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INITIAL EXPERIENCE WITH USING FRAMELESS IMAGE-GUIDED RADIOSURGERY FOR THE TREATMENT OF BRAIN METASTASES

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Aim: **Recent technologic advances have led to the development of frameless radiosurgery. We report our initial results using frameless image-guided radiosurgery for the management of brain metastases.** ***Methods***: **Over a 2-year period, 16 patients harboring 28 lesions were treated in our institution. 12 of 16 patients were treated in a single fraction, but 4 patients were treated using fractioned stereotactic radiotherapy in 3–5 fractions. The maximum target diameter, as determined by T1 — weighted contrast — enhanced magnetic resonance imaging were < 4 cm in all patients. 8 patients (50%) received WBRT (3 Gy in 10 fractions to a total dose of 30 Gy) prior to stereotactic radiosurgery, and were treated with SRS for either lesion progression or new lesions. The total treatment volume for each patient was the sum of the treatment volumes for all treated metastases. The median total treatment volume was 18.63 cm^3 (range 1,85–47.03 cm^3).** ***Results***: **Median overall survival time of entire group were 10 months (95% confidence interval 7.470–12.530 months). Of the 3 (11.11%) lesions that showed complete response, all were associated with breast cancer. Partial response was seen in 8 (29.62%) cases. Stable disease was seen in 13 (48.14%) cases, but 3 (11.11%) cases showed progression of disease.** ***Conclusion***: **Further studies are needed to to match the treatment results with other available modalities to optimize and individualize care of patients with brain metastases.**
Key Words: **brain metastases, frameless image-guided radiosurgery.**

Brain metastases represent an important cause of morbidity and mortality and may occur in 20–40% of patients with cancer [1]. The incidence of brain metastases has increased over time as a consequence of the increase in overall survival for many types of cancer and the improved detection by magnetic resonance imaging (MRI).

Current treatment options for brain metastases include surgical resection, stereotactic radiosurgery, whole brain radiation therapy (WBRT), hypofractionated stereotactic radiotherapy, and more recently chemotherapy aģents with some degree of central nervous system activity [2, 3].

In the last 20 years radiosurgery in addition to surgery and whole-brain radiotherapy, by virtue of its noninvasive nature and high lesion control rates, has emerged as one of key options for patients with brain metastases [4].

Radiosurgery has been demonstrated to result in superior local control compared with WBRT alone. Frame-based methods of radiosurgery using either LINAC or gamma unit devices are well established.

Frameless image guidance as applied to radiosurgery describes a method whereby high-resolution imaging is obtained at the time of treatment for patient positioning purposes and implies that patient immobilization is not obtained with rigid skeletal fixation, but rather with the noninvasive use of a mask.

Frameless image-guided methods in the setting of single-fraction radiosurgery have as their primary advantage the potential for improved patient comfort. As there no sedation or anesthesia is used, no vital monitoring is required. Frame-based radiosurgery methods have a long history, and the reliability of these methods is not in dispute. In contrast, since image-guided methods are relatively new, few reports are available detailing clinical results for common applications of this technology.

Since 2010, Novalis frameless image-guided radiosurgery (IGRS) system is available in Riga East Clinical University Hospital and we report our initial results using frameless IGRS for the management of brain metastases.

MATERIAL AND METHODS

The records of patients with brain metastases who were treated with IGRS in Riga East Clinical University Hospital of one or more lesions between January, 2010 and March, 2012 were retrospectively reviewed. Approval of Riga East Clinical University Hospital Medical ethics committee was obtained.

Over a 2-year period, 16 patients harboring 27 lesions were treated in our institution. Patients were offered treatment for metastatic disease of the brain with one or more metastases and a Karnofsky Performance Scale score of 70 or greater at time of initial presentation to our clinic. In the patient sample were represented 5 male and 11 female patients with mean age 59.88 years (min = 45, max = 75, SE = 2,194). The majority (n = 8) of patients had brest cancer metastases (Table 1). 12 patients demonstrated metachronos development of metastasis, whereas the others revealed synchronous development. There were 11 cases that presented with one metastasis, 3 cases with two metastases, 1 case with five metastases and 1 case with six metastases.

12 of 16 patients were treated in a single fraction, but 4 patients were treated using fractioned stereotactic radiotherapy in 3–5 fractions (Table 2). The maximum

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Abbreviations used: fSRT – hypofractionated stereotactic radiotherapy; IGRS – image-guided radiosurgery; MRI – magnetic resonance imaging; SRS – stereotactic radiosurgery; WBRT – whole brain radiation therapy.

target diameter, as determined by T1-weighted contrast — enhanced MRI were < 4 cm in all patients. Eight patients (50%) received WBRT (3 Gy in 10 fractions to a total dose of 30 Gy) prior to stereotactic radiosurgery, and were treated with SRS for either lesion progression or new lesions. Other eight patients did not have WBRT during the study period.

