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Editorial

Dear colleagues,
Dear friends of International Neuro-oncology,
Dear members of WFNOS,

It was a pleasure and privilege to welcome almost 1000 of you to this 5th World Meeting of Neuro-oncology Societies. Zurich was a great place, we spent lively and scientifically rewarding hours in the pleasant lecture hall and owe our thanks to the local organizing team, headed by Michael Weller and our colleagues from EANO as well as the staff of the Vienna Medical Academy.

The topics of our recent issue reflect burning issues in neuro-oncology. Our magazine reviews on an optimal treatment of an alkylator-based regimen, recent developments in meningioma as well as pediatric glioma, and metastases provide insight into an immunotherapy concept for recurrent PCNSL.

This issue of the magazine features our French neuro-oncology colleagues from ANOCEF. Having a look at their achievements, we may need to remind ourselves that WFNOS was not only initiated by 3 large neuro-oncology societies—SNO, ASNO, and EANO—but hosts several national neuro-oncology societies.

The new board of EANO has launched a young neuro-oncologists’ initiative. Anna Berghoff from Vienna, who leads this initiative with Carina Thomé from Heidelberg, explains background and may trigger applications from many of our younger readers. With the utmost important topic, Kathy Oliver from the International Brain Tumor Alliance explains background for a new initiative of the European Union. The European References Networks (ERNs) are planned to increase collaborative, cross-border approaches to treating brain tumor patients with a focus on underserved areas in Europe.

Please have a look at the exciting scientific and practical news from neuro-oncology practice. The editors share their hotspots to prioritize reading.

On behalf of EANO, I would like to very much welcome Young-Kil Hong as the new WFNOS president. SNO and EANO have passed on the torch to ASNO and look forward to the preparations for the next World Meeting in Seoul in 2021.

With warm regards,

Wolfgang Wick
President of EANO
Dear Members and Colleagues of SNO, EANO, ASNO, and WFNOS:

I thank you for the opportunity and privilege to provide you with a summary of SNO’s accomplishments over this past year. I would like to recognize the leadership of our officers: our vice-president, Terri Armstrong, and our treasurer, Gelareh Zadeh. I also would like to recognize the work of the members of our Executive Council and of our Board of Directors.

We have just returned from a great meeting in Zurich for WFNOS 2017. The weather for the most part contributed to a great meeting, but more importantly the quality and excitement of the talks and presentations were the highlights of the meeting. Together with our colleagues from our sister societies, we were happy to see so many participants from all corners of the globe. This family of practitioners in the sciences and clinical practice of neuro-oncology show an unbeatable spirit of creativity and quest for knowledge that bodes well for each member society. The collaborations that come out from these meetings are bound to provide the next set of impressive results to be presented in future years. These meetings also make one aware that our patients only benefit from the sharing of knowledge and experience, thus ensuring that any patient has access to very similar care regardless of where he or she is seen. In spite of this, it is clear that much more has to be done on this front for some of the neediest parts of our world!

SNO would like to recognize and thank the leadership of EANO and in particular Michael Weller for this meeting. In addition to the venues for the talks, the social programs were excellent and well attended. The banquet dinner on top of a mountain peak surrounded by clouds made one feel the spirit of Switzerland.

SNO continues to thrive in terms of its impact, its membership, its ability to provide exciting annual meetings, and its educational content. We would be very excited if we could match the success of WFNOS 2017 with our SNO 2017 meeting in San Francisco. Under the leadership of our scientific program chairs (Drs Manish Aghi, Vinay Puduvalli, and Frank Furnari), the theme for the SNO 2017 meeting will be the CANCER MOONSHOT initiatives which have been announced by the NIH/NCI and supported in a rare spirit of bipartisanship by the US Congress.

Keynote speeches provided by Dr Jennifer Doudna from UC Berkeley, widely regarded as one of the main inventors of the Crispr/Cas9 genetic editing technology, and by Dr Carlo Croce, from Ohio State University, will certainly be the feather in the cap for additional exciting oral presentations. We thus hope that as many members of WFNOS societies attend and visit San Francisco!

Finally SNO wishes to provide our next WFNOS President and host of the next WFNOS meeting in Seoul, Dr Young-Kil Hong, our most heartfelt congratulations and wishes for a great meeting in 2021!

Respectfully yours,

E.A. (Nino) Chiocca, MD PhD
Pediatric Ependymomas: A Plea for International Cooperation

Didier Frappaz

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Abstract

Ependymomas account for 10% of brain tumors in children, and are thus the third most common pediatric tumor of the central nervous system (CNS). They may arise from ependymal cells that are spread along the entire neuraxis. More than 90% of ependymomas occurring in children are located intracranially, with two-thirds in the infratentorial and one third in the supratentorial regions. More than half of pediatric ependymomas occur in children younger than 5 years of age. Males are more often affected, with a sex ratio of 2:1. There are no environmental factors described up to now. However, some predisposing factors are described: patients with Turcot or Gorlin syndrome may develop intracranial ependymomas, and those with neurofibromatosis type 2 may develop spinal ependymomas.

For the SIOP Ependymoma group

Ependymomas are located in or close to the ventricular system, though intraparenchymal tumors are described. These plastic tumors tend to infiltrate the surrounding regions: in the posterior fossa, extension into the cerebellopontine angle through the foramina of Luschka and/or toward the cervical region through the foramen of Magendie is a typical feature of an ependymoma rather than that of a medulloblastoma. This explains why the complete removal is sometimes difficult and should be attempted only by skilled pediatric neurosurgeons. Magnetic resonance imaging usually shows a decreased T1-weighted signal intensity, with gadolinium enhancement that may or may not be heterogeneous, and a heterogeneous T2-weighted hyperintensity. Cystic components may be seen in supratentorial tumors. Ependymomas are localized at time of diagnosis in more than 90% of cases. The initial staging should include a spinal MRI (if feasible preoperatively) and a CSF cytological study prior to therapy. Ependymoma tends to recur locally, though with improved local therapy this becomes less true. Staging should thus be repeated at time of relapse.

Ependymomas were divided by the World Health Organization (WHO) 2007 classification into 3 histology-based grades whatever their site of origin.1 WHO grade I tumors included myxopapillary ependymomas, typically located in the spine, and subependymomas, mostly located intracranially. They occur predominantly in adults and are usually associated with favorable patient outcomes, though spinal myxopapillary spinal tumors of children have a tendency to recur and disseminate much more than their adult counterpart.2 The majority of ependymomas are WHO grade II (classic) and grade III (anaplastic) tumors. Classic WHO grade II ependymomas may show a papillary, clear cell, or tanyctic phenotype. WHO grade III (anaplastic) ependymomas are defined by a high mitotic count, microvascular proliferation, and tumor necrosis. Differential diagnoses include neurocytoma and metastasis of a papillary adenocarcinoma. Of note, ependymoblastomas are not ependymal tumors, though they were included in the past in some series of ependymomas, thus blurring the results. The reproducibility of this classification has been questioned, and its value to determine event-free survival and overall survival was a matter of debate especially in younger children.3 Moreover, this classification did not take into account the site. A better understanding of the cell of origin was provided by genome-wide DNA methylation profiling.4 This innovative technology has suggested that the cell of origin of supratentorial tumors differs from that of infratentorial and spinal tumors. Ependymoma can be subdivided into at least 9 subgroups with etiological, clinical, demographic, prognostic, and molecular specificities. Each
anatomical zone may be divided into 3 subpopulations: spine (SP), posterior fossa (PF), and supratentorial region (ST). WHO grade I subependymoma (SE) is named ST-SE, PF-SE, and SP-SE according to its site, and occurs in adults only. The 2 remaining spinal subgroups match the histopathological classification of WHO grade I myxopapillary ependymoma (SP-MPE) and WHO grade II/III ependymoma (SP-EPN). The 2 remaining subgroups in the posterior fossa are called PF-EPN-A and PF-EPN-B. PF-EPN-A tumors are seen mostly in infants and young children: they show an aggressive behavior with a high recurrence rate and poor clinical outcome. In contrast, PF-EPN-B tumors are found mainly in adolescents and young adults and are associated with a better prognosis. The 2 remaining subgroups in the supratentorial region are called ST-EPN-v-rel avian reticuloendotheliosis viral oncogene homolog A (RELA) and ST-EPN–Yes-associated protein 1 (YAP1). The former is characterized by fusions between a gene with unknown function, C11orf95, and the nuclear factor-kappaB effector, RELA. The ST-EPN–RELA subgroup is more frequent (75%), and occurs in children and adults. It may have more aggressive behavior, though this is not clear, as clear-cell ependymomas with branching capillaries carry this fusion gene and have a good prognosis. The 2016 WHO classification of central nervous system tumors recognizes the supratentorial molecular variant, ST-EPN–RELA, as a separate pathological disease entity. The ST-EPN–YAP1 is characterized by recurrent fusions to the oncogene YAP1 and is diagnosed mainly in childhood. Multivariate survival analyses suggest that molecular subgrouping may become in the close future a major prognostic factor that will be used to tailor therapeutic options according to initial prognostic data. However, these data are currently based on retrospective analysis of heterogeneous series, and though numbers are huge, this requires prospective validation. The European Ependymoma Biology Consortium program “Biomarkers of Ependymomas in Children and Adolescents” (BIOMECa), attached to the SIOP Ependymoma II protocol, is intended to prospectively validate these prognostic factors in a prospective randomized series of patients. Apart from molecular subgrouping, it will aim at confirming the universally recognized 1q gain as a major prognostic factor and validating other factors such as tenascin C in posterior fossa tumors.

Treatment

The removal of ependymoma is crucial. For children with raised intracranial pressure due to a posterior fossa tumor, shunting is the initial step. It may be obtained via ventriculo-cisternostomy or ventriculo-peritoneal shunt or external drainage. Complete removal remains the major prognostic factor in most series. It may be achieved in one or several steps, with similar outcome, though increased risk of sequelae. This explains why the procedures of the SIOP Ependymoma II protocol, which is currently running, includes a central review of initial and postsurgical imaging, with central surgical advice for a second look when feasible, either by the initial or by a more skilled surgeon. These advices are organized nationally. Though both PF-EPN-A and PF-EPN-B tumors benefit from gross total resection, the impact of resection may not be equivalent: survival rates are uniformly poor for incompletely resected PF-EPN-A, even after completion of radiation therapy, while a subset of patients with gross totally resected PF-EPN-B tumors do not recur, even in the absence of radiotherapy. The standard of postoperative care in localized ependymoma is to deliver local radiation therapy when feasible. A dose of 59.4 Gy is delivered in most cases, though in the youngest children and in those who underwent several surgeries and/or have poor neurological status, this dose should be decreased to 54 Gy in order to avoid major sequelae, including radionecrosis. Radiation margins depend on the accuracy of the immobilizing device but are usually on gross total volume with a clinical total volume of 0.5 cm and a planning target volume of 0.3 to 0.5 cm³. Iterative general anesthesia may be required in the youngest children and requires a dedicated radiotherapy and anesthetic team; hypnosis may be an alternative. The role of proton therapy, especially in the youngest children, is still under investigation. With the systematic use of focal radiation, a 7-year progression-free survival rate of 77% may be achieved. The role of postradiation chemotherapy is explored in older children with complete removal through a randomization versus observation: half of the children will receive a 15-week alternating cycle of vincristine, etoposide, and cyclophosphamide with vincristine cisplatin in the SIOP Ependymoma II study. A similar randomization is proposed on the other side of the Atlantic by the Children’s Oncology Group ACNS0831 protocol. For those children who have an inoperable residue, the role of an 8 Gy radiotherapy boost on top of the standard radiation and the addition of pre- and postchemotherapy are currently being explored in the SIOP Ependymoma II protocol. For infants, since the late 1990s, the fear of neuropsychological sequelae due to radiation delivery on a developing brain has led to the design of chemotherapy-only programs. Their goal is to avoid or at least delay the delivery of radiation. Several series have been published. Based on the best results of the literature, a 41% five-year relapse-free survival may be expected. Histone deacetylase inhibitors have been shown to be effective in decreasing proliferation in vitro and in vivo. Their clinical utility is currently being explored by randomization on top of chemotherapy in the infant stratum of the SIOP Ependymoma II study. Finally, a registry is opened for those children under 21 that may not enter into one of the randomizations. All children will benefit from biological investigations organized by the BIOMECa program.
At time of relapse, the role of surgery should be highlighted. Irradiation of the infants who received first-line exclusive chemotherapy is part of the discussion with parents: the delay obtained by chemotherapy may or may not appear sufficient to avoid neurological sequelae. Reirradiation of children previously irradiated is encouraged.21 The extent of the fields (focal reirradiation and/or craniospinal irradiation) remains a matter of debate. Further profiling, chemotherapy, and innovative treatment should all be discussed in a multidisciplinary setting. Phase II chemotherapy studies have shown a low response rate.21 To date, anti-angiogenic drugs,22 tyrosine kinase32, or gamma secretase38 inhibitors have shown modest efficacy. An elegant in vitro test has unexpectedly suggested that 5-fluorouracil may be active in some subgroups of ependymoma.25 However, it did not translate into a meaningful clinical activity.26

Ependymal tumors are a biologically heterogeneous disease. Future therapy will probably take into account this heterogeneity, though current protocols are intended to validate definitively the concept of molecular subgroups. Participation in international cooperative trials is encouraged, and particularly the collection of fresh frozen samples to perform innovative research. As surgery is the main prognostic factor, referral of difficult cases to specialized teams is encouraged. The future will tell whether postradiation chemotherapy has a role in older children and whether the concept of histone deacetylation may add to chemotherapy in the youngest patients. Profiling of tumors at the time of relapse is warranted both to understand the pathways of resistance and to propose innovative strategies.

References


Unsolved Problems in the Medical Treatment of Gliomas: PCV or PC?

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Introduction

The combination of radiation therapy plus chemotherapy with procarbazine, lomustine, and vincristine (PCV) is the postsurgical treatment of choice in high-risk low-grade gliomas and in anaplastic oligodendrogial tumors, based on results of studies demonstrating the superiority of adding chemotherapy to treatment with local irradiation.1–3 Interest in adding chemotherapy to the treatment of oligodendrogial tumors arose from observing objective responses with PCV-like chemotherapy in small series of patients with recurrent disease.4,5 Two independent studies, one by the European Organisation for Research and Treatment of Cancer (EORTC) and the Medical Research Council Clinical Trials Group (EORTC 26951)6 and the other by the Radiation Therapy Oncology Group (RTOG 9402),7 randomized patients with anaplastic oligodendroglia or oligoastrocytoma after surgery to receive treatment with PCV plus radiotherapy or radiotherapy alone. The 2 trials differed slightly in study design, chemotherapy dose, and number of planned cycles. Chemotherapy was prior to irradiation in RTOG 9402 and after radiation in EORTC 26951; the doses of lomustine and procarbazine (PC) were higher and there was no dose ceiling for vincristine in the RTOG 9402 trial. Four cycles were planned in the RTOG 9402 trial, compared with 6 in the EORTC 26951 trial. Despite these differences, both trials demonstrated that the addition of PCV to radiation therapy undoubtedly increased overall survival for patients harboring the 1p/19q codeletion, now recognized as true oligodendrogial tumors according to the recent World Health Organization (WHO) classification for brain tumors,6 and grade III gliomas with oligodendrogial tumors with mixed morphology without the 1p/19q codeletion but with isocitrate dehydrogenase 1 mutations.7,8 These results led to major changes in the standard treatment of these diseases. However, it took more than 15 years to confirm the benefit of PCV. The EORTC 26951 trial began recruitment in 1996 and required 6 years to include 368 patients,6 while the RTOG 9402 trial began in 1994 and required 8 years to include 291 patients.10 The first reports of effectiveness date from 2006 and final results were published in 2013.1,2 (Table 1). PCV also produced regressions in low-grade gliomas11 and it was tested as first-line adjuvant treatment in the RTOG 9802 randomized trial, which compared radiation versus radiation plus PCV in low-grade gliomas with a high risk of relapse. This trial initially demonstrated an increase in progression-free survival12 and subsequently a clear increase in overall survival in the patients treated with radiation plus PCV (13.3 vs 7.8 years; hazard ratio [HR] for death, 0.59; P = 0.003).1 Total of 251 patients were included in the trial between 1998 and 2002, and mature results were not published until 2016.1 It thus took 18 years to change the standard of treatment of low-grade gliomas.13

PCV has a long trajectory in neuro-oncology, dating from a phase II study reported in 1975,14 and has since been demonstrated to be an active combination in numerous phase II and several phase III studies.15–24 PCV was more active in anaplastic astrocytoma than in glioblastoma,25–27 and better results were obtained in tumors with oligodendroglial components than in anaplastic astrocystoma.20,23 PCV was the control arm in several phase III trials in morphologically defined anaplastic tumors21,24–27 and in high-grade (III and IV) gliomas20,28 in different settings. Results of randomized clinical trials showed that PCV was more effective than carmustine (BCNU)21 or lomustine/teniposide (CCNU/VM26).29 However, a retrospective review of patients treated in the RTOG protocols with radiotherapy plus either PCV or BCNU found no differences between the 2 treatments.30 Furthermore, although temozolomide has lower toxicity than PCV, it has never been shown to be more effective than the PCV combination.27,28,31 (Table 1). Nevertheless, temozolomide was more effective than procarbazine alone in a randomized phase II trial for patients with relapsed glioblastomas.32

After more than 20 years of clinical trials, PCV has now come into its own as a standard treatment in neuro-oncology. Nevertheless, over these years, there has been rising concern about the role of vincristine in the PCV regimen. Since it is now clear that patients treated with PCV will have long survival, the dual objective of preserving quality of life and avoiding unnecessary toxicity has taken on a more prominent role.

