

C linear and nodular, D normal or hydrocephalus only) presentation. Type I LM is defined by the presence of tumor cells in the cerebrospinal fluid (CSF) (confirmed LM) whereas type II LM is defined by typical clinical and MRI signs (probable or possible LM). Here we explored the clinical utility of these EANO ESMO LM subtypes. **PATIENTS AND METHODS:** We retrospectively assembled data from 254 patients with newly diagnosed LM from different solid tumors, including as main primary tumors breast cancer (n=98, 45%), lung cancer (n=65, 25.5%) and melanoma (n=51, 13.5%). Survival curves were estimated using the Kaplan-Meier method and compared by Log-rank test. **RESULTS:** Median age at LM diagnosis was 56.5 years (range 20–82 years). Typical clinical LM symptoms or signs were noted in 225 patients (88.5%); only 13 patients (5%) were clinically asymptomatic. The most common MRI subtype was A seen in 117 patients (46%). Types B (n=33, 13%), C (n=54, 21%) and D (n=50, 19.5%) were less common. Tumor cells were observed in the CSF in 186 patients (73%) whereas the CSF was equivocal in 24 (9.5%) and negative in 44 (17.5%) patients. Patients with confirmed LM had inferior outcome than patients with probable or possible LM (p=0.0063). Type I patients had inferior outcome than type II patients (p=0.0019). Nodular disease was a negative prognostic factor in type II LM, but not in type I LM (p=0.0138). **CONCLUSION:** The presence of tumor cells in the CSF appears to have a greater prognostic role than the neuroimaging presentation. EANO ESMO LM subtypes are highly prognostic and should be considered in the design of clinical trials.

#### 42. IDENTIFICATION OF BRAIN METASTASIS VULNERABILITIES USING METPLATFORM

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The diagnosis of brain metastasis involves high morbidity and mortality and remains an unmet clinical need in spite of being the most common tumor in the brain. Exclusion of these cancer patients from clinical trials is a major cause of their limited therapeutic options. In this study, we report a novel drug-screening platform (METPlatform) based on organotypic cultures which allows identifying effective anti-metastasis agents in the presence of the organ microenvironment. We have applied this approach to clinically relevant stages of brain metastasis using both experimental models and human tumor tissue (by performing patient-derived organotypic cultures). We identified heat shock protein 90 (HSP90) as a promising therapeutic target for brain metastasis. Debio-0932, a blood-brain barrier permeable HSP90 inhibitor, shows high potency against mouse and human brain metastases from melanoma, lung and breast adenocarcinoma with distinct oncogenic profiles at clinically relevant stages of the disease, including a novel model of local relapse after neurosurgery. Furthermore, we have also used METPlatform to perform unbiased proteomics of brain metastases *in situ*. By applying this analysis to brain metastases treated with the chaperone inhibitor, we uncovered non-canonical clients of HSP90 as potential novel mediators of brain metastasis and actionable mechanisms of resistance driven by autophagy. Combined therapy using HSP90 and autophagy inhibitors showed synergistic effects compared to sublethal concentrations of each monotherapy, demonstrating the potential of METPlatform to design and test rationale combination therapies to target metastasis more effectively. In conclusion, our work validates METPlatform as a potent resource for metastasis research integrating drug-screening and unbiased omic approaches that is fully compatible with human samples and questions the rationale of excluding patients with brain metastasis from clinical trials. We envision that METPlatform will be established as a clinically relevant strategy to personalize the management of metastatic disease in the brain and elsewhere.

#### 43. DELAYS IN ADJUVANT STEREOTACTIC RADIOSURGERY REDUCE LOCAL CONTROL FOR RESECTED BRAIN METASTASES

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**OBJECTIVE:** For resected brain metastases (BM), stereotactic radiosurgery (SRS) is often offered to minimize local recurrence (LR). Although the aim is to deliver SRS within a few weeks of surgery, a variety of socioeconomic, medical, and procedural issues can cause delays. We evaluated the relationship between timing of postoperative SRS and LR.

