BSCI-06. FREQUENCY OF BRAIN METASTASIS FROM BREAST AND LUNG CANCER IN THE UNITED STATES – A POPULATION-BASED ASSESSMENT
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BACKGROUND: Brain metastases (BM) are the most common central nervous system tumor in the United States and occur with increasingly frequency due to improved screening and therapeutics leading to improved survival. Current estimates of frequency of BM vary significantly by cancer site and are typically not population-based. Population-based estimates of incidence have recently become possible due to collection of data on BM identified at autopsy, and both breast and lung tumors have been shown to be the most common primary malignancies that eventually metastasize to the brain. METHODS: Data from Surveillance, Epidemiology, and End Results (SEER) 2010-2016 diagnosis were used to estimate BM incidence. For breast cancer, we linked data from SEER-Medicare (2008–2012 diagnoses for individuals 65+)

INTRODUCTION: Brain metastases remain one of the most dreaded consequences of late stage cancer, yet their incidence has risen as survival from primary cancers has improved. We have recently reported that tumors harbored within the brain, specifically, sequenter T-cells within the bone marrow through immune evasion. Sequential loss of tumor-imposed loss of S1PR1 receptor from the T-cell surface. Stabilization of the receptor on T-cells frees T-cells from sequestration and licenses T-cell activating therapies for intracranial tumors. While this phenomenon was initially observed in glioblastoma, its role in promoting immune evasion in brain metastases remains less clear. METHODS: Blood, bone marrow, and tumors were collected from mice bearing intracranial tumors commonly metastatic to the brain, including lung carcinoma (LLC), melanoma (B16F10), or breast carcinoma (E0771) and analyzed by flow cytometry. T-cell S1PI counts were assessed in each compartment. Correlation analyses were conducted between T-cell counts and S1PI levels on T-cells in the bone marrow across intracranial and subcutaneous murine tumors.

RESULTS: T-cell lymphopenia and accompanying accumulation of T-cells in the bone marrow was observed in the murine models of lung carcinoma, melanoma, and breast cancer, but only when these tumor lines were implanted intracranially. Sequestered T-cells in tumor-bearing mice showed decreased surface S1PI levels in a manner correlating with their sequestration. CONCLUSION: S1PI-mediated bone marrow T-cell sequestration is a novel mode of cancer-induced T-cell dysfunction in intracranial tumors. Preventing receptor internalization abrogates T-cell sequestration and licenses T-cell activating therapies in glioblastoma. Sequestration is now observed in models of brain metastases. Pharmacologic strategies to stabilize S1PI, reverse sequestration, and restore circulating T-cell numbers are anticipated to improve immunotherapeutic efficacy for brain metastases.

Blood-brain-bone-tumor barriers (BBB and BTB) and interstitial transport may constitute major obstacles to the transport of therapeutics in brain tumors. In this study, we examined the impact of focused ultrasound (FUS) in combination with microbubbles on the transport of two relevant chemotherapeutic agents. Imaging of experimental data with physiologically based pharmacokinetic (PBPK) modeling suggests that FUS in combination with microbubbles increases the endothelial cell transmembrane transport and uptake. PBPK modeling indicates selective increase in transvascular transport of the non-targeted small chemotherapeutic doxorubicin through small vessel-wall pores size with a narrow range (Diameter: 10-50nm). Our work provides a quantitative framework for the optimization of FUS-drug combinations to maximize intratumoral drug delivery and facilitate the development of novel therapeutic strategies against brain metastases.

BSCI-09. MECHANISMS OF ENHANCED DRUG DELIVERY IN BRAIN METASTASES WITH THE ASSISTANCE OF ULTRASOUND-INDUCED BLOOD-TUMOR BARRIER DISRUPTION
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BACKGROUND: Blood-brain/blood-tumor barriers (BBB and BTB) and interstitial transport of therapeutic chemotherapeutic doxorubicin and the antibody-drug conjugate ado-trastuzumab emtansine (T-DM1). Using an orthotopic xenograft model of HER2-positive breast cancer brain metastasis and quantitative microscopy we demonstrate multi-fold increases in the extravasation of both agents (7-fold and 2-fold for doxorubicin and T-DM1, respectively) and we provide evidence of increased drug penetration (>100μm vs. < 20μm and 42±7μm vs. 12±4μm for doxorubicin and T-DM1, respectively) after application of FUS as compared to control

