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12. OUTCOMES AFTER SURGICAL RESECTION OF MELANOMA BRAIN METASTASES IN THE AGE OF CHECKPOINT INHIBITOR TREATMENT

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NEURO-ONCOLOGY ADVANCES

Abstracts

Society for Neuro-Oncology Virtual Conference on Brain Metastases, August 14, 2020, held in association with the AANS/CNS Section on Tumors

04. ASSESSMENT OF EFFICACY AND SAFETY OF OSIMERTINIB FOR PATIENTS WITH INTRACRANIAL METASTATIC DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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INTRODUCTION: Intracranial metastatic disease (IMD) is a serious and life-altering complication for many patients with cancer. Targeted therapy may address limitations of current treatments as an additional agent to achieve intracranial disease control in some patients with IMD. Osimertinib is a mutant epidermal growth factor receptor (EGFR) inhibitor that can penetrate the blood-brain barrier and inhibit tumor cell survival and proliferation in patients with non-small cell lung cancer (NSCLC) with specific EGFR mutations. The purpose of this study is to assess the efficacy and safety of osimertinib in the management of IMD. METHODS: Studies reporting intracranial outcomes for patients with EGFR-mutant NSCLC and IMD treated with osimertinib were included. Among 271 records identified in MEDLINE and EMBASE, 15 studies fulfilled eligibility criteria. Outcomes were pooled using a random-effects model. Risk of bias was assessed using the Cochrane Risk of Bias tool and modified Newcastle-Ottawa scale. Information extracted included study characteristics, intracranial efficacy measures, and safety measures. Meta-analyses were conducted to pool applicable outcomes. RESULTS: 15 studies reporting on 324 patients were included in the analysis. Combined CNS ORR and CNS DCR were calculated to be 64% (95% CI, 53–76%; n = 195), and 90% (95% CI, 85–93%; n = 246). Risk ratios for CNS ORR and CNS DCR were calculated to be 1.44 (95% CI, 1.06–1.96; n = 52) and 1.13 (95% CI, 0.96–1.33; n = 52). Included studies reported complete intracranial response rates of 7–23%, median best decrease in intracranial lesion size of 40–64%, and grade 3+ adverse event rates of 19–39%. CONCLUSIONS: Findings reported here support a potential role for osimertinib for patients with EGFR-mutant NSCLC and IMD. Clinical decision-makers would benefit from the inclusion of patients with IMD in future trials to identify factors that predict responses to targeted therapy.

06. MALIGNANT SUBDURAL EFFUSION FROM DURAL METASTASES: A CASE REPORT AND REVIEW OF AVAILABLE LITERATURE

Juan Silvestre Pascual, John Emmanuel Torio, and Gerardo Legaspi; University of the Philippines - Philippine General Hospital, Manila, Philippines

Dural metastases from a distant primary site is a relatively uncommon entity. Two complications from this that have similar imaging findings and clinical presentation are subdural hematoma and subdural effusion. Multiple cases of subdural hematoma have been reported, but only eight other cases of subdural effusion have been reported in the literature. Here we present a case of subdural effusion as a complication from dural metastasis from a sigmoid adenocarcinoma in a 43 year old female. We also review the available literature, discussing the possible patho-etiologies, clinical presentations and imaging findings, as well as outcomes. We note the high recurrence rate (seen in 66% of all reported cases, including ours) and poor prognosis (days to months) of these cases.

07. RETROSPECTIVE ANALYSIS OF SALVAGE SURGERY FOR LOCAL PROGRESSION OF BRAIN METASTASIS PREVIOUSLY TREATED WITH STEREOTACTIC IRRADIATION: DIAGNOSTIC CONTRIBUTION, FUNCTIONAL OUTCOME, AND PROGNOSTIC FACTORS

