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Original Research Article

Preoperative radiosurgery for brain metastases (PREOP-1): A feasibility trial

S Rogers [a,1,*], L Schwyzer [b], N Lomax [a], S Alonso [a], T Lazeroms [a], S Gomez [a], K Diahovets [c], I Fischer [c], S Schwenne [a], A Ademaj [a,d], S Berkmann [e], A Tortora [f], S Marbacher [b], L Remonda [g], G.A. Schubert [b,h], O Riesterer [a]

[a] Radiation Oncology Centre KSA-KSB, Kantonsspital Aarau, Tellstrasse, 5001 Aarau, Switzerland
[b] Dept. of Neurosurgery, Kantonsspital Aarau, Tellstrasse, 5001 Aarau, Switzerland
[c] Dept. of Neuropathology, Kantonsspital Aarau, Tellstrasse, 5001 Aarau, Switzerland
[d] Doctoral Clinical Science Program, Medical Faculty, University of Zürich, 8032 Zürich, Switzerland
[e] Neurochirurgie Baden, Husmatt 1, 5405 Baden, Switzerland
[f] Dept. of Neurosurgery, Presidio Ospedaliero Universitario Santa Maria Della Misericordia Udine, Italy
[g] Dept. of Neuroradiology, Kantonsspital Aarau, Tellstrasse, 5001 Aarau, Switzerland
[h] Dept. of Neurosurgery, RWTH Aachen University, Aachen, Germany

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ABSTRACT

Purpose: Preoperative radiosurgery (SRS) of brain metastases (BM) aims to achieve cavity local control with a reduction in leptomeningeal relapse (LMD) and without additional radionecrosis compared to postoperative SRS. We present the final results of a prospective feasibility trial of linac-based stereotactic radiosurgery (SRS) prior to neurosurgical resection of a brain metastasis (PREOP-1).

Methods: Eligibility criteria included a BM up to 4 cm in diameter for elective resection. The primary endpoint was the feasibility of delivering linac-based preoperative SRS in all patients prior to anticipated gross tumour resection. Secondary endpoints included rates of LMD, local control and overall survival. Exploratory endpoints were the level of expression of immunological and proliferative markers.

Results: Thirteen patients of median age 65 years (range 41–77) were recruited. Twelve patients (92 %) received preoperative radiosurgery and metastasectomy and one patient went directly to surgery and received post-operative SRS, thus the primary endpoint was not met. The median time between referral and preoperative SRS was 6.5 working days (1–10) and from SRS to neurosurgery was 1 day (0–5). The median prescribed dose was 16 Gy (14–19) to a median planning target volume of 12.7 cm^3 (5.9–26.1). Five patients completed 12-month follow-up after preoperative SRS without local recurrence or leptomeningeal disease. The patient who received postoperative FSRT developed LMD after six months. There was one transient toxicity (grade 2 alopecia) and nine patients have died from extracranial causes. Patients reported significant improvement in motor weakness at 6 months ($P = 0.04$). No pattern in changes of marker expression was observed.

Conclusion: In patients with large brain metastasis without raised intracranial pressure, linac-based preoperative SRS was feasible in 12/13 patients and safe in 12/12 patients without any surgical delay or intracranial complications.

Introduction

Brain metastases (BM) are a common cause of morbidity and mortality in cancer patients. Stereotactic radiosurgery (SRS) is the high dose per fraction, small volume irradiation of BMs that aims to spare the normal brain, and is preferred to whole brain radiotherapy (WBRT) in patients with up to 10 BMS in the absence of leptomeningeal disease (LMD), due to the neurocognitive impairment [1,2] and alopecia associated with WBRT. Neurosurgical resection of BMs may be indicated to obtain histology or to relieve neurological symptoms. For BMs greater

* Corresponding author.
E-mail address: susanne.rogers@ksa.ch (S. Rogers).
[1] 0000-0003-0094-1890.

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than 2 cm in diameter, retrospective series report better local control and overall survival with the combination of surgery followed by SRS than with SRS alone [3]. Relevant clinical outcomes following postoperative SRS include rates of cavity local control, LMD, radionecrosis and neurocognitive function. Two randomised trials have demonstrated the benefit of postoperative SRS with regard to neurocognitive preservation as compared with WBRT (at 6 months 48 % vs 15 %, $p < 0.001$) [1] and to cavity local control as compared with observation (at 1 year 72 % vs 43 %) [4]. Cavity local control rates were superior with WBRT (81 %) [5] vs 61–72 % with postoperative SRS [4,5] but there was no difference in overall survival as extracranial disease was the predominant cause of death.

LMD is the spread of cancer cells along the brain's meningeal layer. Diffuse LMD, also known as sugarcoating, can occur as part of disease progression, however nodular LMD is attributed to the iatrogenic dissemination of tumour cells into the cerebrospinal fluid (CSF), at resection and an incidence of LMD of 16 % is seen after surgery alone [4]. Distant or close nodular LMD is mediated by the dissemination of tumour cells into CSF, whereas adjacent LMD and cavity recurrences may be attributed to a geographical miss of tumour cells at delineation of a poorly-defined surgical cavity. The risk of LMD (nodular and diffuse) is 6.5 times greater with postoperative SRS than with primary SRS [6]. LMD is thus a frequent (11 %-28 %) pattern of relapse following metastasectomy and radiotherapy to the surgical cavity [4,7–10], and consensus guidelines recommend a 5–10 mm extension along the dura in the event of pre-existing contact [11] to reduce leptomeningeal failure. Reported risk factors for LMD are large and/or multiple metastases, distant brain failure, infratentorial location and breast histology [12]. Piecemeal, rather than en bloc, resection may also be contributory [12].

