HÔTEL LE MAROIS
FRANCE AMÉRIQUES

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11th Edition

BRAIN METASTASES RESEARCH AND EMERGING THERAPY CONFERENCE

PROGRAM CHAIRS

- Manmeet Ahluwalia (US)
- Fabrice Barlesi (FR)
- Frédéric Dhermain (FR)
- Emilie Le Rhun (CH)
- Philippe Métellus (FR)
- Riccardo Soffietti (IT)
- Michael Weller (CH)
- Manfred Westphal (DE)

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SNO Society for NeuroOncology
GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS
PARIS-SACLAY CANCER CLUSTER
Ramsay Santé - 1 - Hôpital privé Clairval

SUMMARY

WELCOME LETTER

Dear Friends,

We are delighted to welcome you to Paris for the Eleventh Annual Brain Metastases Research and Emerging Therapy Conference.

Past successful editions have conforted us to organize again the conference.
The meeting will be held, as for previous editions under the auspices of EORTC, EANS, EANO and SNO, also in association with the Gustave Roussy Cancer Campus and Paris-Saclay Cancer Cluster.

This initiative is devoted to accelerate therapeutic discoveries and, to improve care of patients with metastatic CNS malignancies. We anticipate that this cross-sectional meeting will provide a deeper dive into basic and translational research and, also stimulate innovative and insightful clinical trial on brain metastatic patients.

These pre, intra and post diagnosis issues of great unmet need will be addressed in a dynamic and interactive framework.

Several topics will be specifically discussed like challenges in precision medicine management and, the actual role of liquid biopsies for CNS metastases patients. The increasing place of new local treatments and, combined strategies in the era of targeted therapies and immune check point inhibitors will also be addressed.

We are convinced that this conference would constitute an unparalleled platform to share basic, translational and clinical data and explore new treatment paradigms in this patient population.

Finally, the scientific committee hopes that this meeting will provide a fantastic opportunity to develop networking with all professionals involved in brain metastases management and, lay the foundation for future collaborative projects.

The program chairs
Manmeet Ahluwalia (US), Fabrice Barlési (FR), Frédéric Dhermain (FR),
Emilie Le Rhun (CH), Philippe Métellus (FR), Ricardo Soffietti (IT),
Michael Weller (CH), Manfred Westphal (DE)

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L'Houcine Ouafik (FR)

Matthias Preusser (AT)

Matthias Simon (DE)

Riccardo Soffietti (IT)

Patricia Steeg (US)

Roger Stupp (US)

Claudio Tatsui (US)

Martin J. van den Bent (NL)

Erik Van de Kelft (BE)

Andreas von Deimling (DE)

Jeffrey S. Wefel (US)

Tobias Weiss (CH)

Michael Weller (CH)

Manfred Westphal (DE)

SCIENTIFIC PART

ABSTRACTS

OPENING LECTURE - WEDNESDAY, OCTOBER 4TH, 2023 - 19.00

BRAIN METS : THE NEW FRONTIER IN NEURO-ONCOLOGY ?
Michael Weller (CH)

Michael Weller,
University Hospital Zurich, Department of Neurology, Switzerland

Despite a much higher incidence, compared to primary brain tumors, metastatic disease to the central nervous system has been relatively deprioritized by the neuro-oncology research community for decades. Only the last view years have seen emerging initiatives that have brought the challenge of CNS metastases to the forefront of neuro-oncology research. This includes the challenges of establishing clinically relevant animal models, the use of high throughput technology to explore in what way brain metastases differ from metastases at other organ sites, and eventually the development of dedicated clinical trial initiatives to address the challenge of brain metastases. There are divergent developments in solid brain metastases versus leptomeningeal metastases. For solid brain metastases, several agents have been demonstrated to induce responses or at least prolonged disease control, when given systemically, resulting in new controversies on the best place for various radiotherapy approaches in this setting. For leptomeningeal metastases intrathecal drug delivery has regained interest and current evidence suggests that the potential of this privileged approach to the site of disease should not be underestimated. A highly active and successful research community has formed that has placed this field at the forefront of oncology research with novel approaches to classify, diagnose, monitor and treat metastases to the central nervous system.

SESSION 1 – THURSDAY OCTOBER 5TH 2023 – 09.10

Clinical and Translational Insights into Brain Metastases of Breast Cancer

[1]Khan, I., [1]Wu. A.M.L., [1]Zhang, W.,[1]Rahman, S., [1]Kumar, D., [1]Gril, B., [2]Swenson, R., [1]Zimmer, A., [1]Steeg, P.S.

[1] Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute and;
[2] Chemistry and Synthesis Center, National Heart, Lung and Blood Institute, NIH, Bethesda, MD, USA.

The blood-tumor barrier (BTB) is a potent obstacle to the delivery and efficacy of drugs for the treatment of brain metastases. The BTB is formed when tumor cells traverse the normal blood-brain barrier (BBB) and use its matrix as a substrate for proliferation and migration to form a metastatic colony. We previously reported that the BTB is heterogeneously permeable to probes and drugs, with 85% of lesions more permeable than the BBB, but only 10% of lesions having enough drug uptake to induce an apoptotic response in tumor cells. In addition to paracellular permeability, occurring when continuous tight junctions and cell adhesions between capillary endothelial cells are broken, transcytotic pathways through the capillary endothelia can mediate permeability. To determine how transcytotic pathways function through the BTB, we compared the distribution of three far-red labeled ligands: Transferrin receptor (TfR) peptide, Low density lipoprotein receptor 1 (LRP1) peptide and Albumin. Each was injected into two hematogenous models of brain metastases (231-BR and JIMT1-BR), circulated for two different times. TfR distributed to uninvolved brain but showed poor uptake in metastases, while LRP1 was poorly distributed overall. Albumin demonstrated a frequent, intense distribution in virtually all metastases (For 231-BR and JIMT1-BR models- $P < 0.0001$) in contrast to low distribution in uninvolved brain. Albumin transcytosis was distinct from a Biocytin-TMR paracellular marker distribution; albumin also targeted both macro and micro metastases effectively ($P<0.0001$). The data identify a potential transcytotic pathway to potentially improve drug uptake in brain metastases.

Translation of preclinical brain metastasis prevention experiments to the clinic is hampered by the lack of acceptable prevention trial designs. We will describe a secondary brain metastasis prevention phase I trial and exploratory endpoints based on cell-free DNA mutations.

In separate experiments we investigated an aspect of breast cancer with regard to patient age: Young patients diagnosed with breast cancer have aggressive disease and higher rates of brain metastases. Investigations of primary tumors from young and older patients has revealed no set of age-specific mutations, prompting the hypothesis that the host's age regulates brain metastatic ability. In four model systems young mice were injected with brain-tropic breast cancer cells side-by-side with older mice, and the younger mice developed 2-3 fold greater brain metastases. FACS analysis demonstrated that the myeloid (microglia, infiltrating macrophages) compartment is altered in the metastatic brain by age, and pretreatment of young mice with a colony stimulating factor-1 receptor (CSF-1R) inhibitor significantly prevented brain metastasis formation. We will present a translational investigation of CSF-1R inhibitors for brain metastases.

The data illuminate characteristics of the BTB that may be important for rational drug design for CNS malignancies.

SESSION 2 – THURSDAY OCTOBER 5TH 2023 – 09.30

The role of the neurosurgeon: the EANS perspective

Matthias Simon
Prof. & Chair, Dept. of Neurosurgery, University of Bielefeld OWL, Bethel, Bielefeld, Germany
Chair, EANS Neuro-oncology Section

Patients with brain metastases often have a grim prognosis with a median overall survival of less than 12 months even in selected patient cohorts. However, current progress in treating cancer has resulted in an increasing number of patients considered for neurosurgical management. Neurosurgical interventions usually aim at obtaining a tissue diagnosis, relieving mass effect and thereby maintaining or even improving the patient's clinical status, and prolonging survival by controlling CNS disease.

Most patients with single brain metastases should be considered for open resections. Recent data suggest that there may even be a relationship between extent of resection and survival. Surgical indications in cases with multiple metastases are more controversial, but there is evidence to suggest that resections are helpful in some patients, e.g. those with few ("oligometastases") rather than many tumors. Repeat resections may also be beneficial in selected cases. Posterior fossa metastases with their attendant risk for brainstem compression and hydrocephalus may require urgent surgical treatment and are a good example for surgery aiming at preserving or improving neurological function. Functional outcomes are of utmost importance in brain metastases surgery. In particular neurological deficits have a major negative prognostic impact, and surgery for brain metastases probably warrants the routine use of intraoperative monitoring, awake craniotomies and other surgical adjuncts similar to glioma operations. Issues such as frailty and age, i.e. the preoperative status of the patients beyond functional health scores have also attracted some attention from researchers lately.

The EANS perspective on brain metastases and their treatment of course includes the use of stereotactic biopsies and radiosurgery in addition to open resections in order to complete the neurosurgical armamentarium for such patients. An EANS tumor section study will address the issue of repeat surgery for brain metastases. Neurosurgical treatment algorithms for brain metastases are changing. The molecular biology of the brain tumor may differ from its primary tumor which may require neurosurgeons more often to resect or biopsy lesions in order to identify druggable targets even if the primary cancer is known. Finally, the great variation of patient outcomes which often reflects advances in medical oncology vis-à-vis control of the CNS disease may likely warrant to think of brain metastases less often as a specific neuro-oncological condition, and result in a more "oncological" (i.e. primary cancer-centered) approach to the patient with brain metastases.

SESSION 2
THURSDAY, OCTOBER 5TH, 2023 - 09.50

Brain metastases - an interdisciplinary challenge: The radiation oncology position

Giuseppe Minniti,
Department of Radiological Science, Oncology and Anatomical Pathology, Umberto I Hospital, University Sapienza, Policlinico Umberto I, Rome, Italy

Brain metastases are common complications occurring in 10–50% of cancer patients and represent a major challenge in oncology. Whole-brain radiation therapy (WBRT) has been the mainstay of treatment for decades; however, more advanced radiological technologies and systemic therapies are changing the therapeutic framework of several tumors. Stereotactic radiosurgery (SRS) has been shown to be effective in reducing the detrimental effects on cognitive function and quality of life associated with WBRT, while maintaining an equivalent survival benefit. So far, SRS has become the standard of care for patients with multiple brain metastases.
Together with the improvement of radiotherapy techniques, the development of new systemic therapies, immunotherapy, or targeted therapies, has represented a fundamental achievement in the management of brain metastases. For patients with actionable oncogenic mutations, such as BRAF-mutant melanoma, HER2-mutant breast cancer, and EGFR-mutant non-small cell lung cancer, targeted therapies have shown excellent intracranial response rates of 30-60% or higher. Likewise, immunotherapy has had a substantial impact on several types of cancer, including metastatic melanoma.
Numerous studies have demonstrated significant activity of these agents in the context of patients with brain metastases. Thus, the current clinical findings raise the question whether the use of initial systemic treatments could obviate the need for SRS in such patients. Although this approach can be observed for asymptomatic brain metastases, omission of SRS as first-line therapy should be considered with caution in large and/or symptomatic lesions. Currently, the use of systemic agents with or without radiotherapy is field in rapid expansion, as evidenced by over 200 ongoing clinical trials registered. Future studies, including overall survival, preservation of neurocognitive function, and incidence of treatment-associated neurological toxicity, will help clarify the “changing” role of SRS in the management of brain metastases. Additionally, optimal timing of radiation dose fractionation of radiotherapy and the development of biomarkers that can help identify who is most likely to benefit from different treatments will need to be determined in future research.

SESSION 2
THURSDAY, OCTOBER 5TH, 2023 - 10.10

INSIGHTS FROM NEURO-ONCOLOGISTS

Prof. Riccardo Soffietti,
Division of Neuro Oncology, Department of Neuroscience «Rita Levi Montalcini»,
University of Turin and Institute of Cancer Research and Cure (IRCCS) Candiolo, Turin, Italy.

New targeted agents require new concepts of monitoring. Advanced MRI and PET with old and new tracers should increase the capabilities of detecting early responses and relapses, as well as the minimal residual disease. Volumetric measurements of tumor burden and also algorithms of AI are being implemented in clinical trials. Monitoring of molecular response by liquid biopsy increasingly parallel the evaluation of response by neuroimaging. Prevention of brain metastasis is another hot topic: new targets, both in the tumor and microenvironment, critical for brain colonization, are druggable in early clinical trials. Targeting synapses between neurons and tumor cells is a new frontier of treatment.

SPINAL TUMORS SESSION - **THURSDAY, SEPTEMBER 5TH, 2023 - 10.45**

Treatment of ambulatory patients with metastatic epidural spinal cord compression: emerging treatment modalities

Erik Van de Kelft, MD, PhD,
University of Antwerp, Belgium.
Department of Neurosurgery, Vitaz, Sint-Niklaas, Belgium

Approximately 10% of patients with spinal metastases develop metastatic epidural spinal cord compression (MESCC) which undiagnosed and treated can lead to the loss of ambulation. Timely diagnosis and efficient multidisciplinary treatment are critically important to optimize neurologic outcomes. This presentation aims to determine the most efficient treatment modalities for ambulatory patients with MESCC, based on two recent reviews.

We conducted a systematic review and meta-analysis on the treatment of mobile patients with MESCC regarding outcome described as local control (LC), ambulatory function, quality of life (QoL), morbidity and overall survival.

In general, different treatment modalities exist, as stand alone or in combination: classical radiotherapy (RT), Stereotactic Body RT (SBRT), reconstructive surgery with gross tumorectomy, 'separation surgery' or decompressive surgery in combination with spinal fixation.

