until October 2018. We also searched the Chinese databases Wanfang Data, Wanfang Med Online, China National Knowledge Infrastructure, and Chongqing VIP Information for RCTs published until September 2019. Trials including > 10 patients were selected. The primary outcomes were overall survival (OS) and intracranial progression-free survival (PFS). We used a frequentist random-effects model for network meta-analysis and assessed the certainty of evidence using the GRADE approach. RESULTS: Among 8798 abstracts, 106 RCTs (9452 patients) met inclusion criteria. Median sample size was 67 (range 25–554). All trials included adult patients with histologically proven NSCLC and >1 BM proven on CT/MRI. Of trials that reported performance status (e.g. ECOG or KPS, n=67), 63/67 excluded patients with non-favorable performance status. Interventions assessed included surgery, WBRT, SRS, targeted therapies (i.e. EGFR/ALK inhibitors), and chemotherapy. Compared to WBRT alone, several interventions demonstrated a statistically significant increase in median OS, including non-targeted chemotherapy + surgery (MD: 415.3 days, 95% CI: 31.3–799.4), WBRT + EGFRi (MD: 200.2 days, 95% CI:146.3–254.1), and EGFRi alone (MD: 169.7 days, 95% CI: 49.7–289.7). Among all interventions, only WBRT + EGFRi showed a significant improvement in median PFS (MD: 108.0 days, 95%CI: 48.5–167.5). CONCLUSIONS: Our preliminary analyses indicate an OS and PFS benefit on the addition of EGFR inhibitors to WBRT for the treatment of BMs from NSCLC. Further analyses of hazard ratios for OS/PFS are underway, and subgroup analyses are planned. These data support the growing role of targeted therapies in the treatment of BMs, particularly in susceptible mutant tumours.

61. EXPRESSION OF ANDROGEN RECEPTOR IN BREAST CANCER BRAIN METASTASIS

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INTRODUCTION: Treatment options for women with breast cancer brain metastases (BrM) are generally limited to surgery and/or radiotherapy because most systemic therapies do not cross the blood-brain barrier. Androgen receptors (ARs) are frequently expressed in breast cancer and anti-androgenic therapies have been shown to penetrate the central nervous system. In this study, we analyzed the expression of AR in breast cancer BrM to identify patients who may benefit from anti-androgenic therapies. METHODS: Consecutive BrM resected in our institution (July 1999-June 2013) were identified from the Anatomic Pathology departmental database. Cases that were signed out as breast origin given the available immunohistochemical profile and clinical history were included. A tissue microarray was constructed using 1 mm cores in triplicates and studied by immunohistochemistry for AR, ER, PR and HER2 (SP107, SP1, IE2, 4B5; Ventana Medical Systems, Tucson AZ, USA). HER2 gene amplification was determined by INFORM HER2 DNA and Chromosome 17 (both by Ventana Medical Systems, Tucson AZ, USA). Immunohistochemistry was used as a surrogate to determine intrinsic subtypes. RESULTS: Among 61 breast cancer BrM with available tissue blocks, AR was expressed in 38 (62%) cases. Among BrMs of luminal A subtype (ER+, PR+/-, HER2-, Ki67<16%), 50% expressed AR (n=1/2). Within the luminal B subtype (ER+, PR+/-), all 15 HER2+ BrM expressed AR (100%), while only 50% of HER2- BrM expressed AR (n=8/16). Among 14 BrM of HER2+ subtype (ER-, PR-), 71% expressed AR (n=10/14). Only 30% of triple negative BrM (ER-, PR-, HER2-) were AR+ (n=4/14). CONCLUSION: Almost two-thirds of breast cancer BrM expressed AR. HER2+ luminal B and HER2+ subtypes were most likely to be AR+, while only 30% of triple negative BrM were AR+. Our data suggests that certain subtypes of breast cancer BrM are more likely to be AR+ and could serve as a potential therapeutic target.