The incidence of LMD following preoperative SRS is reported to be 0–7 %, similar to WBRT [13–15] which strongly suggests that preoperative SRS can sterilise cells that might be disseminated at surgery. Preoperative SRS takes advantage of the clearer delineation of an intact contrast-enhanced brain metastasis with the consequent benefits of a smaller planning margin of 0–2 mm (2–10 mm in the postoperative setting [11]), and resection of the irradiated volume, which both reduce the risk of radionecrosis. In addition, there is no delay to the irradiation of any additional metastases if performed synchronously with preoperative radiosurgery rather than postoperatively. Preoperative SRS is compelling, with promising retrospective reports of efficacy with minimal toxicity [14,16] and should now be evaluated prospectively to ensure high local control rates and a low incidence of LMD. The PREOP-1 trial was designed to document prospectively the feasibility of linac-based preoperative SRS in routine clinical practice and to optimise the interdisciplinary workflow prior to launching the PREOP-2 randomised trial comparing with postoperative fractionated stereotactic radiotherapy (FSRT).

Materials and Methods

Ethics approval was obtained (2020–00262) and this prospective single centre trial was registered with the German Clinical Trials Registry (DRKS00023579).

Inclusion and exclusion criteria

All patients were presented at a multidisciplinary neuro-oncology tumour board where a recommendation for resection of a BM was made, followed by a subsequent recommendation to offer participation in the PREOP-1 trial. All patients provided informed consent.

Eligibility criteria included a BM up to 4 cm in diameter for resection and up to three other BMs for radiosurgery, anticipated gross tumour resection, an estimated prognosis of at least 6 months and no contraindication to steroids or MRI. A prior histological diagnosis of a solid cancer and a Karnofsky performance status of at least 70 % were required.

Exclusion criteria included signs of raised intracranial pressure requiring urgent decompression surgery, germ cell tumour, small cell lung cancer and lymphoma histology, and LMD in CSF or on MRI other than directly adjacent to brain metastasis for resection. Prior therapy to the BM for resection and prior WBRT were not permitted.

Endpoints

The primary endpoint was the feasibility of delivering preoperative SRS in all patients prior to the scheduled date of brain metastasectomy.

Secondary endpoints were the rates of LMD, cavity local control, overall survival, neurological death, radionecrosis, toxicity (CTCAE v5.0) and patient-reported quality of life (QoL).

Exploratory endpoints included any change in the centre of mass of the BM for resection between the MRI for treatment planning and the diagnostic MRI. Furthermore, the levels of proliferation (Ki67) and of B- (CD3, CD4) and T-cell infiltration (CD8) were compared by immunohistochemistry between the primary tumour and the resected, irradiated BM.

Interdisciplinary workflow

The date for elective neurosurgical resection was set by the treating neurosurgeon and SRS could be delivered up to and including the day of resection as either an inpatient or an outpatient (Fig. 1). The protocol did not dictate the date of neurosurgery, which was set by the neurosurgeon according to capacity and clinical indication.

Treatment planning technique

A CT with contiguous 0.6 mm slices [17] in a customised radiosurgery mask (Brainlab, Germany) was fused rigidly and with deformable registration (Brainlab Elements) with a 1.5 T T1 Gd-enhanced VIBE planning MRI. A 1 mm planning target volume (PTV) margin was added to each BM. The single fraction dose was prescribed according to PTV volume, modified from Prabhu *et al* [18] (Supplementary Table 1) to cover 98–99 % of the PTV [19], with a maximum dose between 125 and 143 % (equivalent to prescribing to the 70–80 % isodose surface (% IDS) when normalised to the maximum point dose). Treatment plans for preoperative SRS were generated using Brainlab Elements Cranial SRS v1.5 and v3.0.

Treatment delivery

SRS was delivered on a Truebeam STx linear accelerator with Novalis Radiosurgery platform (Brainlab/Varian, USA) with high definition MLC leaves (2.5 mm), a 6 degrees of freedom (DoF) couch and stereoscopic Exactrac kV x-ray 6D image guidance (Brainlab). Follow-up MRIs were performed every 3 months after resection and time to local recurrence, nodular leptomeningeal recurrence, new brain metastases and radionecrosis were calculated from the date of neurosurgery. Patient follow-up was censored at death or last contact up to 26.08.22.

Quality of life (QoL)

QoL was assessed by the validated EORTC core questionnaire (QLQ C-30) [20], and the additional brain module (BN20) [21]. Questionnaires were completed prior to SRS, and subsequently at three monthly intervals for 12 months.

Statistical analysis

Survival was censored at death or on 26.08.2022 when the last patient reached 12-month follow-up. The survival analysis was performed using the Kaplan-Meier survival estimator and QoL questionnaires were analysed using R programming (version 4.2) with main packages