SBRT seems to be an extremely promising treatment modality being integrated into treatment algorithms and provides durable LC. Surgery has an important role, but does not improve LC or survival in absence of instability or neurologic deficit. In case of high-grade MESCC in the absence of a neurologic deficit, the role of surgery is still debatable as some studies demonstrate good LC for SBRT without preceding surgery. However separation surgery can provide safe margins for the ablative dose of SBRT to the entire tumor volume within the constraints of spinal cord tolerance. With the excellent results of separation surgery and SBRT, the role of highly invasive en-bloc resections is diminishing given the complication rate and morbidity of these procedures.

SPINAL TUMORS SESSION - **THURSDAY, SEPTEMBER 5TH, 2023 - 11.10**

Intradural spinal metastases: going beyond the anecdote

Steven Knafo,
Paris, France

Intradural extramedullary spinal metastases (IESM) of non-neurogenic origin are rare and often misdiagnosed. IESM must be distinguished from «drop metastases» and leptomeningeal carcinomatosis after a thorough diagnosis workup including brain MRI, PET-CT and CSF study. More than half of IESM cases are revealed by a motor deficit due to spinal cord compression and are associated with brain and systemic metastatic localizations. Whenever the general status of the patient is acceptable, surgical resection of IESM followed by adjuvant radiotherapy should be offered, ensuring neurological improvement and a median OS of 24 months.

SPINAL TUMOR SESSION - **THURSDAY, OCTOBER 5TH, 2023 - 11.30**

Considerations in the surgical management of intramedullary metastases

Manfred Westphal,
Institute for Tumor Biology, UK Eppendorf, Hamburg Germany

Metastases to the CNS become increasingly frequent as systemic therapies become more efficient and patients enjoy much longer life spans after the diagnosis of cancer. This is also reflected by an increasing number of metastases to the spinal cord. Nevertheless these lesions are still considered rare and a sign of endstage disease.

More than 60% of intramedullary metastases originate from lung and breast cancer but in principle, all malignancies have been found at least anecdotally to metastasize to the spinal cord. The prognosis is poor and few patients survive more than 12 months. Upon MRI imaging, there is consistent contrast enhancement, extensive edema extending upwards and downwards along the fiber tracts and occasionally necrosis. Most lesions are singular.

As the mechanism of metastasis is by hematogenic route, the tumors are located anywhere inside the cord, - different from ependymoma which is regularly central in its origin or subependymoma which also has a central root although being excentric. When located close to the surface, exophytic growth may lead to meningeal seeding and associated meningeal carcinomatosis.

Surgical removal of symptomatic lesions aims at preventing paraplegia or tetraplegia, establishing the histology and even molecular pathology in search of specific drug targets. In contrast to ependymoma, metastases may be locally infiltrative from their surface and therefore tend to locally recur. In contrast to astrocytoma, there is no migratory infiltration along fiber tracts, explaining the strictly local tendency to recur. Unless reaching the surface of the cord, the lesions are approached mostly through the midline with the intention to debulk as much as possible. Laminotomy limited to the extent of the lesion is the optimal exposure. In most patients, surgery is followed up with radiation. Systemic chemotherapy has to take possible molecular targets into consideration as well as the history of regimes already used for the primary tumor.

Overall, metastases to the spinal cord are a growing concern but it becomes apparent that also in these lesions, patients can benefit at least temporarily from aggressive removal. To learn more about the optimal strategies for these tumors, registries may be established by national or international consortia.

SPINAL TUMORS SESSION
THURSDAY OCTOBER 5TH 2023 – 11.50

Advancements in surgical treatment of spinal metastasis

Claudio E. Tatsui,
Professor, Department of Neurosurgery, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

The introduction of spine stereotactic radiosurgery (SSRS) has led to significant improvement the local control of spinal metastasis. Surgical management focuses in maintaining spinal stability and decompression of the spinal cord, to allow adequate delivery of tumoricidal doses of conformal radiation to the spinal tumor. In this context, adequate imaging for proper target delineation and the aggressiveness of surgery are important considerations in the multimodality management of these patients. We present three recent innovations in the surgical management of spinal metastasis used in combination with SSRS: 1- A review of the implantation of 491 carbon fiber-peek pedicle screws in 69 patients and the quantification of the imaging artifacts compared to a similar cohort of individuals who received titanium hardware confirms significant reduction in imaging artifacts in post-operative MRI, facilitating SSRS planning and image follow up; 2- A review of the utilization of spinal Laser Interstitial Thermotherapy (sLITT) as an alternative to open surgery in 160 cases treated between 2014 and 2023, describing the technique and clinical outcome. A sub analysis of a matched cohort of 40 cases treated with open surgery or sLITT followed by SSRS confirmed similar local control and reduced morbidity, shorter hospitalization, faster return to oncological management in patients treated with sLITT; 3: Pre-clinical studies (computational models, in vitro and in vivo) of the utilization of Tumor Treating Fields (TTFields) to be used in a clinical trial as an adjunct to surgery for management of radiation refractory spinal tumors. In conclusion, the multimodality management of spinal metastasis is evolving, and surgical advancements must be incorporated to improve clinical outcome.

NEUROCOGNITION, REHABILITATION AND SUPPORTIVE CARE - **THURSDAY, OCTOBER 5TH, 2023 - 14.00**

Neurocognition and Rehabilitation in Brain Metastases

Jeffrey W. Wefel,
Section of Neuropsychology, Department of Neuro-Oncology, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, USA

Patients with brain metastasis frequently encounter neurocognitive function (NCF) deficits during the course of their illness. NCF deficits may be caused by disease factors and/or treatment for the metastasis, including surgery, radiation therapy, chemotherapy, and immunotherapy. Improvements in survival time have contributed to increased emphasis on improving survivorship. This presentation will review data on the nature and prevalence of NCF deficits, prevention and management strategies for NCF deficits, and future directions.

NEUROCOGNITION, REHABILITATION AND SUPPORTIVE CARE
THURSDAY, OCTOBER 5TH, 2023 – 14.30

Dilemma's in supportive care in brain metastases

D. Brandsma,
Neurologist Netherlands Cancer Institute, Amsterdam, The Netherlands

Supportive care stems from the 1960's-1970's to minimize toxicities of cancer therapy, so treatments could be continued. Now, supportive care has evolved to care that is aimed at improving quality of life of the patient and his/her family in a broad scope, during any stage of cancer and treatment.
In patients with brain metastases, supportive care encompasses the treatment of neurological symptoms due to the tumor, treatment of seizures, rehabilitation for cognitive dysfunction, psychological and social support for the patient and his/her family, and support at end-of-life decisions.
In this presentation, two specific dilemma's in supportive care for patients with brain metastases will be discussed: treatment of hydrocephalus due to concomitant leptomeningeal metastases and treatment of cerebral radiation necrosis. Both medical and ethical considerations of the complex, shared-decision making in patients with these cancer- or treatment-related complications are shown, using two clinical cases.

DIGITAL TRANSFORMATION: A NEW PARADIGM IN MULTIDISCIPLINARY APPROACH FOR BRAIN METASTASES PATIENTS – THURSDAY OCTOBER 5TH 2023 – 17.00

Rethinking Brain Metastases

Roger Stupp, MD,
Malnati Brain Tumor Institute of the Lurie Compr. Cancer Center,
Northwestern University, Chicago, IL / USA

Brain metastases are not a diagnosis, but a manifestation of a variety of cancers. The onset brain metastases is commonly late in the disease course (yet metastases seeding may occur early and specific trigger will awaken cells from their dormant state), and is often considered a sign of very advanced disease with little valid treatment options. The observed increased incidence of brain metastases is owed to the better and more readily available diagnostic procedures, (MRI), baseline screening of cancer patients, and last but certainly not least progress in cancer therapy over the past two to three decades.

While brain metastases are not a diagnosis per se but a manifestation of an initial tumor that originated in another organ, there are certain characteristics that distinguishes CNS metastases from other metastatic manifestations. Not only is there the blood brain barrier an obstacle for the penetration of our drug therapies, the blood-brain barrier is also preventing or delaying development of metastatic deposits in the central nervous system. Brain metastases may form early in the disease course, yet remain dormant for months or years.

Management of brain metastases is built on several paradigms. I) the blood-brain barrier prohibits the penetration of effective drugs into the brain, thus only surgery and/or radiotherapy can elicit a response. II) Local control in the brain is a most important goal. III) overall prognosis is poor with an expected “average survival” of around 6 months. For these reasons most clinical trials historically excluded patients with brain metastases. Recent looser eligibility criteria may allow for trial participation of patients with “treated and stable” brain metastases, an ill-defined subgroup.

Trials investigating local treatment modalities are selecting patients based on practical considerations, patient fitness for the intervention, location, size and accessibility of the brain metastases (with various numbers of mets allowed) while ignoring the underlying cancer’s and histological subtype’s specific natural history and biology. In isolation and in their heterogeneity, these trials are doomed to fail demonstrating a survival benefit.

We need to rethink our approach to brain metastases and clinical trials in this condition. Can we design window-of-opportunity trials that will allow to understand distribution, tissue concentration and biological effect of our systemic intervention. Rather than exploring novel therapeutics as single agents in large trials that also allow inclusion of some patients with brain metastases, maybe specific clinical and translational trials can better respond to important fundamental questions. Treatment strategies need to consider systemic disease control as much than the brain. Isolated CNS control is not a useful outcome. Strategies to evaluate novel agents for their potential to prevent or delay metastases formation in an earlier stage disease setting may not only be a powerful avenue for drug development in a crowded market, but also more meaningful for our patients.

HIGHLIGHTS IN BM MANAGEMENT - FRIDAY, OCTOBER 6TH, 2023 - 10.10

CSF liquid biopsy in the management of brain metastases: Integration of clinical pathways and research standardization

Andreas von Deimling,
Neuropathology Heidelberg and CCU Neuropathology German Cancer Center, Heidelberg, Germany

Metastases to the brain are readily diagnosed if a primary tumor is known and morphological and immunohistological findings match accordingly. However, conflicting data may arise if metastatic manifestation has undergone major change or if a patient has developed additional cancer different from the established primary. In the case of cancer of unknow primary (CUP) a wide range of immunohistochemical analyses may point to the origin. Nevertheless, the classical tools may not suffice and molecular analyses are warranted. DNA sequencing may be employed for the detection of tumor relevant mutations. While DNA sequencing may detect a pathognomonic mutation, most alterations on the DNA level do occur in many different tumors. Therefore, DNA sequencing does assist greatly in the identification of potentially druggable targets, but much more rarely is able to unequivocally identify a distinct tumor type. A molecular approach addressing tumor lineage is determination of the global tumor methylome. This diagnostic approach has initially been developed for brain tumors with an according brain tumor classifier. Meanwhile, methylation profiling is also successfully used for sarcomas and a sarcoma classifier has been forwarded. Copying these models for carcinomas runs in a resolution problem. A Carcinoma classifier would need to cover such a high number of entities which would not allow clear separation of each tumor type. Therefore, an alternative approach is development of organ specific epithelial classifiers. In the longer run this would imply for the diagnosis of CUP running the molecular data by several classifiers. In this presentation, the development of non-primary brain tumor classifiers and their application to brain metastases will be discussed.

HIGHLIGHTS IN BM MANAGEMENT - **FRIDAY, OCTOBER 6TH, 2023 - 10.27**

Artificial intelligence for imaging of brain metastases

Norbert Galldiks,
University Hospital Cologne – Cologne, Germany

Although a variety of imaging modalities are used or currently being investigated for patients with brain tumors including brain metastases, clinical image interpretation to date uses only a fraction of the underlying complex, high-dimensional digital information from routinely acquired imaging data. The growing availability of high-performance computing allows the extraction of quantitative imaging features from medical images that are usually beyond human perception. Artificial intelligence is broadly a set of advanced computational algorithms that basically learn the patterns in the data provided to make predictions on unseen data sets. Using machine learning techniques and advanced statistical methods, subsets of such imaging features are used to generate mathematical models that represent characteristic signatures related to the underlying tumor biology and may be helpful for clinical applications, e.g., the assessment of prognosis or treatment response, and the identification of molecular markers. The identification of appropriate, characteristic image features as well as the generation of predictive or prognostic mathematical models is summarized under the term radiomics. Radiomics can be coupled with artificial intelligence because of its better capability of handling a massive amount of data compared with the traditional statistical methods. Together, the primary purpose is to extract and analyze as much and meaningful hidden quantitative data as possible to be used in decision support. This presentation summarizes the current status of artificial intelligence including radiomics in patients with brain metastases.

HIGHLIGHTS IN BM MANAGEMENT - FRIDAY, OCTOBER 6TH, 2023 - 11.05

CSF liquid biopsy in the management of brain metastases : Integration of clinical pathways and research standardization

Alireza Mansouri,
Pennsylvania State University

Background:
Effective diagnosis, prognostication, and management of central nervous system (CNS) malignancies traditionally involves invasive brain biopsies that pose significant risk to the patient. Sampling and molecular profiling of cerebrospinal fluid (CSF) is a safer, rapid and non-invasive alternative that offers a snapshot of the intracranial milieu while overcoming the challenge of sampling error that plagues conventional brain biopsy.

