ORIGINAL ARTICLE

Cavity volume changes after surgery of a brain metastasis—consequences for stereotactic radiation therapy

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Abstract

Purpose For a large or symptomatic brain metastasis, resection and adjuvant radiotherapy are recommended. Hypofractionated stereotactic radiotherapy (HFSRT) is increasingly applied in patients with a limited number of lesions. Exact target volume definition is critical given the small safety margins. Whilst technical advances have minimized inaccuracy due to patient positioning and radiation targeting, little is known about changes in target volume. This study sought to evaluate potential changes in the resection cavity of a brain metastasis.

Methods In all, 57 patients treated with HFSRT after surgical resection of one brain metastasis between 2008 and 2015 in our institution were included in this study. Gross tumor volume (GTV) of the initial metastasis and the volume of the resection cavity in the post-operative, planning, and follow-up MRIs were measured and compared.

Results The mean cavity size decreased after surgery with the greatest change of –23.4% (±41.5%) occurring between post-operative MRI and planning MRI ($p < 0.01$). During this time period, the cavity volume decreased, remained stable, and increased in 79.1, 3.5, and 17.4%, respectively. A further decrease of –20.7% (±58.1%) was perceived between planning MRI and first follow-up ($p < 0.01$). No significant difference in pattern of change could be observed depending on the volume of initial GTV, size of the post-operative resection cavity, initial or post-resection FLAIR (fluid-attenuated inversion recovery) hyper-intensity, postsurgical ischemia, or primary tumor. The resection cavities of patients with post-operative ischemia were significantly larger than resection cavities of patients without ischemia.

Conclusion The resection cavity seems to be very dynamic after surgery. Hence, it remains necessary to use very recent scans for treatment planning.

Keywords Resection cavity dynamics · Hypofractionated stereotactic irradiation · Neuro-oncology · Adjuvant radiotherapy · Constriction of the surgical bed

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Volumenveränderungen der Resektionshöhlen nach Operation von Hirnmetastasen – Konsequenzen für die stereotaktische Strahlentherapie

Zusammenfassung

Hintergrund Die empfohlene Therapie für große und symptomatische Hirnmetastasen ist die chirurgische Resektion mit nachfolgender Bestrahlung der Resektionshöhle. Bei Patienten mit einer begrenzten Metastasenanzahl werden zunehmend stereotaktisch fraktionierte Konzepte (HFSRT) angewandt. Aufgrund der geringen Sicherheitssäume, die bei der HFSRT verwendet werden, ist die genaue Definition des Zielvolumens entscheidend. Während lagerungsbedingte Ungenauigkeiten durch technische Fortschritte weitgehend minimiert werden konnten, sind bisher wenige Informationen über Veränderungen der Zielvolumina bekannt. Ziel dieser Studie war es, Veränderungen der Resektionshöhlen von Hirnmetastasen zu untersuchen.

Methoden In die Studie wurden 57 Patienten eingeschlossen, die zwischen 2008 und 2015 an unserer Klinik eine HFSRT der Resektionshöhle einer Hirnmetastase erhalten hatten. Das Tumorvolumen (GTV) der Metastase und die Volumina der Resektionshöhlen in der postoperativen Magnetresonanztomographie (MRT), im Planungs- und Nachsorge-MRT wurden gemessen und verglichen.

Ergebnisse Die durchschnittliche Größe der Resektionshöhle nahm im Verlauf ab, wobei die größten Veränderungen von $-23{,}4\%$ ($\pm41{,}5\%$) zwischen dem postoperativen MRT und dem Planungs-MRT auftraten ($p<0{,}01$). In diesem Zeitraum wurde die Resektionshöhle in $79{,}1\%$ der Fälle kleiner, blieb in $3{,}5\%$ gleich und nahm in $17{,}4\%$ zu. Eine weitere signifikante Reduktion des Resektionshöhlenvolumens um $-20{,}7$ ($\pm58{,}1\%$) trat zwischen dem Planungs-MRT und der ersten Nachsorge auf. Signifikante Zusammenhänge zwischen der Veränderung der Resektionshöhlenvolumina und dem initialen Volumen der Metastase (GTV), der Größe der postoperativen Resektionskavität, der FLAIR(„fluid-attenuated inversion recovery)-Hyperintensität, der postoperativen Ischämie oder des Primärtumors konnten nicht nachgewiesen werden. Patienten mit postoperativer Ischämie hatten eine signifikant größere Resektionshöhle als Patienten ohne postoperative Ischämie.

Schlussfolgerung Nach Operation von Hirnmetastasen treten Änderungen der Resektionshöhlenvolumina auf. Daher ist es notwendig, aktuelle Bildgebungen zur Bestrahlungsplanung zu verwenden.

