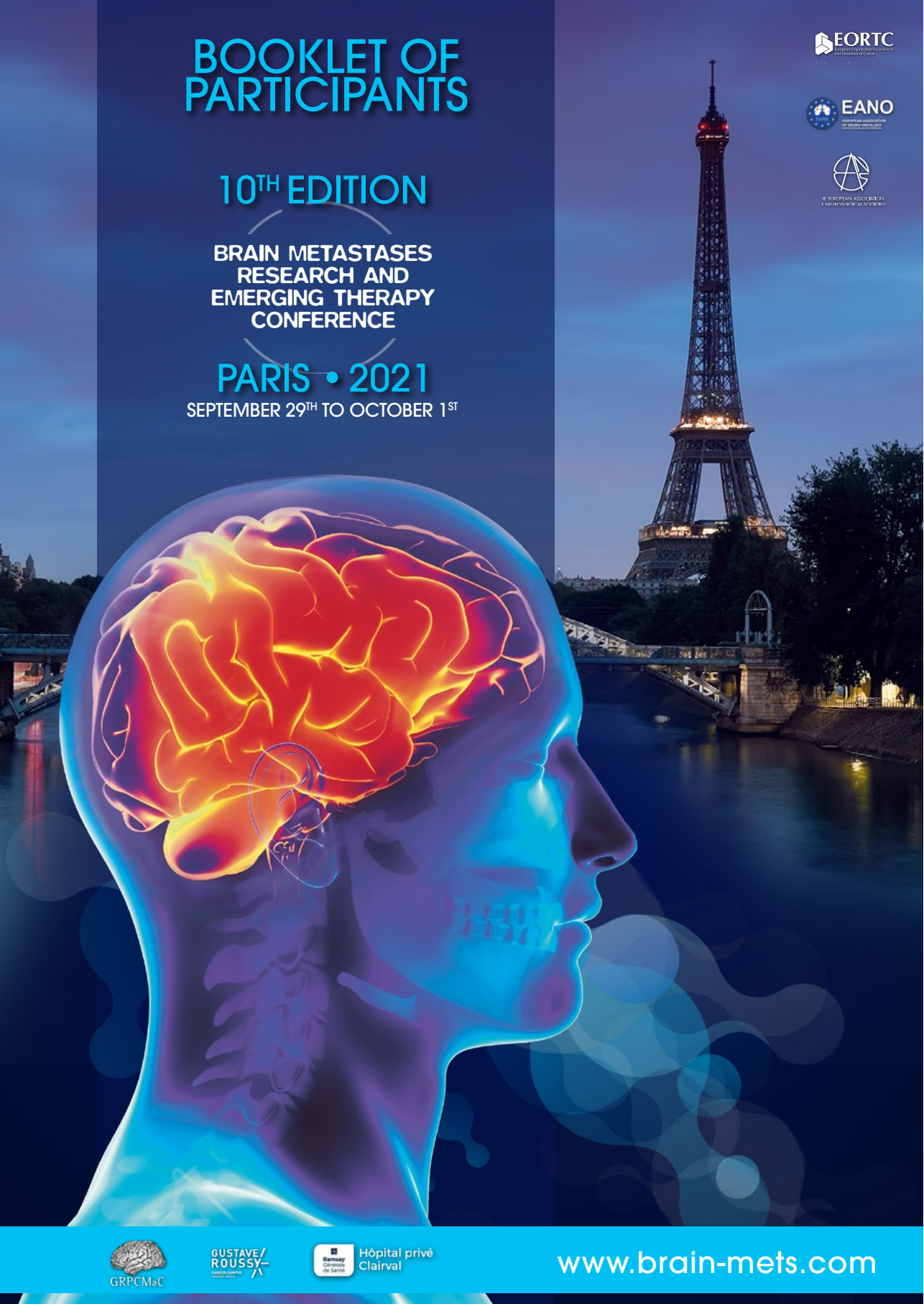
BOOKLET OF PARTICIPANTS

10TH EDITION

BRAIN METASTASES RESEARCH AND EMERGING THERAPY CONFERENCE

PARIS • 2021

SEPTEMBER 29TH TO OCTOBER 1ST



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SUMMARY

Organization

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WELCOME LETTER

WELCOME TO THE 10TH EDITION OF BRAIN METS MEETING!

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

The 2019 edition encouraged us to once again organize this conference. This year the meeting will be held under the auspices of EORTC, EANS & EORTC.

This initiative brings the multidisciplinary approach needed to develop Brain Metastases projects across several tumor types and disciplines such as breast cancer, lung cancer, melanoma, imaging, radiation oncology, pathology and molecular. It is expected that this cross-sectional meeting will stimulate innovative and insightful research in a collaborative environment and improve the standard of care and methodology of clinical research.

The overarching goal of the meeting is to generate a set of research priorities that would stimulate integrated scientific and clinical investigation directed at understanding basic processes of Brain Metastases and translating such insights to clinical care.

The organizing committee hopes that this meeting will provide an exceptional opportunity for you to share your collective expertise ranging from basic science to new treatments in order to facilitate ongoing studies and lay the foundation for future.

PROGRAM CHAIRS:

Manmeet Ahluwalia, Fabrice Barlési, Frédéric Dhermain, Emilie Le Rhun, Philippe Métellus, Riccardo Soffietti, Michael Weller, Manfred Westphal

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Manuel Valiente (SP)
Martin J. van den Bent (NL)
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SCIENTIFIC PART

ABSTRACTS

OPENING LECTURE - **THURSDAY, SEPTEMBER 30TH, 2021 - 08.30**

The Zap-X Radiosurgical Robot

Professor John R. Adler, Jr. MD,
Stanford University – Stanford, USA

Radiosurgery (SRS) is a widely accepted and oftentimes preferred procedure for managing a broad array of human pathologies, especially all types of metastases; brain SRS is estimated to be used globally in almost 200,000 patients every year, with metastasis being the most common indication. However, based on cancer and other disease incidences, it is estimated that more than 3 million patients in middle income and wealthy countries would today be best treated with radiosurgery were it available to them. The fact that so many patients lack access to state-of-the-art brain treatments represents an important public health concern. Believing that cost, complexity and the availability of radiation therapy vaults are primary impediments to the wider availability of SRS throughout the world, the Zap-X radiosurgical robot was created. The Zap-X is the first ever self-shield therapeutic radiation device, designed to avoid the cost and complexity of being sited inside a shielded vault, has been traditionally required. Optimized specifically for the brain and head & neck regions, the Zap-X robot combines image-guided targeting, a radically new rotating collimator design and a compact S-band linear accelerator to accomplish state-of-the-art radiosurgery. With a total of 7 installations worldwide, the Zap-X robot is still undergoing a rapid evolution, yet the core technology promises to dramatically increase the availability of high-quality radiosurgery for brain metastasis patients worldwide.

BASIC SCIENCE & TRANSLATIONAL RESEARCH IN BRAIN METASTASES
THURSDAY, SEPTEMBER 30TH, 2021 - 09.10

Exploiting organ adaptation to solve therapeutic resistance

Manuel Valiente
Centro Nacional de Investigaciones Oncológicas – Madrid, Spain

The ability of a tumor to adapt to its surroundings involve modulation of various signaling pathways, which might include specific therapeutic targets. In addition, inhibition of a certain target or signaling pathway in cancer cells is frequently counterbalance by the activation of an alternative molecular network, which emphasizes the general need for combination strategies.
I will provide an example to illustrate the influence of the context in therapeutic sensitivity, in particular I will discuss the emergence of resistance to a non-targeted approach such as radiation.
We found that metastatic cells switch from a radiation-sensitive state, while growing in vitro, to a radiation-resistant state, when they grow in the brain. Such state allows cancer cells from experimental lung and breast cancer brain metastasis to resist to a variety of fractionated radiation protocols applied in vivo. By deconstructing the different aspects required during organ colonization, including metastasis initiating properties as well as the ability to establish interactions with the microenvironment, we reproduced the emergence of radio-resistance. Unbiased analysis of the transcriptomic changes present under conditions inducing resistance to therapy allowed us to identify potential candidates. Both a genetic approach and a pharmacologic one blocking one of such candidates were sufficient to sensitize brain metastases from breast and lung cancer to radiotherapy in vivo. We further explored the potential benefit of such biomarker, which is compatible with liquid biopsy, in patients with brain metastasis from various primary sources concluding that it identifies those ones that would benefit from radiotherapy. On the contrary, patients with high levels of the biomarker could be offered a blood-brain barrier inhibitor targeting the mechanism underlying radio-resistance, which we demonstrate is sufficient to turn patient-derived organotypic cultures from relapsed radiation-insensitive brain metastases into radiation-sensitive tumor entities.
In summary, the plasticity used by metastases to get adapted to a specific context (i.e. the brain) is also key to understand resistance to available therapies, such as radiotherapy. Given the potential of organ-dependent plasticity as a source of novel effective therapeutics, we have developed a novel drug-screening platform (METPlatform) that we have validated in both experimental and human brain metastasis and primary brain tumors.

BASIC SCIENCE & TRANSLATIONAL RESEARCH IN BRAIN METASTASES
THURSDAY, SEPTEMBER 30TH, 2021 - 09.30

Microenvironment

Professor Adrienne Boire,
Memorial Sloan Kettering Cancer Center – New York, USA

The tumor microenvironment plays a critical regulatory role in central nervous system metastases. Leptomeningeal metastases, (LM) face substantial microenvironmental challenges, including inflammation and sparse amounts of micronutrients including iron. To investigate the mechanism by which cancer cells overcome these constraints, we subjected cerebrospinal spinal fluid (CSF) from patients with LM to single-cell RNA-Seq. Cancer cells, but not macrophages, within the CSF express the iron-binding protein lipocalin-2 (LCN2) and its receptor SCL22A17. These macrophages generate inflammatory cytokines that induce cancer cell LCN2 expression, but do not generate LCN2 themselves. In mouse models of LM, cancer cell growth is supported by the LCN2/SLC22A17 system and can be inhibited by iron chelation therapy. We are currently translating these observations into a Phase I clinical trial.

CHALLENGES IN CLINICAL PRACTICE (1): CANCER OF UNKNOWN PRIMARY (CUP)
THURSDAY, SEPTEMBER 30TH, 2021 - 10.20

Radiotherapy

Dr Frédéric Dhermain,
Institut Gustave Roussy – Villejuif, Paris.

Even if SCMC and IMT present clearly different natural histories, treatments and outcomes, most of radiotherapy (RT) indications are in post-operative situations. We will describe some pre-operative indications of RT, underlying the importance of clearly defining the key endpoints for patients in each scenario. The choice of the optimal timing and technique of RT will highly depend on histo-clinical and radiological parameters. We will present in detail several scenarios for an optimal and personalized RT fractionation. Finally, we will summarize the respective role of RT in the management of SCMC and IMT in a perspective of a 'patient-centered' management, guided by modern molecular and radiological tools.

CHALLENGES IN CLINICAL PRACTICE (2): CANCER OF UNKNOWN PRIMARY (CUP)
THURSDAY, SEPTEMBER 30TH, 2021 - 10.40

How neuropathology can be informative?

Johan Max Kros, MD, PhD.,
Laboratory for Tumor Immuno-Pathology, Dept. Of Pathology, Erasmus Medical Center – Rotterdam, The Netherlands.

Recent progress in treatment strategies for common cancers has resulted in focus on the development of therapies for metastatic sites, including brain. For the development of novel therapeutic strategies using chemotherapeutic agents or immune modulators, not only the primary tumors, but also their diaspora needs to be adequately characterized. Complex issues as tumor heterogeneity in time and place, and the multiple interactions with the tumor cellular and molecular environment, are accountable for our limited knowledge of today. Stimulation of basic and translational research in this field is, therefore, mandatory.
The ontogeny of cerebral metastases is a multi-step process that starts with the dissociation of tumor cells from the primary site and their transformation into migrating phenotypes that enter the blood stream. Subsequent events include the adhesion of the cells to the blood vessels and their penetration through the barriers of the brain, after a dormant stage followed by outgrowth into the neuropil. The characteristics of the tumor cells and their surroundings involved in the subsequent steps are relevant to strategies aimed at their interception and elimination. The mutational status, expressional profiles and micro-environmental specificities of primary tumors including the nature and intensity of the immune response, may well be predictive of the chance of cerebral seeding. The same parameters are important to treatment of the primary tumors, but also to intracerebral (or CSF located) metastases. Besides many homologies between the primary tumors and their cerebral seeds there may well be important genetic and expressional discordances that are relevant for the choice of site-specific therapy. Obviously, the immune response in primary tumors is different from that at the metastatic sites behind the blood-brain barrier. In addition, tumor colonization-promoting actions of glial cells and microglia are relevant to the invasion of the tumor cells in brain. For diagnostic purposes the tumor cells and their derivatives in the blood stream are easily accessible. However, an important issue is their representation of the tumor tissue for the sensitivity and specificity of diagnostic assays. The acquisition of tissue from the primary tumors is relevant for screening for genetic mutations and expressional patterns predictive of response to targeted drugs. Because of discrepant genomic and expressional parameters between the primary tumors and their brain metastases, the characterization of the intracerebral tumors is important as well. It is expected that environmental parameters including the immune response will also be taken into consideration in future diagnostic algorithms. Diagnostic procedures to tumor cells and their derivatives in the blood stream are promising because of their easy accessibility. However, issues of critically low numbers of circulating tumor cells (CTCs) and exosomes, and low concentrations of circulating tumor-associated nucleic acids, have hampered their diagnostic exploitation so far. It is to be expected that progress in technical developments and more translational studies will solve the current problems and better adjust therapies to combat brain metastatic disease.