Objectives:
1. Provide an overview of the role of CSF in the dissemination of systemic cancer to the brain.
2. Highlight current advances in CSF-based liquid biopsy in brain metastases.
3. Present our data on CSF based diagnostic signatures in brain metastases.
4. Conclude with recommendations for research and clinical applications

Body:
An outline of the literature suggesting possible routes of tumor cell entry into the CNS, bypassing the blood-brain barrier, is presented. Subsequently, we show that the number of brain lesions in contact with a CSF space correlate directly with the likelihood of positive cytology in brain metastases patients without LMD undergoing radiosurgery. With strong evidence that tumor cells are present in the CSF earlier than currently accepted, we posit that the CSF is a valuable resource for studying brain metastases. Through a systematic review of the literature, we identify the most validated biomarkers established for brain metastases, while also highlighting major challenges and gaps. We then present our own proteomics data, using as little as 30uL, to distinguish brain metastases from other tumors while also proposing a potential biomarker. We conclude by outlining strategies on improving liquid biopsy research while also proposing areas where a clinical impact can be made.

HIGHLIGHTS IN BM MANAGEMENT - **FRIDAY, OCTOBER 6TH, 2023 - 11.40**

Prospects of antibody drug conjugate (ADC) therapy in CNS metastases

Matthias Preusser,
Medical University of Vienna

Antibody-drug conjugates (ADCs), a class of targeted cancer therapeutics combining monoclonal antibodies with a cytotoxic payload via a chemical linker, have already been approved for the treatment of several cancer types, with extensive clinical development of novel conjugates ongoing. CNS metastases are associated with high mortality and morbidity, necessitating novel treatment approaches. Pharmacotherapy of CNS metastases can be limited by restricted drug delivery across the blood–brain or blood–tumour barrier, although emerging data indicate clinically relevant intracranial ADC activity in patients with brain metastases from HER2-positive breast cancer. This talk will summarize the available data on the activity of ADCs from trials involving patients with CNS metastases and discuss their clinical implications and future directions.

HIGHLIGHTS IN BM MANAGEMENT - FRIDAY, OCTOBER 6TH, 2023 – 11.57

Stereotactic Radiosurgery for patients with Brain Metastases.

Dr Frederic Dhermain
Gustave Roussy, Department of Radiation Oncology, Paris-Saclay University, Villejuif, France.

Survival of patients with solid metastat¬ic cancer has dramatically improved in the last decade with the advent of precision medicine, sophisticated surgical techniques and diffusion of dedicated machines for stereotactic radiosurgery (SRS). With improved extra-cranial con¬trol and prognosis in more patients, optimizing intracranial control while minimizing 'late' neurotoxicity (beyond one year) has become essential. Even if Whole-Brain Radiotherapy (WBRT) keeps some rare but solid indications, SRS has supplanted it for 'limited' brain metastases (BM) as supported by recent interna¬tional guidelines1and reviews2, with a doubling of SRS use with a concomitant decline in WBRT. SRS allows for increased local tumor control while sparing normal brain tissue minimizing toxicities, which potentially improves neurocognition and quality of life3. The growth of SRS has led to a list of 'hot questions'. (1) The limit in the number/volume of BM appropriate for SRS over Hippocampal-Avoidant WBRT tech¬niques4. (2) For operable BM, the best sequencing of SRS, before or after surgery. (3) The best timing of SRS when combined with immunotherapies and/or with targeted-drugs5. (4) The optimal SRS dose/fractionation and the question of decreasing total dose for selected patients6. (5) The best machine for SRS delivery. In daily practice, beyond ongoing trials, BM management represents an excellent model for hyper-personalized management. Each patient is unique, with an individual expected survival difficult to anticipate and an increasing panel of therapeutic possibilities. Finally, there will be only one proposal, fruit of an open discussion within a multidisciplinary tumor board, offering the best benefit/risk balance to each patient.

References

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HIGHLIGHTS IN BM MANAGEMENT - **FRIDAY, OCTOBER 6TH, 2023 - 12.35**

What's Hot in Breast Cancer CNS Metastasis?

Nancy U. Lin, MD,
Dana-Farber Cancer Institute, Boston, MA, USA

CNS involvement occurs in up to half of patients with HER2-positive advanced disease, 25-45% of patients with advanced triple-negative breast cancer, and 10-15% of patients with advanced ER-positive/HER2-negative breast cancer. While radiation therapy remains a mainstay of treatment, the role of systemic therapy has substantially expanded in recent years, particularly for patients with HER2-positive breast cancer. HER2-targeted agents with intracranial activity include lapatinib, neratinib, tucatinib, high-dose trastuzumab with pertuzumab, ado-trastuzumab emtansine, and trastuzumab deruxtecan. For patients with HER2-positive leptomeningeal disease, intrathecal trastuzumab and the triplet of tucatinib-capecitabine-trastuzumab are associated with clinical activity. In HER2-positive patients, an increasingly common clinical question is when to recommend consideration of systemic therapy in lieu of radiation therapy, and conversely, when systemic therapy should be switched versus continued after local therapy. For patients with ER-positive breast cancer, data are more sparse, however case series and small phase 2 studies support the use of a variety of endocrine agents and combinations as well as some targeted agents (e.g. abemaciclib, alpelisib). Multiple novel endocrine therapies are in clinical trials, some of which cross the intact blood-brain barrier and are being investigated in patients with CNS involvement. For patients with triple-negative breast cancer, chemotherapy can be considered; however, efficacy is generally lower and survival shorter than other breast cancer subtypes. Across subtypes, there is strong rationale to study antibody drug conjugates (for example, targeting HER2, HER3, or Trop2) in patients with both brain metastases and leptomeningeal disease.

SCIENTIFIC PART

SELECTED ORAL PRESENTATIONS

FRIDAY, OCTOBER 6TH, 2023 - 08.00

The preliminary results of a randomized trial on the effect of WBRT or GKRS on cognitive performance in patients with 11-20 brain metastases (CAR-Study B)

Patrick Hanssens,
Patrick Hanssens [1] ,Eline Verhaak [1] , Wietske Schimmel [1], René Post [2], Terry Wiersma [2], Xynthia Kavelaars [3], Joris Mulder [3], Margriet Sitskoorn [4], Karin Gehring [1],

1. Department of neurosurgery/gamma knife center, Elisabeth-tweesteden hospital, Tilburg, NETHERLANDS
2. Department of radiation oncology, The netherlands cancer institute, Amsterdam, NETHERLANDS
3. Department of methodology and statistics, Tilburg university, Tilburg, NETHERLANDS
4. Department of cognitive neuropsychology, Tilburg university, Tilburg, NETHERLANDS

Background:
Maintaining cognitive functions for patients with brain metastases (BM) is an increasingly important treatment goal. Both whole brain radiation therapy (WBRT) and Gamma Knife radiosurgery (GKRS) have demonstrated their efficacy in treating multiple BM, resulting in comparable overall survival (OS) rates. The primary aim of Cognition and Radiation (CAR)-Study B was to compare cognitive outcomes after WBRT or GKRS in patients with 11-20 BM.
Methods: Patients with 11-20 newly diagnosed BM on a triple-dose contrast-enhanced MRI-scan, expected survival >3 months, and Karnofsky Performance Status (KPS)≥70 were included and randomized 1:1 (minimization) to WBRT (n=40) or GKRS (n=41), using the following stratification factors: age, histology, total BM volume, systemic treatment, KPS, and baseline Hopkins Verbal Learning total recall (HVLT-R) score. Cognitive functioning was measured with neuropsychological assessment (NPA) pre-treatment (WBRT n=35, GKRS n=39), and at 3 (n=23, n=28), 6 (n=15, n=20), 9 (n=9, n=12), 12 (n=8, n=10), and 15 (n=8, n=9) months post-treatment, using parallel tests. A decline of ≥5 points in immediate HVLT-R total recall score was considered a cognitive failure. Data were monitored at interim with Bayesian statistics. Inclusion would be halted if the Bayesian posterior probability of a higher cognitive failure rate in one group versus the other was >0.975 at T3 or T6. To analyze OS, Kaplan-Meier curves were used.

Results:
An interim analysis was performed in April 2022 after 81 patients were enrolled. Median OS did not significantly differ between the WBRT and GKRS groups (p = .933): 6.6 months (95% CI, 6.0 to 7.3 months; 5 patients (13.9%) censored) and 8.9 months (95% CI, 3.5 to 14.2 months; 6 patients (15.4%) censored). As the posterior probability of 0.978 of a higher cognitive failure rate in the WBRT group versus the GKRS group at 6 months exceeded the threshold of 0.975, inclusion in the study was halted. In the WBRT group, 66.7% of the patients (6 out of 9 patients with NPA data) showed a decline in HVLT-R TR score whereas in the GKRS group, 11.8% of the patients (2 out of 17 patients with NPA data) showed a decline, based on a mean posterior probability of decline of 40.6% for the WBRT group and 12.5% for the GKRS group. This difference also appeared at 3 months, with a mean posterior probability of decline of 39.6% for the WBRT group and 23.2% for the GKRS group (90.3% evidence), and persisted at 9, 12 and 15 months after treatment.

Conclusion:

Based on the interim analysis, inclusion in CAR-Study B was halted. The probability of experiencing a decline in verbal memory at 6 months was higher in the WBRT group in comparison to the GKRS group. Potentially confounding factors, such as intracranial tumor status, have not yet been accounted for. Definitive outcomes from the completion of CAR-Study B are impending, and these findings might offer supplementary insights to aid clinicians, patients, family members, and other caregivers in shared decision-making.

Keywords: Brain metastases, Cognition, Whole brain radiation therapy, Gamma Knife radiosurgery

FRIDAY, OCTOBER 6TH, 2023 - 08.10

Tumor lineage-specific immune response in brain metastatic disease: opportunities for targeted immunotherapy regimen?

Shiva Najjary [1],

1. Pathology, Erasmus mc, Rotterdam, NETHERLANDS

Background:
Metastases in the brain are the most severe and devastating complication of cancer. The incidence of brain metastasis is increasing. Therefore, the need of finding specific druggable targets for brain metastasis is demanding. The aim of this study was to investigate the brain (immune) response to brain metastases of the most common tumor lineages, viz., lung adenocarcinoma and breast cancer.

Material & Methods:
Targeted gene expression profiles of 11 brain metastasis from lung adenocarcinoma (BM-LUAD) were compared to 11 brain metastasis from breast cancer (BCBM) using nCounter PanCancer IO 360™ Panel of NanoString technologies. The most promising results were validated spatially using the novel GeoMx™ Digital Spatial Profiler (DSP) Technology. Additionally, Immune cell profiles and expression of drug targets were validated by multiplex immunohistochemistry.

Conclusion:
This is the first report on differences in the brain immune response between metastatic tumors of different lineages. We found more active immune response in BM-LUAD as compared to BCBM. In the BM-LUAD, 138 genes were upregulated as compared to BCBM (adj. p-value ≤ 0.05). Conversely, in BCBM 28 genes were upregulated (adj. p-value ≤ 0.05). Additionally, We found a far more extensive infiltration of immune cells in BM-LUAD as compared to BCBM. Genes related to CD45+ cells, T cells and cytotoxic T cells showed to be expressed higher in BM-LUAD compared to BCBM (adj. p-value = 0.01, adj. p-value = 0.023, adj. p-value = 0.023, respectively). The spatial quantification of the immune cells using the GeoMx DSP technique revealed the significantly higher quantification of CD14 and CD163 in tumor regions of BM-LUAD as compared to BCBM. Importantly, the immune checkpoint VISTA and IDO1 were identified as highly expressed in the BM-LUAD. Multiplex immunohistochemistry confirmed the finding and showed that VISTA is expressed mainly in BM-LUAD tumor cells, CD3+ cells, and to less levels in some microglial cells in BM-LUAD. Taken together, targeted immune therapy should be considered to treat patients with BM-LUAD.

Keywords: Brain metastases; Gene expression; Immune infiltration; Immune response; Breast cancer, Lung adenocarcinoma.

FRIDAY, OCTOBER 6TH, 2023 - 08.20

Does size matter? Response of melanoma brain metastases to immune checkpoint inhibitors

Sophie Derks [1],
Li Shen Ho [1], Stephan Koene [2], Arjen Joosse [3], Maja De Jonge [3], Joost Jongen [1], Martin Van Den Bent [1], Marion Smits [2], Astrid Van Der Veldt [3],

1. Neuro-oncology, Erasmus mc, Rotterdam, NETHERLANDS
2. Radiology&nuclear medicine, Erasmus mc, Rotterdam, NETHERLANDS
3. Oncology, Erasmus mc, Rotterdam, NETHERLANDS

Background:
Melanoma is known for its high propensity to metastasise to the brain. The efficacy of immune checkpoint inhibitors (ICIs) has been demonstrated in patients with MBM. However, little is known about the association between MBM response to ICIs and clinical and radiological features on baseline MRI. Here, we aimed to assess whether baseline variables, such as size of MBMs, are associated with MBM response to ICIs.

Material & Methods:
Between 2012 and 2021, patients with ICIs after the diagnosis of MBM were included at Erasmus MC Cancer Institute, Rotterdam, the Netherlands. Only patients with a baseline MRI were included. Prior to and during treatment with ICIs, clinical (e.g. age, sex, WHO performance status, status of extracranial disease [ECM]) and radiological (e.g. largest diameter [mm], location, aspect on T1-, T2-, DWI and post-contrast weighted MRI) variables were collected. Al MRI data were verified by a radiologist in training (SK) and an experienced neuro-radiologist (MS). The primary endpoint was best overall response rate (bORR) per lesion according to RANO-BM, measured from the start of ICI treatment until disease progression. Secondary outcomes were intracranial progression free survival (iPFS) and overall survival (OS). Cox proportional hazard analysis was performed for time-to-event analyses, with $p<0.05$ defined as significant (Likelihood ratio test).

