Simultaneous stereotactic radiosurgery of multiple brain metastases using single isocenter dynamic conformal arc therapy: a prospective monocentric registry trial

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Abstract

Background Single-isocenter dynamic conformal arc (SIDCA) therapy is an efficient way of delivering stereotactic radiosurgery (SRS) to multiple metastases simultaneously. This study reports on the safety and feasibility of SRS with SIDCA for patients with multiple brain metastases.

Methods All patients who received SRS with this technique between November 2017 and June 2019 within a prospective registry trial, were included. The patients were irradiated using a VersaHD® linear accelerator (LINAC) from Elekta (Stockholm, Sweden). Follow-up was performed every three months, including a clinical and radiological examination with cranial magnetic resonance imaging (MRI). The data were analyzed using descriptive statistics and the Kaplan-Meier method.

Results 65 patients with 254 lesions (range 2–12) were included in this analysis. Median beam on time was 23 minutes. The median follow-up at the time of analysis was 13 months (95% CI 11.1–14.9). Median overall survival and median progression-free survival was 15 months (95% CI 7.7–22.3) and 18 months (95% CI 11.1–24.9), respectively. Intracranial and local control after 6 months was 73.0% and 97.5%, respectively. During follow-up, CTCAE grade 1 adverse effects (AE) were experienced by 29 (44.6%) patients (18 of them therapy-related (27.7%)), CTCAE grade 2 AEs by 4 (6.2%) patients (one of them therapy-related (1.5%)) and CTCAE grade 3 by 3 patients (4.6%) (none of them therapy-related). 2 lesions (0.8%) in 2 patients (3.1%) were proven as radiation necrosis.

Conclusions Simultaneous SRS using SIDCA seems to be a feasible and safe treatment for patients with multiple metastases.

Introduction

Brain metastases (BM) occur in approximately 30% of all cancer patients[1]. Without treatment, BM are often associated with a dismal prognosis and a survival of only about one month[2]. Singular or solitary metastases are treated locally with stereotactic radiosurgery (SRS) or surgical resection preferably in combination with adjuvant (stereotactic) radiotherapy[3–5]. The surgical resection is most often chosen in case of large and/or symptomatic lesions as an operation can immediately relieve the patient from the burden of space-occupying effects.

However, almost 80% of all patients with BM have more than one metastasis[1, 2]. For 2–4 metastases of limited size, SRS is the first choice as this procedure achieves a fast and effective treatment with a high local tumor control and only rare side effects[6]. For patients with multiple BMs, whole brain radiotherapy (WBRT) is the mainstay of treatment[7]. WBRT is thought to delay neurological symptoms and prolong cranial control; but patients with poor performance at baseline are unlikely to benefit[8]. Moreover, WBRT is associated with a spectrum of toxicities that often result in irreversible cognitive decline even within a few months after treatment[9–11].

Through the improvement of systemic therapy with e.g. immunotherapy targeting PD-1 or PD-L1, the survival of patients is steadily improving even in advanced cancer stages[12]. This also includes patients who have been treated with WBRT for multiple BMs. As a result, BM patients are now more frequently affected by a treatment-associated long-term neurocognitive decline; therefore, recent approaches are trying to preserve cognitive function following WBRT. One of these approaches is to administer memantine as a neuroprotective agent during treatment[10]. Another is to spare the hippocampus during WBRT (HA-WBRT) to avoid memory impairment[9, 13]. A phase III trial by Brown et al. from 2020 addresses a combination of both approaches[14]: In here, HA-WBRT plus memantine showed significantly better preservation of cognitive function and patient-reported symptoms than regular WBRT plus memantine. For better local control rates, a simultaneous/sequential boost to the metastases can be added to WBRT[15–18]. The ongoing multicentric HIPPORAD (NOA-14) trial addresses this approach (results are pending)[15].

A different approach is the use of single high dose SRS for more than four BMs while sparing the remaining brain parenchyma[6, 19]. Yamamoto et al. have applied SRS to up to ten BMs in a multicentric prospective non-randomized observational study and showed that survival and toxicity for patients with five to ten BMs was non-inferior to patients with two to four BMs[20]. Even the long-term effects after median 12.0 months (range 0.3–67.5 months) were non-inferior[21]. According to further reports by Yamamoto et al., even more than ten BMs may be eligible for SRS in carefully selected patients[22, 23].