HOW NEUROPATHOLOGY CAN BE INFORMATIVE? - **THURSDAY, SEPTEMBER 30TH, 2021 - 11.00**

Brain Metastasis from Unknown Primary Tumor: How do I manage?

Riccardo Soffietti,
Department of Neuro-Oncology, University of Turin – Turin, Italy.

Steroids are widely used in neuro-oncology albeit the indications for use have very different implications at different timepoints of the respective disease.

At the time of diagnosis due to a neurological deficit, steroids are mostly used to counteract edema. For unequivocal diagnosis of metastasis or high grade glioma, resolution of symptoms is already a good indicator, that the lesion can be safely treated by resection or if inaccessible by radiosurgery. In cases where lymphoma cannot be ruled out on the initial imaging, steroids should be withheld until securing the histology by biopsy.

At the time of initial treatment, the use of steroids depends on the modality. For surgical tumor removal, the routine use of intraoperative steroids is controversial except for intramedullary tumors. There is widespread use in the presence of marked edema and continuation of steroids for the first postoperative days but there is widespread acceptance that this should be tapered as soon as possible. For radiosurgery, periprocedural use of steroids is a regular practice. In case of biopsy only, steroids will not be administered routinely for biopsy but maintained for the lesion as long as there is symptomatic edema

At the time of adjuvant treatments, steroids may be necessary to control reactive edema from radiation or from intracavitary treatments. In the current debate as to how many treatment effects are mediated by immunological phenomena, the outlook for the use of steroids is negative as there is solid evidence that they are definitively immunosuppressive. As the efficacy of radiosurgery, - mostly for metastases, is also increasingly recognized to have an immunological component this immunosuppressive effect gains relevance. A negative effect of steroids prescribed during radiation in glioblastoma has been suspected from the analysis of three large clinical cohorts, presumably due to protecting tumor cells from the genotoxic stress of chemotherapy and radiation. Likewise, the elevated glucose levels during steroid treatment are thought to have a negative influence on the clinical course of gliomas in general.

At the time of palliatiion, steroids can well be used for a short time in high doses but might abruptly be stopped to shorten a burdensome final disease phase. Also, consideration has to be given to the fact that prolonged palliative use of steroids in patients with maintained mobility causes severe muscle wasting so that patients may lose mobility as one of their main elements of QoL.

CONTROVERSIAL TREATMENTS FOR CNC METASTASES
THURSDAY, SEPTEMBER 30TH, 2021 - 11.40

Surgery first or SRT first?

Dr Frédéric Dhermain,
Institut Gustave Roussy – Villejuif, Paris

Point °1. Still indications for Whole-Brain RT with/without Hippocampal Avoidance?

Point°2. Take into account the paradigm shift through Targeted-Drugs & Immunotherapies!

Point °3. If WBRT is indicated, arguments for HA with WBRT +/- Memantine are debatable…

Point °4. There will be always more 'Normal Brain Sparing' with Radiosurgery Vs WBRT-HA

Point°5. Increasing availability/ cost-effectiveness of Radiosurgery Machines up to 10 BMs

CONTRA: PRO SRT FIRST - **THURSDAY, SEPTEMBER 30TH, 2021 - 11.45**

Contra: Pro SRT first

Stephanie Combs,
Institute of Radiation Medicine (IRM), HMGU – Munich, Germany.

Surgical resection of brain metastases followed by stereotactic radiotherapy (SRT) achieves high local control rates with a superior neurocognitive outcome compared to whole-brain radiotherapy. Preoperative SRT has been proposed as an alternative radiotherapy strategy. Multiple retrospective and prospective series reported local control rates between 80% to 90 % at 1 or 2 years comparable to adjuvant SRT outcomes. Besides these first encouraging outcome data, preoperative SRT brings several important benefits: (1) Postoperative SRT requires relatively large planning target volumes due to the inherent size of resection cavities, the inclusion of surgical tracts and areas of meningeal adhesion, as well as the need for isotropic target expansions. In contrast, preoperative SRT allows for more precise target volume definition with smaller target volumes and reduced exposure of surrounding normal brain tissue. Moreover, lower radiation doses may be adequate in the absence of post-surgery hypoxia. For instance, Prabhu et al. (Prabhu et al. JRBOP 2021) reported a median prescription dose of 15 Gy in a multicenter trial achieving local control rates similar to post-operative SRT. These dose benefits were mirrored by low reported rates of adverse events and at the same time leave more room for SRT deliveries close to sensible organs at risk (e.g. brainstem, optic chiasm), salvage SRTs nearby, and single fractionation SRT in borderline large brain metastases. (2) The delivery of preoperative SRS is not subject to the postoperative clinical course, which may lead to higher compliance rates. In a phase II trial, 20% of patients enrolled before surgery did not receive the intended postoperative SRT (Brennan et al. IJROBP 2014). (3) The much-needed systemic chemotherapy can be initiated more rapidly because there is no delay to ensure adequate wound healing before the start of SRT. (4) For postoperative SRT there are concerns about tumor cell spreading and formation of leptomeningeal disease relapse (Johnson et al. IJRBOP 2016) with reported leptomeningeal relapse rates of 28 % to 45 % in the course after treatment. It is hypothesized that pre-operative radiation may confer lethal damages to metastatic tumor cells that are spilled during surgery. Thus, the occurrence of leptomeningeal disease relapse could be reduced. For example, retrospective data from a multicenter study (Prabhu et al. JRBOP2021) achieved promising results with a leptomeningeal disease relapse rate of only 7.6 % after 2 years.

To conclude, preoperative SRT constitutes a safe and effective radiotherapy modality which the potential to confer improved outcomes by reducing the rate of post-surgery leptomeningeal disease relapse and early start of post-operative systemic therapies.

FLUORESCENCE GUIDED SURGERY FOR BRAIN METASTASES? SHARED EXPERIENCE AND CLINICAL EVIDENCE LEVEL - **THURSDAY, SEPTEMBER 30TH, 2021 - 12.05**

Fluorescence guided surgery for brain metastases? - Shared experience and clinical evidence level - Part 2

Nils Ole Schmidt,
Department of Neurosurgery, University Medical Center - Regensburg, Germany.

Brain metastases are the most frequent intraparenchymal tumors of the brain with an increasing incidence. In patients eligible for surgery, complete tumor removal is the most important predictor of overall survival and neurological outcome.
Fluorescein sodium is a leakage tracer that accumulates in cerebral regions of blood-brain barrier disruption. It can be used as a neurosurgical fluorescent tracer for the indirect identification of tumor tissue and therefore facilitating the resection of brain tumors including brain metastases. Recent results of our experience with more than 300 cases of fluorescein-guided microsurgeries for the resection of brain metastases has demonstrated its safety and value for increasing the extend of resection with minimal morbidity. Furthermore, the introduction of intraoperative imaging of brain tumors with fluorescence-guided confocal laser-endomicroscopy (CLE) allows the additional visualization of microstructures in the surgical field during tumor resection. With fluorescein sodium providing the sufficient image contrast a non-invasive and repeated intravital visualization of intratumoral and perilesional microstructures such as the metastasis brain parenchyma-interface is possible. This novel technique has the potential to improve intraoperative diagnosis, surgical resection and to facilitate clinically relevant scientific activites by providing unprecedented in-situ insights of brain metastasis. Currently a multicenter phase II trial is already ongoing and comparing fluorescein-INtra-VItal microscopy versus conventional frozen section diagnosis for intraOperative histopathological evaluation (INVIVO).
Taken together, fluorescence-guided microsurgery using fluorescein sodium is feasible, safe and an effective technique to improve visualization and resection of brain metastasis.

CONTRA: PRO SRT FIRST - **THURSDAY, SEPTEMBER 30TH, 2021 - 12.20**

Immunotherapy alone versus immunotherapy + Stereotactic Radiation in newly diagnosed melanoma brain metastases

Dieta Brandsma[1] and Giuseppe Minniti[2],
1 Antoni van Leeuwenhoek Hospital – Amsterdam, The Netherlands
2 Istituto Neurologico Mediterraneo Neuromed – Pozzilli, Italy

Prior to the introduction of immunotherapy (immune checkpoint inhibitors: anti-PD1, anti-CTLA4) and targeted therapy (BRAF and MEK inhibitors), patients with melanoma brain metastases (BM) had a median survival of 4-5 months.1
Immunotherapy and targeted therapy have significantly improved outcomes of patients metastatic melanoma, also in case of BM.2,3 A recently reported median overall survival of melanoma patients with BM ranged from 14 to 23 months.4
Due to this prolonged survival, an increasing number of patients suffering from BM is treated by stereotactic radiation (SRT) for BM during immunotherapy. A potential synergistic effect of combinational treatment for melanoma BM was suggested based on an international meta-analysis.5 However, there are raising concerns on the long-term cerebral toxicity of SRT of BM, as cerebral radiation necrosis risk in patients treated with immunotherapy and SRT may be increased.6 On the other hand, immunotherapy without SRT in patients with asymptomatic, small melanoma BM can induce long-lasting cerebral responses.3
In this session, the risks and benefits of combinational immunotherapy and stereotactic radiation versus immunotherapy alone for melanoma BM will be discussed.

References

1.Davies MA, Liu P, McIntyre S, Kim KB et al. Prognostic factors for survival in melanoma patients with brain metastases. Cancer 2011; 117:1687-96.
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5.Lehrer EJ, Peterson J, Brown PD et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: an international meta-analysis of individual patient data. Radiother Oncol 2019; 130:104-112.
6.Dia K, Bian SX, Routman et al. Stereotactic radiosurgery and ipilimumab for patient with melanoma brain metastases. J Neurooncol 2018; 139:421-9.

WILL ARTIFICIAL INTELLIGENCE CHANGE THE MANAGEMENT ?
SEPTEMBER, OCTOBER 30TH, 2021 - 14.45

Will artificial intelligence change the management ? Pro

Stephanie Combs,
Institute of Radiation Medicine (IRM), HMGU – Munich, Germany.

Artificial intelligence (AI) techniques are expected to have a significant impact on multiple areas of daily life. Besides natural language processing, picture analysis has become one of the major applications that is already being dominated by AI techniques. Likewise in medicine, AI-based image analyses may open up new options for personalization of medicine. The field of radiomics describes the high throughput extraction of quantitative imaging features that are then fed into machine learning models to predict clinical outcomes. Alternatively, AI techniques called «deep neural networks» can directly analyze medical imaging data. Both approaches have been shown to predict histological and molecular features or disease progression in different cancer types using computed tomography, magnetic-resonance imaging (MRI), and positron emission tomography. In brain metastases patients, AI techniques will have a large impact on clinical management on multiple levels: AI-based analyses of MRI imaging have been used to predict local control with an area under the curve (AUC) of up to 0.79 (Mouraviev et al. Neurooncology 2020). Such imaging-based prediction models may be used to pre-therapeutically stratify patients into groups with a high or low risk of local recurrence. High-risk patients could then be administered to more aggressive treatment regimens. For instance, high-risk patients could be treated with dose-escalated stereotactic radiotherapy alone or as definitive ablative treatment. Other authors have analyzed the prediction of intracranial progression-free survival (Zhao et al. Translational Lung Cancer Research 2020), brain metastases velocity, and the occurrence of leptomeningeal disease relapse (Che-Yu et al. Neuro-Oncology Advances 2020). Such prediction models may be helpful to guide the selection of systemic therapies and follow-up regimens.

In patients with brain metastases as a single occurrence of cancer with unknown primary, non-invasive AI-based histological subtyping may be used to guide the search for an underlying primary tumor. Kniep et al. (Radiology 2020) demonstrated effective prediction of histology up to an AUC of 0.82 for melanoma histology.

Likewise, multiple authors have demonstrated effective differentiation of post-radiotherapy necrosis from tumor progression. This may be a helpful tool to guide the important decision for salvage therapies or anti-necrotic therapies. Besides image analyses, deep neural networks provide large benefits for three-dimensional image segmentation which constitutes a central part of the radiotherapy workflow. Automatized segmentation of brain metastases may reduce operator dependence and speed up the working time, especially in the era of multi-brain metastases treatments. AI-based radiotherapy treatment planning may speed up the process further.

Alternatively, AI techniques have been trained to automatically analyze frozen sections intra-operatively to differentiate the histological types of brain tumors with expert level performance ultimately guiding neurosurgical interventions (Hollon et al. Natur Medicine 2020).

To conclude, AI will change the management of brain metastases significantly by allowing medical imaging-based risk stratification and personalization of therapy, characterization of histological subtypes based on pathological slides and MR-imaging, differentiation of radiation necrosis from metastases, and automatic radiotherapy treatment planning of brain metastases.