Results:
Ninety patients were included with a total of 478 MBM at baseline. Median follow-up since the start of ICIs was 22.2 (interquartile range [IQR] 9.0-43.7) months. Forty-five (50%) patients had at least one target lesion ≥10mm, and 75 (83.3%) patients had ECM at baseline. Eighteen (20.0%) patients had previously received BRAF-MEK-inhibitors, six (6.7%) patients ICIs, and one (1.1%) both. Immune checkpoint inhibitors at baseline consisted of combination therapy (44.4%) or monotherapy with anti-PD-1 (51.1%) or anti-CTLA-4 (4.4%). Median iPFS was 7.28 months, and median OS was 22.2 months. Of the total of 478 lesions at baseline, 245 (77.8%) were <10mm in largest diameter, whereas 58 (19.2%) were ≥10mm. After exclusion of 175 lesions with previous/concurrent local treatment (resection and/or stereotactic radiotherapy [SRT]) or missing follow-up MRI, 303 of 478 lesions were eligible for further

analysis. Treatment response was found in 41.9% (CR=29.4%, PR=12.5%) of lesions.
Univariate analysis showed that target lesions (median iPFS 5.4 months) had a significantly ($p<0.001$) higher probability of progression than smaller lesions (median iPFS not reached). In multivariate analysis, increasing baseline largest diameter was significantly associated with higher probability of progression (HR 1.08, [95% confidence interval 1.05-1.12], $p<0.001$), whereas lesion location (frontotemporal HR 1.01 [0.40-2.55] $p=0.98$, parieto-occipital HR 0.71 [0.27-1.90] $p=0.50$, ref. infratentorial) was not.

Conclusion:
These preliminary results indicate that size of MBM at the start of ICI treatment is associated with treatment response. The larger a lesion, the higher the probability of progression. If confirmed, this supports a policy to treat larger lesions with surgery or radiotherapy in patients with multiple MBM.

Keywords: advanced melanoma, brain metastases, immune checkpoint inhibitors, response assessment

FRIDAY, OCTOBER 6TH, 2023 - 08.30

Patient derived breast cancer brain metastasis initiating cell: a novel preclinical model for studying the whole metastatization process

Stefania Faletti [1],
Cristina Richichi [1], Daniela Osti [1], Elena Ceccacci [1], Camilla Cerutti [1], Massimiliano Del Bene [2], Bianca Pollo [3], Monica Patanè [3], Giovanni Bertalot [4], Francesco Di Meco [2], Giuliana Pelicci [1],

1. Experimental oncology, Istituto europeo di oncologia, Milano, ITALY
2. Neurosurgery, Fondazione ircss istituto neurologico carlo besta, Milano, ITALY
3. Neuropathology, Fondazione ircss istituto neurologico carlo besta, Milano, ITALY
4. Unità operativa multizonale di anatomia patologica, Trieste, ITALY

Introduction and Objectives:
Brain metastasis from breast cancer (BCBM) are lethal tumors occurring in 10-15% of IV stage breast cancers. While surgery and stereotactic radiation are the gold standard treatments for oligometastatic diseases, limited therapeutic options are available to treat widespread cancer dissemination. A critical hindrance to the design of novel therapeutic approaches is the narrow set of experimental models recapitulating the whole metastatization process. Hence, we aimed to isolate patient-derived metastasis-initiating cells (MICs) to furnish novel preclinical models resembling the stem-like population which is thought be the main source of BCBM dissemination and progression.

Method:
We isolated MICs from fresh human BCBM specimen by culturing them as stem-enriching tumorspheres and we characterized them in term of i) markers expression by RT-qPCR, FACS and IHC analysis, ii) tumorigenicity by orthotopic xenotransplant, iii) growth and self-renewal ability by in vitro/in vivo assays, iv) firm adhesion to organ-specific endothelial cells, v) metastatization potential by intracardiac/intranipple injection and vi) drug responsiveness screening. Further, we transcriptionally profiled MICs-driven organ-specific metastasis.

Results
BCBM-derived MICs highly expressed epithelial markers (Gata3, cytokeratin-18/-19/-5 and -14), reminiscence of the epithelial nature of the primitive tumor. MICs grew indefinitely in stem cell medium and successfully formed spheres in serial clonogenic assays. Similarly, their ability to form tumors when orthotopically injected in mice brain was maintained upon serial transplantation and under in vivo limiting dilution conditions, suggesting their endowment with stem-like traits. Coherently, about 90% of MICs were positive to the expression of putative stem cell markers such as CD15, CD24 and CD44. Compared to the whole BCBM of origin, MICs transcriptomic profiling revealed an up-regulation of drug resistance signatures, which are often linked with stem-like traits, and that were functionally validated by a high throughput drug screening.

We took advantage of a representative MICs sample, hereafter PR60 MICs, to further appraise MICs as a preclinical model recapitulating the whole metastatization process. Under shear stress, that mimics in vivo hemodynamic conditions, PR60 MICs firm adhesion to human brain endothelial cells was strikingly increased compared to non-brain endothelium, indicating a retention of a brain-tropism. PR60 MICs metastatic potential was tested upon either intracardiac or intranipple transplantation. Independently of the route of injection, PR60 MICs metastatized to mice brain and bones, wholly mirroring the clinical course of the patient they had been derived from. PR60 MICs-driven brain metastasis recapitulated patient tumor histology, cytoarchitecture and marker expression. Transcriptomically, PR60 MICs, whose expression profile had a very high correlation with the BCBM of origin, retain the ability to form intra-nipple tumors whose transcriptomic landscape resembles that of patient primitive breast tumor. PR60 MICs-derived brain and bone metastasis reveal a distinct expression profile suggesting that they are able to colonize different organs rewiring their transcriptomic landscape.

Conclusions:
Altogether, we established a robust and versatile MIC model that reliably mirrors the brain metastasis of origin and mimics the different steps of brain metastatic dissemination for in vitro and in vivo studies. This model has the potential to provide further knowledge for future therapy development for BCBM management.

Keywords: Preclinical models, Cancer stem cells, Breast cancer brain metastasis

FRIDAY, OCTOBER 6TH, 2023 - 08.40

Molecular profiling of cell-free DNA from cerebrospinal fluid is a promising tool to diagnose leptomeningeal metastasis.

Berit Van Linder [1],
Els Verhoeven [1], Lisa Jongejan [1], Kim Monkhorst [1], Joop De Langen [2], Daan Van Den Broek [3], Tom Van Wezel [1], Dieta Brandsma [4], Mirjam Boelens [1],

1. Department of pathology, Netherlands cancer institute, Amsterdam, NETHERLANDS
2. Department of thoracic oncology, Netherlands cancer institute, Amsterdam, NETHERLANDS
3. Department of laboratory medicine, Netherlands cancer institute, Amsterdam, NETHERLANDS
4. Department of neuro-oncology, Netherlands cancer institute, Amsterdam, NETHERLANDS

Background:
Leptomeningeal metastasis (LM) is associated with a poor prognosis and limited treatment options. Confirmation of LM is based on cytological examination of the cerebrospinal fluid (CSF), diagnosing the patient with definitive LM. However, its sensitivity is limited, leading to delayed or missed diagnoses of LM. Previous work from our institute showed that circulating tumour cell (CTC) analysis by flow cytometry is more sensitive to detect malignant cells in CSF than cytology. In this study, we examined the sensitivity of next generation sequencing (NGS) in diagnosing LM by analysing driver mutations in CSF

Method:
CSF cell pellet-derived DNA (CSF-cell-DNA), CSF supernatant-derived cell-free DNA (CSF-cfDNA) and blood plasma-derived cfDNA (plasma-cfDNA) was isolated from a group of eleven patients with definitive LM from a solid tumour with a known driver mutation. NGS was performed to examine the presence of these driver mutations. Next, we used a group of 72 suspected LM patients (based on clinical symptoms and/or radiological lesions) and compared the results of CSF-cfDNA analysis, CTC analysis and cytology.

Results
Using CSF-cell-DNA, driver mutations were exclusively found in the examined LM patients with positive CSF cytology. As expected, variant allele frequencies (VAF) of the driver mutations were dependent on the estimated tumour cell percentage (TCP). Interestingly, CSF-cfDNA analysis showed driver mutations for all definitive LM patients, including those with initial negative CSF cytology. The average VAF of oncogenic driver mutations was around 50%, suggesting that the majority of CSF-cfDNA was derived from tumour cells. For plasma-cfDNA, the observed VAFs of driver mutations were very low, indicating a negligible contribution to cfDNA in CSF. Next, we used a group of 72 patients with a suspicion of LM to compare the sensitivity of CSF-cfDNA to that of CSF cytology. For 81% of these patients, CSF-cfDNA and cytology showed consistent results (43% both positive, 38% both negative, confirming definitive LM or no LM respectively). For the remaining 19% of patients, driver mutations were detected in CSF-cfDNA while CSF cytology was negative (possible or probable LM). This group will be further analysed.

Conclusions:
This study demonstrates that molecular profiling of CSF-cfDNA is a promising tool to diagnose LM. Besides, knowledge of driver mutations in the CSF could support choice of treatment. To further examine the exact sensitivity and specificity of CSF-cfDNA in diagnosing LM, we are currently studying the possible and probable LM patients and incorporating each patient's follow-up and CSF-CTC analysis.

Keywords: Leptomeningeal metastasis, cerebrospinal fluid, cell-free DNA, next generation sequencing

FRIDAY, OCTOBER 6TH, 2023 - 08.50

Dissecting the role of CSF2Rb-STAT5 signaling in tumor-associated inflammation in brain metastasis

Aylin Möckl [1],
Anna Salamero-Boix [1], Florian Klemm [2], Tijna Alekseeva [1], Alexander Schäffer [1], Michael Schulz [1], Katja Niesel [1], Julian Anthes [1], Dominic Menger [1], Karl H Plate [3], Johanna A Joyce [2], Lisa Sevenich [1],

1. Georg-speyer-haus, Georg-speyer-haus, Frankfurt, GERMANY
2. Department of oncology, University of lausanne, Lausanne, SWITZERLAND
3. Institute of neurology, Edinger institute, Frankfurt, GERMANY

Tumor microenvironment (TME)-targeted therapies are emerging as promising treatment options for different cancer types. Tumor-associated macrophages and microglia (TAMs) represent the most abundant non-malignant cell type in brain metastases (BrM) and have been proposed to modulate metastatic colonization and outgrowth. We utilized the colony stimulating factor 1 receptor (CSF1R) inhibitor BLZ945 to target TAMs at different stages of the metastatic cascade and observed anti-tumor responses in preclinical prevention and intervention trials in breast-to-brain metastasis models. However, anti-tumor activity was only transient and adaptive resistance mechanisms prevented long-term therapeutic efficacy. Transcriptional analysis revealed the induction of compensatory CSF2Rb-STAT5 signaling in a subset of TAMs leading to neuroinflammatory gene signatures in association with wound repair responses that fostered tumor recurrence. We employed different strategies to block the CSF2-mediated TAM activation, including CSF2 neutralization, genetic silencing of CSF2Rb and pharmacologic inhibition of STAT5. CSF1R inhibition combined with CSF2 neutralization or CSF2Rb knockout led to a complete loss of the remaining TAM population. However, depletion of the CSF2-activated TAM population resulted in only minor improvement of the therapeutic response. In contrast, combination of CSF1R blockade with STAT5 inhibition led to a restoration of the TAM population together with phenotypic normalization and amelioration of neuronal damage. Importantly, this intervention strategy resulted in sustained tumor control1. Transcriptomic analyses of TAMs and other BrM-associated cell types in response to CSF1R inhibition compared to CSF1R-CSF2Rb vs CSF1R-STAT5 inhibition will help to identify mechanisms that mediate TAM normalization and will provide evidence for optimized TAM-targeted therapies to further improve therapeutic efficacy and mitigate the risk of neurotoxicity.

FRIDAY OCTOBER 6TH, 2023 - 9.00

Should we screen cancer patients for brain metastases?

Olav E Yri [1],
Guro L Astrup [1], Astrid T Karlsson [1], Marianne J Hjermstad [1], Nina Aass [1], Stein Kaasa [1],

1. Oncology, Oslo university hospital, Oslo, NORWAY

Background:
Patients with lung cancer, breast cancer or melanoma frequently develop brain metastases (BMs) causing symptoms affecting quality of life (QoL). One may postulate that early detection of BMs could prevent symptom development, reduce need for surgery and WBRT and facilitate SRS/SRT. Routine screening for BMs is not established and the benefit thereof is debated. We compared BMs characteristics and treatments in patients diagnosed with BMs due to clinical symptoms with those in patients with incidentally diagnosed BMs. We hypothesized that those incidentally diagnosed would have smaller and fewer BMs, less often need surgery and more frequently amenable to SRS/SRT and that these patients reported higher QoL at time of diagnosis.

Material & Methods:
Patients with non-small cell lung cancer (NSCLC; N=360), breast cancer (any subtype; N=129) and melanoma (N=148) were identified from a prospective, observational study including patients with first-time BMs. Patients were categorized as “asymptomatic” (i.e. diagnosed during screening for study participation, diagnostic procedures without suspecting BMs and/or metastatic screening) or “symptomatic” (diagnostics due to clinical symptoms). We compared proportions of factors relevant to BMs treatment and prognosis between the groups and patient-reported symptoms at time of study inclusion using EORTC QLQ-15 PAL and BN20.