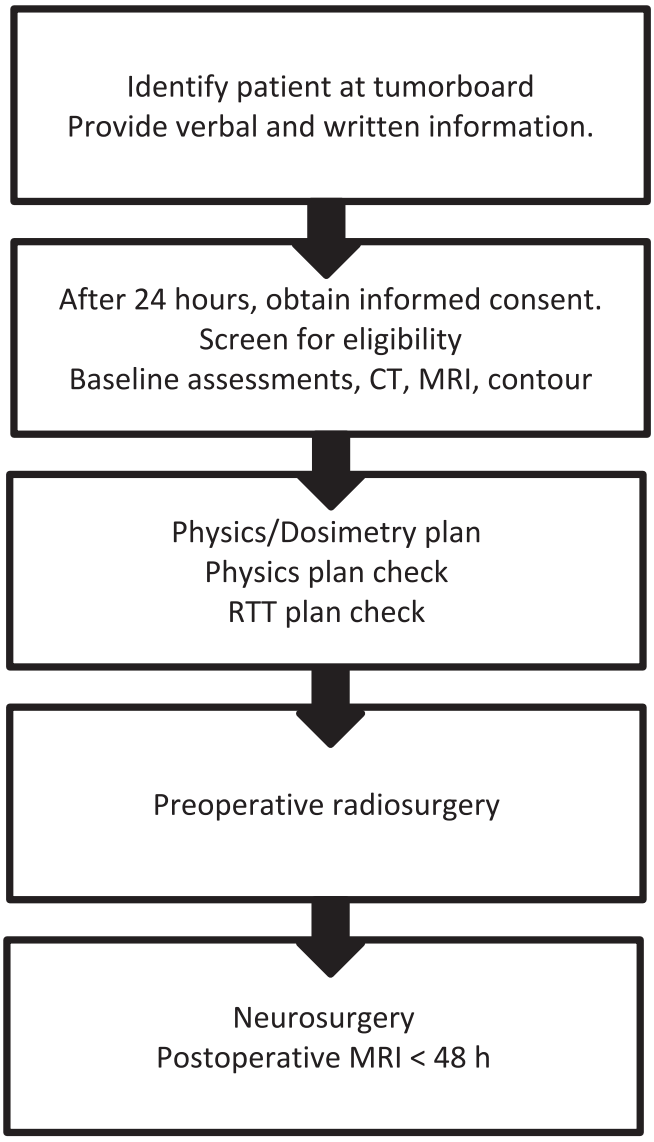


Fig. 1. Preoperative SRS workflow.

'survimer' and 'ggplot2' otherwise descriptive statistics were applied (R and IBM SPSS 24). All statistical tests were two-tailed and p-values $\leq$ 0.05 were considered significant.

Results

Thirteen patients were approached and recruited between November 2020 and February 2022. The key demographics are summarised in Table 1. The median encompassing dose of preoperative SRS was 16 Gy (range 14–18), the median GTV was 9.6 cm^3 (range 4.1 to 16.3) and the median PTV was 12.7 cm^3 (range 9–26) (Table 2). The median time between tumour board referral and linac-based SRS was 6.5 working days (1–10) and 8.5 days in total (1–14) (Table 3). Neurosurgery took place a median of one working day later (0–5) and a median of 1.5 days including non-working days (1–7). The median time from tumour board to metastasectomy was 7 working days (range 2–15) and a median of 12 (range 2–34) days in total. Dexamethasone (12–16 mg) was administered according to medical indication and no patients experienced progressive neurological symptoms between referral and neurosurgery.

Six of twelve (50 %) patients received preoperative SRS and metastasectomy within 6 working days of the tumour board decision. The other six received surgery 8 to 15 days after the tumour board referral.

Table 1
Summary of patient demographics.

Patient Characteristics	**N = 13**
Gender M:F	4: 9
Age (yrs) median (range)	65 (41–77)
Karnofsky performance status (%) median (range)	80 (70–100)
Histology	
–Non-small cell lung cancer	5
–Melanoma	2
–Oesophageal cancer	2
–Colorectal cancer	3
–Breast cancer	1
Median number of BMs per patient (range)	1 (1–3)
Disease-specific Graded Prognostic Assessment Score median (range)	2.5 (0–4)
Synchronous: metachronous BM	3: 10 (23 %)
Location of BM for resection	
–frontal lobe	9
–parietal lobe	1
–cerebellum	3
Symptomatic BM for resection Y: N	9:4 (69.2 %)
–neurocognitive symptoms	6/8
–cerebellar symptoms	2/8
–Broca's aphasia	1/8
Time to BM from diagnosis of primary in months median (range)	18 (0–81.2)
Extracranial metastases Y:N	10:3 (77 %)
Synchronous systemic treatment Y:N	4:9 (25 %)
–Immunotherapy	2/3
–Tyrosine kinase inhibitor	1/3
–Chemotherapy	1/3

BM = brain metastasis

Table 2
Dosimetric features of preoperative SRS plans.

Dosimetric features of preoperative SRS treatment plans (N = 13)	Median (range)
Diameter of brain metastasis (cm)	3.5 (2.6–4.4)
Gross tumour volume (GTV) (cm^3)	9.6 (4.1 to 16.3)
Diameter of planning tumour volume (cm)	3.7 (2.8–4.7)
Planning tumour volume (PTV) (cm^3)	12.7 (9–26)
Radiosurgery dose (Gy)	16 (14–19)
Prescription isodose (%)	70.4 (69.1–77.7)
Maximum dose (Gy)	23.7 (19.7–25.3)
Dose to 99 % of PTV (Gy)	16.1 (11.7–18.4)
Mean dose to PTV (Gy)	20.3 (17.2–22.2)
Dose to 2 % of PTV (Gy)	22.9 (19.2–25)
Conformity index	1.1 (1.1–1.3)
Gradient index	2.4 (2.2–2.7)
Volume of structure 'brain –GTV' receiving 10 Gy (cm^3)	12.7 (7.5–21.5)

Table 3
Clinical outcomes following preoperative SRS delivered to 12 patients.

Clinical outcomes after preoperative SRS (n = 12)	Median (range)
Total number of days from referral to SRS (n = 12)	8.5 (1 – 14)
Number of working days from referral to SRS (n = 12)	6.5 (1–10)
Total number of days from SRS to resection (n = 12)	1.5 (0–7)
Number of working days from SRS to resection (n = 12)	1.0 (0–5)
Total number of days from referral to resection (n = 12)	12.0 (2–34)
Number of working days from referral to resection (n = 12)	7.0 (2–15)
Leptomeningeal recurrence (n = 6)*	0/6
Local control (n = 6)	5/6 (83 %)
Distant brain failure (n = 6)	2/6
Salvage SRS/WBRT (n = 6)	2/6
Alive at last follow-up Y:N (n = 12)	4: 8
Neurological death	0/8

*Follow-up MRIs were available for 6 of 12 patients who received preoperative SRS.

