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Adjuvant radiotherapy after brain metastasectomy: analysis of consecutive cohort of 118 patients from real world practice

Pavel Fadrus[1, 2*], Vaclav Vybihal[1, 2*], Ivana Roskova[1, 2], Iveta Selingerova[3], Martin Smrcka[1, 2], Radim Jancalek[4, 5], Jiri Sana[6, 7], Ondrej Slaby[6, 7], Petr Pospisil[8, 9], Ludmila Hynkova[8, 9], Jan Garcic[8], Renata Belanova[10], Jan Kristek[10], Andrea Sprlakova-Pukova[11], Zdenek Mackerle[4, 5], Vilem Juran[1, 2], Marek Sova[1, 2], Eduard Neuman[1, 2], Hana Valekova[4, 5], Radek Lakomy[7, 12], Milos Holanek[7, 12], Roman Hrstka[3], Michaela Svajdova[8, 9, 13], Katerina Polachova[8, 9], Ivana Kolouskova[12, 14], Pavel Slampa[8, 9], Tomas Kazda[3, 8, 9]

[1]Department of Neurosurgery, University Hospital Brno, Czech Republic
[2]Department of Neurosurgery, Faculty of Medicine, Masaryk University, Brno, Czech Republic
[3]Research Center for Applied Molecular Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic
[4]Department of Neurosurgery, St. Anne's University Hospital Brno, Brno, Czech Republic
[5]Department of Neurosurgery, St. Anne's University Hospital Brno, Faculty of Medicine, Masaryk University, Brno, Czech Republic
[6]Department of Biology, Faculty of Medicine, Central European Institute of Technology, Masaryk University, Brno, Czech Republic
[7]Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic
[8]Department of Radiation Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic
[9]Department of Radiation Oncology, Faculty of Medicine, Masaryk University, Brno, Czech Republic
[10]Department of Radiology, Masaryk Memorial Cancer Institute, Brno, Czech Republic
[11]Department of Radiology and Nuclear Medicine, University Hospital Brno and Masaryk University, Brno, Czech Republic
[12]Department of Comprehensive Cancer Care, Faculty of Medicine, Masaryk University, Brno, Czech Republic
[13]Department of Radiation and Clinical Oncology, General Hospital Rimavska Sobota, Rimavska Sobota, Slovakia
[14]Faculty of Medicine, Masaryk University, Brno, Czech Republic
*These authors contributed equally and share the first co-authorship.

ABSTRACT

Background: The aim of this retrospective study is to analyze a consecutive cohort of brain metastasis (BM) patients treated off clinical trials through combination of surgery and radiotherapy over the last 15 years in a tertiary neurooncology center.

Materials and methods: All BM patients operated between 2007–2019 received adjuvant linac-based radiotherapy categorized to whole brain radiotherapy (WBRT) and tumor bed stereotactic radiotherapy. Survival outcomes and local control was analyzed.

Results: In total, 118 patients were enrolled, those with stereotactic radiotherapy (41%) had better baseline characteristics mirrored in longer overall survival (OS) [18 *vs*. 7.1 months, $p < 0.001$; hazard ratio (HR) 0.47, $p = 0.004$] with median follow-up of 58 months. Cumulative incidence for local, distant, and extracranial control was not significantly different between groups, with 12-month cumulative control of 22% *vs*. 18%, 44% *vs*. 29%, and 35% *vs*. 32% for stereotactic and WBRT group, respectively. WBRT was an independent factor for better distal brain control.

Conclusions: Real world data demonstrating significantly better overall survival in patients treated with postoperative targeted radiotherapy compared with postoperative WBRT is presented, with no significant difference in cumulative incidence for local or distant brain control. The majority of patients with targeted radiotherapy had a fractionated dose schedule with outcomes comparable to single-dose radiation trials of postoperative targeted radiotherapy.

Key words: brain metastases; surgery; radiotherapy; tumor cavity; overall survival

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Address for correspondence: Tomas Kazda, Department of Radiation Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic, tel: +420 543 131 187; e-mail: tomas.kazda@mou.cz

Introduction

The increasing incidence and prevalence of brain metastases (BM) confirm earlier predictions about the growing importance of patient-centered care for this population. Although the exact incidence is unknown, the commonly reported incidence of BM is 20–30% for all patients with solid tumors, with most of them originating from primary lung tumors and melanoma, especially in those with extracranial metastatic disease to any distant site [1]. Despite the growing portfolio of modern systemic treatments for BM, local therapies remain the cornerstone of management. Eventually, the majority of patients with small asymptomatic BM treated with upfront osimertinib (BM from non-small cell lung cancer) [2, 3], dabrafenib plus trametinib (BRAF-mutant melanoma) [4], ipilimumab and nivolumab (melanoma) [5], tucatinib and trastuzumab (HER2-positive intracranial metastatic breast cancer) [6], or other types of targeted therapy are usually referred to some kind of local treatment later during the natural course of the intracranial disease.