Results:
Of 637 patients (median age 68 years [27-96], female 58%), 121 (19%) were “asymptomatic” (lung: 70/360; 19.4%, breast 21/129; 16.3%, melanoma 30/148; 20.3%). Asymptomatic patients more frequently had single BM (47.9% vs 30.5%, p<0.001), tumors <40 mm in largest diameter (96.5% vs 80.8%, p<0.001), and fewer were prescribed corticosteroids (48.8% vs 84.5%, p<0.001). Asymptomatic patients more often had extracranial metastases (ECM; 88.4% vs 73.1%, p<0.001), and synchronous diagnosis of BMs and ECM (51.2% vs 29.7%, p<0.001). There was no difference in age or sex distribution or proportion of patients with ECOG 0-1 (p=0.16), progressive ECM (p=0.3) and ≥5 BMs (p=0.08) between the groups.

As initial BM treatment, asymptomatic patients were more often treated with SRS/SRT (53.7% vs 32.6%, p<0.001) or systemic treatments (10.7% vs 1.0%, p<0.001); less often with surgery (1.7% vs 19.6%, p<0.001) or WBRT (28.1% vs. 42.1%, p=0.005). Overall survival did not differ (mOS 7.4 vs 6.2 months, p=0.86).

Most frequently recorded clinical symptoms leading to diagnostic procedures were headaches, nausea, visual disturbances, dizziness and aphasia. At study inclusion, There was no difference in self-reported levels of QoL, physical function or fatigue at study inclusion, but patients in the symptomatic group reported higher levels of sleep disturbances ($p=0.03$), headache ($p=0.03$), motor dysfunction ($p<0.001$) and communication deficits ($p<0.001$) and less pain ($p=0.02$).

Conclusion

Our findings indicate that earlier detection of BMs could prevent or reduce symptoms and reduce the need for surgery or WBRT as initial treatments. If relevant for treatment considerations in the individual patient, our findings support screening of patients with high risk of developing BMs.

Keywords : Screening, symptoms

FRIDAY OCTOBER 6TH, 2023 - 9.10

Predictive and prognostic value of radiomics in patients with non-small cell lung cancer and brain metastases treated by PD-(L)1 inhibitors

Clémence Henon, MD, PhD [1,2]
Lizza Hendriks, MD, PhD [3], Alexandre Carré, PhD [4], Laura Mezquita, MD, PhD [1,5,6], Sylvain Reuzé, PhD [4], Samy Ammari, MD, PhD [7], Mihaela Aldea, MD [1], Charlotte Robert, PhD [4], Cécile Le Pechoux, MD [8], Clarisse Audigier-Valette, MD [9], Julien Mazieres, MD, PhD [10], Corentin Lefebvre, MD [10], Audrey Rabeau, MD [10], Boris Duchemann, MD 11, Angela Botticella, MD [8], David Planchard, MD, PhD [1], Eric Deutsch, MD, PhD [4,8], Benjamin Besse, MD, PhD [1,12], and Roger Sun, MD, PhD [4,8]

1 Department of Medical Oncology, Gustave Roussy Cancer Campus, Villejuif, France
2 Early phase trial department, Gustave Roussy Cancer Campus, Villejuif, France
3 Department of Pulmonary Diseases, GROW School for Oncology and Reproduction, Maastricht University Medical Center, Maastricht, The Netherlands
4 UMR 1030, ImmunoRadAI, Gustave Roussy Cancer Campus, Villejuif, France
5 Department of Medical Oncology, Hospital Clínic, Barcelona, Spain
6 Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi I Sunyer Biomedical Research Institute, Barcelona, Spain
7 Department of Radiology, Gustave Roussy Cancer Campus, Villejuif, France
8 Department of Radiation Oncology, Gustave Roussy Cancer Campus, Villejuif, France
9 Department of Pulmonary Diseases, Centre Hospitalier Toulon Sainte-Musse, Toulon, France
10 Department of Pulmonary Diseases, Centre Hospitalier Universitaire de Toulouse, Université Paul Sabatier, Toulouse, France
11 Department of Medical Oncology, Institut Bergonie, Bordeaux, France g Department of Pulmonary Diseases, Hôpital d'Avicenne, Paris, France
12 Paris-Sud University, Orsay, France

Background:
The incidence of brain metastases (BMs) in patients treated for advanced non-small cell lung cancer (NSCLC) is between 20 to 50% in published cohorts. While Immune Checkpoints Inhibitors (ICIs) are current standard of care for metastatic NSCLC in the first-line or beyond settings, around 50% and 30% of patients will have a systemic and brain tumor response, respectively. Importantly, the determinants of BMs response to ICIs remain largely unknown, partly due to the limited accessibility to BMs tumor samples. This study aims to evaluate a non-invasive approach based on baseline brain MRI radiomics to uncover novel predictive and prognostic factors in the BM+ NSCLC population treated by ICIs.

Methods:
We performed a retrospective multicenter study involving five European centers. We enrolled BMs+ NSCLC consecutive patients treated between 2011 and 2021. In order to ensure the specificity of the radiomic model, we generated two cohorts of patients treated either by ICIs (Evaluation cohort) or by chemotherapy (Control cohort) with a 2:1 ratio. We assessed both individual BMs and overall brain response using a modified RANO (Response Assessment in Neuro-Oncology) method. We further developed a radiomic model to predict BMs control/progression to ICIs at the first brain follow-up imaging. The ICIs cohort was divided into two datasets used for model training with 5-fold cross-validation and model testing. Finally, we aggregated the BMs control/progression prediction results and generated a radiomic score to predict patient overall survival, and compared its robustness with clinical prognostic factors.

Results:
The ICIs and Chemotherapy cohorts comprised 94 and 49 patients, respectively, among which 56 (59.6%, N = 227 BMs) and 39 (79.6%, N = 192 BMs) had available brain follow-up imaging. Overall, brain response rates were 33.3% in the ICIs cohort versus 50.0% in the Chemotherapy cohort (p-value = 0.084). Our machine learning strategy relied on extreme gradient boosting algorithm (xgboost), and focused on BMs of largest diameter ≥10mm. After learning on the ICIs training set (N = 52 BMs), our model could predict individual BMs progression upon ICIs with an area under curve (AUC) of 0.77 (95% CI [0.56-0.98], p-value = 0.03) in the test set (N = 24 BMs). In comparison, the AUC in the Chemotherapy cohort (N=81 BMs) was of 0.69 (95% CI [0.49-0.89]) and did not reach statistical significance (p-value = 0.08). Finally, we defined a radiomic score stratifying ICIs cohort patients between High-Risk or Low-Risk groups, according to the predicted individual BMs progression. High-risk patients were associated with worse overall survival (OS) (median OS of 6.3 months, 95% CI [3.02-10.49]) compared to Low-risk patients (median OS of 11.87 months, 95% CI [7.02-21.90]) with a p-value = 0.042. The prognostic value of the radiomic score on OS was further validated in a multivariate analysis (HR=1.99, 95% CI [1.103-3.616], p=0.022).
Conclusions: This is the first study to explore the value of radiomics at the lesion and patient level in the ICIs-treated BMs+ NSCLC population. The applicability of this approach should be evaluated in prospective cohorts.

Keywords
Non-small Cell Lung Cancer; Brain Metastases; Immune Checkpoint Inhibitors; Radiomics.

FRIDAY OCTOBER 6TH, 2023 - 9.20

Brain metastases stereotactic re-irradiation for local recurrence after radiotherapy: safety and efficacy in a monoinstitutional experience

Fodor Andrei [1], Deantoni Chiara [1], Villa Stefano [2], Roncelli Francesca [3], Bailo Michele [3], Torrisi Miriam 1, Gagliardi Filippo [3], Snider Silvia [3], Gigliotti Carmen [5], Perna Lucia [5], Broggi Sara [5], Del Vecchio Antonella [5], Barzaghi Raffaella [3], Mortini Pietro [6], Di Muzio Nadia [7],

1. Department of radiation oncology, Irccs san raffaele scientific institute, Milan, ITALY
2. Department of radiation oncology, Irccs san raffaele scientific instittute, Milan, ITALY
3. Department of neurosurgery and gamma knife radiosurgery, Irccs san raffaele scientific institute, Milan, ITALY
4. Department of radiation oncology, Irccs san raffaele scientific institute, Milan, ITALY
5. Medical physics, Irccs san raffaele scientific institute, Milan, ITALY
6. Department of neurosurgery and gamma knife radiosurgery, Irccs san raffaele scientific institute and vita-salute san raffaele university, Milan, ITALY
7. Department of radiation oncology, Irccs san raffaele scientific institute and vita-salute san raffaele university, Milan, ITALY

Objectives:
To present our results of salvage Stereotactic Radiotherapy(SRT)/Radiosurgery(RS) for recurrent BM after previous radiotherapy(RT).

Methods:
From 01/2018- 07/2022, 134 BM in 30 patients (pts) were re-irradiated (ReRT). Two pts were treated 2 times for different relapses. Median ReRT BM per patient was 2(1-21). Site of primary was lung for 17 pts, breast for 11, melanoma for 2, colon for 1, and prostate for 1. Time interval between first BM RT and ReRT was 14(4.2-39.2)months. Previous RT on the same volume was performed as whole-brain(WB) radiotherapy in 14 pts(2 with simultaneous integrated boost), CyberKnife SRT(CK) in 7, Volumetric Modulated Arc Therapy SRT(VMAT) in 4, Gamma Knife RS(GK) in 3 pts, and in 1 as tumor bed RT. Median dose delivered was 30(12-50) Gy in 1-10 fractions. ReRT was performed with CK(23 pts), GK(8), and TomoTherapy(1). Median ReRT volume was 3.45(0.3-31.76)cc. Median delivered dose 30(16-37.5)Gy, in 5(1-5) fractions(fr), at the 77(48-95)% isodose. CTCAEv 5.0 was used to report toxicity.

Results:
Median follow-up after ReRT was 9.7(0.7-54.4)months. Median age of pts at ReRT 56.1(40.9-70.7) years. Acute toxicity was low: 21/30(70.0%) evaluable pts did not present any toxicity, 7 pts(23.3%) G1 toxicity, and 2 pts(6.7%) G2 toxicity, and were more frequent in treatments performed in 1 fr(4/9,

44.4%), than in fractionated treatments(5/23, 21.7%). Six radionecrosis(RN) were registered, all in pts who survived ≥13 months, but only 5 were ReRT lesions. Local control, evaluable in 30 pts, was: complete response in 4 pts, partial response in 16, stable disease in 6, and progressive disease in 4 pts. Two pts underwent a second ReRT, and 1 patient a third ReRT. Two pts were operated on for RN (N=1), and relapse (N=1). Median overall survival(OS) was 10 months; 12, 24- and 36-month OS were 39.1%, 24.8%, and 18.6% respectively (See fig. 1). Median local relapse-free survival was 22 months; 6-, 12-, 24- and 36-month LRFS were 79.8%, 60.1%, 36.1% and 36.1% (Fig. 2a). Median intracranial relapse-free survival was 10 months; 6-, 12-, 24- and 36-month ICRFS were 63%, 40.8%, 28% and 28% respectively(Fig. 2b). Initial WB did not reduce ICRFS at either the first or second event (p=0.14 and 0.13, respectively)

Conclusions:
ReRT of recurrent BM is safe, with low toxicity, and effective with responses in 86.7% of pts. RN were recorded in ≤1% of ReRT lesions at a median of 13.5 months after ReRT. A prospective study is necessary to confirm these results.

Keywords : brain metastasis, re-irradiation, stereotactic radiotherapy, radiosurgery

FRIDAY OCTOBER 6TH, 2023 – 9.30

Challenges in Immunotherapy for Central Nervous System Metastases: Revisiting Concepts in Organotropism and Therapeutics

Carlos Eduardo Da Silva Isidoro [1], Flávia Cristina Rosa [1],

1. Universidade cidade de são paulo, São paulo, BRAZIL

Background:
Metastasis are defined as secondary disseminations of the primary malignant tissue. When talking about the central nervous system (CNS) there are main differences between approaches. Immunotherapy is a well-known technique, being capable of great results, by this study it's expected to understand the challenges when considering immunotherapy for CNS and to stimulate more research around the technique.

Material & Methods:
The key-words: Immunotherapy, Brain metastases and Brain Neoplasms were used in the NIH library and PubMed. The studies were included if they were written in English, written after 2013 and excluded if they were not related to the objective of the study or didn't have enough data to prove it´s findings. After the analysis 11 studies were used and 1 was excluded.

Results & Conclusions:

After the research, where found six main tumor immune escape mechanisms, the first one being: the modified blood-brain barrier, that is turned into the blood-tumor barrier, being dysfunctional, more permeable and tortuous, resulting in accumulation of the drugs and affecting the therapeutic dose[1]; the second one being the production of immunosuppressive signals by the tumor, resulting in less activity of the antigen-presenting cells (APC) and the recruiting of regulatory T-cells, by the action of tryptophan and kynurenine produced by the metastatic cells[11]; the third challenge is the control of the therapeutic dose when using cytokines, because of the uncontrolled dissemination and the action of the tumor metabolites[11]; the fourth adversity being the less effectivity of the microglial cells into presenting antigens when compared with other APCs of non-nervous tissue, resulting in more mechanisms for organotropism[3]; the fifth one is the low presence of natural killer cells and the cells have partial or limited functionality as shown by Kmiecik, Justyna et al. [7]; the last challenge being the action of the PD-L1, produced by the metastatic cells, by binding the PD-1, produced by the activated T-cells, resulting in apoptosis of the tumor-infiltrating lymphocytes and the suppression of the immune system by turning the CD4+ into T- regulators. To conclude, most challenges can affect the treatment and the efficacy of the prognosis. Although, new studies and techniques are being developed in order to solve the challenges.