Although Yamamoto et al. have demonstrated non-inferiority, a major problem of SRS of multiple metastases is the cumulative duration of multiple treatments[24]. When using conventional multi-isocenter linear accelerator (LINAC) based SRS, plans get exponentially more complex with each additional metastasis, as dose contributions of one lesion's plan to the other lesions have to be taken into account. Since each metastasis is treated with a separate isocenter, additional time is required for patient setup and verification. For three BMs, this can easily add up to treatment times of 60 minutes. Therefore, not only the treatment planning, but also the irradiation itself is a time-consuming process.

To solve this problem, specific algorithms have been developed for VMAT or dynamic arc therapy, in which a single isocenter is used while all metastases are simultaneously treated[25, 26]. Brainlab (Munich, Germany) has developed a specific single-isocenter 4π dynamic conformal arc (SIDCA) algorithm and included it in their Elements Multiple Brain Mets SRS software. Using this solution, up to 12 BMs have been irradiated simultaneously in this study, with approximately 20 minutes total beam-on time in most cases. To the best of our knowledge, the Department of Radiation Oncology of the University Hospital, LMU Munich has been the first center worldwide to use this technique to irradiate multiple BMs simultaneously using a VersaHD® LINAC (Elekta, Stockholm, Sweden). Moreover, there are only a few reports of clinical experience with this new technique. In this study the safety and feasibility of SRS using SIDCA was analyzed. The aim of the study was to prove that SRS is a safe, time-efficient and effective alternative to WBRT.

Materials And Methods

Study design and participants

All patients included in this analysis were irradiated with SRS using SIDCA of at least 2 metastases of all tumor entities except lymphoma, germinoma or small-cell lung cancer. Patients with disseminated cerebral metastases or signs of leptomeningeal disease received other treatments (such as WBRT) instead. Metastases needed a diameter of at least 3 mm and a maximum of 25 mm as a requirement for being treated with SRS. With a margin of 1 mm from the GTV, the smallest planning target volume (PTV) diameter was 5 mm, which corresponds to the isocentric width of one leaf of the VersaHD® multileaf (Elekta, Stockholm, Sweden).

Planning and Prescription

In addition to a contrast enhanced planning computed tomography (CT) scan (with iodine-based contrast agents), all patients received magnetic resonance imaging (MRI) scans with gadolinium-based contrast agents, both with a slice thickness of 1 mm. Planning CT and MRI were ideally not older than one week (maximum two weeks old) at the time of irradiation; usually both were done on the same day to reduce matching discrepancies. The delineation and planning were accomplished using the Elements Multiple Brain Mets® SRS application by Brainlab (Munich, Germany), see an example case in Fig. 1. The dose prescription for each metastasis was dependent on the size and its proximity to organs at risk (mainly optical pathway and brainstem) and was usually 18 Gy for metastases of 4.2–15.0 cm^3 size and 20 Gy for < 4.2 cm^3 (prescribed to the 80% isodose). For large metastases close to critical structures 15 Gy to the 80% Isodose could be perscribed. Additionally, the number of targets was taken into account during dose prescription. As a higher number of target volumes increases the individual lesion-based V10 and V12 values (brain volume which received 10 Gy or 12 Gy, respectively), Sahgal et al. recommended to reduce the dose for each target by 1–2Gy[27]. Following this recommendation, the prescription dose of each target was usually decreased by 1 Gy once the number of metastases exceeded 5. For the PTV, the metastasis' volume was isotropically expanded with a margin of 1.0 mm. IGRT was achieved using ExacTrac® (Brainlab, Munich, Germany) which was connected HexaPOD®-System (Elelkta, Stockholm, Sweden)[28]. Through this IGRT could achieve variation which were smaller than 0.1 mm.

Prophylactic antiedematous treatment

For irradiation, a prophylactic dexamethasone scheme was administered which usually consisted in 4-2-0 mg on the day of irradiation, followed by 2-1-0 mg, 1-1-0 mg, and 1-0-0 mg within the first 3 days of treatment. The dosage was adjusted depending on the size or location of the metastases or the presence of edema and comorbidities (e.g. diabetes), requiring appropriate reduction. For prevention of gastric ulcers, pantoprazole 40 mg per day was prescribed during the days of dexamethasone treatment.

Follow-up

To monitor the intracranial local tumor control and the formation of new metastases, thin-sliced contrast enhanced MRI was performed every 3 months after treatment. Whenever new metastases were detected, further treatment with SRS, WBRT or surgery was evaluated. In case of an increase in size of the metastases after irradiation, differentiation between treatment reaction and tumor progression was

performed using fluoroethyl-L-tyrosine positron emission tomography (FET PET)[29]. In case of inconclusive findings of FET PET, a stereotactic biopsy was performed. In addition to monitoring the intracranial control, the patients were clinically and neurologically examined during the follow-up visit. A change in treatment regimens or extracranial tumor control was recorded as well. The reported AE were described using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistics

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM, Armonk, New York, USA). Descriptive analysis was performed to describe patient and treatment characteristics. Survival analysis was performed using Kaplan-Meier estimators.