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BACKGROUND: Stereotactic irradiation (STI) is a primary treatment for patients with newly diagnosed brain metastases. Some of these patients experience local progression, which is difficult to differentiate from radiation necrosis, and difficult to treat. Just a few studies have clarified the prognosis and effectiveness of salvage surgery after STI. We evaluated the diagnostic value and improvement of functional outcomes after salvage surgery. METHODS: We evaluated patients with brain metastases treated with salvage surgery for local progression from October 2002 to July 2019. These patients had undergone salvage surgery based on magnetic resonance imaging findings and/or clinical evidence of post-STI local progression and stable systemic disease. We employed two prospective strategies according to the eloquency of the lesions. Lesions in non-eloquent areas had been resected completely with a safety margin, utilizing a fence-post method; while lesions in eloquent areas had been treated with minimal resection and postoperative STI. Prognostic factors for survival were analyzed. RESULTS: Fifty-four salvage surgeries had been performed on 48 patients. The median age of patients was 64 years. The median diameter of the enhanced lesions was 35 mm (range 19–58 mm). The median overall survival was 20.2 months from salvage surgery and 37.5 months from initial STI. Primary cancers were lung 31, breast 9, and others 8. Local recurrence developed in 13 of 54 lesions (24%). Leptomeningeal dissemination occurred after surgery in 3 patients (5.6%). Primary breast cancer (breast vs. lung: HR: 0.17), (breast vs. others: HR: 0.08) and RPA class 1–2 (RPA 1 vs. 3, HR: 0.13), (RPA 2 vs 3, HR: 0.4) were identified as good prognostic factors for overall survival (OS) in multivariate analyses. CONCLUSION: We insist that salvage surgery leads to rapid improvement of neurological function and clarity of histological diagnosis. Salvage surgery is recommended for large lesions especially with surrounding edema either in eloquent or non-eloquent areas.

11. ASSOCIATION OF TUMOR EXPOSURE TO CEREBROSPINAL FLUID SPACES TO LEPTOMENINGEAL DISEASE IN PATIENTS WITH BRAIN METASTASES

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BACKGROUND: Development of leptomeningeal disease in patients with brain metastases is associated with extremely poor survival. Identification of the underlying pathogenesis of leptomeningeal disease is unknown. METHODS: This retrospective case control study included consecutive adult patients with at least one cerebral metastasis from a known extracranial primary solid malignancy and at least 3 month follow up (n=366). Patients were treated with radiotherapy with or without surgical resection and primary outcome was development of leptomeningeal disease. RESULTS: The overall rate of leptomeningeal disease was 15.0%. Rates of development of leptomeningeal disease correlated with the presence of a dural based lesion (*65.7% vs. 9.7%; P<0.0001),* intraventricular lesion (*29.4% vs. 14.3%; P=0.0897),* and with dural based lesions with sulcal or cortical enhancement (*100% vs. 12.9%; P<0.0001*). Rates of developing leptomeningeal disease were not independently associated with surgical resection (*17.2% vs. 14.2%; P=0.4859*), however did occur significantly more often with piecemeal, as opposed to *en bloc*, resection (*31.3% vs. 8.1%; P=0.0138)* or when the ventricle was entered (*61.5% vs. 18.9%; P<0.0001)*. CONCLUSIONS: Metastases that are in contact with cerebrospinal fluid spaces are associated with a higher rate of subsequent leptomeningeal disease, with or without surgical resection. Future studies should investigate the use of neoadjuvant radiation, whole brain radiation therapy or adherence to strict surgical technique in high risk brain metastasis patients to mitigate this probability.

12. OUTCOMES AFTER SURGICAL RESECTION OF MELANOMA BRAIN METASTASES IN THE AGE OF CHECKPOINT INHIBITOR TREATMENT

Ramin Morshed[1], Jason Chung[1], Vivek Sudhakar[2], Daniel Cummins[1], Jacob Young[1], Mariza Daras[1], and Manish Aghi[1]; [1]UCSF, San Francisco, CA, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA

BACKGROUND: Metastasis of melanoma to the brain is associated with poor outcomes. Recent trials demonstrate improved survival after treatment with immune checkpoint inhibitors. OBJECTIVE: To examine the impact that checkpoint inhibitor treatment has on overall survival (OS) and cen-

