phase stages, the use of robust tissue-based analyses exploring the mechanism of action, such as dose response modeling and multisite tissue biopsies, may have mitigated some of these concerns and led to wider acceptance by the community. Bevacizumab and cilengitide clearly benefited from retrospective analyses of human tumor tissue to identify susceptible treatment populations, while the enthusiasm for TTFields is perhaps in part tempered by the lack thereof. Collectively, the evolution of these treatments underscores the value of extensive, targeted tissue sampling in furthering development of new adjunctive therapies.

Open surgical resection of tumors with such targeted tissue acquisition for analysis will continue to play a key role in prospective clinical trial designs. Comparison of pretreatment and posttreatment tissue profiles represents a valuable line of investigation by delving into mechanisms of therapeutic action as well as mechanisms of treatment failures.[10,11] It also provides an opportunity to investigate a number of key fundamental steps along an agent's path to clinical success, such as: does the agent successfully traffic to the tumor, if so how much, and does the agent then actually have its hypothesized effects at the biochemical or cellular level? Thus, early-phase trials can and should include posttreatment molecular endpoints when possible, in addition to safety endpoints. Immunotherapy and immune checkpoint inhibition represent exciting novel therapeutic approaches for neuro-oncology, particularly based on their success in metastatic cancers. Large phase III trials studying blockade of the programmed cell death protein (PD)1/PD ligand 1 axis with monoclonal antibodies for newly diagnosed and recurrent glioblastoma are under way, but initial reports have been concerning for negative results. As in the development of many previous novel agents, tissue-based mechanism studies have been largely lacking in the preclinical phases. However, an Alliance-supported trial currently enrolling focuses on a biomarker as a primary endpoint; patients with recurrent glioblastoma indicated for surgery are randomized to receive pembrolizumab, a PD1 inhibitor, either before or after surgery (NCT02852655). The resected tumor tissue will then be analyzed for the profile of tumor-infiltrating T cells, and comparison will be made between the 2 groups. This study represents a tremendously valuable opportunity to explore the impact and the potential challenges of checkpoint inhibition for malignant gliomas in the clinical setting, and should the large phase III trials end up negative, this pilot study will be very informative.

Advances in imaging, biomarkers, and molecular characterization of gliomas, in conjunction with new targeted therapies, will continue to improve and transform the management of these tumors. Multimodality imaging can now more accurately reflect ongoing biological processes within these tumors, such as the presence of oncogenic mutations or cells undergoing malignant transformation. Novel biomarkers, such as circulating tumor DNA, show promise in detecting early recurrence or monitoring treatment response.[3,7,24] Lastly, the new classification scheme revolving around molecular characterization will provide a

necessary corollary to these novel diagnostic tools. It remains indisputable, however, that clinical validation of these novel diagnostic tools will also require systematic correlation with human tumor tissue obtained through surgery. These samples, ideally gathered prospectively, will provide a pivot upon which we can expand our understanding of the complex network of oncological processes driving these tumors.

Malignant gliomas are incredibly challenging disease entities, in many ways due to the inter- and intratumoral heterogeneity that is a hallmark of them. Experience to date hints that future successes in malignant gliomas rest in neuro-oncology entering the era of precision medicine, where validated biomarkers and targeted personalized therapies are seamlessly integrated into the management paradigm. Accordingly, systems supporting surgical resection and patient-specific tumor tissue analysis must be built and organized to guide the decision making for therapy. As our overall approach to the management of malignant gliomas evolves, so should the framework of surgical management. The clinical benefits of maximal safe resection are well founded and well reported. However, the oncological neurosurgeon must now look beyond maximal cytoreduction itself and recognize the value of thoughtful acquisition and analysis of tumor tissue. Modern neurosurgeons must consider themselves surgical neuro-oncologists, and engagement and participation of surgeons into clinical trials, particularly early-phase trials, should be encouraged and valued. In turn, we should provide our surgical trainees with the training and tools in neuro-oncology to help them participate and contribute in multidisciplinary collaborative efforts aiming to advance the understanding of brain tumor biology and ultimately improve the outlook of our patients.

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Update on Radiation Combinations in the Treatment of Patients with Malignant Brain Tumors: From Radiosensitizers to Immunotherapy

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Abstract

Advances in radiosensitizers and immunotherapy have ushered in a new frontier in brain tumor treatment. The brain has often been viewed as a sanctuary site due to the blood–brain barrier, and thus the 2 primary modalities of therapy included surgery and radiation therapy (RT). More recently systemic therapies have played a greater role as either combination therapy, radiosensitizers, or immunotherapy. Two novel radiosensitizers are being developed for the treatment of brain metastases. RRx-001, for example, is a small molecule that accelerates the NO2 to NO conversion of deoxyhemoglobin, and the agent 2-dexoyglucose (2-DG) is a nonmetabolized glucose analogue that interferes with ATP formation. Poly(ADP-ribose) DNA polymerase inhibitors are promising due to their distinct radiobiological effects. Veliparib and olaparib are among the most studied, with randomized trials exploring their use in gliomas and brain metastases. Immunotherapy, including immune checkpoint inhibitors, may play a role for both primary gliomas and brain metastases. RT has been shown to enhance the function of cytotoxic T lymphocytes, induce infiltration of cytotoxic T lymphocytes, and enhance function. Trials are presently exploring use of both programmed cell death protein (PD)1 and PD ligand 1 blockade in glioblastoma patients with radiation. Similarly several immunotherapies are being investigated with either stereotactic radiosurgery or whole brain radiation therapy for brain metastases. In this review, the use of radiosensitizers and immunotherapy agents with RT will be discussed broadly.

Keywords: brain metastases, brain tumors, gliomas, immunotherapy, radiation therapy, radiosensitizers.

Radiosensitizers and Immunotherapy in Brain Tumors

Advances in radiosensitizers and immunotherapy have ushered in a new frontier to brain tumor treatment. Brain tumors, however, are a diverse class sharing only similar anatomic location. Both primary brain malignancies and brain metastasis have widely diverse histologies and molecular phenotypes. With the blood–brain barrier, the brain has often been viewed as a sanctuary site, and thus the 2 primary modalities of therapy included surgery and radiation, with decreased benefit from systemic agents due to lack of brain penetration. However, more recently systemic therapies have played a greater role as either combination therapy, radiosensitizers, or immunotherapy. While temozolomide (TMZ) has played a pivotal role for glioblastoma (GBM), only a subset of patients benefit from the treatment.[1] The use of alternative systemic agents that may potentiate the effects of radiation therapy (RT) is becoming increasingly appealing. Similarly, for brain metastases, a variety of systemic agents are being explored primarily based on histology and immune profile. In this review, the use of radiosensitizers and immunotherapy agents currently under investigation with RT will be discussed.

Radiosensitizers

The guiding concept of radiation sensitization is to increase the biologic effect of radiation, such as increased DNA damage, decreased DNA repair, decreased hypoxia, or increased G2/M cell cycle blockade, leading to improved tumor control and increased patient survival.[2] Poly(adenosine diphosphate-ribose) DNA polymerase (PARP) inhibitors are promising radiosensitizers due to their roles in DNA repair.[3] PARP inhibitors work against PARP1, a nuclear enzyme involved in the recruitment of repair proteins used in base excision repair, and single-strand break repair. PARP1 may also play a role in nonhomologous end-joining.[4] The primary investigation of PARP inhibitors has been in potentiating radiation and chemotherapy effects, the latter in the context of homologous repair deficient tumors. For radiation the primary mechanism of action is inducing damage to nucleotides, leading to single-strand and double-strand breaks. Thus, PARP inhibitors in combination with radiation have an appealing mechanism to inhibit or delay DNA repair and likely convert more single-strand breaks to double-strand breaks.[4]

While several PARP inhibitors are currently being evaluated in a variety of tumors, including talazoparib and niraparib, veliparib and olaparib are among the most studied, and there are randomized trials exploring their use in

Table 1. Clinical trials involving immunotherapy and radiation therapy[12,13]

Clinical Trials Number	Phase	Disease Type	Treatment Groups
NCT02667587	II	Newly diagnosed GBM, MGMT-methylated	Nivolumab + TMZ + RT vs placebo + TMZ + RT
NCT02617589	III	Newly diagnosed GBM	Nivolumab + RT vs TMZ + RT
NCT02336165	II	Newly diagnosed unmethylated MGMT, recurrent glioblastoma	MEDI4736 + standard RT vs MEDI4736 + bevacizumab
NCT02530502	I/II	Newly diagnosed GBM	RT + TMZ + pembrolizumab → TMZ + pembrolizumab
NCT02313272	I	Recurrent glioma	Hypofractionated stereotactic radiation + pembrolizumab + bevacizumab
NCT02696993	I/II	Brain metastases	Nivolumab + SRS; nivolumab + WBRT; nivolumab + ipilimumab + SRS; nivolumab + ipilimumab + WBRT
NCT02115139	II	Melanoma brain metastases	Ipilimumab + WBRT
NCT02097732	II	Melanoma brain metastases	Ipilimumab → SRS → ipilimumab vs SRS → ipilimumab
NCT01703507	I	Melanoma brain metastases	Ipilimumab + WBRT vs ipilimumab + SRS
NCT02107755	II	Melanoma brain metastases	Ipilimumab + SRS
NCT02858869	pilot	Melanoma and NSCLC	Pembrolizumab + SRS
NCT01950195	I	Melanoma brain metastases	Ipilimumab + SRS
NCT02662725	II	Melanoma brain metastases	Ipilimumab + SRS

gliomas. The US National Cancer Institute (NCI)–funded Alliance for Clinical Trials in Oncology (Alliance) A071102 is a randomized phase II/III trial evaluating the use of veliparib in combination with TMZ in the adjuvant setting in patients with GBM tumors exhibiting hypermethylation of the O^6 methylguanine DNA methyltransferase (*MGMT)* gene promoter. Preclinical data supporting this trial suggested that only patients with *MGMT* methylated tumors would benefit from the combination, a group of patients for whom TMZ concurrent with radiation might be most beneficial.[5] A phase I trial performed by the NCI-funded American Brain Tumor Consortium attempted to combine veliparib with radiation and TMZ but failed to identify a suitable recommended phase II dose due to significant hemotoxicity.[6] Thus, attempts to combine radiation with veliparib have focused on patients least likely to benefit from TMZ, namely with *MGMT* unmethylated tumors, for whom TMZ could be withheld. The Australian Veliparib, RT, and TMZ trial in newly diagnosed unmethylated MGMT glioblastoma (VERTU) is a single-arm study in which patients receive RT with veliparib followed by adjuvant TMZ and veliparib.[4]

An ongoing novel approach to radiosensitize gliomas involves a combination with an agent that interferes with an essential metabolic process. 2-Dexoyglucose (2-DG) is a nonmetabolized glucose analogue that acts as a competitive inhibitor of glycolysis. It is transported across the blood–brain barrier by the glucose transporter GLUT-1 and thus has good penetration into the CNS. Intracellularly, it is trapped and accumulates in cells similar to the mechanism of 18-fluorodeoxyglucose: 2-DG is phosphorylated by glycolytic enzymes and the phosphorylated 2-DG (2-deoxyglucose-P) is trapped intracellularly. Inhibition of hexokinase activity by 2-DG interferes with ATP formation and results in tumor cell death.[7] While it has positive attributes by selectively targeting metabolically active tumor cells, 2-DG has also been associated with Q-T prolongation. The current phase I/II trial in gliomas is assessing the toxicity and tolerability of 2-DG with hypofractionated radiation of 5 Gy as a radiosensitizer.[7]

Two novel radiosensitizers are being developed for the treatment of brain metastases. First, RRx-001 is a small molecule initially designed by the aerospace industry. It works in part as a radiosensitizer by increasing blood flow and thus oxygenation of tumors through nitric oxide. RRx-001, which binds to hemoglobin, accelerates the NO_2 to NO conversion of deoxyhemoglobin. It works locally under hypoxic conditions, and subsequently the radiosensitive effects through nitric oxide are in vasodilation and inhibiting DNA repair enzymes.[8] Nitric oxide is relatively benign. The higher levels of oxidative stress with H_2O_2 and superoxide in tumors in comparison to normal tissues result in the preferential generation of reactive peroxynitrite in the presence of higher nitric oxide levels.[7] This accounts for the increased specificity and decreased toxicity with RRx-001. The dose limiting toxicity in a phase I trial of 25 patients treated with either weekly or biweekly infusions was infusional pain related to the release of NO at the site of injection.[7] Outside of preclinical models, 2 clinical reports examining whole brain radiation therapy (WBRT) with RRx-001 reported an intracranial response. A patient with melanoma and 2 hemorrhagic edematous lesions of 2.6 cm and 3.3 cm

after a single intravenous dose of RRx-001 of 5 mg/m^2 4 days before WBRT resulted in symptomatic improvement within 48 hours. By 4 months after radiation, there was a reduction in size in the largest dimension down to 1.0 cm and 2.3 cm of the respective lesions. A second report of a melanoma patient with at least 18 lesions after receiving RRx-001 of 5 mg/m^2 4 days before WBRT as well as twice weekly doses during the 2 weeks of radiation also showed response. The patient at 4 months had disappearance of 13 of 18 lesions, with shrinkage of the remaining 5 lesions.[8] Presently BRAINSTORM is a phase I/II dose escalation trial of RRx-001 designed to be administered twice weekly for 2 weeks with WBRT (30 Gy in 10 fractions) with the option for weekly maintenance.[8]