Results

Overall, 65 patients, 35 (53.8%) male and 30 (46.2%) female, were treated with SIDCA. The first patient underwent SRS in November 2017 and the last patient in June 2019. The median age at the time of SRS was 61.5 years (range 22–85 years). With 40 (61.5%) patients, the most frequent entity was non-small-cell lung cancer (NSCLC), including 34 adenocarcinomas, 2 squamous cell carcinomas and 4 neuroendocrine carcinomas, followed by melanoma with 10 (15.4%) patients and breast cancer with 7 (10.8%) patients. Figure 2 shows the entities of the cohort. 25 (38.5%) patients had no extracranial metastases and 40 (61.5%) patients had extracranial metastases at the time of treatment. The median Karnofsky Performance Status at the time of radiosurgery was 90% (range 50–100%). The median follow-up at the time of data analysis was 13 months (95% CI: 11.1–14.9 months). Details of the patient characteristics are listed in table 1.

Overall, 254 lesions were treated. 2 (0.8%) were located in the brainstem. Details on the location of metastases are given in table 1. The number of treated lesions per patient per therapy session was median 3 (range 2–12). The median beam-on time of the simultaneous treatment of all metastases at once was 23 minutes (range 12–38 minutes). There was a significant correlation between number of metastases and beam-on time (Pearson 0.516; 95%-CI 0.324–0.676; $p < 0.001$). The median dose to each metastasis was 19 Gy (range 15–20Gy). Figure 3 shows a successful treatment of a patient with 5 metastases.

In total, 32 (49.2%) patients experienced AEs. In the first month after treatment, 7 (10.8%) patients experienced acute AEs CTCAE grade 1, such as fatigue, vertigo or cephalgia, all of which could all be related to the SRS. One (1.5%) patient, who received irradiation of 4 melanoma-metastases, experienced seizures CTCAE grade 2 due to intralesional hemorrhage a week after treatment. Overall, no acute AEs CTCAE grade 3 were reported. During follow-up, 28 (43.1%) patients presented AEs: 22 (33.8%) patients experienced CTCAE grade 1 (11 of them therapy-related (16.9%)), 4 patients (6.2%) experienced CTCAE grade 2 (one of them therapy-related (1.5%)) and 3 (4.6%) patients CTCAE grade 3 (none of them therapy related). The AEs are listed in detail in table 2.

Until December 2019 30 (46.2%) patients had died, 5 of them with cerebral progressive disease. Most of the patients (26.2%) died within the first 3 months after radiosurgery. Detailed information is given in Fig. 4. The median overall survival (OS) was 15 months (95% CI 7.7–22.3). In the follow-up period 36 (55.4%) patients had neither a malignant progressive lesion nor new metastases in the brain after radiosurgery.

14 (5.5%) lesions of 11 (16.9%) patients were progressive in size after treatment. Local control of the irradiated lesions after 6 months was 97.5%. 1 (0.4%) lesion, irradiated with 15 Gy, had a histopathologically verified tumor progression 6 months after radiosurgery. This patient additionally had multiple new metastases one year after therapy and was then treated with WBRT (30 Gy in 10 fractions). 21 months after SRS and 6 months after WBRT, the patient developed 3 new metastases: 1 was surgically resected and the rest were treated with a further SRS treatment.

Moreover, 18 (27.7%) patients developed new brain metastases after their first radiosurgery during the follow-up period. After the first intracranial progression, 8 patients received WBRT and 8 patients received a second series of SRS. 2 patients also received a third radiation series: one of them was treated with SRS after a WBRT and the other one was treated with a third SRS course. 2 patients are still under active surveillance after showing only limited progression. The median cerebral progression-free survival was 18 months (95% CI 11.1–24.9). The intracranial control rate was 73.0% after 6 months.