Schlüsselwörter Resektionshöhlendynamik · Hypofraktionierte stereotaktische Radiotherapie · Neuroonkologie · Adjuvante Strahlentherapie · Volumenreduktion der Operationshöhle

Introduction

Brain metastases constitute the most common intracranial malignancy in adults, with an estimated annual incidence of around 26,000 cases in the US [6, 30]. They occur in 5 to 40% of patients with malignant diseases [20]. Most common primary sites are pulmonary cancer, breast cancer, gastrointestinal cancer, and melanoma [10, 24]. Whilst refined systemic treatment options lead to an increased overall survival for many types of primary cancers, prognosis of patients presenting with brain metastasis remains poor [8, 27]. Patients presenting with up to three brain metastases are candidates for local treatment [5, 16, 19, 32]. Recent studies have shown that neurosurgical resection and radiosurgery may be equieffective in the treatment of single brain metastases [23]. Surgical resection is preferred in larger (>2 cm) and symptomatic lesions [19, 21]. Adjuvant radiotherapy (RT) is required even after complete resection, as 2-year local recurrence rates without adjuvant treatment are approximately 60% [12, 16, 17, 22]. Radiosurgery (SRS) or hypofractionated stereotactic radiotherapy (HFSRT) is increasingly becoming the method of choice in the treatment of resection cavities [1, 4, 11, 15, 15, 28, 31]. Previously, we have shown this approach to combine low toxicity with excellent local control [5, 16, 26]. Recent studies confirmed the advantages of SRS over whole-brain radiotherapy (WBRT) after surgical resection of patients with limited numbers of brain metastases. Local control is comparable and neurotoxicity may be reduced [5, 14]. The advantage of stereotactic treatment techniques is the ability to keep safety margins small and subsequently spare healthy brain tissue. Therefore, precise knowledge about the location of the volume to treat is critical for treatment results. Whilst technical advances have minimized inaccuracy due to patient positioning and radiation targeting, little is known about anatomical changes to the brain that take place after surgery. After the resection of brain metastases, volume changes occur due to removal of tumor mass [2]. Fluctuations in the size of the resection cavity itself have been in the focus of previous studies. However, the results varied from volume increase in around 30% of the cases to other studies reporting a constriction in >90% [2, 5, 25]. The aim of this study was to evaluate volume changes within the resection cavity and to establish a recommendation for reimaging and radiation start.

Patients and methods

Patients

57 patients treated with HFSRT after surgical resection of a large or symptomatic brain metastasis between 2008 and 2015 in our institution were included in this study. Median age was 62 years (range 33–82 years), most common primaries were non-small cell lung cancer (NSCLC; 16 cases/28%); gastrointestinal cancers (16 cases/28%), and breast cancer (11 cases/19%). General performance status was adequate in most patients with a median Karnofsky index of 90% (range 60–100%). Patients' characteristics are shown in Table 1.

Out of 57 patients, 49 had an early post-surgical MRI (up to 96 h after surgery). The median time from surgery to the early post-surgical MRI was 1 day (1–4 days). In another 5 patients an MRI was performed within a delayed timeframe after surgery of 26–100 days (median 58 days). In the analysis of the changes in cavity volume, these delayed MRIs were treated as postoperative MRIs since all of those patients also received a planning MRI. A planning MRI was available in 47 patients. Median time between post-surgical MRI and planning MRI was 23 days (7–58 days). Median time from surgery to planning MRI was 31 days (range 8–122 days). Median time from the planning MRI to the initiation of irradiation was 7 days (range 1–25 days). First, second, third, fourth, and fifth follow-up MRI were defined as 4–8 weeks, 3–6 months, 6–12 months, 12–24 months, and 24–36 months after radiotherapy, respectively. At this time, an MRI was available in 45 patients for first, 42 patients for second, 35 patients for third, 27 patients for fourth, and 15 patients for fifth follow-up.

Methods

Delineation of gross tumor volume (GTV) of the initial metastasis, volume of the resection cavity, and of the residual tumor (if present) was carried out on contrast enhancing T1-weighted MRI. Surrounding edema was defined as hyper-intensity in fluid-attenuated inversion recovery (FLAIR) images. Contouring of the structures mentioned above was done in early post-surgical MRI, delayed post-surgical MRI, planning MRI, and follow-up MRI. The post-surgical ischemic area was contoured in the ADC sequence of the early post-surgical MRI. Volumetric evaluations were performed using the Eclipse 13.0 treatment planning software (Varian Medical Systems, Palo Alto, CA, USA). Cavity size was compared between post-operative MRI, planning MRI, planning CT, and follow-up exams. Changes in cavity size, which are stated as percentages of post-operative volume, include only patients with post-surgical MRI. Changes in cavity size of <5% were considered within the fluctuation

Table 1 Patients' characteristics

	n	%
Median age		
62 years (range 33–82 years)		
Median time from first diagnosis of primary tumor to first diagnosis of brain metastases		
27 months (range –1–289 months)		
Sex		
Male	27	47
Female	30	53
Primary tumor		
Breast cancer	11	19
NSCLC (adenocarcinoma)	12	21
NSCLC (squamous cell cancer)	4	7
Gastrointestinal cancer	16	28
Malignant melanoma	10	18
Gynecological cancer	2	4
Others (RCC, thymoma)	2	4
Resection status		
Complete resection	32	56
Residual tumor	17	30
Unknown	8	14
Extracerebral tumor mass		
Yes	35	61
No	22	39
Number of lesions		
1	50	88
2	3	5
3	3	5
4	1	2
Recursive partitioning analysis (RPA) class		
1	14	25
2	42	74
3	1	2
Graded Prognostic Assessment (GPA) score		
0–1	2	4
1.5–2	21	37
2.5–3	20	35
3.5–4	12	21
Mean resection cavity size (cm³)		
8.8 ± 6.2		

n number of patients, *NCLC* non-small cell lung cancer, *RCC* renal cell cancer

margin and subsequently regarded as a stable cavity size. The value given for absolute changes in the resection cavity volume (in cm³) includes all patients.

