Original Research Article

Local control and overall survival after frameless radiosurgery: A single center experience

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Introduction: Stereotactic radiosurgery (SRS) has been increasingly advocated for 1–3 small brain metastases. The goal of this study was to evaluate the clinical results in patients with brain metastases treated with LINAC-based SRS using a thermoplastic mask (non-invasive fixation system) and Image-Guided Radiotherapy (IGRT).

Material and Methods: In this single-institution study 48 patients with 77 brain metastases were treated between February 2012 and January 2014. The prescribed dose was 20 Gy or 18 Gy as a single fraction. SRS was performed with a True Beam STX Novalis Radiosurgery LINAC (Varian Medical Systems). The verification of positioning was done using the BrainLAB ExacTrac X-ray 6D system and cone-beam CT.

Results: In 69 of 77 treated brain metastases (90%) the follow-up was documented on MR imaging performed every 3 months. Mean follow-up time was 10.86 months. Estimated 1-year local control was 83%. In 7/69 brain metastases (10%) local failure (LF) was diagnosed. Median progression free survival (PFS) was 3.73 months, largely due to distant brain relapse. A GTV of ≤2.0 cm³ was significantly associated with a better PFS than a GTV >2.0 cm³. Extracranial stable disease and GTV ≤2.5 cm³ were significant predictors of OS. We observed 2 cases of radiation necrosis diagnosed by histology after surgical resection. No other cases of severe side effects (CTCAE ≥3) were observed.

Conclusion: LINAC-based frameless SRS with the BrainLAB Mask using the BrainLAB ExacTrac X-ray 6D system for patient positioning is well tolerated, safe and leads to favorable crude local control of 90%. In our experience, local control after frameless (ringless) SRS is as good as ring-based SRS reported in literature. Without invasive head fixation, radiotherapy is more comfortable for patients. Whole brain radiotherapy makes the dose uniform, so it can be used to salvage patients who develop less side effects compared with patients who are treated with it, will develop less side effects compared with patients who are treated with whole brain radiotherapy (WBRT), especially concerning neurocognition [7]. It can also be used to salvage patients who have a high incidence of up to 65% during the disease trajectory, dependent on primary tumor type, and can cause significant morbidity and mortality [1,2]. Stereotactic radiosurgery (SRS) has become a standard of care over the years in patients with 1–3 small brain metastases [3–6]. It is effective regarding in-field control and patients who are treated with it, will develop less side effects compared with patients who are treated...
underwent WBRT as primary therapy [8–10]. Local control after SRS ranges between 70% to 90% [11–14].

In patients treated with linear accelerator (LINAC)-based SRS the head immobilization was generally realized by invasive head fixation using a stereotactic ring, at least during the first decades. Due to the development of LINACs with image-guided radiotherapy (IGRT) capability, the head positioning can now be accomplished with a thermoplastic mask. The advantage of the mask is that it is more convenient for the patients, is not invasive and the treatment planning can be done one or more days before the delivery of the treatment.

In this retrospective single-institutional study we investigated local control (LC) as a primary endpoint in patients undergoing SRS for brain metastases. Intracranial progression-free survival (PFS), distant intracranial tumor control (DC), overall survival (OS) and side effects were secondary endpoints.

Material and Methods

Patient characteristics

In this single-institution study 48 patients harboring 77 brain metastases were treated by SRS between February 2012 and January 2014. The patient characteristics are summarized in Table 1.

Median age was 58 years (range 22 to 79 years), 25 (52%) men and 23 (48%) women were included. The most common primary tumors were non-small-cell lung cancer, malignant melanoma and breast cancer (Table 1). Extracerebral metastases were found in 36/48 patients (75%). Twelve of 48 patients (25%) had only brain metastases. Eighteen of 48 patients (37.5%) had stable extracranial disease and 30/48 patients (62.5%) were staged as having progressive disease.