A symptomatic radiation necrosis (RN) was diagnosed in 3 (4.6%) patients, of which 2 (0.8%) lesions in 2 (3.1%) patients were histopathologically verified. One of them was treated with steroids due to symptoms such as vertigo CTCAE grade 2 with nystagmus, which were almost identical to the initial symptoms. The other patient experienced vertigo and cephalgia CTCAE grade 1, but did not require any antiedematous treatment. Another patient developed a symptomatic RN in two metastases, which was clinically and radiologically diagnosed, but no biopsy was performed. Both lesions were irradiated with 20 Gy. The patient suffered from paresis of his left arm and was first treated with dexamethasone and then with bevacizumab in analogy to Levin et al. after insufficient response[30, 31]. 9 lesions (3.5%) in 7 (10.8%) patients were interpreted as pseudo-progression by an experienced neuroradiologist.

A total of 38 (58.5%) patients were treated with immunotherapy at some point during the course of their disease. 12 patients (18.5%) received immunotherapy within a time-period of 4 weeks before and after treatment. 14 patients (21.5%) received tyrosine kinase inhibitors (TKI). 4 of these patients (6.2%) were treated throughout the course of disease, during and after radiotherapy. Overall, these patients had only few AE, most of which were unrelated to the cranial irradiation (such as thyroiditis in 1 patient, or alopecia in 2): 2 patients (3.1%) experienced cephalgia CTCAE°I, and 2 patients (3.1%) fatigue CTCAE°I. However, 1 patient with malignant melanoma, who received nivolumab until shortly before radiotherapy, suffered from a cranial hemorrhage in the irradiated metastases a week after radiotherapy and died a month later. The symptoms included aphasia CTCAE°I and seizure CTCAE°II. No RN was detected among the patients who received immunotherapy at the time of radiation. Detailed information about immunotherapy and small molecule treatment is listed in table 1.

Discussion

Systemic treatment is of growing importance in the treatment of patients with metastatic disease. Even BM, which for a long time were not considered susceptible to systemic treatment due to them blood-brain-barrier, have been shown to be regressive under new systemic agents[32]. The best intracranial control seems to be achieved with a combination of immunotherapy and radiosurgery while not having a significantly higher rates of RN[33]. For metastatic melanoma patients, Goyal et al. stated that this combination “obviate(s) the need for whole brain radiation”[34]. Additionally, a study by Minniti et al. from 2019 showed promising results in the combination of nivolumab or ipilimumab and SRS[35]. Patients with metastatic NSCLC showed a similar pattern: Magnuson et al. presented in a retrospective multi-institutional analysis that patients who received upfront SRS followed by epidermal growth factor receptor (EGFR) TKI had superior outcome concerning OS compared to the patients who received EGFR-TKI primarily, with SRS as a salvage option[36]. Another study by Lanier et al. suggests that immunotherapy after SRS improves OS and reduces the rate of neurological deaths of patients with melanoma or NSCLC[37]. In addition to the benefits in treatment outcome, SRS also offers practical advantages for oncological treatments in general: by limiting the duration of the treatment to one day (compared to two weeks for WBRT with 30 Gy in 10 fractions), the systemic treatment does not have to be paused or postponed for too long, so that treatment can be started or continued in cases of acute systemic progression.

To date, SRS has mostly been limited to patients with a certain number of metastases[6, 19]. The question remains whether there is a limit to how many metastases can be irradiated using SRS. Hatiboglu et al. suggested, that the total tumor volume has a greater influence on the whole brain dose than the number of metastases[38]. In fact, a dosimetric analysis by Becker et al. showed that theoretically 40 metastases of different sizes could be irradiated radiosurgically with Gamma Knife® before reaching a whole brain dose of 8 Gy, corresponding to the dose of a single fraction WBRT, had been reached[39, 40]. As already mentioned above, Yamamoto et al. were able to show that SRS of 5–10 metastases is non-inferior to SRS of 2–4 metastases[20]. Treatment of more than 4 metastases might still be a reasonable approach; this is also recommended as an option in the NCCN guidelines for viable cases (Version 1.2020). However, it is important to find a suitable radiation technique for this treatment.

This study tested the simultaneous irradiation of multiple metastases using SIDCA on a VersaHD® LINAC from Elekta (Stockholm, Sweden). Other techniques such as VMAT using HyperArc® (Varian Medical Systems, Palo Alto, California, USA) were tested before with good results[26, 41, 42]. From a pure dosimetrical point of view, SIDCA was compared with VMAT in a 2019 study: The SIDCA plans were reevaluated using Monaco® (Elekta, Stockholm, Sweden) as VMAT plans. According to the study, SIDCA can potentially ensure better protection of healthy brain tissue and superior treatment efficiency with a steeper dose gradient if the target volume is nearly spherical, while for non-spherical volumes VMAT was able to achieve higher conformity[43]. Using SIDCA, the safety and feasibility was now clinically tested within this trial. As described in the results, the AEs were only very limited, most of them only being CTCAE grade 1. Only 3 patients experienced seizures CTCAE grade 3: one resulted from intracranial

