OTHER

OTHR-01. USING COGNITION TO PREDICT RISK OF MEDICAL DECISION-MAKING IMPAIRMENT IN BRAIN CANCER

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BACKGROUND: Medical decision-making capacity refers to the ability to make informed decisions about medical treatment. Understanding is the most cognitively demanding aspect of medical decision-making and requires the ability to comprehend medically-related information and then use that information to make decisions about diagnosis, prognosis, and treatment options. In previous papers, we have shown that knowledge about specific cognitive abilities that affect understanding in brain cancer could be used to construct actuarial equations designed to help clinicians identify persons with brain cancer or brain metastases at risk of understanding impairment. METHODS: In total, 184 participants (67 with brain metastasis, 41 with non-brain metastasis, 29 with malignant glioma, and 47 healthy controls) were recruited. All participants were administered a neuropsychological battery that included a performance-based measure of medical decision-making capacity. Impairment cutoffs were calculated from control group performance. Using the cognitive scores that were most highly associated with understanding, logistic and linear regression models were used to construct actuarial equations designed to predict intact/impaired understanding and understanding scores, respectively. RESULTS: As expected, both brain cancer groups had poorer understanding than controls and approximately 50% of both brain cancer groups exhibited impaired understanding. Over 24% of the non-brain metastasis group exhibited impaired understanding. Significant associations were found between understanding and all administered cognitive variables, with the strongest correlations noted as between understanding and measures of executive function, verbal memory, and verbal fluency. Using these cognitive variables, we were able to construct predictive equations that showed strong psychometric properties. CONCLUSIONS: These data demonstrate how cognitive measures can estimate medical understanding in persons with cancer. Clinically, these findings suggest that poor verbal memory, executive function, and/or phonemic fluency function could serve as "red flags" for reduced consent capacity in this patient population, and thus signal that a more comprehensive medical decision-making capacity evaluation is warranted.

OTHR-03. ENHANCEMENT OF T1W-GAD MRI IS ASSOCIATED WITH POST-SRS LOCAL CONTROL OF NSCLC BRAIN METASTASES

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BACKGROUND: Local control (LC) of brain metastasis (BM) is an important clinical endpoint. To date predictors of LC have been limited to patient and treatment related factors. Quantitative imaging features predictive of LC have not been well described for BMs treated by stereotactic radiosurgery (SRS). This study aimed primarily at assessing quantitative imaging predictors of LC that may be used for tailored SRS treatment of BM patients. METHODS: A cohort of non-small cell lung cancer (NSCLC) treated with SRS alone were identified. Post-operative SRS, radiosurgical boost, or prior WBRT cases were excluded. All patients underwent pre-SRS and follow-up T1-Gad MR imaging (termed here T1-SRS and T1-FWU). BM regions were outlined using T1-SRS during treatment planning. LC was assessed for each treated lesion by a Radiation Oncologist. Intensity histograms were normalized to account for inter-individual brain signal heterogeneity. For each BM, computed predictor factors were derived from established LC markers (volume), features associated with tumor shape (compactness, eccentricity), and signal intensity distribution in BM region (percentiles, standard deviation). RESULTS: A total of 106 NSCLC BMs in 82 participants (41 female) were examined. Mean follow-up time was 9±9 months (median 6.5 months). Kaplan-Meier (KM) curves for LC were split by the predictor factors, with split threshold ranging between -0.5 and 0.5 of sample standard deviation, optimized to maximize the difference between lower and upper curves. KM curves for lower volume ($p=0.02$), lower eccentricity ($p=0.004$), higher intensity standard deviation ($p=0.02$), and higher 95th intensity percentile ($p=0.05$) resulted in significantly higher LC. CONCLUSION: Volume, eccentricity, intensity standard deviation, and 95th intensity percentile were found to predict LC. Intensity standard deviation and intensity percentile as predictors of LC merit validation in larger, independent datasets or in future prospective studies.