**METHODS:** We retrospectively identified a consecutive series of BM patients managed with resection and adjuvant SRS, recommended within two weeks of surgery, at our institution from 2012–2018. We assessed the correlation between time to SRS, as well as other demographic, disease, and treatment variables, and LR, distant recurrence (DR), and overall survival (OS). **RESULTS:** 133 patients met inclusion criteria. Median age was 64.5 years. Approximately half of patients had a single BM, and median BM size was 2.9 cm. Gross total resection was achieved in 111 (83.6%) patients, and >90% received fractionated SRS. Median time to adjuvant SRS was 37.0 days and LR rate was 16.4%. The factor most predictive of LR was time from surgery to SRS. Median time from surgery to SRS was 34.0 days for patients without LR, versus 61.0 days for those with LR (p<0.01). LR was 2.3% with SRS administered ≤4 weeks postoperatively, compared to 23.6% if delayed >4 weeks (p<0.01). Local recurrence-free survival (LRFS) was also improved for patients who had SRS at ≤4 weeks (p=0.02). Delayed SRS was also predictive of DR (p=0.02), but not OS. **CONCLUSIONS:** We demonstrate that the strongest predictor of failure of postoperative SRS for BM is the delay to SRS. A cut-off of 4 weeks is a reliable predictor of increased LR. Every effort should be made to perform SRS within 4 weeks of surgery, and if this cannot be achieved, other RT modalities, such as brachytherapy or preoperative SRS, should be strongly considered.

#### 44. EFFECT OF STEREOTACTIC RADIOSURGERY ON NON-SMALL CELL LUNG CANCER BRAIN METASTASIS: CONTINUED CORRELATIVE RADIOBIOLOGIC ANALYSIS OF DNA AND RNA GENOMIC PROFILES FROM PHASE-II CLINICAL TRIAL NCT03398694

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**BACKGROUND:** Stereotactic radiosurgery (SRS) is an increasingly common modality used with or without surgery for the treatment of brain metastases (BM). However, the effects of SRS on tumors *in vivo* is unknown.

**METHODS:** Patients were treated with SRS prior to surgery as per clinical trial NCT03398694. Resected tumor was divided into two groups: 'center' and 'periphery' with respect to SRS treatment. Tissue were analyzed by DNA and RNA sequencing and compared between the two and to non-irradiated tumor. **RESULTS:** DNA analysis showed at the individual level, matched comparison of SRS samples from the center or periphery of the same tumor had mutational burden differences. RNA analysis revealed no differentially expressed genes between center and periphery, but there were 62 and 192 differentially expressed genes between the center or periphery and non-irradiated control, respectively. At an individual level, matched center and periphery tumor had an average of 16641 differentially expressed genes. Comparing total number of up- and downregulated genes with SNP and Indel mutations of matched patient samples, in patients with higher mutational burdens in peripheral tumors as compared to center there was a higher number of upregulated genes. Reciprocally, when mutation burden was higher in center tumor, total number of genes that were either up- or downregulated were about the same. Pooled analysis revealed significant downregulation of oncogenes, such as TP63 and RECQL4, in the SRS group. DO enrichment analysis also revealed pathways related to NSCLC and lung carcinoma significantly altered in radiation cohort. **CONCLUSION:** In summary, this study demonstrates that SRS alters the molecular and genomic profile of NSCLC BM. It results in downregulation of oncogenes and pathways related to lung cancer. Additionally, by sampling the tumor at the center and periphery, there are differential effects of the dose gradient on the cellular and molecular response to ionizing radiation.

#### 45. DELAY OR FAILURE TO ADMINISTER STEREOTACTIC RADIOSURGERY TO THE CAVITY AFTER SURGERY FOR BRAIN METASTASES. AN INTENTION-TO-TREAT ANALYSIS

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**BACKGROUND:** Data regarding the efficacy of adjuvant stereotactic radiosurgery (SRS) for resected brain metastases (BM) is often limited to patients completing SRS within a specified timeframe. We performed an intention-to-treat analysis to determine local recurrence (LR) for all BM patients referred for SRS. **METHODS:** We retrospectively identified resected BM patients referred for SRS between 2012 and 2018. Patients were divided based on delay to SRS into four categories: 1) ≤4 weeks, 2) >4–8 weeks, 3) >8 weeks, and 4) never received. We investigated the relationship between