METHODS: We retrospectively evaluated all operative cases of image-guided Ommaya reservoir insertion from 2004–2014 by the senior author (JFM). Patient demographic data, surgical outcomes, and peri-operative complications were collected.

A systematic review was performed using Medline and Embase databases using Medical Subject Headings (MeSH) and relevant keywords as regular expressions (1960 to January 2016). The literature search was limited to the English language and for a total of 2670 articles. No randomized controlled trials were identified. Quality of evidence was rated based on the Methodological Index for Non-Randomized Studies (MINORS) score. Data extraction and statistical analysis for the systematic review are in progress.

CONCLUSIONS: Our findings suggest improved accuracy and decreased complications using an image-guided approach compared with a traditional approach. Our results support routine use of intra-operative image guidance for proximal catheter insertion in elective Ommaya reservoir placement for intraventricular chemotherapy.

P13.06 DURAL METASTASES FROM BREAST CANCER - CASE SERIES
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Intracranial metastases from solid tumors are increasingly common, often brain or leptomeningeal metastases. Dural metastases are under-reported, present diagnostic and therapeutic challenges, and may mimic subdural hematoma or meningioma. This report describes 4 recent patients with dural metastases from breast cancer. A 60 year old woman, without known cancer, had 5 months of increasing headaches, left weakness, and focal seizures. Imaging showed an enlarging right frontal extracerebral enhancing mass with edema, initially thought to be a meningioma. At surgery the tumor involved overlying bone, replaced the dura, and invaded brain. Pathology was metastatic adenocarcinoma, ER/PR positive and Her-2 negative. Investigations showed a right breast primary and lung metastases. She received chemotherapy (1960 to January 2016), letrozole and pamidronate. The tumor remains controlled after 40 months. The 3 other patients all had prior known breast cancer, 2 ER/PR positive and Her-2 negative, and 1 triple negative, ages 45–70 years. Two had known systemic metastases prior to neurological presentation. Presenting symptoms included headache, seizures, focal weakness, and confusion. All had new or progressive systemic metastases, including bone, at diagnosis of dural metastases. Two had resection of dural metastases, 1 with complicated postoperative course, with eventual improvement in both. Two received cranial RT, 1 refused RT, and all received hormonal or chemotherapy, with ongoing clinical or MRI control. These cases illustrate the complexity of dural metastases. Although patients often have extensive metastatic disease, treatment can improve symptoms and prolong survival.

P13.07 PHASE II STUDY OF SYSTEMIC HIGH-DOSE METHOTREXATE AND INTRALIPIDOSAL CYTARABINE FOR TREATMENT OF BREAST CANCER WITH LEPTOMENIGEAL METASTASES
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BACKGROUND: Metastatic breast cancer frequently leads to brain metastases and, less commonly, leptomeningeal carcinomatosis (LC). Once cerebro-spinal fluid (CSF) involvement occurs the prognosis is poor with median survival between 3–7 months. There are limited treatment options available, but none offer significant survival benefit. Methotrexate, given systemically at high doses (HD-MTX 3.5–8 gm/m2), achieves cytotoxic concentrations in the CSF and has been shown to prolong survival in patients with LC. Intrathecal (IT) liposomal cytarabine has been shown to increase time to neurologic progression in patients with breast cancer and LC. The combination of these two agents in LC has not been studied extensively but our preliminary data indicated that this approach is feasible and may offer therapeutic benefit.

METHODS: A single arm, phase II study was designed to include patients with leptomeningeal LC as per patient’s care teams. No22). Patients had an abnormal MRIing and/or CSF confirmation of LC and were allowed to have parenchymal (brain) metastatic disease, but controlled systemic disease. Eligible patients who gave informed consent underwent re-staging and CSF flow study. Patients were treated with systemic HD-MTX (8 gm/m2) every two weeks and with intrathecal liposomal cytarabine at 50 mg per injection every two weeks (on HD-MTX off weeks). Response was assessed clinically, and with MRI of the brain and spine, and CSF cytology. Adverse events were monitored and recorded.