OTHR-04. INCIDENCE AND SURVIVAL OUTCOMES IN UROTHELIAL CARCINOMA BRAIN METASTASES

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INTRODUCTION: Urothelial carcinoma is a common malignancy with ~79,000 new cases diagnosed annually. However, urothelial brain metastases (UBM) are encountered uncommonly. Herein we evaluate their national prevalence, predictors, and treatment outcomes in the contemporary era. METHODS: The characteristics, management, and overall survival (OS) of UBM patients (2010–2015) were evaluated using the National Cancer Database, which comprises >70% of all newly diagnosed cancers in the U.S. OS was analyzed with Kaplan-Meier methods and log-rank tests. National outcomes were compared to our institutional cohort of UBMs. RESULTS: Out of 208,600 patients diagnosed with urothelial carcinoma, 8.4% presented with stage IV disease--of these only 216 (1.2%) had BMs at the time of diagnosis. Patients presenting with bone, liver, or lung metastases were more likely to present with synchronous BMs. Brain involvement demonstrated significantly worse median OS (3.9mos, 95%CI: 3.1–4.9) than non-BM stage IV disease (10.9mos, 95%CI: 10.6–11.2, $p< 0.001$). Compared to non-BM stage IV disease, UBMs were more likely to have surgery for metastatic disease and receive radiotherapy ($p< 0.001$); but were less likely to have primary resection or chemotherapy. In multivariable analysis of stage IV urothelial cancer, BMs demonstrated significantly worse OS (HR 1.43, 95%CI: 1.20–1.72, $p< 0.001$). In our institutional data, 10 urothelial cancer patients developed BMs; of which 7 were male, median age and KPS at diagnosis were 64.9yo (IQR 56.4–72.0) and 85 (IQR 75–100). Four patients had synchronous metastases; the median number of BM lesions was 2 (IQR 1–2), with a median size of 2.6cm (IQR 1.6–3.3). All 10 underwent GTR, 3 also with SRS and 7 with WBRT, associated with a median OS of 16.5mos. CONCLUSION: Our results confirm the rarity of UBMs and suggest that BM screening may only be indicated in stage IV patients with neurological symptoms. Systemic therapies demonstrate improved OS in these patients.

OTHR-05. THE ABILITY TO MAKE INFORMED TREATMENT DECISIONS IS COMPROMISED IN ADULTS WITH ADVANCED STAGE CANCER

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OBJECTIVE: To investigate medical decision-making capacity (MDC) in patients with advanced stage cancer. METHODS: Participants were 113 newly diagnosed adults with brain metastases and 41 adults with metastatic cancer without brain metastases who were recruited from an academic medical center and 40 demographically-matched healthy controls recruited from the community. We evaluated MDC using the Capacity to Consent to Treatment Instrument (CCTI) Vignette B and its four clinically relevant consent standards (expressing a treatment choice, appreciation, reasoning, and understanding). Capacity impairment ratings (no impairment, mild/moderate impairment, and severe impairment) on the consent standards were also assigned to each participant using cutoff scores derived statistically from the performance of the control group. RESULTS: Both of the metastatic cancer groups (with and without brain metastasis) performed significantly below controls on consent standards of understanding and reasoning. The brain metastasis group performed below the non-metastatic cancer group on understanding. Capacity compromise was defined as performance ≤1.5 standard deviations (SD) below the control group mean. Using this definition, approximately 65% of the participants with brain metastases and 51% of participants with metastatic cancer without brain metastases were impaired on at least one MDC standard. CONCLUSION: Over half of participants with metastatic cancer regardless of whether they have brain disease have reduced capacity to make treatment decisions. The finding of impaired MDC in patients without brain metastases is surprising and suggests this group likely exhibits cognitive deficits that impact their ability to understand and reason about different treatment options. The reasons underlying this impairment will be investigated. This highlights the importance of routine clinical assessment of MDC in all patients with metastatic cancer when important treatment decisions are being discussed. These results also indicate a need for the development and investigation of interventions to support or improve MDC in this patient population.

OTHR-06. ANALYSIS OF GENOMIC ALTERATIONS IN 154 BRAIN METASTASES

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Brain Metastases (BM) are associated with poor prognosis. Understanding the genomic alterations (GA) that drive tumor metastasis to the brain will increase our ability to identify patients at risk for BM, and provide better opportunities to implement targeted therapies. We performed a retrospective review of genomic alterations in 154 patients with BM from various primary sites (80 Lung, 22 Breast, 16 Melanoma, 5 Kidney, 4 Colorectal, 4 Prostate, and 23 carcinomas from unknown primary (UP). All cases were analyzed by a next generation sequencing assay the detects mutations in the coding region of 327 genes and rearrangements involving 37 genes.

The most commonly mutated genes were; *TP53, CDKN2A/B, KRAS, MYC, RB1, NF1, PIKC3A, STK11,* and *PTEN*. A comparison of GA in our BM cases with unmatched primary tumors from COSMIC revealed differences in the frequency of mutated genes: *TP53* (Lung 85% vs 38%, Breast 63.6% vs 26.0%) *CDKN2A/B* (Lung 33.7% vs 7%, Melanoma 56.2% vs 18%, Kidney 40% vs 2%, UC 34.7% vs 9%), *ERBB2* (Breast 36.3% vs 4%), MYC (Breast 36.36% vs 0.3%), *TERT* (Melanoma 62.5% vs 25%, Kidney 40% vs 2%), *APC* (Colon 100% vs 48%), *KRAS* (Colon 100% vs 31%), *PTEN* (Prostate 50% vs 7%), *TSC1* (Kidney 40% vs 2%), *STK11* (UC 26.0% vs 6%). Our results demonstrate a higher frequency of *TP53* mutations (p=0.001) in metastatic lung cancer, and a higher frequency of *MYC* amplification (p=0.01) in metastatic breast cancer, when compared to primary tumors. The present study demonstrates significant differences in the frequency of mutations between primary tumors and BM. Such differences may play an important role in the pathogenesis of BM and may allow for targeted strategies utilizing existing therapies.