62. PRESENCE OF EXTRACRANIAL TUMORS INFLUENCES RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN A PRE-CLINICAL MODEL OF MELANOMA BRAIN METASTASIS

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Up to 75% of patients with melanoma develop brain metastases. While immune checkpoint inhibitors (ICI) targeting PD-1 and CTLA4 have revolutionized the treatment of metastatic melanoma, responses within the immune-specialized microenvironment of the brain are not well understood and there is a paucity of animal models to investigate the effect of ICI intracranially. We characterized responses to checkpoint inhibitors in a syngeneic mouse model of melanoma brain metastasis with concurrent intracranial and subcutaneous melanoma. D3UV3 cells (obtained from David Fisher's laboratory) were derived using UVB irradiation from D4M.3A melanoma cell line and implanted into the striatum using stereotactic injection or subcutaneously injected into the flank of C57BL/6 mice. Mice were then treated with anti-PD-1 antibody, anti-CTLA4 antibody, a combination of anti-PD-1 and anti-CTLA4, or isotype controls. While mice with intracranial melanoma alone had no response to monotherapy with anti-PD-1 or anti-CTLA4 antibody (p=1 and 0.1, respectively), and only a slight response to combination therapy (p=0.049), mice with concurrent subcutaneous tumors had significantly improved responses to anti-PD-1, anti-CTLA4 and combination treatment (p=0.002, 0.01 and 0.01 respectively compared to mice with intracranial tumors alone with equivalent treatment). These results demonstrate that the presence of an extracranial tumor influences response to ICI in pre-clinical mouse models of melanoma brain metastasis. We have therefore established a pre-clinical model with concurrent intracranial and extracranial tumors to better recapitulate the clinically observed context of melanoma brain metastases and lead to a better understanding of the setting in which ICI are effective for patients with this devastating complication.

64. AN ENT2-DEPENDENT, CELL-PENETRATING, AND DNA-DAMAGING LUPUS AUTOANTIBODY CROSSES THE BLOOD-BRAIN BARRIER TO TARGET BRAIN TUMORS

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The blood-brain barrier (BBB) limits conventional antibody-based approaches to brain tumors. ENT2, an equilibrative nucleoside transporter, facilitates penetration of autoantibodies into live cells and is expressed in the BBB. PAT-DX1 (also known as Deoxymab-1 or DX1) is an ENT2-dependent, cell-penetrating, and DNA-damaging lupus autoantibody that is synthetically lethal to cancer cells with defects in the DNA damage response. PTEN loss renders sensitivity to DX1 and is common in primary and metastatic brain tumors. We show that DX1 is toxic to spheroids derived from primary PTEN-deficient glioblastoma (GBM), and crosses the BBB to suppress the growth of orthotopic GBM and breast cancer brain metastases. Mechanistically, we find the ENT2 inhibitor dipyridamole blocks DX1 penetration into brain endothelial cells and transport across the BBB *in vitro* and *in vivo*, consistent with ENT2-mediated uptake of DX1 into brain tumors. Autoantibodies that hijack nucleoside transporters to cross cell membranes may open new frontiers in brain tumor therapy.

65. INVASIVE HISTOPATHOLOGY DRIVES POOR OUTCOMES IN SURGICALLY RESECTED BRAIN METASTASES

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BACKGROUND: Brain metastasis (BrM) patients treated with surgery and radiotherapy frequently experience local recurrence (LR), leptomeningeal metastasis (LM), and poor overall survival (OS). We sought to correlate the presence of invasive or circumscribed histopathological growth pattern, observed in the BrM lesion and surrounding brain, with these outcomes, and to study molecular mediators of parenchymal invasion. METHODS: We assessed the HGP of H&E-stained slides from 164 surgically resected BrM from 147 patients. HGP was correlated with incidence of LR, LM and OS. Single-cell RNA sequencing (scRNAseq) was performed on three invasive HGP patients, sampling the metastasis center (MC) and surrounding brain (SB) outside of the contrast-enhancing region. Orthotopic patient-derived xenograft models (OPDX) were established from N=30 brain metastasis via intracranial propagation. RESULTS: 56/164 BrM specimens (34%) showed a circumscribed growth pattern between the tumor and adjacent brain (cHGP) while 108/164 (66%) showed significant invasion of tumor lobules or single cells into the brain parenchyma (iHGP). iHGP was associated with LR, LM and shortened OS in BrM patients. OPDX models of BrM retain features of patient BrM, including HGP. scRNAseq identified abundant cancer cells in SB that overexpressed a number of genes involved in cell survival, invasion and metastasis compared to matched cancer cells in MC. Validation of these targets with immunohistochemistry in patient and OPDX tissues revealed cold-inducible RNA binding protein (CIRBP) overexpression in iHGP patient and OPDX BrM. Modulation of CIRBP expression in OPDX and cell line models of iHGP BrM delayed BrM progression and extended OS. CONCLUSION: iHGP is a poor prognostic indicator in patients with surgically resected BrM, establishing HGP as an

important prognostic factor that should be considered by clinicians treating BrM patients. We identify CIRBP as a functional mediator of this process.