WILL ARTIFICIAL INTELLIGENCE CHANGE THE MANAGEMENT ?
THURSDAY, SEPTEMBER 30TH, 2021 - 14.50

Will artificial intelligence change the management? Contra

Norbert Galldiks, University Hospital Cologne – Cologne, Germany.

An overview of how advanced imaging techniques may help to overcome shortcomings of anatomical MRI for response assessment in patients with brain metastases who are undergoing stereotactic radiosurgery, immunotherapy, or combinations thereof will be presented.

Study results suggest that parameters derived from amino acid PET, diffusion- and perfusion-weighted MRI, MR spectroscopy, and newer MRI methods are particularly helpful for the evaluation of the response to radiosurgery or checkpoint inhibitor immunotherapy and provide valuable information for the differentiation of radiotherapy-induced changes such as radiation necrosis from brain metastases. The evaluation of these imaging modalities is also of great interest in the light of emerging high-throughput analysis methods such as radiomics, which allow the acquisition of additional data at a low cost.

Preliminary results are promising and should be further evaluated. Shortcomings are different levels of PET and MRI standardization, the number of patients enrolled in studies, and the monocentric and retrospective character of most studies.

CONTRA: PRO SRT FIRST - **THURSDAY, SEPTEMBER 30TH, 2021 - 15.05**

QoLand cognitive function assessment end points…

Linda DIRVEN,
Leiden University Medical Center – Leiden, The Netherlands

Traditional outcomes in studies with brain metastases patients comprise progression-free and overall survival as well as local tumor control. Other outcomes that are increasingly considered important reflect the patients' functioning and well-being, such as symptoms and impairments, functioning in daily life and other aspects of health-related quality of life. In this presentation, both the value and difficulties of assessment of health-related quality and cognitive functioning will be discussed. Next, possible solutions will be discussed to capture relevant information on the patient's functioning and wellbeing, while reducing the patient burden and subsequently prevent poor compliance with assessments of these outcomes over time.

INTERACTIVE CASE REPORTS WITH ELECTRONIC VOTING SYSTEM -
FRIDAY, OCTOBER 1ST, 2021 - 08.00

Checkpoint-inhibition therapy for brain metastases from lung cancer is improved by depletion of intratumoral tumor-associated macrophages and microglia (TAM/M)

Philipp Karschnia[1,2]; Tao Xu[3]; Esther Fitzinger[1]; Julia C. Saliger[1]; Jens Blobner[1,2]; Nico Teske[1,2]; Iven-Alex von Mücke-Heim[3]; Sigrid Langer[3]; Marcel Konhäuser[1]; Hellen Ishikawa-Ankerhold[4]; Niklas Thon[1,2]; Joerg-Christian Tonn[1,2]; Louisa von Baumgarten[1,2,3],

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4 Department for Cardiology, Ludwig-Maximilians-University - Munich, Germany

Background: Brain metastases dramatically limit prognosis of lung cancer patients. Unlike systemic disease, brain metastases from lung cancer poorly respond to checkpoint-inhibition therapy. Targeting the immunosuppressive tumor-associated macrophages and microglia (TAM/M) and their receptor CSF1R may increase efficacy of checkpoint-inhibitors.

Methods: Cranial windows were prepared in fully immunocompetent, transgenic CX3CR1GFP/wt-mice with green-fluorescent TAM/M. Intracranial injection of red-fluorescent Lewis Lung Carcinoma-cells was performed, and mice received one of the following three treatments: PD1-inhibition only (n=8); PD1-inhibition combined with an anti-CSF1R-antibody (exhibiting limited blood-brain-barrier permeability under physiologic conditions, n=8); or PD1-inhibition combined with a small molecular CSF1R-inhibitor (exhibiting high blood-brain-barrier permeability, n=7). Tumor growth and TAM/M were followed by repetitive two-photon laser scanning microscopy over weeks.

Results: Following intracranial injection, metastases were detected in all three treatment groups within eight days. In mice receiving PD1-inhibition only, metastases showed exponential growth which was paralleled by intra- and peritumoral accumulation of TAM/M. Treatment with an anti-CSF1R-antibody resulted in significantly lower numbers of intratumoral TAM/M given increased tumoral blood-brain-barrier permeability, but did not substantially affect peritumoral TAM/M or TAM/M localized in the healthy contralateral hemisphere. In contrast, treatment with a small molecular CSF1R-inhibitor not only reduced the number of intratumoral TAM/M, but also of peritumoral and contralateral TAM/M.

Compared to PD1-inhibition only, the addition of either an anti-CSF1R-antibody or a small molecular CSF1R-inhibitor resulted in decreased tumor growth (tumor size on day 12: 8.3 mm2 (PD1-inhibition only) versus 0.9 mm2 (PD1-inhibition + anti-CSF1R-antibody) versus 2.5 mm2 (PD1-inhibition + small molecular CSF1R-inhibitor)) (p = 0.01). The beneficial effects of the small molecular CSF1R-inhibitor in reducing tumor growth were similar to those of the anti-CSF1R-antibody.

Conclusion: Targeting intratumoral TAM/M using CSF1-inhibition may increase the efficacy of checkpoint-inhibition therapy for brain metastases from lung cancer. Such an approach may warrant further evaluation in preclinical and clinical studies.

MOLECULAR NEUROPATHOLOGY - **FRIDAY, OCTOBER 1ST, 2021 - 09.40**

Molecular neuropathology : What story does the tissue tell?

Patrick HARTER,
Edinger-Institute (Neurological Institute) – Frankfurt am Main, Germany

Although brain metastases are the most common intracranial neoplasms, knowledge about their cellular composition and molecular profiles are rare. Brain metastases are not a single cancer entity, they contain a heterogeneous group of tumors with variable clinical behaviour. Insights into the distinct tissue compositions with a special regard to the immune architecture and its clinical relevance will be presented. Furthermore, novel neuropathological tools will be introduced, which might help in identifying (i) predictive signatures for immunotherapies and (ii) the source of cancers with unknown primary.

STEREOTACTIC RADIATION IN BM MANAGEMENT - **FRIDAY, OCTOBERR 1ST, 2021 - 11.05**

Stereotactic Radiotherapy (SRT) versus Whole-Brain Radiotherapy (WBRT) for patients with Multiple Brain Metastases: a multidisciplinary decision.

Dr Frédéric DHERMAIN,
Institut Gustave Roussy – Villejuif, Paris

Among the few ongoing trials still proposing WBRT as the 'reference arm' for patients with multiple BMs (with or without Memantine, with or without HA), the NCT03550391 trial seems to be the one that could best answer the two coupled questions: what impact will have a modern (Hippocampal-Avoidance) HA-WBRT choice on survival and neurocognition? Other registered trials are either 'not yet recruiting' or don't propose HA systematically in the WBRT arm or are slowly recruiting. Consequently, because there is no 'level 1 evidence-based' data to definitively conclude pro or against HA-WBRT versus SRT in patients with multiple BMs, a case by case inter-disciplinary discussion will be 'the best option'.

In our daily practice, outside ongoing trials, the individual decision should integrate several key factors including clinical, radiological data (volumetric and dynamic) and also the histo-molecular profile, if possible based on the more recent tissue available. The 'worst candidates' for exclusive SRT will present the following and paradoxically 'opposite' characteristics: either (1) an asymptomatic patient with a very favorable expected survival, a high velocity index and 'targetable' lesions/ potentially responders to immunotherapies (IT) with an 'intermediate' total cumulative volume of BMs. This subgroup of patients could be treated with frontline exclusive systemic treatments, delaying SRT or WBRT for future progression, or (2) a highly-symptomatic patients with an expected survival of less than 3-4 months, with a high-velocity index, no 'targetable' lesions and a bulky total cumulative volume. This subgroup of patients would be proposed for WBRT +/- HA or best supportive care. All other patients should potentially benefit from a multi-disciplinary discussion favoring a personalized combination of SRT and Systemic treatment.

Choosing between Systemic treatments versus RS versus a Combination of both versus WBRT

	Systemic Treatment (ST)	SRT	Combination of ST and SRT *	Modern WBRT with HA
Molecular Profile	Targetable	Non targetable	Targetable	Non targetable
Number of BMs	More than 10	4 to 10	4 to 10	More than 10
Total Cumulative Volume of BMs	More than 15-20 cc	Less than 15-20 cc	Less than 15 cc	More than 20 cc *(surgery if needed)*
Velocity Index	high	low	intermediate	high
Survival[T]	>3 months	>3 months	> 6 months	3 to 12 months
Neurological status	No Symptom	Symptomatic	+/- Symptomatic	Symptomatic

SurvivalT: expected median overall survival based on DS-GPA dedicated index. DS-GPA: disease-specific Graded Prognostic Assessment. ST: systemic treatment, mostly targeted-drugs and/or immunotherapies. RS: radiosurgery (1 fraction), HFSRT: hypo-fractionated stereotactic radiotherapy (3-5 fractions / 1 week). SRT*: if possible, before ST or 'concomitant' with ST (within 1 half-life of the drug).

What's hot in lung cancer

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Based on chemoimmunotherapy with atezolizumab or durvalumab being the new standard of care for extensive disease small cell lung cancer and apparent lack of benefit from hypocampal avoidance WBRT, the current research foci are defining the effect of chemoimmunotherapy alone in patients with asymptomatic brain metastases and moving toward stereotactic radiotherapy for treatment emerging brain metastases rather than prophylactic cranial irradiation in extensive disease.
The standard for patients with advances non-small cell lung cancer is upfront immunotherapy alone or in combination with chemotherapy. Knowledge on the of these regimens in patients with brain metastases is limited, mainly due to their exclusion from randomized clinical trials. The effectiveness of these approaches alone in patients with asymptomatic brain metastases remains to be answered, as well as their combination with stereotactic radiotherapy. First line targeted therapy has become the standard of care for most oncogenic driver NSCLC. The concept of brain as a sanctuary and thus the primate of local radiotherapy needs to be revised because of excellent brain penetrance of later generation TKIs and in view of the long survival patients can expect. The hot topic here is to define the right timing of stereotactic radiotherapy, both for patients with asymptomatic or symptomatic brain metastases.

SCIENTIFIC PART

SELECTED ORAL PRESENTATIONS

FRIDAY, OCTOBER 1ST, 2021 - 08.00

Checkpoint-inhibition therapy for brain metastases from lung cancer is improved by depletion of intratumoral tumor-associated macrophages and microglia (TAM/M)

Philipp Karschnia[1], Tao Xu[2], Esther Fitzinger[1], Julia Saliger[1], Jens Blobner[1], Nico Teske[1], Iven-Alex Von Mücke-Heim[2], Sigrid Langer[2], Marcel Kohnhäuser[1], Hellen Ishikawa-Ankerhold[3], Niklas Thon[1], Joerg-Christian Tonn[1], Louisa Von Baumgarten[1],

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Background: Brain metastases substantially limit survival of lung cancer patients. Unlike systemic disease, brain metastases from lung cancer poorly respond to checkpoint-inhibition therapy. It is unclear whether the immunosuppressive tumor-associated macrophages and microglia (TAM/M) and their receptor CSF1R may represent a therapeutic target to improve efficacy of checkpoint-inhibition therapy.

Methods: Cranial windows were prepared in fully immunocompetent, transgenic CX3CR1GFP/wt-mice with green-fluorescent TAM/M. Red-fluorescent Lewis Lung Carcinoma-cells were intracranially injected, and mice received one of the following three treatments: PD1-inhibition only (n=8); PD1-inhibition combined with a CSF1R-antibody (exhibiting limited blood-brain-barrier permeability under physiologic conditions, n=8); or PD1-inhibition combined with a small molecular CSF1R-inhibitor (exhibiting high blood-brain-barrier permeability, n=7). Repetitive two-photon laser scanning microscopy was performed to follow tumor growth and TAM/M over weeks.

Results: Metastases were detected in all three treatment groups within eight days following intracranial injection. In mice receiving PD1-inhibition only, metastases showed exponential growth which was paralleled by intra- and peritumoral accumulation of TAM/M. Treatment with a CSF1R-antibody resulted in significantly lower numbers of intratumoral TAM/M due to increased tumoral blood-brain-barrier permeability, but did not substantially affect peritumoral TAM/M or TAM/M localized in the healthy contralateral hemisphere. Contrary, treatment with a small molecular CSF1R-inhibitor not only reduced the number of intratumoral TAM/M, but also of peritumoral and contralateral TAM/M.
When compared to PD1-inhibition only, the addition of either a CSF1R-antibody or a small molecular CSF1R-inhibitor resulted in decreased tumor growth (tumor size on day 12: 8.3 mm2 (PD1-inhibition only) versus 0.9 mm2 (PD1-inhibition + CSF1R-antibody) versus 2.5 mm2 (PD1-inhibition + small molecular CSF1R-inhibitor)) (p = 0.01). The beneficial effects of the small molecular CSF1R-inhibitor in reducing tumor growth were similar to those of the CSF1R-antibody.

Conclusion: The combination of checkpoint-inhibition therapy with CSF1-inhibitors targeting intratumoral TAM/M may result in decreased growth of brain metastases from lung cancer. Such a therapeutic approach may therefore warrant evaluation in preclinical and clinical studies.

