OTHR-09. IDENTIFYING EPIDEMIC SIGNATURES IN LUNG ADENOCARCINOMAS THAT PREDICT DEVELOPMENT OF BRAIN METASTASIS

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INTRODUCTION: Metastases are the most common adult brain tumor with half spreading from lung cancers and they reduce median overall survival by 16 months. There are two main patient-specific predictors of brain metastasis, Epigenetic signatures predict disease recurrence in other cancers and identifying brain metastasis methylation-based signatures may allow for treatment approaches to high-risk patients that prevent their development. METHODS: In 207 lung adenocarcinomas, multivariate cox time to brain metastasis analyses including clinically-relevant variables (lung tumor size and TNM nodal score) along with significant covariates on univariate analyses were performed. DNA was extracted from 142 of these tumors and profiled on the Illumina Infinium EPIC array. A general boosted regression classification model used differentially methylated CpG sites significantly predicting time to brain metastasis in a 70% training cohort cox analysis (p<0.05). Resulting methylation-based risk scores were compared to size and nodal status in a multivariate analysis of the independent 30% testing cohort. RESULTS: Of 207 patients with 72 brain metastatic events, tumor size (HR=1.5, 95% CI 1.1–2.0, p=0.011), N status (3 vs. 0, HR=9.9, 95% CI 3.1–31, p=0.0001), EGFR status (HR=0.4, 95% CI 0.2–0.8, p=0.014), and age (HR=0.7, 95% CI 0.5–1.0, p=0.039) independently predicted their development. Multivariate-based risk significantly predicted time to brain metastasis in a univariate analysis of the testing cohort (p=0.03). A multivariate analysis of testing cohort patients identified methylation score as the only independent predictor of brain metastases (HR=4.5, 95% CI 1.3–17, p=0.038) accounting for tumor size and N score. CONCLUSIONS: Genome-wide DNA methylation signatures predict brain metastasis development in lung adenocarcinomas independent of tumor size and nodal disease. The design of a nomogram combining methylation and other clinical factors may be used to determine patient-specific brain metastasis risk scores to guide patient counselling, extent of treatment, and screening.

OTHR-10. THE NATIONAL DISTRIBUTION OF NEWLY-DIAGNOSED BRAIN METASTASES IN ADULTS VARIES WIDELY BY PATIENT DEMOGRAPHICS

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INTRODUCTION: Metastases are oft-cited as comprising approximately half of all adult intracranial neoplasms, and their national composition remains unclear. METHODS: The patient demographics and histologic distribution of newly-diagnosed brain metastasis (BM) patients aged >18yo without a prior history of cancer (2010–2015) were evaluated using the National Cancer Database, which comprises >70% of all newly-diagnosed patients in the U.S. RESULTS: Multivariate analysis yielded a newly-diagnosed BM between 2010–2015. The most common sites of brain metastases overall were lung (82% of metastatic cases), breast (4.1%), melanoma (3.2%), kidney (2.9%), and colorectal (1.8%). The overall 1-year survival was 5.3% (95% CI 5.1%–5.5%), respectively. The distribution of primary sites for newly-diagnosed BMs varied by sex, age, and race. Compared to males, more females had BMs from breast (8.4% versus 0.8%) and fewer had BMs from kidney (1.9% versus 3.8%), melanoma (1.9% versus 4.5%), and esophagus (0.3% versus 2.0%). In young adults, particularly those 20–29yo, BMs were more likely from melanoma, genitourinary (in males), and soft tissue than adults in middle and advanced age. Lung carcinomas comprised fewer BMs in Hispanics (66%) compared to Whites (82%), Blacks (83%), and Asian/Pacific Islanders (85%). BMs from kidney and genitourinary primaries were higher in Hispanics (7.3% and 2.4% of BMs, respectively) than in Whites (2.8% and 0.3%, respectively), Blacks (1.8% and 0.1%, respectively), and Asian/Pacific Islanders (2.6% and 0.2%, respectively). Melanoma was more frequent in Whites (3.8% of BMs) and Hispanics (2.5%) compared to Blacks (0.3%) and Asian/Pacific Islanders (0.6%). CONCLUSIONS: Our results illustrate the national distribution of newly-diagnosed BMs and investigate how the distribution varies by patient demographics.