Veliparib has also been evaluated in the setting of brain metastases. It was tested in a global, randomized controlled trial with WBRT. Veliparib is orally bioavailable and crosses the blood–brain barrier. It was first examined in a multihistology phase I trial in patients with non–small cell lung cancer (NSCLC), breast cancer, melanoma, and renal and colorectal cancers, among others. The study of 81 patients tested dose tolerance of veliparib from 10 to 300 mg orally twice a day with WBRT to 30 Gy in 10 fractions or 37.5 Gy in 15 fractions.[9] The phase I trial dose escalation portion did not reach the predefined criteria for the maximum tolerated dose, but there was amplification of the adverse effects of nausea and vomiting among the highest dose cohort of 300 mg b.i.d.[9] The adverse event profile at 200 mg b.i.d. was similar to that of WBRT alone. Doses of veliparib from 20 to 200 mg b.i.d. demonstrate similar antitumor activity, and other studies in preclinical models found that 50 mg daily demonstrated significant reduction in poly(ADP-ribose) in peripheral blood mononuclear cells and tumor tissue while also effectively crossing the blood–brain barrier. Thus the subsequent phase II trial examined 50 mg with WBRT.[9] In order to assess a more homogeneous cohort, the phase III global randomized trial studied only NSCLC at the 2 doses of 50 mg and 200 mg twice daily versus placebo twice a day with WBRT.[10] The primary endpoint was overall survival. In 307 patients in a 1:1:1 randomization of 50 mg b.i.d., 200 mg b.i.d., or placebo twice daily, the study found no significant differences in overall survival among the different groups.[10] The majority of patients across the treatment groups had a graded prognostic assessment (GPA) score of $\leq$2.5 and a Karnofsky performance status of $>$80. The median overall survival was 185 days for patients receiving placebo and 209 days for those receiving veliparib without any statistically significant difference. These results were similar to the disease-specific estimate of median survival for the disease-specific GPA of NSCLC patients with brain metastases.[10]

Several other radiosensitizers have failed to improve over radiation alone in a number of trials. These have included trials with WBRT, including motexafin gadolinium, efaproxyn, bortozemib, thalidomide, teniposide, topotecan, paclitaxel, and cisplatin.[7] Of note, other PARP inhibitors also being assessed include talazoparib and niraparib,[4] which may yield positive results. The use of valproic acid (VPA) as a histone deacetylase inhibitor has also been considered to have radiosensitizing potential in addition to its anti-epileptic drug properties.[11] While studies have reported that patients with GBM receiving an anti-epileptic agent may have higher overall survival than those receiving standard chemoradiation therapy alone, the benefit remains controversial. Retrospective analysis suggested that patients taking VPA specifically had better survival in comparison to other anti-epileptic drugs. Also, a recent prospective phase II trial was performed in 37 patients with GBM receiving VPA 25 mg/kg concurrently with TMZ chemoradiation and reported a median survival of 29.6 months. While controversial, further data and investigation are needed into this and other agents that may potentiate RT.

Immunotherapy and radiation

Immune checkpoint inhibitors lead to activation of T cells, which may traffic across the blood–brain barrier to interact with tumor. Primary brain tumors may evade the immune system through upregulation of immune checkpoints and possible immunosuppression.[12] Monoclonal antibodies promote immune-mediated antitumor activity by inhibiting the immune function–mediated cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) receptors. PD protein ligand (PD-L1) is upregulated in GBM through oncogenic signaling, possibly through phosphatase and tensin homolog loss and interleukin-10 signaling.[13,14] RT has also been shown to enhance the function of cytotoxic T lymphocytes. RT may induce an infiltration of cytotoxic T lymphocytes and enhance their function. It may also induce anti–CTLA-4 agents inhibiting T-cell function and increasing the CD8+ T cell/regulatory T cell ratio in cases of melanoma.[15] Thus, PD-1 and PD-L1 blockers may have a further role in CNS management with the use of radiation.

In preclinical models, radiation has been examined with immunotherapy that included among other mechanisms vaccination, PD-1 blockade, and CTLA-4 blockade. In mice, radiation plus a vaccination of irradiated glioma cells was associated with increased survival of 40% to 80%, compared with 0% to 10% for other groups studied.[16] A benefit of PD-1 blockade with stereotactic radiosurgery (SRS) specifically has also been shown in a mouse model. In comparison to mice treated with radiation, anti–PD-1 therapy, or a combination, only those receiving combination therapy had a higher percentage survival alive beyond 180 days after treatment.[17] Other mouse carcinoma models have identified response with anti-CTLA antibody and fractionated radiation therapy.[18] CD137 activation, CTLA-4 blockade, and focal radiation therapy have been examined in an immunocompetent, intracranial GBM model. Mice treated with triple combination therapy had 50% greater survival.[19] In other murine

models the use of anti–PD-1 and anti–CTLA-4 agents showed improved survival and increased tumor infiltrating leukocyte populations compared with single modality with concurrent radiation.[16] There are conflicting data regarding timing or sequencing of therapy, with some animal models showing no difference in tumor response in relation to timing of RT and delivery of immunotherapy.[18] For instance, in one animal model, CTLA-4 blockade delivered simultaneously with radiation or delivered a couple of days after showed no difference in survival among the mice.[19]

Increased PD-1 expression in circulating monocytes has been identified as a biomarker for tumor-induced immunosuppression and may serve as a prognostic factor for potentially worse survival outcomes in clinic.[13] In one study, GBM patients with lower PD-L1 expression had higher median overall survival than those with higher PD-L1 expression, suggesting that lower expression may be associated with less immunosuppression and more immune activity against the tumor glioma.[20] RT with immune checkpoint blockade is being investigated to assess if the addition of PD-1 and PD-L1 inhibitors may improve the outcomes or toxicity profile of standard therapy. For instance, a multi-institutional trial opened as a phase I/II will evaluate outcomes in GBM receiving radiation and pembrolizumab with TMZ (NCT02530502). Next, durvalumab or MEDI4736, a PD-L1 inhibitor, is being examined for unmethylated MGMT GBMs with standard radiotherapy (NCT02336165).[12] The impact of checkpoint inhibitors during adjuvant treatment of GBM is currently being evaluated in the NCI-funded NRG-BN002 trial (NCT02311920), which will evaluate the anti–CTLA-4 antibody ipilimumab alone or in combination with the anti–PD-1 antibody nivolumab for patients with newly diagnosed GBM.

Brain metastases have clonal populations of cells different from the rest of the brain and a unique microenvironment that may influence immunotherapy. There may be more immune infiltrates in metastases than in primary brain tumors.[21] PD-L1 expression in brain metastases varies by histology. In a series evaluating PD-L1 expression in various tumors, including melanoma, NSCLC, breast, renal, colorectal, and small cell, less than 10% showed significant expression.[22] There was greatest expression among NSCLC and melanoma, with a correlation between PD-L1 expression and tumor infiltrating lymphocytes.[22] Institutional series have examined the combination of radiation and immune checkpoint blockade. In another study specific to melanoma brain metastases, PD-L1 expression was found in over 50% of the cases, and among those cases over 40% expressed PD-L1 in more than 5% of tumor cells.[23] The largest body of data for use of PD-L1 with radiation is for melanoma and NSCLC.

Ipilimumab is a human monoclonal antibody that blocks CTLA-4 and allows for T-cell activation and proliferation to enhance the immune response to cancer. In a retrospective review of 70 patients with brain metastases treated with SRS or WBRT, the 33 patients receiving immunotherapy had a median survival of 18.3 months in comparison to the 37 patients who did not receive ipilimumab, with a median survival of 5.3 months. While there were limited data among the cohort to evaluate sequencing of therapy, among 10 evaluable patients, 40% who received ipilimumab prior to RT had a partial response in comparison to only 10% among the cohort of 22 evaluable patients who did not receive ipilimumab therapy at all with radiation.[24] Another retrospective institutional study, of 77 patients, in which 37% received ipilimumab, found that patients treated with SRS and ipilimumab had a median survival of 21.3 months versus 4.9 months for those not receiving ipilimumab. Most interestingly they identified that the correlation remained significant even after adjusting for additional factors such as performance status. Secondly there was not an increased need for use of salvage WBRT.[25]

The sequencing of radiotherapy and immune checkpoint inhibitors is of interest. In a study of patients with brain metastases, the one-year survival for patients receiving SRS before ipilimumab was greater at 65% in contrast to 56% for those receiving it concurrently and 40% for those receiving it after SRS.[26] Similarly another study, of 75 patients with 566 brain metastases, showed greater tumor lesion response at 6 months from SRS for patients receiving ipilimumab, nivolumab, or pembrolizumab within 4 weeks of their SRS.[27] Those receiving concurrent therapy had by 6 months a decrease of 94.9% in comparison to 66.2% for those not receiving checkpoint inhibitors within 4 weeks. Prospective clinical trials are investigating different combinations of RT with immune checkpoint blockers in this setting. For instance, new trials are currently evaluating intracranial tumor control at 6 months and the timing of immune therapy or immune checkpoint inhibitors in relation to SRS.[28]

Vaccines are also being developed for primary brain tumors, showing some evidence for their use. Vaccines developed from dendritic cells and tumor lysate with tumor antigens, such as the epidermal growth factor receptor variant III vaccine, have shown promise.[29] For instance, in a placebo controlled phase II trial of ICT-107, a vaccine composed on autologous dendritic cells and tumor antigens, progression-free survival was increased by 2 months for those receiving the vaccine.[30] Radiation may assist in serving as a primer for the immunogenic effects by facilitating tumor antigen uptake by dendritic cells and cross presentation on major histocompatibility complex I. Thus, RT may assist in the tumor-specific, cytotoxic T lymphocytes associated with the immune mechanism.

In conclusion, although there may be challenges to combining and sequencing brain tumors, radiosensitizers, and immunotherapy, the opportunities and potential for novel applications are promising. For brain tumors, brain metastases are typically underrepresented in trials

despite being among the most common intracranial lesions. Despite their large population, patients with brain metastases are often excluded from clinical trials with novel agents due to concerns regarding confounding outcomes and tolerability.[12] Primary gliomas also offer a novel frontier for the use of immunotherapy to standard adjuvant chemotherapy and radiation, particularly for patients with GBM less likely to respond to TMZ, such as with unmethylated *MGMT*. As studies work to define the role of RT and radiosensitizers and immunotherapy, further analysis is needed to assess the timing of RT and these treatments.

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British Neuro Oncology Society Conference 2017

Approximately 250 people with an interest in neuro-oncology attended part or all of "Engaging Science, Enhancing Survival" in Edinburgh June 21–23, 2017. In addition to our guest speakers, including a number from North America, Denmark, and Italy, and wide representation from throughout the UK, there were also proffered papers from Greece, Hong Kong, and India.

As well as the plenary sessions, including the Clerk Maxwell Cancer Lecture and the Stephen Baker Memorial Lecture, there were proffered papers, posters, and lunchtime seminars and exhibitions by sponsors. There were often parallel sessions so that attendees could choose between science, clinical, and allied patient care topics such as quality of life and palliative care. Bursaries were available to ensure that those starting out in the field could attend. Of course, the social and networking opportunities were not ignored, with a Welcome Reception at Dynamic Earth and the Conference Dinner taking place at the Playfair Library.

BNOS would like to thank the various organizations and charities whose sponsorship made this meeting possible: AbbVie, BrainLab, Medac, Brainstrust, Brain Tumour Research, B Braun, Bristol-Myers Squibb, Cancer Research UK, Codman, Integra, International Brain Tumour Alliance, Medtronic, Mercian, Novartis, Renishaw, Severn, Storz, The Brain Tumour Charity, TrusteDoctor, and Vitaflo.

Council would also like to acknowledge the hard work of the Edinburgh team led by Imran Liaquat. Sessions were filmed and will be made available on the BNOS website, and the abstracts of the proffered papers and posters are available to all via the conference website. This report is intended to provide a flavor of the conference via some of the themes that stood out amongst the sessions that I attended.

Glioma Stem Cells

Glioma stem cells underpin malignancy and recurrence via their angiogenic and invasive nature and resistance to chemoradiation. The vascular microenvironments of neural and glioma stem cells differ, with two types of signaling, maintaining quiescence amongst the former and the perivascular invasion characteristics of the latter. New insights into the genomic and epigenomic landscapes of glioma were discussed frequently. Whilst the former, of course, continues to be studied, e.g. helping understanding of how IDH mutation confers better prognosis via a significant enrichment of genes involved in apoptosis and endoplasmic reticulum stress response, inhibitors of epigenetic regulatory proteins are now also a focus. Hence, there were papers describing development of animal models to replicate both aspects and not just single nucleotide variations. Insights into neuronal differentiation as a potential therapeutic avenue for GBM were also presented. Preclinical data were presented demonstrating that a subset of Ascl1-expressing patient-derived glioma stem cell lines can be induced to differentiate into neurons, leading to pronounced tumor suppression and extended survival.

The FOXG1 and SOX2 transcriptional factors found in high levels in glioma drive unconstrained self-renewal of neural stem cells. This is effected by preventing premature differentiation via control of the core cell cycle apparatus and epigenetic machinery. As SOX2 and OLIG2 progenitors are absent in adult brain, but cycling rapidly in the fetal brain, work is now progressing to investigate whether the Zika virus (which is known to result in congenital birth defects while having little effect when nonpregnant adults are infected) penetrates and targets glioma stem cells.

Early Diagnosis

It can be argued that there is no advantage to be gained from earlier diagnosis of adult brain tumors as there is no evidence that this would positively affect outcome, but just increases the period of anxiety for patients and their families. However, the contrary view was made strongly that a long symptomatic period prior to diagnosis (particularly in those with more subtle symptoms than seizures) leads to poor quality of life, frustration, and psychological damage. Early diagnosis therefore should be a priority, and a better triage procedure is required to help GPs know whom to refer for urgent imaging. Analysis of open-access computed tomography referrals for possible CNS malignancy by Lothian-based GPs for 2010–2015 showed a rate of only 1.6% of scans positive for brain tumor—headache (either alone or in combination with other symptoms) being the most common complaint among patients with positive scans.