RESULTS: The study was closed 3.5 years after the first patient was enrolled due to low accrual. Three patients have been enrolled and treated (13.6% of planned accrual). All patients were female with median age of 50 (range 46–60). The median Karnofsky Performance Status (KPS) at the time of enrollment was 70%. Mean interval between the diagnosis and initiation of therapy was 1.2 months. Median progression free survival (PFS) was 1.4 months (range 1.3–8.2) and overall survival (OS) was 8.2 months (range 3.5 – 11.3). The median number of HD-MTX and IT liposomal cytarabine doses administered per patient was 3 for each drug. The regimen was well tolerated, with no significant hematologic toxicity. Transient grade 3 transaminitis was noted in all three patients.

CONCLUSIONS: Breast cancer with leptomeningeal metastases presents as a therapeutic challenge. Radiotherapy and standard chemotherapy provide limited benefit. Maximizing cytotoxic concentrations of chemotherapeutics in the CSF is desirable and may offer a therapeutic advantage. Preliminary results from this prospective single-institution study demonstrate the feasibility and thus this approach is currently being explored in a limited number of patients with encouraging survival data. Our accrual limitations highlight the challenges of conducting studies in “orphan diseases” such as LC and underscore the importance of multi-center collaboration.

P13.08 THE VALIDATION OF MELANOMA GPA AND CHOWDHURY OVERALL SURVIVAL SCORE IN PATIENTS WITH MELANOMA BRAIN METASTASES TREATED WITH GAMMA KNIFE SURGERY
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INTRODUCTION: Melanoma is the most aggressive form of skin cancer. Nearly half of the patients with stage IV melanoma develop brain metastases. The median survival of patients after diagnosing melanoma brain metastases (MBM) is 4–5 months. Some patients have local control with Gamma Knife surgery (GKS). We retrospectively included 64 patients treated with GKS alone from MBM from 1st of January 2008 to 31st of December 2014 in our institution. Patients were divided in categories based on M-GPA: 0–1, 1.5–2.0, 2.5–3.0 or 3.5–4.0 points and the Chowdhury overall survival (OS) score: low-, moderate- or high-risk. We validated a new overall survival risk score in patients treated with GKS. We validated both risk scores in our patient cohort.

METHODS: We retrospectively included 64 patients treated with GKS alone from MBM from 1st of January 2008 to 31st of December 2014 in our institution. Patients were divided in categories based on M-GPA: 0–1, 1.5–2.0, 2.5–3.0 or 3.5–4.0 points and the Chowdhury overall survival (OS) score: low-, moderate- or high-risk. We validated the Gamma Knife surgery (GKS) patients treated with GKS. We validated both risk scores in our patient cohort.

RESULTS: Median follow-up time was 52 months (15–97 months). Median overall survival after GKS in this cohort was 6 months. With respect to the M-GPA 5 patients (7.8%) had a score of 0–1 with a corresponding OS of 2 months. Thirty patients (46.9%) scored 1.5–2.0 points resulting in a median OS of 5 months. An OS of 6 months was observed in 14 patients (21.9%) with a p-value of 0.042 and between M-GPA 0–1 and M-GPA 1.5–2.0 with p = 0.010. Regarding the Chowdhury OS score 18 patients (28.1%) had a low-risk score (0–3 points) with a median overall survival of 13 months. Nineteen patients (29%) received a high-risk score (4–6 points) resulting in a median OS of 7 months. Seventeen patients (26.6%) scored as high risk (6.5–10 points) and appeared to have a median OS of 3 months. The difference in OS between the low-risk and high-risk group and between the moderate-risk and high-risk group, respectively, was statistically significant: p = 0.004 and p = 0.026, respectively.

RESULTS: Median follow-up time was 52 months (15–97 months). Median overall survival after GKS in this cohort was 6 months. With respect to the M-GPA 5 patients (7.8%) had a score of 0–1 with a corresponding OS of 2 months. Thirty patients (46.9%) scored 1.5–2.0 points resulting in a median OS of 5 months. An OS of 6 months was observed in 14 patients (21.9%) with a p-value of 0.042 and between M-GPA 0–1 and M-GPA 1.5–2.0 with p = 0.010. Regarding the Chowdhury OS score 18 patients (28.1%) had a low-risk score (0–3 points) with a median overall survival of 13 months. Nineteen patients (29%) received a high-risk score (4–6 points) resulting in a median OS of 7 months. Seventeen patients (26.6%) scored as high risk (6.5–10 points) and appeared to have a median OS of 3 months. The difference in OS between the low-risk and high-risk group and between the moderate-risk and high-risk group, respectively, was statistically significant: p = 0.004 and p = 0.026, respectively.
CONCLUSION: In this study we validated both the M-GPA and Chowdhry OS score. The Chowdhry OS score proved to be the most accurate score to categorize patients with MBM in risk groups with corresponding OS. So we recommend this median overall survival time. Contrary to Chowdhry et al. the follow-up time in our study was sufficient for the low-risk group to reach the median overall survival time which was 13 months.