Despite these new approaches, indications for surgery still include treatment of large bulky disease (usually over 3–4 cm in the maximal diameter), symptomatic BM not responding to corticosteroids, solitary BM without other metastasis, or newly diagnosed brain lesion suspected to be BM without evidence of extracranial disease [7–9]. Perioperative oncologic management of patients is currently the subject of intensive research covering pre-surgery stereotactic radiosurgery (SRS) (NCT04422639, NCT03741673, NCT03750227, or NCT04474925) as well as post-surgery modifications of adjuvant radiotherapy (RT) with respect to fractionated stereotactic radiotherapy (FSRT) (NCT04114981), along with debate regarding the best contouring of RT target volumes [10]. With the advancement and increased accessibility of modern RT techniques, a paradigm shift is underway in postoperative strategies. Compared with the formerly widespread use of whole-brain radiotherapy (WBRT), current modified WBRT techniques with simultaneous integrated boost to the metastases (WBRT-SIB) and/or selective sparing of hippocampal regions (HA-WBRT) are now only used with caution, for example in patients with high BM velocity or a larger number of BMs (usually > 10–20 BMs) [7, 11].

The aim of this retrospective study is to analyze a consecutive cohort of BM patients treated by combination surgery with adjuvant radiotherapy over the last 15 years in a tertiary neurooncology center equipped with linear accelerators, and to compare this real-world data to published clinical trials.

Materials and methods

Patients selection

All patients who underwent comprehensive local therapy (metastasectomy followed by radiotherapy) for newly diagnosed BM between 2007 and 2019 in the neurooncology center of Brno, Czech Republic, were included in this analysis as follows. Surgery was performed in the University Hospital Brno or the St. Anne's University Hospital Brno. Radiotherapy and accompanying comprehensive cancer care were provided at the Masaryk Memorial Cancer Institute. All patients were discussed at a Multidisciplinary Tumour Board consisting of: neurosurgeon, medical oncologist, radiation oncologist, neurologist, neuroradiologist, and/or pathologist. All patients signed the informed consent for anonymized/pseudonymized analysis of their clinical data for research purposes. Clinical data were obtained from the electronic medical records of the respective hospital information systems. Available magnetic resonance (MR) images were used for local control analysis. MR was scheduled every 2–4 months according to local practice and the availability of scan slots. Local control at the surgical site and distal parts of the brain were separately evaluated on MR by an attending radiologist. Leptomeningeal pattern of dissemination was evaluated separately in proximity to the resection cavity and distal brain. Ambiguous findings were reviewed by a neuroradiologist or discussed in the aforementioned multidisciplinary tumor board. Available imaging methods were used to assess extracranial progression, most commonly by computed tomography (CT) or positron emission tomography (PET/CT). The study was approved by the ethical committee of the University Hospital Brno No. EK-FNB-17-06-28-01.

Neurosurgery

Metastasectomy was performed with the goal of maximum safe resection. Functional pre-sur-

gery navigation MR study was performed as needed based on the location of BM. Depending on the location, number, shape, size, cystic or solid nature, and/or growth velocity of BM, the neurosurgery technique and tactic were adapted, including neuronavigation, intraoperative stimulation mapping, awake craniotomy, intraoperative ultrasound, or fluorescence guided surgery. The radicality of the re-section was evaluated utilizing postsurgery MR or CT study with intravenous contrast agent administration no longer than 72 hours after surgery.