A potential infrared spectroscopic method based on a serum sample is being developed as a cancer/no cancer test (95% sensitivity and 88% specificity). It takes 10 minutes and could be utilized in a GP practice. This was thought to be economically viable, the incremental cost-effectiveness ratio per quality-adjusted life year

(QALY) being far below the National Institute for Health and Clinical Excellence (NICE) threshold of £20,000–£30,000 (although the cost of additional secondary care if a case were diagnosed earlier was not included). However, there are also other factors to be considered, such as: would a GP feel able to withhold referral after a negative test even though symptoms had justified invoking the test in the first place?

Biomarkers

It was encouraging to hear that the WHO 2016 biomarker-based classifications appear to be well established. Indeed it was suggested that the next classification will be significantly different again and that the review time span of 9 years may be too long. In particular, IDH wild-type astrocytoma is considered only a provisional entity within the new classification, as these can have very variable prognoses. There is a growing view that they can be further classified into molecularly high grade (harboring EGFR, H3F3A, or TERTp mutations) and lower grade. The former are a distinct, rapidly progressive subgroup without histopathological grade 4 characteristics but suspected to represent early glioblastomas ("baby GBMs"), whereas the latter lack all of these biomarkers, the most favourable survival being noted in those with MYB amplification.

It was thought that adult glioma patients should be informed as to their IDH mutation and MGMT promoter status and their implications, as they have such a dramatic effect on treatment response and outcomes.

The role of biomarkers in the subclassification of medulloblastoma (first to 4 and now to 7 or possibly 12 subgroups) is now evident in impact on treatment, most notably the possibility of reducing aggressive treatment in the better-prognosis subgroups so as to limit the significant long-term toxicity.

Imaging

One might be forgiven for thinking that biomarker assays could now drive all diagnosis and treatment decision making; however, tumors are notoriously heterogeneous and plastic over time and it is not always possible to obtain the repeated tissue samples required to conduct assays. Hence, while identification of biomarkers is now vital, there is definitely still a role for (ever more) sophisticated imaging techniques and integrated diagnostic phenotypic-genotypic methods. For example, MR perfusion imaging may replace conventional MRI techniques that fail to detect the regions of low tumor cell density remaining after resection but which are responsible for subsequent tumor recurrence, diffusion-weighted MRI may identify non-enhancing IDH wild-type tumors despite an initially innocuous imaging appearance, and PET/CT can differentiate tumor phenotypes and between disease progression and radionecrosis.

Despite the significant engineering challenge, a multimodality imaging tool for concurrent spectroscopy and MRI has been built via the EU-funded INSERT project (INtegrated SPECT/MRI for Enhanced stratification in Radio-chemo Therapy). A prototype is now available, providing simultaneous biological readouts aligned with high quality anatomical information, which should enhance stratification and early treatment response assessment without the confounding problem of pseudoprogression seen when MRI alone is utilized.

Surgery

Formal surgical trials are rare. For example, although a systematic review of studies investigating efficacy and safety of 5-aminolevulinic acid (5-ALA)–guided resection has identified 46 formal surgical trials, they are mostly only deemed Level 2–3 evidence. Although use of 5-ALA correctly identifies tumor tissue, there are sensitivity and specificity limitations. Hence, it was encouraging to hear of proposals for 2 prospective multicenter trials to compare intraoperative imaging techniques (MRI and ultrasound) and 5-ALA with white light microscopy.

The Bristol team reported, however, that although awake surgery and intraoperative MRI are the most effective individual aids in preventing damage to functional brain while maximizing the extent of resection, and despite high levels of patient satisfaction, using them together is demanding for the anesthetic and nursing teams and for the patient, at 10 hours the theater times being about 2 hours longer than for a standard craniotomy. Hence the combination is mostly only used for grade 2 tumor resections and those grade 3–4 tumors possibly implicating eloquent areas.

It was depressing to hear of the very slow uptake of use of 5-ALA across the UK; an audit of neuro-surgical centers and their catchment areas shows that even though only one unit has no interest in using it, and all others have surgeons trained in its use, only 43% of centers have fully implemented its use, with a further 23% using it to a limited extent. The only 2 (foreign) studies which calculated cost-effectiveness provide a cost per QALY of £6500–£7400 (although only one takes into consideration all medical costs)—but even so the barrier remains one of funding. As all efforts to obtain full NHS approval for its use have failed (and the recent approval of 5-ALA in the USA is not expected to have any significant impact on UK usage), surgeons should perhaps be creative in finding savings elsewhere in order to fund its use. For example, in Southampton, measures have been introduced to ensure high rates of elective admissions and reduced length of stay (LOS). Their median LOS for intrinsic tumors is 1 day (versus 6 days nationally). Mean LOS (vs national) is 2.5 (6.4) days for high-grade glioma, 2.9 (6.5) days for metastases, and 4.7 (9.2) days for benign tumors—all the lowest in the UK—without compromising readmission, reoperation, or mortality

rates. (The use of the National Neurosurgical Audit Program [NNAP] and Get It Right First Time [GIRFT] data for benchmarking was recommended.) Not only has this proven popular with patients, but it has improved efficiency, reduced cost, cancellations, and waiting times and has more widespread implications across the NHS.

Local Drug Delivery

We know that residual cancer cells remain at the margin even after gross total resection and that targeting this invasive region is vital in the development of new therapies. Hence there is significant interest in locally delivered chemotherapy.

The Nottingham team is delivering combined temozolomide and etoposide directly into the resection cavity in a thermo-setting biodegradable paste and this has achieved significant extension to overall survival in an orthotopic rat model. Similarly encapsulated disulfiram nanoparticles have been developed in Wolverhampton to protect the drug from degradation, thereby extending its half-life; and this in combination with copper significantly inhibits glioma in orthotopic xenograft mouse models at a very low dose.

In Bristol, convection-enhanced delivery of panobinostat-loaded nanomicelles allows administration of the water insoluble histone deacetylase inhibitor in a high-grade glioma rat model. An added sophistication being studied in Edinburgh is that of coupling a prodrug with the use of a nontoxic and catalytic implant to trigger local release of cytotoxic agents. The prodrug is initially rendered nontoxic by masking the functional groups key to its mode of action, which are then unmasked by palladium in the implant. As the palladium device catalytically unmasks the prodrug, the treatment course would not be limited by the lifetime of the implant and could be readily repeated in cases of recurrence.

An example of local delivery which has reached man is that of irinotecan incorporated into biodegradable hydrogel microspheres for injection into the postsurgical cavity wall. A phase I study in Birmingham has shown less local swelling and wound healing issues than have been demonstrated for carmustine wafers despite early offloading. However, this shorter period of exposure is compensated for by a much higher than expected activation of irinotecan to its active metabolite.

Radiation Therapy

Even with stereotactic radiosurgery alone (without whole brain irradiation) recent studies have demonstrated that around half of patients suffer memory impairment. Hence, having identified that a considerable proportion of patients receiving radiosurgery for isolated metastases receive significant radiation to the hippocampus, a proposed new prospective study in Wales will correlate detailed radiation dosimetry, neurocognitive function, and functional MRI measurements of organs at risk.

It was interesting to hear that TTField treatment is now being considered in the UK. In Nottingham an early study has shown antiproliferative effects on pediatric brain tumor cell lines at clinically deliverable field settings, and implantable multiple deep brain stimulation electrodes may address the compliance issues associated with the Optune system.

There is also a focus on identifying novel therapeutics to overcome inherent radioresistance. Irradiation of glioblastoma cells can, for example, promote enhanced motility and invasiveness, both in vitro and in vivo, through activation of myotonic dystrophy kinase–related CDC42-binding kinase, thought to offer a potential new target. Radiosensitization can also be engendered in glioma stem cells by poly(ADP-ribose) polymerase (PARP) inhibitors, the most developed being olaparib, which is being studied in the PARADIGM clinical trials, and an ataxia–telangiectasia mutated kinase (ATM) inhibitor soon to enter man. A UK consortium is developing a multi-arm/multistage trial in collaboration with AstraZeneca to test their portfolio of DNA damage response candidates.

Proton Beam Therapy

In 2016 the NHS sent 210 patients to the USA and Switzerland for proton beam therapy at a cost of £114,000 each (compared with 136 in 2015 and 104 in 2014). Two proton beam installations in the UK, both considered national centers, are being built, with Manchester due to start clinical practice in summer 2018 (their cyclotron was delivered on June 22!) via 3 gantries (plus a fourth research facility). University College London Hospitals (UCLH) will follow in 2021. The first priority is to repatriate patients who would otherwise have gone abroad before commissioning more “core” indications in pediatrics (particularly medulloblastoma) and adults (sarcoma, head and neck, selected cases of meningioma, orbital cancer, chordoma, and other base-of-skull cancers) and then eventually adding evaluative trials for further indications. Once both centers are fully functional, it is anticipated that 1500 patients will be treated per year (1% of current patients treated with photon radiotherapy, a far lower proportion than planned in Holland, for example). A 14-hour clinical day and total operation from 6 am until 11 pm each day will be in place with implications regarding contracts and many other logistical aspects. All patients will be consented and planned for both photon and proton therapy as a contingency, and outcomes data will be collected for all patients. Specific clinical requirements such as exclusion of metal from the treatment area and

how to maintain clear separation of the target site from neighboring structures were discussed.

There are, of course, other single gantry commercial proton beam facilities coming onstream throughout the UK imminently. While these are unlikely to be able to handle more complex cases, they are likely to create pressure on NHS commissioners to include a broader range of indications.

Clinical Management

The recently available relative wealth of clinical trial data in low-grade gliomas still leaves many unanswered questions. For example:

- Which subset of patients do not benefit from chemoradiation?
- How should one treat IDH wild-type patients?
- What is the optimal timing for initiating treatment for particularly indolent tumors?
- Can one delay treatment in order to reduce the cognitive deficit without loss in efficacy?
- Why does it take about 4 years before the survival curves of the best and poorer prognosis patients separate?
- Can one reduce or fractionate radiotherapy or ensure hippocampal sparing?
- Is proton beam therapy superior to traditional photon therapy?
- What is the impact of using chemotherapy alone on survival?
- Are temozolomide, PCV, and nitrosoureas equivalent?
- What is the impact of a neoadjuvant tumor lysate vaccine?
- Are IDH or checkpoint inhibitors effective?

A number of other studies are in progress or opening imminently, but the difficulty caused by long survival times means that valid surrogate endpoints are required. Those suggested were progression-free survival (but only if treatment does not alter vascular permeability), change in the rate of progression (if, in addition to excluding anti-angiogenic agents, one can measure this prior to initiating therapy), and response rate.

Of course, one also has to consider additional management factors and not just survival advantage—for example, the psychological effect of providing patients with an estimate of projected survival possible if biopsy, and hence biomarker assay, has been conducted, or the reduction in seizures resulting from surgery and irradiation even if not associated with radiological or clinical response (although there is a suggestion that seizure response may be an early indicator of response to chemoradiation).

Seizures are, of course, a common presenting symptom or may develop later, meaning that antiepileptic agents are often given prophylactically with significant adverse effects. Hence, if as suggested by a study in meningiomas, existence of preoperative seizures may be a significant predictor of postoperative seizures, it may be possible to withhold anti-epileptic drugs in some patients. While seizures are less common in high-grade gliomas, it has been found that secondary, transformational high-grade gliomas (as opposed to primary, de novo ones) and the presence of IDH mutation are associated with increased likelihood of seizure at presentation.

Increased survival in childhood cancer also comes with difficulties in follow-up, whether of survival or of the many potentially significant long-term side effects (neurocognitive, psychosocial, growth and development, organ dysfunction, fertility and reproduction, carcinogenicity), which may only become evident years after treatment. In the face of the current very limited evidence of their value in restoring subsequent fertility, a research study is under way in Edinburgh to carry out tissue and oocyte preservation in prepubertal children prior to their treatment.

The Elderly

The vast majority of the increased incidence of brain tumors is due to gliomas occurring in patients over 70 years in whom there is poorer prognosis due to more aggressive biology (for example, IDH mutation is rare and EGFR amplification common), frailty, comorbidities, and issues with access to care. Fitness to treat is difficult to define and often evident only after the event. A number of studies in this age group have now been published and it was recommended that up to age 69 the aim should be maximum resection and chemoradiation, and likewise in older patients who are MGMT promoter positive (or temozolomide alone if they can't tolerate radiotherapy). There was a call for a new study of chemoradiation versus temozolomide alone after gross resection in MGMT promoter positive patients over age 70, although concern was raised in the audience as to the dramatic decline in performance status that can accompany craniotomy in such elderly patients.

Diet

In answer to the considerable interest shown in diet (the impact of lifestyle factors on survival was number 1 on the list of priorities for research identified by the James Lind Alliance), 2 parallel multicenter open-label phase II randomized trials of the modified ketogenic diet are due to open in patients with high-grade gliomas receiving chemoradiotherapy (the primary endpoint will be overall survival) and in patients with low-grade gliomas (primary endpoint: symptom levels). Many factors have had to be taken into consideration during trial design, including how to ensure that patients accept randomization and do not "self-prescribe," and the amount of dietetic support available.

Immuno-therapeutics

Once it was realized that the CNS is not totally immune privileged, that leukocytes can traffic to the CNS, and that there are lymphatics in the brain, it was natural to try to emulate the dramatic results achieved with immunotherapy (vaccines and anti–CTLA-4, PD1, and PDL-1 checkpoint inhibitors) for metastatic CNS disease in melanoma and lung in primary glioma.