Neurosurgery was delayed by three to nine days in three patients due to COVID-related lack of theatre or intensive care capacity, and bank holidays. One patient had to await transfer from a regional hospital, and another required twelve days to consent to neurosurgery. The median follow-up was 6 months (range 0.6–12). A follow-up MRI was available for eight surviving patients, of whom seven received preoperative SRS. None of the seven developed LMD and one had a local recurrence (Fig. 2). The 80 % local control rate was equivalent to that observed in a *meta*-analysis of postoperative radiosurgery [22].

The eighth patient went directly to surgery to optimise use of theatre availability and received postoperative FSRT (5 x 6 Gy to a PTV of 19.6 cm^3 as compared with the intended 1 x 18 Gy to a PTV of 5.24 cm^3 preoperatively). This patient developed two small nodular leptomeningeal recurrences after six months which have been controlled with SRS to date. There was one related toxicity (alopecia grade 2) at three months in a patient who received SRS to two adjacent BMs, which recovered completely by six months. None of the seven patients had evidence of clinical or radiological radionecrosis. Six patients completed 12-month follow-up and the median overall survival was 6.3 months (range 0.6–18.6). Four patients are still alive and nine patients have died: six from visceral metastases, one from intracranial progression of a non-resected BM and two from unrelated causes (massive haemoptysis/haematemesis and postoperative pneumonia). Overall survival in this group of patients was lower than has been reported [14], but no patients died from intracranial disease progression. Several patients had synchronous brain metastases and the aggressive course of the extracranial disease could not be anticipated, however there was a positive correlation between predicted and observed survival (Supplementary Fig. 1).

We observed neither extensive necrosis in the BMs (mean 11 %, range 0–50 %) compared with the primary extracranial tumours (mean 45 %, range 3–70 %), nor a consistent decrease in tumour-infiltrating lymphocytes CD-3, −4 and −8 in the metastases at a mean of one day between radiosurgery and resection (Fig. 3). Paired QoL data, at baseline and after six weeks, were available for seven patients and at six months for five patients. The only parameter with a statistically significant change was an improvement in motor weakness at 6 months ($P = 0.04$). In both symptomatic and asymptomatic patients, QoL was otherwise stable during the duration of follow-up (Supplementary tables 2 and 3).

With regard to the change in volume of the BM for preoperative SRS whilst the patients received 12–16 mg dexamethasone during the 4–19 day interval between diagnostic and planning MR scan in 10 evaluable patients, 4/10 (40 %) BMs showed a reduction in volume and 6/10 (60 %) increased in volume (Supplementary Fig. 2). Treatment planning was performed with image distortion correction on a diagnostic scan acquired within 24 h for the other 3 patients. There was no correlation between the time interval between the diagnostic and planning MRI scans and the percentage change in volume of the brain metastases (median 8.5 %, range −11 –(+81)) (Supplementary Fig. 2) or in the centre of mass [23] (median 1 mm, range 0–3.2) (Supplementary Fig. 3), although the lesion with the greatest change in volume (81 %) also had the greatest change in centre of mass (3.2 mm) (Supplementary Fig. 4).

Discussion

The PREOP-1 trial was able to demonstrate that preoperative SRS was feasible in 12/13 patients (92 %) and safe in 12/12 patients as no patients suffered any adverse events between referral and resection. Five

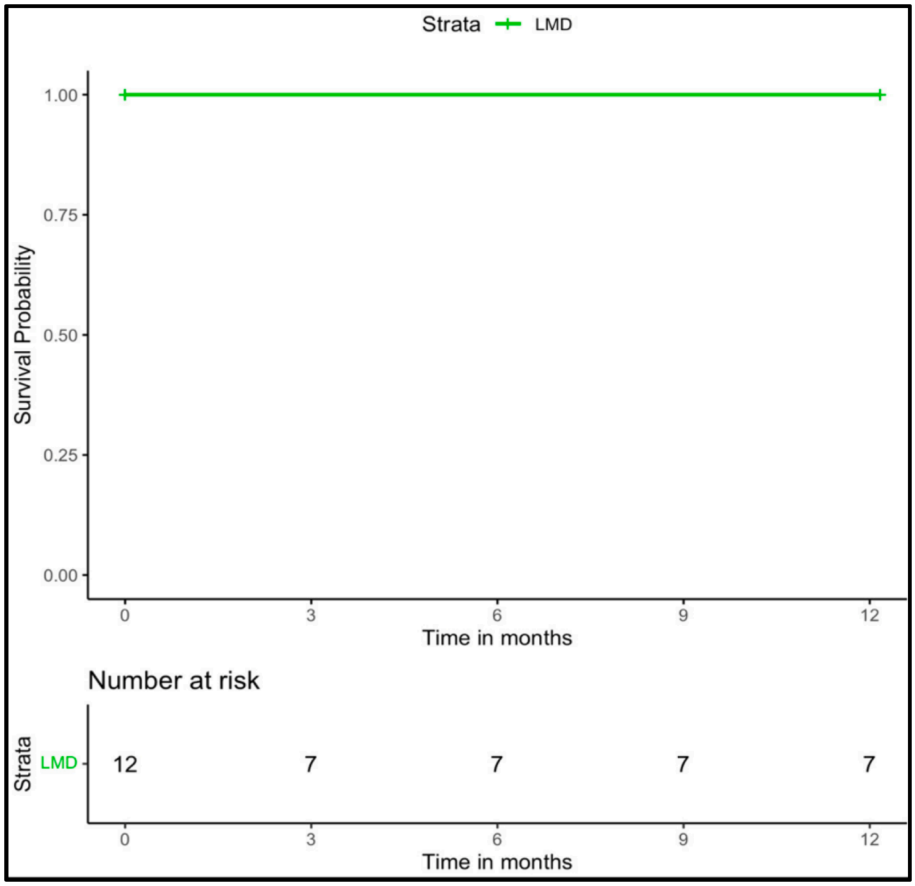


Fig. 2. Kaplan-Meier estimate of the probability of Fig. 1a: leptomeningeal disease-free survival (100%), Fig. 1b: local control (80%) and Fig, 1c; overall survival following preoperative SRS. **a**. There were no cases of leptomeningeal disease (nodular or classical) after preoperative radiosurgery. **b**. The cavity local control rate was 80% after preoperative radiosurgery. **c.** Overall survival after preoperative radiosurgery.

