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Abstract 315: IMPACT OF THE NUMBER OF METASTATIC BRAIN LESIONS ON SURVIVAL AFTER GAMMA KNIFE RADIOSURGERY

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Objective: The number of brain metastases (BMs) plays an important role in the decision making between stereotactic radiosurgery (SRS) and whole-brain radiation therapy

Methods: We analyzed the survival of 444 SRS-treated patients with BM as a function of BM number. 113 patients were treated with repeat SRS for local recurrence and distant brain relapse. Survival analyses were performed with Kaplan-Meier analysis as well as univariate and multivariate Cox proportional hazards models.

Results: The median survival for all patients was 9.8 months (95% CI 8.5-11.3). Patients with BMs were categorized as those with 1, 2-4, 5-10 and >10 BMs. Median overall survival for patients with 1 BM was superior to those with 2-4, 5-10 and >10 BMs (14.3 months vs. 10.3 months vs. 6.8 months vs. 6.0 months, $p = 0.0001$). Survival of patients with 5-10 BMs did not differ from those with >10 BMs (6.8 months vs. 6.0 months, $p = 0.8288$). On multivariate analysis, age younger than 50 years ($p = 0.02$, HR 0.51, 95% CI 0.45 - 0.95), number of lesions ≥ 5 ($p = 0.02$, HR 1.43, 95% CI 1.05 - 1.94), Karnofsky performance status ≥ 80 ($p < 0.0001$, HR 0.51, 95% CI 0.39 - 0.69) and absence of extracranial metastases ($p < 0.01$, HR 0.53, 95% CI 0.33 - 0.87) had significant impacts on overall survival.

Conclusions: The contribution of BM number to overall survival is modest and should be considered as one of the many variables considered in the decision between SRS and whole-brain radiation therapy. Our finding confirm correlation between the survival outcome and the number of lesions treated SRS. According to our data, the median survival of patients with 2-4 metastases in the brain is significantly higher compared with a group of patients who have 5-10 or more lesions.

Abstract 327: Treatment Effect of Gamma Knife Radiosurgery for Germinomas in Pineal Gland

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Objective: Germinomas in pineal gland is uncommon, so radiation therapy is generally accepted of primary treatment of choice, but there is controversy of optimal treatment strategy for pineal germinomas. We assessed treatment effect of Gamma Knife Radiosurgery (GKS) for germinomas in pineal region.

Methods: Between October, 1994 and December 2013, 18 patients with pineal germinomas were treated with GKS. 13 cases were treated with combined GKS and booster whole brain radiotherapy (70 Gy), while 5 cases were treated using GKS only. The mean radiosurgical tumor volume was 4.6 ml (range 0.5-36 ml). The mean dose delivered to the tumor center was 25.6 Gy (range 20-45) and to the tumor margin was 14.6 Gy (10-22.5Gy).

Results: All patients underwent serial MRI scanning and mean duration of imaging follow-up was 40.6 months (range 23-148). Among 18 patients, 14 patients underwent shunts or external ventricular drainages (EVD) and biopsies were performed in all patients. Follow-up MR images were revealed complete response in 8 patients and partial response in 5

patients, while in 5 patients, it initially showed a partial response followed by no response after 8.3 months. Clinical outcome was showed better their symptoms in 13 patients and stable in 5 patients.

Conclusions: GKS is safe and effective treatment of pineal germinomas, and treatment combining radiosurgery with booster radiotherapy showed better results than the radiosurgery only treatment.

Abstract 329: Using Machine Learning to predict the overall survival after Gamma Knife radiosurgery for brain metastases

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Objective: It is extremely important for cancer research to predict outcomes and detect the key features from complex datasets. The Machine Learning (ML) is a powerful tool to achieve these goals. The purpose of this study is to apply the ML to predicting the overall survival (OS) after Gamma Knife radiosurgery (RS) in case of patients with brain metastases (BS).

Methods: We retrospectively evaluated the total data of 589 patients with 34 patient characteristics who had received the RS in the period from 2009 to 2016. The data were gathered in the self-designed database. 146 patients were excluded from analysis due to incompleteness of the data. 443 patients with 7 features (age, Karnofsky performance status (KPS), total volume of all lesions, maximal volume of the lesion, number of lesions, presence of extracranial metastases, diagnosis) were included into analysis and subdivided into two sets - training and testing ones. We applied three ML algorithms (the Decision Tree (DT), the k-nearest neighbors algorithm (kNN) and the Random Forest (RF)) to the task of classification to predict OS.