Prospective randomized double-blind trials are now in place to study the dendritic cell vaccines in glioma with results from the DCVax trial expected in 12–18 months. The outcome of the other study (ICT-107, utilizing "off the shelf" rather than personalised antigens) may, however, be compromised or delayed, as it has been reported that recruitment has been suspended while the company explores strategic options for further financing.

Unfortunately the single peptide vaccine rindopepimut was shown to be inferior to the control arm, but results from a phase II study with the multipeptide vaccine IMA950 are awaited. The REO-Glio trial—which adds reovirus, an oncolytic virus, and granulocyte-macrophage colony-stimulating factor pretreatment to standard-of-care chemoradiation in adult glioma—will open summer 2017 at 4 sites.

Drug Discovery

Understandably, perhaps there was competition between speakers as to whether it is surgery or radiation treatment that plays the central role in the management of patients with brain tumors. Current methods of drug discovery via genomics and identification of molecular targets are proving of no real success, while being very long and costly, and hence phenotypic screening via high-throughput microscopy and stem cell technology, with target deconvolution only at a late stage, is now coming to the fore.

Clinical Trial Design

Medulloblastoma provides a master class in international collaboration to conduct effective trials despite there being only 650 cases per year in the EU (and 150 high-risk cases). However, achieving consensus means that time from concept to a trial starting is too long, especially as the design must be flexible enough to allow additional new therapies to be slotted in as they become available.

Unfortunately, the picture is not the same in adult brain tumors. Data from the National Cancer Research Institute Clinical Studies Group show huge inequality across the country regarding access to brain tumor trials. Recruitment is challenging, with barriers being, amongst others, resources, differing patient pathways, and lack of trials. The majority of patients don't remember their physicians speaking to them about possible trial participation, and it was admitted that when under time pressure in clinic, this may not occur. Twenty-six percent of patients wanted to take part in a study but were unable to due to the lack of an appropriate trial or inclusion/exclusion criteria. Twenty-five percent of potential patients are lost for preventable reasons, such as distance from a participating hospital. In order to address this and recruit **all** brain tumor patients in the UK, **all** centers should take part in trials, whereas currently many feel that the setup effort is not worthwhile if they are only likely to have a handful of appropriate patients.

Qualitative Research

A rather different (but again quite worrying!) topic listed all the different types of biases that can affect physician and surgeon decision making and the advice these practitioners give to patients. It was recommended that best practice tumor boards, and not just multidisciplinary meetings, be used to ensure that views of other similar specialists are taken into consideration.

Attendees were also introduced to the role of qualitative research via semi-structured, face-to-face interviews. Examples largely focused on patient satisfaction with awake craniotomy, gamma knife radiosurgery, "wait and see" management in low-grade glioma, end-of-life care, or information provision prior to surgery, but this technique can also be used to elicit physicians' views, such as: how do they feel about elective surgical resampling of malignant tumors to guide treatment? or do they (and the family) experience the loss of the relationship after their patient dies?

Conclusions

It is interesting to look back at the reports I have written after this conference in previous years and to identify trends. This year the scientific papers were thoroughly sprinkled with epigenetics, and everyone—scientists, surgeons, and oncologists alike—were talking about the tumor margin and invasiveness!

While we still have a long way to go to improve outcomes (the latest "great white hope," immunotherapy is still a long way from proving fruitful!), there is a staggering amount of information available from ever more sophisticated imaging techniques, and biomarker classification and advanced radiotherapy modalities are allowing less aggressive regimes to reduce side effects.

Internationally, neuro-oncology must be congratulated on reusing clinical trial data to extract every last drop of information! One frequently heard results from repeated subgroup analyses of completed trials, and there were more and more

demands for new stratification factors to be built into trial design. However, much more needs to be done in the UK before recruitment of adult patients into trials emulates that achieved in pediatrics.

Management information (for example, benchmarking data and qualitative research), long the domain of business, is now finding its place in medicine, and there is obviously room for thinking creatively as far as NHS cost constraints are concerned.

Appendix

The Young Investigator of the Year Award, jointly funded by BNOS and Brain Tumour Research, was made to Harry Bulstrode, University of Cambridge.

The best poster prize was awarded for "18F-methylcholine PET/CT, in vivo magnetic resonance spectroscopy imaging and tissue enzyme biomarkers of choline metabolism in primary brain gliomas" by Matthew Grech-Sollars (Imperial College, London).

The best scientific oral presentation was "A human iPS cell-based model of medulloblastoma demonstrates co-operativity between SHH signalling and mutation in an epigenetic modifier" by Jignesh Tailor (St George's University Hospital, London)

The best clinical oral presentation was "The impact of visual impairment on Health-Related Quality of Life (HRQoL) scores in brain tumour patients" by Sana Sharrack (University of Cambridge)

BNOS 2018 will be held July 4–6 in Winchester.

Abstracted from a report prepared by Maryanne Roach on behalf of the BNOS Council and BNOS 2017 organizing committee. Full version on BNOS website http://www.bnos.org.uk

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Indian Society of Neuro-Oncology Annual Conference Report 2017

The 9th Annual Conference of the Indian Society of Neuro-Oncology (ISNO) was successfully organized by Kidwai Memorial Institute of Oncology (KMIO) and hosted by the National Institute of Mental Health and Neuro-Sciences (NIMHANS) at the NIMHANS Convention Center in Bangalore from March 10th to 12th, 2017.

The ISNO Executive Committee (EC) acknowledges and appreciates the hard work of all members of the organizing team led admirably by Dr Lokesh (KMIO) and Dr Vani Santosh (NIMHANS) and executed through the untiring efforts, utmost sincerity, and dedication of Dr Uday Krishna as the Organizing Secretary of ISNOCON 2017.

The conference had more than 300 registrations, including over 100 top-notch faculty from several leading national and international academic institutions, who presented and discussed the various aspects of clinical and basic neuro-oncology. The international faculty list comprised luminaries such as Dr Minesh Mehta (Radiation Oncologist, Miami, Florida, USA), Dr Vinay Puduvalli (Neuro-Oncologist, Ohio, USA), Dr Felice Giangespero (Neuro-Pathologist, Italy), Dr Santosh Kesari (Neuro-Oncologist, Santa Monica, USA), Dr Eng Siew-Koh (Radiation Oncologist, Australia), Dr Zarnie Lwin (Medical Oncologist, Australia), Dr Girish Dhall (Pediatric Oncologist, UCLA, USA), Dr Garnie Burkhoudarian (Neurosurgeon, Santa Monica, USA), and Dr Venkata Yenugonda (Clinical Pharmacologist, Santa Monica, USA).

The 2 main themes of the meeting were “2016 Update of WHO Classification of Central Nervous System (CNS) Tumors and Impact on Management” and “Novel Therapies in Neuro-Oncology and Impact on Management.” The meeting started with the ISNO Educational Session in the form of 3 parallel Workshops on Radiation Oncology, Basic/Translational Neuro-Oncology, and Neurosurgery under the dynamic leadership of Dr Rakesh Jalali, Dr Vani Santosh, and Dr Arivazhagan, respectively.

The formal scientific session started on Day 1 with the theme “2016 Update of WHO Classification” and “Impact on Management in Clinical Practice.” A focused session on recent updates in “Pediatric Neuro-Oncology” followed

the WHO update. This was followed by the ISNO Award Session and the prestigious ISNO President's Oration by Dr Rakesh Jalali. The first day ended with formal inauguration of the meeting by distinguished guests and luminaries (see photograph).

Day 2 of the conference was themed "Novel Therapies in Neuro-Oncology" and "Impact on Management" in various fields such as skull-base tumors, adult diffuse gliomas, molecular mechanisms of resistance, retreatment, and immunotherapy. This was followed by the much-awaited Ab Guha Oration. Dr Minesh Mehta, world-renowned Radiation Oncologist and presently the Deputy Director of the Miami Cancer Institute, Florida, USA, delivered the prestigious Ab Guha Oration tracing the journey in the management of "Low Grade Gliomas." This was followed by the very exciting "Do Not Miss It" session on 6 landmark papers in various fields of neuro-oncology with potential to shape/change practice. The day ended with a multidisciplinary discussion on interesting and challenging case capsules (Tumor Board).

Day 3 of the conference started with parallel "Meet the Expert" sessions on "Immunotherapy" and "Germ Cell Tumors," followed by scientific presentations on "Nanotechnology in Neuro-Oncology" and "Basic Biology of Glioblastoma." This was followed by the Proffered Paper session, a lively debate on "Integration of Molecular Techniques in Routine Neuro-oncologic Practice" and the "Indian CNS Tumor Registry" initiative.

A number of cash prizes, grants, and awards were given during ISNOCON 2017 as follows:

"ISNO President's Award for Best Clinical Researcher" for 2017 was awarded to Dr Tejpal Gupta, Radiation Oncologist, Tata Memorial Centre, Mumbai for his research work on medulloblastoma.

"ISNO Annual Award for Outstanding Work in Neuro-Oncology" for 2017 was awarded to Dr Shilpee Dutt, Principal Investigator and Scientist, ACTREC, Tata Memorial Centre, Mumbai for her innovative biological research on glioblastoma resistance models.

ISNO Students' Awards for 2017. Two awards were given in this category:

(1) Clinical Neuro-Oncology: Dr Archya Dasgupta, Clinical Research Fellow, Radiation Oncology, ACTREC, Tata Memorial Centre, Mumbai for his original research on the radiogenomics of medulloblastoma
(2) Basic/Translational Neuro-Oncology: Dr Jyothi Nair, Research Fellow, Shilpee Dutt Lab, ACTREC, Tata Memorial Centre, Mumbai for her PhD-related work on resistance mechanisms in glioblastoma

ISNO 2017 Travel Grants: Twenty-eight top-scoring abstracts of a total of 80 abstracts (8 abstracts in the ISNO Award Session and 20 abstracts selected for Oral Presentation in the Proferred Papers Session) were given ISNO Travel Grants to attend ISNOCON 2017, consisting of a cash prize of Rs 5000 and a citation.

ISNO 2017 Poster Awards: Four best posters of the 52 abstracts selected for Poster Presentation, one each from Neurosurgery, Radiation Oncology, Neuropathology, and Basic Neuro-Oncology were selected for Poster Awards consisting of a cash prize of Rs 3000 and a citation.

ISNO 2017 Training Fellowship: Dr Vibhay Pareek, pursuing DNB in radiation oncology at Jupiter Hospital, Mumbai was awarded the "ISNO Training Fellowship" for 2017. He is entitled to complete a 4- to 6-week training course on "Radiosurgery in Neuro-Oncology" under the tutelage and mentorship of Dr Rakesh Jalali at Tata Memorial Centre, Mumbai.

The 10th Annual Conference of the Society (ISNOCON 2018) is being organized and hosted by the All India Institute of Medical Sciences (AIIMS), New Delhi from March 10th to 12th, 2018 under the able leadership of Dr Ashish Suri (Organizing Secretary) and Dr Chitra Sarkar (Organizing Chairperson). You can e-mail at isnocon2018@gmail.com or visit our website at www.isno.in for more details.

Dr Tejpal Gupta, Professor, Radiation Oncology, Tata Memorial Centre

Joint Secretary, Indian Society of Neuro-Oncology

Supporting Family Caregivers as Part of Neuro-Oncology Patient Care

Cristina Cruz, MPH
Margaretta S. Page, RN, MS

The needs of the neuro-oncology patient are significantly different compared with those of patients affected by other cancers. Though the treatment of radiation and chemotherapy is one commonality to other cancer treatments, high-grade glioma patients can suffer from physical decline as well as significant changes in mood, behavior, and cognition, causing distress for both patients and their caregivers.[1] These neurologic-specific symptoms can be overwhelming to caregivers, particularly cognitive decline and personality changes that occur in a patient who may outwardly appear to be fine. These caregivers are known to experience "poorer social functioning, more mental health concerns and higher carer burden than carers of patients with other cancers."[2]

In a recent publication of the European Association of Neuro-Oncology's palliative care guidelines, EANO acknowledges the role of the family caregiver in patient care and the psychosocial effects of the illness on these caregivers.[3] The guidelines recognize the benefits of addressing this caregiver strain through psychoeducational interventions, employing specialized neuro-oncology staff who can assess needs and by encouraging providers to treat family members as part of the care team. More research is needed to understand the best sustainable practices to support family caregivers, since they serve as a strong component of the neuro-oncology patient's care team. This article presents one approach to supporting the loved ones caring for a brain tumor patient—a caregiver/family support program embedded within the neuro-oncology clinic at the University of California, San Francisco (UCSF).

Creating a Caregiver Program

The Gordon Murray Neuro-Oncology Caregiver Program at the UCSF's Division of Adult Neuro-Oncology was created in response to a need identified by a former neuro-oncology caregiver. The program's goal is to increase caregiver preparedness across the trajectory of the illness, with hopes to sustain or improve quality of life among patients' caregivers and subsequently improve patients' quality of life and health outcomes.

In 2011, Randi Murray collaborated with other former cancer caregivers and cancer survivors to initiate the Brain Tumor Initiative,[4] which would raise funds to further develop the neuro-oncology care and research offered at UCSF. At its inception, the caregiver program was tasked with allocating staff to provide guidance and informational resources to prepare neuro-oncology caregivers for the different symptoms and side effects brain tumor patients can experience. The Gordon Murray Caregiver Program was the most novel component of the initiative's charge, and it remains the only clinic-based caregiver support program in neuro-oncology practice today.