Vincristine, the Blood–Brain Barrier, and Antitumor Activity

The blood–brain barrier (BBB) is a physical and biological barrier that protects the brain from pathogens and toxic molecules and regulates hypometabolic exchanges between the brain and blood to maintain brain homeostasis. Only highly lipophilic molecules can cross the BBB by passive paracellular diffusion. However, the BBB is disrupted physiologically in restricted zones of the brain close to the third and the fourth ventricles, the circumventricular organs, and around brain metastases or high-grade primary tumors, such as glioblastoma. These disrupted areas constitute the so-called blood–tumor barrier (BTB), where anarchic, disorganized, and leaky blood vessels increase permeability and allow the passage of certain drugs without lipophilic properties. In fact, this phenomenon is the main reason why gadolinium enhancement reveals the disruption of the BBB in high-grade brain tumors, while this disruption seems absent in low-grade tumors, which commonly do not enhance.33–35 The brain adjacent to tumor (BAT) includes invasive
escaping tumor cells infiltrated through a normal brain. This infiltrative pattern is seen around the enhanced part of T1 gadolinium images with T2 and T2/fluid attenuated inversion recovery sequences in high-grade tumors and is the most frequent pattern for low-grade tumors, indicating a generally preserved BBB, although some parts may have small disruptions that are not enough to leak gadolinium.36

Five main physicochemical parameters are involved in the ability of drugs to cross the normal BBB: size (molecular weight); lipophilicity; electrical charge; protein plasma binding; and susceptibility to transport by efflux pumps and transporters. Some mathematical models, including the “rule of five” developed by Lipinski,37 have been designed to predict in silico the ability to cross the BBB, but not all these predictions are consistent with experimental data.38 A combination of in silico, in vitro data and in vivo data can better predict this ability. Nowadays pharmacokinetic studies of new drugs are performed in blood and cerebrospinal fluid (CSF) to test the ability to cross the BBB, and the detection of drug levels in CSF is widely used as a surrogate marker of brain penetration. However, CSF is isolated from the brain and blood by the arachnoid and pia mater, which prevent diffusion from both the blood to CSF and from CSF to the brain through the CSF transport systems and limit diffusion to 1–2 mm.39,40 The distribution of drugs into CSF is thus not necessarily representative of drug distribution in brain parenchyma or in tumor tissue.

Given the lipid-soluble properties and preclinical pharmacokinetic data on both lomustine and procarbazine, it was expected that they would cross the capillaries of T1 gadolinium images with T2 and T2/fluid attenuated inversion recovery sequences in high-grade tumors and is the most frequent pattern for low-grade tumors, indicating a generally preserved BBB, although some parts may have small disruptions that are not enough to leak gadolinium.36

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PCV, procarbazine, lomustine and vincristine; NCOG, Northern California Oncology Group; RT, radiotherapy; BCNU, carmustine; HGG, high-grade gliomas; OS, overall survival; AA, anaplastic astrocytoma; GB, glioblastoma; DFMO, eflornithine; AG, anaplastic gliomas; AO, anaplastic oligodendroglioma; RTOG, Radiation Therapy Oncology Group; BUdR, bromodeoxyuridine; ISRCTN, International Standard Registered Clinical Society Study Number; TMZ, temozolomide; EORTC, European Organisation for Research and Treatment of Cancer; AOA, anaplastic oligoastrocytoma; LGG, low-grade gliomas; PFS, progression-free survival; NOA, Neurooncology Working Group of the German Cancer Society; CIMP, CpG island methylator phenotype; CT, chemotherapy; TTP, time to progression; mPCV, modified PCV; CCNU/VM-26, lomustine/teniposide
both normal brain and tumor and maintain constant drug concentrations in the tumor and the BAT, which is thought to have a normal BBB. It was further expected that vincristine would cross the BBB, due in part to its lipophilicity (log P: 1-octanol/water partition coefficient of 2.5–2.8), However, there were no further data to support this assumption, and moreover, its molecular weight (825 daltons) indicates a low capillary permeability coefficient (6.4 x 10^-7 cm/s) that is insufficient for an efficient diffusion across the lipid membranes of the BBB endothelium. Moreover, even if drug levels in CSF were a proven surrogate marker of levels in brain, vincristine has not been found in CSF after intravenous administration in adults and children with malignant hematological diseases with nondisrupted BBB. In addition, vincristine does not fulfill all the necessary in silico conditions for passing the BBB, although preclinical studies have found that vincristine crosses the BBB by previous radiotherapy but does not accumulate in the brain in sufficient concentrations.

The antitumor activity of vincristine is also controversial. While it seems to be one of the most active drugs in vitro, its efficacy in vivo has yet to be demonstrated by today’s standards. In fact, its use was discontinued in an early trial, since it was found to reduce the efficacy of carmustine when the 2 agents were combined.

### PCV Regimen

Procarbazine is a cell cycle phase–nonspecific prodrug and derivative of hydrazine whose mechanism of action has not yet been clearly defined. Lomustine is a lipid-soluble alkylating agent nitrosourea compound that alkylates DNA and RNA, can cross-link DNA, and inhibits several enzymes by carbamoylation. It is a cell cycle phase–nonspecific agent. Vincristine is a naturally occurring vinca alkaloid. Vinca alkaloids are antimicrotubule agents that block mitosis by arresting cells in the metaphase. Vincristine is thought to act by preventing the polymerization of tubulin to form microtubules, as well as by inducing depolymerization of formed tubules. Like all vinca alkaloids, vincristine is cell cycle phase specific for M phase and S phase.

The combination of the 3 drugs in the PCV regimen is administered every 6–8 weeks. It is a quite complicated schema that combines oral and intravenous administration. It is also relatively inconvenient for the patient, as it requires regular visits to the hospital for the intravenous administration of vincristine.

### Table 2. Characteristics of drugs included in the PCV regimen

<table>
<thead>
<tr>
<th></th>
<th>Vincristine</th>
<th>Procarbazine</th>
<th>Lomustine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Vinca alkaloid: acting as antimicrotubule</td>
<td>Alkylating agent: cell cycle phase nonspecific</td>
<td>Alkylating agent: nitrosourea</td>
</tr>
<tr>
<td><strong>Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipophilicity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Molecular weight (daltons)</td>
<td>825</td>
<td>221</td>
<td>234</td>
</tr>
<tr>
<td><strong>Dose (every 6 weeks)</strong></td>
<td>1.4 mg/m² (max 2 mg)</td>
<td>60–100 mg/m², once daily</td>
<td>110–130 mg/m² in one dose</td>
</tr>
<tr>
<td>days 8 &amp; 29</td>
<td>days 8 to 21</td>
<td>day 1</td>
<td></td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Intravenous</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Extensively metabolized, mainly hepatic (CYP3A4–CYP3A5)</td>
<td>Hepatic (CYP450) and renal</td>
<td>Extensive hepatic metabolism (CYP450)</td>
</tr>
<tr>
<td><strong>Terminal half-life elimination</strong></td>
<td>Range of 19–155 hours</td>
<td>1 hour</td>
<td>16–72 hours</td>
</tr>
<tr>
<td><strong>Main adverse effects</strong></td>
<td>• Peripheral neurotoxicity</td>
<td>• Myelosuppression</td>
<td>• Myelosuppression</td>
</tr>
<tr>
<td></td>
<td>• Myelosuppression</td>
<td>• Nausea and vomiting</td>
<td>• Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>• Constipation</td>
<td>• Neurotoxicity</td>
<td>• Nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td>• Hyponatremia–SIADH</td>
<td></td>
<td>• Pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td>• Hair loss</td>
<td></td>
<td>• Visual disturbances</td>
</tr>
<tr>
<td><strong>Blood–brain barrier (BBB)</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug present in CSF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rule of five (Lipinski)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>In silico prediction</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Expected to cross intact BBB?</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

SIADH, syndrome of inappropriate antidiuretic hormone secretion
low-grade gliomas. In general, tolerability is low and dose reductions and treatment delays due to hematological toxicity are common. In the RTOG 9402 trial, only 54% of patients were able to receive the 4 planned cycles before radiation therapy and 25% of patients had to stop due to toxicity. In the EORTC 26951 trial, the median number of cycles was 3 of the 6 planned cycles, and in the RTOG 9802 trial of low-grade gliomas, of the 6 planned cycles, the median number of cycles was 3 for procarbazine, 4 for lomustine, and 4 for vincristine.

PCV versus PC

There is some doubt that the addition of vincristine provides any advantage over PC alone. Clinical trials comparing PC versus PCV have not been conducted so far. Only 2 retrospective analyses have compared PCV with PC. Vesper et al treated 61 patients with PCV and compared their outcome with that of 84 patients treated with PC from 1990 to 2003. All the patients had morphologically diagnosed oligodendrogliomas or oligoastrocytomomas. A multivariate analysis adjusted for prognostic factors found no differences in progression-free survival between the 2 cohorts (HR 0.81; 95% CI 0.53–1.25; \( P = 0.346 \)). However, neurological toxicity was more frequent in patients treated with PCV: 12% grade 2 and 4% grade 3 sensory toxicity in PCV versus 0% in PC (\( P = 0.002 \)); 4% grade 2 motor toxicity in PCV versus 0% in PC (\( P = 0.26 \)). Surprisingly, myelotoxicity was higher for patients treated with PC: 57% grade 2; 25% grade 3, and 2% grade 4 in PC versus 30%, 17%, and 2%, respectively, in PCV (\( P < 0.001 \)). More recently, Webre et al retrospectively compared 21 patients who received PC and 76 patients who received PCV. With a median follow-up of 9.9 years, they found no differences in progression-free or overall survival. Findings on toxicity were similar to those in the study by Vesper et al: 14.5% neurotoxicity in PCV versus 0% in PC; 23.8% myelotoxicity in PC versus 5.3% in PCV (\( P = 0.02 \)). The authors attribute the greater frequency of myelotoxicity in the PC group to the younger age of patients receiving PCV (PCV: median age, 37; range, 16.7–66.7 vs PC: median age, 47.8; range 23.9–65.7; \( P = 0.05 \)), which increased their tolerability of higher doses of chemotherapy. In fact, the absence of vincristine in the PC schema did not decrease the frequency of dose reductions (PC, 38.1% vs PCV, 35.5%; \( P = 0.83 \)) or treatment delays (PC, 28.6% vs PCV, 30.6%; \( P = 0.88 \)). Although these data must be interpreted with caution, since these were retrospective studies, they seem to indicate that the only toxicity that could be reduced by eliminating vincristine is neurological, while myelotoxicity seems somewhat higher with PC than with PCV. Nevertheless, it is intriguing that both studies found an increase in myelotoxicity when one of the objectives of eliminating vincristine was to reduce toxicity. This seemingly contradictory finding may be due to a potential interaction between procarbazine and vincristine. Both procarbazine and vincristine are metabolized in the liver through cytochrome P450. Vincristine has a long terminal half-life and the 2 drugs coincide on day 8, when vincristine is administered and oral procarbazine starts for 15 days. We can hypothesize that the interaction of the 2 drugs could lead to a decrease in procarbazine plasmatic levels through an unknown pharmacological mechanism, which would improve the hematological tolerability of PCV over PC. While this is only hypothetical, it is a paradoxical effect that merits further investigation.

Conclusion

PCV has become the standard of treatment for oligodendroglial tumors as defined in the recent WHO classification—1p/19q codeleted tumors—and for low-grade gliomas at high risk of relapse, though it took more than 20 years to demonstrate a role for this chemotherapy regimen in the treatment of these patients. PCV has been used over the last 29 years as the control arm of multiple randomized studies. However, the role of vincristine in this schema remains unclear. Available data in patients do not demonstrate that vincristine reaches the tumor in adequate concentrations, as it seems to cross only a disrupted BBB. In particular, low-grade gliomas seem to have an intact BBB, as they do not show gadolinium enhancement on MRI, suggesting that in these patients, vincristine would have no benefit, as it would not cross the BBB. On the other hand, eliminating vincristine from the chemotherapy combination would have the advantage of facilitating administration by eliminating the intravenous treatment, which now requires patients to go to the hospital for treatment. In addition, eliminating vincristine would likely reduce some neurotoxicity, though not that due to procarbazine, which is also a neurotoxic drug. Two separate retrospective noncontrolled studies reached the same conclusion: vincristine can be omitted because progression-free and overall survival were similar for PCV and PC. However, neither study found a decrease in dose reductions or treatment delays with PC. Moreover, although neurotoxicity was lower in patients treated with PC, myelotoxicity was slightly higher, raising the hypothesis that procarbazine and vincristine may interact in liver metabolism. However, no data on this hypothesis are currently available. Taken together, these findings indicate that the inclusion of vincristine is still an unsolved problem in neurooncology. Faced with this problem, we can continue as is or search for solutions. Continuing as is would not necessarily present problems, as vincristine is not an expensive drug and it is not clear that toxicity would be reduced by its omission. However, there are 3 strategies that could help to find solutions. Firstly, a randomized non-inferiority trial could be performed to compare PCV with PC. If this
trial were conducted in a histology with shorter outcome, such as glioblastoma, it would avoid the long wait for results that is required in other histologies, although it would then be necessary to evaluate whether results in glioblastoma were transferable to oligodendroglial tumors and low-grade tumors. Nevertheless, such a trial would be ethically and clinically correct, as both PC and PCV contain lomustine, the standard control arm for recurrent glioblastoma, according to EORTC guidelines. In fact, some evidence from earlier studies suggests that PCV could be more active than BCNU or CCNU/VM26 (Table 1). Secondly, a thorough brain distribution and pharmacokinetic study of PCV would shed light on the ability of vincristine to cross the BBB but not on its role in terms of clinical benefit. Finally, consensus guidelines to eliminate vincristine would at least provide an easier treatment schedule and reduce peripheral neurotoxicity, maybe at the cost of greater myelotoxicity.

