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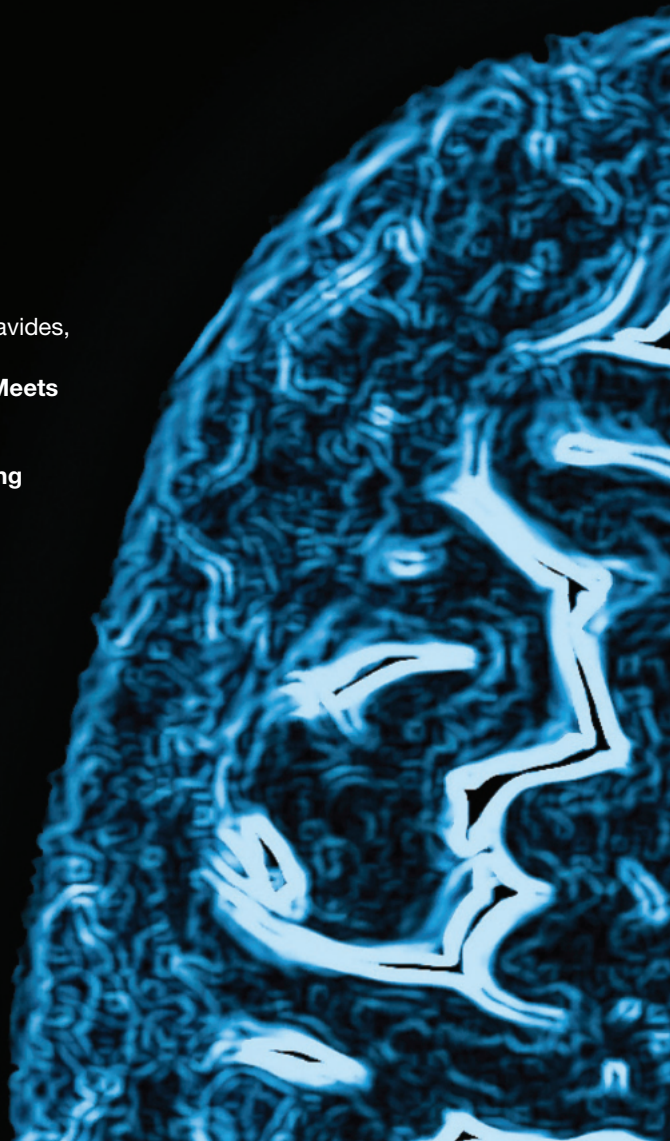
World Federation of Neuro-Oncology Societies magazine

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



World Federation of Neuro-Oncology Societies magazine

Editorial

Dear international neuro-oncology community, dear users of the magazine,

over the past years, the WFNOS magazine has evolved into a publication of activities within WFNOS, portraits of national neuro-oncology societies, as well as news and views from our field in perspectives that may not be seen in regular scientific journals. In addition, we made the effort to provide you with high-quality reviews, focus articles, and opinion papers from several areas of our field. This peer-reviewed activity cost the biggest effort and—in hindsight—might have stretched the mission of the magazine too far.

In the view of all of you—by your usage of the content—and the critical discussions in the boards of EANO and SNO as well as discussions amongst the WFNOS members, the main appeal of the magazine is to picture international activities, collaboration, and brief news and views in neuro-oncology. We seem not to benefit from another source of original or review papers. Instead, for this scientific information we prefer to rely on the main journals—*Neuro Oncology* and *Neuro Oncology Practice*. There is also increasing demand for some short, real-time interactions in a structured format outside the main meetings.

With this diagnosis, the next step seemed logical. From 2019 on, we will provide you with most of the content of the magazine, but enhanced day-to-day information without a formal regular article section on a new website. Responsibilities, teams, and most importantly the international structure will remain; we will hopefully involve some of you with a clear vision, how a WFNOS website should allow communication, what information is suitable, and what content may be better placed elsewhere. Most importantly, the main focus remains quality, interprofessional and international appeal, as well as adherence to the mission of the WFNOS.

At this stage, it is my great need to thank the handling editors Roberta Rudà and Nick Butowski, the national editors, and the production team. We will continue their work in the new format.

For now, I look forward to receiving some feedback on the plan to enhance the WFNOS magazine to the next level, and remain with kind regards,

Wolfgang Wick

EANO President 2016–2018

Editorial

Dear Friends and Colleagues in Neuro-Oncology,

I would like to invite you to read the second issue of the WFNOS Magazine for 2018. The editors have again produced another outstanding edition highlighting important areas of neuro-oncology. These include updates from the 2018 ASCO meeting, highlighted papers from *Neuro-Oncology* and *Neuro-Oncology Practice*, synopsis of the EORTC phase III trial of the proteosome inhibitor marizomib with standard of care, the Dutch approach to the use of protons, and reports from the Spanish Group for Research in Neuro-Oncology (GEINO) and the Egyptian Group for Neuro-Oncology (EGNO). In addition, there is an interview with Susan Chang providing career advice, and advice from Ingela Oberg on the important issue of how to break bad news.

This year's SNO meeting on November 15–18 will be in New Orleans and will focus on clinical trials. The hope is that Education Day and the Scientific Meeting will help participants improve the quality of the trials that they are conducting. In addition, a major emphasis will be on increasing the accrual into these clinical trials. A large task force has been working on identifying the barriers to clinical trials accrual and proposing strategies to overcome these issues. A townhall at SNO will allow these findings to be presented and feedback to be obtained from the neuro-oncology community. Another focus is to increase the participation of nurses, physician assistants, and other allied health workers in the meeting, and additional events and content have been specifically developed on November 14 for them. We hope that many of you can join us at this meeting.

Patrick Y. Wen

SNO President

Success Through Mentorship, Opportunity, and Teamwork

Susan M. Chang, MD

Director, Division of Neuro-Oncology, Department of Neurological Surgery, University of California, San Francisco (UCSF)

In 2017 I had the honor of being selected by the Society for Neuro-Oncology as the recipient of the distinguished Victor Levin award. I saw this as a great opportunity to acknowledge and thank my mentors, collaborators, and colleagues who have encouraged and supported me along my career. I am often asked by junior faculty and trainees about what I see as the keys to success in our field, and I thought that this would be an appropriate venue to address that topic and share my experience around the evolution of my career. Ultimately, I believe that achieving success hinges on three things: effective mentorship; the ability to recognize and seize opportunities; and the capacity to work as part of a team. You may have a brilliant mind and a strong work ethic, but without those three ingredients, I think it's difficult to get to a place where you can really make a significant impact.

Dr. Victor Levin

Beginning with mentorship, it was especially meaningful to receive the Victor Levin award, as Dr Levin was really instrumental for not only building the neuro-oncology program at UCSF but the whole field. I remember first meeting him in 1996 at the inaugural SNO meeting and being impressed with his passion and energy to find new treatments for patients, something that he continues to pursue. I think that one of the things that also distinguishes him is that he has done so much to educate and mentor others in the field. In 1995 I submitted a review on chemotherapy for glioma to *Current Opinions in Oncology*, for which Dr Levin was the editor. He sent me a letter thanking me for my contribution. It was really a proud moment in my early career, and receiving the award named in his honor from him was a true privilege.

Dr. Ian Tannock with the editions of the "Basic Science of Oncology" textbook

The importance of mentorship is exemplified by Dr Ian Tannock, who guided me during my fellowship in medical oncology at the Princess Margaret Cancer Center in Toronto. Beyond his innate ability as a wonderful educator, he had a great love of continued learning and would never accept that things could not be improved upon. Dr Tannock remains one of the most influential figures in my work not only because he was the person who introduced me to the challenges of clinical trial design, but because he also instilled in me the concept of translational research. As a clinician he authored a textbook on the basic science in oncology and he really impressed upon me the importance of not divorcing the clinical entity from the

underlying science. As a result of that, when I became a neuro-oncologist at UCSF, I would attend the Costello lab meetings and participate in their journal club so that I would know what was happening on the research side. This also allowed me to share the clinical aspect of the disease with the scientists. And I think that has served me incredibly well, not just for leading an oncology program that is deeply entrenched in translational work, but also for building relationships beyond my immediate clinical colleagues that ultimately help us get over hurdles in bringing improvements to patients.

I joined UCSF in 1992 as a neuro-oncology fellow and had the very good fortune to be mentored by an incredible team, which included Mike Prados and Dr Charlie Wilson. I was impressed by how inclusive Mike was about engaging members to work on projects and the incredible focus of Dr Wilson and his drive to get results. Around this time I participated in a teaching scholars course where I had to complete a questionnaire asking what my career goals might be. And looking back, I had quite a low bar—"design and conduct clinical trials in Neuro-Oncology, publish an article in JCO and give a presentation at ASCO."

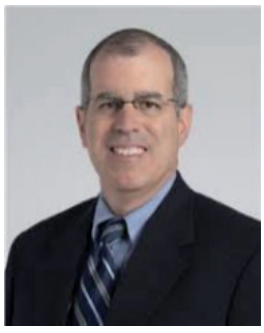
It was such a low bar that by 1998, together with Mike Prados and a great group of collaborators at the North American Brain Tumor Consortium, I was already the PI of several clinical trials, published a paper in JCO, and was able to present the results of the work at ASCO. Having accomplished those early goals, I realized there was still much to do, especially because 10 years later, despite the promise of targeted therapies, we were faced with so many negative results. I continue to be involved in the development of new treatments with my colleagues at UCSF and through consortium-based studies.

As I gained experience in the field, I became interested in how we were assessing response to therapy in our patients and some of the challenges we were facing. In 1996 I wrote an application to attend the inaugural joint ASCO-AACR workshop on Methods of Clinical Cancer Research, or what I considered a boot camp, in which I outlined the fact that what we were seeing on the MRIs after therapies was not always an accurate reflection of the biology—it was often a transient treatment effect, and it was a major obstacle to directing appropriate therapy, evaluating response to treatments, and determining valid clinical endpoints. This problem remains a major challenge for the field. At a meeting in Barcelona in 2008, Martin Van den Bent and Patrick Wen and I began having some informal discussions around what we were seeing in MRIs following treatment with bevacizumab. We recognized that there was both a need and an opportunity to initiate a major shift in the field. So with David MacDonald and Mike Vogelbaum, we formed the Response Assessment in Neuro-Oncology (RANO) executive committee and began working on guidelines for clinicians to use to interpret these often misleading imaging findings.

With any large-scale changes to everyday clinical practice, one of the biggest hurdles is reaching a consensus. And RANO was no exception. These were difficult problems and it was critical that everyone agreed with how to address them. I cannot understate the importance of inclusivity in this setting and giving everyone a chance to be heard. So while consensus did not necessarily come easily, the collaborative spirit of this group, the willingness to volunteer time, effort, and expertise, and our ability to work together carried the day. The resulting guidelines for high-grade glioma were published in 2009 to supplement the MacDonald criteria, followed by subsequent multiple guidelines that deal with so many aspects of neuro-oncology. I'm especially proud of being a part of this community of colleagues and the RANO effort is a career highlight for me.