66. CLINICAL CHARACTERISTICS AND RESULTS OF PEDIATRIC SOLID TUMORS WITH BRAIN METASTASES: EXPERIENCE FROM A SINGLE REFERRAL CANCER CENTER

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BACKGROUND: 80% of childhood cancer are located in low- and middle-income countries (LMIC). The most common form of presentation is disseminated or metastatic disease. The rate of survival has not been equitable across the world, since in these countries only 1 of 5 children are cured. OBJECTIVE: To evaluate the clinical and histopathological features of patients with metastatic pediatric solid tumors, in a single referral cancer center in Honduras. METHODS: We conducted a retrospective review of patients diagnosed with pediatric solid tumors from January 2010 to April 2020. Among the 260 patients through a collection form, we obtained: sociodemographic characteristics, clinical presentation at diagnosis, common histological subtypes, sites of metastasis, treatment and outcome at the time of follow-up. RESULTS: During the last 10 years, 260 cases of childhood cancer were referred to our center for treatment. 127 patients (48.8%), have a solid tumor, patients ranged in age from 1 to 18 years and distribution for sex were 38% for males and 62% females. At the time of initial diagnosis 40/127 (31%) have advanced disease (stages III and IV). We found brain metastases in 22/40 cases (55%), the primary cancer was localized at CNS in 13/22 (59%) and the most common extracranial tumors causing brain metastases were neuroblastoma (4/22), rhabdomyosarcoma (3/22), retinoblastoma (2/22). Currently in the follow-up there were 18/22 (82%) died and 4/22 (18%) are in treatment with palliative intent. CONCLUSION: There is a lack of information about the epidemiology of brain metastases among children with solid tumors in the low/middle income countries (LMIC) where the prognosis of metastatic disease is very poor, despite efforts, multimodal therapy and multidisciplinary management, in absence of other options like bone marrow transplantation, and reliable access to high-quality medicines. For our countries, timely diagnosis is still the main determining factor for cure.

67. INCREASED RISK OF BREAST CANCER BRAIN METASTASIS WITH EGFR AND KI-67 EXPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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PURPOSE: This study aims to conduct a systematic review of the literature to identify biomarkers associated with breast cancer brain metastasis (BCBM). METHODS: A systematic search was conducted in PubMed, Embase, Web of Science, and Cochrane for relevant literature up until October 1, 2018. Case reports, conference abstracts, and expert opinions/letters were excluded. Studies were included if they investigated risk factors for BCBM in a cohort of patients with locoregional or metastatic breast cancer of any subtype. RESULTS: From the 4866 studies that were screened, 117 were selected for inclusion and review. Twenty-eight unique biomarkers were investigated, of which three (EGFR, Ki-67, and p53) were assessed by more than two authors. In a pooled analysis of 3 studies, EGFR expression was associated with an increased risk of BM (RR 3.48, 95% CI 2.27–5.32, I^2=0%, p-interaction = 0.39, n= 571 patients). In a pooled analysis of 5 studies, increased Ki-67 expression was associated with an increased risk of BM (RR 2.91, 95% CI 1.96–4.32, I^2=59%, p-interaction = 0.05, n= 1,178). In a pooled analysis of 4 studies, p53 expression was not associated with a statistically significant risk of BM (RR 1.42, 95% CI 0.98–2.06, I^2=53%, p-interaction = 0.10, n= 738). CONCLUSION: This study summarizes the various biomarkers investigated for a role in breast cancer brain metastasis. Two biomarkers, EGFR and Ki-67 were identified as having a statistically significant increased risk of BCBM while p53 was not found to be statistically significant. Future studies are needed to develop more robust prediction models, as well as evaluate the other biomarkers identified in this study, which could help clinicians identify patients at high risk of breast cancer brain metastasis.