Treatment planning was carried out according to standard of care procedure. Clinical target volume (CTV) was defined as the resection cavity (encompassing residual tumor, if present) and a safety margin of 2–3 mm. Planning target volume (PTV) was generated with an additional margin of 1–2 mm to the CTV. Treatment planning was car-

ried out using iPlan RT Dose treatment planning software (BrainLAB AG, Munich, Germany) or Eclipse software.

35 Gy was applied in 7 fractions (daily dose of 5 Gy). Dose prescription was to the 95–100% isodose line. Dmean (PTV), Dmax (PTV), and Dmin (PTV) were 35.24 Gy (±0.52), 36.7 Gy (±0.74), and 33.34 Gy (±0.51), respectively. Irradiation was performed with a Clinac Trilogy linear accelerator equipped with a 120 HD multileaf collimator (Varian Medical Systems, Palo Alto, CA, USA) and 6 MV photons. A high-precision treatment set-up was applied using a frameless thermoplastic mask system (BrainLAB AG, Munich, Germany). Daily image-guided radiotherapy (IGRT) was performed with the ExacTrac stereoscopic X-ray imaging system.

Local recurrence and loco-regional recurrence were calculated from the first day of radiation therapy until the date of tumor recurrence. For the evaluation of OS, the time interval between the start of radiation therapy to the date of death or the last contact was calculated. Recurrence was documented if stated as such in the MRI report.

All patients were treated in accordance with the Declaration of Helsinki. A written informed consent for the use of scientific data was obtained from all patients. This study was approved by the Ethics Committee of the Technical University Munich, Faculty of Medicine.

Statistical evaluation

Continuous data were expressed as means ± standard deviation (SD) or median and range, categorical data as frequency counts or percentages.

Statistical analysis was performed by two-sided students' t-test. A p-value of 0.05 was defined as the threshold for statistical significance within a confidence interval of 95%. All calculations and figures were done with the software packages Graphpad Prism 7 (Graphpad Software Inc, USA).

Results

Outcome

At time of analysis, 36 patients had died and 21 patients were still alive. Median follow-up time was 54.0 months. The median OS of the complete cohort was 24.1 months (range 2.2–102.6 months). The OS of patients that had received prior radiation to the brain was 7.9 months (range 7.7–9.2 months). Patients receiving additional radiotherapy for asymptomatic brain metastasis had a median OS of 40.5 months (range 17.6–60.2 months). With a median OS of 35.5 months, breast cancer was the entity with the best prognosis (range 4.7–73.2 months).

In 32 patients (56%) the metastasis was resected completely. In 17 patients (30%) residual tumor was suspected based on early postoperative MRI. Resection status was unknown in 8 (14%) patients. Mean volume of residual tumor was $0.4 \pm 0.4\,cm^3$. Mean residual tumor volume in planning MRI was $0.7 \pm 1.0\,cm^3$. Comparing the early post-operative MRI to planning MRI, 5 patients had a local progression and local recurrence was suspected in 4 patients. The median time between imaging in patients with progressive disease or recurrence was 28 days (range 11–56 days), in patients without progression or recurrence 21 days (range 12–50 days). This difference in time between patients with and without recurrence was not statistically significant ($p = 0.12$).

Of the 57 analyzed patients, 34 (59.5%) experienced a cranial progression. In one patient (1.7%) the recurrences was isolated within the field of HFSRT, in 11 patients (19.3%) the recurrence was in- and out of field, and in 22 patients (38.5%) only distant recurrences occurred. The 1-year local recurrence rate was 16.9%. The 1-year loco-regional recurrence rate was 48.8%. No difference in local recurrence between patients with or without suspicion of residual tumor was observed ($p = 0.91$). During the course of observation, 19 patients received salvage treatment in the form of whole-brain radiotherapy with or without radiosurgery for further recurrences, 9 patients in the form of radiosurgery only, and one patient in the form of HFSRT.
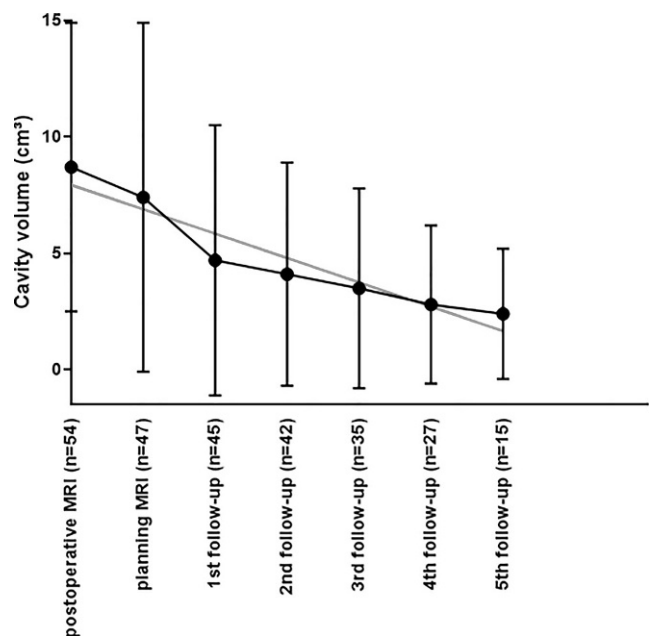