There are so many other instances about how critical teamwork is to success. On a local level, our Department holds a Program Project Grant that has been funded since the 1970s and a CNS Specialized Program of Research Excellence (SPORE) award from the National Cancer Institute (NCI) that has been funded since 2002. The continuous success of these programs has all to do with Dr Berger's leadership and this incredible team and



Members of the
Response Assessment in Neuro-Oncology
(RANO)Executive Committee
Martin Van den bent, Patrick Wen, David Macdonald, Michael Vogelbaum

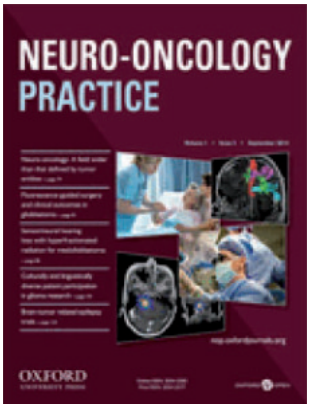
our culture of collaboration. We genuinely have fun working as a team, which makes the work seem less onerous and taxing. A major focus of these intra-programmatic awards has been to advance novel neuroimaging technologies, and I am fortunate to serve as co-PI with Dr Sarah Nelson on several noninvasive imaging studies, and she has been a brilliant collaborator and friend. Our group is especially interested in imaging metabolic and physiologic changes within a tumor that may be able to give us an earlier indication about progression or response to treatment than can currently be achieved with standard MRI. Instituting standard operating procedures to identify patients, acquire the multiparametric images, and procure image guided samples was critical in serving as the basis for numerous studies. We were able to show the value of these tools in detecting changes, culminating with the first-in-patient hyperpolarized carbon 13 imaging of a brain tumor last year. Partnering with the lab of Joe Costello, we have since added genomic data to the rich patient cohort. These are methods that we continue to be really excited about and I believe are going to have a profound impact on our ability to diagnose patients and guide treatment.

A clear example of mentorship, opportunity, and teamwork that has had a major impact on my career is my involvement in SNO. In 1998, Dr Berger was the president of SNO and the meeting was hosted in San Francisco. He asked me to lead the meeting. It was an opportunity that I was initially apprehensive about, since I had not organized any meeting before, but Dr Berger reassured me that I would be fine. Jan Esenwein was instrumental in guiding me through that meeting. Accepting that first step to take on something that may seem like an isolated event or project can often spark a chain of other doors to open, and that was the case with my leading the meeting in 1998.

Since then, through my involvement with SNO, I have been able to serve on the Board of Directors in several roles, including being President of the society. Through his amazing example, Ab Guha instilled in me the serious need for us to be more integrated globally in order to share advances and information. During my own SNO presidency, one of my biggest priorities was to build a larger and more integrated international coalition of physicians and researchers. Working with Chas Haynes and EANO and ASNO leadership, the World Federation of Neuro-Oncology Societies (WFNOS) was created and we began sending a SNO representative to the ASNO and EANO meetings every year and vice versa, which increased international attendance at all these meetings overall, instead of just getting together every four years at the WFNOS meeting.

I am grateful to so many of my international colleagues from EANO and ASNO whose friendship has enriched my life. These collaborations foster international fellowships and educational opportunities, exposing trainees across the globe to different modes of practice. But one of the biggest advantages about global teamwork is that we are seeing more multi-site international clinical trials and more data sharing, which exponentially increases our knowledge base.

In 2012, Al Yung, then editor-in-chief of *Neuro-Oncology*, asked me to serve as the editor of a special international supplement dealing with practical issues in neuro-oncology and topics related to quality of life and survivorship. Again this was a small opportunity, but one that I really wanted to take on because there was a need for more of this type of information for the global community. SNO had already acknowledged the importance of these issues and had a QoL component to the education day. But we did not realize just how much it was needed. It



Executive editors for Neuro-Oncology Practice
EANO- Wolfgang Grisold
SNO-Jeffrey Wefel
ASNO- Rakesh Jalali

quickly became one of the most downloaded and cited issues of the journal, and in 2014, SNO and Oxford University Press invited me to be the editor-in-chief of *Neuro-Oncology Practice*, a new journal which would be dedicated to publishing articles on quality of life, survivorship and caregiver issues, and applying the results of clinical trials to everyday practice. One of the most important aspects of this journal is that my co-editors from SNO, EANO, and ASNO help to solicit articles from their respective regions and it has really become an incredible resource and learning tool for the international community.

The opportunity to serve on other teams has been another rewarding aspect of my career. Several of these include service to the NCI and scientific advisory boards of many philanthropic foundations, such as the Sontag Foundation, the American Brain Tumor Association, Cancer.net (the patient portal for ASCO), the National Brain Tumor Society, and the Brain Tumor Charity. Working with such dedicated groups whose mission is to improve the care of our patients through patient and caregiver education and resources, to support the research efforts in neuro-oncology, and to invest in the future careers of young investigators of the field has extended my community of friends and colleagues.

While working on clinical trials, publishing in JCO, and presenting at ASCO fulfilled my initial ideas of success, I remained focused on issues related to the quality of life of my patients. Kris Hardin was one of my patients who found joy and comfort in painting beautiful and colorful pieces, and her artwork adorns our clinic space, reminding us that while we strive to improve survival for our patients, optimizing their quality of survival is paramount in the care we provide.

Over the past several years I was presented with some very big opportunities on that front and have also come to realize that teamwork really extends beyond working with my colleagues. Our patients and their caregivers are very much a part of the team, and without their help and support we would never be able to make progress. Of course this is exemplified at every scientific meeting through their courage and altruism in their willingness to participate in clinical trials, as well as through partnerships to advance research and education. But they also keep us focused on—to quote Jashiri Blakely—the "heart and soul of neuro-oncology," the needs of the patient and caregiver. With the generous support of Sheri Sobrato Brisson and working with my colleagues Drs Hervey Jumper and Oberheim Bush, we have initiated a new survivorship program that combines neuro-oncology, neurosurgery, neuropsychology, physical and integrative medicine, and psycho-oncology. This is what I hope the future will be for all patients undergoing treatment anywhere in the country.

I was also given the opportunity to launch a program specifically for caregivers at UCSF. The UCSF Neuro-Oncology Gordon Murray Caregiver Program is named for one of our patients, Gordon Murray, whose family

Kris Hardin and examples of her Beautiful paintings

and close friends came to us and spearheaded the idea. This involves not only providing caregivers with practical resources and support groups, but also reaching out to them at known points of stress throughout the trajectory of the illness to help with difficult transitions. We have also supported the Milton Marks family camp for the last four years focused on patients who have young children in the home, offering a fully supported weekend of fun, relaxation, counsel, and community. It has been an unbelievably rewarding experience to be able to launch this program, and the effect that it has had on our patients and their families has been wonderful. This was entirely funded through philanthropy, and with the help of my colleague Margaretta Page, we now have a program that provides an additional layer of support to caregivers. We hope this model can become the standard for all practices, nationally and internationally.

I am so fortunate to work with my current team at UCSF, with colleagues who have an incredible passion and commitment to the care of patients and clinical research. I now find myself in the position of mentoring others and I hope to be able to pay forward all the wonderful mentorship I myself received over the years, to pass on opportunities for others to seize, and to continue to promote the collaboration and teamwork without which we would achieve so little. And finally I'd like to express my enormous gratitude to my family—my mom, aunt, and children and especially my husband Doug—whose unwavering love and support throughout my career and genuine enthusiasm for my work have provided the base for all of my success.

The Spanish Group for Research in Neuro-Oncology (GEINO): Past, Present, and Future Perspective

María Martínez-García,[1] Juan Manuel Sepúlveda,[2] and Manuel Benavides,[3] on behalf of GEINO

[1]Medical Oncology, Hospital del Mar, Barcelona, Spain;
[2]Medical Oncology, Hospital 12 de Octubre, Madrid, Spain;
[3]Medical Oncology, Hospital Carlos Haya, Málaga, Spain.

The Spanish Group for Research in Neuro-oncology (GEINO) was founded in November 1998 as a result of the enthusiasm of a group of professionals. The group was initially created by specialists in medical oncology under the name of GENOM (Spanish Group of Medical Neuro-Oncology), and in October 2010 it was renamed GEINO, reflecting its actual spirit of multidisciplinarity and with the intention to gather all specialists involved in the management of and research in neuro-oncology. In February 2002, it obtained official recognition as a nonprofit scientific society. Currently, more than 80 hospitals from all over Spain are active members of the group. GEINO is composed of more that 250 researchers from different specialties across the country (Figure 1). The official website is www.geino.es.

The aims of the group are:

- Promote high standards of quality of care for neuro-oncology patients
- Develop clinical and translational research in the field
- Provide continuous training for professionals

Quality of care in neuro-oncology

As part of its interest in improving the quality of the management of patients affected by these diseases, GEINO has developed guidelines and protocols that can be found on the group's website and that have been recently updated. The GEINO guidelines include:

- Low-grade glioma guidelines
- Malignant glioma guidelines
- Anaplastic astrocytoma guidelines
- Anaplastic oligodendroglioma and oligoastrocytoma guidelines

Furthermore, GEINO, as part of the aim of providing high quality of care all over Spain, receives patient consultations online, offering a service that tries to help those affected by central nervous system tumors.

Clinical and translational research

The development of academic and investigator initiated clinical trials has been one of the earliest fundamental interests of the group. So far, 14 clinical trials have been carried out by GEINO. Currently 4 clinical trials are open and actively recruiting patients (Table 1).

The group has been also committed to donate research grants for which all GEINO members can apply. To date 6 GEINO research grants have been awarded (Table 2).

This passionate clinical and translational research has resulted in several publications during the past years, some of which are summarized here (see references).

Academic conferences and courses

GEINO is committed to education and continuous training for professionals, and as part of this task, organizes several scientific meetings, including the GEINO Educational Symposium. This annual meeting has national and international participation, and the main interest is to report advances and research findings in the field of neuro-oncology. So far 9 editions have been accomplished, and we are looking forward to the next symposium, which will be held in Barcelona on November 29 and 30, 2018. The group is also proud of

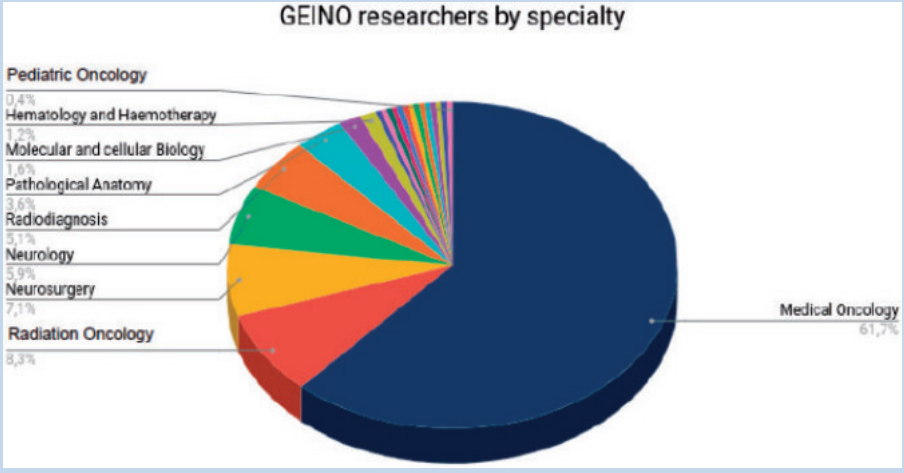


FIGURE 1. GEINO members by specialty

Table 1. Ongoing GEINO Clinical Trials

STUDY NAME	TITTLE
OLIGO-PALBO GEINO 13	Safety and Efficacy of PD0332991 (Palbociclib), a Cyclin-dependent Kinase 4 and 6 Inhibitor, in Patients With Oligodendroglioma or Recurrent Oligoastrocytoma Anaplastic With the Activity of the Protein RB Preserved (NCT02530320)
TEM 6-12 GEINO 14-01	Phase IIB randomized, multicenter, of continuation or non-continuation with 6 cycles of Temozolomide after the first 6 cycles of standard first-line treatment in patients with glioblastoma (NCT02209948)
CRIZO-GLIO GEINO 14-02	Phase Ib, open-label, multicentre, dose-escalation study, followed by an expansion phase to asses the safety and activity of the combination of Crizotinib with Temozolomide and radiotherapy in patients with newly diagnosed glioblastoma (NCT02270034)
GEINOCANN-GEINO 16-01*	Phase Ib clinical trial, multicenter study to evaluate the combination of THC - CBD with Temozolomide and radiotherapy in patients with newly diagnosed glioblastoma (NCT03529448)
GEINOGLAS GEINO 16-02	Phase Ib/ randomized phase II Study Combining Glasdegib (SHH pathway inhibitor) with temozolomide in patients with newly diagnosed Glioblastoma (NCT03466450)