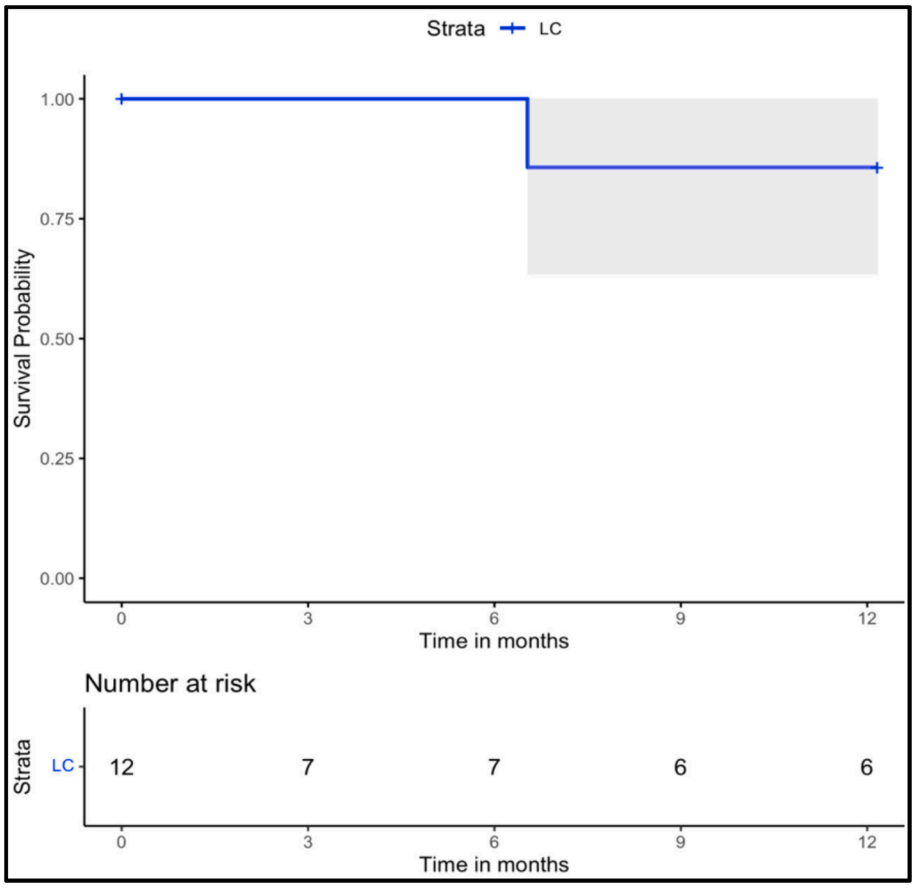


Fig. 2. (*continued*).

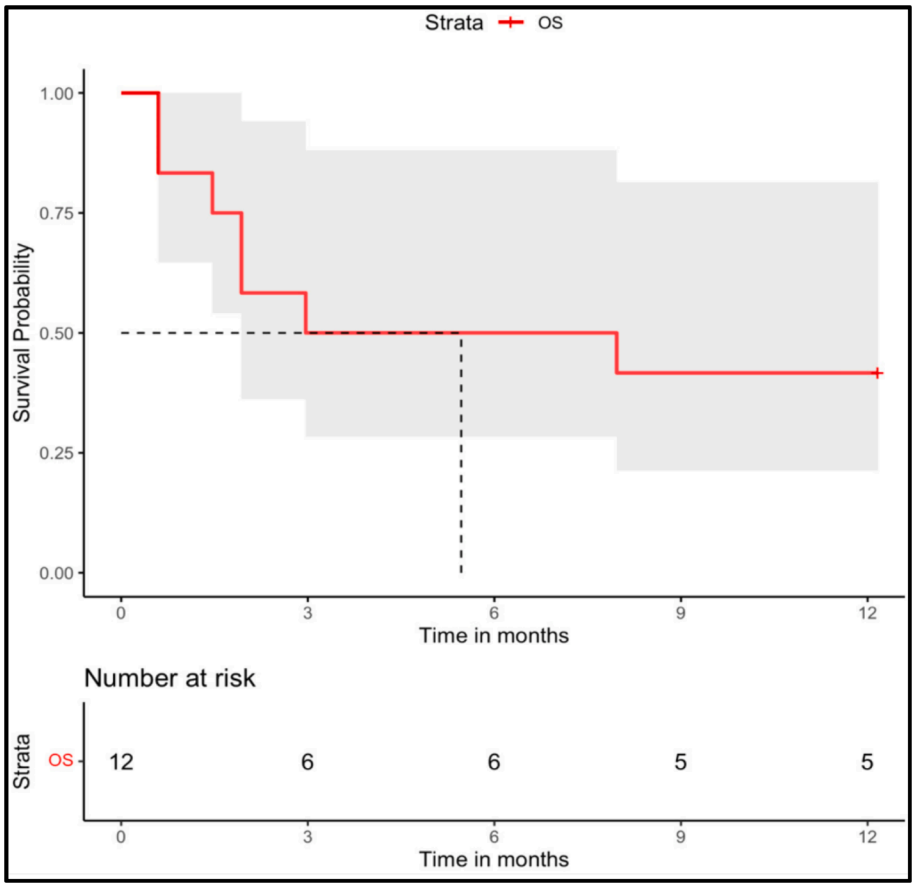
working days were estimated to be a realistic timeframe however the interval to planned resection was variable [median 7 (range 2–15) working days]. The median time from referral to SRS was 6.5 working days (range 1–14) and the main delay to initiation of SRS was patient-related factors such as time to informed consent to surgery and transfer from a peripheral hospital. The patient who was operated on directly had been scheduled for preoperative SRS and resection on the same morning. Radiosurgery on the day of neurosurgery had been successfully performed in two patients previously, however from this case forwards, preoperative SRS was delivered up to the day prior to resection to maximise feasibility.