The program's multidisciplinary team aims to prepare caregivers for their roles by offering resources, health care navigation, and emotional support through proactive outreach, one-on-one consultations, peer support opportunities, and educational offerings. The staff includes a medical director, nurse coordinator, social worker, and program analyst, who are an active part of the adult neuro-oncology clinic team (see **Table 1** for further details on staff job descriptions).[5]

Offering Support Across the Disease Trajectory

The Caregiver Program's theory for its programming and outreach is based on Paula Sherwood's stress response model [6] for family caregivers of patients with a primary malignant brain tumor. In Sherwood's model, which is rooted in Lazarus and Folkman's work on stress and coping, caregivers have both internal and external resources that are accessed to address the patient's evolving care needs. Sherwood models neuro-oncology caregivers' emotional and physical stress responses to be a result of the caregivers' primary appraisal of the patient's health status and care needs (i.e., assistance with activities of daily living and independent activities of daily living, changes in cognitive functioning, low KPS score[7] and a secondary appraisal of the internal and external resources that he or she has available to address those needs. A caregiver's internal resources are their physical and emotional traits or characteristics. These resources can include the caregiver's sense of mastery, self-efficacy, physical health, and emotional health. External resources include more tangible forms of support such as financial means, health information, hired caregivers, peer support, or respite care. The number and quality of these resources moderate the caregiver's stress responses, which can present in many ways, affecting both physical and emotional health.

There are several touch points in the Caregiver Program where caregivers are supported across the disease trajectory (see **Table 2** for further details on each program component). Staff connect with caregivers to assess needs for support at each of these time points. When the program was first created, an internal assessment form was created as part of the intake process. Currently, program staff use a framework that guides conversations with caregivers to assess needs for support or resources that may fall under informational, practical, social, or emotional concerns.

The program is designed to both supplement and strengthen a caregiver's internal and external resources. Dedicated caregiver support staff serve as an extra line of support that is consistently available to family members

Table 1. Gordon Murray Caregiver Program Team Job Descriptions

Team Member	Role
Medical Director	Leadership, vision, oversight of development of the program. Offers prioritization of program elements and progress. Develops national and international agendas by creating policy initiatives for long term goals to improve caregiver outcomes. Leads caregiver research initiatives, and evaluates program and caregiver outcome data. Financial oversight and fiscal support.
Nurse Coordinator, with expertise in neuro-oncology	Operational development and day-to-day management of the Caregiver program. Provides clinical expertise and direct care to caregivers and families of neuro-oncology patients. Offers education about the disease and needs of the neuro-oncology caregiver to caregivers and other health professionals involved with caring for brain tumor patients along the disease trajectory. Serves as consultant to others in the department, medical left, and community at large. Participates in application of and evaluation of evidence-based solutions in the care of the caregiver. Participates in clinical research.
Neuro-oncology social worker	Provides psychosocial assessments, crisis intervention, consultation, education, and linkage to supportive services and community resources that are specifically offered and intended for the neuro-oncology caregiver. Participates in program goal setting and outcome evaluations. Facilitates monthly neuro-oncology caregiver support group.
Program Analyst	Provides administrative and operational support to the Caregiver Program. Develops documentation for program implementation toolkit, needs assessment tools, and program evaluation procedures. Manages all program internal and external communications and marketing. Collaborates with clinic team to triage caregiver concerns. Meets all caregivers of newly diagnosed patients at first visit to the Neuro Oncology clinic.

above the assistance provided by the clinic's staff. Program staff help caregivers cope with the psychosocial effects of the disease through connecting caregivers to peer support, local counseling services, and monthly support groups. Caregivers are also encouraged to contact the program staff to discuss strategies to manage the stress of caregiving. Caregivers can meet with staff in the caregiver program room, a separate space decorated with soft lighting and calming colors, for more extensive conversations to discuss concerns that may not always be shared in front of the patient. Additionally, the program offers several resources to educate caregivers about what to expect at different stages of the disease trajectory[8] and parenting resources[9] to talk about the effects of the disease on the patient's children.

To fortify the caregiver's external resources, the program connects family members to existing caregiver support services and materials that can increase family members' ability to provide care for patients. This includes informational resources regarding organizing care, understanding the disease and managing symptoms, financial assistance programs, respite programs, assistance with navigating home health care, and other cancer support services. For example, the program collaborated with fellows in UCSF's Palliative Care program to create a manual that educates caregivers about what to expect during a patient's transition to hospice.[10] Recently, more resources have been curated for patients accessing different types of care, such as clinical trials or palliative care, to be shared by providers in the clinic. A caregiver lending library was also recently created to offer self-help and stress management books that caregivers can review on their own time.

Educating Providers on Supporting the Neuro-Oncology Caregiver

Since the program began, there have been more opportunities to offer education to other providers about supporting the neuro-oncology caregiver as part of a brain tumor patient's care. In addition to serving as guest faculty in the UCSF Palliative Care Fellowship Training program, the program's nurse coordinator travels to hospices throughout the Bay Area to provide in-service education to hospice nurses, social workers, and chaplains about the disease-specific needs of brain tumor patients and their families at end of life.[11] The goal of this outreach is to not only shed light on the patient's symptoms at end of life, but also to explore how the neurologic deficits that these patients

Table 2. Gordon Murray Caregiver Program Caregiver Outreach

Outreach	Target Population	Time Point of Service	Objectives of Outreach
Inpatient Education Outreach	Families of postoperative patients with newly diagnosed glioma	Prior to discharge from hospital	Prepare caregivers for caring for patient postop, regarding: • Medication management • Addressing seizures • Health care navigation
New to Clinic Introductions	Patients/caregivers who are visiting the clinic for their first appointment and are receiving their diagnosis, prognosis and treatment plan	At conclusion of consult with neuro-oncologist	Provide initial caregiver resources: • Introductory health information • Caregiver handbook • ABTA resources • Peer caregiver support info.
GBM Outreach Calls: Proactive outreach across 3 phone calls to address common concerns during first stage of standard of care treatment	Caregivers of newly diagnosed glioblastoma patients	Two weeks and 4 weeks after first clinic appointment; After post-radiation MRI follow-up appointment	See Table 3 for more details
Hospice Transition Counseling	Families of patients who have recently been recommended to hospice	Upon MD referral, or upon request from caregiver	• Educate family members on services available through hospice • Explain symptoms at end of life to prepare families on what to expect
Bereavement Outreach	Caregivers of patients who have died	One month or later after patient's death	• Assess for bereavement support needs • Connect caregivers to grief support groups or other grief counseling

experience can impact the family during the final stage of the illness.

Evaluating the Program's Impact

Research is still developing to fully understand how supporting caregivers can impact their mastery and self-efficacy to care for patients with brain tumors. The program has been able to develop services and outreach in response to the most common caregiver needs identified through the literature and interactions with family members. In a 2011 study conducted among patient–caregiver dyads within UCSF Neuro-Oncology's clinic, caregivers identified the following areas as being of high importance and in need of improvement in the clinic's practice: emotional support to manage their anxiety and stress and getting connected with caregivers who have experienced similar situations.[12] Other areas that caregivers identified as very important included understanding how to manage symptoms, knowing the side effects from treatment, and managing the uncertainty of the patient's prognosis. Today, some of the most common referrals the Caregiver Program team receives from the providers in the clinic are in regard to guidance with accessing disability benefits, managing challenging patient behaviors, hiring in-home health support, and providing emotional support when transitioning the patient to hospice care.

Thus far, the program has relied on distributing annual feedback surveys that have asked broad questions about the support received from the Caregiver Program to guide programming decisions. Now that the program has established itself within the clinic and among fellow UCSF partners in care, the program's next goals are to measure outcomes and analyze the program's impact to identify

other ways to best meet caregiver needs. Over time, the information from these outcome measures will be used to refine the program's resources and standard operating procedures for caregiver outreach.

The first step in this next phase of the program is to concretely measure the effect of the support provided to caregivers. The program team will use the Caregiver Preparedness score[13] as the primary outcome measure for caregivers of newly diagnosed glioblastoma (GBM) patients who are offered proactive outreach. The Preparedness Scale is a self-assessment tool that asks caregivers questions about how prepared they feel to manage aspects of the patient's care, such as emergent care needs, navigating health care services, and the stress of caregiving. This measure most closely aligns with the support currently provided to caregivers, assessing the social, emotional, practical, and informational domains. The goal is to measure caregivers' preparedness prior to the first GBM outreach call for a pre-measurement and then after the post-radiation MRI follow-up appointment to collect a post-measurement (see **Table 3** for more details on the GBM outreach protocol for caregivers of newly diagnosed GBM patients).

Most recently, the program has decided to build a database to collect and store these caregiver outcomes data hosted through the REDCap[14] electronic data capture tool. This tool will allow staff to electronically distribute needs assessments and surveys to caregivers in a secure manner. Caregivers will be able to privately and objectively state where they need assistance as they review lists of some of neuro-oncology caregivers' most common concerns. Pre- and post- outcome measures will be collected more consistently with this systematized distribution of assessments. This database will also store demographic data about caregivers to identify trends among the program's high utilizers, allowing the team to further understand caregiver needs.

Strategies for Supporting Caregivers with Current Infrastructure

The Caregiver Program as it exists today within the UCSF adult neuro-oncology clinic would not be possible without the generosity of the donors involved in the Brain Tumor Initiative. Philanthropic dollars provided for the program's staffing costs, allowing for the development and launch of the program in its first 3 years. Now that the program staff's salaries have been allocated to the department's budget, the program relies on donations only to finance ongoing programming, evaluation, and resource development.

The chief goal of the program is to serve as a model for caregiver support so that, in time, these services can be made available in all neuro-oncology practices. Until this support service can be made available everywhere, there are a few strategies that can be utilized among providers in the clinic to prepare family members for their new caregiving roles. To successfully implement these strategies, clinics should work with all providers to establish buy-in and create consistent, sustainable practices so that patients and their families receive equitable care.

One of the first steps to effectively supporting caregivers is to recognize their role in the patient's care and to regularly assess their needs to effectively care for the patient at home. Caregiver needs should be assessed at each appointment to offer timely, effective interventions. This is especially relevant for caregivers of high-grade tumor patients, who tend to have rapid decline.

Secondly, resources should be readily available to address common caregiver concerns. Most often, caregivers are not aware of what they will need until they are well into managing the logistics of treatment. This makes anticipating needs somewhat difficult. At UCSF Neuro-Oncology, caregivers of newly diagnosed patients are provided a manual that provides a comprehensive overview on symptoms and side effects throughout different stages of treatment, along with a review of helpful resources and tools for these different stages. Families are also offered disease-specific resources from the American Brain Tumor Association (ABTA). ABTA (abta.org) provides concise resources designed for both patients[15] and caregivers[16] and has a listing of brain tumor–specific support groups available in each state.

Lastly, a listing of cancer support services available in the areas where patients live should be curated and shared among providers. Patients travel from several different counties within California to have an appointment at UCSF Neuro-Oncology such that the program's social worker has become very familiar with many of the resources available to patients throughout the state. Over time the social worker has curated a county-specific list of caregiver support services and other frequently requested providers where patients and caregivers can be referred. The team often references these resources as clinicians inquire about referrals for patients and families receiving treatment locally. Similar resources can be organized and stored on a shared drive within the clinic, where providers can access them as needed.

Currently there is no reimbursement process for caregiver support services, and funding for dedicated staff to provide these services as part of patient care is not widely available. Advocacy efforts for federal policy changes to include and reimburse caregiver services must continue, as family caregivers have increasingly become an extension of the health care team. The profile of the unpaid family caregiver is more visible as patients live longer with

Table 3. Gordon Murray Caregiver Program—GBM Outreach Protocol

GBM Outreach Time Point	Outreach Objectives	Performance Objectives	Talking Points
Call 1: Two weeks after first appointment at UCSF Neuro-Oncology	1. Orient caregiver to working with health care team at Neuro-Oncology 2. Assess caregiver's ability/limitations to fulfill caregiver duties	1. Caregiver will learn resources available to him/her during treatment at Neuro-Oncology 2. Caregiver to identify their informal "support" team among friends/family 3. Caregiver will identify progress toward starting treatment, re: transportation, finding providers, etc.	1. How has it been organizing appointments/care for the next steps in treatment plan? Have you been able to communicate with the team? 2. Do you know who to contact in Neuro-Onc? 3. Who else is helping you take care of the patient? 4. Normalize common concerns during XRT treatment (i.e. fatigue, getting to appointments, etc.)
Call 2: Four weeks after first appointment at UCSF Neuro-Oncology	1. Prepare caregiver for supporting patient/making arrangements during radiation 2. Health care navigation 3. Arranging for disability/work leave 4. Address financial concerns, offer navigation	1. Caregiver will learn skills to navigate discussions with family, children, patient re: caregiving duties or disease 2. Caregiver will navigate concerns about arranging time off for or paying for treatment (insurance navigation)	1. How have you and your family been managing the new changes in routine? 2. Now that your loved one has begun treatment, have you had any concerns about paying for treatment or accessing insurance coverage? 3. Are you able to navigate any of these concerns with your radiation-oncology team? 4. Have you had any issues making arrangements with your employer or the patient's employer for time-off during treatment? Disability benefits?
Call 3: After post-radiation MRI follow-up appointment at UCSF Neuro-Oncology	1. Confirm caregiver's understanding of next steps in treatment, and address information needs 2. Transitioning back to work/developing a new routine after radiation treatments 3. What to expect next 4. Staying in touch with Neuro-Oncology team between MRI scan	1. Help caregiver adapt to new stage in treatment 2. Help caregiver problem solve outreach/resource identification to navigate new transition 3. Discuss resources/coping strategies for living with uncertainty of illness and disease trajectory	1. How will you need to support the patient after your last visit with the neuro-oncologist? Do you feel prepared to manage the next stage of treatment? 2. Will you be going back to your old routine in any way? 3. Do you have other support to help take care of your loved one during this transition back to work, etc.? 4. Do you think you'll be able to make time for self-care in new routine?

improved treatment. For brain tumor patients, however, small steps to support their family caregivers may lead to long strides in better patient care and better coping among patients and families so that everyone impacted by the disease can have a better quality of life.