P13.06 SURVIVAL AND RELAPSE OF BRAIN METASTASES AFTER COMPLETE RESECTION OF A SINGLE BRAIN METASTASIS WITHOUT POSTOPERATIVE WHOLE BRAIN RADIOTHERAPY - A RETROSPECTIVE STUDY

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INTRODUCTION: In 2011, the EORTC 22952–26001 study showed that omission of postoperative whole brain radiotherapy (WBRT) after complete resection or stereotactic radiation for oligometastatic brain metastases (BM) does not decrease overall or functionally independent survival despite high intracranial relapse rates. Postoperative WBRT appeared to have a (transitory) negative impact on some aspects of health-related quality of life (HRQOL). A review observation with close monitoring of MRI with 9.5 months follow-up was not detrimental for HRQOL. Based on these results, the Dutch guideline on management of BM was adapted and it was advised to omit direct postoperative WBRT after complete resection of a single BM. In this retrospective study we analyzed intracranial tumor relapses, overall survival and functionally independent survival in patients with a single BM who underwent a complete resection without postoperative radiotherapy (either whole brain or locally) in two Dutch cancer centers.

METHODS: Sixty-six patients treated between June 2011 and December 2014 in the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam and the Brain Tumor Center, Erasmus MC University Medical Center Cancer Institute, Rotterdam were evaluable. Complete resection was defined as removal of the macroscopic complete resection and absence of tumor tissue on a postoperative contrast-enhanced brain MRI performed within 72 hours after resection. Follow-up brain MRIs were performed every 3 months, or earlier in case of new neurological symptoms. In case of an intracranial relapse BM, a multidisciplinary Neuro-oncology team decided on salvage therapy (radiotherapy, re-resection, systemic therapy or symptomatic palliative). Primary outcomes were overall survival and functionally independent survival. Secondary outcomes were intracranial local and distant recurrence of BM.

RESULTS: Twenty-five patients had lung cancer, 17 melanoma, 10 breast cancer and 14 patients other tumor types. Median overall survival was 13 months (95% CI: 9.6–16 months) and median functionally independent survival was 10.5 months (95% CI: 6.5–14.5 months). Local BM relapse rate was 58% within a median time of 13 months (range: 1.5–21 months). Distant BM relapse rate was 53% with a median time to relapse of 9.5 months (range: 1–30 months). Forty-four percent of all local or distant brain relapses were symptomatic. Distant BM relapse from melanoma occurred significantly earlier than in other tumor types (median time 4 months, range: 1.5–14 months (p=0.005)). WBRT as salvage therapy for relapsed BM was given in 33% of all patients.

CONCLUSION: BM relapses and (functionally) independent survival in this retrospective study were similar to the EORTC 22952–26001 study. WBRT could be avoided in 67% of all patients. In melanoma patients, distant BM relapse occurred significantly earlier than in other tumor types.

P13.10 INTRACRANIAL RESPONSE TO NIVOLUMAB IN NSCLC PATIENTS WITH UNTREATED OR PROGRESSING CNS METASTASES

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BACKGROUND: Central nervous system (CNS) metastases occur in about 30% of patients (pts) with advanced non-small cell lung cancer (NSCLC). Local treatment strategies (e.g., radiotherapy or surgery) result in limited local tumor control and are frequently complicated with neurocognitive impairment. Nivolumab is an anti-PD1 immune checkpoint inhibitor which has been recently approved by the FDA as a second line treatment of NSCLC. Data regarding its intracranial activity is lacking.

METHODS: We retrospectively reviewed efficacy and safety of nivolumab administered intravenously at a dose of 3mg/kg q2 weeks in five pts with advanced NSCLC and new or progressing intracranial metastases which were diagnosed before or within 1 month after starting the treatment.