Keywords : brain metastasis, lung cancer, tumor-associated macrophages and microglia, checkpoint-therapy, CSF1R

FRIDAY, OCTOBER 1ST, 2021 - 08.10

Adaptation of colorectal cancer cells to the brain microenvironment: The role of IRS2

Inbal Greenberg[1], Klein Anat[1], Grossman Rachel[2], Sokol Ethan[3], Yeini Eilam[4], Ofek Paula[4], Satchi-Fainaro Ronit[4], Liang Bertrand[5], Reuveni Hadas[5], Rubinek Tami[1], Wolf Ido[1],
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Colorectal cancer (CRC) reflects the fourth most frequent etiology of brain metastasis (BM). Yet, molecular mechanisms supporting it are unknown. We aimed to explore drivers enabling adaptation of CRC cells to the brain and decipher mechanisms facilitating the process.
We analyzed the FoundationOne database, which contains genomic alterations data of cancer-related genes in over 16,000 human CRC primary and metastasis samples. Increased prevalence of IRS2 gene amplification was observed in 13% of BM, compared to only 3% of primary tumors or other metastatic sites. IRS2 is a cytoplasmic adaptor mediating effects of insulin and IGF-1 receptors and is involved in more aggressive behavior of different cancer types. In agreement with the genomic data, immunohistochemistry of human clinical samples showed increased expression of IRS2 protein in BM. We constructed an in vitro system mimicking the brain microenvironment using cultured human astrocytes or their conditioned media. Under these conditions, IRS2-overexpressed CRC cells survived better and formed larger 3D spheres. IRS2-silenced CRC cells showed a mirror image. Moreover, in an intracranial CRC BM mouse model, IRS2-overexpressed cells generated larger brain lesions, while silencing IRS2 dramatically decreased tumor outgrowth and extended survival. Interestingly, transcriptomic analysis revealed enrichment of oxidative phosphorylation (OXPHOS) and Wnt/β-catenin pathways by IRS2. Indeed, IRS2-expressing cells showed increased mitochondrial activity and glycolysis-independent viability. Furthermore, IRS2-expressing cells had increased β-catenin transcriptional activity. Interestingly, β-catenin or IRS2 inhibition (using NT219) in IRS2-expressing cells decreased their viability, β-catenin transcriptional activity, and OXPHOS gene expression, suggesting involvement of IRS2 in modulating OXPHOS through β-catenin. β-catenin is known to confer 5-FU resistance; consequently, we showed that combination of 5-FU and NT219 worked in synergy, inhibited the formation of BM, and extended animal survival.
These data reveal the unique genomic profile of CRC BM and suggest IRS2 inhibition as a novel target for treatment of these patients.

FRIDAY, OCTOBER 1ST, 2021 - 08.20

Selection of intrinsically chemoresistant tumor cells by the brain environment drives chemoresistance in breast cancer brain metastasis

Uceda Rebeca[1], Vennin Claire[1], S. Margarido Andreia[1], Gooijer Mark[2], Citirikkaya Ceren[2], Van Tellingen Olaf[2], Wesseling Pieter[3],
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Resistance to chemotherapies is commonly seen in the clinic in a range of cancer types, especially in metastatic diseases [1, 2]. As first-line treatments involve chemotherapeutics, when these fail, metastases develop and their treatment plan becomes even more challenging due to cross-class multidrug resistance [3-5]. In particular, first-line treatment of patients with brain metastases comprises radiation and tumor resection [6, 7], and systemic treatments are not commonly applied due to frequently observed chemoresistance and blood brain barrier (BBB) impermeability [8-10]. Here, we dissected the intrinsic and microenvironmental mechanisms driving chemoresistance in our drug-naïve breast cancer brain metastasis (BCBM) model (Margarido et al., under revisions). We showed, for the first time, that in vivo selection of chemotherapy-responsive MMTV-PyMT breast tumors in the brain results in reduced response to chemotherapy by the BCBM. We demonstrate that BCBM chemoresistance is not caused by the properties of the BBB nor by previous exposure to chemotherapy. Instead, we found that in vivo selection in the brain trigger an upregulation of Breast Cancer Resistance Protein (BCRP) in the tumor cells, which causes chemoresistance.

Keywords : Breast Cancer Brain Metastasis (BCBM), Blood Brain Barrier (BBB), Breast Cancer Resistance Protein (BCRP)

References : Briz, O., et al., What «The Cancer Genome Atlas» database tells us about the role of ATP-binding cassette (ABC) proteins in chemoresistance to anticancer drugs. Expert Opin Drug Metab Toxicol, 2019. 15(7): p. 577-593., Yardley, D.A., Drug resistance and the role of combination chemotherapy in improving patient outcomes. Int J Breast Cancer, 2013. 2013: p. 137414., Longley, D.B. and P.G. Johnston, Molecular mechanisms of drug resistance. J Pathol, 2005. 205(2): p. 275-92., Gote, V., et al., Drug Resistance in Metastatic Breast Cancer: Tumor Targeted Nanomedicine to the Rescue. Int J Mol Sci, 2021. 22(9).

FRIDAY, OCTOBRE 1ST, 2021 - 08.30

T lymphocyte IFN-enhances the ability of breast cancer cells to pass the blood-brain barrier

Dana Dana Mustafa[1],
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To develop brain metastasis, tumor cells must penetrate the blood-brain barrier (BBB). The molecular mechanisms utilized by tumor cells and underlying the penetration are largely unknown. Previously we found that the interaction of primary tumor cells with infiltrating T lymphocytes enhances the development of brain metastasis of estrogen receptor-negative (ER-) breast cancer. We discovered that T lymphocytes induce the expression of Guanylate-Binding Protein 1 (GBP1) in primary tumor cells and increase their ability to cross the in vitro BBB model and the in vivo mouse model1. GBP1 is a downstream target of IFN-□ which is a product of T lymphocytes. In the current study, we investigated the molecular contribution of the IFN-□ pathway in enabling MDA-MB-231 breast cancer cells to cross the in vitro BBB. We identified CD8+ cells as the subset with the strongest stimulatory effect on breast cancer cell transmigration. We investigated the role of the IFN-□ pathway by two methods: inhibiting the IFN-g receptor in breast cancer cells and neutralizing the soluble IFN-□. Both methods impaired the transmigration ability of breast cancer cells through the BBB. Importantly, the study highlighted the biological differences between recombinant and native IFN-g. Moreover, the CXCL-9,-10,-11/CXCR3 axis, dependent on IFN-□ signaling activity, was overexpressed in primary breast cancer samples of patients who developed brain metastasis.
Our study demonstrates the prominent role of the IFN-□ pathway in the formation of brain metastasis of ER- breast cancer and offers targets to design future therapies for preventing breast cancer cells to cross the BBB.

Keywords : T lymphocytes, Brain Metastasis, Breast cancer, BBB

FRIDAY, OTOBER 1ST, 2021 - 08.40

Deciphering the impact of cancer cell´s secretome and its derived-peptides on breast cancer brain metastasis

Ana Sofia Ribeiro[1], Rita Carvalho[1], Liliana Santos[2], Inês Conde[1], Ricardo Leitão[2], Fernando Schmitt[3], Célia Gomes[2], Ana Paula Silva[2], Joana Paredes[1],
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Introduction
Brain metastases present the poorest survival rates, lack efficient therapies and remain the major clinical problem in breast cancer surveillance. Thus, we aim to dissect the initial steps of the brain metastatic process and focus on the paracrine interaction between breast cancer cells and the brain microenvironment. Our goal is to identify a brain cancer cell secretome signature, since it has been seen as a promising source for the discovery of new biomarkers involved in metastatic progression.

Material and Methods
Breast cancer cells 231, and their brain, bone and lung organotropic variants have been used. Their secretome was collected from collagen embedded 3D-spheroids cultures and high throughput proteomic Label Free Quantitation analysis was performed in order to identify brain enriched metastatic signature. Further, the secretomes were then used to challenge different components of the brain pre-metastatic niche, such as the blood-brain-barrier (BBB) permeability and microglia.
Nude mice were pretreated with secretomes and BBB integrity was assessed in vivo by near-infrared fluorescence imaging, and ex vivo by collagen IV and albumin immunostaining in the prefrontal cortex. Human brain vascular hCMEC/D3 ECs monolayers integrity was assessed by measuring the transendothelial flux of a 4 kDa fluorescent dye, the TEER, and the expression of tight and adherens junction proteins (ZO-1 and β-catenin). Microglia activation was determined by its phagocytic capacity and p-Stat3 expression. VGF mRNA expression and protein expression was analyzed in the TCGA database and the in series of primary breast tumors and brain metastasis from breast cancer patients.

Results and Discussions
We found a 25 secretome protein signature specifically deregulated in the secretome of brain tropic variants. Importantly, their secretome caused a significant disruption of BBB permeability, whereas all organotropic cell promoted microglia activation. Interestingly enough, we validated this results using an in vivo secretome induced model, where pretreated mice with secretome from brain tropic cells promoted an increase in the accumulation of the fluorescent dye in the brain, a decrease of collagen IV and an increase of albumin immunoreactivity further indicating structurally and functional alterations in the in vivo BBB integrity. So far, we identified VGF (nerve growth factor inducible) as a key mediator in this process. In detail, the exposure of in vitro BBB model to exogenous TLQP-21, a VGF-derived peptide, caused a similar cell permeability compared to the secretome of brain tropic cells, an effect that was abolished in the presence of a TLQP-21 receptor antagonist. In contrast, only a slight increase in microglia phagocytosis and p-Stat3 expression was observed upon VGF treatment. Importantly, VGF expression was found both at the cancer cells and in the tumor's adjacent stroma, being its co-expression associated with HER-2 overexpressing and basal-like tumors, the molecular subtypes of breast cancer that metastasize more frequently to the brain.

Conclusion
In conclusion, our data shows a specific breast cancer brain metastatic signature. So far, we identified VGF as a key mediator in this process, being associated with a poor prognosis for breast cancer patients.

Keywords : Brain Metastasis, Breast cancer, cancer secretome, VGF, pre-metastatic niche

FRIDAY, OCTOBER 1ST, 2021 - 08.50

Impact of Tucatinib on Progression Free Survival in Patients with HER2+ Metastatic Breast Cancer and Brain Metastases

Thomas Bachelot[1], Nancy U. Lin[2], Rashmi K. Murthy[3], Sara Hurvitz[4], Virginia Borges[5], Mafalda Oliveira[6], Catherine Oakman[7], Sarah Khan[8], Cynthia Lynch[9], Kelly Westbrook[10], Catherine Doyle[11], Matthea Reinish[12], Marco Colleoni[13], Dennis Slamon[14], Gabriel Hortobagyi[3], Eric P. Winer[15], Jorge Ramos[16], Wentao Feng[17], Sibylle Loibl[18],

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Background: Tucatinib (TUC) is an oral tyrosine kinase inhibitor highly specific for HER2. TUC is approved in multiple regions for use in combination with trastuzumab (T) and capecitabine (C) in adult patients (pts) with advanced unresectable or metastatic HER2+ breast cancer, including pts with brain metastases (BM), who have received 2 prior anti-HER2–based regimens. In the pivotal HER2CLIMB trial, TUC added to T and C resulted in statistically significant improvements in PFS and OS in HER2+ metastatic breast cancer pts with and without BM (Murthy, NEJM 2020). We present exploratory analyses of PFS by type of BM in HER2CLIMB.

Methods: HER2CLIMB (NCT02614794) pts were randomized 2:1 to receive TUC or placebo combined with T and C. All pts had baseline brain MRI. BM were classified as untreated, treated stable, or treated and progressing. PFS per investigator and OS were analyzed by treatment arm in stable BM pts (treated stable) and active BM pts (untreated + treated progressing), using standard RECIST 1.1 assessing disease in both body and brain.

Results: At baseline, 291 pts (48%) had BM: 198 (48%) in the TUC arm and 93 (46%) in the control arm. In pts with stable BM (n=117), median (95% CI) PFS was 7.5 mo (5.4, 9.6) in the TUC arm vs 5.0 mo (2.0, 5.6) in the placebo arm (HR: 0.56; 95% CI: 0.33, 0.96; P=0.03). In pts with active BM (n=174), median PFS was 7.6 mo (5.7, 8.5) in the TUC arm vs 4.1 mo (3.1, 4.3) in the placebo arm (HR: 0.38; 95% CI: 025, 0.58; P<0.00001). In pts with treated progressing BM (n=108), median PFS was 7.6 mo (5.7, 9.6) in the TUC arm vs 4.1 mo (3.1, 4.3) in the placebo arm (HR: 0.36; 95% CI: 0.21, 0.63; P=0.0002). In pts with untreated BM (n=66), median PFS was 6.9 mo (5.5, 9.6) in the TUC arm vs 3.6 mo (1.5, 7.5) in the placebo arm (HR: 0.47; 95% CI: 0.24, 0.92; P=0.02).

Conclusions: Addition of TUC to T and C significantly improved PFS regardless of BM type, indicating delay of progression not only in the body but also in the brain. Patients with active BM (typically excluded from HER2+ MBC trials) had substantially longer PFS with TUC treatment.