*Not yet recruiting

Table 2. GEINO research grants

YEAR	TITTLE	RECIPIENT
2012	Histological, radiological and molecular analysis of the response to bevacizumab in patients with relapsed glioblastoma. Search for predictive markers	Dr. Hernández-Laín. Hospital Universitario 12 de Octubre, Madrid
2012	Possible utility of early pre-RDT magnetic resonance imaging (PRMR) for the monitoring of high-grade gliomas	Dr. Majós. Hospital Universitario de Bellvitge, Barcelona
2013	Study of circulating endothelial cells in glioblastoma, prognostic and clinical value	Dr. Vaz. Hospital Universitario Ramón y Cajal, Madrid
2014	Study of the secretome in immunohistological subtypes of glioblastoma and in long- and short- term survival groups	Dr. Reynés. H. U. La Fe, Valencia
2015	Study of the MGMT methylation status by pyrosequencing in patients with glioblastoma (GBM) included in the GENOM 009 trial	Dr. Balañá. ICO Hospital Universitario Germans Trias i Pujol, Barcelona
2016	Mutational status of IDH and expression of immunoregulatory factors in circulating tumor DNA and correlation with the primary tumor in patients with glioma	Dr. Cabezas. Hospital Clínico Universitario San Carlos, Madrid

its neuro-oncology course, of which 13 annual editions have been held, gathering every year almost 100 participants from different specialties (Figure 2). GEINO has also organized several online seminars and workshops during the past decades, with the aim of updating the latest advances in the field.

Relationship with other scientific societies

GEINO is registered as a cooperative group within the Spanish Society of Medical Oncology (SEOM). Moreover, GEINO collaborates with other Spanish scientific societies such as:

- SEN (Spanish Society of Neurology)
- SEAP-IAP (Spanish Society of Anatomical Pathology)
- SENEC (Spanish Society of Neurosurgery)
- SENR (Spanish Society of Neuroradiology)
- SEMN (Spanish Society of Nuclear Medicine)

The group also undertakes several initiatives with patient associations, for example, ASATE (Spanish Association of Patients with Brain Tumors) and IBTA (International Brain Tumour Alliance).

GEINO members attend scientific meetings held by EANO, WFNOS, and other important neuro-oncology societies. There is a common interest to consolidate the collaboration with WFNOS, EANO, as well as other neuro-oncology groups, in order to join efforts in the fight against these terrible diseases.

FIGURE 2. Conferences and courses
GEINO Neuro Oncology course 2014. Madrid, Spain.

FIGURE 2. Conferences and courses
GEINO Symposium 2015 Madrid, Spain. Organizing committee and guest speakers.

FIGURE 2. Conferences and courses
GEINO board meeting May 2018 Madrid, Spain.

References: some of GEINÓs international publications

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The Egyptian Group of Neuro Oncology (EGNO): the History Meets the Future

Khaled Abdel Karim, MD, PhD

Professor of Clinical Oncology, Ain Shams University, Cairo, Egypt

Secretary General of the EGNO

How did we start?

Ten years ago, neuro-oncology practice in Egypt was of interest to merely a few Egyptian oncologists. A group of leading pioneers in cancer management in the country gathered in April 2008 to form EGNO as part of the parent Egyptian Cancer Society (ECS). This was the first step toward gaining recognition of such a specialty in a country with 90 million inhabitants with years of struggling to establish a national cancer registry, and throughout the past decade EGNO tried to fulfill its goals along many tracks.

The role of EANO

EGNO has evolved gradually from being an idea to becoming an initiative after many of its founding members started to participate in the meetings of the European Society of Neuro Oncology (EANO) in 2010. Many Egyptian neuro-oncologists became EANO members and were therefore part of the formation of the World Federation of Neuro-Oncology Societies (WFNOS), which was meant to be an international platform for collaboration among neuro-oncology societies around the world.

Spreading the specialty and MDT

EGNO inspired the formation of the first specialized neuro-oncology academic unit in Ain Shams University, which is one of the top universities in Egypt, in 2010. This unit gathered a group of dedicated oncologists, and some of them received special training in pediatric neuro-oncology and radiotherapy with our colleagues from the pediatric cancer hospital 57357, enabling them to establish special protocols for pediatric CNS tumors. The National Cancer Institute of Egypt had also formed a special CNS group, which is currently conducting many studies, such as a phase II study on hippocampal sparing in radiotherapy for glioma. The early results of such a study can be adopted by EGNO to be standard of care in glioma radiotherapy planning.

EGNO also participated in forming specific multidisciplinary teams (MDTs) of neuro-oncologists in a number of Egyptian oncology centers. These teams included oncologists, neurosurgeons, neuropathologists, and neuroradiologists to plan ahead patients' management, discuss cases, and give lectures all over the country.

Bringing the world to Egypt

EGNO has arranged alone and in collaboration with many Egyptian universities multiple neuro-oncology conferences, where a number of international figures were invited to Egypt to present their experiences helping young neuro-oncologists to update their knowledge. We were honored to welcome Professors Martin van den Bent, Riccardo Soffietti, and Evangelia Razis to Cairo in the past few years.


WELCOME TO EANO 2018

Neuropathology as a cornerstone

The neuropathology group at Ain Shams University was the first in the country to study MGMT in GBM through immunohistochemistry years ago. Currently, they are conducting a study about the role of PDL1 expression and its possible effect on the management of GBM in collaboration with EGNO.

First glioma group in the country

Having a glioma group in Egypt was a major step to register all the glioma cases diagnosed yearly. This was led by a fellow medical genetics specialist from Ismailia, who initiated a funded project by the government to create the first genetic mapping of glioma in Egypt. The collaboration with EGNO in the second phase of such a project will spread the call to all the oncology centers all over the country to collect data and tissue samples, opening a new frontier for research, especially with the rising interest in the field of immune and targeted therapy for CNS tumors.

Treating elderly patients with GBM

Two phase II and III studies were conducted in Egypt in the past few years at Kasr El Einy and Ain Shams Universities to explore the advantages of hypofractionated radiotherapy protocols in elderly patients with GBM with or without concomitant chemotherapy. EGNO is leading a second interim analysis of the results of both studies as a foundation for reaching new guidelines in the management of this group of patients, especially with the presence of some earlier reports that discussed chemotherapy as the main line of treatment in frail patients.

Radiosurgical re-irradiation of GBM

The Gamma Knife Center, Cairo, Nasser Institute, is initiating a project in collaboration with EGNO aiming at discussing the efficacy of radiosurgery with Gamma Knife in re-irradiation of GBM and high-grade glioma as salvage after failure of chemotherapy and where re-surgery is not feasible. Such a protocol will adopt the fractionated Gamma Knife ICON radiosurgery (mask based).

Salvage chemotherapy for GBM

EGNO is initiating a protocol for salvage treatment of GBM using bevacizumab with rechallenge of temozolomide in good performance patients at time of recurrence.

“If you don’t publish, I can’t see you”

Years ago, Professor Weller, an eminent neuro-oncologist, said that in a conference. Since then, EGNO

has encouraged its members to get their work presented in international meetings like those held by EANO, ESMO, and WFNOS and to be published in many peer reviewed journals. Such movements had helped us to further collaborate with the EORTC brain tumor group and to be contacted by some international pharmaceutical companies to participate in some of their funded research about new therapies for CNS tumors.

Challenges

The lack of funds in a developing country makes it difficult to finance large projects that could not be done in multiple centers except without the help of pharmaceutical companies. With the establishment of research and ethical committees in the academic centers, many internationally operated third party companies are operating in Egypt to monitor and supervise such scientific research to ensure that the international standards in conducting research are met.

Opportunities

In a heavily populated country like Egypt, we have more than 50 oncological academic departments, government hospitals, and research centers. Many of these have their own labs and research units which are internationally accredited and monitored. Egypt, with the help of many European countries, has established a special funding authority: the Science and Technology Development Fund (STDF), which helped to fund much basic science research in the field of neuro-oncology. This means that EGNO is ready to be involved in international trials, as the infrastructure for such trials is already present.

What EGNO needs from WFNOS

WFNOS has done a great job in publishing this magazine and in organizing their first conference in Zurich in 2017. Still we are looking forward to the next step for helping neuro-oncology societies like EGNO to be active participants in international multicenter research, to use our data as part of reaching neuro-oncology guidelines, and to help our younger oncologists to find their way to better training programs and workshops that could improve their skills and performance in the growing field of neuro-oncology in Egypt.

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EORTC 1709/CCTG CE.8: a randomized phase III trial assessing the addition of marizomib to standard of care in patients with newly diagnosed glioblastoma

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The standard of care for patients with newly diagnosed glioblastoma includes maximum safe resection, involved-field radiotherapy (RT), and concomitant and up to 6 cycles of maintenance temozolomide (TMZ) chemotherapy (TMZ/RT→TMZ). Despite this intense treatment, the prognosis remains poor, with a median overall survival of approximately 16 months in contemporary clinical trials.[1] Within the last 5 years, several novel drugs failed to prolong the overall survival of patients with newly diagnosed glioblastoma in randomized clinical trials, including bevacizumab, targeting vascular endothelial growth factor (VEGF), and the integrin inhibitor cilengitide.[2–4] Similarly, no immunotherapeutic approach such as vaccination or immune checkpoint inhibition has conferred a survival benefit in glioblastoma patients so far.[5]

Consequently, novel therapeutic strategies and targets are urgently needed. The proteasome has long been considered a promising candidate for therapeutic targeting in various types of cancer.[6] Several proteasome inhibitors have shown pronounced antiglioma activity in preclinical models.[7, 8] However, despite these compelling data, no clinically meaningful activity was seen with proteasome inhibitors such as bortezomib in glioblastoma patients.[9] A major drawback of most of the currently available proteasome inhibitors is their poor ability to cross the blood–brain barrier. The emergence of marizomib (MRZ), a novel, brain-penetrant irreversible pan-proteasome inhibitor, now offers the opportunity to assess the activity of this therapeutic approach in the setting of primary brain tumors. Marizomib was derived from a marine actinomycete and inhibits the proteolytic chymotrypsin-like, trypsin-like, and caspase-like activities of the 20S unit of the proteasome.[10] It has been explored in several preclinical models demonstrating antiglioma activity as a single agent.[11, 12] In monkeys, drug levels in the CNS reached approximately 30% of those measured in peripheral blood.[13]

Most importantly, marizomib was successfully investigated in phase I studies in patients with newly diagnosed as well as recurrent glioblastoma. In the MRZ-108 study,