Keywords: Immunotherapy, Brain metastases, Brain Neoplasms

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SCIENTIFIC PART

POSTERS

POSTER 1

Effect of Thymoquinone (TQ).nanoparticle to protective NeuroToxcity cells induced by Ehrlich ascites carcinoma (EAC) & lead in vivo study

Maha Ibrahim [1], Ammar Bayoumi [1],

1. Medical research, Msf, Jeddah, SAUDI ARABIA

Cancer is the major cause of death and many factors that lead to its occurrences, such as environmental pollution and pesticides and other factors. Ehrlich carcinoma development depends on many things associated with the environment. The present study aimed to evaluate the potential protective effects of the active ingredient of Nigella Sativa is a Thymoquinone (TQ). TQ nanoparticle research aims to improve TQ's pharmaceutical effects, such as targeting capacity, bioavailability, and avoiding unspecific binding. Different formulations of TQ nanoparticles were tested against several of brain damage & cancer , whereby the studies showed greater effectiveness of TQ nanoparticle than free TQ. These formulations included nanostructured lipid carriers (NLCs), solid lipid nanocarriers (SLNs), polymeric, noisomely, and liposomal. Using Nanoparticle formulation, against Ehrlich ascites carcinoma (EAC) & lead-induced damage in the prefrontal cerebral cortex, hippocampus, and cerebellum can lead to a variety of neurological disorders, such as brain damage, mental retardation, behavioral problems, nerve damage, in male mice. Thymoquinone (TQ) is a promising anticancer molecule that inhibits cancer cell growth and progression in vitro experimental animal model . Despite the promising anticancer activities of TQ, its translation to the clinic is limited by its poor bioavailability and hydrophobicity. As such, we and others encapsulated TQ in nanoparticles to improve its delivery and limit undesirable cytotoxicity. These TQ-nanoparticle formulations showed improved anticancer and anti-inflammatory activities when compared with Cisplatin is a chemotherapy drug used to treat brain damage cancer. Here, we provide an overview of the various TQ-nanoparticle formulations, highlight their superior efficacy and discuss up-to-date solutions to further enhance TQ bioavailability and anticancer activity, thus improving potential for clinical translation.

Materials and Methods
The Ehrlich Tumor Cells Inoculation & lead
Dose of lead using by injection of 350 mg/kg lead
the nano TQ treatment is able to fix dopamine, serotonin unbalance In a record time during the period of neuro damage symptoms, which contributes to solving the problems and symptoms of Brain da singe symptoms and their complications.

Effect of Thymoquinone (TQ)nanoparticle on Ehrlich tumor cells induced tumor and inflammation on serum TNF-a levels in experimental rats. Statistical analysis was done

by Prism software and graphs were automatically generated according to p value. * to **** indicate least to maximum significant difference (high to low p value). ns indicates non-significant values. Each value represents the mean± SEM of the group. Tumor with thymoquinone nanoparticles dose show significantly decreased TNF-a and significantly increase of GSH levels.
Effect of Thymoquinone (TQ)nanoparticle on induced neurotoxicity on serum dopamin & sertonine levels in experimental mice. Statistical analysis was done by Prism software and graphs were automatically generated according to p value.

Results showing significantly balance of serum dopamin & sertonine level
No siginficant correlation between Thymoquinone (TQ)nanoparticle group and Cisplatin treated groups .

Keywords: Nigella Sativa , Thymoquinone (TQ), TQ nanoparticle, kidney toxicity, Ehrlich ascites carcinoma

POSTER 2

Molecular mechanisms involved in the development of brain metastasis from lung adenocarcinoma and breast cancers and their brain metastases

Shiva Najjary [1],

1. Pathology, Erasmus mc, Rotterdam, NETHERLANDS

Background
Up to 50% of patients with common cancers will develop brain metastases and incidences of this devastating complication are still rising. In recent work we found a significant stronger immune response to brain metastases from lung adenocarcinoma (LUAD) as compared to those from breast cancer (BC). Importantly, we discovered the higher expression of the drug target VISTA in the brain metastases of the LUAD. The aim of the current study was to investigate the molecular mechanisms driving the formation of brain metastasis from the two different cancer lineages. In addition, we aimed to examine the expression level of the drugable molecules between primary tumors and their brain metastasis.

Material & Methods
Primary tumors and their matched brain metastasis samples of 11 LUAD and 11 breast cancer (total = 44 samples) were included in this study. RNA was extracted from the FFPE samples and the targeted gene expression profiles were measured using the PanCancer IO360™ Panel that includes 770 cancer-related genes (NanoString technology). Data were analysed using the nSolver software.

Conclusions
We identified 12 common up-regulated genes in brain metastasis, despite the origin of the primary tumor. Pathway analysis revealed higher metabolic stress in breast cancer-brain metastases compared to lung cancer metastases. Importantly, by comparing the primary tumors of BC and LUAD with their brain metastasis, we found that VISTA is predominantly expressed in the primary tumors of LUAD and their matched brain metastasis. The present study shows that different cancer lineages utilize various genes/pathways to metastasize to the brain. Moreover, primary LUAD and their brain metastasis express high levels of VISTA highlighting the possibilities for targeted therapy.

Keywords: Brain metastases; Gene expression; Molecular mechanism; Breast cancer, Lung adenocarcinoma.

POSTER 3

Dynamics in lesions during and after MR-guided Laser Interstitial Thermal Therapy – TLVMC experience

Shiva Najjary [1],

Tal Shahar [1], Lottem Bergman [1], Ariel Agur [1], Segev Gabay [1], Rachel Grossman [1], Ido Strauss [1],

1. Neurosurgery, Tel aviv medical center, Tel aviv, ISRAEL

Background
MR-guided laser interstitial thermal therapy (MRgLITT) is a minimally invasive technique used for treating deep-seated brain lesions. However, the radiological changes following ablation remain incompletely characterized. The goal of this current study is to retrospectively examine the outcome and describe the radiological volume changes that occur after MRgLITT ablation of brain tumors.

Material & Method
We retrospectively collected clinical and imaging data of all adults' patients that underwent MRgLITT of brain tumors (primary and metastatic) between 2020-2023 at the Tel-Aviv Medical Center. Lesions' volume, length and diameter were measured before, during and in follow-ups on T1-weighted images with contrast. The post-operative ablation volume was compared to Medtronic thermal damage estimate (TDE). Local control was assessed at last follow-up.

Results
Twenty patients (average age 57±11 years) were available for follow-up. Most lesions (n=11) were metastatic, and the rest 9 patients had high grade gliomas. Mean follow-up was 8±7.5 months. Average preoperative tumor volume was 2.26±1.96 cc, and immediate postoperative at the end of the ablation was 4.65±2.5 cc. During follow-up the average lesion volume was as follow: one week 7.7±4.85 cc, 1-2 months 4.8±3.22 cc, 3 months 4±3 cc, 6 months 2±1.86 cc and 9 months 1.2±1.2 cc. The forward extension of the enhancing lesion from the tip of the catheter post-ablation averaged 3.4±2 mm. Notably, all high-grade glioma tumors experienced failure (local/distant progression) after 3-6 months.

Conclusions
MRgLITT can lead to an initial enlargement in lesion volume during the first months after ablation, with an average forward thermal damage of approximately 3 mm.

Keywords: MR-guided laser interstitial thermal therapy (MRgLITT), Brain tumor, Brain metastases

POSTER 4

Endothelin receptors (ETR) prime targets for the development of new therapeutic stategies against ETR + brain metastases

Amaury Herbet [1],
1. 91, Cea, Saclay, FRANCE

Background
Advances in imaging and therapy, including immunotherapy, have contributed significantly to the overall survival rates of cancer patients. However, despite these remarkable advancements, brain metastases continue to pose a significant challenge, affecting 20-30% of cancer patients. Current treatments struggle to effectively target brain metastases due to the limited permeability of the blood-brain barrier (BBB) to biotherapeutics. Endothelin type A (ETA) and B (ETB) receptors play a crucial role in driving tumor progression across various cancers (melanoma, ovarian, prostate...) including glioblastoma (GBM).1 Efforts to inhibit these receptors signaling pathways using antagonistic drugs have been extensively studied in clinical trials.2,3 However, these attempts have faced challenges as a result of the elevated endothelin (ET) concentrations in the tumor microenvironment and their remarkably high affinity for their respective receptors, leading to limited success.

Material & Methods
To target ET receptors, we have developed the patented chimeric antibodies Rendomab B49 (xiRB49) against ETB and Rendomab A63 (xiRA63) against ETA. xiRB49, conjugated to monomethyl auristatin E, showed remarkable efficacy against ETB+ human melanoma in a preclinical model, and we demonstrated the ability of xiRA63 to target human ETA+ GBM stem cell line in the brain after its intravenous administration in a preclinical orthotopic xenograft mouse model.4 However, alteration of the BBB has not always been observed in cancer brain metastasis. To overcome the challenge of delivering therapeutic agents to the brain, we are investigating antibody nanoparticle (mAb-NP) formulations administered via the nasal route. Preliminary evaluations of the efficacy of these formulations have been performed on an in vitro human nasal barrier model.

Conclusions
We have demonstrated a promising increase in permeability of mAb-NP over mAb alone across the in vitro nasal barrier model. We are now working on the in vivo demonstration of mAb delivery to the brain and its biodistribution through the nose-to-brain pathway prior to designing an in vivo experiment to demonstrate the therapeutic effect of the formulated drug mAb on melanoma brain metastasis.

Keywords: Nose to brain, Melanoma metastasis, Endothelin receptors, Therapeutics antibody
References: Rosanò, L., Spinella, F. & Bagnato, A. Nat Rev Cancer 13, 637–651 (2013). 2. Carducci, M. A. et al. Cancer 11r., Carducci, M. A. et al. Cancer 110, 1959–1966 (2007)., Kefford, R. et al. Molecular Cancer 9, 69 (2010)., Hautiere, M. et al. Eur J Nucl Med Mol Imaging (2023).

POSTER 5

Comparative effectiveness of immune checkpoint inhibition versus chemotherapy in combination with radiation therapy among patients with NSCLC and brain metastasis undergoing neurosurgical resection

David Wasilewski [1], Josefine Radke [2], Ran Xu [1], Matthias Raspe [3], Anna Trelinska-Finger [4], Zoe Shaked [1], Tizian Rosenstrock [1], Paul Poeser [1], Schumann Elisa [5], Judith Lindner [6], Frank Heppner [5], David Kaul [7], Norbert Suttorp [3], Peter Vajkoczy [1], Nikolaj Frost [3], Julia Onken [1],

1. Department of neurosurgery, Charite university medical center berlin, Berlin, GERMANY
2. Institute of pathology, University medical center greifswald, Greifswald, GERMANY
3. Department of infectious diseases and pulmonary medicine, Charite university medical center berlin, Berlin, GERMANY
4. Charité comprehensive cancer center, Charite university medical center berlin, Berlin, GERMANY
5. Department of neuropathology, Charite university medical center berlin, Berlin, GERMANY
6. Department of pathology, Charite university medical center berlin, Berlin, GERMANY
7. Department of radiation oncology, Charite university medical center berlin, Berlin, GERMANY

Introduction and Objectives:
Patients with brain metastases (BrM) from non-small cell lung cancer (NSCLC) have regularly been excluded from prospective trials including therapy with immune checkpoint inhibitors (ICIs). Real-world data demonstrating the benefit of ICIs, specifically in patients following neurosurgical BrM resection, are still scarce. We evaluated the association of radiation therapy with immune checkpoint inhibition (RT + ICI) versus classic therapy involving radiation and chemotherapy (RT + CTx) regarding overall survival (OS), extracranial and intracranial progression-free survival (ecPFS and icPFS) in NSCLC patients undergoing BrM resection.

Methods:
Eligible patients involved individuals that were subjected to craniotomy with BrM resection with histologically confirmed NSCLC. A single-center, 1:1 propensity-matched effectiveness study at the largest neurosurgical clinic in Germany to assess the effect of treatment with RT + CTx vs. RT + ICI on OS and PFS.

Results:
From the whole cohort (N=384), the two cohorts of interest included 108 patients (31%) with RT + CTx and 63 patients (18%) with RT + ICI following neurosurgical metastasis removal (before matching). Median age was 64 years (57-72 IQR). Median follow-up time (IQR) for the total cohort was 47.90 months (28.17-70.07 months) with 89 (23.2%) of patients being censored and 295 (76.8%) being dead at the end of follow-up, in December 2021. After covariate equalization using propensity score matching (62 patients per group) patients receiving RT + CTx after neurosurgery had significantly decreased OS (11.8 months; 95% CI; 9.1 – 15.2 months) as compared to patients with RT + ICIs (23.0 months; 95% CI; 20.3 – 53.8 months; p=.00033). Whereas, ecPFS) was significantly higher in patients treated with RT + ICIs (24.3 months; 95% CI; 21.3 – not estimable months; p=.0065) compared to patients with RT + CTx (10.4 months; 95% CI; 7.4 – 42.1), icPFS did not significantly differ between patients that were treated with RT + ICIs (18.4 months; 95% CI; 15.4 – not estimable months; p=.18) vs. patients treated with RT + CTx (10.4 months; 95% CI; 7.4 – 42.1 months).