The present work complies with the principles laid down in the Declaration of Helsinki and was approved by the appropriate ethical committees in the institution in which it was performed.

| Table 1 | Patients’ characteristics (others: bladder carcinoma, hypopharynx carcinoma, oropharynx carcinoma, colon carcinoma, unknown primary). |
|---------|-------------------------------------------------------------------------------------------------------------------------------------|
| Number of Patients | 48 |
| Number of treated Brain metastases | 77 |
| Number of brain metastases at the first SRS | |
| n = 1 | 10 | 20.8% |
| n = 2 | 11 | 22.9% |
| n = 3 | 6 | 12.5% |
| n = 4 | 8 | 16.7% |
| n ≥ 5 | 13 | 27.1% |
| Local Failures | 7/69 | 10% |
| Age | Median | 58 |
| Gender | Male | 25 |
| Female | 23 |
| Primary tumor site | NSCLC | 27 | 56.3% |
| Melanoma | 9 | 18.8% |
| Breast cancer | 7 | 14.6% |
| Others | 5 | 10.4% |
| Extracranial Metastases | Yes | 36 | 75.0% |
| No | 12 | 25.0% |
| Extracranial stable disease | Yes | 18 | 37.5% |
| No | 30 | 62.5% |
| RPA classification | I | 2 | 4.3% |
| II | 45 | 93.8% |
| III | 1 | 2.1% |

Radiation therapy

Radiotherapy planning was based on computed tomography (CT) with 2 mm slice thickness in the early phase of the study and 1 mm afterwards, i.e. when most patients were treated. Patients were immobilized in a thermoplastic mask (BrainLAB, Feldkirchen, Germany), as shown in Fig. 1.

The gross tumor volume (GTV) for each brain metastasis was defined on gadolinium enhanced magnetic resonance imaging (GdT1-MRI, Siemens ESPREE, Siemens Medical Systems, Erlangen, Germany) with 1 mm slice thickness (MP-Rage sequence) [15]. For each patient a planning CT and an MRI were performed at the same day. The radiosurgery was performed two days after the planning CT/MRI. Treatment planning was performed with iPlan RT Image 4.1.1 (BrainLab, Feldkirchen, Germany). The planning target volume (PTV) was defined as GTV plus 1 mm. Irradiation dose was prescribed to ensure coverage of at least 80% of the PTV with the prescription dose. The target volume covered 100% of the prescribed dose; the allowed maximum dose in the PTV was 125%. The prescribed dose was 20 Gy or 18 Gy (80% isodose) as a single dose. The dose of 18 Gy was used when the brain metastases were located within or next to the brain stem. SRS was performed with a True Beam STX Novalis Radiosurgery LINAC with 6 MeV photons. Patient positioning and positioning verification was done using the BrainLAB ExacTrac® X-ray 6D system and subsequent cone-beam CT (CBCT). Using infrared markers, which are detected by a camera system, the patient was moved automatically into treatment position. First, two radiographs were taken registered to digitally reconstructed radiographs (DRR) calculated from the CT used for treatment planning. From this information the deviation of the patient’s actual position from his/her intended value was computed and the corresponding shift was applied. To test the correctness of the positioning procedure a cone-beam CT scan was performed and the resulting dataset was registered with the planning CT.

Follow-up

Patient follow-up after SRS included MRI and physical examination at 6–8 weeks. Subsequent follow-up was every 3 months. Local failure was defined as an increase of the maximum diameter of the treated brain metastasis. RANO criteria were used. Distant intracranial failure was defined as new brain metastases or leptomeningeal enhancement outside the previously irradiated volume. The primary endpoint for this study was local control (LC). LC was evaluated for each treated brain metastasis. Secondary endpoints included distant intracranial tumor control (DC), intracranial progression-free survival (PFS), overall survival (OS) and side effects were secondary endpoints.
effects after SRS. PFS was defined as time to local failure, intracranial progression or death.