Table 1. Distribution of tumor types in 16 patients

Tumor type	Number of patients	Number of metastases
breast	8	13
melanoma	2	3
lung	3	7
ovary & cervix	2	3
non-Hodkin's lymphoma	1	1

Table 2. Treatment modalities used

Treatment modality	Number of patients	Target (volume range)	Marginal dose (range)
IGRS	9	25.12 cm^3 (2.03–47.03)	18 Gy (15–24)
WBRT + IGRS	3	8.15 cm^3 (1.85–15.79)	18 Gy (18–20)
WBRT + fSRT	4	22.36 cm^3 (6.80–39.47)	15.35Gy in 3–5 fractions

The treatment isodose volume for each metastasis was calculated using GammaPlan software. The total treatment volume for each patient was the sum of the treatment volumes for all treated metastases. The median total treatment volume was 18,63 cm^3 (range 1,85–47.03 cm^3).

Patients were followed up with contrast-enhanced MR imaging at 6–8 weeks following SRS treatment and then every 3 months until the end period of data collection or patient demise.

Response criteria to treatment used were defined on the basis of MRI scans as follows: complete response (CR), as complete resolution of the enhancing lesion, partial response (PR), >50% reduction in the size of the lesion, stable disease (SD), no change in the dimension of the lesion, or < 50% reduction, and progression of disease (PD), > 25% increase in the size of the lesion.

Survival was calculated from the date of radiosurgery to the last follow-up evaluation or death.

Radiosurgery technique. Patients were immobilized during computed tomography (CT) and treatments using the BrainLAB non-invasiv stereotactic immobilization mask system.

MRI scan was available for each patient to help to define the target volume. The tumor was delineated using MRI images and after that co-registration between CT and MRI images was done in order to transfer target volume to CT images that are used for dose calculations. The clinical target volume (CTV) was defined as the union of GTVs delineated on MRI images as well as on CT-scans. No margin was added for subclinical extension. The margin for the planning target volume (PTV) was 1 mm in all directions added to the CTV.

Stereotactic radiosurgery (SRS) was planned with Eclipse™ (*Varian Medical Systems INC, USA*) treatment planning system (TPS) using volumetric intensity modulated dose delivery by RapidArc™ (*Varian Medical Systems INC, USA*) or intensity modulated radiation therapy (IMRT) with 7–9 intensity modulated treatment fields (Fig. 1). Treatment plan was normalized to 80% isodose line and normalized 100% isodose line encompassed the PTV. Linear accelerator NovalisTx™ equipped with a high-definition multileaf collimator (MLC 120HD) was used for SRS delivery. All plans were delivered using photon energy 6 MV and dose rate of 1000 monitor units (MU) per minute. For patient position correction, ExacTrac® 6D (3 transversal directions and 3 rotations) Image-Guided Radiotherapy (IGRT) System (BrainLAB *GMBH, Munich, Germany*) was used.

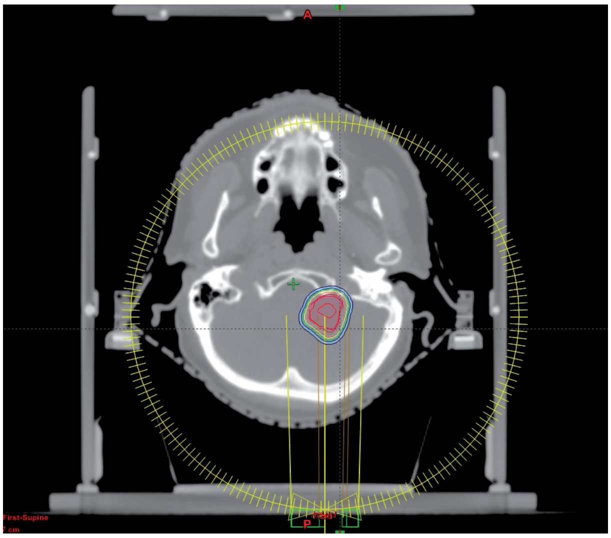

Fig. 1. CT images with isodose lines showing a treatment plan of brain metastasis

Quality assurance procedures. All treatment plans were verified from dosimetric point of view via complex verification procedure, which included dose plane measurements and point dose measurements in phantom and Winston — Lutz test. Dose plane measurements were performed using Gafchromic EBT 2 films end evaluated performing gamma index method. Generally results were considered acceptable if more than 90% of evaluated points passed gamma criteria 1 mm/5%. Point dose measurements were performed using pinpoint 3D (*PTW, Freiburg, Germany*) ionization chamber. The tolerance level for the point dose measurements was set to 3%. The treatment unit was considered to be appropriate for treatment delivery if isocentre sphere, as measured via Winston — Lutz test, did not exceeded 1 mm.