OTHR-11. TUMOR RELATED IMPAIRMENTS OF NEUROCOGNITIVE FUNCTIONS IN PATIENTS WITH BRAIN METASTASES

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OBJECTIVE: To study whether the neurocognitive functions were affected by brain metastases in patients, and what are the potential risk factors. METHODS: A total of 172 patients with brain metastases were retrospectively analyzed. Prior to radiotherapy of brain metastases, the neurocognitive function was evaluated by a wide range of tests including MOCA, VFT, HVLT-R, TMT-A, TMT-B and TOL. Kappa test was used to analyze the consistency of physical examination and neurocognitive assessments results. The related factors were analyzed by univariate analysis and multivariate analysis. RESULTS: 53 out of 172 patients (30.8%) were identified with cognitive impairments by physical examination. The assessment with neurocognitive scales revealed that there were 148 cases of cognitive impairment (86.0%) and 24 cases of non-cognitive impairment (14.0%). Kappa=0.025, indicating that the difference between neurocognitive assessment results and physical examination was significant. The univariate analysis on the factors related to neurocognitive impairment revealed that the factors that may affect the neurocognitive functions included age, KPS, m-GPA score, RPA classification, whether the original tumor was under control, with or without brain metastases. After adjusting for education, the multivariate analysis showed that age≥45 years old, KPS≤70, RPA classification >2 and m-GPA score ≤3 were independent risk factors for neurocognitive impairment. CONCLUSION: Patients with brain metastases were found to have various degrees of neurocognitive impairment prior to radiotherapy. The neurocognitive functions of patients can be more precisely evaluated by a comprehensive scale assessment. Age, KPS, RPA, and m-GPA score are the main factors associated with neurocognitive impairment.

OTHR-12. DRIVING RECOMMENDATIONS IN PATIENTS WITH NEWLY DIAGNOSED BREAST CANCER BRAIN METASTASES

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BACKGROUND: Approximately 5% of all patients with breast cancer develop breast cancer brain metastases (BCBM). Medical and legal guidance on health conditions associated with driving may vary by state. The paucity of data to guide clinicians’ recommendations on driving in the setting of BCBM prompted this review of clinical practice. The primary objective is to determine the frequency of provider-documented driving recommendations with secondary objectives to define associated clinical factors. METHODS: University of Michigan’s (UM) DataDirect tool retrospectively searched databases dated 10/02/2012 to 11/02/2018 using ICD 9 and 10 codes for breast cancer (C50.910, C50.912, C50.915, C51.091, C51.095, 174.9, 175.9) and for brain metastases (C79.31, D49.6, D43.2, 198.3, 239.6). Eligibility criteria were: age ≥18, BCBM, UM pathologist confirmation of breast cancer, CNS imaging at time of diagnosis performed within 30 days of diagnosis, UM consultation with radiation oncology, neuro-oncology, neuropsychology, or neurology within 4 weeks of BCBM diagnosis. Chart abstraction included clinical and demographic factors for descriptive analysis. RESULTS: Only 87 of the 188 identified subjects (46%) met eligibility criteria. The most common exclusions were non-breast cancer brain lesion (n=40), neither UM imaging nor pathology (n=23) and no intra-parenchymal brain metastases (n=22). Of the 87 eligible subjects, 21 (24%) had documented recommendations against driving. Five of the 7 subjects with documented seizure history within 4 weeks of diagnosis also had documented recommendation against driving. There were several other factors that affected this decision, for example, anti-epileptic drugs of which 13 had documented driving recommendations. CONCLUSIONS: The minority of patients (24%) with newly diagnosed BCBM had a documented recommendation against driving. Seizure activity was strongly associated with driving recommendations. The subjective nature of the effects on anti-epileptic drugs of which 13 had documented driving recommendations. CONCLUSIONS: The minority of patients (24%) with newly diagnosed BCBM had a documented recommendation against driving. Seizure activity was strongly associated with driving recommendations. The subjective nature of the factors related to neurocognitive impairment revealed that the factors that may affect the neurocognitive functions included age, KPS, m-GPA score, RPA classification, whether the original tumor was under control, with or without brain metastases. After adjusting for education, the multivariate analysis showed that age≥45 years old, KPS≤70, RPA classification >2 and m-GPA score ≤3 were independent risk factors for neurocognitive impairment. CONCLUSION: Patients with brain metastases were found to have various degrees of neurocognitive impairment prior to radiotherapy. The neurocognitive functions of patients can be more precisely evaluated by a comprehensive scale assessment. Age, KPS, RPA, and m-GPA score are the main factors associated with neurocognitive impairment.