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REPORT FROM ASCO 2017

With regard to CNS tumors, the 2017 annual meeting of the American Society of Clinical Oncology (ASCO) included 9 oral presentations that focused on primary brain tumors and brain metastases. There was a clinical science symposium on maximizing the approach to central nervous system tumors.

Martin van den Bent presented the final results of the TAVAREC trial, which was a randomized phase II of patients with recurrent grade II/III glioma without 1p/19q codeletion. One hundred and fifty-five patients were randomized to receive temozolomide with or without bevacizumab in first recurrence. Overall survival (OS) rate at 12 months (primary endpoint) was similar in both of the arms, 61% in the temozolomide arm and 55% in the temozolomide with bevacizumab arm. Neurocognitive function was similar in both groups. Overall survival was longer in tumors with isocitrate dehydrogenase 1 or 2 (*IDH1/2*) mutations compared with *IDH* wild-type tumors (15 mo vs 10.7 mo, $P = 0.001$). The study demonstrated that addition of bevacizumab to temozolomide failed to improve progression-free survival (PFS) or OS in this patient population.

Mizuhiko Terasaki discussed the results of the randomized, double-blind, phase III trial of 88 human leukocyte antigen A24–positive glioblastoma patients refractory to temozolomide from 20 Japanese hospitals. Patients in the experimental group received a personalized peptide vaccination (4 peptides chosen from 12 peptide candidates). Median OS in the vaccine group at 8.4 months was similar to the OS of 8.0 months in the best supportive care group (control arm).

Fred Lang presented the results of the phase Ib randomized study of the oncolytic adenovirus DNX-2401 with or without interferon gamma for recurrent glioblastoma. OS-12 and OS-18 rates for all patients enrolled were 33% and 22%, respectively, regardless of treatment assignment, and support an ongoing phase II study of DNX-2401 for recurrent glioblastoma.

Andrew B. Lassman presented the efficacy analysis of ABT-414 with or without temozolomide in patients with epidermal growth factor receptor (EGFR)–amplified, recurrent glioblastoma. He reported an objective response rate (ORR) of 10% (2 complete response [CR] and 9 partial response [PR] in 115 patients and disease control rate of 52% [CR + PR + stable disease] and PFS6 rate of 26%. Report of the phase II European Organisation for Research and Treatment of Cancer study of ABT-414 is expected to be presented at the 2017 Annual Society of Neuro-Oncology Meeting in San Francisco.

Thomas Graillon presented the CEVOREM study, a phase II trial of everolimus and octreotide in 20 patients with refractory and progressive meningioma. The combination resulted in a PFS6 of 58% and PFS12 of 38% and may warrant further evaluation in this patient population with limited medical therapy options.

Oral presentations in brain metastases in the CNS section included a phase I study of AZD3759, the first EGFR inhibitor primarily designed to cross the blood–brain barrier to treat patients with EGFR-mutant non-small-cell lung carcinoma with CNS metastases. The use of AZD3759 was associated with the intracranial ORR of 63% by investigators' assessment in 19 evaluable patients and extracranial ORR of 50% (10 of 20 evaluable patients). Cambridge Brain Mets Trial 1 (CamBMT1), a phase Ib proof-of-principle study of afatinib penetration into cerebral metastases was presented. The study showed that it is feasible to conduct a window-of-opportunity study of targeted agents in patients with operable brain metastases.

Three oral presentations focused on therapeutic options for patients with brain metastases from melanoma. Michael Davis presented a phase II study of dabrafenib and trametinib in 4 cohorts of patients with *BRAF* mutant melanoma brain metastases. The cohorts A, B, and C enrolled asymptomatic patients, while cohort D included symptomatic brain metastases. The patients in cohorts A (radiation naïve) and B (prior treatment) had good performance status and harbored *BRAF V600E* mutations. Cohort C included patients with *BRAF* V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy, and cohort D included *BRAF* V600D/E/K/R-positive patients. The investigator-assessed intracranial responses by Response Evaluation Criteria in Solid Tumors v1.1 criteria were 58%, 44%, 56%, and 59% in cohorts A, B, C, and D, respectively. A phase II study of a combination of ipilimumab and nivolumab in patients with brain metastases from melanoma was presented by Hussein Tawbi. Response rates of 55% and an intracranial PFS6 of 67% were reported among 75 patients enrolled in the study.

Georgina Long from the Melanoma Institute, Australia, presented preliminary results of a randomized phase II study of nivolumab or nivolumab plus ipilimumab in melanoma patients with brain metastases. The median intracranial PFS was 4.8 months in the nivolumab and ipilimumab arm and 2.7 months in the nivolumab alone arm. Response rates of 50% were seen in the combination arm of nivolumab and ipilimumab in 20 patients who were treatment naïve.

A phase II trial of bevacizumab and temozolomide for upfront treatment of elderly patients with newly diagnosed glioblastoma was part of the poster discussion. Leia Nghiemphu reported that use of bevacizumab and temozolomide as an upfront treatment resulted in a median OS of 12.3 months (14.8 mo for those with methylation of O^6-methylguanine-DNA methyltransferase [MGMT], 10.0 mo for unmethylated MGMT) in patients with newly diagnosed glioblastoma age $\geq$70 and Karnofsky performance status $\geq$60. The poster session covered almost all subfields of neuro-oncology. There was an educational session on brain metastases and different therapies in gliomas.

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Interview

Howard Colman, MD, PhD

Director of Medical Neuro-Oncology, Professor of Neurosurgery, Neurology, and Internal Medicine (Oncology), Huntsman Cancer Institute, University of Utah

1. **How do you currently use NGS technology in your current practice? Eg, whole-genome sequencing (WGS), whole-exome sequencing (WES), transcriptome sequencing, targeted gene panels, and why? All patients, trial patients? For diagnosis or treatment?**

   At Huntsman Cancer Institute at the University of Utah, we currently perform NGS sequencing on most patients with primary brain tumors when there is sufficient tissue. In terms of NGS technology, we have used various commercial and local variations, including mutation hotspot panels, targeted exome (and promoter) panels, whole exome sequencing, and for selected cases combined DNA and RNA sequencing. Our experience indicates that both whole exome sequencing and larger targeted panels that provide adequate coverage of important brain tumor genes (including fusions) are sufficient for most diagnostic and treatment information in gliomas and other primary brain tumors. Good coverage of cancer predisposition mutations and more recently information on mutational load and microsatellite instability status are also important for identification of patients with unsuspected germline mutations and those that may be candidates for treatment with checkpoint inhibitors or other immunotherapies. The one technology we have found insufficient are so-called hotspot panels that are mainly aimed at identifying specific point mutations. These panels are often optimized for targeted therapies in other solid tumors and fail to identify many of the key alterations (larger mutations, deletions, and gene fusions) important in brain tumors. While not currently part of our clinical practice, RNA sequencing in combination with DNA sequencing provides the potential for even more sensitivity for detection of some alterations, particularly gene fusions. As technology improves and costs go down, this approach may become more common in routine practice.

   Results of NGS are used in our clinical practice in several ways, including: clarifying diagnosis, determining clinical trial eligibility, and identifying patients who may be candidates for targeted or checkpoint therapies. In terms of diagnosis, NGS is most useful in situations where current WHO criteria still leave some ambiguity regarding diagnosis or prognosis. This is particularly relevant in gliomas that are wild type for IDH1 by initial immunohistochemical testing. While many of these tumors harbor alterations similar to GBM in genes such as EGFR, PTEN, NF1, and/or TERT promoter, there is a distinct subset of tumors in which the NGS results can influence diagnosis or prognosis. Some of these tumors harbor alterations in BRAF or other genes suggestive of a different diagnosis (eg, ganglioglioma, pilocytic astrocytoma), and some turn out to be IDH mutated by sequencing even when initial IHC results are negative. NGS results are also necessary for enrollment in an increasing number of clinical trials that include specific molecular alterations as inclusion criteria. While still a minority of patients, there are also a select set of gliomas, meningiomas, craniopharyngiomas, and others that are candidates for targeted therapies based on alterations in specific genes, including: BRAF mutations and fusions, ROS1 and TRK fusions, SMO mutations, etc. The recent FDA approval of checkpoint inhibitors for all solid tumors with microsatellite instability also raises the potential to treat brain tumors with this alteration or high mutational burden with immunologic agents.

2. **What are you most interested in learning with NGS? Eg, identification of driver mutations, detection of resistance mechanisms, quantification of mutational burden, evaluation of tumor gene expression, diagnosis of germline mutations**

   While the utility and information needed from NGS varies by patient and tumor type, we are generally most interested in the pattern of driver mutations and alterations, quantification of mutational burden and microsatellite status, and diagnosis of germline mutations. As described above, the pattern of specific driver gene mutations and alterations can be very informative for clarifying diagnosis (and prognosis) in certain WHO diagnostic categories that can include a more heterogeneous molecular group of tumors (eg, IDH wild type gliomas). Within diagnostic categories the specific driver alterations can be important to identify rare subsets of patients who may derive benefit from targeted therapies, although definitive data for efficacy of these alterations and associated treatments are often lacking for brain tumors relative to other solid tumors. Mutational burden and microsatellite status are used to identify those patients who may benefit from use of checkpoint inhibitors or other immune modulators. This can be important for enrollment in clinical trials, but now also potentially for “on-label” use with the recent FDA approval for MSI-high tumors.

   We have also successfully identified a number of patients with previously unsuspected germline alterations based on NGS results that demonstrate alterations that are not typically found in particular brain tumor types. Specific germline mutations that we have identified include RET, SDH, BRCA, TP53, and biallelic mismatch repair mutations. Appropriate identification of these unsuspected alterations and referral of these patients and their families to cancer genetics can have important implications. Implementation of appropriate testing and screening for the patient and extended family members can potentially prevent or facilitate early diagnosis of additional cancers.

3. **What is the long-term utility of NGS in neuro-oncology? Eg, to predict responders to immunotherapy, either through RNA-Seq based gene**

expression or mutational burden, could also drive significant clinical uptake of clinical NGS testing. Is there applicability to ctDNA for early diagnosis/ more representative view of tumor heterogeneity?

There are several potential ways NGS testing and technologies may evolve in terms of long-term utility in neuro-oncology. First, while the success of targeted therapies in general have been disappointing in brain tumors relative to other solid tumor types, there are a number of potential situations where accumulating data suggest promising efficacy, such as BRAF alterations. These alterations can be seen commonly (but not universally) in some histologic diagnoses (eg, ganglioglioma, pilocytic astrocytoma) but rarely in others (eg, IDH wild-type astrocytoma). There are also very promising data in other solid tumors for specific targeted therapies for alterations that occur very rarely in brain tumors, such as ROS1 and TRK fusions. If developing data show clearly for efficacy of individual agents for specific alterations, then NGS is potentially necessary for all patients with these diagnoses in order to make sure that all of the rare patients with these alterations get the appropriate therapies. Second, there is promise based on recent data and FDA approvals that checkpoint inhibitors may have efficacy for brain tumors with microsatellite instability (and possibly high mutational burden), but specific data for brain tumors are still in development. Thus, importance and uptake of NGS in routine practice will depend in some degree on observation of clear benefit of targeted, immunotherapy, or other treatments in selected brain tumor populations. Lastly, as technologies improve, there is the potential for comprehensive NGS testing to replace several of the individual molecular tests that are done as part of the standard evaluation of many brain tumors. For example, NGS and related technologies can potentially be used to quantify copy number alterations and gene methylation. So, one can imagine that in the future, we could perform one test as part of initial evaluation of a tumor sample that results in all the relevant diagnostic data (IDH, 1p/19q), prognostic/predictive data (eg, MGMT methylation), and alterations relevant to targeted and immunotherapies, and germline information.

Circulating tumor DNA (ctDNA) analysis and so-called liquid biopsies from blood or CSF are showing some promising data for specific applications such as diagnosis of IDH mutant gliomas. If additional data indicate good sensitivity and specificity of these technologies for IDH and other brain tumor alterations, this approach may be particularly useful for initial diagnosis of patients with non-enhancing MRI abnormalities. In these situations, additional information from ctDNA testing may be used to suggest likelihood of diagnosis of infiltrating glioma or other brain tumor which would be useful for making the decision for early surgical intervention or initial close observation. While these technologies also have the potential to be used for monitoring disease status and perhaps indicate evidence of disease response or recurrence, or resistance to specific therapeutic agents, the data for this application in brain tumors to date are currently lacking.

Interview

John de Groot, MD

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1. How do you currently use NGS technology in your clinical practice?

Our overall goal is to utilize patient- and tumor-specific information to optimize treatment for patients with primary brain tumors. We currently use the Clinical Laboratory Improvement Amendments (CLIA) MD Anderson–developed NGS targeted sequencing panel called Oncomine for most of our newly diagnosed and recurrent glioma patients who are *trial eligible* and have undergone surgery at MD Anderson. This panel includes over 120 of the most commonly mutated genes in cancer as well as copy number alterations (CNAs). Patients operated on outside of our institution may already have NGS results, commonly from Foundation Medicine. The mutation and CNA information is primarily used to identify patient eligibility for clinical trials using molecularly targeted therapies. Mutational burden derived from NGS may also be an eligibility requirement for enrollment on some immunotherapy clinical trials.