METHODS: Experiments were performed in nude mice following resection of BM with 22-gauge needle. BM were emulsified and suspended in saline with the ratio of 1:1 (BM:saline) and injected into the tail vein. Presence of BM was confirmed by IVIS. Luminescence imaging was performed weekly following injection. BM were harvested at week 4 post injection. BM mice were treated with EPR (PR) or PR+HER2. CONCLUSION: Frequency of synchronous and period BM varies by originating site as well as subtype. The new BM variable in SEER allows for estimation of this important statistic, while the SEER-Medicare linked data allows for estimation of FUS, both on a population-level for the US population. These estimates are useful to clinical practice and critical for estimating morbidity and mortality due to BM.
Abstracts

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The compression of brain tissue by a tumor mass is believed to be a major cause of the clinical symptoms seen in patients. However, the biological consequences of these physical stresses on the brain tissue are unknown. Using clinical pathological, computational, and functional electrophysiological studies, we characterized a subgroup of primary and metastatic brain tumors, classified as nodular based on the growth pattern, exert compressive solid stress on the surrounding brain tissue, leading to a decrease in local vascular perfusion, as well as neuronal death. We demonstrated a causal link between solid stress and neurological dysfunction, by applying and removing cerebral compression, mimicking the mechanics of tumor growth and surgical resection respectively. Finally, we showed that treatment with lithium reduced solid stress-induced neuronal death and improved motor coordination in mice. Our results indicate that brain tumor-generated solid stress impairs neurological function in patients and show lithium as a potential therapeutic intervention to counter these effects.

BSCI-11. STROMAL PLATELET DERIVED GROWTH FACTOR RECEPTOR-B (PDGFRβ) PROMOTES BREAST CANCER BRAIN METASTASIS

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Stromal platelet-derived growth factor receptor-beta (PDGFRβ) has emerged as an actionable mediator of breast tumor-stromal communication. As a receptor tyrosine kinase, PDGFRβ is activated by its ligand, PDGF-BB, which is released by neighboring tumor epithelium and endothelium. However, how PDGF signaling mediates breast cancer (BC) initiation, progression, and metastasis remains unclear. To evaluate PDGFRβ in this disease, we developed a mouse model of stromal-specific PDGFRβ activation using the Fip-cea transgene previously published by our group. Mesenchymal-specific activation of PDGFRβ promotes preferential experimental breast metastasis of PDGFRβ-expressing mammary tumor cells when injected intravenously and accelerates intracranial tumor growth of these cells. Mammary tumor cells expressing low levels of PDGFRβ do not exhibit a similar increase in brain metastases in PDGFRβ mutant mice. To our knowledge, this is the first example where genetic manipulation of the stroma leads to an increased incidence of BCBM. Our pre-clinical data suggests that primary breast tumors that express high PDGFβ could preferentially metastasize to the brain. The establishment of this preclinical model, which mimics the stroma and tumor microenvironment of breast cancer, allows us to develop novel preclinical models to test the efficacy of current and novel treatments to prevent and treat BCBM metastases.