bleeding after a massive progression, the other from leptomeningeal disease, and the last one occurred after receiving WBRT due to disseminated intracranial progress. Furthermore, 5 (7.6%) patients experienced CTCAE grade 2 AEs, one of which was cephalgia due to post-therapeutic edema, which could be treated with dexamethasone. One patient experienced seizures due to improper medication intake of anticonvulsive medication. Another one due to intracranial hemorrhage a week after SRS. The last two patients had alopecia following systemic treatment. Concerning RN, the incidence with 4 lesions (1.6%) in 3 patients (4.6%) was lower compared to other literature[44]. This can probably be explained with the small margin of 1 mm and the rationally adapted median dose to the PTVs of 19 Gy. The prophylactic administration of dexamethasone might have been a protective factor as well. Altogether, simultaneous SRS with SIDCA showed only few side effects in this prospective monocentric registry trial.

Unfortunately, the number of patients receiving parallel immunotherapy was too low, and their follow-up too short to show any significant additive effect, higher toxicities or abscopal effects. This aspect will be highlighted further in the future.

Conclusions

The simultaneous radiosurgical irradiation of multiple metastases using SIDCA could be applied safely and efficiently in this prospective monocentric registry trial. Long-term observations for patients with over 4 metastases, especially in combination with systemic treatment, are needed for further validation of this finding.

List Of Abbreviations

AE adverse effects

CT computed tomography

CTCAE common terminology criteria for adverse events

EGFR epidermal growth factor receptor

FET PET fluoroethyl-L-tyrosine positron emission tomography

HA-WBRT hippocampal avoidance whole brain radiotherapy

LINAC linear accelerator

MRI magnetic resonance imaging

NSCLC non-small-cell lung cancer

PTV planning target volume

RN radiation necrosis

SIDCA single-isocenter dynamic conformal arc

SRS stereotactic radiosurgery

TKI tyrosine kinase inhibitors

WBRT whole brain radiotherapy

Declarations

Ethics approval and consent to participate

The declaration of Helsinki has been obeyed in all points.

This study was approved by the ethics committee of the LMU University Hospital Munich (Nr. 573-15). Informed consent was obtained from all participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Brainlab (Munich, Germany) supported this project. Apart from that, the authors declare that they have no competing interests.

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Authors' contributions

RB drafted the Manuscript. RB and AK collected the data. RB, IH, JH, SG and MN were involved in treatment planning. RB, AK, IH and DF performed statistical analysis. JH, SG and MR were physicist advisors. RF evaluated and interpreted magnetic resonance imaging. NT gave surgical advice. SC, CB and MN supervised the project. All authors read and approved the final manuscript

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Tables

Due to technical limitations the Tables are available as downloads in the Supplementary Files.