Statistical methods. Survival probability was estimated with the Kaplan — Meier method. Log-rank test was used to test wether there was a difference between the survival time of different groups of treatment. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS).

RESULTS

Median overall survival time of entire group were 10 months (95% CI 7.470–12.530 months) (Fig. 2).

Overall survival depending on the type of therapy (p = 1.01): WBRT+FSRS (4 patients) — median overall survival were 14 months (95% CI 2.240–25.760 months); WBRT+SRS (3 patients) — median overall survival were 7 months (95% confidence interval 2.199–11.801 months);

SRS (9 patients) — median overall survival were 10 months (95% confidence interval 5.842–14.158 months).

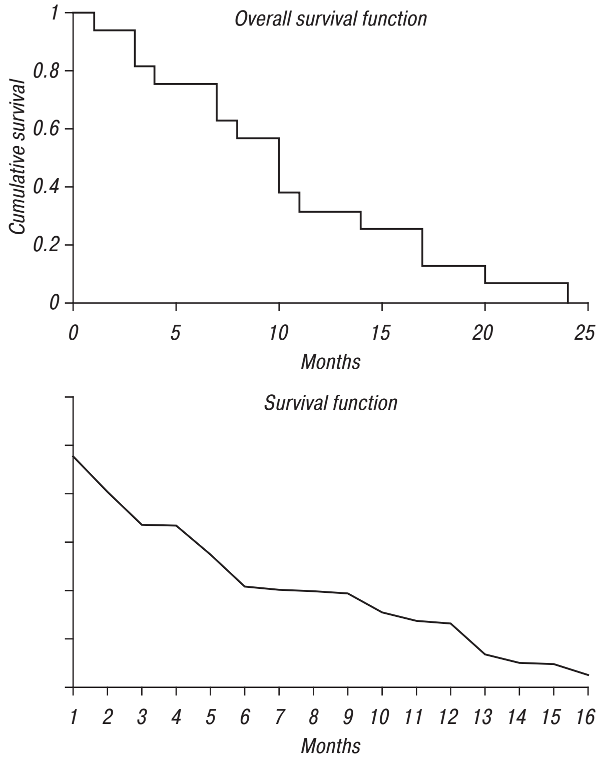

Fig. 2. Median overall survival time for entire group — 10 months (95% CI 7,47–12,53 months)

Regarding overall survival depending on the type of tumor (p = 1.07): breast cancer (8 patients) — 11.375 months (95% CI 8.21–11.78 months); lung cancer (3 patients) — 10.33 months (95% CI 3,8–16.867 months); melanoma (2 patients) — 9 months (95% CI 0–24.68 months).

5 (31.25%) patients developed new metastases following radiosurgery treatment.

Of the 3 (11.11%) lesions that showed CR, all were associated with breast cancer. PR was seen in 8 (29.62%) cases (Fig. 3, 4), and were associated with breast cancer in 5 cases and 1 each with ovary, lung and non-Hodkin's lymphoma cancers. SD was seen in 13 (48.14%) cases. These patients included 5 with breast cancer, 5 with lung cancer, 1 with melanoma, 1 with cervix, and 1 with ovary cancers. 3 (11.11%) cases showed PD — 2 melanoma cancer, and 1 lung cancer patients.

At the time of data analysis, 9 of the 16 patients in our study group were still alive, 7 had died during the reporting period.

During follow up, brain radionecrosis was registered in one patient with melanoma 12 month after SRS. Diagnosis was suspected by MRI (at the moment SPECT and PET examinations are not available in Latvia) and confirmed by histological examination after operation which was done because of suspected progression of the disease with mass efect.

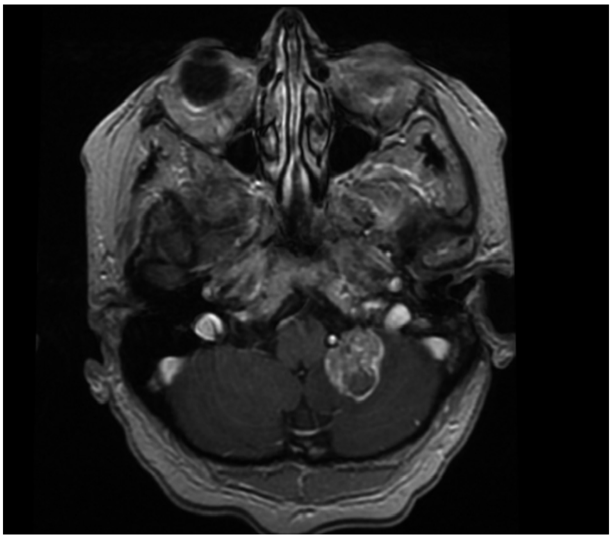

Fig. 3. Patient 60-year-old woman with posterior fossa lesion secondary to metastatic breast cancer