OTHR-13. A DEEP LEARNING APPROACH TO DETECT CANCER METASTASES TO THE BRAIN IN MRI

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BACKGROUND AND OBJECTIVE: Brain metastases have been found to account for one-fourth of all cancer metastases seen in clinics. Magnetic resonance imaging (MRI) is widely used for detecting brain metastases. Accurate detection of the brain metastases is critical to design radiotherapy to treat the cancer and monitor their progression or response to the therapy and prognosis. However, finding metastases on brain MRI is very challenging as many metastases are small and manifest as objects of weak contrast on the images. In this work we present a deep learning approach integrated with a classification scheme to detect cancer metastases to the brain on MRI. MATERIALS AND METHODS: We respectively extracted 101 metastases images from 10192 slices of images in a total of 336 scans from our PACS and manually marked the lesions on T1-weighted contrast enhanced MRI as the ground-truth. We then randomly separated the cases into training, validation and test sets for developing and optimizing the deep learning neural network. We designed a 2-step computer-aided detection (CAD) pipeline by first applying a fast region-based convolutional neural network method (R-CNN) to sequentially process each slice of an axial brain MRI to find abnormal hyperintensity that may correspond to a brain metastasis and, second, applying a...
random under sampling boost (RUSBoost) classification method to reduce the false positive metastases, RESULTS: The computational pipeline was tested on real brain images. A sensitivity of 97.28% and false positive rate of 2.72% were achieved over the images were achieved by using the proposed method. CONCLUSION: Our results demonstrated the deep learning-based method can detect metastases in very challenging cases and can serve as CAD tool to help radiologists interpret brain MRIs in a time-constrained environment.

OTHR-14. TREATMENT MONITORING OF IMMUNOTHERAPY AND TARGETED THERAPY USING FET PET IN PATIENTS WITH MELANOMA AND LUNG CANCER BRAIN METASTASES: INITIAL EXPERIENCES
Norbert Galldiks, Diana Abdulla, Matthias Scheffler, Viola Schweinsberg, Max Schaak, Nicole Kreuzberg, Jenny Landsberg, Philipp Lohmann, Garry Ceccon, Jan-Michael Werner, Eren Celik, Maximilian Ruge, Martin Kocher, Simone Mannritz, Gereon Fink, Karl-Josef Langen, Juergen Wolf, and Cornelia Mauch