**Statistical methods**

LC, PFS and OS were measured using the Kaplan–Meier method. All analyses were performed with SPSS 22.0.0.0 (IBM, New York, USA) and R-Statistics [16]. Cox regression and Log Rank test were used to analyze subgroups of patients concerning LC, DC and OS. A competing risk analysis was performed with R-Statistics.

Several variables (recursive partitioning analysis (RPA) classification, GTV, gender, extracerebral metastases) were evaluated as possible predictors of outcome. GTV size was dichotomized not only by median, but also by other cut-offs in order to identify the most relevant definition of small or large, i.e. the cut-off with biggest separation of the Kaplan-Meier curves.

**Theory/calculation**

As brain metastases can lead to significant morbidity and mortality efficient and safe treatment becomes more and more important. In this work we wanted to present our data in a single center with LINAC-based frameless radiosurgery. We included all patients treated by radiosurgery from February 2012 to January 2014 and performed a retrospective analysis.

**Results**

**Patient characteristics**

Patient characteristics are described in Materials and Methods and listed in Table 1. At the time of the first SRS only 10 patients (21%) had a single brain metastasis. Thirty-eight (79%) patients had two or more brain metastases. Thirteen (27%) patients had n ≥ 5 brain metastases.

**Treatment parameters**

Treatment parameters are listed in Table 2.

Most of the brain metastases were treated with a single dose of 20 Gy (75 brain metastases, 97.4%). Two of 77 brain metastases (3%) were treated with a dose of 18 Gy. The median GTV was 0.4 cm³ (average 1.06 cm³; range 0.1 cm³ to 6.8 cm³). Sixty-three of 77 brain metastases (82%) were ≤ 2.0 cm³, 14/77 metastases (18.2%) had a size between 2.1 cm³ and 6.8 cm³.

Nine of 47 patients (19%) had WBRT before SRS. The median time between WBRT and SRS was 17 months (range 8–33 months). In 12/47 (24%) patients we performed WBRT as a salvage therapy in case of intracranial progression after SRS. The median time to salvage therapy was 6 months (range 1–12 months).

**Local and distant control**

Mean follow-up time was 10.9 months (range 1–43 months). Local control was estimated for every single treated brain metastasis of each patient. To evaluate local control, patients were censored when they died. Because some patients were treated with more than one SRS (competing risks), in case of death all brain metastases of the respective patient were censored in order to analyze every treated metastasis separately. A competing risk analysis was performed (s. Fig. 2), and the risk of death was higher than the risk of local progression.

Estimated 1-year local control was 83%, using the Kaplan-Meier method (Fig. 3). In 7/89 brain metastases (10%) local failure was detected on MRI. Median time to local failure was 4.8 months.
In 4 cases of local recurrence on MRI the diagnosis was established by imaging follow-up. Two brain metastases with local failure were resected. The third patient was treated with SRS after biopsy confirmed local recurrence.

Women (41.4 vs. 24.5 months in men, p = .011) and patients with a GTV ≤ 2.0 cm³ (38.4 vs. 8.9 months, p = .001) had a longer time without local failure. In the multivariate analysis only small GTV remained significant (p = .037).

Progression-free survival

Median intracranial progression-free survival (PFS) was 3.73 months (range 1–14 months). In 4 cases of local recurrence on MRI the diagnosis was established by imaging follow-up. Two brain metastases with local failure were resected. The third patient was treated with SRS after biopsy confirmed local recurrence.

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A GTV of ≤ 2.0 cm³ was significantly associated with a better PFS than a GTV > 2.0 cm³ (median PFS 4.38 vs. 3.19 months, p = .038).

In the multivariate Cox regression test GTV > 2.0 cm³ (p = .009) and breast cancer (p = .001) were associated with a worse PFS.

Overall survival

Thirty-three of 48 patients died during follow-up. The median survival was 8 months (95% CI 2.82–13.11; range 0.66 months to 45 months). The estimated 1-year survival rate was 35.6% using the Kaplan-Meier method (Fig. 5).