The new World Health Organization 2016 guidelines integrate histologic diagnosis with tumor molecular markers. Although the majority of information can be obtained from immunohistochemistry (IDH1 R132H) and fluorescence in situ hybridization (1p/19q), the widespread availability of NGS testing complements the integrated pathologic diagnosis. The information used from CLIA-based testing may also be useful in the management of patients with rare mutational variants (eg, low-grade glioma harboring noncanonical mutations in IDH1 [R132C, R132G, etc] or IDH2). Additionally, the diagnosis of rare tumors may benefit from NGS testing. For example, an IDH1/2 negative lower-grade glioma with a BRAF V600E mutation may be consistent with a pleomorphic xanthoastrocytoma (PXA) and not an IDH wild-type anaplastic astrocytoma.

Additionally, we consent patients who are treated at MD Anderson to our prospective longitudinal tumor profiling protocol, which is the foundation of our research database that collects demographic, clinical, therapeutic, radiographic, and biospecimen (tumor, circulating tumor [ct]DNA, etc) NGS sequencing data. Currently, tumor tissue is subjected to a 200 gene targeted gene panel, whole exome sequencing, and RNA sequencing platforms. Although tumor and liquid biopsy data are obtained using non-CLIA NGS panels, this information can be used to identify and retrospectively analyze molecular cohorts and clinical outcomes data.

2. What are you most interested in learning from NGS?

We are most interested in learning gene mutations, CNAs (deletions and amplifications), mutational burden, and fusions. Although the latter is not yet available in our in-house panel, there are several clinical trials that enroll patients based on gene fusions (fibroblast growth factor receptor, neurotrophic tyrosine kinase receptor, etc). In circumstances where a patient treated with a targeted therapy develops progression and undergoes resection, the tumor is resequenced to identify resistance mechanisms. This may enable the patient to be treated with combination therapies to target resistance pathways.

3. What is the long-term utility of NGS in neuro-oncology?

Many challenges remain before the value of NGS can be fully realized in neuro-oncology. Tumor heterogeneity is a formidable challenge to developing effective targeted therapies for brain tumor patients. The information from NGS may provide an overall picture of target expression within the tumor, but there are also a few examples of targeted therapy that leads to clinical benefit in patients. Next-generation sequencing using single cell methodologies is being developed and may enhance the ability to optimally tailor therapies to each patient's tumor. Additionally, there are gene amplification events that occur in extrachromosomal DNA that are not being detected with NGS platforms. Another major issue in neuro-oncology relates to the difficulty in repeatedly accessing the tumor for analysis. There is a critical need to optimize blood-based ctDNA and exosomal analyses to evaluate tumor biology over time and to integrate this information with imaging, neurologic function, and clinical outcomes.

Interview

Patrick Y. Wen, MD

Director, Center For Neuro-oncology,
Dana-Farber Cancer Institute,
Professor of Neurology, Harvard Medical School

1. How do you currently use NGS technology in your practice? Eg, whole-genome sequencing (WGS), whole-exome sequencing (WES), transcriptome sequencing, and targeted gene panels and why? All patients, trial patients? For diagnosis or treatment?

For almost all patients with adequate tumor tissue, at Dana-Farber Cancer Institute, we perform a targeted NGS panel called Oncopanel that surveys exonic DNA sequences of 447 cancer genes and 191 regions across 60 genes for rearrangement detection, as well as providing information on copy number alterations and mutational burden. In addition, we usually conduct whole-genome array comparative genomic hybridization, or more recently, Oncoscan for additional copy number information. This information is used to select patients for trials with specific targeted therapies, or in the case of tumors with high mutational load, for trials with checkpoint inhibitors.

In collaboration with Accelerated Brain Cancer Cure (ABC2), our Chief of Neuropathology, Keith Ligon, is leading a multicenter study called ALLELE using WES for patients with newly diagnosed glioblastoma (GBM). We are using this especially for one of our multicenter trials called INdividualized Screening trial of Innovative Glioblastoma Therapy (INSIGhT) for newly diagnosed GBM with unmethylated MGMT. This is a biomarker-driven Bayesian adaptive design trial which utilizes the information generated by the WES from the ALLELE study for randomization of patients into specific treatment arms with targeted molecular agents.

2. What are you most interested in learning with NGS?Eg, identification of driver mutations, detection of resistance mechanisms, quantification of mutational burden, evaluation of tumor gene expression, diagnosis of germline mutations

We are interested in driver mutations, copy number alterations, gene fusions, and mutational burden primarily.

3. What is the long-term utility of NGS in neuro-oncology? Eg, to predict responders to immunotherapy, either through RNA-Seq based gene expression or mutational burden, could also drive significant clinical uptake of clinical NGS testing. Is there applicability to ctDNA for early diagnosis/more representative view of tumor heterogeneity?

In the long term it is likely that as the cost of testing continues to decrease and the turnaround time improves, most brain tumor patients will undergo NGS testing of some form. This will allow patients to be selected for specific targeted molecular therapies and immunotherapy trials. There is also growing interest in developing personalized vaccines based on the presence of neoantigens, and if these approaches are successful, the need for WES will expand.

Ideally, technology will eventually improve sufficiently to allow ctDNA to be readily detected. This will provide valuable information on the molecular alterations in the tumor and potentially allow early diagnosis as well as early detection of the development resistance.

Hotspots in *Neuro-Oncology 2017*

Riccardo Soffietti

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Chemotherapy for adult low-grade gliomas: clinical outcomes by molecular subtype in a phase II study of adjuvant temozolomide

Wahl M et al. Neuro Oncol. 2017;19(2):242–251

Optimal adjuvant management of adult low-grade gliomas is controversial. The recent update of the World Health Organization classification of brain tumors 2016, based on molecular subtype definitions, has the potential to individualize adjuvant therapy but has not yet been evaluated as part of a prospective trial.

In the February issue of *Neuro-Oncology*, Wahl and colleagues from the University of California San Francisco have published the results of a single-arm mono-institutional phase II trial on upfront chemotherapy with temozolomide for grade II gliomas after incomplete resection. Patients received monthly cycles of standard temozolomide for up to 1 year or until disease progression. For patients with available tissue, molecular subtype was assessed based upon 1p/19q codeletion and isocitrate dehydrogenase 1 R132H mutation status. The primary outcome was radiographic response rate; secondary outcomes included progression-free survival (PFS) and overall survival (OS). One hundred twenty patients were enrolled with median follow-up of 7.5 years. Overall response rate was 6%, with median PFS and OS of 4.2 and 9.7 years, respectively. Molecular subtype was associated with rate of disease progression during treatment ($P < 0.001$), PFS ($P = 0.007$), and OS ($P < 0.001$). Patients with 1p/19q codeletion demonstrated a 0% risk of progression during treatment. In an exploratory analysis, pretreatment lesion volume was associated with both PFS ($P < 0.001$) and OS ($P < 0.001$).

In conclusion, this study suggests that patients with high-risk low-grade glioma receiving adjuvant temozolomide may display a high rate of radiographic stability and favorable survival outcomes while meaningfully delaying radiotherapy. Patients with 1p/19q codeletion are potential candidates for omission of adjuvant radiotherapy, but further work is needed to directly compare chemotherapy with combined modality therapy. This important study has shown 2 main limitations. First, the response evaluation was based on Macdonald criteria with measurement of the enhancing tumor only and not on the more modern Response Assessment in Neuro-Oncology criteria, which include measurement of the non-enhancing tumor as well. Second, the predictive capacity of methylation of O^6-methylguanine-DNA methyltransferase for response to temozolomide was not analyzed.

Phase III randomized study of radiation and temozolomide versus radiation and nitrosourea therapy for anaplastic astrocytoma: results of NRG Oncology RTOG 9813

Chang S et al. Neuro Oncol. 2017;19(2):252–258

The primary objective of this multi-institutional randomized phase III study was to compare the overall survival (OS) of patients with newly diagnosed anaplastic astrocytoma (AA) receiving radiotherapy (RT) and either temozolomide (TMZ) or a nitrosourea (NU). Secondary endpoints were time to tumor progression (TTP), toxicity, and the effect of isocitrate dehydrogenase 1 (IDH1) mutation status on clinical outcome.

In the February issue of *Neuro-Oncology*, Chang and colleagues have reported the final results. Eligible patients with centrally reviewed, histologically confirmed, newly diagnosed AA were randomized to receive either RT+TMZ (n=97) or RT+NU (n=99). The study closed early because the target accrual rate was not met.

Median follow-up time for patients still alive was 10.1 years (1.9–12.6 y) and 66% of the patients died. Median survival time was 3.9 years in the RT+TMZ arm (95% CI, 3.0–7.0) and 3.8 years in the RT+NU arm (95% CI, 2.2–7.0), corresponding to a hazard ratio (HR) of 0.94 (P=0.36; 95% CI, 0.67–1.32). The differences in progression-free survival (PFS) and TTP between the 2 arms were not statistically significant. Patients in the RT+NU arm experienced more grade $\geq$3 toxicity (75.8% vs 47.9%, $P < 0.001$), mainly related to myelosuppression. Of the 196 patients, 111 were tested for IDH1-R132H status (60 RT+TMZ and 51 RT+NU). Fifty-four patients were IDH negative and 49 were IDH positive, with a better OS in IDH-positive patients (median survival time 7.9 vs 2.8 y; P=0.004, HR = 0.50; 95% CI, 0.31–0.81).

In conclusion, RT+TMZ did not appear to significantly improve OS or TTP for AA compared with RT+ NU. RT+TMZ was better tolerated. IDH1-R132H mutation was associated with longer survival.

This study is important as it suggests that for treatment of newly diagnosed AA, the choice of the alkylating agents to be associated with radiotherapy does not impact the outcome.

Point/counterpoint: randomized versus single-arm phase II clinical trials for patients with newly diagnosed glioblastoma

Grossman SA et al. Neuro Oncol. 2017;19(4):469–474

In this article, which appeared in the April issue of *Neuro-Oncology*, Grossman and colleagues discussed the pros and cons of single-arm versus randomized phase II studies in patients with newly diagnosed glioblastoma (GBM), taking into account such factors as (i) the availability of appropriate controls, (ii) the interpretability of the resulting data, (iii) the goal of rapidly screening many novel agents using as few patients as necessary, (iv) utilization of limited financial and patient resources, and (v) maximization of patient participation in these studies.

In conclusion, phase II trials are critically important in the development of novel therapies for patients with newly diagnosed GBMs. These trials represent the initial evaluation of activity in this disease and are specifically designed to triage novel compounds and approaches into those that do and do not deserve further study. While it often appears that there is a conflict between

randomized and single-arm phase II trial designs, in reality each has its place in furthering effective drug development. Since the vast majority of experimental drugs tested in patients with newly diagnosed GBM have been clinically ineffective, designing small single-arm phase II studies to eliminate ineffective therapies early is reasonable. However, larger randomized phase II trials are important to reduce confounders and false positives. Investigators should carefully consider the trial endpoint, the availability of appropriate controls, and how trial results will be used to inform further development of the experimental therapy when choosing a design. Ultimately, single-arm and randomized phase II trials (as well as adaptive and integrated designs) provide useful tools for evaluating the efficacy of novel therapeutics in newly diagnosed GBM when applied in an appropriate fashion.

Leptomeningeal metastases: a RANO proposal for response criteria

Chamberlain M et al. Neuro Oncol. 2017;19(4):484–492

Leptomeningeal metastases (LM) currently lack standardization with respect to response assessment. A Response Assessment in Neuro-Oncology (RANO) working group with expertise in LM developed a consensus proposal for evaluating patients treated for this disease. In the April issue of *Neuro-Oncology*, Chamberlain and colleagues proposed 3 basic elements for assessing response in LM: a standardized neurological examination, cerebrospinal fluid (CSF) cytology or flow cytometry, and radiographic evaluation. The group recommends that all patients enrolling in clinical trials undergo CSF analysis (cytology in all cancers; flow cytometry in hematologic cancers), complete contrast-enhanced neuraxis MRI, and in instances of planned intra-CSF therapy, radioisotope CSF flow studies. In conjunction with the RANO Neurological Assessment working group, a standardized instrument was created for assessing the neurological exam in patients with LM. Considering that most lesions in LM are nonmeasurable and that assessment of neuroimaging in LM is subjective, neuroimaging is graded as stable, progressive, or improved using a novel radiological LM response scorecard. Radiographic disease progression in isolation (ie, negative CSF cytology/flow cytometry and stable neurological assessment) would be defined as LM disease progression.

This is the first attempt to standardize the criteria for evaluating response in clinical trials on leptomeningeal diseases, and now they are being validated in several US and European prospective studies. Moreover, such a standardization may serve as a guide also in the daily clinical practice to optimize the management of this difficult category of patients.

The Neurologic Assessment in Neuro-Oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria

Nayak L et al. Neuro Oncol. 2017;19(5):625–635

The Macdonald criteria and the Response Assessment in Neuro-Oncology (RANO) criteria define radiologic parameters to classify therapeutic outcome among patients with malignant glioma and specify that clinical status must be incorporated and prioritized for overall assessment. But neither provides specific parameters to do so. A standardized metric to measure neurologic function would permit more effective overall response assessment in neuro-oncology.

An international group of physicians including neurologists, medical oncologists, radiation oncologists, and neurosurgeons with expertise in neuro-oncology drafted the Neurologic Assessment in Neuro-Oncology (NANO) scale as an objective and quantifiable metric of neurologic function evaluable during a routine office examination. Nayak and colleagues reported in the May issue of *Neuro-Oncology* the proposal for a NANO scale, which was tested in a multicenter study to determine its overall reliability, interobserver variability, and feasibility.

Overall, the NANO scale is a quantifiable evaluation of 9 relevant neurologic domains based on direct observation and testing conducted during routine office visits. The score defines overall response criteria. A prospective, multinational study noted a $>$ 90% interobserver agreement rate with kappa statistic ranging from 0.35 to 0.83 (fair to almost perfect agreement), and a median assessment time of 4 minutes (interquartile range, 3–5). This new scale should be validated in prospective clinical trials in the different brain tumor subtypes.