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tral nervous system (CNS) progression in a cohort of patients undergoing surgical resection of melanoma brain metastases. METHODS: This retrospective, single-center study included patients undergoing first-time surgical resection of melanoma brain metastases. A multivariate Cox proportional model was used to estimate the association of patient and treatment factors with OS and CNS progression. RESULTS: 85 patients underwent first-time resection of 97 melanoma brain metastases with a median follow-up of 9.5 months. Checkpoint inhibitors (Pembrolizumab, Ipilimumab, and/or Nivolumab) were used in 55.1% of cases (19 pre-op; 47 post-op; median 9 cycles). Patients treated with checkpoint inhibitors had similar peri-op systemic disease status and KPS but had been treated with more systemic agents and had more instances of CNS progression prior to surgery. Median OS and time to CNS progression for the cohort were 1 year and 237 days, respectively. In a multivariate Cox regression model, age (HR 1.03 by decade; p=0.02), treatment with a checkpoint inhibitor (HR 0.27; p<0.0001), prior radiotherapy (HR 2.44; p=0.007), and number of brain metastases at the time of surgery (HR 1.05 per metastasis; p=0.04) were significant predictors of OS. Checkpoint inhibitor treatment was associated with longer OS from surgery (median 3 vs 0.5 yrs, log-rank p=0.004). However, patients who underwent craniotomy after prior checkpoint inhibitor treatment had poor OS (median 0.56 yrs). Prior radiotherapy was also associated with poor OS (median 0.53 yrs). CONCLUSIONS: While checkpoint inhibitor treatment was associated with improved survival in this surgical cohort of melanoma brain metastases, patients who require surgical resection after checkpoint inhibitor treatment or radiotherapy are poor surgical candidates.

13. MANAGEMENT OF BRAIN METASTASES FROM SMALL CELL LUNG CANCER USING SRS

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PURPOSE/OBJECTIVE(S): The management of brain metastases in patients with SCLC has become controversial in the MRI era. We examine our institutional experience treating patients with SCLC with stereotactic radiosurgery. We hypothesize that an SRS strategy in well-selected patients with close MRI surveillance will result in acceptable tumor control, and without disproportionate future neurological symptoms associated with intracranial disease. MATERIALS/METHODS: Patients with a diagnosis of high grade neuroendocrine lung cancer who had undergone SRS between 2013 and 2019 were identified and divided into two groups: SRS-primary and SRS-salvage. SRS-primary was defined as patients who, at time of SRS, had not received previous PCI or WBRT. SRS-salvage was defined as patients who had received previous PCI or WBRT. Primary outcome was intracranial progression free survival. Secondary outcomes included overall survival and neurologic symptom free survival (N-SFS), defined as time to development of neurologic symptoms attributed disease. RESULTS: Twenty patients were identified with median follow-up of 14.1 months. 11 patients were identified as SRS-primary, 9 as SRS-salvage. Among SRS-primary, median PFS and OS were 6.1 months (range 0.9 – 14.5 months) and 15.6 months (4.1–43.5) respectively. N-SFS was 11.2 months (range 3.6–40.0). 3 of 11 patients developed neurological symptoms attributable to disease. 3 underwent salvage SRS and 2 salvage WBRT. None died from intracranial disease. Among SRS-salvage, median PFS following PCI/WBRT was 9.8 months (range 1.8 – 23.6 months) and OS following salvage SRS 5.5 months (range 1.1 – 27.8 months). 3 of 9 patients developed further brain metastases post-SRS. 1 patient died from intracranial disease. CONCLUSION: Among well-selected patients followed with MRI surveillance, our data suggest SRS as primary management of brain metastases from SCLC may be reasonable. Symptomatic intracranial disease was uncommon after SRS, and no patients undergoing upfront SRS died from intracranial disease. Prospective data are required to validate these results.