RESULTS: Pt baseline characteristics were as follows: median age 78 years (range 57–88); 2 males; 4 smokers; ECOG: PS 0/1/2 - 2 pts/1 pt/2 pts; histological subtype: adenocarcinoma/squamous-cell carcinoma/NSCLC NOS 3 pts /1 pt/1 pt; EFRG WT/ALK neg/KRAS M all/all/all pts. Four pts had parenchymal brain metastases, three pts had leptomeningeal disease. All pts were asymptomatic and did not receive corticosteroids or brain irradiation. Dramatic response in the brain was observed in two pts (including 1 pt with leptomeningeal spread demonstrating a complete response in the CNS); time-to-response comprised 5 weeks and 9 weeks; all responses are still ongoing at the time of the report (18+ weeks, 19+ weeks). In one pt stabilization of leptomeningeal carcinomatosis for 10 weeks was achieved. Systemic responses and intracranial responses were largely concordant. No treatment-related or CNS-metastases related grade ≥ 3 adverse events were observed.

CONCLUSIONS: Nivolumab has promising intracranial activity and favorable safety profile in pts with NSCLC and untreated/progressing CNS metastases. Nivolumab CNS activity warrants further evaluation.

P13.11 OUTCOME EVALUATION OF OLIGOMETASTATIC PATIENTS WITH SINGLE, LARGE BRAIN METASTASES TREATED WITH GROSS TOTAL RESSECTION (GTR) FOLLOWED BY HYPOFRACTIONATED STEREOTACTIC RADIOSURGERY (HSRS) ON THE TUMOR BED

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INTRODUCTION: In case of large brain metastases (BM), treatment option include whole-brain-radiotherapy (WBRT), surgery, single dose radiosurgery (SRS) or Hypofractionated stereotactic radiosurgery (HSRS). None of these, when given as a single modality ability to obtain and adequate local control rate. Therefore a combined approach, if feasible, is recommended. The aim of this study was to evaluate the benefit of a combined treatment, gross total resection (GTR) followed by adjuvant hypofractionated-sterotactic-radiotherapy (HSRS) on the tumor bed, in oligometastatic patients with single, large BM.

METHODS AND MATERIALS: From January 2011 to March 2015, 69 patients with single, large BMs, controlled primary tumor and extracranial disease were treated. All patients underwent gross total resection (GTR) followed by HSRS on the tumor bed with a total dose of 30 Gy in 3 daily fractions. Clinical outcome was evaluated by neurological examination and MRI 2 months after RT and then every 3 months. Local progression was defined as radiographic increase of the enhancing abnormality in the treated brain volume and brain distant progression (BDP) as the presence of new brain metastases or leptomeningeal enhancement outside the treated brain volume. Surgical morbidity and radiation-therapy toxicity, local control (LC), brain distant progression (BDP), and overall survival (OS) were evaluated:

RESULTS: The median preoperative volume and maximum diameter of BMs was 18.45 cm³ (range 4.06–64.23 cm³) and 3.6 cm (range 2.1–5.4 cm); the median clinical target volume (CTV) was 29 cm³ (range 4.06–203.10 cm³) and the median planning target volume (PTV) was 55.19 cm³ (range 17.18–282.90 cm³). The median follow-up was 24 months (range 4–33 months). The 1-and 2-year LC in site of treatment was 100%; the brain distant progression rate was 53% with a median time to relapse of 9.5 months (range: 1–30 months). Systemic responses and intracranial responses were largely concordant. No treatment-related or CNS-metastases related grade ≥ 3 adverse events were observed.

CONCLUSIONS: Multimodal approach, surgery followed by HSRS, can be an effective treatment option for selected patients with single, large brain metastases from different solid tumors.

KEYWORDS: brain metastases, surgical resection, hypofractionated-stereotactic-radiotherapy

P13.12 LONG TERM SURVIVAL OF PATIENTS TREATED BY GAMMA KNIFE RADIOSURGERY WITH A TOTAL OF 5 TO 21 BRAIN METASTASES

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PURPOSE: To analyse the long term survival of patients treated by Gamma Knife radiosurgery (GKRS) with more than 4 brain metastases (BM).

METHODS AND MATERIALS: Between December 1999 and December 2007, we treated 88 patients with more than 4 BM by GKRS. We analysed the median survival (MS) according the number of BM (5 to 21) and histology (mainly lung, melanoma and breast cancer).

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