In published retrospective series, the preoperative SRS dose was reduced by up to 20 % as compared with the RTOG 9005 prescription for primary SRS for brain metastases. In the PREOP-1 trial, the prescribed dose was at the upper limit that was delivered without complications in the PROPS-BM cohort [14] and was approximately 10 % less than the RTOG 9005 prescription dose [24]. There are no established metrics for preoperative SRS. We did not generate trial plans however the volume of the structure 'brain-GTV' that received 10 Gy in a single fraction, was recorded. The median volume of 'brain-GTV' that received 10 Gy was 12.7 cm^3 (range 7.5–21.5), which is just above the 10 cm^3 recommendation for non-resected brain metastases [25]. At 12 months follow-up, there have been no signs of clinical or radiological radionecrosis, in contrast to the 10.3 % incidence in our review of the postoperative FSRT literature [10].

Surgical trauma induces immune suppression, acute inflammation and release of pro-angiogenic factors [26]. The rupture of tumour architecture contributes to tumor cell proliferation and migration, cell release and survival in the circulation; adhesion to the endothelial wall and extravasation; escape from immune surveillance and trigger of the angiogenic switch [26]. Cell inactivation through preoperative SRS could therefore plausibly reduce subsequent tumour seeding. Kotecha *et al* recently published a first report of differences in the levels of expression of immune cells in brain metastases after preoperative SRS as compared with the primary tumour for 22 patients from the PROPS-BM cohort [27]. Patients were treated with a median preoperative SRS single fraction dose of 18 Gy (range 15–20 Gy) similar to the 16 Gy (14–19 Gy) in our series. After a median interval of 67.8 h to neurosurgery, the rate of pathological necrosis was significantly higher in irradiated brain metastases than in the corresponding non-irradiated primary tumours ($p < 0.001$). A decrease in all immunomodulatory cell populations was found in irradiated metastases compared to primary tumours: CD3 + ($p = 0.003$), CD4 + ($p = 0.01$), and CD8 + ($p = 0.01$) We did not observe any significant necrosis in the metastases compared with the primary tumours or a consistent change in tumour-infiltrating lymphocytes in the metastases at a median of one day after SRS (Fig. 3). The mean time to neurosurgery in the PROPS-BM series was nearly three days as compared with one day in our study, but the authors reported that increased tumour necrosis and differences in expression of immunomodulatory factors did not appear to be time dependent [27]. Interpretation of any impact of preoperative SRS in such studies is confounded by the mixed histologies, the comparison of a primary tumour with a metastasis, any effect of surgical trauma and exposure to immunotherapy however.

An advantage of preoperative SRS is the subsequent resection of the irradiated tissue, which should reduce the risk of radionecrosis, particularly if re-irradiation is indicated. Six patients required subsequent irradiation to new BMs. Four received SRS, one received partial brain RT and one needed WBRT after developing more than 20 brain metastases at the same time as extensive extracranial metastases.

No patient who received preoperative SRS developed a nodular leptomeningeal recurrence in contrast with our series of postoperative



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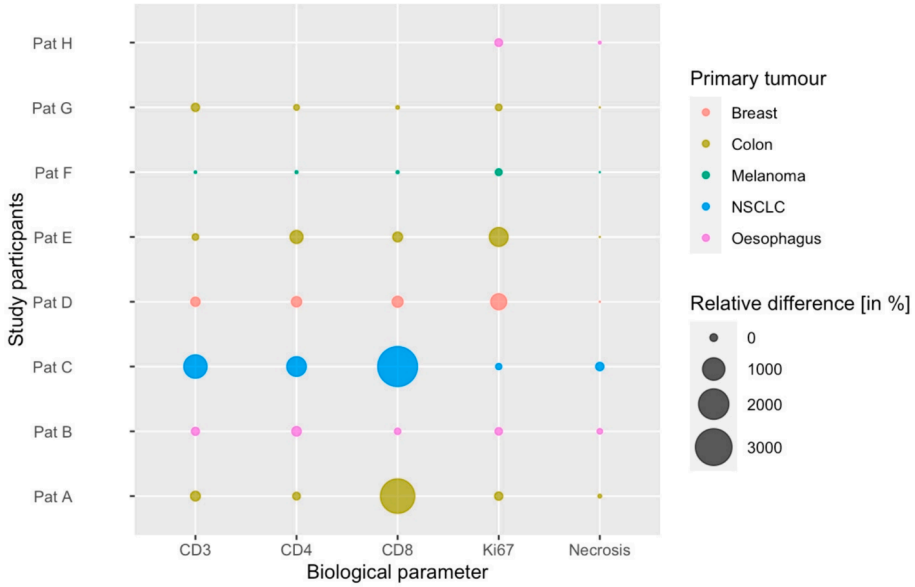

Fig. 3. Depiction of the relative difference (percentage change in counts per 10 low power fields) of tumour-infiltrating lymphocytes (CD3, 4 and 8) and markers of proliferation (Ki67) and necrosis in 7 patients with matched tissue from the primary tumour and a preoperatively irradiated metastasis. Six patients had sufficient tissue available for the assessment of all markers.

FSRT, where nodular LMD was evident in 7/40 (17.5 %) and a cavity local control rate of 82.5 % at 1 year was achieved, similar to the median local control rate of 83.1 % (71–98.9 %) and LMD of 14.9 % (7–34 %) reported in the FSRT literature [10]. The local control rates of 83 % (5/6 metastases) achieved with preoperative SRS in both this small study and 84.5 % (214/253 metastases) in the much larger PROPS-BM cohort [14] are again similar.