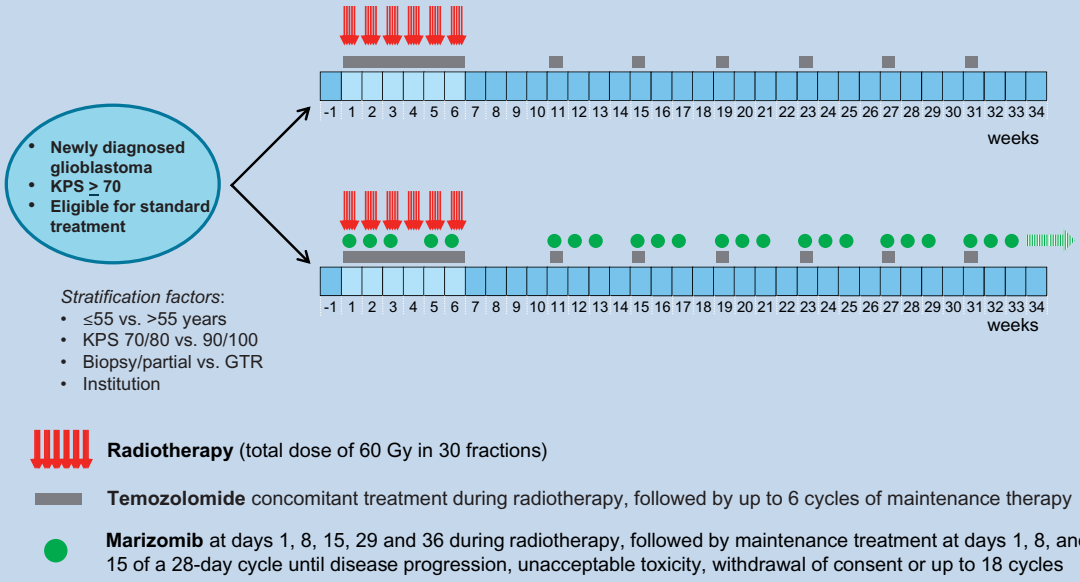

Figure 1. Design of the EORTC 1709/CCTG CE.8 trial.

marizomib was evaluated in patients with recurrent glioblastoma either as a single agent or in combination with bevacizumab. Median overall survival was 9.4 months.[14] The MRZ-112 trial explored the addition of marizomib to radiochemotherapy and maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma, aiming at defining the recommended dose for further studies. Patients were enrolled in separate cohorts for concomitant (TMZ/RT+MRZ) and maintenance (TMZ+MRZ) treatment using a 3 + 3 dose-escalation design with a subsequent dose-expansion cohort at the recommended dose in concomitant followed by maintenance treatment. Most frequent side effects included fatigue, nausea, vomiting, and headaches, as well as CNS-related adverse effects, including hallucinations and ataxia. The recommended marizomib dose for further evaluation was determined to be 0.8 mg/m^2 in combination with standard of care.[15]

Because of its promising antiglioma activity in various preclinical models as well as the data obtained in the MRZ-108 and MRZ-112 studies, marizomib will now be investigated in the EORTC 1709/CCTG CE.8 trial, a multicenter, randomized, controlled, open label phase III superiority study (ClinicalTrials.gov Identifier: NCT03345095). Patients with newly diagnosed glioblastoma, who are eligible for standard TMZ/RT→TMZ, are candidates for study participation. The trial will enroll a total of 750 patients who will be randomized 1:1 to receive standard treatment alone or standard treatment plus marizomib (Figure 1). Stratification factors include institution, age, Karnofsky performance status, and extent of surgery. Marizomib will be administered until tumor progression, untolerable toxicity, withdrawal of consent, or up to 18 cycles after completion of radiotherapy.

The primary objective of this study is to compare overall survival in patients receiving marizomib in addition to TMZ/RT→TMZ with patients receiving standard treatment only. The testing strategy is defined to assess this objective in both the intent-to-treat population and the subgroup of patients with tumors harboring an unmethylated O^6-methylguanine-DNA methyltransferase promoter. Secondary endpoints include progression-free survival, safety, neurocognitive function, and quality of life.

An accompanying translational research program has been set up which involves, among others, the assessment of baseline proteasomal activity in tumor tissue as well as longitudinal measurements of proteasomal activity in peripheral blood. The study will be opened at 50 EORTC sites in Europe and done as an intergroup collaboration with the Canadian Cancer Trials Group (CCTG) with 25 sites in Canada and additional sites in the US. The first study sites in Europe and Canada were activated for enrollment in July 2018 and the activation of most sites is expected at the beginning of 2019.

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Selection of Brain Tumor Patients for Proton Therapy: the Dutch Approach

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Abstract

Proton therapy is a radiation technique which can reduce toxicity in selected patients compared with standard photon radiotherapy. A careful patient selection is essential to offer proton therapy to patients who will benefit the most in terms of prevention of toxicity and to validate the clinical benefits compared with photons. In the Netherlands, where proton therapy has been introduced in 2018, selection criteria for patients eligible for proton therapy must be described in a National Indication Protocol.

After extensive deliberation and close collaboration among experienced radiation oncologists in neuro-oncology, a national consensus on the selection of patients for proton therapy was reached which is supported by the neuro-oncologists. This paper describes the development of the Dutch National Indication Protocol for Neuro-Oncology. The proposed protocol is currently under appraisal of the National Health Care Institute to advise about inclusion in basic health insurance.

Introduction

Several well-established and highly developed radiotherapy techniques are available for the treatment of central nervous system tumors. With the most common radiation modality, photon therapy, tumors can be irradiated with very high precision. Yet, photon therapy has some limitations, including an inevitable irradiation of surrounding (brain) tissue with lower dose. Proton therapy is an alternative radiation modality which has been applied for many years worldwide and becomes increasingly available in Europe. The physical principles of proton beams offer possibilities for superior dose distributions compared with photon treatment, as is shown by many in silico dose planning comparative studies.[1–3] Based on these in silico planning studies, the main application in which protons could produce a clinical benefit is reduction of radiation-induced side effects by reducing the dose to normal tissue. The translation of dosimetric advantages to clinical advantages is challenging. For many critical organs or normal tissues, it is observed that the probability of side effects is directly associated with the radiation dose that is received by that organ. The severity of toxicity following a given dose of radiotherapy is organ specific.[4–6]

Ideally, the validation of the benefits of proton therapy should be performed in a randomized controlled trial with radiation-induced toxicity as a primary endpoint. Yet, many radiation-induced complications can have a long latency time, with incidences increasing over more than 15 years, requiring very long monitoring of patients.[7–9] A randomized controlled trial would take many years to be completed. Given the fact that technological advances evolve rapidly, current techniques will be regarded as outdated within several years, and it is expected that randomized trials will not generate applicable data. To clinically validate the benefit of protons, performance of randomized controlled trials comparing photon and proton therapy is therefore often not feasible.

In the Netherlands, 3 proton therapy centers have been opened in 2018: Groningen PTC in Groningen, Holland PTC in Delft, and ZON PTC in Maastricht. A careful selection of those patients who are expected to benefit most from proton therapy is needed.

In the Dutch health insurance system, all primary and curative care is financed from private mandatory insurance. For this purpose, insurance companies must offer a core universal insurance package for universal primary curative care for a fixed price. The government decides on the content of the universal package. Insurance companies are not allowed to refuse an applicant for the universal package. The system is financed from payroll taxes paid by employers, the government, and the premiums paid directly by the insured. Additional services can be offered by the insurance companies at extra costs. For these services, additional conditions for acceptance may apply.

The Dutch Health Council (in Dutch, Gezondheidsraad) and the National Health Care Institute (in Dutch,

Zorginstituut Nederland) have advisory functions for the Minister of Health for the decisions on the content of the standard insurance package.

Some indications are generally accepted for proton therapy worldwide and are therefore considered standard indications. In the Netherlands, proton therapy is part of the universal insurance package and is regarded as an insured provision for the standard indications of pediatric tumors, chordomas and chondrosarcomas of skull base or spine, and ocular melanoma. For selection of patients with other indications for proton therapy, the model-based approach was chosen by the Dutch Society for Radiation Oncology (DSRO, in Dutch NVRO).[10] In the model-based approach, the potential benefit of proton therapy in reducing side effects is estimated by use of Normal Tissue Complication Probability (NTCP) models. This concept was approved by the Dutch Health Council and the National Health Care Institute. It is estimated that with this approach, about 3% of all patients in the Netherlands who have an indication for radiotherapy will be eligible for proton therapy.[11] The criteria that must be fulfilled in order to be eligible for proton therapy (and reimbursement in the universal insurance package) are described in a National Indication Protocol. For every indication, a tumor-specific protocol is written by radiation oncologists with expertise in this area.

Before the indication for proton therapy can be regarded as insured care, the indication protocol should be approved by the National Health Care Institute. In this paper, the development and realization of the proposed National Indication Protocol for Neuro-Oncological tumors is described.

Search for NTCP models

All radiation oncologists working in the Netherlands are members of the DSRO. Within the DSRO, radiation oncologists with expertise of specific tumors are organized in platforms. These platforms are engaged in regulating and improving radiotherapy treatment for certain tumors and developing national guidelines. The platforms have an advisory function for the board of the DSRO. The development of national indication protocols for proton therapy is a combined effort between the tumor-specific platforms and the National Platform for Proton Therapy (NPPT, in Dutch LPPT). For the National Indication Protocol on Neuro-Oncology, the National Platform for Radiotherapy in Neuro-Oncology (NPRNO, in Dutch LPRNO) established a committee consisting of radiation oncologists with expertise in neuro-oncology and interest in proton therapy. Because the model-based approach is highly dependent on the use of reliable NTCP models, the first step for the committee in the development of the protocol was to perform a systematic search for NTCP models estimating the risk of toxicity after radiation of organs to a certain dose. Structures that are known to be relevant for radiation-induced toxicity are often called organs at risk (OARs) in radiotherapy. In neuro-oncology the most relevant OARs are the brain, brainstem, cochlea, cornea, lens, retina, lacrimal gland, optic nerve, chiasm, pituitary, hypothalamus, cerebellum, and hippocampus.

For the Dutch National Indication Protocol for neuro-oncological tumors, a detailed search strategy was composed in cooperation with a trained librarian of the Leiden University Medical Center. For the National Indication Protocol, several medical databases were searched using a systematic query, which was optimized for every individual database. The results of the search strategies were first screened by members of the committee in order to select papers containing NTCP models. NTCP models for neurocognitive function, endocrine disorders, ototoxicity, radionecrosis, and dry eyes were found. The selected papers were then more thoroughly reviewed and the quality of the NTCP models was assessed according to the TRIPOD criteria.[12] The results of this search will be published elsewhere. During a meeting of the DPRNO, the committee presented the results of the search strategy and the evaluation of the available NTCP models to the members of the DPRNO. The members of the DPRNO concluded that the available evidence and the quality of the available NTCP models were insufficient for use for patient selection. The use of nonvalidated NTCP models—for instance, a model developed by Gondi et al. relating hippocampal dose to neurocognitive function impairment—was considered but rejected after comprehensive deliberation.[13]

Patient selection

Because of the conclusion from the search, a different approach for patient selection other than the model-based approach and the use of NTCP models was required. After extensive and comprehensive discussion within the national platform as well as with neuro-oncologists, it was agreed that the therapy should be offered to patients who are expected to benefit the most, in accordance with the principles of the model-based approach.

Most of the radiation-induced side effects in neuro-oncology that are expected to be reduced by proton therapy have a long latency time.[9,14] The members of the DPRNO therefore agreed that the highest potential gain in quality of life and costs is to be expected for patients with a good prognosis. In order to define a favorable prognosis, neuro-oncologists were consulted and asked to share their expert opinion on this topic. Good prognosis was defined as 10-year overall survival of at least 50%, which was approved by both radiation oncologists and neuro-oncologists.