OTHR-07. ESTIMATING INCIDENCE PROPORTION OF BRAIN METASTASES AT DIAGNOSIS AND LIFETIME INCIDENCE AMONG CANCER PATIENTS DIAGNOSED FROM 2010–2015 IN CANADA

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INTRODUCTION: The incidence of brain metastases (BM) among Canadian cancer patients is unknown. We aimed to estimate the incidence proportion (IP) of BM at the time of all cancer diagnoses and during follow-up of cancer patients with the top six primary tumours that are most likely to metastasize to the brain. METHODS: Data on BM at diagnosis from 2010–2015 was obtained from the Canadian Cancer Registry (CCR). Site-specific IPs of BM was estimated for patients from provincial registries that achieved ≥90% complete data. These estimates were applied to the total number of newly diagnosed primary cancers to estimate total number of BM at diagnosis from 2010–2015 in Canada. To estimate the number of lifetime BM that arise from six selected primary cancers including lung, breast, skin melanoma, colorectal, kidney/renal pelvis and esophagus, we applied IP estimates reported in the literature. RESULTS: We identified 1,105,905 cancer cases in the CCR from 2010–2015, of which 519,950 (47%) were from the six primaries. The annual average number of patients with BMs at diagnosis from all cancer sites was approximately 2,800 and was highest for lung cancer(2,400).The site-specific IPs of BM at diagnosis were: lung (9.6%;95% CI: 9.3–10.0%), esophageal (2%;95%CI:1.5–2.7%), kidney/renal pelvis (1.3%;95%CI:1.0–1.5%), skin melanoma (1.1%;95%CI:0.9–1.3%), colorectal (0.3%;95%CI:0.2–0.3%), and breast (0.2%;95%CI:0.2–0.3%).Using clinical and population data from the literature, we estimated that nearly 7,400 lifetime BM cases occur annually for these six primaries. CONCLUSIONS: Each year in Canada, approximately 2,800 BMs from all primary cancers are found at the time of diagnosis and approximately 7,400 lifetime BM occur annually from the six selected primary tumours.

OTHR-08. PREDICTION OF RISK OF CENTRAL NERVOUS SYSTEM METASTASIS FOR AJCC 8TH EDITION STAGE III MELANOMA PATIENTS

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Among common solid tumors, melanoma has the highest risk of CNS metastasis. Improved understanding of the incidence, risk factors, and timing of CNS metastasis is needed to inform surveillance strategies for at-risk patients. Clinical data were extracted from two institutions for AJCC 8th edition stage III melanoma patients, diagnosed from 1998–2014 who had negative baseline CNS imaging within 4 months of diagnosis. The cumulative incidence of CNS metastasis was calculated in the presence of the competing risk of death from stage III presentation, and at benchmark time points 1-, 2-, and 5-years post-diagnosis. The cohort (N=1,918) consisted of patients from major melanoma centers in the US (50.6%) and Australia (49.4%). The first site of distant metastasis was CNS only for 3.9%, CNS and extra-cranial sites (ECS) for 1.9%, and ECS only for 31.2% of patients (N=1918); 15.5% of patients who developed distant metastases (N=708) had CNS involvement at first diagnosis of stage IV disease. Cumulative incidence of CNS metastasis from stage III diagnosis was 3.7% (95% Confidence Interval (CI): 2.9–4.6) at 1-year; 9.6% (95% CI: 8.3–11.0) at 2-years; and 15.9% (95% CI: 14.2–17.7) at 5-years. In multivariable analyses, risk of CNS metastasis was significantly higher for males; younger patients; increasing AJCC stage group; scalp primary tumor site, acral melanoma subtype, and increased primary tumor mitotic rate. Conditional analyses showed that only high primary tumor mitotic rate (>9 per mm2) was significantly associated with risk of subsequent CNS metastasis among patients who survived without CNS recurrence 1-, 2-, and 5-years after the diagnosis of stage III disease. Similar rates of CNS metastasis were observed between these two large, geographically-distinct stage III melanoma patient cohorts. These results provide a framework for developing evidence-based surveillance strategies and for evaluating the impact of contemporary adjuvant therapies on the risk of melanoma CNS metastasis.

OTHR-09. IDENTIFYING EPIGENETIC 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 from 26 to 12 months. There are no robust 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 generalized 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=0.01), N status (N3 vs. N0, 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. Methylation-based risk scores 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 metastasis (HR=4.3, 95%CI 1.1–17, 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 profile other clinical factors may be used to determine patient specific brain metastasis risk values 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 cancers in the U.S. RESULTS: 91,686 adults presented with 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 and 5-year OS rates for all BMs were 27.0% (95% CI [26.7%-27.3%]) and 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%). CONCLUSION: Our results illustrate the national distribution of newly-diagnosed BMs and investigates how the distribution varies by patient demographics.