Results: For evaluating the classification quality, we use the accuracy metrics, which means the number of correct predictions. The predictors had the following classification accuracy in the cross - validation estimation as well as in the held-out dataset: the DT 78% and 61,6 % , the KNN 88,6 % and 69,9%, the RF 78,4 % and 67,6 % respectively . We have found that the most important features for predicting the OS are the total volume of the lesions, the maximal volume of the lesion, the age and the number of metastases. The features are mentioned in order of priority.

Conclusions: This research is just a first step to apply the ML algorithms to prediction outcomes in case of patients with BS in the Moscow Gamma Knife center. The kNN shows the better results in the cross - validation than the other algorithms; and besides, the most important feature is the total volume of the lesions. The accuracy of the study can be improved by the number of patients and completeness of the patient data. It could be more correct to apply the other metrics to evaluate the classification. The database system integration with the machine learning algorithms can lead to a new level in development of both the predictive models and the making decision process within the clinical practice.

Abstract 342: Frameless Stereotactic fractionated high resolution radiotherapy using Gamma Knife Icon for the treatment of Glioblastoma

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Objective: Treatment of glioblastoma is still one the biggest challenges in neurosurgery. Latest improvements in treatment protocols including surgery, radiation therapy and

enhanced MRI-scan), KPS ≥ 70 and life expectancy of at least 3 months. Before randomisation, patients complete a comprehensive neuropsychological test battery to assess cognitive functioning (HVL-R, COWA, WAIS Digit Span and Digit Symbol, TMT A and B, Grooved Pegboard). In addition, patients fill-out 3 questionnaires concerning health related quality of life (FACT-BR), depression, anxiety (HADS), and fatigue (MFI). Randomisation is stratified by the cumulative tumour volume in the brain, systemic treatment, KPS, histology, baseline HVL-R Total Recall score (a memory task) and age. Follow-up for both groups is scheduled at 3, 6, 9, 12 and 15 months after treatment with cognitive testing, questionnaires and MRI-scans.

Results: The primary endpoint is the between-group difference in the percentage of patients with significant memory decline at 3 months. Significant decline is defined as a 5-point decrease from baseline in HVL-R Total Recall score, based on the Reliable Change Index (RCI) with correction for practice effects. Secondary endpoints include cognitive functioning over time, health related quality of life, depression and anxiety, fatigue, overall survival, local control and development of new brain metastases. A power analysis based on Bayesian stopping rules suggests that the trial will be halted when 46 patients (23 in both groups) are enrolled. An independent statistician will perform monitoring of this trial using Bayesian statistical methods.

Conclusions: This trial is currently recruiting. Results of this study are relevant in clinical decision-making and may be used to inform individual patients with BM more precisely about the cognitive effects they can expect from treatment. Knowledge gained from this trial may be used to change clinical practice (in the Netherlands).

Trial registration: Clinicaltrials.gov identifier: NCT02953717

Abstract 218: GAMMA KNIFE RADIOSURGERY FOR BRAIN METASTASES: PROGNOSTIC FACTORS FOR SURVIVAL AND LOCAL CONTROL

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Objective: To evaluate the efficacy of Gamma Knife Radiosurgery (GKRS) in the treatment of single and multiple brain metastases.

Methods: From October 2010 to June 2016 582 patients were treated with GKRS for brain metastases at N.N. Burdenko Neurosurgery Institute of Moscow. Overall survival was calculated from the day of GKRS until death. Local recurrence was defined as radiologic growth of the irradiated lesion, while distant brain recurrence was the evidence of brain lesion outside the previous irradiated field. The correlations within patient and disease characteristics and the outcomes of survival and disease control were analyzed.

Results: At the time of analysis 322 patients (55,3%) were dead. The overall survival at 1 year was 43%. On multivariate analysis, age younger than 50 years ($p = 0.0242$; HR 0.5132; 95% CI 0.4495 - 0.9459), number of lesions ≥ 5 ($p = 0.022$; HR 1,4303; 95% CI 1,0530 - 1.9428), Karnofsky performance status ≥ 80 ($p < 0.0001$; HR 0,5132; 95% CI 0,3788 - 0.6954) and absence of extracranial metastases ($p < 0.0114$; HR 0,533; 95% CI 0,3274 - 0.8678) had significant impacts on overall survival.