References

29. Jeremic B, Jovanovic D, Djuric LJ et al. Advantage of post-radiotherapy chemotherapy with CCNU, procarbazine, and


Radiation Therapy for Intracranial Meningiomas: Current Results and Controversial Issues

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Abstract

Meningiomas are common primary brain tumors. According to World Health Organization (WHO) classification, most meningiomas are benign lesions, whereas a minority of them are classified as atypical or malignant. Surgical resection is the cornerstone of meningioma therapy and represents the definitive treatment for the majority of patients, especially those with benign tumors at favorable locations. Beyond surgery, external beam radiation therapy (RT) is frequently used to increase local control after incomplete resection of a benign meningioma arising at unfavorable locations, or after surgical resection of atypical and malignant meningiomas, even following macroscopic removal. The current review summarizes the published literature on the use of RT for intracranial meningiomas, with an emphasis on outcomes for either benign or nonbenign tumors. The efficacy of RT given adjuvantly or at tumor recurrence and the safety and efficacy of different radiation techniques have been examined.

Keywords: meningioma, radiation therapy, fractionated radiotherapy, stereotactic radiosurgery

Introduction

Meningiomas are the most common primary intracranial tumors and account for more than one third of all central brain tumors. Based on local invasiveness and cellular features of atypia, meningiomas are histologically characterized as benign (grade I), atypical (grade II), or malignant (grade III) by World Health Organization (WHO) classification. Surgical excision is the treatment of choice for accessible intracranial meningiomas; following apparently complete resection of a WHO grade I meningioma, the reported local control is up to 90% at 10 years and 80% at 15 years. Beyond surgery, external beam radiotherapy (RT) is frequently used to increase local control after incomplete resection of a benign meningioma arising at unfavorable locations, or after surgical resection of atypical (grade II) and malignant (grade III) meningiomas, even following macroscopic removal.

Both fractionated RT and stereotactic radiosurgery (SRS) have been employed after incomplete excision/progression of a benign meningioma with a reported 10-year local control in the region of 75%–90%; in contrast, lower local control rates have been observed following radiation for atypical and malignant meningiomas. Despite RT being an essential part of the management of meningiomas, several issues remain controversial, including the efficacy of radiation treatment for atypical and malignant meningiomas, the timing of the treatment (early versus delayed postoperative RT), the optimal radiation technique, and dose/fractionation schedules.

We have provided a literature review on the effectiveness of fractionated RT and SRS for intracranial meningiomas with the intent to define their role in the context of different clinical situations. Safety and efficacy of different radiation techniques were also examined.

Histopathologic Classification

According to the latest WHO classification, tumors with low mitotic rate (less than 4 per 10 high power fields [HPF]) are classified as benign (WHO grade I). For atypical meningiomas or brain invasion, a mitotic count of 4–19 per HPF is a sufficient criterion for the diagnosis. As for the previous WHO classifications, atypical meningiomas can also be diagnosed on the basis of the presence of 3 or more of the following properties: sheetlike growth, spontaneous necrosis, high cellularity, prominent nucleoli, and small cells with a high nuclear-cytoplasmic ratio. Malignant (WHO grade III) meningiomas are characterized by elevated mitotic activity (20 or more per HPF) or frank anaplasia with histology resembling carcinoma, melanoma, or sarcoma. In addition, clear cell or chordoid cell meningiomas are specific histologic subtypes classified...
as grade II, and rhabdoid or papillary meningiomas are specific histologic subtypes classified as grade III. When these criteria are applied, the majority of meningiomas are classified as benign, 20%–30% as atypical, and 1%–3% as malignant.

Radiotherapy for Benign Meningiomas

Postoperative conventional RT has been reported as effective either following incomplete resection or at the time of tumor recurrence. Using a dose of 50–55 Gy in 30–33 fractions, local control rates are in the region of 75%–90% (Table 1).20–24 In a series of 82 patients with skull base meningiomas who received conventional RT, Nutting et al23 reported 5-year and 10-year tumor control rates of 92% and 83%, respectively. In a series of 101 patients treated with 3D conformal RT, Mendenhall et al24 reported local control rates of 95% at 5 years and 92% at 10 and 15 years, respectively, and cause-specific survival rates of 97% and 92%, respectively. The reported control and survival after subtotal resection and RT are similar to those observed after complete resection, and better than those achieved with incomplete resection alone.15 There is little evidence that timing of RT is important, as local control and survival rates are similar whether the treatment is given postoperatively or at the time of recurrence.22–24

The toxicity of conventional RT, including the risk of developing neurological deficits, especially optic neuropathy, brain necrosis, cognitive deficits, and pituitary deficits, is relatively low (Table 1).20–24 Radiation-induced brain necrosis with associated clinical neurological decline is a severe complication of RT; however, it remains exceptional when doses less than 60 Gy are used. Hypopituitarism is reported in 5%–15% of patients. Radiation injury to the optic apparatus, presenting as decreased visual acuity or visual field defects, is reported in 0%–3% of irradiated patients. Other cranial deficits are reported in less than 1%–4% of patients.

Assuming that RT is of value in achieving tumor control, more sophisticated fractionated radiation techniques, including fractionated stereotactic radiotherapy (FSRT) and intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT), have been employed in patients with intracranial meningiomas. New techniques allow for more precise target localization and accurate dose delivery as compared with conformal RT, resulting in low radiation doses to surrounding sensitive structures, such as the optic pathway and the brainstem.

A summary of recent published series of FSRT/IMRT for skull base meningiomas is shown in Table 1.25–32 A 10-year local control of 90%–100% and overall survival up to 100% have been reported with the use of either FSRT or IMRT for the control of large complex-shaped meningiomas, and this is associated with low incidence of radiation-induced optic neuropathy, cavernous sinus cranial nerve deficits, and hypopituitarism. In a series of 506 patients with a skull base meningioma who received FSRT (n = 376) or IMRT (n = 131), Combs et al31 observed similar local control rates of 91% at 10 years for patients with a benign meningioma; similar tumor control rates have been observed in other published series,25–27,30,32 suggesting that both techniques are effective as primary and salvage treatment for meningiomas, with a local control at 5 and 10 years similar to that reported with conformal RT and limited toxicity.

Table 1. Summary of selected published studies on the fractionated radiation therapy of benign meningiomas

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (n)</th>
<th>Technique</th>
<th>Volume (mL)</th>
<th>Dose (Gy)</th>
<th>Follow-up (months)</th>
<th>Local Control (%)</th>
<th>Late Toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldsmith et al, 1994</td>
<td>117</td>
<td>CRT</td>
<td>NA</td>
<td>54</td>
<td>40</td>
<td>89 at 5 and 77 at 10 years</td>
<td>3.6</td>
</tr>
<tr>
<td>Maire et al, 1995</td>
<td>91</td>
<td>CRT</td>
<td>NA</td>
<td>52</td>
<td>40</td>
<td>94</td>
<td>6.5</td>
</tr>
<tr>
<td>Nutting et al, 1999</td>
<td>82</td>
<td>CRT</td>
<td>55–60</td>
<td>41</td>
<td>92 at 5 and 83 at 10 years</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Vendrely et al, 1999</td>
<td>156</td>
<td>CRT</td>
<td>NA</td>
<td>50</td>
<td>40</td>
<td>79 at 5 years</td>
<td>11.5</td>
</tr>
<tr>
<td>Mendenhall et al, 2003</td>
<td>101</td>
<td>CRT</td>
<td>NA</td>
<td>54</td>
<td>64</td>
<td>95 at 5, 92 at 10 and 15 years</td>
<td>8</td>
</tr>
<tr>
<td>Henzel et al, 2006</td>
<td>84</td>
<td>FSRT</td>
<td>11.1</td>
<td>56</td>
<td>30</td>
<td>100</td>
<td>NA</td>
</tr>
<tr>
<td>Tanzler et al, 2010</td>
<td>144</td>
<td>FSRT</td>
<td>NA</td>
<td>52.7</td>
<td>87</td>
<td>97 at 5 and 95 at 10 years</td>
<td>7</td>
</tr>
<tr>
<td>Minniti et al, 2011</td>
<td>52</td>
<td>FSRT</td>
<td>35.4</td>
<td>50</td>
<td>42</td>
<td>93 at 5 years</td>
<td>5.5</td>
</tr>
<tr>
<td>Slater et al, 2012</td>
<td>68</td>
<td>Protons</td>
<td>27.6</td>
<td>57</td>
<td>74</td>
<td>99 at 5 years</td>
<td>9</td>
</tr>
<tr>
<td>Weber et al, 2012</td>
<td>29</td>
<td>Protons</td>
<td>21.5</td>
<td>56</td>
<td>62</td>
<td>100 at 5 years</td>
<td>15.5</td>
</tr>
<tr>
<td>Solda et al, 2013</td>
<td>222</td>
<td>FSRT</td>
<td>12</td>
<td>50/55</td>
<td>43</td>
<td>100 at 5 and 10 years</td>
<td>4.5</td>
</tr>
<tr>
<td>Combs et al, 2013</td>
<td>507</td>
<td>FSRT/IMRT</td>
<td>NA</td>
<td>57.6</td>
<td>107</td>
<td>91 at 10 years</td>
<td>1.8</td>
</tr>
<tr>
<td>Fokas et al, 2014</td>
<td>253</td>
<td>FSRT</td>
<td>14.4</td>
<td>55.8</td>
<td>50</td>
<td>92.9 at 5 and 87.5 at 10 years</td>
<td>3</td>
</tr>
</tbody>
</table>

CRT, conventional radiation therapy; FSRT, fractionated stereotactic radiation therapy; IMRT, intensity modulated radiation therapy; NA, not assessed.
Proton irradiation can achieve better target-dose conformity compared with 3D-conformal RT and IMRT and the advantage becomes more apparent for large volumes. Distribution of low and intermediate doses to portions of irradiated brain are significantly lower with protons compared with photons. The reported tumor control after proton beam RT is 90% at 5 years, similar to that observed with fractionated photon techniques (Table 1).28,29

SRS, delivered as single fraction or, less frequently, as multiple 2–5 fractions, has been extensively employed in patients with residual/recurrent meningiomas. The main radiation techniques include Gamma Knife, CyberKnife, and a modified linear accelerator (LINAC).33–37 In its new version, Gamma Knife uses 192 radioactive cobalt-60 sources (each with 3 different apertures of 4 mm, 8 mm, and 16 mm, respectively) that are spherically arrayed in a single internal collimation system via collimator helmets to focus their beams to a center point. A highly conformal but inhomogeneous dose distribution and high central tumor dose can be achieved through the optimal combinations of the number, the aperture, and the position of the collimators.15,33 CyberKnife (Accuray, Sunnyvale, California) is a relatively new technological device that combines a mobile LINAC mounted on a robotic arm with an image-guided robotic system.34,35 Patients are fixed in a thermoplastic mask and the treatment can be delivered as single-fraction or multifraction SRS. LINAC is the most frequently used device for delivery of SRS in the world and uses multiple fixed fields or arcs shaped using a multileaf collimator with a leaf width of between 2.5 and 5 mm.15,36,37 Dose conformity can be improved by the use of intensity modulation of the beams or VMAT, with results similar to those achieved with the Gamma Knife and the CyberKnife. The superiority in terms of dose delivery and distribution for each of these techniques remains a matter of debate. Currently, no comparative studies have demonstrated the clinical superiority of a technique over the others in terms of local control and radiation-induced toxicity for patients with brain tumors.

A summary of main recent published series of SRS in skull base meningiomas is shown in Table 2.38–50 Large recently published series report actuarial control rates in the range of 90%–95% at 5 years and 80%–90% at 10 and 15 years using a median dose to the tumor margin of 13–16 Gy. The rate of tumor shrinkage varied in all studies, ranging from 16% to 69%, and tended to increase in patients with longer follow-up. Similarly, a variable improvement of neurological functions has been shown in 10%–60% of patients. The rate of significant complications at doses of 13–15 Gy (as currently used in the majority of cancer centers) is less than 8%, being represented by either transient or permanent complications. The risk of clinically significant radiation-induced optic neuropathy for patients receiving SRS for skull base meningiomas is 1%–2% following doses to the optic chiasm below 10 Gy, although this percentage may significantly increase for higher doses.51–57 A few studies have reported the use of multifraction SRS (2 to 5 daily fractions) for relatively large meningiomas located near critical structures. Using doses of 21–25 Gy delivered in 3–5 fractions, a few series report a local control of 93%–95% at 5 years, and this has been associated with low cranial nerve toxicity.42,50,58–60

Despite the frequent use of RT, several issues remain a matter of debate. For example, when is the right time and what is the right fractionation approach when RT is considered? Do all meningioma-suspect lesions require histological verification of the diagnosis? Is radiation an alternative to surgery?

### Table 2. Summary of selected published studies on stereotactic radiosurgery of intracranial meningiomas

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (n)</th>
<th>Technique</th>
<th>Volume (mL)</th>
<th>Dose (Gy)</th>
<th>Follow-up (months)</th>
<th>Local Control (%)</th>
<th>Late Toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krell et al, 2005</td>
<td>200</td>
<td>GK</td>
<td>6.5</td>
<td>12</td>
<td>95</td>
<td>98 at 5 and 97 at 10 years</td>
<td>4.5</td>
</tr>
<tr>
<td>Kollova et al, 2007</td>
<td>368</td>
<td>GK</td>
<td>4.4</td>
<td>12.5</td>
<td>60</td>
<td>98 at 5 years</td>
<td>15.9</td>
</tr>
<tr>
<td>Feigl et al, 2007</td>
<td>214</td>
<td>GK</td>
<td>6.5</td>
<td>13.6</td>
<td>24</td>
<td>86.3 at 4 years</td>
<td>6.7</td>
</tr>
<tr>
<td>Kondziolka et al, 2008</td>
<td>972</td>
<td>GK</td>
<td>7.4</td>
<td>14</td>
<td>48</td>
<td>87 at 10 and 15 years</td>
<td>7.7</td>
</tr>
<tr>
<td>Colombo</td>
<td>199</td>
<td>CK</td>
<td>7.5</td>
<td>16–25*</td>
<td>30</td>
<td>96</td>
<td>3.5</td>
</tr>
<tr>
<td>Skeie et al, 2010</td>
<td>100</td>
<td>GK</td>
<td>11.1</td>
<td>13</td>
<td>32</td>
<td>90.4 at 5 and 10 years</td>
<td>6</td>
</tr>
<tr>
<td>Halasz et al, 2011</td>
<td>50</td>
<td>Protons</td>
<td>27.4</td>
<td>13</td>
<td>36</td>
<td>94 at 3 years</td>
<td>5.9</td>
</tr>
<tr>
<td>Pollock et al, 2012</td>
<td>251</td>
<td>GK</td>
<td>7.7</td>
<td>15.8</td>
<td>62.9</td>
<td>99.4 at 10 years</td>
<td>11.5 at 5 years</td>
</tr>
<tr>
<td>Santacroce et al, 2012</td>
<td>3768</td>
<td>GK</td>
<td>4.8</td>
<td>14</td>
<td>63</td>
<td>95.2 at 5 and 88.6 at 10 years</td>
<td>6.6</td>
</tr>
<tr>
<td>Starke et al, 2014</td>
<td>254</td>
<td>GK</td>
<td>NA</td>
<td>13</td>
<td>71</td>
<td>93 at 5 and 84 at 10 years</td>
<td>6.4</td>
</tr>
<tr>
<td>Ding et al, 2014</td>
<td>177</td>
<td>GK</td>
<td>3.6</td>
<td>13</td>
<td>47</td>
<td>93 at 5 and 77 at 10 years</td>
<td>9</td>
</tr>
<tr>
<td>Sheean et al, 2014</td>
<td>763</td>
<td>GK</td>
<td>4.1</td>
<td>13</td>
<td>66.7</td>
<td>95 at 5 and 82 at 10 years</td>
<td>9.6</td>
</tr>
<tr>
<td>Marchetti et al, 2016</td>
<td>143</td>
<td>CK</td>
<td>11</td>
<td>21–25**</td>
<td>44</td>
<td>93 at 5 years</td>
<td>5.1</td>
</tr>
</tbody>
</table>

GK, GammaKnife; CK, CyberKnife; *16–25 Gy delivered in 2–5 fractions in 150 patients; **21–25 Gy delivered in 3–5 fractions.
Grade I meningiomas are slow-growing tumors; however, a minority of them can grow more rapidly. Although asymptomatic incidentally discovered meningiomas and small postoperative lesions can be managed by observation only with MRI at intervals of 6–12 months, an early postoperative radiation treatment after incomplete surgical resection is a reasonable approach for the majority of meningiomas to prevent the development of neurological deficits and to treat smaller tumor volumes (minimizing the risk of long-term radiation-induced toxicity). Interestingly, the presence of molecular alterations (i.e., telomerase reverse transcriptase, Akt-1, or Smoothened mutations) are associated with different degrees of aggressiveness of meningiomas.19 Future research is needed to investigate the predicting value of different molecular markers on tumor recurrence and biological behavior, with the aim of selecting which patients will benefit from adjuvant therapy.