Keywords : HER2CLIMB, HER2+ Metastatic Breast Cancer, Brain Metastases, Tucatinib

References : Murthy et al. N Engl J Med. 2020;382:597-609, , ,

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Nude mice were pretreated with secretomes and BBB integrity was assessed in vivo by near-infrared fluorescence imaging, and ex vivo by collagen IV and albumin immunostaining in the prefrontal cortex. Human brain vascular hCMEC/D3 ECs monolayers integrity was assessed by measuring the transendothelial flux of a 4 kDa fluorescent dye, the TEER, and the expression of tight and adherens junction proteins (ZO-1 and β-catenin). Microglia activation was determined by its phagocytic capacity and p-Stat3 expression. VGF mRNA expression and protein expression was analyzed in the TCGA database and the in series of primary breast tumors and brain metastasis from breast cancer patients.

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Keywords : HER2CLIMB, HER2+ Metastatic Breast Cancer, Brain Metastases, Tucatinib

References : Murthy et al. N Engl J Med. 2020;382:597-609, , ,

FRIDAY, OCTOBER 1ST, 2021 - 09.00

Clinical impact of MRI screening for brain metastases in resected stage III melanoma

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Background: Melanoma has a high propensity to metastasize to the brain, especially in advanced disease stages. Therefore, screening for brain metastases (BMs) is often routinely performed in patients with stage IV melanoma. Knowledge of intracranial disease can change the treatment strategy, since local therapies (surgical resection, stereotactic radiosurgery [SRS]) and systemic therapies (targeted therapies [TTs], immune checkpoint inhibitors [ICIs]) have shown efficacy in melanoma BMs. In 2018, adjuvant systemic treatments were introduced in the Netherlands for patients with resected stage III melanoma. Since then, a final screening for both extracranial (CT and/or 2-Deoxy-2-[fluorine-18] fluoro-d-glucose positron emission tomography/CT [18F-FDG-PET/CT]) and intracranial disease (MRI) has been routinely performed in these patients prior to treatment initiation. Here, we evaluated the clinical impact of MRI screening for BMs in patients with resected stage III melanoma.

Material & Methods: In this retrospective cohort analysis, we included all patients with resected stage III melanoma who underwent screening MRI of the brain between August, 1st, 2018, and January, 1st, 2021. The following data were collected from our hospital's electronic health record system: reported American Joint Committee of Cancer (AJCC) stage at initial referral; diagnosis of new extracranial disease on screening CT and/or PET-CT; diagnosis and size of BMs on screening MRI (neuro-radiologists' reports); and treatment plan prior to and after MRI.

Results: We identified 191 patients with resected stage III melanoma who had been screened for BMs: 21 were initially referred with melanoma stage IIIA, 70 with stage IIIB, 95 with stage IIIC, and 5 with stage III of unknown primary . Extracranial disease was detected at screening in 25 patients (13.0%): 1.0% in stage IIIA, 4.1% in stage IIIB, 7.9% in stage IIIC, and 0.0% in stage III of unknown primary. Overall, in 5 out of 191 patients (2.6%), the screening MRI revealed BMs; all were asymptomatic. 4 patients had initial stage IIIC and 1 had stage III of unknown primary. 2 patients had a single BM, 1 had 3 BMs and dural metastases, 1 had 6 BMs, and 1 had 10 BMs. All BMs had a diameter <10mm, except for one BM in the patient with 10 BMs, which had a diameter of 18mm (including hemorrhage). 2 out of 5 patients with BMs also had concurrent extracranial disease

after screening, which had already resulted in a change in treatment strategy (from adjuvant to stage IV treatment). Therefore, in patients with resected stage III melanoma without extracranial disease after restaging, MRI of the brain led to a change in treatment strategy in only 3 out of 166 patients (1.8%). None of the 5 patients with BMs received local therapy as first-line treatment.

Conclusions: The clinical impact of MRI screening for BMs in patients with resected stage III melanoma appears to be low and requires further evaluation.

Keywords : advanced melanoma, brain metastases, screening, magnetic resonance imaging, adjuvant therapy

FRIDAY, OCTOBER 1ST, 2021 - 09.10

Detection of circulating tumor cells in cerebrospinal fluid for patients with suspected breast cancer leptomeningeal metastases: a prospective study

Darlix Amélie[1], Pouderoux Stéphane[2], Lehmann Sylvain[3], Thezenas Simon[4], Bievelez Alexis[4], Jacot William[2], Cayrefourcq Laure[5], Menjot de Champfleur Nicolas[6], Leaha Cristina[7], Alix-Panabières Catherine[5],

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Introduction

The diagnosis of breast cancer (BC) associated leptomeningeal metastases (LM) is confirmed by the detection of tumor cells in the cerebrospinal fluid (CSF) using conventional cytology (gold standard). However, even with optimal CSF sample volume and time to analysis, the sensitivity (Se- of this technique is low, demanding repeated samples. Here, we aimed to evaluate the value of circulating tumor cell (CTC) detection in CSF using the CellSearch® system for LM diagnosis.

Methods

This prospective, monocentric study included adult BC patients with suspected LM. CSF samples from 1-3 lumbar puncture(s) were analyzed: protein level, conventional cytology (60 drops), and CTC detection with the CellSearch® system (60 drops, first lumbar puncture only). Se and specificity (Sp) were calculated, using the results of the conventional cytology as the gold-standard.

Results

Forty-nine eligible patients were included (Jan 2017-Jan 2020): median age 51.8, 95.9% women, 20.4% HER2+ BC, 93.8% previously diagnosed with metastatic BC, 89.8% with clinical symptoms. Among them, 40 were evaluable (CTC detection failure: n=8, eligibility criteria failure: n=1). Median sample volume was 3.0 mL for conventional cytology samples (median time to analysis: 22min) and 3.3 mL for CTC samples. Of the 40 evaluable patients, 18 had a positive cytology (on

sample n=°1/n°2: n=16/n=2) and were therefore diagnosed with LM using the gold-standard. Protein level was elevated in 88.2% of these patients, compared with 45.1% of patients with negative CSF cytology (p=0.005). CTCs were detected in these 18 patients (median 5824 CTCs, range 93-45052). CTCs were also detected in 5/22 patients with a negative cytology (median 2 CTCs, range 1-44). Among them, one patient (44 CTCs) was diagnosed with a cytologically-proven LM 9 months later, while there was no further argument for LM in the other patients' history (1-3 CTC), who died of the extra-cerebral disease after a median of 5.2 months (range 0.9-25.9). The detection of □1 CTC in CSF was associated with a Se of 100.0% (IC95% 82.4-100) and a Sp of 77.3% (IC95% 64.3-90.3) for the diagnosis of LM. Considering the number of CTC as a quantitative value, we determined the cut-off maximizing the Youden index using the ROC analysis. The detection of at least 93 CTC in CSF was associated with a Se and a Sp of 100.0% for the diagnosis of LM. It was associated with a Se of 75.1% (IC95% 61.6-88.4) and a Sp of 100% for the diagnosis of confirmed or probable LM as defined by the ESMO-EANO guidelines. Interestingly, HER2+ CTC were detected in CSF in 73.3% of patients with a HER2- tumor.

Conclusion
CTCs were detected with the CellSearch® system in all patients diagnosed with a cytologically-proven LM, as well as in a few patients without a cytological confirmation of LM. The prognosis of these patients with CSF cytology-/CTCs+ needs to be further investigated in a larger cohort.

Keywords : Leptomeningeal metastases, breast cancer, circulating tumor cells
Results: We identified 191 patients with resected stage III melanoma who had been screened for BMs: 21 were initially referred with melanoma stage IIIA, 70 with stage IIIB, 95 with stage IIIC, and 5 with stage III of unknown primary . Extracranial disease was detected at screening in 25 patients (13.0%): 1.0% in stage IIIA, 4.1% in stage IIIB, 7.9% in stage IIIC, and 0.0% in stage III of unknown primary. Overall, in 5 out of 191 patients (2.6%), the screening MRI revealed BMs; all were asymptomatic. 4 patients had initial stage IIIC and 1 had stage III of unknown primary. 2 patients had a single BM, 1 had 3 BMs and dural metastases, 1 had 6 BMs, and 1 had 10 BMs. All BMs had a diameter <10mm, except for one BM in the patient with 10 BMs, which had a diameter of 18mm (including hemorrhage). 2 out of 5 patients with BMs also had concurrent extracranial disease

FRIDAY, OCTOBER 1ST, 2021 - 09.20

Evaluation of predictive markers for the patterns of metastatic disease in patients with pulmonary adenocarcinoma with a focus on brain metastases

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Background: The majority of patients diagnosed with pulmonary adenocarcinoma present at an advanced stage of the disease and most of them will develop metastases during follow up. Finding predictive biomarkers for the development of metastatic disease during diagnostic workup is important to guide therapeutic strategies. In this study we sought histologic and molecular parameters predictive of (brain) metastatic potential in the primary tumours.

Materials & Methods: A set of four histologic criteria including growth pattern, inflammation, desmoplasia and nuclear grading, as well as a diagnostic genetic panel customized for lung cancer alterations, were evaluated in biopsy and resection specimens of 339 patients presenting with metastases from pulmonary adenocarcinoma, and correlated with metastasis in brain and other sites. Survival data were associated with clinical staging and the metastatic sites.

Results: Predominantly papillary tumours showed a strong propensity to develop brain metastasis. In addition, the presence of an Epidermal Growth Factor Receptor mutation was associated with the occurrence of brain metastases but appeared independent of the dominant growth pattern. We observed a major difference in dominant growth pattern between the primary tumours and the corresponding metastases.

Conclusion: Routine histopathology and genetic biomarkers of primary pulmonary adenocarcinoma specimens predict to some extent the development of cerebral metastasis. These parameters are by themselves insufficiently specific to reliably predict metastatic behaviour. This is, however, a first step towards the development of a predictive algorithm on which therapeutic strategies can be based. We are currently investigating additional parameters to improve the specificity of our predictive model.

Keywords : pulmonary adenocarcinoma, brain metastases, predictive markers

FRIDAY, OCTOBER 1ST, 2021 - 09.30

Brain metastases - Impact of extent of resections

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Background:
Surgical resection of brain metastases may improve symptoms and prolong survival in selected patients. Gross total resection is usually attempted, but the identification of tumor margins during surgery may be difficult. Further, fear of inflicting damage to eloquent areas may result in subtotal resection. It is uncertain whether gross total resection improves survival compared to subtotal resection in patients with single brain metastases. We investigated the association between overall survival and extent of resection in this patient population.

Method:
We reviewed the medical records of all adults undergoing first-time surgery for a single brain metastasis between 2011 and 2018 at a large, regional referral cancer center. Only patients with MRI 12-48 hours post-operatively to evaluate extent of resection were included in the analyses. Gross total resection was defined as no visible residual tumor on the post-operative MRI as described by the neuroradiologists. We grouped patients according to extent of resection for statistical analyses: a subtotal resection group and a gross total resection group. In cases of ambiguity regarding remnant tumor, patients were classified as having subtotal resection.

Results:
We included 373 patients (52% females) and most common primary cancers were lung (35%) and melanoma (24%). Gross total resection was identified in 238 patients (64%). Median overall survival for all patients was 11.0 months; 8.0 (6.2-9.8) in the subtotal resection group and 13.0 (9.7-16.3) in the gross total resection group. The groups had similar rates of surgical complications and post-operative neurological deficits. In a multivariate regression analysis including known prognostic preoperative factors (age, performance status, extracranial metastases and status of extracranial disease), gross total resection was significantly associated with longer overall survival compared to subtotal resection (HR 0.68, p=0.002). Post-operative radiotherapy administered within 6 weeks after surgery did not significantly alter the hazard ratio estimates for gross total vs. subtotal resection when included in the regression analysis (HR: 0.68 vs. HR: 0.69).

Discussion/Conclusion:
Our study suggests improved survival for gross total resection compared to subtotal resection in patients with single brain metastases, when adjusting for prognostic preoperative factors and post-operative radiotherapy. Further, the similar rates of surgical complications after subtotal vs. gross total resection indicate that we should not discard the importance of gross total resection in surgery for brain metastases. Future studies should include patient reported outcome measures to better understand the quality of these patients lives.

Keywords : Brain metastases, surgery, gross total resection, survival

SCIENTIFIC PART

POSTERS

POSTER 1 - CATEGORY: CHALLENGES IN CLINICAL PRACTICE

Overall survival after radiotherapy for brain metastases; a historic cohort study of 1566 NSCLC patients

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Background
Radiotherapy (RT) is a treatment cornerstone in brain metastases (BM) from non-small cell lung cancer (NSCLC). Use of stereotactic radiosurgery (SRT) has increased the last 10 years, but overall survival (OS) remains poor. To avoid overtreatment, it is important to identify patients unlikely to benefit from RT in terms of extended survival time and/or symptom relief. We analyzed OS and use of RT at a large cancer referral center from introduction of SRT in 2006 through 2018 to characterize patients with short and long survival after RT.

Material and Methods
1566 NSCLC patients were treated with RT for BM with either SRT (n=435/28%) or WBRT (n=1131/72%) as initial RT. Clinical data were retrieved from patient records. OS was estimated from start of RT to death of any cause. 30 days, 90 days and >1 year OS were calculated.