BSCI-12. COMPREHENSIVE GENOMIC ANALYSIS OF BRAIN METASTASES FROM MULTIPLE CANCER TYPES

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PURPOSE: Brain metastases occur in approximately 5–10% of patients with cancer, and the incidence has increased over the past decades. The most common primary tumors responsible for brain metastases are lung cancer, melanoma, renal cell carcinoma (RCC), breast cancer and colorectal cancer. The heterogeneous mechanisms by which genetically abnormal tumors drive the formation of brain metastases remain unclear. Here, we conducted comprehensive genomic and transcriptional analysis with paired primary tumor tissue (or extracranial metastasis tissue) and brain metastasis tissue using whole-exome sequencing (WES), mRNA-Seq and global methylation profiling. METHODS: Frozen, paired brain metastasis tissue and primary tumor tissue (or extracranial metastasis tissue) and white blood cells were acquired from RCC (n=12), breast cancer (n=17), lung cancer (n=15) and melanoma (n=14) patients, followed by extraction of DNA and RNA. WES and mRNA-Seq were performed on the Illumina HiSeq 4000 platform. For methylation profiling, DNA was analyzed using Illumina Infinium MethylationEPIC Beadchip arrays. RESULTS: Somatic mutations or methylation of VHL gene were identified in 81.8% of RCC patients. Gene Set Enrichment Analysis revealed significant enrichment for hypoxia pathway transcripts in RCC brain metastases relative to primary tumors. The most commonly altered genes in breast and lung cancer patients were TP53 mutations with frequencies of 50.0% and 73.5%, followed by ERBB2 alterations (43.8%) in breast cancer patients and mutually exclusive alterations of EGFR (33.3%) and KRAS (26.7%) in lung cancer patients. Mutually exclusive alterations of NRAS (42.9%) and BRAF (42.9%) in melanoma were also observed in a causative pathway pattern. Gene set and epigenetic analysis revealed characteristics of brain metastases depending on primary cancer types. CONCLUSIONS: Comprehensive genomic analysis of brain metastases from four different cancer types revealed that brain metastases tissues have unique genomic, transcriptional and epigenetic profiles according to histopathology groups. Therefore, the therapeutic strategies should be designed based at least in part on tumor histogenes.

BSCI-13. TUMOR-SPECIFIC TGLI1 TRANSCRIPTION FACTOR MEDIATES BREAST CANCER BRAIN METASTASIS VIA ACTIVATING METASTASIS-INITIATING CANCER STEM CELLS AND ASTROCYTES IN THE BRAIN METASTASES NICHES

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Breast cancer is the second leading cause of brain metastases in women; patients with breast cancer brain metastasis (BCBM) survive only 6–18 months after diagnosis. Mechanisms in breast cancer (BC) brain metastasis (BM) remain unclear and need to be studied in order to design ineffective treatments and dismal prognosis. Truncated glioma-associated oncogene homolog 1 (tGLI1) belongs to the GLI1 family of zinc-finger transcription factors and functions as a tumor-specific gain-of-function mediator of tumor invasion and angiogenesis. Whether tGLI1 plays any role in metastasis of any tumor type remains unknown. Using an experimental breast metastasis mouse model, via intracardiac implantation, we showed that ectopic expression of tGLI1, but not GLI1, promoted preferential metastasis to brain. Conversely, selective tGLI1 knockdown using tGLI1-specific antisense oligonucleotides led to decreased metastasis of intracardially inoculated breast cancer cells. Furthermore, intracranial implantation mouse study revealed tGLI1 enhanced intracranial colonization and growth of breast cancer cells. Immunohistochemical staining of patient samples showed that tGLI1, but not GLI1, was increased in lymph node metastatic primary tumors, and that tGLI1 was expressed at higher levels in BCBM specimens compared to primary tumors. Whether tGLI1 plays any role in radiosensitivity is unknown; we found radiosensitive BCBM cell lines and patient specimens expressed higher levels of tGLI1 than radiosensitive breast cancer stem cells (CSCs) are highly metastatic and radiosensitive, we examined whether tGLI1 promotes BCBM and radiosensitivity through activating CSCs. Results showed that tGLI1 transcriptionally activates stemness genes CD44, Nanog, Sox2, and OCFC4, leading to stem cell activation. Furthermore, we observed that tGLI1-positive CSCs strongly activated and interacted with astrocytes, the most abundant brain tumor microenvironmental cells known to promote tumor growth, in vitro and in vivo. Collectively, our findings establish a novel role of that tGLI1 plays in promoting breast cancer preferential metastasis to brain, radiosensitivity, and astrocytes in the metastatic niche.

BSCI-14. SYNTHETIC METASTATIC BRAIN DISEASE MRI IMAGES CREATED USING A GENERATIVE ADVERSARIAL NETWORK TO OVERCOME DEEP MACHINE LEARNING CHALLENGES IN HEALTHCARE

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Deep Machine Learning (DML) in commercial applications such as recognizing animal species in photographs occurred through analyzing large volumes of public data. To achieve similar success in brain tumor imaging, additional factors must be addressed such as the need to follow strict regulatory protocols, work with limited datasets, and protect patient privacy. Generative adversarial network (GAN) restricted to intracranial disease is one possibility to overcome these challenges and enable training on small annotated datasets with new samples. Large fabricated breast metastases (BM) training datasets derived from patient MRI using GAN models may enable DML of BM MRI studies. METHOD: We randomly selected 82 glioma...