The main application of the superior physical properties of protons in neuro-oncology is the sparing of normal brain tissue. Several studies have shown that irradiation of normal brain can cause changes in the neurocognitive

function.[9,14–17] These neurocognitive deficits are among the most important long-term side effects resulting from treatment of brain tumors, and radiation of the brain in particular. It comes on top of the neurocognitive decline that may be caused by the brain tumor itself and has a vast impact on the activities of daily living and thereby on quality of life of both patients and their families. Besides the brain tissue in general, the hippocampus plays an important role in neurocognitive function, especially in memory. It is common practice in the Netherlands to keep the dose to the aforementioned structures as low as possible. The possibility of sparing of normal brain tissue and the hippocampi was designated to be the main focus in selecting patients for proton therapy.

Not all patients with brain tumors and a favorable prognosis will benefit from proton therapy. In silico planning studies have shown that in tumors with very small volumes the advantages of protons are limited and sometimes even unfavorable because of the larger area of dose fall-off (penumbra) at the edge of a proton beam and the larger setup uncertainties compared with stereotactic radiotherapy or radiosurgery with photons. Therefore it was stated in the protocol that proton therapy should not be offered to patients for whom treatment with stereotactic or radiosurgical radiotherapy is feasible. Furthermore, the requirement of a quality check was added to the protocol. In this quality check, the proton dose distribution plan is compared with a state-of-the-art photon plan. The protocol describes minimal levels of improvement in dose distribution that the proton plan should offer compared with the photon plan, in order for a patient to be eligible for proton therapy. The ultimate decision whether a patient will be treated with proton or photon therapy is made by the treating radiation oncologist in dialogue with the patient (shared decision making). For an individual patient, several other factors besides dose distributions may influence the choice for proton or photon therapy, such as travel distance, waiting time, or personal preferences.

For patients with meningioma, additional inclusion criteria were formulated. Alternative treatment options to avoid radiation of normal brain tissue and/or to postpone radiation for a significant period of time like additional surgery, limiting the target volume for radiation to the progressive postoperative residual tumor, wait-and-scan policy, or a combination of these strategies should be considered before referring a patient for proton therapy. The indication of craniospinal irradiation in adults was proposed and accepted by medical doctors as an additional standard indication. This proposed protocol is currently under appraisal by the National Health Care Institute to advise about inclusion in the basic health insurance.

Discussion

The model-based approach for selecting patients for proton therapy was developed and introduced in the Netherlands to select patients for proton therapy in case a randomized controlled trial is considered inappropriate.[10] Yet, the feasibility of the approach is highly dependent on the availability of validated NTCP models. For neuro-oncology indications, the model-based approach does not fit due to a lack of NTCP models of sufficient quality.

In neuro-oncology, there are several limiting factors in creating NTCP models. First of all, radiation-induced toxicity is often measurable only after a long follow-up time of at least 15 years. Radiotherapy is a rapidly developing area of treatment. Results from studies that started including patients 15 years ago may now be considered outdated, because of the fast development of technical innovations. Outcomes of these studies may not be comparable to the outcomes of patients treated with currently available techniques. Furthermore, the evaluation of outcomes, in particular neurocognitive function, is complex. The neurocognitive function is composed of multiple domains, including executive functions, attention, learning and memory, perceptual-motor speed, and others. These domains can be tested globally by short questionnaires but also by extensive neurocognitive function tests performed by trained professionals. The lack of uniformity in the testing of neurocognitive function makes results of studies difficult to compare.

Although consensus was reached about the selection criteria for proton therapy in patients with neuro-oncological tumors, not all issues could be solved and the proposed National Indication Protocol has some limitations and might need adjustment in time.

An age limit as an eligibility criterion for proton therapy was suggested. Rationale for this would be that the brain of younger people is developing until about the age of 30 years[18] and is more susceptible to radiation toxicity. Moreover, as the life expectancy of younger people is longer than that of older patients, it was proposed that younger patients would benefit longer from the advantages of having less toxicity. Yet in literature, no definite age limit was defined for the maturation of brain tissue. Many radiation oncologists expressed ethical objections against selection based on age since solid evidence from literature to support this is lacking. It was therefore decided not to add an age limit to the list of inclusion criteria.

One of the disadvantages of model-based selection and selection of patients in general from a research perspective is that the group of patients treated with proton therapy will, by definition, have different baseline characteristics than patients treated with photon therapy. This makes comparison of the cohorts very difficult. An alternative approach to compare results would be to compare patients who have been treated with proton therapy to a historical cohort of patients who have been treated with photon therapy in recent years. Another option is to prospectively collect data from a cohort of patients for whom proton therapy was not available at the time of introduction of proton in the Netherlands because of the limited capacity of the proton centers in their

ramp-up phase. For this purpose, a national database and information collecting infrastructure are being created in the Netherlands, collecting data from patients treated with either proton or photon therapy. This project is called ProTRAIT (Proton Therapy Research Infrastructure) and is a collaboration between all university hospitals in the Netherlands. It is supported by a grant from the Dutch Cancer Society.

In order to collect similar data for all patients who will be irradiated for brain tumors in the Netherlands, the relevant OARs will be contoured according to an internationally approved consensus-based atlas, created in collaboration with the European Particle Therapy Network.[19,20] This task force of ESTRO was established to encourage cooperation between particle therapy centers in Europe.

Registration of toxicity and follow-up of patients was also one of the conditions of the National Health Care Institute and the government for proton therapy to become insured care in the Netherlands. With this information, new NTCP models can be developed and validated in order to further improve selection of patients in the future. This also implicates that the national protocol will be evaluated and revised within a few years to incorporate new evidence and information.

Conclusion

The members of the DPRNO had extensive deliberation about the approach toward a model-based National Indication Protocol for neuro-oncology indications. The close collaboration in the Netherlands between experienced radiation oncologists in neuro-oncology resulted in a national consensus on the selection of patients for proton therapy. Cooperation and support from other specialists in neuro-oncology are essential to introduce this approach nationwide and to offer each patient customized care.

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ASCO 2018 Highlights

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The American Society of Clinical Oncology hosted its annual meeting on June 1–5, 2018 in Chicago, Illinois. This year, there were 190 oral and poster presentations related to central nervous system tumors, including primary and metastatic brain tumors, focusing on areas of basic and translational science such as immuno-oncology, molecular pathology, genomics, and the application of precision medicine. Echoing efforts in other solid tumor and hematologic malignancies, understanding and addressing socioeconomic determinants and contributors to outcomes were also presented. Here, we review the meeting highlights.

Dr Ingo Mellinghoff from Memorial Sloan Kettering Cancer Center presented the results from a phase I study of AG-881, an inhibitor of mutant isocitrate dehydrogenase 1 and 2 (IDH1/IDH2). In patients with advanced solid, mutant IDH tumors, including gliomas. In this session, he presented safety, efficacy, and pharmacokinetic/pharmacodynamic data. As of March 2018, 18 patients were still on study, of whom 17 were glioma patients. All patients (glioma and other solid tumors) were treated between the dose range of 10 mg to 400 mg daily. In the glioma cohort, there were no treatment-related deaths. The plasma drug exposure increased linearly between doses 10 mg and 200 mg. In assessing best response in the glioma cohort, 75% (39 of 52 evaluable patients) achieved stable disease. A perioperative study of both AG-881 and AG-120, an oral IDH1 inhibitor, is currently under evaluation.

Dr Michael Platten from Heidelberg University presented the safety and immunogenicity data from NOA-16, a multicenter phase I trial of mutation-specific peptide vaccine targeting IDH1 R132H, in 32 patients with newly diagnosed malignant astrocytomas. Following chemoradiation or 3 cycles of temozolomide, patients were treated with 8 vaccinations over a period of 23 weeks in combination with adjuvant temozolomide. Over 90% of patients received the entire treatment regimen and there were no treatment-limiting toxicities. Additionally, there was evidence of immunogenicity in which patients demonstrated mutation-specific T-cell or humoral-mediated immune responses that were not observed prior to treatment. In parallel with signal suggesting immunogenicity were radiographic findings consistent with pseudoprogression, also indicating possible underlying disease response.

The clinical, molecular, and radiographic features of diffuse gliomas with either fibroblast growth factor receptor 1 (FGFR1) mutations or FGFR3–transforming acidic coiled-coil protein 3 (TACC3) fusions were characterized by Dr Anna Luisa Di Stefano of Pitié Salpêtrierè Hospital. Through their work, Dr Di Stefano and her group identified 50 gliomas with FGFR-TACC3 fusion, across all World Health Organization (WHO) grades, all of which were IDH1-wildtype and co-occurred with amplification of murine double minute 2. The fusion was also found to be a predictor of longer overall survival in glioblastoma patients. FGFR1 mutations were found in 13 of 70 midline gliomas and were associated with K27M mutation, younger age, and longer overall survival (OS). This work highlights that recognition of these alterations are critical as clinical trials targeting FGFR are ongoing.

Dr David Reardon from Dana-Farber Cancer Institute discussed the results of a phase II study of pembrolizumab with and without bevacizumab in patients with bevacizumab-naïve recurrent glioblastoma. A total of 80 patients were included in this analysis. Progression-free survival at six months (PFS6) was 26% in the combination treatment arm in comparison to 6.7% in the pembrolizumab monotherapy arm. Patients on dexamethasone had a poorer survival compared with those who were not. The outcomes of the combination therapy were consistent with historical controls for bevacizumab monotherapy. Immunocorrelative analyses are ongoing.

In the window-of-opportunity clinical trial, Dr Amy Heimberger from the MD Anderson Cancer Center presented data from 15 patients with recurrent glioblastoma who were treated with pembrolizumab before and after surgical resection. Immune effector function and PFS6 were the primary objectives in this study. Median OS has not been reached but median PFS was 7 months. Mass cytometry (CyTOF) and multiplex immunohistochemical analysis following pembrolizumab in resected glioblastoma showed minimal T-cell infiltration. There was evidence of CD68-positive cells particularly at the blood–brain barrier.

Dr Wolfgang Wick from Heidelberg University presented the results from GAPVAC-101, a first-in-human trial of a personalized peptide vaccine in patients with newly diagnosed glioblastoma. In this phase I study, feasibility, safety, and immunogenicity were evaluated. Fifteen patients started and completed APVAC1 (warehouse selected, 7 active peptides against tumor) vaccination; 11 patients subsequently were started on APVAC2 (de novo manufactured, after next-generation sequencing, 2 peptides). Patients treated with APVAC experienced adverse events related to the vaccinations (mostly injection site reactions) and to concurrent treatment. Median OS and PFS were 29 and 14.2 months, respectively. Immunogenicity was demonstrated by CD4+ T-cell responses against neo-epitopes in APVAC2. Pre-vaccination, there was no evidence of immunoreactivity; however, in tissue resected from a patient with recurrent disease, there was a population of tumor-infiltrating lymphocytes with reactivity against one of the APVAC1 peptides.

There was an emphasis on the value of obtaining comprehensive genomic analysis in gliomas as discussed in 2 oral abstracts. Dr Capucine Baldini from Gustave Roussy investigated outcomes of recurrent glioma patients in early-phase clinical protocols. There were 70 recurrent glioma patients included in the analysis, of whom 41 received protocol treatment based upon identification of a clinically actionable target. There was an overall response rate of 21% in IDH-wildtype patients treated as per

molecularly guided protocols, compared with 0% in unselected patients. This work highlighted that molecularly informed trials may be beneficial to specific patient populations.

Dr Mehdi Touat from Dana-Farber Cancer Institute presented the efforts of the ALLELE consortium, which was designed to create an infrastructure for prospective genomic and molecular testing in order to inform biomarker-driven clinical protocols. In this feasibility study, of 65 patients with glioblastoma, 60 underwent prospective genomic testing across multiple centers with a median turnaround time of 22 days. Although there remain challenges to generating real-time functional diagnostics, including cost and delays in analysis and data reporting, information obtained from this testing can be used to guide future trials.