Figures

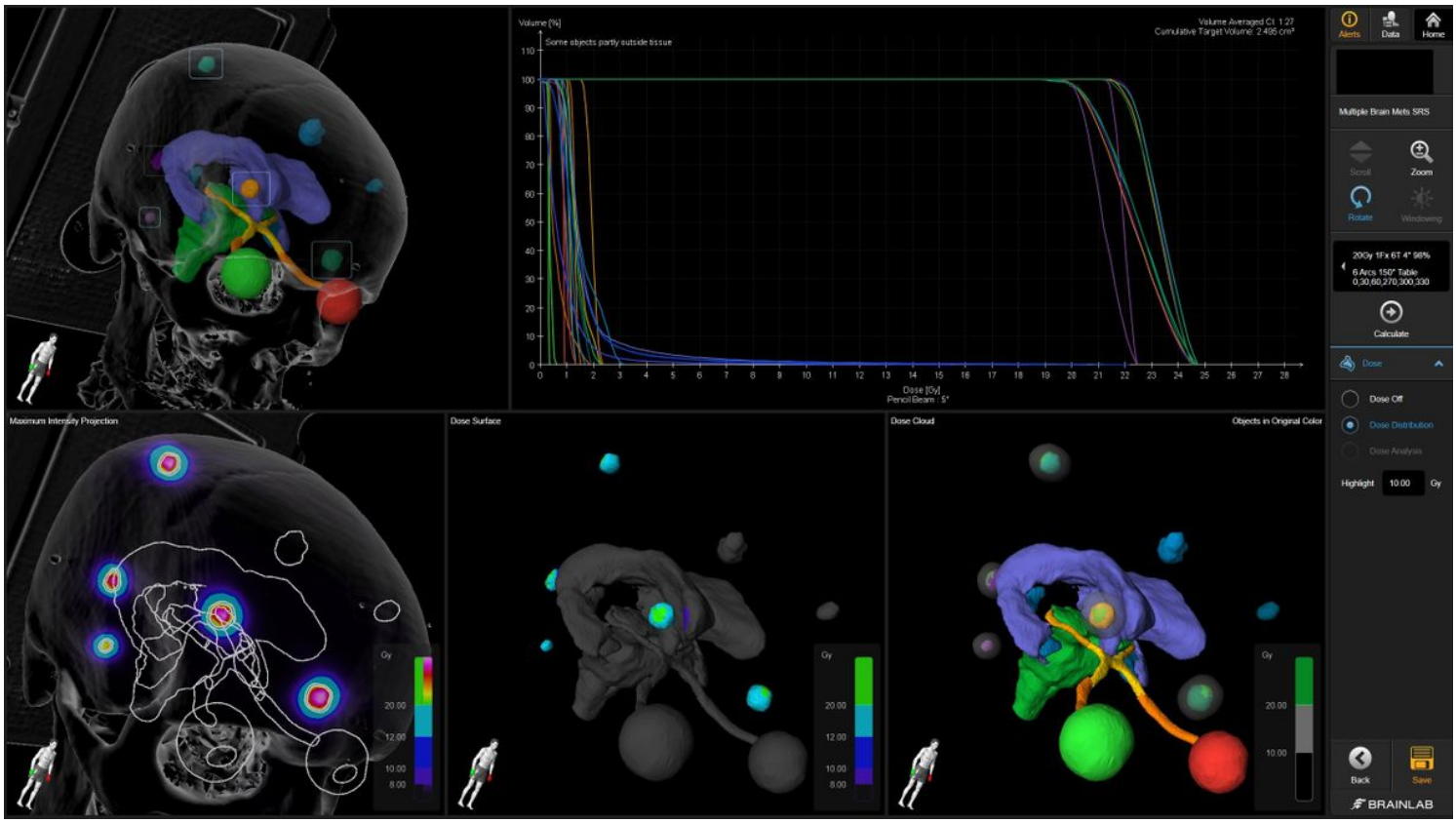

Figure 1

A screenshot of the planning interface of the Multiple Brain Mets® SRS application by Brainlab (Munich, Germany)