In the univariate analysis the following variables were associated with a better survival: age ≤ 58 years (median OS 15.2 vs. 7.2 months, p = .031), GTV ≤ 2.5 cm³ (median OS 11.2 months vs. 5.1 months, p = .005) and stable disease outside the brain (median OS 27 vs. 8.6 months, p = .006). For those variables a multivariate analysis was performed. Extracranial stable disease (p = .015) and GTV ≤ 2.5 cm³ (p = .012) were still significant.

The general practitioners of the patients were contacted in order to obtain the cause of death. Three patients (9%) died because of their cerebral metastases and 3 further patients (9%) died most likely because of their cerebral metastases. In eighteen patients (55%) the cause of death were not the brain metastases, in 3 patients the general practitioners did not know the reason for the patients’ death and in 6 cases we did not receive any reply.

In 46 patients we had information about the extracerebral follow-up. Forty (87%) had progressive disease, 5 patients (11%) were stable and one patient had a complete remission.

Side effects

During follow-up side effects were reported using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

All patients tolerated frameless SRS well with no severe side effects. Only fatigue was reported as acute side effect. We observed two confirmed cases of radionecrosis. In one additional case there was the suspicion of a radionecrosis on MRI follow-up. Even in patients who underwent WBRT before radiosurgery was performed or in patients who underwent WBRT during follow-up as salvage therapy after SRS no severe side effects were seen.
of the BrainLab Mask was reported before [26]. Using infrared
STX Novalis Radiosurgery LINAC with 6 MeV photons. The accuracy
of the frame is used. In our study SRS was performed with a True Beam
cobalt radiation source and for the patient positioning a stereotac-
tic frame is not desirable. The Gammaknife uses a
different vendors is not desirable. The Gammaknife uses a
durability of treatment is shorter. For many, especially smaller,
more [25]. An advantage of the LINAC-based technique is that the
results of the ExacTrac® X-ray 6D suggest that no additional CBCT is needed in the future. The radio-
surgery was performed 2 days after planning CT/MRI. Even com-
plex plans can be calculated and realized by the physicists in this
period. An invasive fixation would not be tolerated for 3 days
and would lead to a higher infection risk.
In our analysis it might be possible that local control is overes-
timated because of the statistical problem of competing risks,
which means that death from extracranial progression resulted in
censoring in the Kaplan-Meier curve. In a competing risk analy-
sis patients had a higher risk to die than to have local recurrence.
In case of local recurrence there was no histology obtained. Only in 2
patients with suspected radionecrosis we obtained a histology
which confirmed radionecrosis. Another patient had the suspicion
of radionecrosis on MRI but we did not perform an operation to
confirm radionecrosis. It is possible that occasional patients with
“local failures” had a radionecrosis instead because we did not always obtain histology.
In our data the histology of breast cancer was associated with
significantly worse PFS, but no effect on overall survival was seen.
This might be a selection bias as we had a small sample size. In lit-
erature patients with the histology of breast cancer have better
survival [27].
In 9/47 patients (19%) WBRT had been performed before SRS. In
these cases radiosurgery was a salvage strategy for symptomatic or
new brain lesions. This explains that 13 patients (27%) had \( n \geq 5 \)
brain metastases when the first SRS was performed.
Diagnosis of new brain metastases was common. Deferred
WBRT remains a possible salvage therapy. In 24% of our patients
salvage WBRT was performed. No additional serious side effects
were seen in case of salvage treatment.
Median OS was 8 months. According to the RPA classification
median OS was between 2.3 and 7.1 months for patients largely