68. FRAMELESS, VAULT-FREE RADIOSURGERY: INITIAL CLINICAL EXPERIENCE WITH THE ZAP-X STEREOTACTIC SYSTEM

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The Zap-X is a novel self-contained and self-shielded dedicated radiosurgery system developed and manufactured by ZAP Surgical Systems, Inc. of San Carlos, California. Intended for the stereotactic radiosurgery (SRS) treatment of benign and malignant intracranial and cervical spine lesions, this gyroscopically stabilized 3 megavolt (MV) linear accelerator (LINAC) provides a unique radiosurgical alternative for selected patients. Beginning in January 2019, a total of 38 metastatic lesions in 24 patients were treated in our facility. Radiation prescription doses ranged from 1500–1900 cGy (single fraction) to 2500 cGy (five fractions), with treatment volumes ranging from .04 to 15.3 cc. Daily treatment times averaged 45 minutes or less. Target coverage, dose homogeneity, and conformality were comparable to the existing Gamma Knife, CyberKnife and LINAC-based radiosurgery treatment systems in daily use at our facility. As with other frameless radiosurgery platforms, the Zap-X proved particularly useful in situations where either surgery or single-fraction radiosurgery was considered a less desirable treatment option; or when fractionated radiosurgery was thought to be radiobiologically advantageous. All treatments were completed without complication. At two months post-treatment, all lesions showed a complete or partial response to therapy based on MRI scan. None of our patients experienced treatment-related skin reaction, cognitive deficit, fatigue or steroid dependency. Among patients who had previously undergone Gamma Knife treatment, there was a clear preference for frameless radiosurgery. In our experience, the Zap-X delivery system offers a high-precision, patient-friendly and cost-effective alternative to traditional dedicated radiosurgical platforms.

69. PERMANENT INTRACAVITARY CS131 BRACHYTHERAPY FOR PREVIOUSLY-IRRADIATED RECURRENT BRAIN METASTASES: INITIAL CLINICAL AND RADIATION SAFETY EXPERIENCE

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OBJECTIVE: Recurrence of previously-irradiated brain metastases (BrM) presents a significant challenge. We describe our initial experience using salvage resection with Cs131 brachytherapy in previously-irradiated BrM. METHODS: Between September 2019 and April 2020, 9 patients with recurrent BrM underwent maximally-safe metastatectomy. Following pathological confirmation of viable recurrence, cavities were implanted with permanent Cs131 brachytherapy (GammaTile, GT Medical Technologies). Prescribed dose was 60Gy at 5mm from the cavity. Postimplant dosimetry (V100) was calculated on postoperative day 1 fused CT/MRI. Intraoperative team exposure was recorded using intraoperative ring dosimetry, and patient dose-rates measured postoperatively informed patient, family and medical-staff exposure modeling. RESULTS: Nine patients (55% female, median age 54) underwent 10 implantations (6 supratentorial, 4 infratentorial). Median preoperative maximum diameter was 3.5cm (2.3–6.3) and histologies included breast, gastrointestinal, lung, kidney and oral cavity squamous cell carcinomas. Five had undergone prior resection or laser ablation. All lesions received >/=1 prior course of stereotactic irradiation a median of 10.1 months (3.7–15.9) earlier. Eight lesions were gross-totally resected. Median number of implanted Cs131 seeds was 16 (12–28) with median seed strength of 61.8U (42.4–98.0). Median postoperative cavity size was well-correlated with the number of implanted seeds (Pearson R=0.75, p=0.03). Median V100 dose coverage of the cavities and uniform 5mm expansion of the cavities were 99% (79–100%) and 79% (51–95%), respectively. Median measured exposure rates were 90mR/hr (28–152) on contact, 9.15mR/hr (2.7–13.9) at 30cm and 1.4mR/hr (0.6–2.3) at 1 meter from the patient. Mean ring dose was 6.83mrem (0–18) for the radiation oncologist and 9.17mrem (0–15) for the neurosurgeon. Modeled lifetime family-member and visitor exposure was 116mrem (52-193mrem), and healthcare worker exposure was 39mrem (17-64mrem), all well below regulatory limits. There were no immediate wound complications or unanticipated neurologic injuries. CONCLUSION: In our early experience, salvage interstitial Cs131 implantation was safely employed for recurrent brain metastases.

70. A PHASE 1–2 CLINICAL TRIAL OF EO1001, A NOVEL IRREVERSIBLE PAN-ERBB INHIBITOR WITH PROMISING BRAIN PENETRATION

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CNS metastasis has become a prominent driver of morbidity and mortality in recent years as new targeted therapies have improved systemic outcomes. Mutations in the ErbB family of kinases are known oncodrivers in many of these cancers. ErbB family member "crosstalk" is associated with rapid development acquired resistance to ErbB TKIs. The development of agents targeting