Fig. 1 Change in cavity volume. *Black* mean cavity volume of resection cavities, *grey* linear regression of cavity volume change over time

Fig. 2 MRI images during therapy. **a** GTV in preoperative MRI; **b** resection cavity in post-operative MRI; **c** resection cavity in planning MRI; **d** resection cavity at first follow-up. *pink* contour to the initial GTV, *magenta* contour to the resection cavity
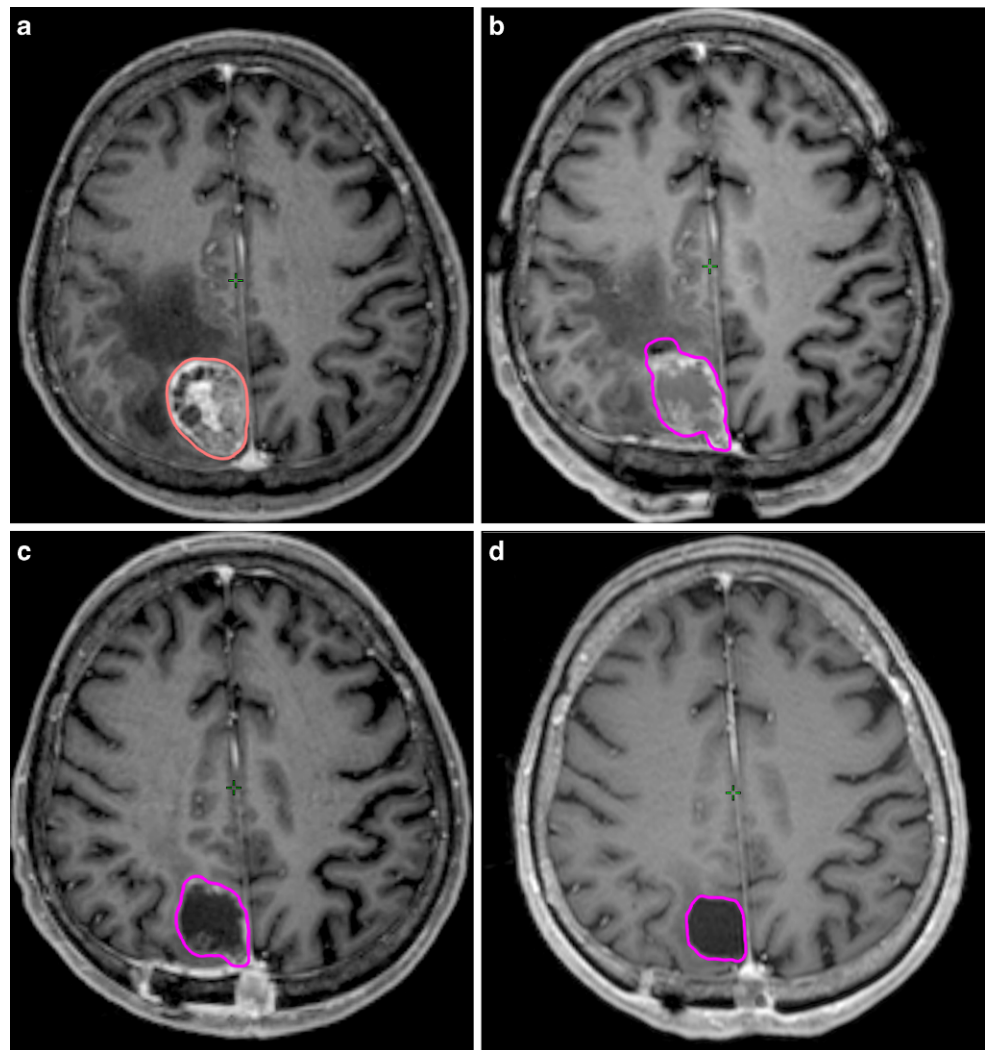
Changes in cavity volume

The mean volumes of the initial GTV and post-operative resection cavity were $15.1\,\text{cm}^3 \pm 14.4$ and $8.7 \pm 6.2\,\text{cm}^3$, respectively. The size of the initial GTV was on average $76.5\% \pm 116.7\%$ larger than the post-operative resection cavity ($p < 0.01$). In very small metastases with a volume below $3\,\text{cm}^3$ (mean GTV $2.2\,\text{cm}^3 \pm 0.56$), the size of the initial GTV was smaller than the initial metastases and made up $85.4\% \pm 48.6\%$ of the postoperative resection cavity. In metastasis with a volume of more than $3\,\text{cm}^3$ (mean GTV $17.56\,\text{cm}^3 \pm 17.25$), the initial GTV was on average twice the size of the postoperative resection cavity ($200.5\% \pm 117.9\%$; $p < 0.01$).