89 patients (19.7%) had recurrence in the radiosurgery field. On multivariate analysis, the only factor associated with a low risk of local failure was brain metastases from breast cancer ($p = 0.0071$; HR 0.2569; 95% CI 0.0954 - 0.6913) and lung cancer ($p = 0.0166$; HR 0.2484; 95% CI 0.0795 - 0.7760)

The median time freedom from new brain metastases was 9.0 months (95% CI 7.5 - 10.5 months). Median distant brain control was 41.9% at 1 year. On multivariate analysis, Karnofsky performance status ≥ 80 ($p < 0.0356$; HR 0,6468; 95% CI 0,4308 - 0.9710) number of lesions ≥ 5 ($p < 0.0001$; HR 2,6292; 95% CI 1,8431 - 3.7507) had significant impacts on the distant brain relapse.

Conclusions: In well-performing patients with stable systemic disease radiosurgery can be

performed as an exclusive treatment for brain metastases. Younger patients could have a greater benefit from the GKRS. Our data confirm correlation between the survival outcome and the number of treated brain metastases .

Abstract 231: Staged Adaptive radiotherapy to reduce complication risks: A hypothesis-generating case study

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Objective: We present the case of a 60 year old female diagnosed in October 2012 with a IIIB poorly differentiated adenocarcinoma of the lung. She was treated with combined chemoradiation, achieved a complete response, and has remained locally controlled. Approximately one year after her diagnosis, she developed the first of several brain metastases. During the next four years she developed sequentially: a 1.9 left frontal lesion; two 5 mm lesions, one in the right temporal and one in the right parietal lobes; a 9 mm right occipital lesion. These lesions were treated on Novalis Brain Lab. The larger lesion received 20 Gy to the 80% isodose, and the three smaller lesions received 24 Gy to the 80% isodose. All lesions achieved a complete response. In October of 2016 a MRI revealed a 4th ventricular lesion measuring 1.3 x 1.25 x 1.13 cm, abutting the posterior pons. Because the lesion was adjacent to the brain stem and prior lesions had shown to be radioresponsive, the decision was made to treat the lesion in two temporally-spaced fractions.

Methods: The lesion was treated on the Icon using a frameless technique. A dose of 8 Gy to the 50% isodose was initially given. Six weeks later a repeat MRI showed significant regression in lesion size. A second fraction of 16 Gy to the 50% isodose was then delivered. The brain stem maximum dose was 7.1 Gy in both fractions.

Results: The 4th ventricular lesion initially measured 2.08 cc and was in apposition to the brain stem. Six weeks after 8 Gy its volume reduced by 71%, which allowed for separation from the brain stem and subsequent delivery of an additional 16 Gy. The patient is now 11 months from treatment. A recent MRI shows an excellent response with minimal enhancement at the site of the prior lesion.

Conclusions: This case illustrates a form of staged adaptive radiotherapy. The approach could be considered whenever the dose to target lesion is constrained due to proximity to critical structures. This approach might also be considered when targets are large. Additionally this method does not have to be limited to two fractions. The frameless Icon system facilitates this type of approach by offering convenience and reproducibility without the need for repeat frame placement. As in this case, its efficacy will be limited by the degree of radioresponsiveness of the target.

Abstract 233: T-cells from glioma recognize specifically autologous tumor and present a viable options for the immunological treatment of patients with glioma

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Objective: T-cells have been shown to play a major role in clinically relevant anti-tumor responses based on i) their role as a positive prognostic factor defined by the T-cell infiltrate concerning patient survival ('immunoscore') and ii) the positive clinical outcome of patients receiving ACT (active cellular immunotherapy). T-cells directed against glioma

radiation for palliation rather than stereotactic radiosurgery. We present our single institution review of the efficacy and safety of treating brainstem metastases aggressively with Gamma Knife Radiosurgery.

Methods: 44 patients with 46 total lesions treated with Gamma Knife Radiosurgery were included. Mean age was 58.7 years, ranging from 22 to 82. Tumor volumes were objectively calculated, treatment effects assessed on imaging and clinical data collected and correlated to the radiosurgical response.

Results: Average survival after diagnosis of brainstem metastasis was 12.4 months, ranging from 1.4 to 58.8 months. Treatment dose ranged from 12 to 20 Gray. At first follow up, 11 patients had complete resolution of treated lesion. At the second and third follow up, 15 and 19 patients, respectively, had a complete response. On average, there was a 64% decrease in tumor size at first follow up after treatment. 25 patients received whole brain radiation therapy (WBRT) in addition to radiosurgery; 19 received radiosurgery alone. There was no difference in overall survival between the two groups ($p=0.1324$). Treatment related toxicity was minimal. Radiation necrosis was reported for one patient with 16 Gray treatment to a 2.06cm³ pontine tumor, but without correlative symptoms. One patient was treated with Bevacizumab® for progressive, but asymptomatic, edema following treatment.