discussion
In our experience local control after frameless SRS was as good as
the previous strategy of frame-based SRS reported in literature.
In a study by Ramakrishna et al. [17] an overall system accuracy similar to the invasive frame-based SRS was reported. An advan-
tage of frameless SRS is that the thermoplastic mask is tolerated better by the patients.
In a study by Becker et al. local control rates for brain metast-
tases at 6 and 12 months of 74% and 61% were reported after frame-based LINAC radiosurgery [18]. In the randomized trial
reported by Kocher et al. 90 patients were treated with radio-
surgery alone and 61 of them had single brain metastases [19].
Local control rates were approximately 75% at 12 months (esti-
mated from the published Kaplan-Meier curves) and 69% at 24
months. In a meta-analysis that also included the Kocher et al. data
186 patients had received radiosurgery, of whom 60% had single
brain metastases [20]. Local control was reported in 80%. Local con-
trol in our study was 90%. Estimated 1-year local control was 83%
using the Kaplan-Meier method. An intrinsic selection bias is pos-
sible as we performed a retrospective single institution study but we had similar results as reported in literature. In the study by
Breneman et al. local control with a frameless system was 80% at
one year [11]. In other institutions reporting their clinical experi-
ence with frameless radiosurgery crude rate for local control was 88% and 90% [21,22] (s. Table 3).
Compared with radiosurgery performed with Cyberknife we
found similar outcomes concerning local control [23,24]. With
the new Gammaknife icon no invasive head fixation is needed any-
more [25]. An advantage of the LINAC-based technique is that the
duration of treatment is shorter. For many, especially smaller,
departments, the increased complexity with equipment from sev-
eral different vendors is not desirable. The Gammaknife uses a
cobalt radiation source and for the patient positioning a stereotac-
tic frame is used. In our study SRS was performed with a True Beam
STX Novalis Radiosurgery LINAC with 6 MeV photons. The accuracy
of the BrainLab Mask was reported before [26]. Using infrared
markers, which are detected by a camera system, the patient is moved automatically into treatment position. During our early
experience we tested the correctness of the positioning procedure
with a cone-beam CT scan and registered the resulting dataset with
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were seen in case of salvage treatment.
Median OS was 8 months. According to the RPA classification
median OS was between 2.3 and 7.1 months for patients largely

| Author      | Year | Patients (n) | Dose (Gy) | Number of Fractions | 1-year Local Control (%) | Crude Local Rate (%) | 1-year OS (%) | Median OS (months) |
|-------------|------|--------------|-----------|---------------------|-------------------------|---------------------|---------------|-------------------|
| Breneman    | 2009 | 53           | 12–22     | 1                   | 80                      | Not available       | 44            | Not available     |
| Bilger      | 2016 | 47           | 18–20     | 1                   | 83.1                    | 90                  | 36            | 8                 |
| Chen        | 2009 | 54           | 14–20     | 1                   | 80                      | 90                  | 28            | 8.6               |
| Kamath      | 2005 | 17           | 12.5–20   | 1                   | Not available           | 86                  | Not available  | 7.1               |
| Nath        | 2010 | 65           | 14–22     | 1                   | 76                      | 88                  | 40            | Not available     |
| Minniti     | 2011 | 102          | 16–20     | 1                   | 91                      | 91                  | 58%           | 15.5              |
treated with primary WBRT [28]. In our analysis most patients were in RPA class II (94%). GTV ≤ 2.5 cm³ and stable disease outside the brain were significant predictors of better OS. Also in the literature extracranial disease status is a well-known prognostic factor for survival [29,30].

Radiosurgery is a well-tolerated and short treatment [31]. No systemic treatment break is needed in case of extracranial progressive disease. This might increase the patients’ chance of extracranial response.

Conclusion
LINAC-based frameless SRS with the BrainLAB Mask using the BrainLAB ExacTrac® X-ray 6D system for patient positioning is well tolerated, patient-friendly, safe and leads to favorable local control (90%, crude local control).

In some patients SRS was performed as salvage treatment after WBRT or WBRBT was performed during follow-up after SRS in case of progression. In a large number of patients after the first radiosurgical treatment repeated SRS in case of progression was performed. No additional side effects were seen.