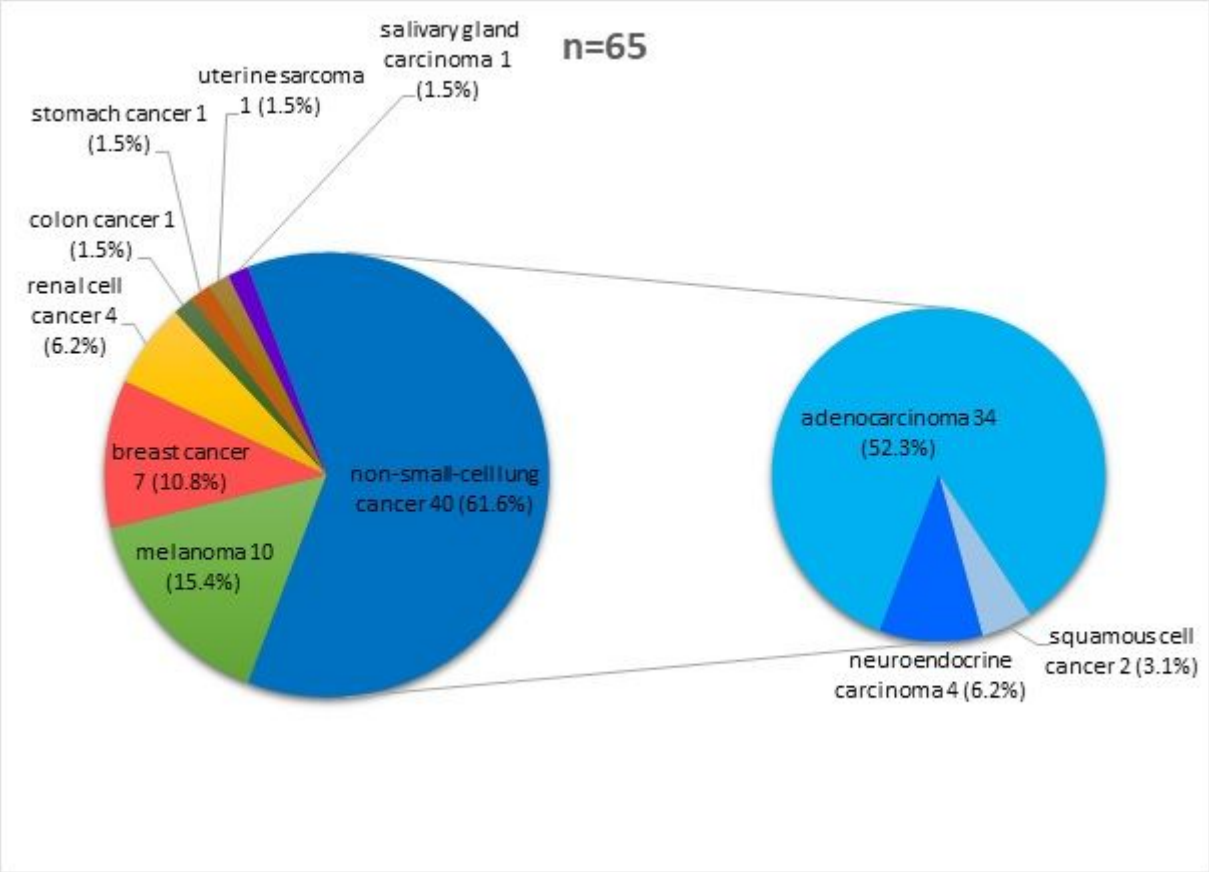

Figure 2

A depiction of the distribution of all entities for all patients (N=65)