Several groups have compared the preoperative metastasis volume and hypothetical preoperative SRS plan with the corresponding post-operative cavity volume to try to refine the patient selection criteria.

Using this approach, a recent publication recommended smaller metastases (<15 cm^3) for preoperative SRS as these tend to be associated with larger postoperative cavities [28]. SRS to a smaller target would certainly be preferable than to a larger target, however fractionation could be used to offset the potential toxicity of irradiating a larger cavity. The minimum effective SRS dose remains to be established, however local control rates appear similar with pre-operative and post-operative irradiation [14].

The major advantage of preoperative SRS is the reported reduction in the incidence of LMD. Cell death following SRS is mediated by double strand cell breaks, free radical-mediated DNA damage, activation of an anti-tumor immunological response, and devascularisation [29]. The latter is reported to occur at doses of 15 Gy or more [30], which in this protocol were applied to PTVs below 22.5 cm^3 (10 of 12 PTVs). It is plausible that SRS-induced cell death impairs the ability of cells disseminated into the CSF at surgery to subsequently establish on the meninges, thus reducing the incidence of nodular LMD. It remains to be elucidated whether there are any disadvantages to doses under 15 Gy for the larger PTVs as the devascularisation mechanism may be less relevant in the preoperative than in the primary SRS setting.

Despite increasing retrospective evidence supporting the utility of preoperative SRS in the clinic, there is some reluctance from clinicians to consider this approach due to concerns about the practicalities. This description of the implementation of preoperative SRS in our clinic should offer some reassurance. Recent retrospective data report higher cavity control rates with preoperative FSRT (3x 8 Gy, BED 10 = 36 Gy) rather than SRS (1x 15 Gy, BED 10 = 31.25 Gy) [31], however given the concerns regarding the delay to surgery for the delivery of a single fraction, there may be a lower acceptance of multifraction preoperative SRS until prospective data are available. Ongoing Phase III trials should help optimise the preoperative fractionation schedules. In the US, patients are being randomised between preoperative and postoperative SRS (NCT05438212) and an Italian trial is comparing pre- and post-operative FSRT in 3 fractions (NCT05545007). The PREOP-1 trial design forms the experimental arm of an open DEGRO/AGO randomised trial (PREOP-2) comparing the efficacy of preoperative SRS against post-operative FSRT (NCT05124236).

The limitations of the study include the small sample size, the single centre design and the incomplete follow-up MRIs due to limited overall survival. The primary aim of the study could be evaluated in all patients however. Although the stringent primary endpoint of achieving preoperative SRS in all patients was not quite met (12/13 patients, 92 %), we were able to confirm that preoperative SRS is feasible in routine clinical practice if performed at least a day prior to elective neurosurgical resection of a brain metastasis. As there were no significant toxicities, we found the risks to be low and not to outweigh the potential benefits, which include less delay to the irradiation of any other brain metastases, delivery of any planned systemic treatment and a lower incidence of LMD. A reduction in frequency of salvage whole brain radiotherapy for LMD would protect against neurocognitive toxicity and resection of the irradiated volume minimises the risk of radionecrosis. If equivalent local control rates and lower incidence of leptomeningeal disease compared with postoperative SRS/FSRT can be achieved without additional toxicity, preoperative SRS has the potential to become a new standard of care for patients with brain metastases indicated for resection and warrants further investigation in a randomised controlled trial.

Ethics Approval

EKNZ 2020-00262

Trial Registration

DRKS00023579

Consent to participate

All patients gave informed consent to participate in this clinical trial and for use of their biological material.

CRediT authorship contribution statement

S Rogers: Writing – original draft, Formal analysis, Conceptualization, Methodology. **L Schwyzer:** Writing – review & editing, Investigation, Resources. **N Lomax:** Writing – review & editing, Formal analysis, Investigation, Resources. **S Alonso:** Writing – review & editing, Investigation, Resources. **T Lazeroms:** Writing – review & editing, Investigation, Resources. **S Gomez:** Writing – review & editing, Investigation. **K Diahovets:** Investigation, Resources. **I Fischer:** Investigation, Resources, Writing – review & editing. **S Schwenne:** Project administration, Data curation. **A Ademaj:** Writing – review & editing, Software, Formal analysis. **S Berkmann:** Writing – review & editing, Investigation, Resources. **A Tortora:** Writing – review & editing, Investigation, Resources. **S Marbacher:** Writing – review & editing, Investigation, Resources. **L Remonda:** Investigation, Resources. **G.A. Schubert:** Writing – review & editing, Resources. **O Riesterer:** Supervision, Writing – review & editing, Investigation, Resources.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [SR has received Speaker's Honoraria from Brainlab.].

Acknowledgement

We would like to thank the patients who participated in the trial.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100798.

References

[1] Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. JAMA 2016;316:401–9.

[2] Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 2009;10:1037–44.

[3] Prabhu RS, Press RH, Patel KR, Boselli DM, Symanowski JT, Lankford SP, et al. Single-Fraction Stereotactic Radiosurgery (SRS) Alone Versus Surgical Resection and SRS for Large Brain Metastases: A Multi-institutional Analysis. Int J Radiat Oncol Biol Phys 2017;99:459–67.

[4] Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol 2017;18:1040–8.

[5] Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 2017;18:1049–60.

[6] Ma R, Levy M, Gui B, Lu SE, Narra V, Goyal S, et al. Risk of leptomeningeal carcinomatosis in patients with brain metastases treated with stereotactic radiosurgery. J Neurooncol 2018;136:395–401.

[7] Atalar B, Modlin LA, Choi CY, Adler JR, Gibbs IC, Chang SD, et al. Risk of leptomeningeal disease in patients treated with stereotactic radiosurgery targeting the postoperative resection cavity for brain metastases. Int J Radiat Oncol Biol Phys 2013;87:713–8.