Radiotherapy

Postoperative RT was categorized in this analysis into techniques involving WBRT (including HA-WBRT or WBRT-SIB) and targeted radiotherapy techniques (SRS, FSRT, or targeted radiation of the metastasectomy bed delivered in more than five fractions). Whole brain radiotherapy was usually performed by 2D treatment planning approach utilizing the Varian Acuity iX RT simulator with ORFIT thermoplastic mask immobilization. 20 Gy in 5 fractions or 30 Gy in 10 fractions were generally prescribed according to performance status and extent of disease. Stereotactic RT plans were prepared using EclipseTM (Varian medical systems, Palo Alto, CA, USA) and delivered on a Varian Clinac iX or TrueBeam STx (Varian medical systems, Palo Alto, CA, USA). Before 2015 the BrainLAB M3 microcollimator was attached to the standard LINAC Varian Clinac 2100C/D, with these plans generated on the BrainLAB BrainSCAN planning system. Immobilization options included invasive (BrainLAB Stereotactic Headring) and non-invasive immobilization (Brain-LAB mask and later the ORFIT thermoplastic mask and CIVCO trUpoint ARCH). The SRS dose was prescribed to 18-24 Gy according to the size of the BM. For FSRT, the total dose was 24-30 Gy delivered in 3-5 fractions. For detection of possible intracranial progression and accurate definition of the target volume, all patients with indications for postoperative SRS or FSRT underwent a planning MR scan no more than 2 weeks before RT. The postoperative cavity was contoured as the gross tumor volume (GTV), with a 1–2 mm margin constituting clinical target volume (CTV). For superficial lesions, the CTV was individually adjusted to cover the adjacent meninges at the discretion of the treating radiation oncologist. The margin for the planning target volume (PTV) was variable according to the method of fixation and available on-board imaging, but generally 1-3 mm in size isotropically in all directions.

Statistical analysis

Treatment and patients' characteristics were described using standard summary statistics. Statistical comparison between WBRT and targeted RT was performed using Fisher's exact test, chi-squared test, or Mann-Whitney test, as appropriate. Overall survival (OS), local brain control (localC), distant brain control (distalC) and extracranial control (extracranialC) were considered as survival outcomes. OS was defined as the time from the date of RT indication to the date of death from tumor cause. localC/distalC/extracranialC was defined as the time from the date of RT indication until local/distant/extracranial progression. Survival probabilities were calculated by the Kaplan-Meier method. Survival curves were compared using the log-rank test. The univariable and multivariable analyses were performed using Cox proportional hazard model for OS and Fine and Gray subdistribution hazard models for LC and DC. The variables included in the multivariable models were selected using backward stepwise elimination. The follow-up was determined using the reverse Kaplan–Meier method. The incidence of post-treatment radionecrosis between WBRT and targeted RT was compared using Fisher's exact test. Radionecrosis was evaluated on follow up scans employing T1-weighted contrast enhancement MR. Considering retrospective nature of this study, several further MRs (if available) were used to distinguish the radionecrosis from other treatment related changes of progression. All statistical analyses were performed using RStudio (version 4.2.2) [10] with a significance level of 0.05.

Results

Patients and treatment

A total of 118 patients met the inclusion criteria. Sixty-four (54%) patients were female. The median age of the entire cohort was 60 years, with median Karnofsky performance status (KPS) of 80%. 78 patients (66%) had a diagnosis of solitary metastasis. The most common primary tumor was lung cancer (39 patients; 33%). WBRT and its variants were

performed in 70 patients (59%), and stereotactic RT to the post-metastasectomy cavity in 48 patients (41%). The majority of patients were treated by stereotactic radiotherapy after 2016 (45/64 *vs.* 3/54, $p < 0.001$). In 2019, all 14 patients were treated by stereotactic RT. The other patients' and BM characteristics are summarized in Table 1 as well as basic radiotherapy data.

Radical resection was achieved in a total of 92/118 (78%) patients. The extent of resection was not re-

Table 1. Patients, brain metastases and radiotherapy characteristics

Variable	Overall (n = 118)	WBRT (n = 70)	Stereotactic RT (n = 48)	p-value
Sex				0.444
Female	64 (54%)	40 (57%)	24 (50%)	
Male	54 (46%)	30 (43%)	24 (50%)	
Age [years]				0.123
Median (IQR)	60 (49, 66)	57 (47, 64)	62 (50, 67)	
Range	26, 80	26, 80	34, 75	
< 59	59 (50%)	40 (58%)	19 (40%)	
≥ 60	59 (50%)	30 (43%)	29 (61%)	
KPS				0.057
≤ 70	32 (27%)	22 (32%)	10 (20%)	
80	49 (42%)	32 (46%)	17 (35%)	
90–100	36 (31.1%)	15 (21.4%)	21 (43%)	
Unspecified	1	1	0	
Year of surgery				< 0.001
2007–2012	29 (25%)	28 (40%)	1 (2.1%)	
2013–2015	25 (21%)	23 (33%)	2 (4.2%)	
2016–2017	33 (28%)	16 (23%)	17 (35%)	
2018– 2019	31 (26%)	3 (4.3%)	28 (58%)	
Scope of surgery				0.424
Radical resection	92 (79%)	56 (81%)	36 (75%)	
Non-radical surgery	25 (21%)	13 (19%)	12 (25%)	
Unspecified	1	1	0	
Number of BM				0.051
1	78 (66%)	40 (57%)	38 (79%)	
2	20 (17%)	13 (19%)	7 (15%)	
3	7 (5.9%)	6 (8.6%)	1 (2.1%)	
> 3	13 (11%)	11 (16%)	2 (4.2%)	
Location of BM				0.007
Cerebellum	51 (45%)	37 (55%)	14 (30%)	
Other	63 (55%)	30 (45%)	33 (70%)	
Unknown	4	3	1	
Extracranial metastases	58 (49%)	33 (47%)	25 (52%)	0.598
Extracranial disease status				0.009
CR-NED	20 (18%)	8 (12%)	12 (25%)	
SD/PR	47 (41%)	23 (35%)	24 (50%)	
PD	47 (41%)	35 (53%)	12 (25%)	
Unknown	4	4	0	