The mean cavity size decreased over time from postoperative MRI to follow-up MRIs as can be seen in Fig. 1. MRI images of one patient at different time points is demonstrated in Fig. 2. The greatest reduction in cavity volume with a mean percentage change of $-23.4\% \pm 41.5\%$ occurred between postoperative MRI and planning MRI ($p < 0.01$). The mean absolute reduction of cavity volume was $1.4\,\text{cm}^3 \pm 2.7\,\text{cm}^3$. In 79.1% of the cases the volume of the cavity size decreased and in 3.5% cavity size was stable. An increase in volume was perceived in 17.4%. All patients with an increased cavity volume in planning MRI showed a reduction in cavity volume in the first follow-up MRI. There was no significant difference in cavity shrinkage between patients with early or delayed postoperative MRI ($p = 0.29$).

The reduction in cavity size was significant for the time between planning MRI to first follow-up ($20.8\% \pm 58.2\%$, $p < 0.01$). Median time from planning MRI to first follow up was 41 days (range 36–77 days).

The size of the initial resection cavity was negatively correlated with proportional size reduction of the cavities between planning and post-surgical MRI, as small cavities tended to experience greater shrinkage ($p = 0.03$; Fig. 3), but was not correlated with reduction in size between post-
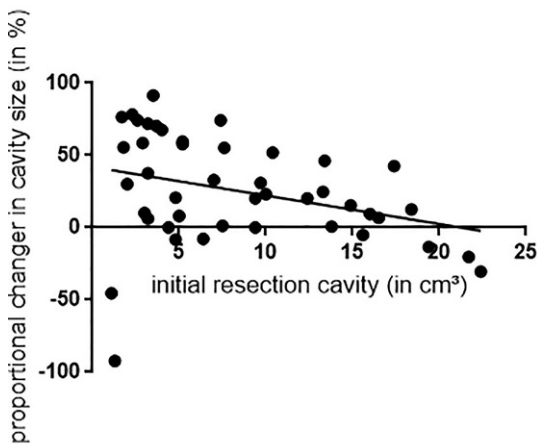
Fig. 3 Correlation of initial cavity size with proportional change. *Dots* represent the cavities with both postoperative and planning MRI available. *Line* respresents the linear regression of proportional change in cavity volume

op MRI and any other point during follow-up ($p = 0.34$). The mean percentage change and mean absolute volume reduction were -28.5% ($\pm 43.9\%$)/$-1.3\,cm^3$ ($\pm 1.7\,cm^3$) and -13.3% ($\pm 23.0\%$)/$-1.5\,cm^3$ ($\pm 3.7\,cm^3$) for cavities with a volume $<10\,cm^3$ and $\geq 10\,cm^3$ in the post-operative MRI, respectively.

No significant difference in pattern of change in cavity size could be observed depending on volume of initial GTV ($p = 0.58$). Neither initial FLAIR hyper-intensity nor post-resection FLAIR hyper-intensity correlated significantly with cavity size reduction ($p = 0.22$ and 0.26, respec-

tively). Patterns in volume change did not significantly differ for different primaries ($p = 0.35$) as can be seen in Fig. 4. The presence of residual tumor mass was not significantly associated with the change in cavity volume ($p = 0.12$).

A post-surgical ischemia was observed in 12 patients with early post-surgical MRI. No significant difference in volume of initial GTV of patients experiencing ischemia and patients without post-surgical ischemia was observed ($18.1\,cm^3 \pm 21.5\,cm^3$ vs. $13.5\,cm^3 \pm 15.7\,cm^3$, $p = 0.5$). The resection cavities of patients with postoperative ischemia were significantly larger than resection cavities of patients without ischemia ($12.8\,cm^3 \pm 10.4\,cm^3$ vs. $7.7\,cm^3 \pm 5.9\,cm^3$, $p = 0.05$). Reduction in cavity size from post-operative MRI to planning MRI did not differ significantly between these two groups ($7.4\% \pm 26.4\%$ for patients with ischemia and $25.5\% \pm 39.1\%$ for patients without ischemia, $p = 0.17$). Volume of ischemic area was not correlated with initial GTV ($p = 0.92$), size of post-surgical resection cavity ($p = 0.86$), or change in cavity size between early post-surgical and planning MRI ($p = 0.09$).

Toxicities

Acute toxicity included skin toxicity CTC I in two patients, hair loss CTC I in four patients, headache and dizziness CTC I in two, and CTC II in one patient. No patient experienced seizures or nausea during radiotherapy.