Discussion/Conclusion:
Patients with NSCLC BrM undergoing neurosurgical resection show increase in OS and ecPFS when treated with RT + ICIs following neurosurgery as compared to patients receiving platinum-based CTx and RT after surgery. No significant impact with respect to icPFS was noted. RT and ICIs should be regularly evaluated as a treatment option for these patients.

Keywords: NSCLC, brain metastasis, immunotherapy, radiation, neurosurgery

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POSTER 6

T cell trafficking and metabolic adaption in brain metastasis

Dominic Menger [1], Anna Salamero-Boix [1], Julian Anthes [1], Michael Schulz [2], Aylin Möckl [1], Katja Niesel [1], Marco Lolies [1], Lisa Sevenich [1],

1. Georg-speyer-haus, institute for tumor biology and experimental therapy, Frankfurt/main, GERMANY
2. Institute for neuropathology, university hospital freiburg, germany (current address), Freiburg, GERMANY

Background:
The increasing incidence of brain metastases (BrM) due to improved therapies for the primary tumor poses increasing challenges to clinicians. The limited therapeutic efficacy of classical therapies such as surgery, radiotherapy, or novel immunotherapies does not show long-term efficacy, resulting in a median survival of patients with brain metastases of only a few months. Therefore, a better understanding of the unique BrM tumor microenvironment (TME) could lead to improved therapeutic efficacy. Of particular interest is a detailed understanding of the T cell compartment that can be observed in BrM, although the brain has been described as an immune privileged organ. Here, we aim to gain deeper insights into T cell biology, infiltration, and adaptation to the TME of BrM to overcome treatment resistance.

Methods and Results:
Using a breast-to-brain metastasis model and RNA sequencing approaches, we analyzed transcriptomic profiles of BrM-associated tumor infiltrating lymphocytes (TILs) and observed an exhausted phenotype that prevents the T cell anti-tumor activity. In addition, changes in several metabolism associated genes and processes were observed in particular in CD8+ T cells. [1] Here, we identified several metabolites which can be targeted and used to improve the immune response to BrM. Furthermore, we investigated in this project the impact of diverse vascular structures on the T cell infiltration to BrM like high-endothelial venules, the glymphatic system or blood vessels. Immune fluorescence staining and spatial transcriptomic data revealed the presence of lymphatic endothelial as well as high-endothelial venules and changes in the polarization of the astroglia system. 3D reconstruction of immune fluorescence staining revealed a close proximity of markers of lymphatic and vascular endothelia cells.

Conclusion:
Taken together, in this project we seek to study the influence of metabolic adaption of the T lymphocyte compartment and infiltration in BrM. First insights confirm the presence of lymphatic structures in the context of BrM as well as a metabolic adaption of infiltrated T cells. Future investigations will analyze and quantify T cell infiltration in relation to the different vascular structures found in the TME of BrM. Furthermore, induced changes in the immune metabolism will reveal the potential of metabolic modulators.

Keywords: T cells, Brain Metastasis, Glymphatic system, Immunometabolism

References: Niesel et al. The immune suppressive microenvironment affects efficacy of radio-immunotherapy in brain metastasis. EMBO Mol Med 13, e13412. (2021) DOI: 10.15252/emmm.202013412,

POSTER 7

Morphophenotypic characterization of melanoma brain metastases immune microenvironment: a multicentre retrospective study

Filippo Nozzoli [1], Marco Gessi [2], Filippo Ugolini [1], Luca Tinunin [1], Luigi Francesco Iannone [3], Alice Esposito [4], Giovanni Muscas [4], Alessandro Della Puppa [4], Isabella Ciardetti [5], Nicola Pimpinelli [5], Vincenzo De Giorgi [5], Isacco Desideri [6], Lorenzo Livi [6], Laura Doni [7], Giovanni Schinzari [8], Ernesto Rossi [8], Mario Mandalà [9], Daniela Massi [1],

1. Section of anatomic pathology, department of health sciences, University of florence, Florence, ITALY
2. Neuropathology, Fondazione policlinico universitario agostino gemelli irccs, università cattolica s. cuore, Rome, ITALY
3. Section of clinical pharmacology and oncology, department of health sciences, University of florence, Florence, ITALY
4. Neurosurgery unit, department of neurofarba, University of florence, Florence, ITALY
5. Dermatology unit, department of health sciences, University of florence, Florence, ITALY
6. Radiation oncology, department of experimental and clinical biomedical sciences, University of florence, Florence, ITALY
7. Oncology, Careggi university hospital, Florence, ITALY
8. Medical oncology, Fondazione policlinico universitario agostino gemelli irccs, Rome, ITALY
9. Oncology, University of perugia, Perugia, ITALY

Introduction and Objectives:
Metastasis to the central nervous system (CNS) is a common and lethal complication of advanced melanoma [1]. The role of immune cells (IC) in melanoma brain metastases (MBM) is only partially fulfilled, as well as the extrinsic mechanisms that drive the polarization of reactive astrocytes, the first step in glial scar formation, remain poorly understood. In the present study, we focused on the microenvironment of MBM including morphological features such as astrogliosis, IC distribution and density, and their prognostic impact.

Methods:
Consecutive MBM patients were retrieved and included in a multicentre, retrospective study. Representative hematoxylin and eosin (HE) stained slides were revised for morphological features. Immunohistochemistry for IC microenvironment was performed with the following antibodies: CD4, CD8, CD68, CD163, FoxP3, HLA-ABC, PD-L1. Score density of CD4, CD8, CD68, CD163 and FoxP3 was assessed through a semiquantitative method [2] and as binary variable (high vs. low). HLA-ABC cumulative H-score was

obtained by multiplying the intensity by the percentage of stained cells [3]. PD-L1 was assessed in tumour cells as well as percentage and dichotomous variable (cut-off: 1%) [4]. Statistical analysis for independent variables were performed with the chi-square test, or the Fisher's exact test. The Kaplan-Meier method was applied to estimate median overall survival (OS), and differences were assessed using the log-rank test.

Results:
Overall, 94 patients were included, among them 65 (69.1%) were male and the median age at diagnosis was 57.5 years. The median follow-up was 12 months, 72 patients (76.6%) died, with a median OS of 20.8 months. 54 patients (57.4%) presented with single MBM at diagnosis. Concomitant extra-cranial metastases occurred in 53/94 patients (56.4%). Upon histopathological review, glial scar was detected in 45/94 cases (47.9%). We found a significant correlation between glial scar and CD163+ infiltration (p=0.001). CD4+ (p=0.012) and CD163+ cells (p=0.048) were predominantly present in the intratumoral and in peritumoral areas, respectively. HLA-ABC H-score (median 130; range 0 – 300) was prevalent in intratumoral areas with high-CD4+ than in those with low-CD4+ cells (p=0.005). 30 patients (31.9%) had PD-L1 expression ≥1%. PD-L1 ≥1% prevailed in high-CD68+ (p=0.047) while CD4+ cells were significantly higher in PD-L1 <1% cases (p=0.030). BRAF mutation occurred in 52 patients (55.3%) and correlated with increased CD68+ macrophages (p=0.038). High-CD68+ showed a favorable impact on OS in patients multiple MBM (p=0.017), whereas peritumoral high-CD4+ (p=0.041) and intratumoral high HLA-ABC H-score (p=0.001)) correlated with prolonged OS in those with single MBM.

Discussion / Conclusion
Our findings showed a different distribution of IC in intratumoral and peritumoral areas of patients with MBM. We identified biomarkers which predict OS in patients with single and multiple MBM. Further studied are needed to validate our results.

Keywords: Melanoma, brain metastases, immune microenvironment, astrogliosis, immunohistochemistry

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P0STER 8

The prognostic impact of performance status and extracranial disease status – can EANO-ESMO brain metastases treatment guideline be further refined?

Olav E Yri [1], Guro L Astrup [1], Astrid T Karlsson [1], Marianne J Hjermstad [1], Nina Aass [1], Ornulf Paulssen [2], Rene Van Helvoirt [3], Marius-Ioan Taran [4], Jo-Asmund Lund [5], Stein Kaasa [1],

1. Oncology, Oslo university hospital, Oslo, NORWAY
2. Oncology and hematology, Telemark hospital trust, Skien, NORWAY
3. Oncology, Sørlandet hospital trust, Kristiansand, NORWAY
4. Oncology and hematology, Vestfold hospital trust, Tønsberg, NORWAY
5. Oncology, More and romsdal hospital trust, ålesund, NORWAY

Background:
Survival and quality of remaining lifetime after the diagnosis of brain metastases (BMs) vary considerably between individual patients. Anti-cancer treatments may provide intracranial tumor control, symptom relief and/or prolonged survival, albeit with significant risk of overtreatment. The 2021 EANO-ESMO guideline for BMs treatment recommends palliative care (PC) for patients with expected survival <3 months, but leaves radiotherapy or systemic treatment as alternative options. What defines "good" and "poor" performance status is not clear-cut in the guidelines. It is challenging for physicians to identify patients with short expected survival and subsequently advise them to refrain from anti-cancer treatment, opting for PC alone. Our research question was how to strengthen physician confidence in identifying these patients and provide helpful information into the shared decision making process that may reduce overtreatment. Our hypothesis was that performance status and extracranial metastatic disease (ECM) status could be the lead factors. We present clinical and patient reported data from 912 patients and relate our findings to the 2021 guideline recommendations.

Material & Methods
A population-based observational study recruiting consecutive patients with first-time BMs (Nov 2017-March 2021) with clinical data collected at inclusion and three-monthly for 24 months; PROMs completed at inclusion and monthly for 12 months. Overall survival (OS) was analyzed from date of BMs diagnosis. ECM status was classified as "controlled" (if absent/stable) or "uncontrolled" (progressive, synchronous BMs/ECM or unknown status). PROMs were analyzed longitudinally.

Results:
912 patients were included (median age 69 years [21-96], 54% female). Most frequent initial intracranial treatment was WBRT (41%) followed by SRS/SRT (34%) and surgery (17%). Median OS (mOS) was 5.9 months (range 0.2 to >55 months). Overall, 30% died within 3 months after BMs diagnosis (WBRT: 42%, SRS/SRT: 17%, surgery: 6%). mOS for patients in ECOG 0-1 (n=519), ECOG 2 (n=214) and ECOG 3-4 (n=163) was 9.9, 4.0, and 2.0 months, respectively. Within each ECOG group, mOS was statistically superior for patients with controlled ECM but clinically meaningful only for ECOG 0-1 (12.8 vs 6.8 months) and ECOG 2 (6.0 vs 3.2), not for ECOG 3-4 (2.3 vs 2.0). Multi-variate analyses associated controlled ECM, <5 BMs and presence of targetable mutations with superior survival for patients with ECOG 0-1 and ECOG 2; with ECOG 3-4 only controlled ECM. Patients with <3 months survival reported no improvement of QoL, physical functioning or fatigue; patients with longer survival reported stable or improved levels over time.

Conclusions:
Intracranial treatments seem beneficial only for patients with ECOG 0-1 and for patients with ECOG 2 with controlled ECM and/or limited number of BMs (i.e. eligible for SRS/SRT). Surgery indications must be considered in the individual patient regardless of ECOG-status. Our data support EANO-ESMO guidelines but the impact of performance status should be more emphasized. “Good” performance status should be restricted to ECOG 0-1. Anti-cancer treatment should be cautiously considered in ECOG 2 as this group appears “intermediary”. With short expected survival, intracranial treatment seems unlikely to improve patient reported symptoms.

Keywords: Guidelines, ECOG, extracranial disease, survival

References: Le Rhun, E., et al. (2021). «EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours.» Ann Oncol.

POSTER 9

Brain-Tumor barrier correlation with immunotherapy: adversities in treatment for brain metastases

Carlos Eduardo Da Silva Isidoro [1], Flávia Cristina Rosa [1],

1. Universidade cidade de são paulo, São paulo, BRAZIL

Background:
Primary tumors are distinguished by the original tissue, being able to produce a variety of different structures and adaptations in the tissue (cellular and molecular) in order to facilitate the outgrowth and penetration. Metastatic cells are adapted with soluble factors, immune inhibitors and external vesicles, the brain metastasis penetrate on the blood-brain barrier accessing the neurovascular unit and the central nervous system.

Material & Methods:
The key-words: Brain Neoplasms, Brain metastases and Immunotherapy were used in the NIH library and PubMed. The studies were included if they were written in English, written after 2013 and excluded if they were not related to the objective of the study or didn't have enough data to prove it´s findings. After the analysis 11 studies were used and 1 was excluded.

Conclusions: After the research, our conclusions were that in order to grow and disseminate the blood-brain barrier is modified by the new vessels developed by the neoplasm, turning into the blood-tumor barrier, that's recognized as leakier and dysfunctional by the heterogeneity of the structure and permeability. Consequently, the modified and dysfunctional barrier is more fragile and does not regulate the substances that pass through it, resulting in accumulation of water and metabolites at the neuroparenchymal space. The distribution of drugs is directly affected, causing accumulation and reducing the efficacy by dysregulation of the therapeutic levels needed for treatment. Glucocorticoids are used to reduce the water edema, but as a side effect it reduces the effectiveness of the immune system as a result the immunotherapy is less therapeutic for brain metastases and cancer cells proliferation.