BACKGROUND: Due to the lack of specificity of contrast-enhanced (CE) MRI, both the response assessment and differentiation of progression from pseudoprogression (PsP) following immunotherapy using checkpoint inhibitors (ICI) or targeted therapy (TT) may be challenging, especially when ICI or log-rank tests and Kaplan–Meier plots were constructed. In a separate value of amino acid PET using O-[18F]fluoroethyl-L-tyrosine (FET) as a problem-solving tool in comparison to CE-MRI in patients with brain metastases (BM) secondary to malignant melanoma (MM) and NSCLC. METHODS: Whole-body PET/CT images from 37 patients with 74 BM (20 to MM (n=20 with 42 BM) and NSCLC (n=11 with 32 BM) who underwent FET-PET scans during the course of disease. All patients had RT prior to ICI or TT initiation (61%) or RT concurrent to ICI or TT (39%). In 13 patients, FET-PET was performed for treatment response assessment of ICI or TT using baseline and follow-up scans (median time between scans, 4.2 months). In the remaining 18 patients, FET-PET was used for the differentiation of progression from PsP related to RT plus ICI or TT. All BM, metabolic activity on FET-PET was evaluated by calculation of tumor/brain ratios. FET-PET imaging findings were compared to CE-MRI and correlated to the clinical follow-up or neuropsychological findings after neuroimaging. RESULTS: In 4 of 13 patients (31%), FET-PET provided additional information for treatment response evaluation, where populations to infer clinicopathological-MRI alone were more responsive patients on FET-PET had a median stable clinical follow-up of 10 months. In 10 of 18 patients (56%) with CE-MRI findings suggesting progression, FET-PET detected PsP. In 9 of these 10 patients, PsP was confirmed by a median stable clinical follow-up of 11 months. CONCLUSIONS: FET-PET may add valuable information for treatment monitoring in individual BM patients undergoing RT in combination with ICI or TT.

OTHR-15. PATIENTS WITH LIMITED STAGE SMALL CELL LUNG CANCER THAT RECUR WITH ISOLATED BRAIN METASTASES HAVE PROLONGED SURVIVAL
Bryan Bonder, Fatemeh Ardestir Lanjani, Ashin Dowlati, and Lisa Rogers

INTRODUCTION: Small cell lung cancer (SCLC) frequently metastasizes to the brain. In patients with limited-stage disease (disease confined to one radiation portal), the incidence of brain metastases after 3 years is 50–60%. We reviewed patients with SCLC and hypothesized that isolated brain recurrence has a unique natural history. METHODS: 471 adult SCLC patients seen at University Hospitals Case Medical Center from 1998 to 2014 were screened. Patients were separated by those with isolated brain metastases and those with other patterns of metastasis. Demographic data including age, race, sex, smoking history and clinical data such as TNM classification, stage, treatment, and time to relapse and death were collected. Median overall survival (mOS) and progression free survival (mPFS) were compared using log-rank tests and Kaplan–Meier plots were constructed. A separate cohort of metastatic SCLC we examined differences in next generation sequencing (NGS) of targeted exomes between primary and metastatic sites including the brain. RESULTS: 281 extensive-stage patients and 40 limited-stage patients were included. 12% (30/281) of the extensive-stage patients and 25% (10/40) of limited-stage patients had isolated brain metastases. Patients with limited-stage disease who developed isolated brain metastases had significantly improved mOS as compared to those who developed other sites of recurrence (24.8 months vs. 20.2 months, p = 0.03). In the remaining patients, mPFS for limited-stage patients with isolated brain metastases was improved compared to other patterns of metastases (mPFS = 18.7 months vs. 10.1 months, p = 0.03). NGS demonstrated that NOTCH1 mutations were identified in all metastatic sites but were only detected in primary tumors. CONCLUSION: In our single center review, patients with limited-stage SCLC who recurred only in the brain had improved survival as compared to those who had other patterns of metastases. Our initial work demonstrates differences in oncogenic gene mutations between the metastatic and primary tumors.

OTHR-16. MOLECULAR PROFILING USING THE 92-GENE ASSAY FOR TUMOR CLASSIFICATION OF BRAIN METASTASES
Andrew Brenner, Raul Collazo, Catherine Schmabel, and Anthony Greco