Asymptomatic radionecrosis was suspected in 5 patients based on MRI in the location of HFSRT: 3 patients had undergone solely postoperative HFSRT; 2 patients had re-

Fig. 4 Patterns of change in cavity volume for different primary cancers. *NSCLC* non-small-cell lung cancer, *GI-Adeno-Ca* gastrointestinal adenocarcinoma
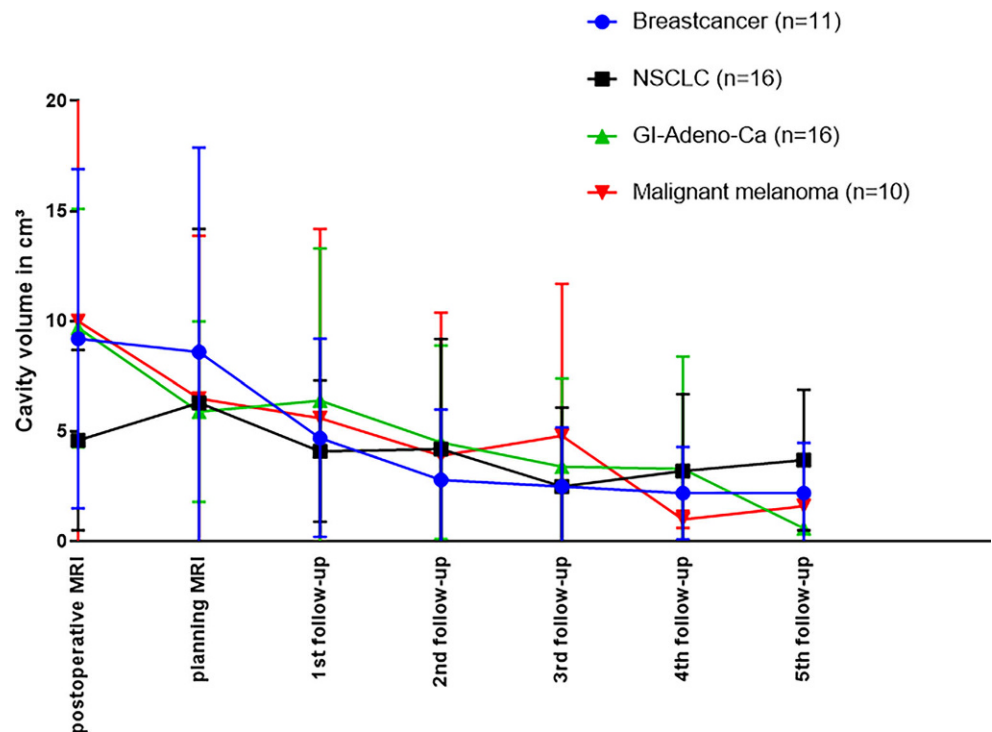
Table 2 Overview of studies on stereotactic radiation to resection cavities

Author (year of publication)	Total number of patients	Median age (years)	Treatment modality (number of patients)	Number of lesions	Radiation dose	Overall survival (1 year/ median)	Local control rate (1 year)	Locoregional control (1 year)	Rate of radio-necrosis (%)	Median cavity size (cm³)	Safety margins (mm)	Specific planning MRI required
Mahajan et al. (2017) [14][a]	128	58 (20–80), 57 (29–79)	SRS (63)	1 41 (63%), 2 14 (22%), 3 10 (15%)	16 Gy (≤10 cc), 14 Gy (10.1–15 cc), 12 Gy (for >15 cc)	17 months	72%	42%	0	8.9 (range 0.9–28.6)	1	Yes (on day of SR)
			Observation (65)	1 38 (60%), 2 18 (29%), 3 7 (11%)	Observation	18 months P=0.24	43% P=0.015	33% P=0.35				
Brown et al. (2017) [4][a]	194	61 (54–66)	SRS (98)	1 75 (77%), 2–4 23 (23%)	24 Gy (Ø <1 cm), 20 Gy (Ø 1–2 cm), 18 (Ø 2.1–3 cm)	12.2 months	~61%	40.7%	4	ø ≤3 cm 59 (60%), ø >3 cm 39 (40%)	2	No
		62 (54–68)	WBRT (96)	1 74 (77%), 2–4 22 (23%)	30 Gy in 10 fractions (n=49), 37.5 Gy in 15 fractions (n=43)	11.6 months	~81% p<0.01	81.5%	0	ø ≤3 cm 58 (60%), ø >3 cm 38 (40%)		
Al Omair et al. (2013) [1][b]	30	70 (41–90)	No prior WBRT 20 (31 cavities)	1 19 (95%), 2 1 (5%)	25–37.5 (5 fractions) 90% Isodose	71%	79%	63	0	nr	2	Yes (a few days before RT)
			Prior WBRT 10 (11 cavities)	1 9 (90%), 2 1 (10%)	25–35 (5 fractions) 90% Isodose	80%	100%		30			
Specht et al. (2016) [23][b]	46	56 (19–84)	HFSRT	1 40 (87%), 2 6 (13%)	35 à 5 Gy, 95–100%	25 months	88%	48%	8.7	14.16 (1.44–38.68)	3	Yes (85%)
Steinmann et al. (2013) [25][b]	33	58 (33–73)	HFSRT	1 33 (100%)	10×4 Gy (n=22), 7×5 Gy (n=7), 5×6 Gy (n=4)	64%	71%	43%	0	9.68 (0.95–52.58)	4	no