Results/Conclusions
Median age was 66, W:52%/M:48%. Sixty-four percent had adenocarcinoma, 64% had extracranial metastases (ECM), 32% had one BM, while 34% had 5 or more. Karnofsky Performance Status (KPS) was >70 in 54% at inclusion.
Median OS was 3 months (2.7-3.4) overall, 7 months (5.7-8.3) in the SRT-cohort relative to 2 (1.8-2.2) in the WBRT-patients. Median OS in the SRT cohort increased from 4 months in 2009 to 9 in 2018, with no change in the WBRT cohort.

Overall, 15% of the patients died within 30 days after start of RT, 45% within 90 days while 20% were alive >1 year.
In the SRT cohort; 8% died during the first 30 days, 27% within 90 days while 35% were alive after 1 year, relative to 18%, 51% and 15% In the WBRT cohort.
Univariate analyses showed that age >70, male sex, histology other than adenocarcinoma, ECM present, multiple BM and KPS ≤70 were significantly associated with shorter survival (p <0.001).

These factors were also significant when analyzed by RT cohort, except age in the SRT cohort. Use of SRT increased in the period from 30% in 2013-2014 to 53% 2017-2018. Moreover three-fraction treatment was more common in the end of the period. We also observed a shift from 3Gy x 10 to 4Gy x 5 in the WBRT cohort.

Summary:
Although some NSCLC patients treated with RT for BM live beyond 1 year, a high proportion dies within 90 days after start of RT. This indicates that RT should be omitted in many patients. Age ≥70, KPS ≤70, ECM present, multiple BM and non-adenocarcinoma histology are factors associated with inferior survival and must be considered before initiating RT. Although results from multivariate analyses are necessary to substantiate this, in order to guide decisions about RT, the findings above indicate important patient characteristics to consider. Moreover, symptom burden and patient preferences should also be emphasized when deciding treatment. It is highly likely that many patients in this cohort may have profited more from best supportive and palliative care than RT.

Keywords : Brain metastases, NSCLC, radiotherapy, overall survival

POSTER 2 - CATEGORY: CNS METASTASES

FEATURES OF TREATMENT OF LEPTOMENINGEAL DISSEMINATION FOR CHILDREN WITH RABHOMYOSARCOMA PARAMENINGEAL LOCALIZATION WITH INTRACRANIAL DISTRIBUTION

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Leptomengeal metastasis (LM) is the spread of tumor cells to the subarachnoid space and membranes of the brain and spinal cord. In children, LM is observed in 8% of cases with rhabdomyosarcoma, Ewing's sarcoma, neuroblastoma, retinoblastoma. Leptomeningeal metastases have an endoneural path of metastasis - spreading along peripheral or cranial nerves and intracranial spreading from adjacent anatomical zones into the brain substance.

Keywords : leptomeningeal dissemination, rhabdomyosarcoma, children, intracranial spread

POSTER 3 - CATEGORY: CNS METASTASES

Trial in Progress: A Prospective, Multicentre Phase 2b Study to Establish Image Interpretation Criteria for 18F-Fluciclovine PET in Detecting Recurrent Brain Metastases after Radiation Therapy (PURSUE)

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Background: Brain metastases represent the most common intracranial tumour in adults, occurring in 10-40% of cancer patients. Most patients undergo multimodal treatment approaches and post-treatment follow-up with conventional MRI (CE-T1-weighted and FLAIR/T2-weighted) of the brain is performed to monitor for disease recurrence. However, owing to the similar appearance of treatment-related changes like radiation necrosis with that of true recurrence, conventional MRI alone suffers from low specificity. Given the high mortality of patients with brain metastases and the considerable treatment-associated morbidity, a need remains for an imaging modality that accurately differentiates recurrence from treatment-related changes. Accurate imaging is key to preventing unnecessary surgery or changes in effective therapy in patients mistaken for disease progression as well as prevent continuation of ineffective therapy if radiation necrosis is incorrectly diagnosed. To this end, 18F-fluciclovine is a synthetic amino acid-based PET imaging agent that has potential to evaluate primary and metastatic brain cancers owing to its low normal background uptake in the brain and increased uptake in brain tumours.

Methods: NCT04410367 is a prospective, open-label, single-arm, single-dose (185 MBq ± 20%) study with a primary objective to establish visual image interpretation criteria for 18F-fluciclovine PET studies of recurrent brain metastases. Up to 40 subjects with solid tumour brain metastases who have undergone radiation therapy will be enrolled across ~10 US sites if they have a reference lesion considered equivocal on MRI for recurrent disease and are planned for craniotomy. Subjects will undergo 18F-fluciclovine PET <42 days after the MRI and 1–21 days before planned craniotomy. Outcome measures comprise the diagnostic performance of 18F-fluciclovine PET at different thresholds of 18F-fluciclovine uptake compared with histopathology, subject- and lesion-level diagnostic performance based on established image interpretation criteria, and safety evaluations. Enrolment began in August 2020 and the trial is open at the time of submission.

Keywords : 18F-Fluciclovine, PET, Recurrent; Brain Metastases; Radiation Therapy

POSTER 4 - CATEGORY: CNS METASTASES

Drug repurposing candidates in the treatment of brain metastases

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Background

Treatment of brain metastases (BM) remains a clinical challenge. Surgery, radiotherapy, and chemotherapy are widely used with targeted therapies and immunotherapies emerging in specific tumors. These drugs impose a major financial burden on health systems in high income countries and remain unaffordable in many low and middle-income countries. Drug repurposing is an alternative development pathway that seeks to reuse existing medications, including non-cancer medications, as a source of new treatment options with limited costs. We aimed to identify non-cancer drugs with supportive evidence to be developed in the treatment of BM.

Materials and methods

A literature-based approach was undertaken to identify non-cancer drugs supported by pre-clinical or clinical evidence for repurposing in BM. Using the 336 drugs listed in the Repurposing Drugs in Oncology (ReDO) database (https://www.anticancerfund.org/en/redo-db), a PubMed query and a clinicaltrials.gov query were performed in June 2021. Drugs with at least one peer-reviewed article reporting an effect against BM (in vitro, in vivo or in humans), or one registered trial to treat BM were considered.

Results

We reviewed 435 abstracts. Out of the 336 initial drugs, 61 (18%) drugs had at least one relevant abstract, and 15 (4%) drugs are or have been tested in BM trials. Based on the quality of the (pre-) clinical and biological evidence, we selected 10 drugs for further consideration in BM research (Table, see att.). No ongoing clinical trials were identified for any of these 10 drugs.

Conclusions

The number of drugs that could be repurposed in BM is not negligible. Several candidates are good candidates for a clinical translation in BM from different tumor types either as single agent or with current standard treatments. In addition, using repurposed drugs to reduce the risk of developing BM represents a field worthy of further exploration.

POSTER 5 - CATEGORY: CNS METASTASES

Incidence and Risk Factor Analysis of Melanoma's Metastatic Disease in the Central Nervous System: a Single Center Retrospective Study

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Background
Melanoma is one the most common tumor that leads to metastatic disease in the central nervous system (CNS). There is not enough evidence in the literature about the real incidence of melanoma's metastatic disease in the CNS in highly melanoma prevalent areas.

Aim
The aim of the present work is to determine the incidence of CNS melanoma's metastatic disease in a subtropical region (Canary Islands, Spain) with high prevalence of melanoma. Additionally, we aim to analyze the possible risk factors associated with the development of CNS metastases.

Methods
A retrospective analysis in a patient cohort with diagnosis of primary melanoma (including superficial melanoma) between January 2013 and May 2016 has been performed. The indicated period was selected to have a minimum follow-up period of five years. Data was extracted from clinical records and non-parametric statistical tests were used to compare patients with and without CNS involvement. Survival analysis was also performed using COX regression analysis, Kaplan-Meier curves and the Log-Rank test.

Conclusion
The incidence of CNS metastases secondary to melanoma in a highly-prevalence region is approximately 4%. The main risk factors associated with melanoma´s CNS metastatic disease were the related with the local and systemic aggressiveness of the disease. The presence of CNS metastases is associated with a worse overall survival.

Keywords : Melanoma; central nervous system; metastasis

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POSTER 6 - CATEGORY: CNS METASTASES

Analysis of the incidence and risk factors for central nervous system metastatic disease in lung cancer: a single center retrospective study

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Background: Lung cancer (LC) is the second most common malignancy and the leading cause of cancer death worldwide. It is one of the most common cancers to metastasize to the central nervous system (CNS). However, CNS imaging is not always included in staging and/or follow-up studies.

Aim: To determine the incidence of CNS metastasis in LC and to identify tumor-specific factors associated with an increased risk of developing CNS metastasis.

Methods: A retrospective analysis in a patient cohort with diagnosis of primary lung cancer (including small cell and non-small cell lung cancer) between January 2015 to December 2018 has been performed. The indicated period was selected to have a minimum follow-up period of two years. Data was extracted from clinical records and non-parametric statistical tests were used to compare patients with and without CNS involvement. Survival analysis was also performed using COX regression analysis, Kaplan-Meier curves and the Log-Rank test.

Conclusion: The incidence of CNS metastases secondary to Lung cancer in a highly-prevalence is approximately 20%. The greatest risk has been identified in young patients with small cell carcinoma. The presence of CNS metastases is associated with a worse overall survival.

Keywords : lung cancer, brain metastasis, CNS

POSTER 7 - CATEGORY: CNS METASTASES

Epidemiological profile and therapeutic results of brain metastases after encephalic radiotherapy in toto

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Introduction : Brain metastases are considered to be the most common malignant brain tumors in adults, and constitute a major challenge in oncology. The objective of our study is to analyze the epidemiological, clinical and paraclinical parameters of patients with brain metastases and treated by encephalic radiotherapy during the year 2020 at the Mohamed VI center of the Ibn Rochd CHU.

Patients and methods :
This is a descriptive retrospective study of 57 patients treated for brain metastases by brain radiotherapy in toto over a period of one year from January 2020 to December 2020 at the Mohamed VI center for the treatment of cancers. . Data was collected using a form duly completed from patient files.

Results : The median age was 54 years with extremes ranging from 33 to 79 years, a female predominance was noted with a sex ratio of 1.11. The evaluation of the general condition made it possible to classify the patients of performance index status ‘1’ in 75.4% of cases.
70.2% of cases had multiple brain metastases, 28% of cases had a single metastasis and 2 cases had three brain lesions. The primary was of bronchopulmonary origin in 57.9% of cases, of mammary origin in 38.6% of cases, and of renal origin in 2 cases. The discovery of brain metastases was synchronous with that of the primary in 49% of cases and metachronous in the rest of the cases.
Most patients showed signs of brain extension at the time of diagnosis. 35% of the patients suffered from a neurological deficit and 47.4% from an intracranial hypertension syndrome. However, the discovery of secondary cerebral localization was fortuitous in 10 cases. +
All patients underwent 3D conformational radiotherapy of the brain in toto with a dose of 30 Gy in 10 fractions in 15.8% of cases, 20 Gy in 4 to 5 fractions in 79% of cases and 16 Gy in 4 fractions in 3 cases. An additional boost of 3 * 3 Gy was received in 4 patients. However, surgical excision before radiotherapy was only performed in 5 cases.
All symptomatic patients were put on corticosteroid therapy initially by the injectable route for three days then relayed by the oral route.
At the evaluation ; 54.4% of patients improved their quality of life with a recovery of their autonomy and an improvement in verbal fluency. 19.3% of cases had a complete response without local recurrence. 15.7% of cases worsened their neurological symptoms and 10.5% of patients were lost to follow-up after the end of brain radiation therapy.
The median survival time was 5.2 months, that of recurrence-free survival of the five operated

patients was 7.8 months.

Conclusion : The characteristics of cerebral metastases and the type of primary cancer are an important determinant for the prognosis ; therapeutic management must take into account the predictive criteria for local control ; and the early detection of this pejorative localization.

Keywords : Brain metastases, encephalic radiotherapy in toto, Epidemiology

POSTER 8 - CATEGORY: PRECLINICAL RESEARCH IN BRAIN METASTASES

Preclinical evaluation of CDK4/6 inhibitor GLR2007 in glioblastoma models

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Introduction and objectives: Glioblastoma multiforme (GBM) is characterized by dysregulation of the cyclin-dependent kinase (CDK)4 and CDK6 pathway, which leads to over-proliferation of tumor cells. CDK4/6 inhibitors abemaciclib, palbociclib, ribociclib, and trilaciclib are approved for treatment of breast cancer or small cell lung cancer, but poor blood–brain barrier (BBB) penetration may limit their efficacy in GBM. GLR2007 is an investigational CDK4/6 inhibitor with the potential for improved penetration across the BBB. These preclinical studies investigated the anti-tumor efficacy in GBM xenograft models and central nervous system distribution of GLR2007.

Methods: Three in vitro assays were used to assess the activity of GLR2007. Inhibition of CDK4/6 enzymatic activity by GLR2007 or palbociclib was calculated. The effect on cell cycle progression was analyzed in U87 MG cells treated with vehicle control or GLR2007 for 24 h. Cell viability was evaluated in U87 MG and U118 MG cell lines after culture for 72 h with GLR2007. In vivo evaluation of the anti-tumor efficacy of GLR2007 versus vehicle, abemaciclib, and/or palbociclib was performed in BALB/c nude mouse GBM xenograft models. Quantitative whole-body autoradiography was used to determine the distribution of [14C]GLR2007 in the tissues of Sprague Dawley rats.