For elderly patients who cannot tolerate surgery or for tumors not safely accessible by surgery, like cavernous sinus meningiomas, RT alone is frequently employed, tumors not safely accessible by surgery, like cavernous sinus meningiomas, RT alone is frequently employed, with reported clinical outcomes similar to those observed for postoperative RT.64 If imaging is highly suggestive of a meningioma, histological verification is not mandatory; however, a regular follow-up is required, since modern imaging tools can suggest the histological diagnosis, but usually not tumor grading.

The optimal radiation technique for benign meningiomas is still a controversial issue. Both SRS and FSRT are safe and effective techniques for the treatment of intracranial meningiomas, affording comparable satisfactory long-term tumor control. In clinical practice, SRS or FSRT should be chosen on the basis of size and location of the meningioma. Currently, single fraction SRS using doses of 13–16 Gy is recommended for small- to moderately-sized meningiomas (<2.5–3 cm), keeping doses to the optic apparatus and to the brainstem below 8–10 Gy and 12.5 Gy, respectively. A few series suggest that multifraction SRS, usually 21–25 Gy in 3–5 fractions, is a feasible treatment option when a single fraction dose carries a high risk of toxicity.42,50,58–60; however, studies with more patients and longer follow-up are required to draw definitive conclusions. FSRT (50–56 Gy in 1.8–2 Gy fractions) would be the recommended radiation treatment modality for lesions >3 cm in size and/or compressing the brainstem and the optic pathway.

Radiotherapy for Atypical and Malignant Meningiomas

Postoperative RT is frequently employed as adjuvant treatment for patients with atypical and malignant meningiomas because of their significant probability of regrowth/recurrence. The Radiation Therapy Oncology Group 0539 study65 has evaluated the 3-year progression-free survival in 52 patients with either newly diagnosed WHO grade II meningioma with gross total resection or recurrent WHO grade I of any resection extent treated with IMRT. Results were compared with those observed in historical control of intermediate-risk meningiomas. Three-year progression-free survival was 96.0% and this was associated with minimal toxicity. No differences in progression-free survival were observed between the subgroups, supporting the use of postoperative RT for gross totally resected atypical meningiomas or recurrent benign meningiomas. Several other retrospective series report variable median 5-year progression-free survival rates of 38% to 100% and median overall survival rates of 51% to 100% after RT.53–80 Although most of the recent studies seem to indicate that adjuvant RT improves progression-free survival and overall survival for atypical meningiomas, the superiority of postoperative RT versus observation in terms of progression-free survival and overall survival remains an unresolved question, especially for totally resected tumors. Selected studies reporting clinical outcomes of patients with atypical meningioma following surgery with or without adjuvant RT are summarized in Table 3.

In a series of 91 patients with atypical meningioma receiving adjuvant RT or not receiving adjuvant RT at Dana-Farber/Brigham and Women’s Cancer Center between 1997 and 2011, Aizer et al75 observed local control rates of 82.6% and 67.8% at 5 years in patients who did and did not receive RT, respectively (p = 0.04). At multivariate analysis, the association between RT and local recurrence was significant (hazard ratio [HR], 0.24; 95% CI, 0.06–0.91; p = 0.04); however, no differences in overall survival were seen between groups. In a series of 108 patients with grade II meningioma who underwent gross total resection at the University of California from 1993 to 2004, Aghi et al67 observed actuarial tumor recurrence rates of 41% and 48% at 5 and 10 years, respectively. Adjuvant RT was associated with a trend toward decreased local recurrence (p = 0.1) in patients who underwent gross total resection; however, only 8 patients received postoperative RT. Better progression-free survival rates in patients receiving postoperative RT compared with those who did not receive RT have been observed in a few other retrospective studies.53,69,73,74,78

On the contrary, other studies have shown no significant advantages in terms of either overall survival or progression-free survival for patients who received adjuvant RT.58,70,71,76,77,79 Yoon et al77 found that regardless of resection status, adjuvant RT had no beneficial impact on tumor recurrence or progression in a series of 158 patients with atypical meningiomas treated at the University of Wisconsin between 2000 and 2010: the 5-year overall survival with and without RT was 89% and
Table 3. Summary of selected published studies on radiation therapy for atypical meningiomas

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>No</th>
<th>Treatment modality</th>
<th>Dose Gy</th>
<th>Median Follow-up (Months)</th>
<th>Progression-free Survival</th>
<th>Overall Survival</th>
<th>Late Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al, 2008</td>
<td>40</td>
<td></td>
<td>Surgery (n = 17)</td>
<td>NA</td>
<td>63.6 (0.6–154.5)</td>
<td>87.1% at 10 years*</td>
<td>89.6% at 10 years*</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + RT (n = 23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aghi et al, 2009</td>
<td>108</td>
<td></td>
<td>Surgery (n = 100)</td>
<td>60.2</td>
<td>39 (1–168)</td>
<td>44% at 5 years</td>
<td>NA</td>
<td>12.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + RT (n = 8)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mair et al, 2011</td>
<td>114</td>
<td></td>
<td>Surgery (n = 84)</td>
<td>51.8</td>
<td>NA</td>
<td>40% at 5 years</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + RT (n = 30)</td>
<td></td>
<td></td>
<td>60% at 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Komotar et al, 2012</td>
<td>45</td>
<td></td>
<td>Surgery (n = 32)</td>
<td>59.4</td>
<td>44.1 (2.7–225.5)</td>
<td>59% at 5 years</td>
<td>NA</td>
<td>No severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + RT (n = 13)</td>
<td></td>
<td></td>
<td>92% at 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hardesty et al, 2013</td>
<td>228</td>
<td></td>
<td>Surgery (n = 157)</td>
<td></td>
<td>52</td>
<td>74% at 5 years 74% at 5 years</td>
<td>NA</td>
<td>No severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RT (n = 71)</td>
<td></td>
<td></td>
<td>at 5 years 60% at 5 years</td>
<td></td>
<td></td>
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<tr>
<td></td>
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<td>SRS, 14 (n = 19)</td>
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<td></td>
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<td>MFSRS, 25 (n = 13)</td>
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<td></td>
<td></td>
<td></td>
<td>IMRT, 54 (n = 39)</td>
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</tr>
<tr>
<td>Park et al, 2013</td>
<td>83</td>
<td></td>
<td>Surgery (n = 56)</td>
<td>61.2</td>
<td>43 (6.2–160)</td>
<td>44.3% at 5 years</td>
<td>90% at 5 years*</td>
<td>No severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + RT (n = 27)</td>
<td></td>
<td></td>
<td>at 5 years 58.7% at 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery (n = 57)</td>
<td>60</td>
<td>4.9 years**</td>
<td>67.8% at 5 years</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + RT (n = 34)</td>
<td></td>
<td></td>
<td>82.6% at 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammouche et al, 2014</td>
<td>79</td>
<td></td>
<td>Surgery (n = 43)</td>
<td>56.2</td>
<td>50 (1–172)</td>
<td>56% at 5 years</td>
<td>81% at 5 years*</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + RT (n = 36)</td>
<td></td>
<td></td>
<td>51% at 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoon et al, 2015</td>
<td>158</td>
<td></td>
<td>Surgery (n = 135)</td>
<td>RT, 57 SRS, 14</td>
<td>32 (0–157)</td>
<td>88 months 59 months</td>
<td>83% at 5 years</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + RT (n = 23)</td>
<td></td>
<td></td>
<td>89% at 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bagshaw et al, 2016</td>
<td>59</td>
<td></td>
<td>Surgery (n = 42)</td>
<td>RT, 54 (n = 18)</td>
<td>26 (3–111)</td>
<td>46 months 180 months</td>
<td>NA</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + RT (n = 21)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>SRS, 15 (n = 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jenkinson et al, 2016</td>
<td>133</td>
<td></td>
<td>Surgery (n = 97)</td>
<td>60</td>
<td>57.4 (0.1–152.2)</td>
<td>75.8% at 5 years</td>
<td>72.7% at 5 years</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery + RT (n = 36)</td>
<td></td>
<td></td>
<td>71.9% at 5 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RT, radiotherapy; NA, not assessed; SRS, stereotactic radiosurgery; RT, external beam radiation therapy; IMRT, intensity modulated radiation therapy.

*For all patients;
**for patients who did not experience recurrence; †for patients who underwent gross total resection.
83%, respectively. Jenkinson et al79 reported similar clinical outcomes of surgery with or without postoperative RT in a retrospective series of 133 patients treated between 2001 and 2010 in 3 different UK centers. Following gross total resection, 5-year overall survival and progression-free survival rates were 77.0% and 82%, respectively, in patients who received early adjuvant RT, and 75.7% and 79.3%, respectively, in patients who did not receive adjuvant RT. Stessin et al72 published a Surveillance, Epidemiology, and End Results–based analysis of the role of adjuvant external beam RT for atypical and malignant meningiomas. A total of 657 patients were identified in the period 1988–2007; of these, 244 had received adjuvant RT. Even with stratification by grade, extent of resection, size and anatomical location of the tumor, year of diagnosis, race, age, and sex, adjuvant RT was not associated with survival benefit. In addition, analysis of cases diagnosed after the WHO 2000 reclassification of meningiomas showed that RT resulted in inferior overall survival. Using the National Cancer Database, Wang et al80 have recently compared the survival outcome in 2,515 patients with atypical meningioma diagnosed according to the 2007 WHO classification, treated with or without adjuvant RT after subtotal or gross total resection. Gross total resection was associated with improved overall survival compared with subtotal resection; however, adjuvant RT was associated with better overall survival in patients who received subtotal resection. The reported toxicity after postoperative RT for atypical and malignant meningiomas is modest, usually being represented by cerebral necrosis and optic neuropathy (Table 3). Neurocognitive decline has been rarely reported, although no published studies have evaluated neurocognitive changes after RT using formal neuropsychological testing.

Radiation dose and timing of RT represent other important variables for outcome. Doses of 54–60 Gy in 2 Gy daily fractions are usually employed in the majority of published series. A few studies employing doses ≥60 Gy showed improved local control62,67,73,81, whereas doses of 54–57 Gy63,77 or less than 54 Gy63,64,68 were apparently associated with no benefits; however, no studies have directly compared different doses, and significant survival advantages observed with higher doses remain speculative. For patients receiving SRS, single doses of 14–18 Gy are typically employed in the majority of radiation centers with similar local control82–93, whereas doses ≤12 Gy are usually associated with inferior local control rates.91 With regard to timing of RT for atypical meningiomas, postoperative RT seems more effective when administered adjuvantly rather than at recurrence, and most authors recommend this approach.63,67,69,73,74,75,78,81 SRS is increasingly being used in the postoperative setting for atypical meningioma.82–93 Hanakita et al87 reported 2-year and 5-year recurrence of 61% and 84%, respectively, in 22 patients treated with salvage SRS; tumor volume <6 mL, margin doses >18 Gy, and Karnofsky Performance Status score of ≥90 were associated with better outcome. Attia et al84 reported clinical outcomes in 24 patients who received Gamma Knife SRS (median marginal dose 14 Gy) as either primary or salvage treatment for atypical meningiomas. With a median follow-up time of 42.5 months, overall local control rates at 2 and 5 years were 51% and 44%, respectively. Eight recurrences were in-field, 4 were marginal failures, and 2 were distant failures. Zhang et al92 treated 44 patients with Gamma Knife either immediately after surgery or as salvage therapy. With a median follow-up time of 51 months, 60-month actuarial local control and overall survival rates were 51% and 87%, respectively. Serious complications occurred in 7.5% of patients. Similar results have been reported in a few other published series.85–91 Overall, data from literature support the efficacy and safety of SRS for patients with recurrent atypical meningiomas; however, its superiority over fractionated RT remains to be demonstrated in prospective randomized trials.

For patients with malignant meningiomas, the reported median 5-year progression-free survival ranges from 29% to 80% using doses of 54–60 Gy delivered in 1.8–2 Gy fractions, with median 5-year overall survival ranging from 27% to 81%.64,65,66,81,94–96 Dziuk et al90 reported the outcome of 38 patients with a malignant meningioma who received (n = 19) or did not receive (n = 19) adjuvant RT. For all totally excised lesions, the 5-year progression-free survival was improved from 28% for surgery alone to 57% with adjuvant radiotherapy (p = NS). Adjuvant irradiation following initial resection increased the 5-year progression-free survival rate from 15% to 80% (p = 0.002). In contrast, the recurrence rate after incomplete resection was similar between groups (100% vs 80%), with no survivors at 60 months in either treatment group. In a series of 24 patients, Yang et al93 observed better overall survival and progression-free survival in 17 patients with malignant meningiomas who received adjuvant RT compared with 24 patients who did not; however, the reported 5-year overall survival and progression-free survival were dismal, being 35% and 29%, respectively. In contrast, several other series confirmed that gross total resection was associated with better clinical outcomes but failed to demonstrate a significant improvement in overall survival and progression-free survival in patients receiving adjuvant RT.64,66,81,96 As with atypical meningioma, higher RT doses appear to improve local tumor control for patients with malignant histology.94,95 In summary, available data do not clearly support the efficacy of adjuvant RT for either incomplete or totally excised atypical meningiomas, and its use is still controversial. While some studies showed trends toward clinical benefit with adjuvant RT, the small number of patients evaluated, different WHO criteria for defining atypical meningiomas over the last decades, and the retrospective nature of published studies preclude any meaningful conclusion of whether adjuvant RT improved outcomes.
relative to nonirradiated patients. The recently closed randomized ROAM/EORTC 1308 trial\(^7\) will help answer the important clinical question of the efficacy of RT versus observation following surgical resection of atypical meningiomas. In this trial, 190 patients have been randomized to receive early adjuvant fractionated RT or active surveillance with serial MRI scans. The primary outcome is time to MRI evidence of local recurrence, and secondary outcomes include time to second-line treatment, time to death, toxicity of treatment, quality of life, neurocognitive function, and health economic analysis. Preliminary results are expected for this year. Malignant meningiomas are highly likely to recur regardless of resection status. No prospective studies have compared surgery plus adjuvant RT versus surgery alone; however, published studies indicate that adjuvant RT is associated with improved progression-free survival and survival, particularly at high doses. Regarding the radiation techniques, fractionated RT given as adjuvant treatment is the most used type of irradiation, whereas SRS is usually reserved for small-to moderate recurrent lesions with reported local control.

Conclusions

RT is an effective treatment for incompletely resected benign meningiomas or for those located in inaccessible surgical sites. Both fractionated RT and SRS are associated with a similar local control, and the choice of technique is mainly based on the volume and site of the tumor. On the basis of the dosimetric advantages of protons, including better conformity and reduction of radiation dose to normal brain tissue, fractionated proton irradiation may be considered in patients with large and/or complex-shaped meningiomas. Controversy exists regarding the role and efficacy of postoperative RT in patients with atypical and malignant meningiomas. The relatively divergent results in the literature are most likely explained by the retrospective nature of series and the relatively small number of patients evaluated; therefore, randomized trials are necessary to clarify the role of adjuvant RT as part of the standard treatment for totally excised atypical and malignant meningiomas, as well as the timing, the optimal dose/fractionation, and technique. Moreover, the development of a molecularly based classification of meningiomas will provide a better understanding of tumor biology and could help predict which patients will benefit from adjuvant therapy.