Conclusions: Stereotactic radiosurgery for metastatic brainstem lesions is a safe and effective treatment. The addition of WBRT does not improve survival. Long term survival is very possible, especially in patients with a good initial Karnofsky score and stable (or treatable) systemic disease. These patients enjoyed a stable to sometimes improved quality of life after treatment. Therefore, we favor the use of radiosurgery over whole brain radiation in patients with brainstem metastasis and good performance status.

Abstract 205: Prognostic factors after Gamma Knife radiosurgery for metastatic brain tumor from non-small cell lung cancer

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Objective: This study was performed to survey prognostic factors of the patients with non-small cell lung cancer (NSCLC) after Gamma Knife radiosurgery (GKRS) for metastatic brain tumors.

Methods: We retrospectively reviewed the medical records of 128 NSCLC patients who underwent GKRS for brain metastases from July 2010 to December 2016. The primary endpoint was progression free survival of the brain metastases. We analyzed variables such as age, sex, RPA class, smoking, pathology, epidermal growth factor receptor (EGFR) mutation, and time to brain metastases as prognostic factors.

Results: Mean age of the patients was 62.3±11.6 years old. The ratio of male : female was 95 : 33. Average number of lesions was 6 and margin dose was 21.11±2.7Gy. As prognostic factors, EGFR mutation and RPA class were statistically significant in progression free survival of brain metastases. Other variables were not statistically significant.

Conclusions: Despite of limitation of this retrospective study, EGFR and RPA class may be proposed as prognostic factors in NSCLC patients after GKRS for brain metastasis. Further randomized controlled studies should be performed to verify these findings.

Abstract 207: Salvage GK radiosurgery for recurrent glioblastoma multiforme

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Objective: Patients with glioblastoma multiforme (GBM) have a poor prognosis with high recurrence rates. Gamma Knife Stereotactic radiosurgery.

Methods: Between 2005 and 2015 in Moscow Gamma Knife Center 98 patients treated with GKRS for recurrent GBM. There are follow up data of only 47 patients. All patients were treated with prior surgery, radiation therapy and chemotherapy. The median time from initial radiation therapy GKRS was 15.5 m. Recurrent disease was treated with GKRS with a median dose 18.0 Gy (range, 10-25 Gy). There are 88 lesions with median of tumor volume was 3.4 cm³ (range, 0.01 - 33.0 cm³). Most of the patients (33) patients had the anti-angiogenic drug therapy (bevacizumab) prior GKRS.

Results: The median of progression-free survival (PFS) was 9.2 months. Actuarial progression-free survival was 40,4% at 1 year. The 12-months overall survival (OS) from GKRS was 63.6%, 2 year - 43.2%; 3 year - 36.8%, respectively. Concerning toxicity, there was 2 (4.2%) grade 4 adverse events within this patient series. Group patients (33 pts) with bevacizumab had no any statistical differences (p=0.2) in PFS and OS with patients how had no targets prior GKRS. Median PFS was 9.0 m and 10.5 m, median OS was 19.8 m and 16.9 m, respectively.

Conclusions: Our outcomes suggest that GKRS with bevacizumab is a feasible treatment option with acceptable salvage survival rate for patients with glioblastoma. It is necessary to investigate the question of the timing of the appointment of bevacizumab and radiosurgery and in what order they should be administered.

Abstract 210: Hypofractionated Stereotactic Radiosurgery for Large (>2 Cm) brain Metastases: a Systematic Review

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Objective: In the single-fraction stereotactic radiosurgery (SRS) era, SRS was limited to small size tumors because local control is less favorable and the risk of radiation-induced brain necrosis is higher when SRS is used in patients with large lesions. However, with recent advent of the image-guided and frameless technique, large brain metastases have been able to be treated with SRS using hypofractionation. We performed a quantitative systematic review to investigate the local control and radiation-induced brain necrosis in patients with brain metastases >2 cm in size who received hypofractionated SRS.

Methods: A literature search was made of the Embase, Pubmed, and Cochrane databases. All searches were made in August 2017. Data on efficacy and safety were extracted and then synthesized into the present review.

Results: Thirty-four clinical studies were identified, the majority of which included no patient comparison group. These studies showed comparable local control and radiation necrosis rates to those of single fraction SRS used in patients with small lesions.

Conclusions: Hypofractionated SRS is effective treatment modality for large brain metastases with better local control and reduced risk of radiation-induced brain necrosis.

Abstract 212: Cognitive outcome after GKRS in patients with 1-10 newly diagnosed brain metastases

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