Dr Priscilla Brastianos from Massachusetts General Hospital presented data from a phase II study of pembrolizumab in leptomeningeal disease from solid tumors. The primary endpoint was OS at 3 months. Eighteen patients were accrued, of whom 15 had breast cancer. Eleven patients were alive at 3 months and the study met its primary endpoint at interim analysis. Also highlighted in this study was the use of cell-free DNA and single-cell RNA sequencing from CSF to monitor disease activity as well as immune response.

Nurse Corner: Breaking Bad News Well

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In the end, the inevitable happens to us all—the only certain thing in life is that we are born to die—and as health care professionals within the neuro-oncology field, we are more used to seeing the implications of this fact over our other peers within other health care settings. But does this common repetition of events make us desensitized to the impending outcome of our patients? How can we help them and their loved ones accept the inevitable, and even achieve a good death? How do we break bad news in a good way—is this something that is up to us as nurses and Allied Health Professionals (AHPs) to do, or do we simply "pick up the pieces" once they have been informed of their diagnosis and prognosis from a senior consultant colleague?

This article aims to explore some of the ways in which these myths are dispelled and how we as nurses and AHPs can help streamline this process and aid in the transition from active treatment to end of life care with greater ease and acceptance. The theme around end of life care is also the topic of this year's Nursing and AHP pre-symposium educational event at EANO Stockholm (October 2018), which I hope many of you will be able to attend and join in the discussions.

For many of us working in neuro-oncology, breaking bad news is part of everyday practice, but how many of us have undergone formal communication skills training, or undergone a course in palliative care or end of life care, or undertaken a counselling degree? Likely not many, or at least not enough of us. We learn as we go along, and experience (whether personal or professional) teaches us invaluable lessons in both empathy and compassion. We learn how to read nonverbal cues and determine when the timing may be right to begin to approach the subject around end of life care with the patient and/or his or her relatives, and we are quick at ascertaining how much information they are likely to be able to retain at any particular time.[1] *How* this is done can greatly influence patients' overall experience of their whole health care encounter, and this is where I think as nurses and AHPs we have a unique opportunity to help lessen the impact of devastation and prepare them for the next steps in a genteel but affirmative manner. Let me give you a common example:

Lisa (fictional name and case) is a 29-year-old mother of two who presented to the emergency department with her first tonic-clonic seizure, witnessed by her husband. A CT scan picked up a likely glioma, and she is discharged home on anticonvulsants and dexamethasone to await an outpatient urgent MRI head scan. An appointment is also made in the neurosurgical clinic the following week to discuss next steps, likely surgery with fluorescence-guided

resection (with 5-aminolevulinic acid [5-ALA]). She is given the number for the neuro-oncology specialist nurse to contact in the interim for advice and support. She rings the following day in a panic.

The specialist nurse speaks to her at length about her seizure and medication and can hear how she audibly calms down over the phone as she understands how the medication will lessen the risks of further seizures and how dexamethasone will act to decrease the tumoral edema. Her main worry had been the children having to witness her having a seizure, or for them to find her unconscious.

The nurse mentions the likely glioma and explains what a primary brain tumor is and that the MRI will provide much more detailed information about its size and location. Lisa is informed about her inability to drive but that she is perfectly safe to cuddle her children for example and undertake normal daily activities with them. The specialist nurse acknowledges that this is a very scary time for them all, and that she is there to offer advice and support as needed. She then talks her through what to expect from her clinic consultation and likely outcomes of anticipated surgery to remove as much of the tumor as is feasible, and that all being well she should be back home again within 3–4 days of her surgery. She is strongly encouraged to bring family members with her to the consultation.

This is where the first anticipatory clue has already been "dropped" that surgery is likely to be discussed and is the foreseen next step. Lisa has been informed she has a potential primary brain tumor, likely a glioma of some description. It gives Lisa a few days to consider the impact this will have (and to come up with further questions for her consultation) and to make preparations for child care arrangements in the interim, as required for her inpatient stay. She is armed with information about her medication and knows her restrictions in what she can/cannot do.

Once at the consultation, surgery is discussed and she is consented for the aforementioned fluorescent guided resection, using 5-ALA. She has been shown her MRI scan so knows where the tumor is located and its size. She is very tearful as the reality dawns on her that she needs brain surgery and has a serious diagnosis in the form of a tumor. After the consultation, the specialist nurse takes her and her husband aside into another room to go through the admissions process in a bit more detail. Here is now the perfect opportunity to prepare them for the next steps and likely outcomes:

The nurse explains that 5-ALA is normally administered as a drink to help the surgeon differentiate between "normal" brain and fluoresced brain tissue (pink) which is infiltrated with active tumor cells. At this stage, the consultant neurosurgeon explains that the 5-ALA only glows pink if the tumor is of a high grade, meaning some form of malignancy, or cancer.[2] The grading of malignancy is yet unknown (eg, World Health Organization [WHO] grades III–IV), and that is what the pathology report will confirm, but we suspect this may represent some form of cancerous tumor, hence the 5-ALA being utilized, as it will enable the surgeon to remove at least 95% of the tumor.

I would strongly recommend using the C-word (cancer) at this stage, even if it is just to say this is what we suspect she is up against. Using terminology like high grade, anaplastic, malignant, etc can cause confusion, and patients end up hearing what they want that to mean. Everyone knows what cancer means, and it gives her and her husband time to prepare themselves mentally while waiting for the surgery. Hope for the best but plan for the worst . . . While being realistic in helping them prepare for a likely cancerous diagnosis, you are also instilling hope in that most (if not all) of the tumor can safely be removed with the aid of 5-ALA. In my opinion, prognosis and life expectancy should NOT be entered into at this stage, as you would need both a full pathology report and all relevant molecular markers to hand to adequately answer this.[3] What you CAN say, though, is that surgery is often the first part of a prolonged treatment pathway, and regardless of the type and tumor grading, it is likely she will require ongoing treatment with oncology afterward. All this will be confirmed with them once the full pathology report has been obtained. Needless to say, these discussions can be quite emotive, so ensure you have time set aside for them not to feel rushed. Offer them plenty of tissues and, above all, time.

In Lisa's case, surgery went well, and she was discharged home within 72 hours with no neurological deficits. Her postoperative scan showed complete resection of her enhancing tumor and her pathology confirmed a glioblastoma (GBM) wildtype (WHO grade IV tumor), requiring chemotherapy and radiotherapy as discussed in the neuro-oncology multidisciplinary meeting.[4] She is seen in clinic the same week for discussion of her results, where her consultant neurosurgeon informs her of the above information and treatment plan. She is crying, as is her husband, but they take comfort in knowing the tumor has been completely removed and that she can have further treatments.

Once again the specialist nurse takes them aside and sits with them quietly for a while, allowing them to grieve, come to terms with their diagnosis, and gather their thoughts. From experience, the patient's being aware of the *diagnosis* and understanding the *prognosis* are two different things, and from an onward treatment perspective, I feel it is important for the patient to know the difference to help be prepared for the forthcoming oncology appointment.[5] This does not mean you have to spell it out in regard to life expectancy.

Normally I start this conversation by asking them about their understanding of their surgical procedure, and if they have fully understood what that implies. I state that even though the surgeon was able to completely resect the tumor (the postoperative scan confirms this), it does not equate to a cure and does not mean the tumor is gone for good. I go on to state that unfortunately, given

time, this tumor *will* resurface—normally in a matter of months rather than years, given her diagnosis.[5] I then state that the aim of surgery is to lessen the pressure effects within the brain and to establish a firm diagnosis, as well as enabling other treatment options such as chemotherapy and radiotherapy to be more effective, and for those treatments to slow down the rate of regrowth. Finally I say that as this is a primary cancer of the brain, our treatment aim is to establish control of the disease for as long as possible (with several arms of treatments available to us), but ultimately we are not looking at a curative process.

In Lisa's case, while this was difficult for them to hear, it did not come as a shock. They had been given potential clues all along as to what this may represent and they had gone home and "Googled" gliomas, so were already well aware of its life limiting implications, should this be a high-grade tumor as initially suspected (and as now confirmed). They were obviously devastated but more from a perspective that their deepest fears had been confirmed, as until now they had naturally been hoping they (and us) would be wrong. They did not ask about prognosis, so this was not discussed at this consultation—but once again they had been given snippets of what to expect from oncology in regard to being an incurable disease that will come back in a matter of months, and that the aim is one of palliation.

They had already made plans for school counselor involvement and had booked a family holiday at the local seaside resort prior to oncology treatments commencing, to create "happy memories" for their children. They thanked the nurse for her unwavering support and professionalism and even stated that she must have a very difficult job breaking bad news every day, but that she had done it in such an empathetic and professional way that they knew what the next steps were at every stage, making them feel prepared and forewarned. They felt that without her support, their journey would not have been as smooth and as well informed. Lisa survived for 10 months.

Apart from being good at breaking bad news, the specialist nurse could offer so much more that would be of great value and support to both the patient and the family. Providing Lisa and her husband with information leaflets about their tumor type and treatment options is imperative and most of us do this without a second thought, but as a specialist nurse, do you always consider obtaining other information that may help them holistically?[6] Do you provide information about where to access financial support and advice, for example, or about local community support groups or charities to contact for peer and online support? About how to access grants for things such as travel reimbursements or how to speak to bereaved children and approach the subject of terminal illnesses with them—where can family members and children go for counseling and support in your area . . . would you know? Do you regularly offer spiritual advice and signpost patients to chaplaincies? How about hospices offering daycare services such as music therapy, mindfulness courses, or dietetic advice in cancer?

There is a myriad of information and support out there for patients, families, and their carers and loved ones, but knowing how and when to access them is a different entity. Being faced with a terminal illness and a very short life expectancy must be like being a rabbit caught in headlights; it can be very difficult for anyone to know where to turn or what to expect, and patients tend to either freeze with fear or bury their heads in the sand, not knowing where to turn. It takes time to achieve acceptance, and we can help them reach that stage in the knowledge they are not alone on this journey—someone to offer them appropriate guidance and support may be all that is required.

Thankfully, through dedicated professionals such as you, more and more is being done to support *everyone* (not only the patient) through this disease trajectory. Throughout the UK, Europe, and the USA there are support programs and even weekend camps for children and family members of those affected by malignant brain tumors, albeit most of these programs are aimed at primary malignant tumors and not metastatic.[7] A network of carer champions is being established to look after the needs of the carers, and more health care professionals (as well as governing bodies) are realizing that we need to look after the carers alongside the patients, as they in turn are the ones looking after the patients. Without them on board, we would not be able to provide our current level of outpatient service.

At this year's Stockholm EANO conference, we have the privilege of once again being able to offer a FREE pre-symposium educational day for nurses and AHPs attending the main symposium thanks to funding from the UK-based Brain Tumor Charity. A lot of the aforementioned topics will be dedicated as speaker slots to further delve into how we can offer these vital services and continue to develop our professionalism and dedicated support to our neuro-oncology cohort. We have a lot to learn from each other, and I hope this year's theme around end of life care does not demoralize you, but rather inspire you to go out there and make a tangible difference to your patients and their loved ones, arguably in their time of greatest need.

Furthermore, I am very excited to announce that as an EANO first, we will also have a dedicated poster viewing section to encourage the submission of nursing and AHP abstracts and research. Furthermore, the previous stand-alone "nursing day" agenda has been fully incorporated into the main symposium events as parallel sessions and breakout sessions over the duration of the conference, minimizing conflicts with other sessions of interest on the main forum. We hope this will encourage more attendees at the nursing symposiums, even if you are not a nurse or AHP. We will also have a "meet the experts" nursing panel and sunrise sessions for our benefit. We hope it will be a great success and a format to use for many years to come.