References

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Central Nervous System Disease in Langerhans Cell Histiocytosis: A Case Report and Review of the Literature

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2Department of Medical Sciences, University of Turin, Turin, Italy
Introduction

Langerhans cell histiocytosis (LCH) is a rare disease of unknown pathogenesis, characterized by intense and abnormal proliferation of bone marrow–derived histiocytes (Langerhans cells). The clinical presentation of LCH is extremely variable, ranging from a single isolated spontaneously remitting bone lesion to a multisystem disease with life-threatening organ dysfunction.

The CNS involvement in LCH is observed in 5%–10% of patients, leading to severe neurological impairment, a negative impact on quality of life, and poor outcome. Here we describe the neurological presentation and response following chemotherapy of a CNS-LCH and a review of the clinical symptoms, histopathologic characteristics, differential diagnosis, and therapeutic approaches.

Case report

In April 2014, a 51-year-old man was referred for weight loss of more than 10 kg in the last year, fever, night sweats, exophthalmos, ataxia, behavioral changes, dysphagia, and dysarthria. No alterations on rheumatologic and blood tests were found. A brain MRI displayed an enhancing lesion in the brainstem and pons with a diffuse involvement of the white matter of cerebral and cerebellar peduncles (Figure 1), while a spinal cord MRI showed multiple localizations in thoracic and lumbar vertebrae. A PET scan with $^{18}$F-labeled fluorodeoxyglucose (FDG) confirmed the presence of high metabolic activity in several bones (shoulders, costal arches, pelvis, hip and thigh bones) and pons. A chest and abdominal CT showed cervical and axillar lymph node involvement.
A bone marrow biopsy was performed in April 2014, and the histological diagnosis revealed LCH (Figure 2A–B). Based on the presence of high-risk LCH (Table 1), in May 2014 we decided to employ cytosine-arabinoside (Ara-C) 500 mg/m² twice daily on day 2–6 and cladribine (Cda) 9 mg/m² daily on day 1–5 every 28 days according to the pilot study of Bernard et al.² After 4 courses of chemotherapy (4 months), the brain MRI showed stable disease (Figure 3), but the patient developed unacceptable adverse events, such as febrile neutropenia and lymphopenia (Common Terminology Criteria for Adverse Events [CTCAE] grade 4), anemia (grade 3), and thrombocytopenia (grade 4).

Table 1. Clinical Classification of LCH

<table>
<thead>
<tr>
<th>SS-LCH</th>
<th>One organ involved (unifocal or multifocal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bone</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
</tr>
<tr>
<td></td>
<td>Lymph node</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
</tr>
<tr>
<td></td>
<td>Central nervous system</td>
</tr>
<tr>
<td></td>
<td>Other locations (thyroid, thymus)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MS-LCH</th>
<th>Two or more organs involved with or without “risk organs”¹¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MS-LCH without involvement of “risk organs” at diagnosis</td>
</tr>
<tr>
<td>Low risk</td>
<td>MS-LCH with involvement of “risk organs” at diagnosis</td>
</tr>
<tr>
<td>High risk</td>
<td>High-risk patients without response to 6 weeks of standard treatment</td>
</tr>
</tbody>
</table>

¹¹“Risk organ” involvement is defined as the presence of at least one of the following:
(i) hematopoietic system (by- or pancytopenia)
(ii) liver (hepatomegaly and/or dysfunction)
(iii) spleen (splenomegaly)


Figure 3. (A–B) Major partial response on contrast T1 and (C) fluid attenuated inversion recovery MRI following 4 courses of Cda/Ara-C and 6 infusions of VBL/PRED.

A bone marrow biopsy was performed in April 2014, and the histological diagnosis revealed LCH (Figure 2A–B). Based on the presence of high-risk LCH (Table 1), in May 2014 we decided to employ cytosine-arabinoside (Ara-C) 500 mg/m² twice daily on day 2–6 and cladribine (Cda) 9 mg/m² daily on day 1–5 every 28 days according to the pilot study of Bernard et al.² After 4 courses of chemotherapy (4 months), the brain MRI showed stable disease (Figure 3), but the patient developed unacceptable adverse events, such as febrile neutropenia and lymphopenia (Common Terminology Criteria for Adverse Events [CTCAE] grade 4), anemia (grade 3), and thrombocytopenia (grade 4).

Considering the poor benefit and the significant toxicity of the Cda/Ara-C regimen, in September 2014 the patient started vinblastine (VBL) 6 mg/m² every 7 days (day 1-8-15-22-29-36) plus prednisone 40 mg/m²/day orally (from day to 28).³ Following chemotherapy, in November 2014 the patient performed a brain MRI that showed a significant reduction of the enhancing brainstem lesion associated with an improvement of gait disturbance, dysphagia and ataxia. No changes in the extent of bone disease were observed. The duration of clinical and radiological response was 10 months, but the patient died from cytomegalovirus pneumonia in September 2015.
Review of the Literature

Etiology

For a long time, LCH has been considered a poorly understood disease due to rarity, uncertain pathobiology, and wide heterogeneity of clinical manifestations. Two hypotheses of LCH have been suggested in the last 30 years: it is either a reactive disease due to an inappropriate immune deregulation or a neoplastic disease. The clonality of LCH was identified in female patients in the 1990s through the demonstration of a proliferation of myeloid progenitor cells with a phenotype similar to epidermal dendritic cells. The description of a patient who had an immunoglobulin gene rearrangement in LCH and B-cells and 2 cases of LCH arising from precursor T-lymphoblastic leukemia/lymphoma further supported the hypothesis of a malignant hematopoietic disease.

Clinical Classification of LCH

The Histiocyte Society has recently proposed a revision of histiocytic disorders based on the integration of clinical presentation and molecular and genetic findings. The new classification defines 5 groups of diseases:

- Langerhans cell histiocytoses include a broad spectrum of clinical manifestations in children and adults with involvement of bones (80%), skin (33%), pituitary gland (25%), liver, spleen, hematopoietic system or lungs (15%), lymph nodes (5%–10%), or the CNS (2%–4% excluding the pituitary). This subgroup includes Erdheim–Chester disease, which typically involves male patients of 55–60 years with a diffuse skeletal involvement, CNS lesions, diabetes insipidus, and exophthalmos. Our patients satisfied all the clinical criteria of this group.
- Cutaneous and mucocutaneous histiocytoses are localized to skin and/or mucosa surfaces, and some of them may be associated with systemic involvement.
- Malignant histiocytoses could be primary or secondary depending on the concomitant presence of a lymphoproliferative disease. They are characterized by rapid progressive tumors with the absence of a specific diagnostic histologic criteria for other myeloid or lymphoproliferative malignancy, a high mitotic activity with atypical mitoses, and cellular atypia.
- Rosai-Dorfman disease involves lymph nodes. The most common presentation is bilateral painless massive cervical lymphadenopathy associated with fever, night sweats, fatigue, and weight loss. Mediastinal, inguinal, and retroperitoneal nodes may also be involved.
- Hemophagocytic lymphohistiocytosis/macrophage activation syndrome is a rare, often fatal syndrome of intense immune activation characterized by fever, cytopenias, hepatosplenomegaly, and hyperferritinemia.

Correlations between Neuropathology, Neurological Symptoms, and MRI in LCH

LCH is characterized by clonal proliferation of cells that express CD1a, C68, and CD207 and by the presence in histiocytic lesions of Birbeck granules (perinuclear cytoplasmic bodies considered to be pathognomonic of normal Langerhans cell of human epidermis).

Three types of lesions have been described in the CNS:

- Circumscribed granulomas: bulky lesions in the meninges or choroid plexus. The composition is similar to Langerhans granulomas in peripheral organs with CD1a reactive cells and CD8-positive T-cell infiltration.
- Granulomas with infiltration of the surrounding brain parenchyma associated with T-cell inflammation and loss of neurons and axons and reactive gliosis. The main localizations are cerebellum, infundibulum, and hypothalamus.
- Neurodegenerative lesions lacking CD1a cells and diffuse inflammatory process CD8++, especially in cerebellum, brainstem, infundibulum, optic nerves, chiasma, and basal ganglia.

The neuropathological findings are correlated with clinical and radiological presentation, thus neuro-LCH could be classified into 3 groups:

- Tumor CNS-LCH represents 45% of neurohistiocytosis and affects mainly young males with a subacute onset characterized by intracranial hypertension, seizures, motor or sensory deficits, cognitive impairment, cranial nerve palsies, and/or cerebellar syndrome. Brain MRI shows a unique intracranial T1 hypointense and T2 hyperintense lesion with a homogeneous contrast enhancement. Although the cerebral hemispheres are most commonly affected, lesions may be localized in other sites, such as the dura mater, brainstem, cerebellum, cranial nerves, nerve roots, choroid plexus, and spinal cord.
- Differential diagnosis is difficult and includes malignant gliomas, cerebral CNS lymphomas, choroid plexus tumors, and brain metastases, but also inflammatory pseudotumor lesions (multiple sclerosis, neuroluciferosis), infectious disease (pachymeningitis), meningiomas, and neoplastic meningitis. The CSF examination is usually normal.
- Neurodegenerative LCH accounts for 45% of neurohistiocytosis. The neurological presentation is dominated by progressive cerebellar ataxia and dysautonomia and pseudobulbar syndrome. More than half of patients suffer from central diabetes insipidus due to hypothalamic-pituitary involvement. Brain MRIs display global cerebellar atrophy with a symmetrical T2 hyperintensity of the cerebellar white matter, a
T1 hyperintensity of the dentate nuclei, and hyperintense T2 areas in the pontine tegmentum and pyramidal tracts. Cortical and corpus callosum atrophy can be seen. Ten percent of patients with neurodegenerative LCH have normal MRI, while 18F-FDG PET shows a hypometabolism in the cerebellum, caudate nuclei, and frontal cortex.

- Mixed forms account for 10% of neuro-LCH. The clinical presentation and neuroradiological findings combine the previous symptoms and type of lesions of the tumor and neurodegenerative forms. Although cerebral granulomatous lesions may improve with specific treatments, cerebellar ataxia tends to worsen over time.

## Principles of Treatment

Patients with one organ system involvement (single-system [SS] LCH) have a better outcome compared with those with multiple organ involvement (multisystem [MS] LCH). Based on this knowledge, Broadbent and colleagues proposed a clinical classification of LCH in order to stratify the risk of early recurrence following treatments and provide a guideline for clinicians, especially for enrollment in clinical trials. Risk organ involvement at diagnosis and response to initial treatment allow for a stratification of patients into low-risk and high-risk subgroups. Furthermore, the absence of a response after 6 weeks of standard therapy defines a “very high risk” patient, who needs an early adjustment of treatment (Table 1).

The Histiocyte Society has conducted several clinical trials in the last years to define the optimal management of LCH. There is general agreement on the indication of chemotherapy in MS-LCH patients. The first international trial, in 1991–1995 (LCH-1 trial), compared the efficacy of VBL plus etoposide in patients with MS-LCH. The study demonstrated the equivalent activity of these drugs in terms of response rate, and the presence of low- and high-risk subgroups based on disease reactivation rate and overall survival.

The second trial (LCH-2) enrolled MS-LCH patients from 1996 to 2000 and evaluated the efficacy of the addition of etoposide to an initial therapy with prednisolone (PRED) and VBL. The standard and experimental arms, respectively, had similar results, achieving response rates of 63% and 71%, 5-year survivals of 74% and 79%, and a disease reactivation rate of 46%.

The LCH-III trial (2001–2008) investigated methotrexate as an adjunctive therapy to the standard combination of PRED and VBL in high-risk MS-LCH. The experimental arm did not show a superiority in terms of control of the disease or overall and reactivation-free survival.

These randomized clinical trials have established VBL and PRED (6–12 weeks of oral steroids and weekly VBL injections followed by pulse of PRED/VBL every 3 weeks for 12 months) as the standard treatment in MS-LCH. Up to date, an effective second-line chemotherapy is not available for high-risk and refractory LCH. A Cda/Ara-C regimen has shown some good results in small series and phase II trials in severe progressive LCH, but also 2 important limitations:

1. Severe toxicities, such as long-lasting pancytopenia and CTCAE grades 3–4 enteritis with massive diarrhea and prolonged hospitalization
2. A long median time to achieve response of around 4 months, and the risk that the clinician prematurely stops the therapy

We employed initially in our patient the Cda/Ara-C regimen due to the severe clinical and neurological impairment, obtaining a stabilization of the disease on MRI. However, the patient developed severe and long-lasting adverse effects, so we switched to a VBL/PRED schedule, achieving a long-lasting response with good tolerability.

## New Insights into LCH Biology and Targeted Therapies

In 2010 the mutation in BRAF serine/threonine kinase (BRAF V600E) was reported in 57% of patients with LCH and was associated with high-risk features and poor short-term response to chemotherapy. In particular, the presence of the mutated BRAF in a hematopoietic stem cell would cause high-risk LCH (multisystemic disease), while a mutation in a differentiated cell type would give a low-risk disease (SS-LCH). Moreover, mutation of BRAF leads to the activation of the Ras/Raf/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase pathways, a possible target of signal-regulated kinase pathways, a possible target of BRAF inhibitors. Haroche et al have reported a significant efficacy of vemurafenib in both MS-LCH and refractory Erdheim–Chester disease. There are a few ongoing trials (NCT02281760, NCT065649972) that are evaluating the role of mitogen-activated protein kinase inhibitors in patients with severe and refractory histiocytic disorders.

The participation of an inflammatory response sustained by specific cytokines and chemokines is not negligible. In this regard, new attractive targets are receptor activator of nuclear factor kappa-B ligand and programmed cell death 1 (PD1) ligand: both receptors are highly expressed in several histiocytic disorders representing therapeutic targets for denosumab and anti-PD1 drugs (eg, nivolumab).

## References


Management of Brain Metastasis: Burning Questions to the Radiation Oncologist

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Q1: Does whole brain radiotherapy (WBRT) still have a role in brain metastasis?

Absolutely, yes. But I can say “in lesser percent of patients than before.” Local treatments like surgery and stereotactic radiosurgery (SRS) have proven to be locally effective with limited side effects and without a detrimental effect on overall survival without the addition of WBRT in patients with limited number of brain metastases (1–4 metastases with level I evidence). Since the radiotherapy devices capable of performing precise treatments like SRS have increased in variety and become widely available and demanded more by the patients, SRS has started to be used more frequently. Even for patients with more than 4 brain metastases, it is being preferred along with the retrospective and single-arm prospective study results. The cumulative volume of the metastases rather than the number appears to be more important for SRS or WBRT decision. For example, in the JLGK0901 prospective observational study, 1194 patients with 1–10 metastases had total cumulative volume of 15 cc and largest tumor limitation of 10 cc. It was shown within this study that patients with 5–10 metastases had similar outcomes as 2–4 metastases, except slightly higher incidence of leptomeningeal dissemination. WBRT has been the mainstay palliative treatment for many decades, with very limited impact on survival compared with best supportive care. The recently published QUARTZ trial in patients with brain metastases from non-small-cell lung cancer (NSCLC) not suitable for resection or SRS (study patient population with KPS < 70 proportion 38%) revealed similar median overall survival of 2 months. Only patients < 60 years had improved survival with WBRT. In the published randomized studies, WBRT in addition to surgery and SRS improves local and distant brain control; however, none of them have been able to show a positive impact on survival. Both quality of life and neurocognitive function have deteriorated in surviving patients. Although in an ad hoc analysis of the Japanese study, addition of WBRT has improved survival in the subgroup of 47 patients with NSCLC and recursive partitioning analysis (RPA) 2.5–4 (favorable prognostic group), this needs to be confirmed prospectively. Nevertheless, in a meta-analysis of the 3 studies, addition of WBRT in 68 patients < 50 years has resulted in similar distant brain control with decreased survival (13.6 vs

Q2: When to employ SRS?