Natural course and prognosis of anaplastic gangliogliomas: a multicenter retrospective study of 43 cases from the French Brain Tumor Database

Terrier LM et al. Neuro Oncol. 2017;19(5):678–688

Anaplastic gangliogliomas (GGGs) are rare tumors whose natural history is poorly documented. In the May issue of *Neuro-Oncology*, Terrier and colleagues on behalf of ANOCEF tried to define their clinical and imaging features and to identify prognostic factors by analyzing all cases of GGGs in the adult prospectively entered into the French Brain Tumor Database between March 2004 and April 2014. After diagnosis was confirmed by pathological central review, clinical, imaging, therapeutic, and outcome data were collected retrospectively.

Forty-three patients with anaplastic GGG (median age, 49.4 y) from 18 centers were included. Presenting symptoms were neurological deficit (37.2%), epileptic seizure (37.2%), and increased intracranial pressure (25.6%). Typical imaging findings were unifocal location (94.7%), contrast enhancement (88.1%), central necrosis (43.2%), and mass effect (47.6%). Therapeutic strategy included surgical resection (95.3%), adjuvant radiochemotherapy (48.8%), or radiotherapy alone (27.9%). Median progression-free survival (PFS) and overall survival (OS) were 8.0 and 24.7 months, respectively. Three- and 5-year tumor recurrence rates were 69% and 100%,

respectively. The 5-year survival rate was 24.9%. Considering unadjusted significant prognostic factors, tumor midline crossing and frontal location were associated with shorter OS. Temporal and parietal locations were associated with longer and shorter PFS, respectively. None of these factors remained statistically significant in multivariate analysis.

In conclusion, this is a large series providing clinical, imaging, therapeutic, and prognostic features of adult patients treated for an intracerebral anaplastic GGG. Our results show that pathological diagnosis is difficult, that survivals are only slightly better than for glioblastomas, and that complete surgical resection followed by adjuvant chemoradiotherapy offers longer survival. It will be important in future studies to investigate new molecular markers (such as BRAF mutations) that could serve as targets for molecular drugs.

Hotspots in *Neuro-Oncology Practice 2017*

Susan Marina Chang, MD

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(1) Sabel M et al. Effects of physically active video gaming on cognition and activities of daily living in childhood brain tumor survivors: a randomized pilot study. Neuro-Oncology Practice 2017;4(2):98–110

Carlson-Green B et al. Feasibility and efficacy of an extended trial of home-based working memory training for pediatric brain tumor survivors: a pilot study. Neuro-Oncology Practice 2017;4(2):111–120

In recent years there has been a significant research effort focused on developing effective interventions aimed at cognitive rehabilitation for children with brain tumors. The article by Sabel et al describes a pilot study on a physical exercise regimen that can be done at home using a video console. While the small study did not show difference in cognitive function before and after intervention, activities of daily living scores were significantly improved, providing a rationale for further exploration of physical exercise as a component of overall rehabilitation. The authors suggest that it may be combined with other active tasks to challenge cognitive ability, possibly for an extended period of time with modulated intensities, and tested in an adequate patient sample.

The article by Carlson-Green et al provides results of a feasibility study using the platform Cogmed® to improve neurocognitive function in children who have been treated for a brain tumor. They found that participants largely enjoyed performing the tasks and that there was significant improvement in working memory, verbal tasks, and visuo-spatial tasks between baseline and 6-month post-intervention scores. Parents also reported improvement in participants' academic and social skills. As with the physical exercise regimen reported by Sabel et al, Cogmed is a home-based intervention, and the inherent flexibility and convenience that it provides has been found to improve compliance.

(2) Hovey EJ et al. Continuing or ceasing bevacizumab beyond progression in recurrent glioblastoma: an exploratory randomized phase II trial. Neuro-Oncology Practice 2017;4(3):171–181

Patients with high-grade glioma are often prescribed bevacizumab at recurrence as part of standard care. However, the question of whether to continue with the therapy (possibly combined with another drug) after further relapse has been a subject of debate among clinicians, with little data to guide practical decisions. The Cabaraet study investigated this important clinical question, and the investigators came to the conclusion that patients who continued bevacizumab beyond disease progression did not have clear survival benefits. This is a highly relevant study for any provider treating patients with glioma.

(3) Likar R, Nahler G. The use of cannabis in supportive care and treatment of brain tumor. Neuro-Oncology Practice 2017;4(3):151–160

Cannabis has a long history as an intervention for cancer pain and in controlling common negative effects of both treatment and tumor. It has been widely used to treat a variety of symptoms, including nausea and vomiting, loss of appetite, mood disorders, and sleep disorders. In this comprehensive review, the authors delve into this history and provide a specific discussion of the different types of cannabinoids and how they may best be used in neuropalliative care. A shift in cultural attitudes towards psychotropic drugs in medicine has led to a resurgence in studies on these compounds, and it is critical for providers to have accurate information when guiding patients who are interested in exploring these therapies.

(4) Dirven L et al. Development of an item bank for computerized adaptive testing of self-reported cognitive difficulty in cancer patients. Neuro-Oncology Practice 2017;4(3):189–196

A common theme in papers examining quality of life is a lack of standardized definitions and assessments, which are essential for making useful comparisons across studies. The professional societies in neuro-oncology are in the best position to make improvements in this area by creating validated tools that can be widely adopted in the neuro-oncology community. This article by Dirven et al—on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group—describes development of a computerized adaptive testing version of each scale of the EORTC Quality of Life Questionnaire (EORTC QLQ-C30). Cognitive deficits are an especially important problem for patients with brain tumor and having an easy-to-use tool facilitates acquisition of data elements that can be used for analysis.

(5) Page MS, Chang SM. Creating a caregiver program in neuro-oncology. Neuro-Oncology Practice 2017;4(2):116–122

This article describes the building and implementation of a dedicated neuro-oncology caregiver program at the University of California, San Francisco. The program has a structure of providing general information to all "new to the clinic" newcomers, proactive extra interventions to caregivers of "newly diagnosed glioblastoma" patients, additional support to a "high-risk transition" group—particularly with reference to their needs of possible palliative and hospice care—and finally a "bereavement" group for counseling and emotional support. An initial evaluation of the program demonstrated that the newly diagnosed glioblastoma and high-risk transition groups had the highest needs, primarily in emotional support and advocacy issues. Overall, the program received positive feedback from caregivers and the authors intend to strengthen their services with more staff, including a dedicated neuropsychologist, and more in-depth interventions in several key areas identified in their preliminary findings.

(6) Pugh S. Essence of survival analysis. Neuro-Oncology Practice 2017;4(2):77–81

One of the most popular features of *Neuro-Oncology Practice* is "Statistics for the Practicing Clinician"—a series

of articles covering statistical methods used in neuro-oncology studies and how to interpret statistical results in order to appropriately counsel patients. In this article, statistician Stephanie Pugh focuses on survival analyses, explaining calculations for both progression-free and overall survival analyses and how to interpret estimates of these critical endpoints that are used in a majority of clinical trials. It also includes the rationale for censoring data from patients lost to follow-up and a detailed explanation of hazard models with illustrative case examples.

The EANO Youngster Initiative: What Does Mentoring Mean to You?

Anna Sophie Berghoff, MD, PhD

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Career development for neuro-oncology youngsters is a main focus of the recently founded EANO youngsters committee. With mentoring being an essential part of every youngster's personal career development, we aim to put a special focus on this topic.

"How to find a good mentor" as well as "how to get most out of your mentoring" are questions every youngster addresses frequently. Therefore, we aim to focus on this essential topic during the EANO youngster track of the upcoming EANO congress 2018. To get started we asked ourselves as well as our mentors "What does mentoring mean to you?" Find enclosed our answers and our mentors'.

Carina Thomé, biologist currently holding a postdoctoral fellow position at the German Cancer Research Center (Heidelberg, Germany)

- Transfer skills and knowledge in science but also in non-science related issues
- Regular meetings and constructive feedback
- Establish and helping with contacts and networks in and outside the community
- Opportunity to present and discuss results and data in the community
- Open minded for new input; however, take, handle, and tolerate criticisms

Wolfgang Wick (mentor of Carina Thomé), head of the neurology department, University of Heidelberg, Germany

- Time for interaction outside the daily working routine
- Time for discussion on conference topics while being at a conference
- Activating an international network for the mentee
- Training of specific skills for presentation, etc.
- Finding role models
- Supporting activity in the neuro-oncology community

Alessia Pellerino, neurology from the University of Turin and her mentors Riccardo Soffietti (head, Dept. Neuro-Oncology, University and City of Health and Science University Hospital of Turin, Italy) and Roberta Rudà (head of the Outpatient Service and Multidisciplinary Brain Tumor Board, City of Health and Science Hospital/University of Turin)

- Since I was a young resident in neurology, my mentors taught me a method in clinical and research practice: they taught me to lead the clinical trials with ethics and intellectual honesty. They remind me to respect patients and their families. Their examples and their careers inspire me and make me love my daily work.
- My mentors gave me the theoretical and practical knowledge to reach a progressive independence as a neurologist through the years. In case of difficult situations, they always stay available for advice and help. They never leave me in troubles and help me to face complications.
- My mentors require hard work and dedication from their team and gave to all collaborators the opportunity to participate in national and international meetings and develop several projects, and write original papers and reviews.
- My mentors know that there are other great neurologists and neuro-oncologists in Europe and the US: in this regard, they stimulate and support young researchers to go abroad in order to share knowledge and gain new stimulating experiences.
- My mentors continuously tell me that an excellent clinical activity needs to be fed and supported by basic and translational knowledge and research.
- My mentors always tell me that a good daily practice should be guided by an adherence to validated international guidelines.

Aleksandar Stanimirović, neurosurgery resident at the clinical center of Serbia

- Giving time and attention to the mentee. A good mentor should always find time to give something back
- Teaching the mentees to keep an open mind to all progress in modern medicine
- Give hope and hold the fear of the mentee, showing him/her to trust in the decisions that are being made and not to be afraid of failure. The mentee must never be paralyzed by the fear of failure or he/or she will never push in the direction of the right vision
- Mustn't be a naysayer
- At the end of the day a good mentor leaves behind outstanding people and doctors, and the field of interest in a better state than it was when he/she began

Dr Danica Grujičić (mentor of Aleksandar Stanimirović), head of the neuro-oncology department of the Clinic of Neurosurgery at the Clinical Center of Serbia

- Transfer of knowledge in a sense of continuous and non-stop patient observation and patient controls
- Training junior colleagues and teaching them different surgical techniques
- Teaching mentees the principles of radio and chemotherapy for brain tumors
- Stimulating younger doctors to better organize the medical care for neuro-oncology patients
- Insisting upon making and publishing scientific papers based on personal and recent experiences

Amelie Darlix, neuro-oncologist at the Montpellier Cancer Institute (France)

- Encourage me to think by myself rather than impose his/her views
- Share his/her clinical experience
- Define short-term and long-term goals with me, in terms of research, scientific publications, and career

- Brainstorm with me in order to make new ideas and projects emerge
- And celebrate successes!

Emilie le Rhun (mentor of Amelie Darlix), neuro-oncologist at Centre Hospitalier Régional et Universitaire (CHRU) de Lille, France

- To help to develop new ideas and translational research projects
- To help to develop a clinical specialty profile
- To define career plans with milestones
- To discuss emerging areas of basic and translational research
- To re-evaluate progress annually

Anna Berghoff, medical oncology trainee at the Medical University of Vienna, Austria

- Show possibilities and guide career development
- Mentoring in a "see one, do one, teach one" manner and encourage mentee to also mentee him/herself younger students (MD students)
- Help with practical question like scholarships or grant applications
- Be patient (especially in the early steps)

Matthias Preusser (mentor of Anna Berghoff), neuro-oncologist at the Medical University Vienna, Austria

- To guide and help develop skills and a personal style. The goal is not to produce a clone of the mentor but persons with their own ideas and ways of thinking and working
- To give advice that is in the best interest of the mentee, even if it is not in the mentor's best interest
- To change the way of mentoring over time to allow a gradual development of the mentee. At some point the mentee should become a mentor on his/her own.
- To be open to learn from the mentee
- Let the mentee make his/her own experiences, including mistakes, but in a positive way

Asgeir Jakola, neurosurgeon and associate professor at the Sahlgrenska University Hospital, Gothenburg, Sweden

- Improves the student's learning and a great opportunity to impact the organization
- Teaches the student how to speak up and be heard = improved communication skills
- Educates the student how to receive constructive feedback in important areas
- Improves the student's interpersonal relationship skills
- Helps the student better understand the organization's culture and unspoken rules, both of which can be critical for success

Roger Henriksson (mentor of Asgeir Jakola), head of the Regional Cancer Centre Stockholm/Gotland

- Listen actively, not only to what's been said but also to what's not said
- Trust the student in finding the best solution for solving problems, but be supportive
- Be curious, ask questions rather than give answers
- Help the student to see things from the positive side, point out the strengths
- Be generous with yourself, your feelings and your experiences

Tobias Weiss, neurology resident at the University Hospital in Zurich, Switzerland

- Strategically guide/support the mentee to reach his/her short- or long-term goals
- Availability and responsiveness
- Bridge contacts and help to establish new networks or integrate into existing structures
- Help to find, judge role models
- Open-minded to continuously improve

Michael Weller, chairman of the Department of Neurology, University Hospital in Zürich, Switzerland

- Promoting focused research of high quality
- Supporting innovative research ideas
- Promoting international cooperation and networking
- Developing excellence in specialized areas of patient care
- Promoting educational and presentation skills