Compared to other technologies, little changes of departmental complexity, workflow and expertise are necessary. Failures in non-treated brain regions are a generally known drawback of any SRS approach. However, they can be salvaged, e.g., by WBRBT or repeat SRS.

Ethics approval and consent to participate
The present work complies with the principles laid down in the Declaration of Helsinki and was approved by the appropriate ethical committees in the institution in which it was performed. All patients were enrolled after giving informed consent.

Consent for publication
Not applicable. Consent for publication has been obtained from the respective person concerning Fig.1.

Availability of data and Materials
Data available on request from the authors.

Competing interests
The authors declare that they have no competing interests.

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No.

Authors’ contributions
AB and FF acquired and analyzed data. AB wrote the manuscript. CN, DM and OO helped to draft the manuscript. RW and VP provided technical assistance and ALG provided clinical supervision. ALG defined the study design. All authors revised the manuscript and then approved the final manuscript.

Disclosure
The authors state that they have not published or submitted the manuscript elsewhere.

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References
[1] Tsao MN, Lloyd N, Wong RKS, Chow E, Rakovitch E, Laperriere N, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev. 2012;4:CDOI3869.
[2] Lassman AB, DeAngelis LM. Brain metastases. Neurrol Clin. 2003 21(1):1–23, vii.
[3] Ahluwalia MS, Vogelbaum MV, Zhao ST, Mehta MM. Brain metastasis and radiosurgery. F1000prime Rep. 2014;6:114.
[4] Wen PY, Loeffer JS. Management of brain metastases. Oncoll Williston Park N. 1999; 13(7):941–54, 957–961, 92.
[5] Ueki K, Matsui M, Nakamura O, Tanaka Y. Comparison of whole brain radiation therapy and locally limited radiation therapy in the treatment of solitary brain metastases from non-small cell lung cancer. Neurrol Med Chir (Tokyo). 1996 Jun;36(6):364–9.
[6] Rades D, Hutterlocher S, Hornung D, Blanck O, Schild SE. Radiosurgery alone versus radiosurgery plus whole-brain irradiation for very few cerebral metastases from lung cancer. BMC Cancer. 2014;14:931.
[7] Linskey ME, Andrews DW, Asher AL, Burri SH, Kondziolka D, Robinson PD, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2010 Jan;96(1):45–68.
[8] Kurtz G, Zadeh G, Gingrich-Hill G, Millar B-A, Laperriere NJ, Bernstein M, et al. Salvage radiosurgery for brain metastases: prognostic factors to consider in patient selection. Int J Radiat Oncol Biol Phys. 2014 Jan 1;88(1):137–42.
[9] Yomo S, Hayashi M. The efficacy and limitations of stereotactic radiosurgery as a salvage treatment after failed whole brain radiotherapy for brain metastases. J Neurooncol. 2013 Jul;113(3):459–65.
[10] Kocher M, Wittrig A, Piroth MD, Treuer H, Seegenschmidt H, Ruge M, et al. Stereotactic radiosurgery for treatment of brain metastases. A report of the DSGR Working Group on Stereotactic Radiotherapy. Strahlenther Onkol Organ Dtsch Röntgenges Al. 2014; 190(6):521–32.
[11] Breneman J, Steinmetz R, Smith A, Lamba M, Warnock RE. Frameless image-guided intracranial stereotactic radiosurgery: clinical outcomes for brain metastases. Int J Radiat Oncol Biol Phys. 2009 Jul 1;74(3):702–6.
[12] Varlott JM, Flickinger JC, Niranjao A, Bhatnagar AK, Kondziolka D, Lunsford LD. Analysis of tumor control and toxicity in patients who have survived at least one year after radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys. 2003 Oct 1;57(2):452–64.