SRS is a high-precision localized irradiation given in single fraction using a firm immobilization and image guidance. Brain metastases generally represent ideal targets for SRS because of their frequently spherical shape and contrast enhancement with sharp margins. I believe one of the most important things for a successful treatment of brain metastases is the quality of the baseline MR imaging. T1 sequences with gadolinium need to be necessarily thin slices like 1 mm. Otherwise, it is possible to miss the treatment of multiple small metastases. In my daily practice, I treat almost all my patients with 1–3 metastases with SRS from any solid tumor histopathology. For patients with 4–10 metastases, especially with the breast cancer, I inform them about the leptomeningeal dissemination risk and usually start with WBRT and use SRS at progression. An MD Anderson Cancer Center (MDACC) study where WBRT and SRS are being compared head to head in this patient population will provide us more guidance.

Technically tumors smaller than 3–3.5 cm are suitable for SRS. However, as the size increases, the radiation dose needs to be reduced because of radiation-related side effects, mainly radiation necrosis. For large metastases, fractionated SRT (fSRT) is a viable option to prescribe a biologically more effective dose with lesser toxicity. Retrospective series and our own experience support fSRT to achieve higher local control and decreased radiation necrosis rates. For patients with large tumors who don’t need prompt surgical decompression or are not suitable for surgery because of comorbidities or systemic disease status, I prefer to give fSRT.

Recent studies also have investigated the role of postoperative cavity
8.2 months). Both subgroup analyses should be assumed as hypothesis generating for further investigation. WBRT as my initial sole treatment choice would be miliary metastases (too many small metastases) or cumulative volume > 15 cc or leptomeningeal infiltration or low KPS. There are ongoing initiatives to reduce the cognitive side effects of WBRT. The use of a neuroprotective compound, memantine, during WBRT has resulted in better cognitive function compared with WBRT + placebo in the phase III Radiation Therapy Oncology Group (RTOG) 0614 trial. Along with the technological developments in radiation oncology, WBRT with hippocampal avoidance and simultaneous integrated boost to the metastases has emerged as a potential improvement for WBRT. In the phase II RTOG 0933 study, hippocampal-avoidance WBRT has resulted in reduced memory deficit and quality of life compared with historical controls and is being investigated in the randomized phase III NRG-CC001 trial “Memantine + WBRT with or without Hippocampal Avoidance.”

SRS is a high-precision localized irradiation given in one fraction using a combination of firm immobilization and image guidance. Small brain metastases represent a suitable target for SRS. The dose is inversely related to tumor size.

The SRS and hypofractionated regimens in cases where high single radiation doses to large tumors or tumors close to critical neural structures will be associated with significant risk of toxicity (so-called stereotactic hypofractioned radiation therapy [SHRT]) have not been compared in a randomized trial. Of course, more reliable results have been published with SRS. Moreover, the radiation schedule for SHRT has not yet been defined. Single dose SRS in the treatment of a limited number (1–3) of newly diagnosed BMs has yielded a local control at 1 year of 80%–90% with symptoms improvement and median survival of 6–12 months. Best prognostic groups have longer survival.

There are no differences in outcome using gamma-knife or linear accelerator.

Salvador Villà, Badalona, Spain

Radiation treatment is essential in the management of brain metastases (BM). In the past, the majority of patients with BM were given whole brain irradiation (WBI), 30 Gy in 10 fractions, and no other schedules have shown superiority in terms of palliation or survival. However, for decision making, the number of BMs is considered. Graded prognostic assessment (GPA) scores 3 different values (0, 0.5, or 1). These scores were assigned for each of these 4 parameters: age (>60, 50–59, < 50), KPS (<70, 70–80, 90–100), number of BMs (>3, 2–3, 1), and extracranial metastases (present, not applicable, none). Our group validated it. However, the revised GPA has found histology to be statistically significant based on retrospective data in a more recent era compared with the database used to derive the old RTOG RPA.

Supportive care measures, which may include anticonvulsants and/or corticosteroids to manage edema, also should be given as necessary. However, anticonvulsant prophylaxis should not be used routinely, and still, in my opinion, some physicians are using it as prophylaxis.

From my point of view, nowadays, WBI is indicated in patients with small cell lung cancer, suspicion of meningeal carcinomatosis, in specific cases of adenocarcinoma of the lung with anaplastic lymphoma kinase mutation due to
the high probability of “miliary” dissemination, in patients with breast cancer and triple negative, with more than 3 or 4 BMs, or in patients with a BM as large as 4 to 5 cm of diameter without surgical indication. We have to take into account that WBI will deteriorate neurocognitive function if patients are alive for more than 3–6 months in a significant proportion of cases. In patients older than 65–70 years I advise to irradiate only in a focal way to the BM which could cause specific symptoms.

The European Organisation for Research and Treatment of Cancer (EORTC) trial 22952 has shown that intracranial progression occurs both at sites treated primarily with SRS or surgery and at new sites not treated before. In this study, intracranial progression was significantly more frequent in the observational arm (delayed WBI) (78%) than in the WBI arm (48%). So, the first conclusion is that WBI is needed for patients with few BMs (1 to 3). Nevertheless, several randomized trials have been unable to show an improved overall survival by adding WBI to surgical resection or SRS. The EORTC trial reported an increased intracranial tumor control while translating into a very modest increase of progression-free survival with WBI, but it does not translate into a prolonged survival time with functional independence or into a prolonged overall survival time. A meta-analysis of these randomized trials comparing SRS alone with SRS + WBI in patients with 1 to 4 BMs suggested a survival advantage for SRS alone in patients aged <50 years without a reduction in the risk of new BMs with adjuvant WBRT; conversely, in patients aged >50 years, WBI decreased the risk of new BMs but did not affect survival. Patients with NSCLC with higher GPA scores (2.5–4.0) had a survival benefit from SRS + WBI compared with SRS alone (median survival 16.7 vs 10.7 months) (special group to be explored).

The impact of adjuvant WBI on cognitive functions and quality of life has been analyzed in some studies. Two trials compared the neurocognitive function of patients who underwent SRS alone or SRS + WBI. In both, after the first 3 months of follow-up, patients had subsequent deterioration of neurocognitive function among long-term survivors (up to 36 months) after WBI or patients treated with SRS + WBI were at greater risk of a decline in learning and memory.

To add SRS to WBI as the standard approach improved overall survival in patients with 1 BM or in patients with GPA score 3.5–4 and 1–3 BM. But, as I said before, I advise to delay WBI in the majority of patients with BM, and consequently the double approach has to be indicated only for specific cases and situations.

Furthermore, many institutions are exploring use of SRS for more than 4 BMs and the results are comparable between number of BMs in terms of survival and toxicity.

Postoperative SRS is an approach to decrease the local relapse following surgery while avoiding the cognitive sequelae of WBI. We have several retrospective and one prospective phase II trial that reported local control rates at 1 year around 80% (70%–90%) and a median survival of 10–17 months. We do not know yet the optimal dose and fractionation, and the effects on survival, quality of life, and cognitive functions, and the risk of radiation necrosis following postoperative SRS seems higher than reported by the EORTC study. The other concern is risk of leptomeningeal relapse in 8% to 13% of patients, especially in those with breast histology.

In summary, SRS (or SHRT) can be used to follow cases of patients with BM: patients with number of BMs up to 4, with diameters up to 3 cm, patients with complete or incomplete resection of 1 or 2 BMs as an adjuvant way, patients older than 65–70 years with large BM, avoiding WBI at all, histologies like melanoma, colon cancer, or kidney which have been considered “radioresistant,” and in necrotic metastases that need higher radiation doses. Delaying (or avoiding) WBI is the final goal.
function 4 months after treatment compared with those receiving SRS alone.

The Alliance trial compared SRS alone versus SRS + WBI in patients with 1–3 BMs using a primary neurocognitive endpoint, defined as decline from baseline in any 6 cognitive tests at 3 months. Overall, the decline was significantly more frequent after SRS + WBI versus SRS alone, with more deterioration in immediate recall, delayed recall, and verbal fluency. A quality of life analysis of the EORTC 22952 trial has shown over 1 year of follow-up no significant difference in the global health related quality of life, but patients undergoing adjuvant WBRT had transient lower physical functioning and cognitive functioning scores and more fatigue.

On the other hand, an effective control of BM may have a positive influence in the neurocognitive outcome treated with BM. As a consequence, a delay in starting WBI does not seem to influence overall survival and improves quality of life. Based on the results of these trials, the American Society for Radiation Oncology recommends not to routinely add adjuvant WBRT to SRS for patients with a limited number of BMs. New approaches (neuroprotective drugs, new techniques of radiotherapy) are being developed. In a randomized double-blind, placebo-controlled phase II trial (RTOG 0614), the use of memantine during and after WBI resulted in better cognitive function over time. Hippocampal-avoidance WBRT using intensity modulated radiotherapy to reduce the radiation dose to the hippocampus is not associated with increased risk of recurrence in the low dose region and could preclude memory deterioration, but we do not have clear evidence so far.

The objective of WBI is palliation. However, WBI has some limitations to control symptoms. Physicians referring patients with BM for consideration of WBI are often overly optimistic when estimating the clinical benefit of the treatment and overestimate patients’ survival. I think that, in particular situations, any radiation to the brain is not indicated. Specifically, in patients with very poor KPS, with multiple BM affected with lung cancer, and with systemic progression, the best supportive care is the good option.
Further Reading


Li J; MD Anderson Cancer Center. A prospective phase III randomized trial to compare stereotactic radiosurgery versus whole brain radiation therapy for <= 4 newly diagnosed non-melanoma brain metastases. http://clinicaltrials.gov/show/NCT01592968


Primary central nervous system lymphoma (PCNSL) is malignant and most commonly of the diffuse large B-cell lymphoma (DLBCL) type that is confined to the CNS at time of diagnosis. PCNSL is a rare disease and accounts for approximately 2.2% of CNS tumors, with an overall incidence rate of around 0.5 cases per 100,000 people per year. The standard therapy at diagnosis is based on high-dose methotrexate (MTX) chemotherapy, which may be combined with other chemotherapeutics (e.g., cytarabine) and followed by consolidation therapies such as whole-brain radiotherapy, intensified chemotherapy, or autologous stem cell transplantation. Therapeutic options for recurrent/progressive PCNSL after MTX-based first-line therapy are poorly defined, and novel treatment concepts based on biological insights are urgently needed to improve patient outcomes. Several studies have shown overexpression of the programmed death 1 receptor (PD-1) and its ligand PD-L1 in PCNSL. Moreover, some case studies have reported response to treatment with anti-PD-1 monoclonal antibodies (immune checkpoint inhibitors). Therefore, we have initiated the clinical trial "Open-label single arm phase II study on pembrolizumab for recurrent primary central nervous system lymphoma (PCNSL)" (NCT02779101). The primary objective of the study is to evaluate the overall response rate and safety in patients treated with pembrolizumab for recurrent or progressive PCNSL after MTX-based first-line therapy. Main inclusion criteria encompass histologically confirmed diagnosis of PCNSL (DLBCL) at initial diagnosis, documented progression or recurrence in cranial MRI after prior MTX-based first-line therapy (with or without prior radiotherapy), measurable disease in cranial MRI (lesion size > 10 x 10 mm), and adequate organ function. The study is being conducted in multiple sites across Europe and is currently accruing patients.
European Reference Networks (ERNs): A New Initiative to Increase Collaborative, Cross-Border Approaches to Treating Brain Tumor Patients

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Rarity is often thought of as an exquisite thing, valuable because it is remarkable for its scarceness. But for more than 4.3 million people throughout the European Union whose lives have been touched by a rare cancer, rarity often means a devastating and lonesome journey. Even in the richest and most powerful countries, patients with rare cancers can be lost in a maze of uneven and inequitable care.

Taken as a whole entity, rare cancers are more common than people may think. Rare cancers represent in total about 22% of all cancer cases diagnosed in the EU each year, including all cancers in children. There is also evidence that 5-year relative survival rates are worse for rare cancers than for common cancers.

Primary brain tumors are considered a rare cancer according to the official RareCare definition of rarity, which identifies cancers with an incidence of < 1/100 000 per year as being rare.

What are European Reference Networks?

In response to the significant unmet needs of people with rare cancers like brain tumors, and in order to ensure that no one with a rare cancer – or indeed with any rare disease – faces inequities in diagnosis, treatment, and support, European Reference Networks (ERNs) have been established under the 2011 EU Directive on Patients’ Rights in Cross-Border Healthcare. The Directive aims to facilitate patients’ access to information and care and thus optimize their diagnosis and treatment options.

The ERNs—virtual networks for the treatment of people with rare diseases, including rare cancers—involve health care providers across the European Union. It is anticipated that ERNs will:

- consolidate expertise and best practice;
- build capacity;
- result in better chances of accurate diagnosis for patients with rare diseases;
- focus on highly specialized treatment;
- generate evidence;
- create and update diagnostic and therapeutic clinical practice guidelines;
- promote new research programs and clinical trials (which will hopefully lead to improved enrollment);
- make economies of scale;
- develop international databases and tumor banks; and,
- improve patient outcomes.

EURACAN is the ERN for rare adult solid cancers

In December 2016, twenty-four European Reference Networks were approved by the EU’s Board of Member States, the formal body which oversees the ERNs. One of the ERNs, called EURACAN, focuses on adult solid tumors, while another ERN (PaedCan-ERN) focuses on pediatric cancers. EuroBloodNet is the ERN for rare hematological cancers and other rare blood diseases, while the Genturis ERN is for rare inherited diseases which may give rise to various cancers.

The mission of EURACAN is “to establish a world-leading, patient-centric and sustainable network of multi-disciplinary, research-intensive clinical centers focused on rare adult cancers.” So far, EURACAN has amassed 66 health care providers in 17 European countries, and 22 associate partners, which include patient advocacy organizations.
Within EURACAN there are 10 “domains” representing the various families of rare cancers: sarcoma, rare gynecological cancer, rare male genital organ/urinary tract cancer, rare neuroendocrine system cancer, rare digestive tract cancer, rare endocrine organ cancer, rare head and neck cancer, rare thoracic cancer, and rare skin and eye melanoma. The tenth EURACAN domain is for brain and CNS tumors. The domain leader for the brain and CNS tumors ERN is Professor Martin van den Bent, Erasmus Medical Center, Rotterdam, the Netherlands.

At the recent kick-off meeting in Lyon, France, for all of the 10 EURACAN domains, Professor van den Bent said:

“We hope that the EURACAN ERN for brain and CNS tumors will enhance the work we already do on a regular and collaborative basis with many of the existing centers of neuro-oncology excellence in Europe. Our objectives will be based on rational, reasonable, and sustainable efforts for brain tumor patients. We will be looking at ways of ensuring that our ERN for brain tumors is not duplicative of other initiatives but rather focuses on delivering new approaches particularly with relation to the very rare adult brain tumors such as medulloblastoma, ependymoma, and BRAF mutated tumors, and do that closely collaborating with existing organizations such as EANO [European Association of Neuro-Oncology] and EORTC [European Organisation for Research and Treatment of Cancer].

### Active patient advocacy engagement in the ERNs

One of the defining aspects of EURACAN’s 10 rare cancer domains, including that of brain and CNS tumors, is the proactive engagement of patient advocates in the networks’ governance boards and committees. Elected “ePAGs” (European Patient Advocacy Group representatives) will sit on the EURACAN main board, steering committee, task force groups, and domain committees ensuring that the patient voice is at the forefront of EURACAN’s work.6

Additionally, patient representatives involved with the 10 domains of EURACAN will “ensure transparency in quality of care, safety standards, clinical outcomes and treatment options; communicate and connect with [their] community; contribute to the definition of research priority areas based on what is important to patients and their families and ensure that [patient perspectives] are embedded in the research activities performed within the ERNs.”7

The European Reference Network for brain and CNS tumors will provide a unique opportunity for clinicians, patient advocates, allied health care professionals, researchers, and other stakeholders to work across geographic borders in Europe and tackle the substantial and
specific challenges of this devastating neuro-oncological disease.