I do hope you will access the EANO website to look at the detailed program in full. There is a prize in store for the best voted nursing/AHP abstract submission, meaning free registration for one lucky participant, so get submitting!

I hope to see you in October (10th–14th, 2018) in Sweden and offer you a warm (Brrr!) welcome to a beautiful, autumnal Stockholm!

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Atypical, Solitary Presentation of Leptomeningeal Metastases from Breast Cancer: A Case Report

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Introduction

Breast cancer is one of the solid tumors most commonly associated with leptomeningeal metastases.[1] Leptomeningeal metastases usually occur in a context of advanced systemic disease, and can be associated with brain intra-parenchymal metastases.[2] Therapeutic options are scarce and have limited efficacy.[3] Current possibilities include systemic treatments and local therapies such as radiation therapy and intrathecal chemotherapy. Leptomeningeal metastases carry a dismal prognosis, with a median survival of less than 6 months in most published series, but some patients experience longer survivals, up to several years.[2,4] Determining the parameters allowing the identification of appropriate candidates for active treatments is challenging. Several prognostic factors have been identified, including the patient's age at the time of leptomeningeal metastases diagnosis, the functional and neurological status, and the delay between cancer diagnosis and leptomeningeal metastases.[5]

Case report

In June 2013, a 62-year-old woman with no medical history was diagnosed by biopsy with a negative hormone receptor, amplified human epidermal growth factor receptor (HER2) ductal carcinoma of the left breast, with a homolateral axillar lymph node involvement (T3N1). Whole body CT scan, bone scan, and brain MRI were normal (M0). She first received neoadjuvant chemotherapy (3 cycles of a regimen consisting of 5-fluorouracil, epirubicin, and cyclophosphamide were followed by 4 cycles of docetaxel and trastuzumab). After completing the whole protocol, she was treated with mastectomy and axillary node dissection. Pathological examination found no residual invasive carcinoma (breast and lymph nodes). The patient was treated with adjuvant radiation therapy delivered to the breast and lymph nodes and trastuzumab. In March 2014, during radiation therapy, she developed acute headache, dizziness, dysarthria, and nausea. The neurological examination revealed cerebellar ataxia. Physical examination was normal. Brain MRI showed large confluent leptomeningeal enhancing nodules located in the vermis and cerebellar hemispheres, associated with a few smaller leptomeningeal nodules in the supratentorial compartment. There was no hydrocephalus. Spinal MRI found leptomeningeal enhancing micronodules at the cervical and lumbar levels. Whole body CT scan showed no visceral progression. The patient was started on corticosteroids and treated with whole brain radiation in April 2014 (30 Gy in 10 fractions). An intraventricular catheter (Ommaya reservoir) was then placed. Repeated CSF examinations found a moderate hyperproteinorachia (0.45 g/L) and the presence of atypical cells suspected to be breast cancer tumor cells.

Intrathecal methotrexate was started in May 2014, associated with a systemic regimen consisting of capecitabine and lapatinib. A first follow-up assessment was performed after 5 injections of intrathecal methotrexate and one cycle of capecitabine-lapatinib. The patient's status was significantly improved. Brain MRI revealed a complete resolution of the macroscopic leptomeningeal nodules, at both the supratentorial and infratentorial levels. It was decided to continue with the same treatment. Unfortunately, the clinical condition of the patient rapidly deteriorated into an acute prothrombotic state a few days after the MRI and she was hospitalized. The physical examination showed petechias and multiple hematomas on the skin. A complete biological workup revealed thrombocytopenia (60 g/L) and an increased prothrombin time. Repeated CSF analysis revealed a moderate hyperproteinorachia (0.45 g/L) and the absence of tumor cells, but brain imaging was not performed. Upon hospitalization she had a respiratory failure, chest CT revealed a massive bilateral pulmonary embolism, and the venous Doppler ultrasound found an extensive thrombus of the left leg. Because of the presence of thrombocytopenia, an inferior vena cava filter placement was programmed, but the respiratory status worsened rapidly and she died 5 days after her admission.

Discussion

This case of a patient diagnosed with breast cancer is atypical by the type of clinical presentation of the leptomeningeal metastases, with neurological symptoms occurring during the adjuvant phase of the initial treatment and in the absence of metastases outside the central nervous system (CNS), and by the radiological findings consisting of large, macroscopic, confluent lesions affecting predominantly the cerebellum. This location in the cerebellum made the management of this patient challenging, and a combination of radiation therapy, intrathecal and systemic chemotherapy, and HER2-targeted therapy resulted in a clear clinical improvement and a complete disappearance of the macroscopic lesions on MRI.

Leptomeningeal metastases commonly occur in the presence of extra-CNS metastases and rarely reveal the metastatic disease. This case report shows that they can occur earlier in the oncological history of patients, including during postsurgical adjuvant treatment and in the absence of brain or extra-CNS metastases. Indeed, leptomeningeal lesions are rarely isolated: in a study of 153 patients with breast cancer–related leptomeningeal metastases, 88% of patients had concomitant extra-CNS metastases.[2]

Besides this atypical presentation, the radiological characteristics of the leptomeningeal metastases were also notable. Brain MRI showed large macroscopic nodular enhancing lesions largely predominant in the posterior

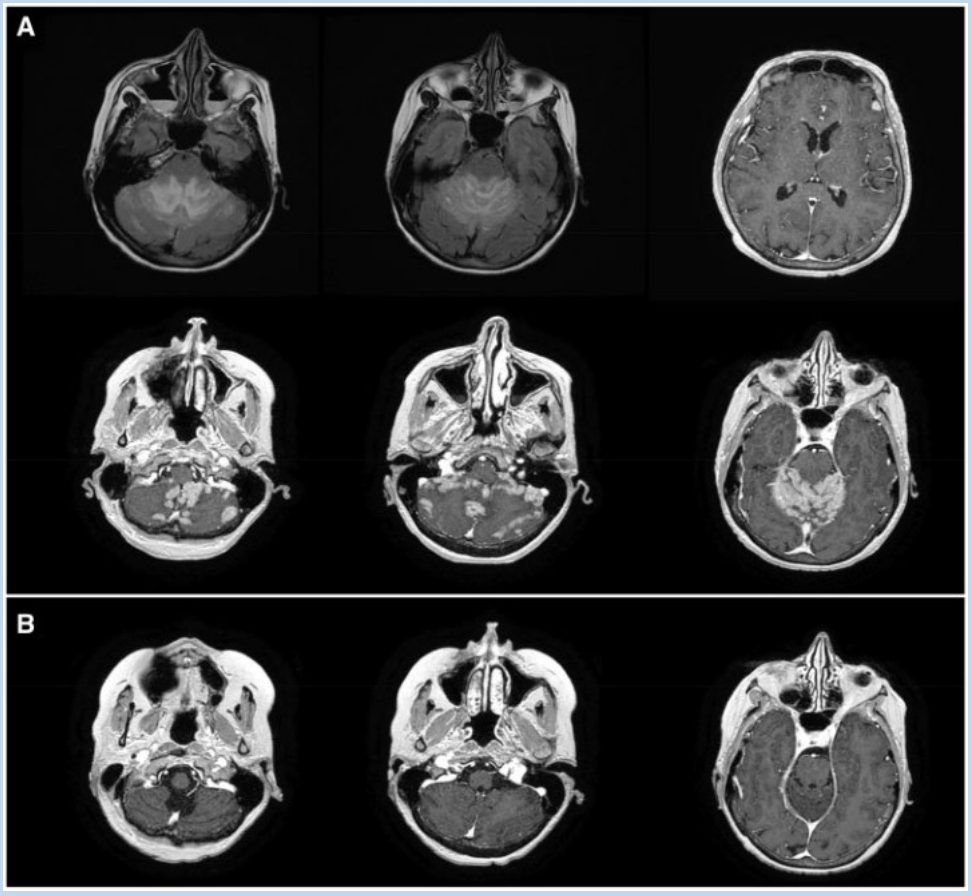

Figure 1. (A) Brain MRI (gadolinium T1-weighted and FLAIR-weighted) at the diagnosis of leptomeningeal metastases showing large confluent leptomeningeal enhancing nodules located within the vermis and cerebellar hemispheres, and a smaller leptomeningeal nodule within the left frontal lobe; (B) brain MRI after the completion of whole brain radiation therapy, 5 administrations of intrathecal methotrexate and one cycle of Capecitabine-Lapatib, showing a complete regression of the leptomeningeal nodules within the posterior fossa.

fossa. Cerebellum is a frequent site of leptomeningeal metastases: in a series of 270 patients with a cytologically confirmed diagnosis of leptomeningeal metastases from various solid tumors, the cerebellum was involved on imaging in 30.1% of cases.[6] Cerebellar lesions can be either nodular, as in our case, or linear. It has been hypothesized that the predominant involvement of the posterior fossa might be linked with postural deposition and collection of tumor cells.[6] The correlation of the location of macroscopic leptomeningeal lesions with outcome has not been investigated yet. It is unknown whether there is a positive or negative impact of cerebellar leptomeningeal involvement in response to treatments or survival.

The management of patients with posterior fossa involvement is indeed challenging for several reasons. First, depending on the size of the leptomeningeal nodules, it can be difficult to obtain a cytological confirmation, as the lumbar puncture might not be possible. Secondly, the risk of intracranial hypertension and/or acute hydrocephalus must be taken into account when considering treating patients with radiation therapy. Due to the possible contraindication of lumbar punctures, the administration of intrathecal chemotherapy can be performed through an intraventricular catheter (Ommaya reservoir).

Overall, this case illustrates the fact that even in the presence of large nodular leptomeningeal metastases responsible for a serious deterioration of the neurological status, active treatments (in this case radiation therapy, intrathecal methotrexate, and systemic treatment) should be discussed, as it can lead to substantial clinical and radiological improvement despite a dramatic situation at diagnosis.

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Hotspots from Neuro-Oncology

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EANO guidelines for the diagnosis and treatment of ependymal tumors

Rudà R, et al. Neuro Oncol. 2018 Mar 27;20(4):445–456.

Ependymal tumors are rare CNS tumors and may occur at any age, but their proportion among primary brain tumors is highest in children and young adults. Thus, the level of evidence of diagnostic and therapeutic interventions is higher in the pediatric compared with the adult patient population.

The diagnosis and disease staging is performed by craniospinal MRI. Tumor classification is achieved by histological and molecular diagnostic assessment of tissue specimens according to the World Health Organization (WHO) classification 2016. Surgery is the crucial initial treatment in both children and adults. In pediatric patients with intracranial ependymomas of WHO grades II or III, surgery is followed by local radiotherapy regardless of residual tumor volume. In adults, radiotherapy is employed in patients with anaplastic ependymoma WHO grade III and in cases of incomplete resection of WHO grade II ependymoma. Chemotherapy alone is reserved for young children $<$12 months and for adults with recurrent disease when further surgery and irradiation are no longer feasible. A gross total resection is the mainstay of treatment in spinal ependymomas, and radiotherapy is reserved for incompletely resected tumors. Nine subgroups of ependymal tumors across different anatomical compartments (supratentorial, posterior fossa, spinal) and patient ages have been identified with distinct genetic and epigenetic alterations, and with distinct outcomes. These findings may lead to more precise diagnostic and prognostic assessments, molecular subgroup-adapted therapies, and eventually new recommendations pending validation in prospective studies.