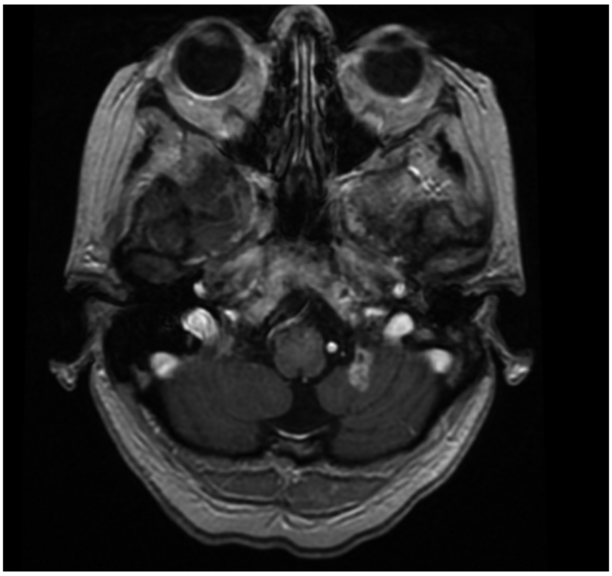

Fig. 4. Follow-up MR image obtained 6 month after treatment showing substantial reduction of metastasis volume (PR to treatment)

DISCUSSION

Brain metastases are a common complication of cancer, with an overall incidence estimated to be 8–11 per 100 000 [5]. Radiosurgery has emerged as a key method of providing definitive local control for brain metastases in addition to surgery and WBRT [6].

The use of frame-based skeletal immobilization for stereotactic procedures has a long history dating back to the 1950s with the introduction of stereotactic systems designed by Leksell, Talaraich, Reichert and Mundinger, Todd and Wells, and others [7].

Stereotactic radiosurgery permits the delivery of a single high dose of radiation to a target of 3–3,5 cm of maximum diameter by using gamma-knife (multiple cobalt sources) or linear accelerator (Linac) through a stereotactic device. The rapid dose fall-off of SRS minimizes the risk of damage to the surrounding normal nervous tissue. Studies have demonstrated that the application accuracy of these devices is on the order of 1 mm [8].

In patients with newly diagnosed brain metastases a decrease of symptoms, a local tumor control (defined as shrinkage or arrest of growth) at 1 year of 80–90% and a median survival of 6–12 months have been reported [9, 10]. Metastases from radioresistant tumors, such as melanoma, renal cell carcinoma and colon cancer, respond to SRS as well as do metastases from radiosensitive tumors. Radiosurgery allows the treatment of brain metastases in almost any location. The type of radiosurgical procedure, gamma-knife or Linac based, does not have an impact on the result [11]. Survival following radiosurgery is comparable with that achieved with surgery [9, 10].

The reliable immobilization and target localization accuracy of invasive frame-based radiosurgery have established the technique as a gold standart, but it is associated with significant disadvantages. Many patients consider head frame placement to be a traumatic experience. Use of the stereotactic frame does have some disadvantages including the procedural discomfort for most patients, with awake placement being typically performed with local anesthetic only. Frame-placement involves risk of bleeding and infection, and requires pre-medication. Furthermore, the care of patients wearing head frames creates a clinical resource burden on the day of care, requiring dedicated nursing and physician support. Frame-based treatment also requires treatment planning to be completed following frame placement on the day of treatment, making it less feasible to incorporate advanced dose planning techniques such as IMRT. Head frames may also slip, compromising treatment accuracy, and potentially resulting in injury to the patient [12].

The disadvantages associated with invasive head frames become of greater concern as more patients receive radiosurgery, and more are being treated on multiple occasions. It becomes important to optimize patient comfort and treatment efficiency.

The use of frameless radiosurgery is evolving and early reports suggest similar outcomes to patients treated with frame-based radiosurgery [13–15]. Also, high control rates are seen for small lesions in which spatial precision in dose delivery is critical [16]. However, the optimal management of brain metastases remains controversial [17].

From our data due to small number of patients in treatment groups its hard to make definite decisions, but our treatment results are compareable to other available studies.

However, surgery continues to play an essential role in the management of lesions complicated by mass effect or after failure of less-invasive treatment methods [18].

In conclusion, we present our early data and experience to control of brain metastases using frameless IGRS method. Further studies are needed to match the treatment results with other available modalities to optimize and individualize care of patients with brain metastases.

STATEMENT OF CONFLICT OF INTEREST

The authors state no conflict of interest.

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