[8] Hsieh J, Elson P, Otvos B, Rose J, Loftus C, Rahmathulla G, et al. Tumor progression in patients receiving adjuvant whole-brain radiotherapy vs localized radiotherapy after surgical resection of brain metastases. Neurosurgery 2015;76:411–20.

[9] Ojerholm E, Lee JY, Kolker J, Lustig R, Dorsey JF, Alonso-Basanta M. Gamma Knife radiosurgery to four or more brain metastases in patients without prior intracranial radiation or surgery. Cancer Med 2014;3:565–71.

[10] Rogers S, Stauffer A, Lomax N, Alonso S, Eberle B, Gomez Ordonez S, et al. Five fraction stereotactic radiotherapy after brain metastasectomy: a single-institution experience and literature review. J Neurooncol 2021.

[11] Soliman H, Ruschin M, Angelov L, Brown PD, Chiang VLS, Kirkpatrick JP, et al. Consensus Contouring Guidelines for Postoperative Completely Resected Cavity

Stereotactic Radiosurgery for Brain Metastases. Int J Radiat Oncol Biol Phys 2018; 100:436–42.
[12] Ahn JH, Lee SH, Kim S, Joo J, Yoo H, Lee SH, et al. Risk for leptomeningeal seeding after resection for brain metastases: implication of tumor location with mode of resection. J Neurosurg 2012;116:984–93.
[13] Patel KR, Burri SH, Boselli D, Symanowski JT, Asher AL, Sumrall A, et al. Comparing pre-operative stereotactic radiosurgery (SRS) to post-operative whole brain radiation therapy (WBRT) for resectable brain metastases: a multi-institutional analysis. J Neurooncol 2017;131:611–8.
[14] Prabhu RS, Dhakal R, Vaslow ZK, Dan T, Mishra MV, Murphy ES, et al. Preoperative Radiosurgery for Resected Brain Metastases: The PROPS-BM Multicenter Cohort Study. Int J Radiat Oncol Biol Phys 2021.
[15] Dharnipragada R, Dusenbery K, Ferreira C, Sharma M, Chen CC. Preoperative Versus Postoperative Radiosurgery of Brain Metastases: A Meta-Analysis. World Neurosurg 2024;182:35–41.
[16] Prabhu RS, Akinyelu T, Vaslow ZK, Matsui JK, Haghighi N, Dan T, et al. Single-Fraction Versus Fractionated Preoperative Radiosurgery for Resected Brain Metastases: A PROPS-BM International Multicenter Cohort Study. Int J Radiat Oncol Biol Phys 2024;118:650–61.
[17] Thrower SL, Al Feghali KA, Luo D, Paddick I, Hou P, Briere T, et al. The Effect of Slice Thickness on Contours of Brain Metastases for Stereotactic Radiosurgery. Adv Radiat Oncol 2021;6:100708.
[18] Prabhu RS, Miller KR, Asher AL, Heinzerling JH, Moeller BJ, Lankford SP, et al. Preoperative stereotactic radiosurgery before planned resection of brain metastases: updated analysis of efficacy and toxicity of a novel treatment paradigm. J Neurosurg 2018;1–8.
[19] Hazard LJ, Wang B, Skidmore TB, Chern SS, Salter BJ, Jensen RL, et al. Conformity of LINAC-based stereotactic radiosurgery using dynamic conformal arcs and micro-multileaf collimator. Int J Radiat Oncol Biol Phys 2009;73:562–70.
[20] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.
[21] Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. Eur J Cancer 2010;46:1033–40.
[22] Akanda ZZ, Hong W, Nahavandi S, Haghighi N, Phillips C, Kok DL. Post-operative stereotactic radiosurgery following excision of brain metastases: A systematic review and meta-analysis. Radiother Oncol 2020;142:27–35.
[23] Hessen ED, van Buuren LD, Nijkamp JA, de Vries KC, Kong Mok W, Dewit L, et al. Significant tumor shift in patients treated with stereotactic radiosurgery for brain metastasis. Clin Transl Radiat Oncol 2017;2:23–8.
[24] Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90–05. Int J Radiat Oncol Biol Phys 2000;47:291–8.
[25] Milano MT, Grimm J, Niemierko A, Soltys SG, Moiseenko V, Redmond KJ, et al. Single- and Multifraction Stereotactic Radiosurgery Dose/Volume Tolerances of the Brain. Int J Radiat Oncol Biol Phys 2021;110:68–86.
[26] Alieva M, van Rheenen J, Broekman MLD. Potential impact of invasive surgical procedures on primary tumor growth and metastasis. Clin Exp Metastasis 2018;35: 319–31.
[27] Kotecha R, Tonse R, Menendez MAR, Williams A, Diaz Z, Tom MC, et al. Evaluation of the impact of pre-operative stereotactic radiotherapy on the acute changes in histopathologic and immune marker profiles of brain metastases. Sci Rep 2022;12: 4567.
[28] Acker G, Nachbar M, Soffried N, Bodnar B, Janas A, Krantchev K, et al. What if: A retrospective reconstruction of resection cavity stereotactic radiosurgery to mimic neoadjuvant stereotactic radiosurgery. Front Oncol 2023;13:1056330.
[29] Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? Int J Radiat Oncol Biol Phys 2014;88:254–62.
[30] Song CW, Park I, Cho LC, Yuan J, Dusenbery KE, Griffin RJ, et al. Is indirect cell death involved in response of tumors to stereotactic radiosurgery and stereotactic body radiation therapy? Int J Radiat Oncol Biol Phys 2014;89:924–5.
[31] Prabhu RS, Akinyelu T, Vaslow ZK, Matsui JK, Haghighi N, Dan T, et al. Single Fraction vs. Fractionated Preoperative Radiosurgery for Resected Brain Metastases: a PROPS-BM International Multicenter Cohort Study. Int J Radiat Oncol Biol Phys 2023.