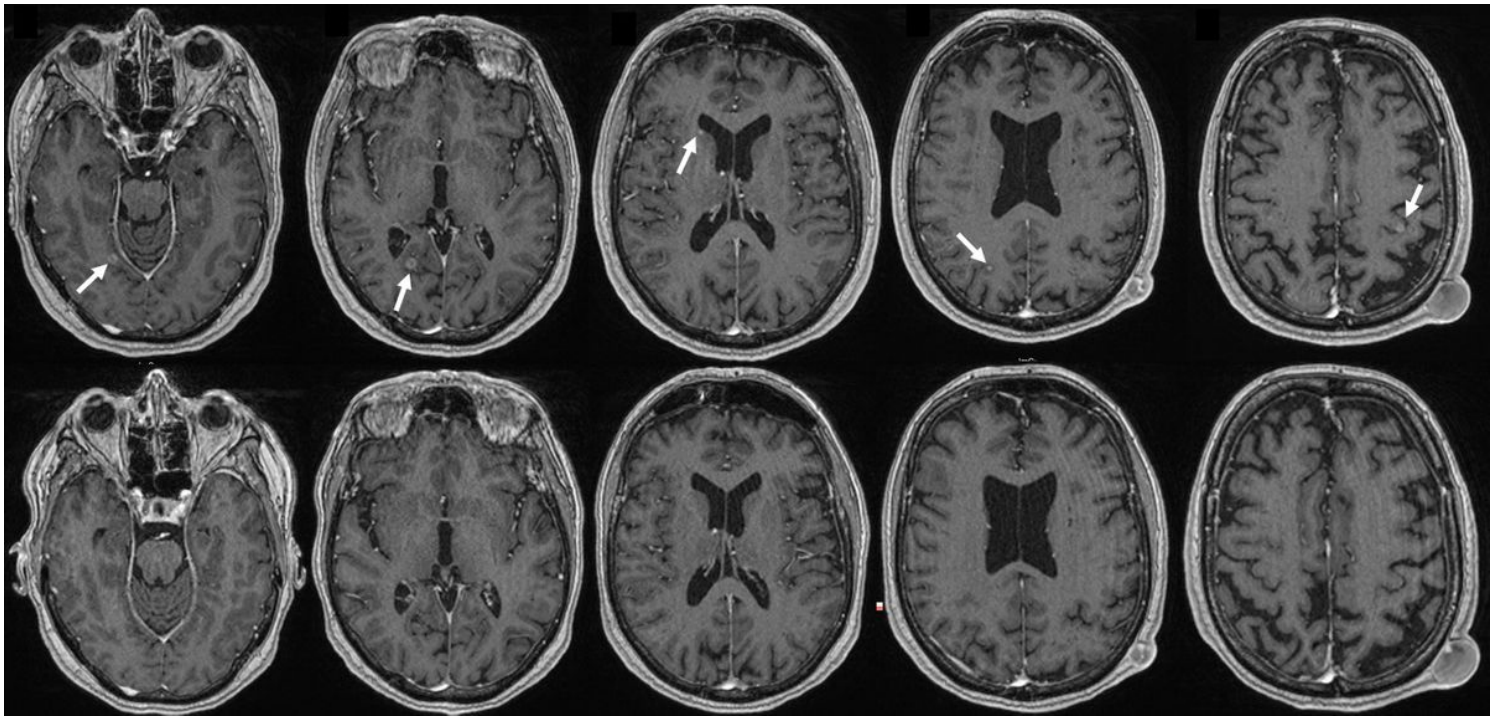

Figure 3

The magnet resonance imaging of a patient with 5 brain metastases of a NSCLC, which were treated simultaneously with stereotactic radiosurgery. The top row shows the T1 sequence at the time of the treatment (the white arrows indicating the metastases); the bottom row shows the equivalent pictures 3 months after treatment. The bubonic extracranial structure on the left is an atheroma.

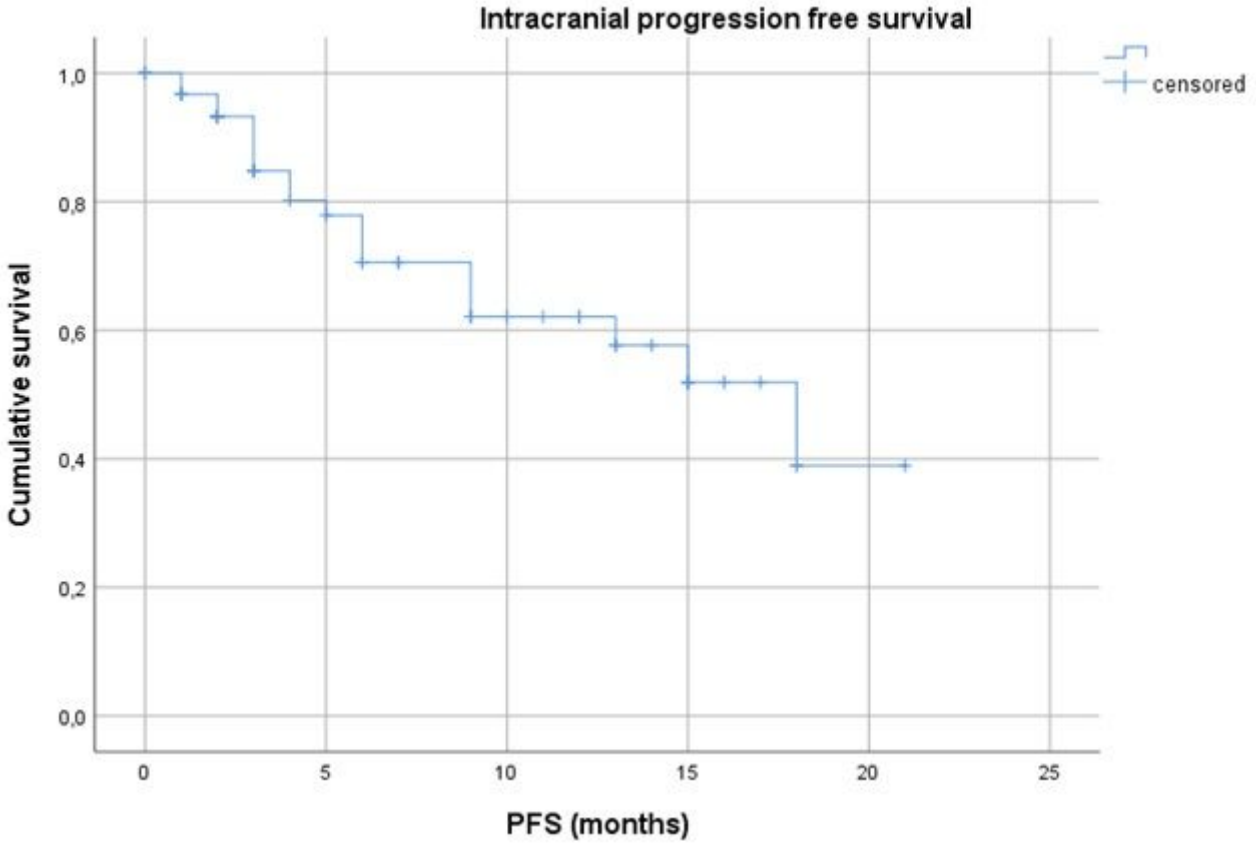

Figure 4

Kaplan-Meyer curves of intracranial progression free survival and overall survival.

Supplementary Files

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- Table1Rev.xlsx
- Table2.xlsx