BACKGROUND: Nearly 200,000 patients are diagnosed with brain metastases in the US annually. Advances in targeted therapies make definitive diagnosis of the primary tumor type important but can be challenging in many cases. The 92-gene assay, a validated genetic assay for 50 tumor types for patients with uncertain tissue of origin diagnoses. Results from a clinical series of brain biopsies and potential impact on treatment were evaluated. METHODS: An IRB approved, de-identified database of clinical and molecular information from biopsies (N=486) was used for testing with the 92-gene assay (CancerTYPE ID, Biotheranostics, Inc.) as part of routine care were reviewed. Descriptive analysis included patient demographics and molecular diagnoses. RESULTS: Analysis included 464 brain biopsies. A molecular diagnosis was provided in 433 (93.3%) tested (5% assay failure rate). 24 different tumor types were found, tumor types most made up the majority (67.4%) with almost one-third of the molecular predictions being Lung (31.2%), followed by Neuroendocrine (NET) (9.9%), Sarcoma (7.9%), Skin (6.4%), Gastroesophageal (6.2%), and Urinary bladder (5.8%). All of these 6 tumor types, for which activity in the CNS has been documented, have immune checkpoint inhibitors or other targeted therapies approved in selected cases by the US Federal Drug Administration (FDA). CONCLUSIONS: Molecular classification of brain metastases can identify distinct tumor types for which there are FDA approved targeted medications. Improving diagnostic precision with the 92-gene assay helps identify a subset of therapy-responsive metastatic brain tumors, thus improving therapy and possibly providing better outcomes and survival.

OTHR-17. PHYLOGENETIC RESOLUTION OF TISSUE-SPECIFIC METASTOGENIC CLONES IN RENAL CELL CARCINOMA
Nelson Moss, Samuel Berman, Salvatore Piscuoglio, Charlotte Ng, Pier Selenica, Rahul Kumar, Jorge Reis Filho and Cameron Brennan

Genomic predictors of organ-specific tropism have been established in several cancers. However, the evolutionary dynamics at work in metastatic carcinoma have yet to be characterized in detail. We identified a cohort of clear cell renal cell carcinoma (RCC) patients who also had multiple metastasectomies, and performed deep sequencing and statistical inference of the metastatic populations to infer clinicopathological and essential genomic features acquired prior to systemic dissemination and site-specific colonization. Exome capture and deep sequencing were performed on tissues from 3 patients with polymetastatic RCC (including 12 metastases, multiple regions of primary tumor, and paired germline tissue) to a mean depth of 250x. Somatic point mutations were called with Mutect, and insertions and deletions with Strelka and VarScan. Validation was performed with a custom NimbleGen panel hybridized to a custom sequence library and sequenced to a mean depth of >500x. Allele-specific copy number and clonal prevalence were established using ABSOLUTE, and analyzed with NGS devices across primary and metastatic lesions to determine clonal architecture. Phylogenetic reconstruction identified ancestral clones, with attendant driver mutations in RCC tumor suppressors (including VHL, SETD2, PBRM1, MTOR) and independent subclonal populations in the metastases of all 3 patients. In an index case with multiple metastases separated in the brain and lung, and soft tissue metastases demonstrate apparent independent ancestors. Conserved loss of known tumor suppressors was also noted in all cases, and in several cases found in conjunction with de novo mutations in known RCC driver genes acquired late in tumor development. In this demonstration of subclonal and evolutionary analysis of multiple paired multi-organ RCC metastases, we identified subclonal populations characterized by alteration of several tumor suppressors which subsequently exhibited organ-specific patterns of metastasis.

RADIATION
RADI-01. PROGNOSTIC FACTORS OF SHORT SURVIVAL FOR BRAIN METASTASES TREATED WITH SRS WITHOUT WBRT
Maciej Harat, Maciej Blok, Roman Makarewicz, and Krzysztof Rosekowski

Nowadays multiple brain metastases (up to 10–15 tumors) are treated with SRS alone. The most common diagnosis-specific Graded Prognostic Assessment and Score for Radiosurgery indices are based on data regarding limited brain metastases (1–4). Moreover, many of patients included in that analyses were treated with WBRT. The aim of this study was to evaluate whether some relevant data were not included due to a retrospective analysis of large datasets. SRS may increase intracranial control of disease, however, treatment of patients with a prognosis of fewer than 3 months survival after SRS may not be clinically reliable. Therefore we conducted an analysis of prospective registry to find the factors that could be useful for very short ones: a after SRS.