Sidebar

For further information about ERNs, please visit http://ec.europa.eu/health/ern/policy_en

For further information about EURACAN, please contact Muriel Rogasik, EURACAN project manager, at muriel.rogasik@lyon.unicancer.fr

For further information on clinical aspects of the European Reference Network for Brain and CNS Tumours, please contact Professor Martin J van den Bent at m.vandenbent@erasmusmc.nl

For further information about patient involvement in the ERNs, please contact Kathy Oliver at the International Brain Tumour Alliance (IBTA), kathy@theibta.org

Notes

2. Ibid.
6. EURORDIS, http://www.eurordis.org/content/epags [accessed 26 April 2017]
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Brain Metastases—A Growing Nursing Concern

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Neuro-oncology nursing is a niche but multifaceted area of nursing practice that is ever expanding in its complexities and in patient numbers. Most of us are involved in the daily management of malignant, high-grade gliomas, whether it be from a surgical or oncological perspective. Some of us also take on expanding roles of managing low-grade glioma patients and those with benign brain tumors. Additionally, some of us manage patients with brain metastases.

Brain metastasis is diagnosed in 10%–40% of all patients with cancer, and the incidence continues to rise as patients are living longer with their primary disease. Brain metastases from systemic cancers are up to 10 times more common than primary malignant brain tumors. Clinical management and understanding of brain metastasis have changed substantially even in the last 5 years—many of these changes are attributable to improvements in systemic therapies, which have led to better systemic control and longer overall patient survival. Over time this leads to increased risk of developing brain metastasis.

This patient cohort opens up a whole new realm of understanding the primary disease trajectory in order to adequately manage the patient’s expectations about prognosis and treatment options, as well as managing side effects of treatments and minimizing adverse effects of them. Patients with brain metastases have complex needs and require a multidisciplinary approach in order to optimize intracranial disease control while maximizing neurological function and quality of life. As nurses and health care professionals, we have a large role to play in ensuring that we minimize the toxic effects of such treatments and that we proactively consider highlighting and addressing these concerns to bring them to the forefront of patient care.

Brain metastases normally manifest themselves with neurological dysfunction alongside functional decline, which can be very difficult to manage, both medically and holistically. As stated by Berghoff et al., treatment options for brain metastases are limited and mainly focus on the application of local therapies such as whole brain radiotherapy (WBRT) and stereotactic radiotherapy (SRS). The inability of many systemic chemotherapeutic agents to penetrate the blood–brain barrier (BBB) has limited their use and subsequently allowed brain metastasis to become a burgeoning clinical challenge. Furthermore, the heterogeneity among and within different solid tumors and their subtypes further adds to the difficulties in determining the most appropriate treatment options. While SRS has broadened therapeutic options for brain metastases, patients respond minimally and prognosis remains poor.

Looking at how we can impact quality of life, given patients’ poor prognosis, Habets et al. performed a prospective study evaluating the impact of brain metastases and SRS on neurocognitive functioning and quality of life by measuring their parameters at 1, 3, and 6 months after SRS. Their study found that over time, SRS does not have an additional detrimental effect on neurocognitive functioning, suggesting that SRS may be preferred over WBRT, a finding echoed by Bender. Quality of life, however, is not only assessed with neurocognitive measures but also based on complications that negatively impact quality of life and sometimes even overall survival. These complications include aspects such as seizures, altered mood, and hypercoagulable states such as venous thromboembolism (VTE). Adequately managing the side effects of antitumor treatments and supportive therapies and attempting to minimize these effects will positively impact on patients’ quality of life.

Patel et al. undertook a retrospective analysis of outcomes and toxicities of pre- and postoperative SRS for resectable brain metastases. Their study found that both treatment arms provided similarly favorable rates of local recurrences, distant recurrences, and overall survival. However, there were significantly lower rates of symptomatic radiation necrosis and leptomeningeal disease in the pre-SRS cohort. Not only does this suggest that further research in a prospective study is warranted, it also lends weight to the argument that by considering a presurgical SRS boost, it may even help improve the patient’s quality of life and minimize long-term effects.

Simple measures like being able to minimize corticosteroids as a result of lessened effects and incidence of radiation necrosis are likely to greatly enhance patients’ quality of life.

At this year’s World Federation of Neuro-Oncology Societies (WFNOS) meeting in Zurich (May 3–5, 2017), and as a result of the aforementioned articles, the nurses’ educational day was dedicated to learning about the care and management of patients with brain metastases. The day was aimed primarily at nurses and allied health care professionals but was open to anyone who wished to gain a deeper understanding about the presenting signs/symptoms and various treatment options as well as current clinical research being undertaken in this expanding and complex field of neuro-oncology.

We learned about the radiological appearances of brain metastasis and about the importance of contrast enhanced imaging and why obtaining diffusion weighted imaging is a crucial part of differentiating abscesses from tumors, and how to assess for leptomeningeal spread. We have heard about how to conduct clinical trials in neuro-oncology with brain metastasis at the forefront, and we have been given in-depth knowledge about breast and lung primary cancers in relation to secondary spread to the brain and subsequent prognosis and treatment options. We have learned about the devastating impact of neoplastic meningitis. Management options for brain metastasis, including surgical and oncological techniques and emerging technologies and advances in medical practice, were also covered on this day.

As patients are living longer with their primary cancer and developing secondary brain metastases, it was felt...
imperative to better equip the nurses and allied health care professionals caring for this patient cohort to be better informed about treatment options and their side effects—in particular focusing on brain metastatic disease, given that this patient group is set to rise even further in the coming years. We hope the WFNOS nurses’ study day has helped in some way to demystify this patient cohort and enable us to provide not only better but also holistic nursing care.

References
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Hotspots in Neuro-Oncology 2017

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Cancers of the brain and CNS: global patterns and trends in incidence

This study examined the geographic and temporal variations in incidence rates of brain and central nervous system (CNS) cancers worldwide. Data from successive volumes of Cancer Incidence in Five Continents were used, including 96 registries in 39 countries. Joinpoint regression was used to estimate the average annual percentage change and its 95% CI.

Globally, there was a large variability in the magnitude of the diagnosis of new cases of brain and CNS cancer, with a 5-fold difference between the highest rates (mainly in Europe) and the lowest (mainly in Asia). Increasing rates of brain and CNS cancer were found in South America, namely in Ecuador, Brazil, and Colombia; in eastern Europe (Czech Republic and Russia), in southern Europe (Slovenia), and in the 3 Baltic countries. Trends were similar between sexes, although decreasing trends in men and women were seen in Japan and New Zealand.

This study showed that important regional variations in brain and CNS cancers exist and that the incidence may be increasing in some countries. Further studies will be required to understand the reasons for these differences and the potential contributions of genetic, environmental, and socioeconomic factors.

Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO)

Brain metastases are a major cause of morbidity and mortality in cancer patients. The management of patients with brain metastases has become an important issue due to the increasing frequency and complexity of the diagnostic and therapeutic approaches. In 2014, the European Association of Neuro-Oncology (EANO) created a multidisciplinary Task Force to draw evidence-based guidelines for patients with brain metastases from solid tumors. These EANO guidelines provide a consensus review of evidence and recommendations for diagnosis by neuroimaging and neuropathology, staging, prognostic factors, and different treatment options. In addition, the EANO Task Force addressed treatment options such as surgery, stereotactic radiosurgery/stereotactic fractionated radiotherapy, whole-brain radiotherapy, chemotherapy and targeted therapy (with particular attention to brain metastases from non–small cell lung cancer, melanoma, breast and renal cancer), and supportive care.

Leptomeningeal metastases: a RANO proposal for response criteria

Leptomeningeal metastases (LM) are a major source of morbidity and mortality in cancer patients for which there is no effective therapy. Currently there is no standardization with respect to response assessment. A Response Assessment in Neuro-Oncology (RANO) working group with expertise in LM (RANO LM working group) developed a consensus proposal for evaluating patients treated for this disease. This proposal included 3 elements in assessing response in LM: a simple standardized neurological examination similar to the Neurologic Assessment in Neuro-Oncology (NANO) score developed for brain tumors but with some minor adaptations for LM, examination of cerebrospinal fluid (CSF) cytology or flow cytometry, and radiographic evaluation. The proposal recommends that all patients enrolling in clinical trials undergo CSF analysis (cytology in all cancers; flow cytometry in hematologic cancers), complete contrast-enhanced neuraxis MRI, and in instances of planned intra-CSF therapy, radioisotope CSF flow studies. Considering that most lesions in LM are nonmeasurable and that assessment of neuroimaging in LM is subjective, neuroimaging is graded as stable, progressive, or improved using a novel radiological LM response scorecard. Radiographic disease progression in isolation (ie, negative CSF cytology/flow cytometry and stable neurological assessment) would be defined as LM disease progression. This proposal by the RANO LM working group is a work in progress. It will require further testing and validation in clinical trials, and additional refinements will likely be necessary. Nonetheless it is an important step in standardizing response assessment in clinical trials in patients with LM.

The Neurologic Assessment in Neuro-Oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria
Neuro Oncol. 2017 May 1;19(5):625–635.

The determination of response of brain tumors to therapeutic agents remains a challenge. Both the Macdonald criteria and the Response Assessment in Neuro-Oncology (RANO) criteria include deterioration in clinical status as part of the determination of progression but do not provide specific parameters for assessing this. The RANO criteria provided guidance on the use of the Karnofsky performance status but this does not provide a reliable assessment of neurologic function. The RANO group developed the Neurologic Assessment in Neuro-Oncology (NANO) scale as a simple objective and quantifiable metric of neurologic function that could be evaluated during routine office examination by nonneurologists in 5 minutes or less. It is designed to be combined with radiographic assessment to provide an overall assessment of outcome for neuro-oncology patients in clinical trials and in daily practice. The NANO scale is a quantifiable evaluation of 9 relevant neurologic domains based on direct observation and
testing. These include gait, strength, ataxia, sensation, visual field, facial strength, language, level of consciousness, and behavior. The score defines overall response criteria and complements existing patient-reported outcomes and neurocognitive testing to provide a global clinical outcome assessment of well-being among brain tumor patients.

To determine its overall reliability, inter-observer variability, and feasibility, a prospective, multinational study was conducted and noted a >90% inter-observer agreement rate with kappa statistic ranging from 0.35 to 0.83 (fair to almost perfect agreement), and a median assessment time of 4 minutes (interquartile range, 3–5).

The NANO scale provides a simple objective clinician-reported outcome of neurologic function with high inter-observer agreement. Its value is being confirmed in ongoing clinical trials, and future studies will determine if it is more useful than simple clinician global assessment of the presence of clinical decline. If validated, it may be incorporated in the future into the RANO criteria to improve assessment of response.

Is more better? The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma: a secondary analysis of EORTC and NRG Oncology/ RTOG
Blumenthal DT, Gorlia T, Gilbert MR, et al.
Since the European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) trial established radiation therapy with concurrent temozolomide (TMZ) followed by 6 cycles of adjuvant TMZ as the standard of care for newly diagnosed glioblastoma (GBM), there has been some controversy regarding the duration of adjuvant TMZ. In Europe most centers conform to the 6 cycles of adjuvant therapy used in the EORTC/NCIC study, while in the United States many centers use 12 cycles of adjuvant TMZ and some treat even longer until progression.

To address this issue, a pooled analysis of individual patient data from 4 randomized trials for newly diagnosed GBM (RTOG 0825, EORTC/NCIC, CENTRIC, and Core) was performed. All patients who were progression free 28 days after cycle 6 were included. The decision to continue TMZ was per local practice and standards, and at the discretion of the treating physician. Patients were grouped into those treated with 6 cycles and those who continued beyond 6 cycles; 624 patients qualified for analysis with 291 continuing maintenance TMZ until progression or up to 12 cycles, while 333 discontinued TMZ after 6 cycles.

Treatment with more than 6 cycles of TMZ was associated with a slightly improved progression-free survival (hazard ratio [HR] 0.80 [0.65–0.98], \( P = .03 \)), in particular for patients with methylated MGMT (\( n = 342 \), HR 0.65 [0.50–0.85], \( P < .01 \)). However, overall survival was not affected by the number of TMZ cycles (HR 0.92 [0.71–1.19], \( P = .52 \)), including the MGMT methylated subgroup (HR 0.89 [0.63–1.26], \( P = .51 \)).

Although the study was retrospective in nature and had inherent limitations, it suggests that continuing TMZ beyond 6 cycles does not increase overall survival for newly diagnosed GBM.

Immunovirotherapy with measles virus strains in combination with anti–PD-1 antibody blockade enhances antitumor activity in glioblastoma treatment
To date oncolytic viral therapies have shown only modest activity. However, there is growing interest in their ability to evoke antitumor pro-inflammatory responses. In this study the combination of measles virus (MV) therapy and anti–programmed cell death protein 1 (anti–PD-1) blockade was to determine if they together can overcome immunosuppression and enhance immune effector cell responses against glioblastoma (GBM).

In vitro, MV infection induced human GBM cell secretion of damage associated molecular pattern (DAMP) (high-mobility group protein 1, heat shock protein 90) and upregulated programmed cell death ligand 1 (PD-L1). MV infection of GL261 murine glioma cells resulted in a pro-inflammatory response and increased migration of BV2 microglia. In vivo, MV + anti–PD-1 therapy synergistically enhanced survival of C57BL/6 mice bearing syngeneic orthotopic GL261 gliomas. MRI showed increased inflammatory cell influx into the brains of mice treated with MV + anti–PD-1. Fluorescence activated cell sorting analysis confirmed increased T-cell influx predominantly consisting of activated CD8+ T cells.

These results demonstrate that oncolytic measles virotherapy in combination with aPD-1 blockade significantly improves survival outcome in a syngeneic GBM model and supports the potential of clinical/translational strategies combining MV with anti–PD-1 therapy in GBM treatment.
Hotspots in Neuro-Oncology Practice 2016/2017

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Seizures and cancer: drug interactions of anticonvulsants with chemotherapeutic agents, tyrosine kinase inhibitors, and glucocorticoids
Benit CP, Vecht CJ.
All neuro-oncologists prescribe anticonvulsant medications as part of routine care for many of their patients, and it is critical to be aware of the potential interactions with other drugs, in terms of both toxicity and altered drug metabolism. Benit and Vecht provide a good review of the pharmacokinetics of anticonvulsants and the current knowledge regarding interactions with chemotherapeutic drugs, tyrosine kinase inhibitors and other targeted agents, and glucocorticoids. In addition to providing a useful reference guide, the authors draw attention to the lack of data on how targeted molecular agents influence the metabolism of anti-epileptic drugs and the significance of individual variability in drug metabolism, which underscores the importance of plasma drug monitoring to prevent organ failure, neurotoxicity, and diminished efficacy.

Glioblastoma in the elderly: making sense of the evidence
Mason M, Laperriere N, Wick W, Reardon DA, Malmstrom A, Hovey E, Weller M, Perry JR.
Standard care for elderly patients with glioblastoma is not always standard. Historically, this population has been excluded from many clinical trials of new agents over concerns that frailty and comorbidities would skew outcome data. Extensive craniotomy is also considered risky in elderly patients and not always offered, even though it is otherwise considered first-line therapy for most malignant gliomas. As a result, there is scattered information on optimal care for these patients despite the fact that they make up a large proportion of the population we see in the clinic. While age is a negative prognostic factor regardless of therapy chosen, there is a growing body of evidence that chemotherapy and radiation are well tolerated by older patients. This article reviews the practical aspects of caring for elderly patients with newly diagnosed glioblastoma, including surgery, radiation, temozolomide, anti-angiogenic agents, and symptom management. Based on available randomized data, the authors provide an easily adoptable algorithm for care that takes into account age, performance status, and MGMT methylation status.