14. DELAYED MRI RESPONSE TO LITT IN PATIENTS UNDERGOING IMMUNOTHERAPY

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Laser interstitial thermal therapy (LITT) is an effective treatment for regrowing lesions after previous radiosurgery to brain metastases, typically resulting in decreased perilesional edema within weeks followed by delayed reduction in lesion size. We have anecdotally observed that patients on immunotherapy (IT) at time of LITT may exhibit a delayed edema resolution response to laser ablation. Post-operative imaging for cases of LITT, performed by the senior author from June 2012-July 2019, for regrowing lesions after prior radiosurgery for brain metastases were retrospectively reviewed. The IT group was defined as any patient receiving IT treatment within 3 months of LITT. Post-operative MRIs obtained at serial time points after surgery (2 weeks, 6 weeks, 3 months, 6 months, and 12 months) were reviewed for treatment response to LITT, defined as change in surrounding edema on T2 FLAIR and change of lesion size on T1-weighted post-contrast images. Out of 60 ablated lesions, 22 were in the IT and 38 were in the non-IT groups. There were no differences in distribution of original cancer pathology (IT: 9 melanoma, 8 lung, 5 other, non-IT: 6 melanoma, 20 lung, 12 other; p>0.05). Time to lesion size response on T1-weighted post-contrast MRI neared but did not reach statistical significance between the IT and non-IT groups: median 3.0 versus 2.25 months (HR 1.5, 0.8–2.5, 95% CI, p=0.08), respectively. However, time to reduction of perilesional edema on T2-weighted MRI was significantly longer in the IT group, compared to the non-IT group: median 2.25 versus 1.5 months (HR 1.5, 0.9–2.5, 95% CI, p=0.04), respectively. These data suggest that IT around the time of LITT may lead to delayed edema reduction on MRI after LITT. We hypothesize IT may enhance normal immune-mediated mechanisms thus increasing perilesional inflammation after LITT. Further studies are needed to corroborate our observations and explore the underlying pathophysiology.

16. GAMMA KNIFE CLINICAL DOSE PROFILE FOR EXTENSIVE BRAIN METASTASES

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BACKGROUND: The use of Gamma Knife stereotactic radiosurgery (GKSRS) for the treatment of extensive intracranial metastases has been expanding due to its superior dosimetry and efficacy. However, there remains a dearth of data regarding the dose parameters in actual clinical scenarios. We endeavored to calculate the radiation dose to the brain when treating >15 brain metastases with GKSRS. METHODS: This retrospective analysis reviewed dosage characteristics for patients requiring single session GKSRS for the treatment of ^{3}15 brain metastases. Forty-two patients met the inclusion criteria between 2008 and 2017. The median number of tumors at the initial GKSRS procedure was 20 (15–39) which accounted for 865 tumors in this study. The median aggregate tumor volume was 3.1cm^3(0.13–13.26) and the median marginal dose was 16Gy (14-19Gy). RESULTS: The median of the mean brain dose was 2.58Gy (range 0.95–3.67Gy) and 79% of patients had a dose <3Gy. The 12Gy dose volume was a median of 12.45cm^3, which was equivalent to 0.9% of the brain volume. The median percentage of brain receiving 5Gy and 3Gy was 6.7% and 20.4%, respectively. There was no correlation between the number of metastases and the mean dose to the brain (p=0.8). A higher tumor volume was significantly associated with an increased mean brain dose (p<0.001). The median of the mean dose to the bilateral hippocampi was 2.3Gy. Sixteen patients had supplementary GKSRS, resulting in an additional mean dose of 1.4Gy (0.2–3.8Gy) to the brain. CONCLUSION: GKSRS is a viable means of managing extensive brain metastases. This procedure provides a relatively low dose of radiation to the brain, especially when compared to traditional whole brain radiation protocols.

17. MELANOMA BRAIN METASTASIS: PRESENTATION, TREATMENT AND OUTCOMES IN THE AGE OF TARGETED- AND IMMUNO-THERAPIES

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BACKGROUND: Melanoma brain metastasis (MBM) prognosis has historically been dismal. However, breakthroughs in targeted and immunotherapies have improved long-term survival in advanced melanoma. As such, MBM presentation, prognosis and multimodality CNS-directed treatment use were reassessed in this contemporary age of treatment. METHODS: This retrospective study evaluated patients treated at Memorial Sloan Kettering Cancer Center between 2010–2019 with a diagnosis of melanoma brain metastases (MBM). Kaplan-Meier methodology was used to describe overall survival (OS). Recursive partitioning analysis (RPA) and time-dependent multivariable Cox modeling were used to assess prognostic variables and associate CNS-directed treatments with OS. RESULTS: Four hundred and twenty-five patients with 2,488 MBM were included. Median OS from MBM diagnosis was 8.9 months (95%CI: 7.9–11.3). RPA demonstrated significantly longer survival in patients diagnosed with MBM between 2015–2019 versus 2010–2014 (13.0 months [95%CI: 10.47–17.06]