Keywords: Brain Neoplasms, Brain metastases, Immunotherapy

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POSTER 10

Tumor progression related to whole brain radiotherapy as a complementary therapy to the resection of brain metastases: systematic review

Flávia Cristina Rosa [1], Carlos Eduardo Da Silva Isidoro [1],

1. Unicid, São paulo, BRAZIL

Background:
Recent studies demonstrated the benefits of isolated surgical resection in the treatment of brain metastases and question the use of whole brain radiotherapy (WBRT) as complementary therapy due to the risk of tumor progression. This study compares both approaches, isolated and combined, to analyze risks and benefits.

Material and methods: The keywords: brain metastases, whole brain radiotherapy, surgical resection and tumor progression were used in the data bases PUBMED and NIH. The studies were included in the analysis if they were written in English, written after 2002 and excluded if they were not related to the objective of the study. After the analysis, 7 studies were selected and 1 was excluded.

Conclusion:
After the research, the findings are that four studies using the WBRT as a complementary therapy to surgical resection of brain metastases increased the risk of tumor development and progression and did not positively influence the quality of life of patients. These studies concluded that the most effective approach for treating patients with brain metastases is surgical resection. Another two studies demonstrated the benefits of WBRT usage, while one study indicated that it doesn't exert influence on tumor progression.
After analyzing the results, it can be concluded that WBRT had a negative impact on tumor progression. Although, it was effective, showing improvement in some cases, it demonstrated importance in influencing the growth of new brain metastases.

Keywords: brain metastases, whole brain radiotherapy, surgical resection, tumor progression.

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metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. Clin Cancer Res. 2007;13(12):3637-3641., Tsao MN, Xu W, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev. 2018;1(1):CD003869. Published 2018 Jan 25.

POSTER 11

Tumor lineage-specific immune response in brain metastatic disease: opportunities for targeted immunotherapy regimen?

Shiva Najjary [1],

1. Department of pathology, Erasmus mc, Rotterdam, NETHERLANDS

Background:
Metastases in the brain are the most severe and devastating complication of cancer. The incidence of brain metastasis is increasing. Therefore, the need of finding specific druggable targets for brain metastasis is demanding. The aim of
this study was to investigate the brain (immune) response to brain metastases of the most common tumor lineages, viz., lung adenocarcinoma and breast cancer.

Material & Methods:
Targeted gene expression profiles of 11 brain metastasis from lung adenocarcinoma (BM-LUAD) were compared to 11 brain metastasis from breast cancer (BCBM) using nCounter PanCancer IO 360™ Panel of NanoString technologies. The most promising results were validated spatially using the novel GeoMx™ Digital Spatial Profiler (DSP) Technology. Additionally, Immune cell profiles and expression of drug targets were validated by multiplex immunohistochemistry.

Conclusions
This is the first report on differences in the brain immune response between metastatic tumors of different lineages.
We found more active immune response in BM-LUAD as compared to BCBM. In the BM-LUAD, 138 genes were upregulated as compared to BCBM (adj. p-value ≤ 0.05). Conversely, in BCBM 28 genes were upregulated (adj. p-value
≤ 0.05). Additionally, We found a far more extensive infiltration of immune cells in BM-LUAD as compared to BCBM.
Genes related to CD45+ cells, T cells and cytotoxic T cells showed to be expressed higher in BM-LUAD compared to BCBM (adj. p-value = 0.01, adj. p-value = 0.023, adj. p-value = 0.023, respectively). The spatial quantification of the
immune cells using the GeoMx DSP technique revealed the significantly higher quantification of CD14 and CD163 in tumor regions of BM-LUAD as compared to BCBM. Importantly, the immune checkpoint VISTA and IDO1 were identified
as highly expressed in the BM-LUAD. Multiplex immunohistochemistry confirmed the finding and showed that VISTA is expressed mainly in BM-LUAD tumor cells, CD3+ cells, and to less levels in some microglial cells in BM-LUAD. Taken together, targeted immune therapy should be considered to treat patients with BM-LUAD.

Keywords: Brain metastases; Gene expression; Immune infiltration; Immune response; Breast cancer, Lung adenocarcinoma.

POSTER 12

The Hamburg Experience: CyberKnife radiosurgery for brain metastases

Sebastian Exner [1], Fabian Fehlauer [1],

1. Cyberknife center, Strahlenzentrum hamburg, Hamburg, GERMANY

Background: Stereotactic radiosurgery (SRS) is increasingly being utilized for the treatment of brain metastases (BMs) due to its lesser detrimental effects on cognition and quality of life compared to whole brain radiation therapy (WBRT). However, SRS techniques lack standardization, and concerns have been raised regarding the potential differences in failure patterns between SRS and WBRT. In this study, our objective is to investigate the efficacy, toxicity, and failure patterns associated with SRS.

Methods and Materials: We conducted a retrospective review of patient outcomes who underwent SRS for BMs between the years 2021 and 2022. We assessed cumulative incidences of local failure, overall distant intracranial failure, and adverse radiation effects.

Results: A total of 91 patients with 345 BMs received SRS treatment in 105 courses. Among these courses, 91 were single fraction SRS with a mean dose of 19.95 Gy at the 70% isodose level (ranging from 18 to 24 Gy at the 70% isodose level), while 8 courses were hypofractionated SRS consisting of three fractions, with a total dose of 24 Gy at the 70% isodose level. The median volume of the planning target volume (PTV) was 14.28 cc (ranging from 0.4 to 62.51 cc). The median clinical follow-up period after SRS was 9.1 months (ranging from 4.1 to 21.6 months). At the 12-month mark, the event rates for local failure, adverse radiation effects, and overall distant intracranial failure were 6%, 8%, and 10.9% respectively. Furthermore, 10% of the patients ultimately required WBRT.

Conclusions: Our findings demonstrate excellent local control and low toxicity associated with Cyberknife for BMs. Additionally, the majority of intracranial failures were observed to be distant in nature. These results support the efficacy of SRS as a treatment option for BMs and emphasize the importance of further investigation to establish standardized techniques for SRS in order to optimize outcomes for patients with brain metastases.

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POSTER 13

Reduction of residual tumor burden is decisive for prolonged survival in patients with recurrent brain metastases – retrospective analysis in 219 patients

Jonas Lin [1], Yannik Kaiser[1], Benedikt Wiestler [2], Denise Bernhardt [3,4], Claire Delbridge[1], Bernhard Meyer [1], Jens Gempt [6] and Amir Kaywan Aftahy [1]

1. Department of Neurosurgery, School of Medicine, Klinikum rechts der Isar, Technical University Munich, Munich, Germany,
2. Department of Neuroradiology, School of Medicine, Klinikum rechts der Isar, Technical University Munich, Munich, Germany,
3. Department of Radiation Oncology, School of Medicine, Klinikum rechts der Isar, Technical University Munich, Munich, Germany
4. German Cancer Consortium (DKTK), Partner Site Munich, Munich, Germany
5. Department of Neuropathology, Institute of Pathology, School of Medicine, Klinikum rechts der Isar, Technical University Munich, Munich, Germany
6. Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background:
Despite advances in treatment for brain metastases, the prognosis for recurrent brain metastases remains poor and requires further research to advance clinical management and improve patient outcomes. Particularly, data addressing the impact of tumor volume and surgical resection with regard to survival remain scarce.

Patients and Methods: Retrospective analysis was conducted on data from adult patients that had presented at TUM Klinikum with recurrent brain metastases between December 2007 and December 2022. A distinction was made between operated and non-operated patients and the residual tumor burden (RTB) was determined by (postoperative) MRI (<72h post-surgery). Survival analysis was performed to analyze the impact of RTB on overall survival (OS) and RTB cut-off values were calculated using maximally selected rank statistics. In addition, further analyses on systemic tumor progression and (postoperative) tumor therapy were conducted.

Results:
219 patients were included in the analysis. Median age at the time of recurrence was 60 years (IQR 52-69). Median preoperative tumor burden was 2.4 cm^3 (IQR 0.8-8.3), and postoperative tumor burden was 0.5 cm^3 (IQR 0.0-2.9). 94 patients (42%) underwent surgery, of whom complete cytoreduction was achieved in 55 (25%). Median overall survival was 6 months (IQR 2-10). Cut-off RTB in all patients was calculated at 0.12 cm^3, showing statistically significant difference ($p = 0.00023$) in overall survival. Cut-off RTB for targeted metastasis patients was calculated at 0.1 cm^3, showing no statistically significant difference ($p = 0.67$). Multivariate analysis has shown preoperative KPSS (HR 0.983, 95% CI, 0.967-0.997, $p = 0.015$), postoperative tumor burden in cm3 (HR 1.03, 95% CI 1.008-1.053, $p = 0.007$) and complete vs. incomplete resection (HR 0.629, 95% CI 0.420-0.941, $p = 0.024$) to be significant, while. Longer survival was significantly associated with having received surgery for recurrent metastases ($p = 0.00063$). In the subgroup of patients with systemic progression a cut-off RTB of 0.97 cm^3 ($p = 0.00068$) was found; patients that had received surgery showed prolonged OS ($p = 0.036$) also in this subgroup. Age was found not to be associated with longer survival did not show a statistically significant association ($p = 0.47$). The combination of RTX and systemic therapy had significant influence on survival ($p = 0.034$).

Conclusion: RTB is a strong prognostic factor for survival in patients with recurrent brain metastases. Operated patients with recurrent brain metastases show a longer survival independent of age and systemic progression. Maximal cytoreduction should be attempted in order to achieve better long-term survival.

Keywords: Recurrent brain metastases, surgery, postoperative MRI, residual tumor burden (RTB), overall survival (OS), neuro-oncology

POSTER 14

Incidence of NTRK genes fusion in adult brain tumours: a longitudinal assessment in 140 patients with cerebral gliomas and brain metastases.

Philippe Métellus[1,2], Clara Camilla [2,3], Emilie Bialek [1], Nathalie Beaufils [3], Christine Vellutini, Eric Pellegrino [3], Christel Pissier, Pascale Tomasini [4], Mannmeet Ahluwalia [5], Isabelle NANNI[3], L'Houcine Ouafik [2,3]

1. Ramsay Santé, Hôpital Privé Clairval, Department of neurosurgery, Marseille, France
2. Aix Marseille Univ, CNRS, INP, Inst Neurophysiopathol, Marseille, France
3. APHM, CHU Nord, Service d'OncoBiologie, Marseille, France
5. Miami Cancer Institute at Baptist Health South Florida, Miami, Florida, USA

Background:
Oncogenic fusion of neurotrophin receptor tyrosine kinase NTRK1, NTRK2, or NTRK3 genes have been found in different types of solid tumours. Nevertheless, the incidence of NTRK gene fusions in these cancers remains quite unexplored. The treatment of patients with TRK fusion cancer with a first-generation TRK inhibitor (such as larotrectinib or entrectinib) is associated with high response rates (>75%), regardless of tumour histology and presence of metastases, with acceptable toxicity profile. Due to the efficacy of TRK inhibitor therapy and the recent Food and Drug Administration and EMA approval of Larotrectinib and entrectinib, it is clinically important to accurately and efficiently identify patients with TRK fusion cancer. In this retrospective study, we provide unique data on the incidence of oncogenic NTRK gene fusions in patients with brain metastases (BM) and gliomas.

Methods:
140 samples fixed and paraffin-embedded tissue (FFPE) of adult patients (59 of gliomas [19 of WHO grade II, 20 of WHO grade III and 20 glioblastomas] and 81 of BM of different primary tumours) are analysed. Identification of NTRK gene fusions is performed using next-generation sequencing (NGS) technology on the Ion Torrent S5XL automaton with the Oncomine Focus RNA assay kit (ThermoFisher). The analysis is carried out using the Ion Reporter software. A minimum of 50,000 mapped reads is required to allow interpretation of the result. A descriptive analysis of the variable of interest included the frequencies of patient's demographics, morphology of brain tumors, transcript fusions and exons skipping, was carried out by SAS® Software.

Results:
Among the 140 samples analysed by NGS, one of 59 glioma specimen was found to harbour ETV6(5)-NTRK3(15) fusion in a diffuse IDH-mutated and 1p19q co-deleted oligodendroglioma – grade II at incidence of 1.69%. Furthermore, in the remaining samples, no other NTRK gene fusions were identified, but transcript fusion as TMPRSS(2)-ERG(4) were detected in pancreas, prostate, endometrium BM and low grade glioma II and FGR3(17)-TACC3(11) was detected in breast BM. Aberrant splicing to produce EGRFex 2-7 skipping within EGFR mRNA, and METex14 skipping within the MET mRNA were found in glioblastoma and pancreas carcinomas BM, respectively.

Conclusion:
Due to the size of the population analysed, this study will provide pioneering data on the incidence of NTRK gene fusions in brain tumors, which could strongly support the relevance of innovative clinical trials with specific targeted therapies (larotectinib, entrectinib) in this population of patients.

ACCREDITATION STATEMENT

10 European CME credits (ECMEC®) by the European Accreditation Council for Continuing Medical Education (EACCME®).

EACCME® Accreditation of event reference #LEE23-00858

We are pleased to inform you that your application for EACCME® accreditation of
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LEARNING OBJECTIVES

- Identify news challenges in precision genomics of Brain Metastases.
- Describe the place of liquid biopsies for Brain Metastases management.
- Describe local treatment strategies for CNS Metastases (stereotactic radiosurgery, surgery, combined treatment).
- Describe the techniques used to assess treatment response.
- Describe molecular based specific systemic treatment in lung, breast and melanoma Brain Metastases.

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Com&Co - Étienne Jarry
15, Bd Grawitz - 13016 Marseille, France
Tel.: +33 (0)4 91 09 70 53 - Fax: +33 (0)4 96 15 33 08
Email: ejarry@comnco.com