[13] Przkal D, Debus J, Lohr F, Fuss M, Rhein B, Engenhart-Cabillic R, et al. Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. J Clin Oncol Off J Am Soc Clin Oncol. 1998 Nov;16(11):3563–9.
[14] Bhattachar AK, Flickinger JC, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for four or more intracranial metastases. Int J Radiat Oncol Biol Phys. 2006 Mar 1;64(3):898–903.
[15] Brant-Zawadzki M, Gillan GD, Fritz WR, MP RAGE: a three-dimensional, T1-weighted, gradient-echo sequence—initial experience in the brain. Radiology. 1992 Mar 1;182(3):769–75.
[16] R: The R Project for Statistical Computing [Internet]. [cited 2017 May 17]. Available from: https://www.r-project.org/.
[17] Ramakrishna N, Rosca F, Friesen S, Tzecani E, Zygmanszki P, Hacker F. A clinical comparison of patient setup and intra-fraction movement using frame-based radiosurgery versus a frameless image-guided radiosurgery system for intracranial lesions. Radiother Oncol. 2010 Apr;95(1):109–15.
[18] Becker G, Jerome B, Engel C, Buchgeister M, Paulsen F, Duffner F, et al. Radiosurgery for brain metastases: the Tuebingen experience. Radiother Oncol. 2002 Feb;62(2):233–7.
[19] Kocher M, Soffetti R, Abacioglu U, Villà S, Fauchon F, Baunert BG, et al. Adjunctive whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952–26001 study. J Clin Oncol 2011;29(2):134–41.
[20] Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. Int J Radiat Oncol 2015;91(4):710–7.
[21] Kamath R, Ryken TC, Meeks SL, Pennington EC, Ritchie J, Buatti JM. Initial clinical experience with frameless radiosurgery for patients with intracranial metastases. Int J Radiat Oncol Biol Phys. 2005 Apr 1;61(5):1467–72.
[22] Chen JCT, Bugoci DM, Gravgian MR, Miller MJ, Arelkano A, Rahman J. Control of brain metastases using frameless image-guided radiosurgery. Neurosurg Focus. 2009 Dec;27(6):E6.
[23] Wang Z, Yuan Z, Zhang W, You J, Wang P. Brain metastasis treated with Cyberknife. Chin Med J (Engl). 2009 Aug 20;122(16):1847–50.
[24] Alongi F, Fiorentino A, Mascou F, Navarria P, Levra NG, Mazzola R, et al. Stereotatic radiosurgery for intracranial metastases: linac-based and gamma-dedicated unit approach. Expert Rev Anticancer Ther. 2016 Jul 2;16(7):731–40.
[25] Wozza B, Mucavic A, Tonn J-C. CyberKnife radiosurgery for brain metastases. 2012;25:201–9.
[26] Minniti G, Scaringi C, Clarke E, Valeriani M, Osti M, Enrici RM. Frameless linac-based stereotactic radiosurgery (SRS) for brain metastases: analysis of patient repositioning using a mask fixation system and clinical outcomes. Radiat Oncol Lond Engl. 2011;6:15h.

[27] Cagney DN, Martin AM, Catalano PJ, Redig AJ, Lin NU, Lee EQ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: A population-based study. Neuro-Oncol. 2017.

[28] Gaspar L, Scott C, Rotman M, Ashell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys. 1997 Mar 1;37(4):745–51.

[29] Park YH, Kim TH, Jung S-Y, Kim Y-E, Bae J-M, Kim Y-J, et al. Combined primary tumor and extracranial metastasis status as constituent factor of prognostic indices for predicting the overall survival in patients with brain metastases. J Korean Med Sci. 2013 Feb;28(2):205–12.

[30] Nieder C, Hintz M, Grosu AL. Predicted survival in patients with brain metastases from colorectal cancer: is a current nomogram helpful? Clin Neurol Neurosurg. 2016 Apr;143:107–10.

[31] Nieder C, Grosu AL, Gaspar LE. Stereotactic radiosurgery (SRS) for brain metastases: a systematic review. Radiat Oncol. 2014 Jul 12;9(1):155.