Clinical outcome assessments in neuro-oncology: a regulatory perspective
Sul J, Kluetz PG, Papadopoulos EJ, Keegan P.
The most widely accepted endpoints used to evaluate clinical trials are overall survival, progression-free survival, and objective response. More recently, clinical outcome assessments (COAs) have been considered in the risk–benefit assessment of clinical protocols. COAs take into account how treatments affect quality of life in terms of patients’ symptoms, function, and overall physical and mental well-being. Sul and colleagues eloquently review the challenges of evaluating COAs in the neuro-oncology field, pointing out that despite their increasing popularity among patients and providers, current measurement tools are extremely heterogeneous in both methodology and quality. They outline the steps needed to develop and validate appropriate instruments to measure COAs from a regulatory perspective in the United States. As stated by the authors, it is the responsibility of health care providers, regulators, and drug developers to promote efforts that encourage effective development and thoughtful use of COAs in clinical trials in conjunction with standard tumor and survival measures. These COAs should be incorporated earlier in the drug development process and take into consideration the concerns that rank highest among patients and caregivers. This article discusses the results of a survey to determine the symptoms and function that patients feel are most important when evaluating new therapies and makes the case for prioritizing COA tools that measure these specific outcomes in clinical trial protocols.

Understanding inherited genetic risk of adult glioma—a review
Genetic risk is an important topic that is often asked about by patients and families. With the recent discovery of inherited genetic variation that increases the risk for adult glioma, Rice and colleagues provide a review of the current knowledge and the potential value and limitations critical for assisting clinicians in counseling patients. In addition, they clearly describe how inherited risk varies by histology and molecular subtypes characterized by acquired mutations within the tumor. Although we can now point to some inherited variations that confer a higher risk for developing brain tumors, such as the chromosome 8 glioma risk variant rs55705857, the overall risk remains so low that testing for these variations is not currently recommended. However, our expanding knowledge of how genetics may influence tumorigenesis is critical to improving treatment options, and the molecular classification of brain tumors may ultimately prove more important than histological classification in predicting their clinical behavior. This article is accompanied by an online companion information sheet on inherited genetic risk of adult glioma, which is a useful resource for clinicians explaining the current state of knowledge to patients and families.

Fertility preservation in primary brain tumor patients
Stone JB, Kelvin JF, DeAngelis LM.
Fertility preservation among patients of child-bearing age who develop brain tumors is an understudied issue in
neuro-oncology. As with other discussions we have with our patients about planning for the future—such as those related to caregiving, advance directives, or hospice—early counseling on fertility preservation should be a routine discussion with young patients and their partners. Despite the high interest that couples have in fertility preservation, this article shows that in the United States there is a deep, unmet need for guidance on this topic and helps provide awareness for oncologists who may assume that their patients are getting relevant information from another source or find the topic inappropriate. Stone et al describe their experience with patients referred for reproductive counseling, which includes discussions on treatment-related fertility risks and fertility preservation. As the authors describe, advances in treatment for many types of primary brain tumors, along with advances in reproductive medicine, have resulted in more young adults being optimistic about beginning families. There were few social, demographic, or clinical characteristics that could predict a patient’s interest in fertility preservation, and the authors recommend that it be offered to all patients of reproductive age regardless of gender, race/ethnicity, marital status, prior children, religion, tumor type, or tumor grade.

Case-based review: primary central nervous system lymphoma
Korfel A, Sclegel U, Johnson DR, Kaufmann TJ, Giannini C, Hirose T.
The case-based review series in Neuro-Oncology Practice is an excellent resource for providers that uses a case report to frame a review of the literature surrounding a particular clinical entity. Korfel et al recently provided an in-depth review of primary central nervous system lymphoma, following the case of a patient presenting only with cognitive and behavioral symptoms. They give detailed information on distinguishing primary central nervous system lymphoma from other neoplastic, inflammatory, and infectious neurological conditions. Once properly diagnosed, they provide an overview of current treatment strategies, including those for elderly patients, as well as a discussion of salvage therapy and experimental agents being tested in ongoing clinical trials. While overall survival remains poor for this disease, management strategies have improved to reduce toxicity, and further studies are under way to better understand the underlying biology of the disease.
ANOCEF (French Speaking Association for Neuro-Oncology)

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The ANOCEF (Association des Neuro-Oncologues d’Expression Française) was created in 1993 as a non-profit organization by Marcel Chatel, who was its first president. Its initial missions were those of a multidisciplinary learned society, then they progressively extended toward supporting research on neuro-oncology under the impulse of its previous successive presidents (Jean-Yves Delattre, Jérôme Honnorat, Olivier Chinot, Luc Taillandier). It has become over the years the natural interlocutor of the public health authorities for all matters to do with neuro-oncology, especially in the framework of the French Cancer Plan. ANOCEF has recently set up a research group named ICGNO (Intergroupe coopérateur de neurooncologie) dedicated to promote clinical research projects and sponsor clinical trials by its own means, and which has been endorsed in 2014 by the French Cancer Institute (INCa).

Education
ANOCEF organizes an annual scientific congress in spring and 2 educational meetings, including one in partnership with the French Society of Neurosurgery, the French Society of Neuroradiology, and the French Society of Neuropathology within the Journées de Neurologie de Langue Française (JNLF). ANOCEF also created in 2004 a postgraduate curriculum with a national degree of neuro-oncology (Diplome Inter Universitaire) involving 13 universities. Three years ago, a curriculum dedicated to nurses was set up. In 2016, 87 participants participated in one or the other curriculum (76 physicians and 11 nurses). ANOCEF has carried out several national guidelines with the aim of improving and standardizing the management of brain tumors throughout the country.

Research
ANOCEF comprises 10 theme working groups covering the different fields of neuro-oncology, whose tasks are to set up clinical and translational research studies. ANOCEF has an executive committee aiming to evaluate and coordinate the projects and to apply for calls. As examples, several ongoing phase III trials have succeeded in obtaining public funding, such as the POLCA trial evaluating the role of deferred radiotherapy in 1p/19q codeleted anaplastic oligodendrogliomas, the BLOCAGE trial evaluating the role of maintenance chemotherapy in elderly patients with primary CNS lymphoma, the CSA trial evaluating the interest of tumor resection versus biopsy in elderly patients with glioblastoma, the DXA trial evaluating the efficacy of dextroamphetamine in brain tumor patients with chronic fatigue. The centers of the ANOCEF network participate also in international trials, especially those conducted by the European Organisation for Research and treatment of Cancer (EORTC), providing in the past years about 20% of the inclusions.

Health Care Networks
Thanks to the National Cancer Plan, ANOCEF is supported by the INCa to structure clinical research on neuro-oncology but also to improve the management of rare cancers through dedicated networks (POLA for anaplastic gliomas, LOC for primary CNS lymphoma, and TUCERA for rare primary CNS tumors). Hence, for complex cases, a colleague anywhere in the country can ask for a histological central review by an expert neuropathologist of the RENOP group, coordinated by Dominique Figarella-Branger, and/or can solicit a national multidisciplinary expert meeting for practical recommendations and second advice. At the moment, ANOCEF provides 8 expert web conferences dedicated to specific CNS tumor types organized on a regular basis at fixed dates and with a designated coordinator (anaplastic gliomas, brainstem tumors, low grade gliomas, meningiomas, spinal cord tumors, primary CNS lymphomas, tumors of adolescent and young adults, neurotoxicities). INCa allows also access for our patients to 26 approved molecular genetics platforms for searching relevant biomarkers for decision making in routine cases, and eventually to 16 early phase trial platforms (CLIP) for innovative therapies.

International Relationships
ANOCEF is the national contact with the European Association of Neuro-Oncology (EANO) and the World Federation of Neuro-Oncology (WFNO). As a
French-speaking society, it aims to develop collaboration with other foreign societies, such as the Belgian Association for Neurooncology (BANO) and the SAKK Swiss Working Group on CNS Tumors. Hence, joint meetings have been held in Lausanne in 2015 and in Bruxelles in 2016. ANOCEF has also a partnership with AROME (Association of Radiotherapy and Oncology of the Mediterranean Area) with an annual joint education meeting of neuro-oncology in the Maghreb (Tunisia, Morocco, Algeria in alternation). Several guidelines adapted to the local health and economic resources have been initiated under AROME and ANOCEF with mixed working groups, and the first one on the “minimal requirements” and standard of care of glioblastoma has been recently published. Educational and training projects with sub-Saharan African countries are also planned as part of a broader project of the French Society of Neurology.

One of our most important priorities for the next months will be to prepare with Jérôme Honnorat and the EANO board the Congress of 2019, which we are proud to host in the beautiful and luminous city of Lyon.
The 5th Meeting of the World Federation of Neuro-Oncology Societies (WFNOS) was hosted by the European Association of Neuro-Oncology (EANO) and held in Zurich, Switzerland May 4–7, 2017. Four years after the last WFNOS convention, in San Francisco, approximately 950 participants discussed the most recent developments as well as controversial topics in neuro-oncology. The meeting started with an educational day jointly organized by EANO and the European Organisation for Research and Treatment of Cancer (EORTC). The organizers set up 2 parallel tracks, focusing on clinical aspects and basic science, respectively. A number of internationally renowned experts reported on the clinical impact of the new World Health Organization (WHO) classification of brain tumors and the current state-of-the-art approaches to rare brain tumors such as primary CNS lymphoma and ependymoma. In a separate session, a comprehensive overview on neurocutaneous syndromes was provided. Additional presentations were devoted to the management of lower-grade (WHO grades II/III) gliomas as well as general aspects of clinical research in neuro-oncology. In parallel, the basic science track covered various aspects of scientific questions currently being addressed in the field. This includes new developments in tumor genetics, metabolic alterations in gliomas, and their therapeutic targeting, as well as an overview on the biological properties of the tumor microenvironment.

The main program over 3 days was characterized by a high density of presentations covering numerous aspects of preclinical and clinical neuro-oncology. The organizers had put a focus on the following topics:

(i) immuno-oncology, (ii) brain and leptomeningeal metastasis, (iii) gliomas, (iv) pediatric tumors, and (v) meningiomas. Several Meet the Expert and plenary sessions dedicated to these contents allowed for comprehensive presentations and in-depth discussion. In the WFNOS session, the acting presidents of ASNO, EANO, and SNO reported on novel developments in local and molecularly targeted treatment of gliomas.

In addition to the 3 parallel sessions of the main meeting, there was a dedicated full-time track for nurses on Friday organized by Ingela Oberg (Cambridge, UK). The nurse session focused on the management of brain metastases covering diagnostic and therapeutic aspects.

Three keynote lectures addressed challenging topics in the field. The EANO keynote lecture was given by Dr Riccardo Soffietti (Turin, Italy), who provided a comprehensive overview of current concepts and challenges of trial design in brain and leptomeningeal metastasis. Dr Koichi Ichimura (Tokyo, Japan) elaborated on the implications of telomerase reverse transcriptase in the biology of brain tumors during the ASNO keynote presentation. Finally, Dr David Reardon (Boston, US), representing SNO, discussed immunotherapeutic approaches which are currently being explored in clinical trials as well as challenges associated with these novel concepts.

A particular highlight of the meeting was the first presentation of the results of the Checkmate 143 trial, the first randomized study assessing the activity of the immune checkpoint inhibitor nivolumab in patients with recurrent glioblastoma. Despite the overall disappointing results, the study demonstrates the high interest in novel immunotherapeutic options which have reached clinical neuro-oncology and are currently being assessed in clinical trials.

Many of the participants were actively involved in the scientific program of the conference, which is reflected by more than 550 submitted abstracts that were included as oral presentations or as part of 2 poster sessions which allowed for intense discussions. In this regard, the Welcome Reception on the bank of Lake Zurich as well as the WFNOS Evening on the Uetliberg over the rooftops of Zurich provided excellent opportunities for scientific and personal exchange.

The 6th Quadrennial WFNOS meeting is scheduled for May 6–9, 2021 in Seoul, South Korea. Information about the program as well as further activities of WFNOS will be available on the WFNOS website (www.eano.eu/wfnos).

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The recently started EANO Youngsters Initiative aims to provide a platform for networking, interaction, and collaboration between young scientists with a special interest in neuro-oncology. Therefore, the EANO Youngsters committee was formed to organize activities specially focusing on young scientists within the EANO. Here, the EANO Youngsters aim to represent the diversity of EANO with a lot of different specialties involved in neuro-oncology as well as to represent the different scientific interests from a clinical as well as a translational and basic science viewpoint. In the following we want to introduce the initiative and ourselves, as well as to provide a broad overview of the planned activities.

The EANO Youngsters committee says “Hello”

The EANO Youngsters committee is in charge of organizing the activities of the newly formed EANO Youngsters initiative. We are all young scientists from different fields of interest and different European countries.

Anna Berghoff is in medical oncology training at the Medical University of Vienna, Austria. She finished the PhD program “Clinical Neuroscience” in 2014 with the main focus on clinical and pathological prognostic factors in brain metastases.

Carina Thomé is a biologist currently holding a post-doctoral posting to the German Cancer Research Center (Heidelberg, Germany) and has her research focus on the interaction of glioma cells with the inflammatory microenvironment.

Tobias Weiss is just about to finish his training in neurology at the University of Zurich. Further, he joined the MD-PhD program in Immunology in 2015 to deepen his research in immunotherapeutic approaches against malignant brain tumors.

Alessia Pellerino completed her neurology residency in 2016 and held a PhD position in neuroscience in the Department of Neuroscience of the University of Turin afterward. She has a particular interest in the design of clinical trials in neuro-oncology with a focus on new therapeutic drugs.

Asgeir Jakola is a neurosurgeon and associate professor at the Sahlgrenska University Hospital, Gothenburg, Sweden. His main clinical as well as certainly research interest is in quality of life in glioma patients after neurosurgical resection.

Amelie Darlix is a neuro-oncologist at the Montpellier Cancer Institute (France). She takes care of patients with both primary and secondary tumors of the CNS, as well as cancer patients with posttreatment cognitive impairment.

Together we aim to address the issues of young neuro-oncology scientists within the EANO and provide a platform for interaction as well as organize dedicated activities. Any ideas for new activities? Do not hesitate to contact us via the Facebook group (see below).

The EANO Youngsters Networking Event

The kick-off for an EANO Youngsters Networking Event was held during the 2016 EANO conference in Mannheim and was repeated during the WFNOS Meeting in Zurich, Switzerland in 2017. The Networking Event provides an informal and casual possibility to connect with other young scientists within EANO. Questions like “How do you perform a TGF beta western blot” or exchanging experiences can be addressed and provide the basis for fruitful collaborations, now or at a later date.

The EANO Youngsters Facebook Group

The EANO Youngsters Facebook group should help to interact with other youngsters more early. Exchange experience and information, ask for advice from the community, and share interesting information, for instance on trials or papers. Not yet connected? Just enter “EANO Youngsters” and join the community!

More to come!

This is only the beginning! We plan our own EANO Youngsters track.
during the next EANO meeting in Stockholm to specially address the interest of young scientists. Currently we are in the planning phase and are trying to put together an exciting first program. Further, we want to fill the Facebook group with more life and share interesting articles in an online journal club with each other. Do not hesitate to forward your ideas for the program to any of the EANO Youngsters committee members. Further, we represent the interest of EANO Youngsters in conducting EANO Summer and Winter Schools.

See the EANO Homepage for more information on the upcoming Summer/Winter Schools.

The EANO Youngsters want you!

After all, any initiative lives off of its participants. So let’s take this opportunity and connect during the EANO Youngsters Networking Event or in the EANO Youngsters Facebook group. We are looking forward to filling this initiative with a lot of activities.

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