Radiologic progression of glioblastoma on therapy—an exploratory analysis of AVAglio

Nowosielski M, et al. Neuro Oncol. 2018 Mar 27;20(4):557–566

In this exploratory analysis of AVAglio, a randomized phase III clinical study that investigated the addition of bevacizumab (Bev) to radiotherapy/temozolomide in newly diagnosed glioblastoma (GBM), the authors analyzed the radiologic characteristics of GBMs on therapy until progression and investigated whether the type of radiologic progression differs between treatment arms and is related to survival and molecular data. Five progression types (PTs) were categorized according to MRI behavior in T1- and T2-weighted images in 621 patients (Bev, $n =$ 299; placebo, $n = 322$). Frequencies of PTs (designated as classic T1, cT1 relapse, T2 diffuse, T2 circumscribed, and primary nonresponder), time to progression/progression-free survival (PFS), and overall survival (OS) were assessed within each treatment arm and compared with molecular subtypes and O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation status. PT frequencies differed between the Bev and placebo arms, except for "T2 diffuse" (12.4% and 7.1%, respectively). PTs showed differences in PFS and OS; with "T2 diffuse" being associated with longest survival. Complete disappearance of contrast enhancement during treatment ("cT1 relapse") showed longer survival than only partial contrast enhancement decrease ("classic T1"). "T2 diffuse" was more commonly MGMT hypermethylated. Only weak correlations to molecular subtypes from primary tissue were detected. In conclusion, these findings are important to predict outcome of GBM patients under treatment; but future prospective studies are still needed.

Radiation-induced cognitive toxicity: pathophysiology and interventions to reduce toxicity in adults

Wilke C, et al. Neuro Oncol. 2018 Apr 9;20(5):597–607.

Radiotherapy is ubiquitous in the treatment of patients with both primary brain tumors as well as disease which is metastatic to the brain. This therapy is not without cost, however, as cognitive decline is frequently associated with cranial radiation, particularly with whole brain radiotherapy (WBRT). The precise mechanisms responsible for radiation-induced morbidity remain incompletely understood and continue to be an active area of ongoing research. In this article, the authors reviewed the hypothetical means by which cranial radiation induces cognitive decline as well as potential therapeutic approaches to prevent, minimize, or reverse treatment-induced cognitive deterioration. Additionally, advances in imaging modalities that can potentially be used to identify site-specific radiation-induced anatomic or functional changes in the brain and their correlation with clinical outcomes were analyzed.

Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: results from exploratory phase I cohorts of CheckMate 143

Omuro A, et al. Neuro Oncol. 2018 Apr 9;20(5):674–686.

Immunotherapies have demonstrated efficacy across a diverse set of tumors supporting further evaluation in glioblastoma. The primary objective of this study was to evaluate the safety/tolerability and describe immune mediated effects of nivolumab $\pm$ ipilimumab in patients with recurrent glioblastoma. Patients were randomized to receive nivolumab 3 mg/kg every 2 weeks (Q2W; NIVO3) or nivolumab 1 mg/kg $+$ ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 doses, then nivolumab 3 mg/kg Q2W (NIVO1$+$IPI3). An alternative regimen of nivolumab 3 mg/kg $+$ ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 3 mg/kg Q2W (NIVO3$+$IPI1) was investigated in a nonrandomized arm.

Forty patients were enrolled (NIVO3, $n = 10$; NIVO1$+$IPI3, $n = 10$; NIVO3$+$IPI1, $n = 20$). The most common treatment-related adverse events (AEs) were fatigue (NIVO3, 30%; NIVO1$+$IPI3, 80%; NIVO3$+$IPI1, 55%) and diarrhea (10%, 70%, 30%, respectively). AEs leading to discontinuation occurred in 10% (NIVO3), 30% (NIVO1$+$IPI3), and 20% (NIVO3$+$IPI1) of patients. Three patients achieved a partial response (NIVO3, $n = 1$;

NIVO3+IPI1, $n = 2$) and 8 had stable disease for $\geq$12 weeks (NIVO3, $n = 2$; NIVO1+IPI3, $n = 2$; NIVO3+IPI1, $n = 4$ [Response Assessment in Neuro-Oncology criteria]). Most patients (68%) had tumor-cell programmed death ligand-1 expression $\geq$1%. Immune mediated effects mimicking radiographic progression occurred in 2 patients. Nivolumab monotherapy was better tolerated than nivolumab + ipilimumab; the tolerability of the combination was influenced by ipilimumab dose. The authors concluded that these safety and exploratory findings were worthy of further investigation of immunotherapies in glioblastoma; however, thus far checkpoint inhibitors in recurrent glioblastomas have failed to show efficacy.

Molecular subtyping of tumors from patients with familial glioma

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Single-gene mutation syndromes account for some familial glioma (FG); however, they make up only a small fraction of glioma families. Gliomas can be classified into 3 major molecular subtypes based on isocitrate dehydrogenase (IDH) mutation and 1p/19q codeletion. The authors hypothesized that the prevalence of molecular subtypes might differ in familial versus sporadic gliomas and that tumors in the same family should have the same molecular subtype. Participants in the FG study (Gliogene) provided samples for germline DNA analysis. Formalin-fixed, paraffin-embedded tumors were obtained from a subset of FG cases, and DNA was extracted. Tissue from 75 families was analyzed, including 10 families containing a second affected family member. Copy number variation data were obtained using a first-generation Affymetrix molecular inversion probe (MIP) array. Samples from 62 of 75 (83%) FG cases could be classified into the 3 subtypes. The prevalence of the molecular subtypes was as follows: 30 (48%) IDH-wildtype, 21 (34%) IDH-mutant non-codeleted, and 11 (19%) IDH-mutant and 1p/19q codeleted. This distribution of molecular subtypes was not statistically different from that of sporadic gliomas ($P = 0.54$). Of 10 paired FG samples, molecular subtypes were concordant for 7 ($\kappa = 0.59$): 3 IDH-mutant non-codeleted, 2 IDH-wildtype, and 2 IDH-mutant and 1p/19q codeleted gliomas. These data suggest that within individual families, patients develop gliomas of the same molecular subtype. Conversely, differences in the prevalence of the molecular subtypes in FG compared with sporadic gliomas were not evident. These observations provide further insight into the distribution of molecular subtypes in FG.

Radiomic subtyping improves disease stratification beyond key molecular, clinical, and standard imaging characteristics in patients with glioblastoma

Kickingereder P, et al. Neuro Oncol. 2018 May 18;20(6):848–857.

The purpose of this study was to analyze the potential of radiomics for disease stratification beyond key molecular, clinical, and standard imaging features in patients with glioblastoma. Quantitative imaging features ($n = 1043$) were extracted from the multiparametric MRI of 181 patients with newly diagnosed glioblastoma prior to standard-of-care treatment (allocated to a discovery and a validation set, 2:1 ratio). A subset of 386/1043 features were identified as reproducible (in an independent MRI test-retest cohort) and selected for analysis. A penalized Cox model with 10-fold cross-validation (Coxnet) was fitted on the discovery set to construct a radiomic signature for predicting progression-free and overall survival (PFS and OS). The incremental value of a radiomic signature beyond molecular (O^6-methylguanine-DNA methyltransferase [MGMT] promoter methylation, DNA methylation subgroups), clinical (patient's age, KPS, extent of resection, adjuvant treatment), and standard imaging parameters (tumor volumes) for stratifying PFS and OS was assessed with multivariate Cox models (performance quantified with prediction error curves). The radiomic signature increased the prediction accuracy for PFS and OS beyond the assessed molecular, clinical, and standard imaging parameters ($P \leq 0.01$). Prediction errors decreased by 36% for PFS and 37% for OS when adding the radiomic signature (compared with 29% and 27%, respectively, with molecular + clinical features alone). The radiomic signature was—along with MGMT status—the only parameter with independent significance on multivariate analysis ($P \leq 0.01$). Overall, this study stresses the role of integrating radiomics into a multilayer decision framework with key molecular and clinical features to improve disease stratification and to potentially advance personalized treatment of patients with glioblastoma.

Hotspots in Neuro-Oncology Practice

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We highlight several articles from *Neuro-Oncology Practice* that represent work on brain cancer survivorship care plans, the importance of patient reported outcomes in spinal cord decompression treatment, the quality of life results from a randomized trial of donepezil for brain tumor patients, and genetic variants that may be associated with fatigue.

(1) Cancer survivorship is a relatively new concept that refers to the entirety of one's life spent living with, through, and beyond the active treatment phase of a cancer diagnosis. Patients and their caregivers often report knowledge gaps associated with their care during different phases of survivorship. In 2005 the Institute of Medicine published a report outlining ways to close these gaps and called for development of a survivorship care plan (SCP) that each patient would receive. An *ad hoc* multidisciplinary group from the Society of Neuro-Oncology Guidelines Committee was organized and produced the first SCP for adult neuro-oncology patients, which is described by Leeper et al (1) and is available on the Society for Neuro-Oncology's (SNO) website. The authors hope this document will facilitate the process of communication between providers, patients, and caregivers, stimulate research, and be adopted and adapted by health care providers.

(2) Researchers from Memorial Sloan Kettering Cancer Center (MSKCC) reported prospective patient reported outcome (PRO) data as a primary endpoint in patients with metastatic spinal cord compression treated with a hybrid approach of surgery and stereotactic radiosurgery (2). In a cohort of 111 patients, the authors demonstrate significant improvement in terms of pain severity, interference of pain with daily life, and symptom burden following this treatment approach. Analysis as per MD Anderson Symptom Inventory (MDASI) scores also revealed reduction of pain severity and significant improvement in patients' general activities following this treatment approach. With a median survival of 16.7 months as expected for this patient population, evaluation of these PROs are critical assessment tools to evaluate the efficacy of such technical advances in surgery and radiosurgery.

(3) Among various strategies studied to minimize well-known effects of radiotherapy -induced neurocognitive decline and resultant impact on health-related quality of life (QoL) in brain tumor patients, several drug-related strategies have been explored to mitigate these effects. Naughton et al report the QoL component of the phase III randomized trial of pharmaceutical intervention strategy using donepezil in brain tumor patients (3). Although the trial had not shown any significant improvement in the chosen primary endpoint of neuro-cognition, the present analysis did show significant improvement in social and emotional well-being and the overall Functional Assessment of Cancer Therapy–Brain (FACT-Br) scores at the 12- week evaluation window. Interestingly, the benefit with donepezil was particularly and significantly more apparent in patients with considerable baseline symptoms. Patients with fewer baseline symptoms, on the other hand, randomized to receive donepezil compared with placebo, reported significantly lower functional well-being at 12 and 24 weeks post evaluation, along with greater fatigue at 24 weeks. These are likely to be important findings, which, if proven in appropriately designed prospective studies, can help us to utilize donepezil judiciously in carefully selected patient populations.

(4) Fatigue is a commonly reported and distressing symptom in patients with cancer. Armstrong et al provide us with unique insights into identification of patients with gliomas likely to have moderate to severe fatigue (4). The study was based on a retrospective evaluation of occurrence of fatigue in 176 consecutive patients (median age, 47 years) with newly diagnosed malignant glioma. Apart from already known factors such as age and poor performance status, unique single nucleotide polymorphisms (SNPs) were also identified to significantly correlate with occurrence and severity of fatigue. Results from multivariate analysis revealed poor performance status, and 2 SNPs were associated with fatigue severity. Both of these genes are important in the circadian clock pathway, which has been implicated in diurnal preference and duration and quality of sleep. No genes in the inflammatory pathway were associated with fatigue in the current study. This encouraging preliminary study adds credence to the possible potential predictor association of unique genetic susceptibility of patients to the development of fatigue because of disease and treatment. A well-designed study is warranted to confirm these encouraging findings and may well prove to be a useful tool in identifying appropriate patient populations while designing various clinical trials, with a possible impact on routine practice as well.

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