Results: GLR2007 potency toward CDK4 and CDK6 was 33.1 and 3.8 times that of palbociclib, respectively. At concentrations >13.72 nM, GLR2007 induced G1 arrest of U87-MG cells. GLR2007 inhibited proliferation in U87-MG cells (half maximal inhibitory concentration [IC50] 15.6±2.4 nM) and U118-MG cells (IC50 23.2±5.2 nM). Anti-tumor efficacy of GLR2007 versus vehicle control was observed in two mouse GBM xenograft models, expressed as tumor growth inhibition (TGI; change in mean tumor volume from baseline as a percentage of change in vehicle group) or increased survival time. Following 21 days of treatment, TGI in BN2289 subcutaneous xenografts was 39.4% and 56.4% for the 25 mg/kg and 50 mg/kg GLR2007 groups, respectively, 34.0% for 25 mg/kg palbociclib, and 24.9% for 25 mg/kg abemaciclib ($P<0.001$ in all groups vs vehicle control). In U87-luc orthotopic xenografts, compared with vehicle controls, median survival time was 50.0% ($P=0.0009$) longer in the 12.5 mg/kg GLR2007 group, similar to the 150 mg/kg abemaciclib group (54.4%, $P=0.0002$), and was 182.6% ($P<0.0001$) longer in mice treated with 50 mg/kg GLR2007. Studies performed in rats demonstrated the distribution of [14C]GLR2007 in whole brain tissue following a single oral dose, with total radioactivity levels in the brain exceeding those in plasma by 2.3–4.5-fold from 2–6 h after dosing.

Conclusions: These preclinical studies suggest the potential of GLR2007 for the treatment of GBM, supported by evidence that GLR2007 showed numerically greater anti-tumor efficacy than approved CDK4/6 inhibitors palbociclib and abemaciclib in GBM xenograft models, and evidence of substantial central nervous system distribution.

Keywords : Glioblastoma multiforme, CDK4/6 inhibitors, Blood–brain barrier penetration

The median survival time was 5.2 months, that of recurrence-free survival of the five operated

POSTER 9 - CATEGORY: RADIATION ONCOLOGY

Trial in Progress: A Multicentre Phase 3 Study to Establish the Diagnostic Performance of 18F-Fluciclovine PET in Detecting Recurrent Brain Metastases after Radiation Therapy (REVELATE)

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Background: Brain metastases occur in up to 40% of patients with cancer and are associated with poor prognosis and considerable levels of recurrence. Consequently, close follow-up with serial brain MRI is performed post-treatment to monitor for recurrent disease. Although conventional MRI (CE-T1-weighted and FLAIR/T2-weighted) is the recommended follow-up modality, it has poor specificity with limited ability to differentiate between true disease recurrence and treatment-related changes such as radiation necrosis. Therefore, alternative imaging options are sought in order to help physicians confidently diagnose treatment-related changes and thus reliably stratify the risk of continuation of a therapeutic regimen, especially given the morbidity associated with current treatments. Amino acid PET imaging agent, 18F-fluciclovine, has increased uptake in brain tumours relative to normal tissue and may be useful for detecting recurrent brain metastases.

Methods: NCT04410133 is a prospective, open-label, single-arm, single-dose (185 MBq ±20%) study with a primary objective to confirm the diagnostic performance of 18F-fluciclovine PET (read with conventional MRI for anatomical reference) for detection of recurrent brain metastases where MRI is equivocal.
Approximately 150 subjects with solid tumour brain metastases who have undergone radiation therapy will be enrolled in this multicentre trial (~18 US sites) if they have a lesion considered equivocal on MRI that requires further confirmatory diagnostic procedures such as biopsy/neurosurgical intervention or clinical follow-up. Subjects will undergo 18F-fluciclovine PET <42 days after the equivocal MRI and 1–21 days pre-biopsy/neurosurgical intervention. Clinical follow-up will occur for 6m post-18F-fluciclovine PET. Secondary objectives include evaluation of subject- and lesion-level 18F-fluciclovine negative and positive percent agreement (equivalent to specificity and sensitivity respectively) for recurrent brain metastases, inter-reader and intra-reader agreement, and safety evaluations. Enrolment began in October 2020 and the trial is open at the time of submission.

Keywords : 18F-Fluciclovine, PET, Recurrent; Brain Metastases; Radiation Therapy

POSTER 10 - CATEGORY: RADIATION ONCOLOGY

Radiotherapy for Brain Mets: Comparing Stereotactic Radiosurgery to Whole Brain Radiotherapy

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Background: New targeted cancer therapies extend patient survival by better tumor control, however a concurrent increase is seen in the number of brain metastases (BM). Radiotherapy is the standard of care for BM, and technological advances allow Stereotactic Radiosurgery (SRS) even in multiple metastases (>4) instead of Whole Brain Radio Therapy (WBRT). While SRS is considered more efficacious and less toxic then WBRT for limited number of BM, only a few comparisons were published for patients with multiple BM. This retrospective analysis compares benefits and toxicity of SRS vs. WBRT in patients with multiple BM.

Methods: We examined radiotherapy plans of 49 patients with multiple brain lesions (>4 lesions, Median 8, inter-quartile range 6) who were treated with SRS (28 patients) or WBRT (21 patients) in Sheba Medical Center between 2010-2018. We reviewed patients' electronic medical records and MRI scans to compare local and distant brain control and used dose to the hippocampi as a surrogate measure for cognitive toxicity.

Results: The patients suffered from NSCLC (n=23) melanoma (n=17), Breast cancer (n=8) and carcinoma of cervix (n=1); average age was 60 (+/- 11.3) and 31/49 patients were females (63.3%). Most patients received systemic treatment when the BM appeared (86%). The metastases cumulative volume was greater in the WBRT than the SRS group (median 9.8cc vs 3.68cc). As expected, response rate was better in the SRS group when comparing SRS / WBRT groups for proportion of complete response (CR) 58% / 24%, partial response (PR) 14% / 4% and stable disease (SD): 3% / 24%. Time to local progression (TTLP) was longer in the SRS group (n.s.) but the time to distant brain progression (TTDP) was significantly greater in the WBRT group (9m vs. 3m regardless of the number or volume of BM, p value= 0.005). Surprisingly, the Median survival (MS) of the WBRT group was significantly longer than the SRS group (10m vs 7m p value=0.046). Regarding treatment toxicity, the bioequivalent dose to the hipocampii was much lower in the SRS group (3.5Gy which is considered safe). Further, when examining steroids use in the two groups, the SRS group used a lower dosage (Median 4 mg vs. 7.3 mg), and for a shorter duration (1 month vs. 7 months). Finally, we found no correlation between primary disease and radiotherapy treatment outcome (TTLP, TTDP, and overall survival).

Conclusion: In patients with multiple brain lesions (4 lesions or more), SRS treatment was better than the WBRT treatment when considering local control, and toxicity as measured by hippocampii exposure to radiation and steroid use. On the other hand, patients in the WBRT group lived longer and had longer TTDP. The main limitation of this study was a difference between the groups in the year of treatment (WBRT was given in earlier years), while a major advantage of this study is that clinical and imaging follow-up continued until patients succumbed to illness.

Keywords : WBRT, SRS, brain metastases, radiation therapy

POSTER 11 - CATEGORY: RADIATION ONCOLOGY

Factors associated with short survival after whole brain radiotherapy for brain metastases in 2140 patients with non-small cell lung cancer

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Background
Brain metastases (BM) occur in about 30 % of non-small cell lung cancer (NSCLC) patients. For the majority of these patients, radiotherapy (RT) is the most applied treatment, either whole brain radiotherapy (WBRT) or stereotactic radiotherapy (SRT). The benefit of WBRT in lung cancer BM treatment is debated and there is a concern that many patients receive WBRT with short survival after treatment, risking adverse side-effects and having less time at home near end-of life. We aimed to identify factors predicting short survival after WBRT in order to aid clinicians and patients in treatment decision making.

Material and methods
We reviewed treatment and medical records of 2140 NSCLC patients treated with RT (WBRT or SRT) as initial treatment for BM in our health care region (57% of the Norwegian population) from 2006 through 2018. Complete medial data were available for the 1496 patients treated at Oslo University Hospital, the largest referral center for RT. Patients who died within 30 days after start of RT were compared to patients living >1 year.

Results
In the entire group (N=2140), median age was 65 year (51% women), with 4% being alive at last follow-up (June 2020, median follow-up time: 49 months (13-167)). 1705/2140 (80%) patients received WBRT as initial treatment, most received 3 Gy x 10 Gy (68%), but the use of 4 Gy x5 increased during the study period.
Median overall survival (mOS) for all 2140 patients was 3 months (2.8-3.2), 3 months in the WBRT group (2.8-3.2) and 7 months (5.7-8.3) in the SRT group (n=435/20%). Seventeen percent of the WBRT patients died within 30 days after start of RT (50% within 90 days); 15% were alive >1 year. Of 1073 WBRT patients with complete medical data who died within 30 days (N=191/1073), 79 % were age >60, 85% had extra-cerebral metastases (ECM), 66% had KPS<70 and 80% had diagnosis specific Graded Prognostic Assessment (DS-GPA) score ≤ 1.0. In patients living >1 year (N=160/1073), 60 % were age <60, 50% had ECM, 26% had KPS<70 and 26% DS-GPA score ≤ 1.0.

Conclusions
Survival times after WBRT is generally poor, but with considerable variation. Therefore, the use of WBRT should be carefully considered individually for each patient. ECM present and KPS<70 were associated with poor prognosis; correspondingly, low DS-GPA was confirmed associated with short survival. Thus, our review confirms that low DS-GPA score may guide the clinicians in decision-making regarding which patients will not benefit from WBRT in terms of OS.

Keywords : Non-small cell lung cancer (NSCLC), brain metastases, whole-brain radiotherapy, survival

POSTER 12 - CATEGORY: RADIATION ONCOLOGY

Development and evaluation of an automated organ at risk contouring atlas in the brain on MRI

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Introduction/objectives:
With modern radiotherapy techniques, organ at risk (OAR) dose can be actively minimized during treatment planning for irradiation of patients with brain tumors or metastases. Therefore, accurate delineation of OARs contributes to avoidance of toxicity. Recently, a European consensus was published of OAR delineation in the brain[1]. Contouring of 34 OARs is time-consuming and automated software tools are available in treatment planning systems (TPS). We developed an automated OAR atlas in our TPS and evaluated its clinical performance compared to manual delineation.

Methods:
Anonymized cerebral MRI scans (0.9x0.9x0.9mm3) of 50 patients undergoing radiotherapy treatment were available. OARs were manually contoured in our TPS (RayStation®) according to the European Particle Therapy Network (EPTN) consensus.1 These OARs were checked by a radiation oncologist. 20 MRI-scans with delineated OARs were used to develop the first version of an automated atlas in RayStation. 50 MRI-scans were used to develop the second version of the atlas. The atlas was applied to the first 20 MRI-scans for evaluation. Two radiation oncologists independently evaluated if adjustments were required for each OAR in the atlas and counted the MRI slices which required adjustments. Spatial overlap between the manual and automated contours was determined by calculating Dice similarity coefficient. Volume difference between the automated and manual contours was also calculated. The radiation oncologists were asked for time required to contour the 34 OARs manually and to adjust the automated OARs for clinical use.

Results:
In the first version of the atlas, adjustments were required in >15% of MRI slices for 7 out of 34 OARs. In the second version, adjustments were required in >15% of MRI slices for only 3 out of these 7 OARs. The seven OARs which required the most adjustments are shown in table 1. For the other 27 OARs, adjustments were required in 4% and 3% of MRI slices in the first and second versions, respectively. Dice similarity coefficient for the second version of the atlas and mean volume difference per OAR are presented in table 1. The outcome of the query from the radiation oncologists was that a significant amount of time was saved as a result of the automated OAR contours with manual fine-tuning compared to manual OAR contouring (approximately 15 minutes per patient versus 90 minutes per patient, respectively).

Conclusion/discussion:
Automated OAR delineation on MRI by the TPS makes OAR contouring according to the EPTN consensus clinically feasible in terms of quality and time. Most OARs are accurately delineated with only a few structures still needing frequent manual adjustments. Improvements were seen after the number of MRI-scans used for the development of the atlas had been increased from 20 to 50. For clinical use, verifying and adjusting of OARs by a radiation oncologist remains necessary. Automated OAR delineation is also relevant in the setting of randomized trials to avoid inter-observer variability and to correlate OAR dose with observed toxicity. In the future, more patients will be included to further improve the accuracy of automated OAR delineation.

Keywords : Brain neoplasms, Organs at risk, Auto-segmentation, Computer-assisted radiotherapy planning, Magnetic Resonance Imaging

References : Eekers, D. B., in ‘t Ven, L., Roelofs, E et al. Radiotherapy and Oncology, 128(1), 37–43. https://doi.org/10.1016/j.radonc.2017.12.013

POSTER 13 - CATEGORY: RADIATION ONCOLOGY

Whole brain radiotherapy for melanoma brain metastases -which patients are likely to live less than three months after treatment?