Table 2 (Continued)

Author (year of publication)	Total number of patients	Median age (years)	Treatment modality (number of patients)	Number of lesions	Radiation dose	Overall survival (1 year/median)	Local control rate (1 year)	Locoregional control (1 year)	Rate of radionecrosis (%)	Median cavity size (cm³)	Safety margins (mm)	Specific planning MRI required
Broemme et al. (2013) [3][b]	42	67 (40–79)	RS (23 cavities) / HFSRT (21 cavities)	1 33 (78%) / 2–3 9 (22%)	SR 12Gy / 4×6Gy (5 patients) / 6×4Gy (6 patients) / 10×4Gy (10 patients)	63.5%	77%	33%	2.4	nr	3	No
Lima et al. (2017) [13][b]	41	Mean+SD 60.27 (9.93) 50.27 (14.64)	HFSRT	1 20 (49%) >1 21(51%)	5×5–6 (26) 10×3 (15)	nr (median OS 28.27)	89.4%	89.6%	0	nr	2	Yes (within 10 days of treatment initiation)
Wang et al. (2011) [27][b]	37	<65 29 (73%) ≥65 8 (27%)	HFSRT	1 24 (65%) 2 12 (32%) 3 1 (3%)	3×8Gy 95% Isodose	nr (~20%)	80%	nr	2.9	nr	2–3	nr
Keller et al. (2017) [9][b]	181	60.6 (26.2–82.5)	HFSRT	1 138 (73%) 2 38 (20%) 3 11 (6%) ≥4 2 (1%)	3×11Gy	62.5%	88%	61%	14.7	7.6 (0.20–48.81)	2	Yes (within 10 days of treatment initiation)
Present Study[b]	57	62 years (range 33–82 years)	HFSRT	1 50 (88%) 2 3 (5%) 3 3 (5%) 4 1 (2%)	35 à 5Gy 95–100%	67.9%	81.7%	51.2%	10.5	7.0 (1.1–36.5 cm³)	3	Yes (85%)

nr not reported, *SRS* stereotactic radiotherapy, *HFSRT* hypofractionated stereotactic radiotherapy, *cc* cubic centimeters

[a]Randomized controlled trials

[b]Retrospective studies on hypofractionated radiotherapy

ceived whole-brain irradiation as well as two further stereotactic treatments to other cerebral lesions. In 4 of these patients, radionecrosis was confirmed histologically. One patient did not undergo surgery.

Discussion

Stereotactic radiation techniques enable precise delivery of relatively high daily doses to the target volume. Therefore, only small safety margins are required and healthy tissue can be spared. A recent randomized controlled trial showed a significant reduction in cognitive deterioration for stereotactic radiation to the resection cavity compared to whole-brain irradiation without compromising overall survival [5]. At the same time, the risk of radionecrosis is higher than in whole-brain radiotherapy as a result of the high daily doses applied [14]. This risk is elevated by prior irradiation, higher doses, and larger irradiation volume [13]. Fractionated radiotherapy is used to reduce the threat of radionecrosis in large lesions. HFSRT with 35Gy in daily fractions of 5Gy was effective and well tolerated with a 1-year local control rate of 83.1%, a 10.5% rate of radionecrosis, and few acute toxicities, as previously demonstrated ([26]; Table 2). The biologically effective dose (BED) that is equivalent to 35Gy à 5Gy depends on the alpha/beta ratio of the irradiated tissue. For breast cancer, lung cancer, and GI cancer cells, with estimated alpha/beta ratios of 4–8, this corresponds to a BED of 65.6 to 96.3Gy [29]. When assuming an alpha/beta of 2 for healthy brain tissue, the equivalent BED is 122.5Gy.

In order to fully exploit the advantages stereotactic radiation provides, exact knowledge of the resection cavity's anatomy at the time of treatment is critical. In this study, anatomical changes before and after radiation therapy were monitored, revealing significant alterations in cavity size over time.

Dimensions of initial metastasis tended to be larger than the corresponding resection cavities. This is not surprising, as metastatic mass effect is reduced by surgery, allowing healthy brain tissue to return to its initial extent. This is particularly visible in large metastases. Small metastases, on the other hand, are frequently resected supramarginally. Hence, there is a statistically significant proportional change in volume size between initial metastasis and resection cavity when comparing smaller with larger lesions. Similarly, Atalar et al. reported an alteration in volume of up to minus 29% when comparing pre-resection tumor and post-resection cavity. In the following time period of up to 33 days after resection, they observed no statistically significant size changes [2]. In our cohort, in contrast, a statistically relevant size reduction occurred from post-operative MRI to planning MRI. Changes in cavity size have