Table 1. Patients, brain metastases and radiotherapy characteristics

Variable	Overall (n = 118)	WBRT (n = 70)	Stereotactic RT (n = 48)	p-value
Primary tumor				0.005
Lung	39 (33%)	30 (43%)	9 (19%)	
Breast	24 (20%)	14 (20%)	10 (21%)	
Melanoma	13 (11%)	7 (10%)	6 (12%)	
GI	10 (8.5%)	2 (2.9%)	8 (17%)	
RCC	13 (11%)	4 (5.7%)	9 (19%)	
Other	19 (16%)	13 (19%)	6 (12%)	
Subtype of breast cancer				0.697
Basal	2 (8.3%)	1 (7.1%)	1 (10%)	
HER2	7 (29%)	3 (21%)	4 (40%)	
LumA	8 (33%)	6 (43%)	2 (20%)	
LumB	7 (29%)	4 (29%)	3 (30%)	
Adenocarcinoma of lung cancer	22 (58%)	17 (59%)	5 (56%)	0.871
Unknown	1	1	0	
Lung cancer — EGFR mutations				0.381
Negative	36 (95%)	29 (97%)	7 (88%)	
Melanoma — BRAF mutation				0.559
Positive	4 (31%)	3 (43%)	1 (17%)	
RT characteristics				
Time from surgery to RT (days)				0.268
Median (IQR)		47 (27, 74)	48 (39, 67)	
Time from indication to start RT (days)				<0.001
Median (IQR)		14 (10, 22)	22 (19, 32)	
Range		3, 83	9, 93	
Type of RT (overview)				
WBRT		56 (80%)	0 (0%)	
WBRT + SIB		12 (17%)	0 (0%)	
HA_WBRT		1 (1.4%)	0 (0%)	
HA_WBRT+SIB		1 (1.4%)	0 (0%)	
SRS		0 (0%)	6 (12%)	
FSRT		0 (0%)	35 (73%)	
Local RT in multiple fractions		0 (0%)	7 (15%)	
RT schedule				
Single fraction		1 (1.4%)	6 (12%)	
3 fractions		0 (0%)	5 (10%)	
10 × 3 Gy		41 (59%)	2 (4.2%)	
5 × 4 Gy		14 (20%)	1 (2.1%)	
5 × 5 Gy		0 (0%)	19 (40%)	
Other		14 (20%)	15 (31%)	
Steroids during RT		56 (81%)	37 (77%)	0.591
Unknown		1	0	
Targeted/immunotherapy after RT		3 (4.3%)	5 (10%)	0.268

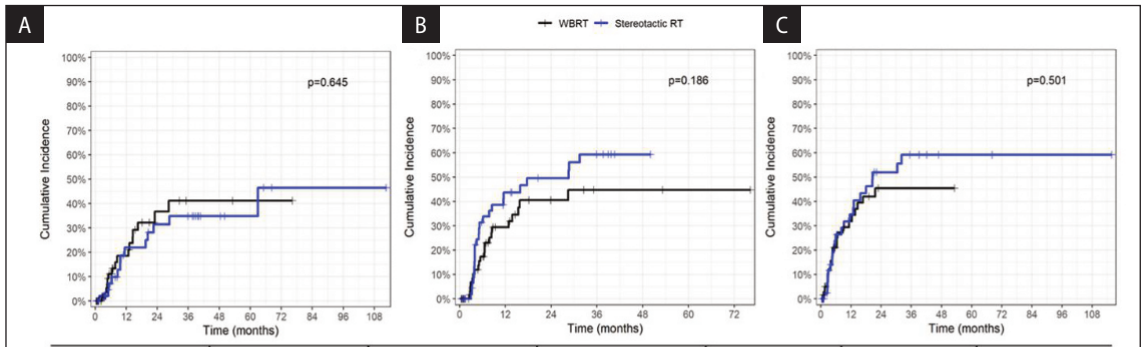
RT — radiotherapy; N — number; WBRT — whole brain radiotherapy; IQR — interquartile range; KPS — Karnofsky performance status; BM — brain metastases; CR-NED — complete response — no evidence of disease; PD — progressing disease; SD/PR — stable disease/partial response; RCC — renal cell carcinoma; HER2 — human epidermal growth factor receptor 2; LumA — luminal A; EGFR — epidermal growth factor receptor; BRAF — proto-oncogene B-Raf murine sarcoma viral oncogene homolog B; SIB — simultaneous integrated boost; HA — hippocampal avoidance; FSRT — fractionated stereotactic radiotherapy; SRS — stereotactic radiosurgery; Gy — Gray