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Introduction and objectives
The value of whole brain radiotherapy in patients with brain metastases and short expected survival is controversial. Cancer patients with ≤3 months expected overall survival (OS) are generally considered to be unfit for further tumor-directed treatments. Brain metastases are frequent in patients with melanoma, and in many cases these patients are unsuited for surgery, stereotactic radiotherapy or systemic treatments. Thus, WBRT may be the only tumor-directed treatment option. To aid treatment decision making in whether to treat with WBRT or not, it is therefore important to identify factors associated with short survival (i.e. ≤3 months) in patients with melanoma brain metastases (MBM). We aimed to identify factors associated with short (≤3 months) and longer (>6 months) survival after WBRT for MBM, including the diagnosis-specific graded prognostic assessment (DS-GPA).

Methods
We identified 294 patients treated with WBRT as first radiotherapy modality for MBM from 2011-2017 at two radiotherapy units. Treatment data for all patients and clinical data for 241 patients were reviewed. We calculated OS from start of WBRT for all 294 patients; factors associated with survival were analyzed for 241 patients with available clinical data. Clinical factors at start of radiotherapy were compared for patients with short OS (≤3 months, N=131) and longer OS (>6 months, N=66) after start of WBRT in a cross-table 2x2 analysis using the Chi-square test.

Results
For the 294 patients (65% male, median age 67 years [27-94]), median OS was 2.8 months. 8 patients were alive at Aug 1st 2021 (median follow-up 75.8 months).161/294 (55%) lived <3 months after start of WBRT (22% <1 month); 77/294 (26%) lived >6 months (14% > 1 year). Compared to patients with OS >6 months, patients with OS ≤3 months were more likely to have age ≥70 (82% vs. 55%), ECOG status >1 (89% vs. 52%), ECM present (68% vs. 39%), BRAF negative or unknown status (74% vs. 52%) and DS-GPA 0-1 (89% vs. 34%).

Discussion/conclusions
Age ≥70, ECOG status >1, presence of extracranial metastases, BRAF negative or unknown status and, correspondingly, DS-GPA score 0-1 were identified as factors associated with survival ≤3 months after WBRT in patients with MBM. In patients with these factors, WBRT should be carefully considered, and most likely be omitted, as these patients may have little benefit in terms of OS, risking burdensome side-effects and less time at home at the end of life. As prognostic factors included in melanoma DS-GPA are age, BRAF status, performance status, number of BMs and presence or absence of extracranial metastases, DS-GPA was confirmed as a prognostic tool useful in WBRT treatment decision making.

Keywords : Melanoma, WBRT, survival

POSTER 14 - CATEGORY: RADIATION ONCOLOGY

Long-term multidimensional assessment of fatigue in patients with brain metastases after Gamma Knife radiosurgery; a study update

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BACKGROUND
In our previous study on fatigue in patients with brain metastases (BM) after Gamma Knife radiosurgery (GKRS), patients' general and physical fatigue increased over 6 months, while mental fatigue decreased during this period. The aim of the current study is to assess longer-term multidimensional fatigue in patients with brain metastases up to 21 months after GKRS.

MATERIAL & METHODS
92 patients with 1 to 10 BM, expected survival >3 months, and Karnofsky Performance Status ≥70 were included. General fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation were measured with the Multidimensional Fatigue Inventory (MFI) before GKRS and every 3 months thereafter up to 21 months. Levels of fatigue between patients and controls at pre-GKRS, 6, 12, and 21 months were compared using independent-samples t-tests. Linear mixed models were used to evaluate the long-term course of fatigue in patients with BM up to 21 months after GKRS (within-group analyses). Additionally, linear mixed models were used to examine differences in fatigue between three time-intervals: pre-GKRS and 6 months, 6 and 12 months, and 12 and 21 months.

RESULTS
Patients with BM experienced significantly higher levels of fatigue on all subscales at pre-GKRS (n=92), 6 (n=53), and 12 months (n=34) after GKRS compared to Dutch controls ($p \leq .007$). At 21 months (n=21), patients experienced significantly higher levels of fatigue for general and physical fatigue but not for mental fatigue, reduced activity, and reduced motivation. Over 21 months, levels of physical fatigue increased significantly, and levels of mental fatigue decreased significantly. Between pretreatment and 6 months, there was a significant increase in levels of physical fatigue, followed by stable fatigue scores between 6 and 12 months and 12 and 21 months. No significant differences between intervals were found for the other fatigue scales.

CONCLUSIONS Results indicate that also in the long term, fatigue is a persistent problem in patients with BM. Except for a decrease in mental fatigue up to 21 months and an increase in physical fatigue up to 6 months, other dimensions of fatigue remained stable up to 21 months after GKRS.

Keywords : Brain metastases, Cancer, Fatigue, Multidimensional Fatigue Inventory, Patient reported outcomes, Radiosurgery
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POSTER 15 - CATEGORY: RADIATION ONCOLOGY

A novel spatiotemporal fractionation concept for irradiating multiple brain metastases

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Background/Purpose: Stereotactic radiosurgery is an established treatment option for brain metastases. While small lesions are safely and effectively treated in a single fraction, larger metastases or metastases located close to critical structures are temporally fractionated to reduce radiation-induced toxicities in the normal brain. In this work, we propose a novel spatiotemporal fractionation (STF) concept that reduces the integral biological dose to the normal brain by optimizing the fractionation scheme of each individual lesion depending on its size and its relative location with respect to the other metastases.

Materials and methods: The proposed approach allows for irradiating different metastases with possibly different doses at every fraction. The optimal fractionation scheme is determined in a biologically effective dose (BED)-based treatment plan optimization process developed inhouse. The method optimizes the dose contribution of each fraction to every metastasis, with the goal of minimizing the integral BED2 in the normal brain, while delivering the prescribed tumor BED10 and constraining the brain volume exposed to BED2 higher than 60 Gy (corresponding to a physical dose of 10 Gy in a single fraction).
The potential benefits of the spatiotemporal fractionation scheme are evaluated for 3 clinical cases each with a large number (> 25) of brain metastases. For each patient, a 3-fraction non-coplanar intensity modulated radiotherapy plan is generated with the proposed fractionation optimization approach and compared to a uniformly fractionated plan delivering the same dose to all metastases in every fraction.

Results: For the same BED10 delivered to the tumor and the same brain volume exposed to high BED2 in both plans, the mean BED2 to the healthy brain can be reduced by 7-9% with the STF plan compared to the uniformly fractionated plan. Exemplary dose distributions for one of the patients are shown in Figure 1 (see supplementary material) for the 2 different plans, while Figure 2 reports their differences in the cumulative physical dose and BED distribution. In the STF plan, small metastases are treated to a high single-fraction dose in alternate fractions. Thereby, the total physical dose can be reduced. Because a good degree of fractionation can nevertheless be achieved in the brain region in between two lesions treated on separate days, this yields a net BED2 reduction in the normal brain. In contrast, larger metastases are treated with similar doses in all fractions, in order to fulfill the dose volume constraint for the brain in the high dose region. This is shown in Figure 3, which plots the maximum fractional dose contribution to each metastasis depending on the size of the lesions.

Conclusion: Conventional fractionation schemes are restricted to treat all metastases to the same dose in every fraction, regardless of their size and location. We demonstrated that improvements can be made by jointly optimizing the fractionation scheme for all metastases based on the cumulative BED2 distribution in the brain, while allowing the fractionation scheme for the individual metastases to be flexible.

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Keywords : Multiple brain metastases, Stereotactic radiosurgery, Spatiotemporal fractionation

POSTER 16 - CATEGORY: RADIATION ONCOLOGY

Brain metastasis velocity can reliably predict overall survival and future prognostic scores in patients treated with intracranial stereotactic radiotherapy

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Introduction
Brain metastasis velocity (cBMV), a novel prognostic parameter taking brain metastases (BM) occurrence dynamics into account, was proposed in 2017. It is calculated as the cumulative number of new BMs after initial stereotactic radiotherapy (SRT) per year. cBMV was quickly picked up in literature and modified using initial number of BMs per year since primary diagnosis (iBMV) and cumulative volume of new metastases since initial SRT per year (vBMV). iBMV and cBMV (but not vBMV) were subsequently externally validated. The literature on BMV metrics has significant limitations, and no paper has yet validated all three parameters simultaneously. The aim of our study was to validate all three scores in a uniform patient cohort treated for BMs with SRT, as well as analyzing if BMV metrics calculated at different times in the patient's management journey can predict future BMV.

Material/Methods
We retrospectively evaluated medical records of 512 patients with BM disease receiving SRT between January 2014 and December 2018. 384 patients met the inclusion criteria. iBMV, cBMV, and vBMV were calculated for 283, 187 and 104 patients respectively. Patient numbers for cBMV and vBMV were lower as patients without distant brain failure could not be included.
Kaplan-Meier survival curves were used to compare overall survival. An attempt to validate all three BMV metrics was made for each metric as a categorical variable using Kaplan-Meier estimators with long-rank tests, and as a continuous variable with cox regression. Furthermore, vBMV and cBMV were recalculated at every time of new distant brain failure. Linear and logistic regression were used to assess the predictive power between different BMVs. A p-value <0.05 was considered significant.

Results
After a median follow up of 14 months (interquartile range: 5–31). 183 patients received a minimum of two treatments and 33 at least three treatments (range: 1–7 courses). cBMV could be validated on a cohort of 187 patients both as a categorical ($p<0.0001$) as well as a continuous variable (HR 1.02, 95% CI 1.02-1.03, $p<0.0001$) both after first and second (but not third and fourth) distant brain failure. iBMV could be validated on a cohort of 284 patients when divided into low and high-risk groups ($p=0.0051$) but not as a continuous variable (HR 1.02, 95% CI 0.99-1.04, $p=0.224$). vBMV could not be validated, neither on a cohort of 104 patients with all primaries ($p=0.9$) nor on a cohort of melanoma patients ($n=36$, $p=0.46$). iBMV and cBMV1 reliably predicted cBMV2, and iBMV also predicts cBMV1 risk groups (for all regressions $p<0.0001$).

Conclusion
This study further validates cBMV and iBMV as reliable and dominant predictors of overall survival in patients with BMs from any primary. This is also the first study to date attempting to validate vBMV although for our patient cohort, this metric was not significant. One of the most significant findings, with the potential of great influence on future clinical practice and treatment decisions, is the reliable prediction of progression based on iBMV and cBMV.

Keywords : Brain metastases, brain metastasis velocity, stereotactic radiosurgery

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POSTER 17 - CATEGORY: RADIATION ONCOLOGY

Results of Nano-Rad first in man study: AGuIX nanoparticles as radiosensitizers for radiotherapy

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Background: The occurrence of multiple brain metastases is a critical evolution of many cancers with a major impact on patients' quality of life and overall survival. A new gadolinium-based nanoparticle, AGuIX, has recently demonstrated its efficacy as a radiosensitizer and MRI contrast agent in several preclinical studies. The objective of this first in man study named Nano-Rad (NCT02820454) was to determine the feasibility and tolerance of intravenous injection of AGuIX in combination with radiotherapy.

Methods & Materials: A monocentric, open-label, 3+3 phase I clinical trial design was used to evaluate the maximum tolerated dose of escalating doses of AGuIX nanoparticles (15, 30, 50, 75 and 100 mg/kg) in combination with whole brain radiation therapy (30 Gy, 10 Fr of 3 Gy) for patients with multiple brain metastases from solid tumors. AGuIX was injected intravenously at 100 mg/mL at an infusion flow rate of 1 mL/min. A multiparametric MRI was performed 2 hours after injection to visualize the distribution of AGuIX in brain metastases and surrounding healthy tissues. Radiotherapy was started 4 hours after injection. Secondary objectives were pharmacokinetics, distribution of AGuIX by MRI, intracranial progression-free survival and overall survival. Safety was evaluated using NCI-CTCAE v 4.03 and tumor response was assessed using RECIST 1.1.

Results: The first in human administration was performed on July 2016 and the last patient (n=15) was recruited on February 2018. Median age is 60 [37-79], median number of brain metastases is 24 [4-50].
An efficient metastases targeting (T1 MRI enhancement) and a persistence of AGuIX one week after administration was observed in all metastases, whatever the histological type of primary cancer was (lung, melanoma, breast and colon). The concentration of AGuIX in metastases was proportional to the injected dose and ranged from 20 to 60 mg/L 2 hours after administration. The plasma elimination half-life was similar for each group (mean 1.3h) and mean urinary excretion was 54 % during the first 24 hours. No dose-limiting toxic effects were observed with a dose escalation up to 100 mg/kg and hence, this was the dose selected for further clinical trials. Of the 14 evaluable patients, 13 had a clinical benefit of treatment with either stabilization or reduction of tumor volume. MRI analyses showed significant correlation between contrast enhancement and tumor responses, thus supporting a radiosensitizing effect of AGuIX.

Conclusions: These results are promising in terms of safety, distribution and efficacy of AGuIX with efficient targeting and persistence of the nano-drug into brain metastases of primary tumors with different histological origins. Evidences of radiosensitizing effects should be confirmed by the randomized multicenter phase 2 study started in March 2019 (NCT03818386).

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