already been demonstrated by prior publications. While Jarvis et al. observed a stable size in 47% of the cases, expansion in 30%, and reduction in 23% [9], Shah et al. reported cavity constriction in >90% resulting in a mean volume reduction of 45%. They observed a significant reduction in cavity size after more than 30 days after surgery [25]. We observed a significant reduction in cavity volume after a median time of 31 days. Even though time between planning and post-resection MRI was not significantly associated with a decrease in cavity size, we can confirm the findings of Shah et al. taking into account the further reduction on cavity size taking place after irradiation. Other than that, no significant factor to predict cavity dynamics was identified in the prior studies conducted. Similarly to previous results, neither initial tumor size, the size of vasogenic edema, nor tumor histology was prognostic for the pattern of volume change. Initial cavity size, on the other hand, correlated negatively with the proportional cavity shrinkage between post-resection and planning MRI. In the further follow-up there was no difference, suggesting a faster response in small cavities. The theory behind the analysis of the resection cavities' dynamics, depending on whether an ischemia was present or not, was the assumption that an ischemia would result in a necrosis and subsequently larger volumes of the resection cavity. Post-surgical ischemia was associated with significantly larger post-surgical resection cavities compared to patients without ischemia. However, the difference in cavity volume was neither significant for the planning MRI nor the MRI at any other time. If necrosis was the relevant factor for a larger cavity volume in the post-surgical MRI, one would expect the difference to increase over time. On the other hand, initial GTV in patients that later experienced necrosis tended to be larger than in patients without necrosis, even though this was not statistically significant. Therefore, it is not clear whether the larger volume of patients with ischemia really is associated with biological processes following ischemia or rather with the fact that ischemia occurs more often in patients with more extensive surgery.

Despite the fact that the reasons for cavity dynamics are not yet clear, implications for RT may be drawn from these findings. A direct comparison of WBRT with stereotactic radiation to the surgical bed revealed higher incidences of local failure in stereotactic radiation [4]. In the study of Brown et al., baseline MRI was performed before randomization, planning MRI was not specifically required, and the local recurrence rate was high compared to other studies [5, 16]. Differences in local control may certainly result from differences in study population or definition of local control. Nevertheless, an increase in cavity volume in some of the patients cannot be fully excluded as a reason for local failure. Moreover, very small or no safety margins were

used, which might be the most relevant factor for the lower local control.

Shah et al. recommended a longer interval between surgery and stereotactic radiation to take advantage of the volume reduction that may occur during this period [25]. The influence of the irradiated volume on the risk of radionecrosis in stereotactic radiosurgery is well established. Particularly the volumes that receive 10 Gy (V10 Gy) and 12 Gy (V12 Gy) have been shown to be predictive for the risk of radionecrosis [3, 18]. Therefore, fractionated therapy is preferred for V10 Gy >10.5 cm³ or V12 Gy >7.9 cm³ [3]. In resection cavities planned for treatment with radiosurgery, a reduction of the risk for radionecrosis through a decrease in target volume can be assumed. However, the vast majority of resection cavities in this study exceeded sizes that can safely be treated with radiosurgery and were therefore treated with hypofractionated stereotactic radiotherapy. Only limited data exist on the effect of an increased radiation volume in hypofractionated stereotactic radiotherapy. The publications available retrospectively analyzed the risk of radionecrosis in a cohort of patients that received 3 × 7.7 Gy (prescribed to the 70%-isodose line) to the postoperative resection cavity of brain metastases. While the analysis with 95 patients demonstrated a predictive value of the V21 Gy, an analysis of 189 patients did not confirm these results, showing no association of the V8 Gy–V22 Gy with the appearance of radionecrosis [7, 11]. Another factor that should be taken into account, when debating on longer waiting periods before adjuvant radiotherapy of the resection cavity is the risk of recurrence or progression. We observed 5 progressions in patients with residual tumor after surgery and 4 recurrences after complete resection. Even though no significant difference in time between surgery and radiation start was observed for patients with and without recurrence/progression, a connection is likely and may not be discernible due to small patient numbers. Therefore, in our experience, HFSRT should begin as soon as wound healing is complete based on most recent MRI.

Limitations to this study include the fact that early postoperative MRI was available in only 70% of the patients and 5 patients received their baseline MRI with a longer interval after surgery. Moreover, neither ischemia nor histology can be omitted as an influence in cavity change due to small patient numbers.

Conclusion

We confirmed a volume change in the resection cavity after surgery of brain metastases. Smaller initial resection cavities experienced a faster proportional decrease in size. Other than that, no predictive factor for the pattern of volume change could be identified. Even if the mechanisms

of decrease in cavity size are unclear, it remains necessary to adapt the process of stereotactic radiation of resection cavities to these findings. As a practical approach, target volume delineation should be based on a planning MRI performed shortly before start of radiation therapy. Older MRIs may result in increased local failure in case of cavity volume increase or unnecessary irradiation of healthy tissue in case of volume reduction. We do not recommend postponing radiation therapy in order to achieve a reduction in cavity size, as recurrence or progression of disease may result from the delay.

Compliance with ethical guidelines

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