ported in one patient; no difference in resection extent was seen between the adjuvant WBRT and stereotactic RT cohorts (p = 0.424). There was a notable upward trend in the number of patients referred for metastasectomy (2007-2015 total of 54/118; 46% *vs.* 64/118; 54% from 2016-2019). These data are summarized in Supplementary File — Table S1.

There were significant differences in the baseline characteristics of patients who underwent different radiotherapy techniques. Patients who underwent stereotactic postoperative radiotherapy were in better overall condition before radiotherapy than those who underwent WBRT (KPS ≥ 90 in 21/48 patients; 44% *vs.* 15/70 patients; 21%). Although there was no difference in the number of patients with extracranial metastasis, there were more patients with controlled extracranial disease in the stereotactic group (75 *vs.* 47%, p = 0.003). Patients in the stereotactic RT group also had a lower number of metastases and fewer infratentorial BM. Conversely, more patients with lung cancer were in the WBRT group, with no difference in the proportion of adenocarcinomas (Tab. 1). Other details about RT procedures are summarized in Supplementary File — Table S2. The incidence of post-treatment radionecrosis is summarized in Supplementary File — Table S3.

Survival and treatment outcomes data

The median follow-up of the whole cohort was 58 months. At time of reporting, 102 (86%) patients had died (68, 97% and 34, 71% in WBRT and stereotactic RT cohort, respectively). Local recurrences were seen in 29 patients, distal recurrences in 45 patients, and extracranial recurrences in 44 patients. 10 patients experienced local (close to initial surgery) and/or distant leptomeningeal metastasis (LM). LM occurred more frequently at the surgical site in the stereotactic RT cohort compared with the WBRT cohort (5 out of 13 with local recurrence *vs.* 1 out of 16 with local recurrence). The median OS of the whole cohort was 10 months [95% confidence interval (CI): 7.1–12 months) and was longer in the stereotactic RT cohort (18 *vs.* 7.1 months; p < 0.001). The cumulative incidence for local, distant and extracranial control were not significantly different between cohorts, with 12-month cumulative incidence for localC of 22% *vs.* 18%, for the 12-month DistalC 44% *vs.* 29%, and for the 12-month extracranialC 35% *vs.* 32% for the stereotactic and WBRT cohorts, respectively. Survival data are summarized in Figure 1 together with 12-, 24-, 36- and 48-month survival/cumulative incidence. When evaluating overall survival according



		Median	12 Month	24 Month	36 Month	48 Month
OS	Overall	10 (7.1, 12)	43% (35, 53)	29% (22, 38)	19% (13, 27)	16% (11, 25)
	WBRT	7.1 (5.0, 11)	33% (24, 46)	19% (11, 30)	10.0% (5.0, 20)	7.1% (3.1, 17)
	Stereotactic RT	18 (11, 30)	58% (46, 74)	44% (32, 60)	31% (20, 47)	31% (20, 47)
			Cumulative incidence of event	Cumulative incidence of event	Cumulative incidence of event	Cumulative incidence of event
localC	Overall		20% (12, 29)	34% (23, 44)	37% (26, 48)	37% (26, 48)
	WBRT		18% (8.9, 31)	37% (21, 52)	41% (25, 57)	41% (25, 57)
	Stereotactic RT		22% (10, 37)	32% (17, 47)	35% (19, 51)	35% (19, 51)
Distal C	Overall		36% (26, 45)	44% (34, 54)	51% (40, 61)	51% (40, 61)
	WBRT		29% (18, 42)	41% (26, 54)	45% (29, 59)	45% (29, 59)
	Stereotactic RT		44% (28, 58)	50% (33, 64)	59% (41, 73)	59% (41, 73)
Extracranial C	Overall		33% (24, 43)	48% (37, 58)	52% (40, 62)	52% (40, 62)
	WBRT		32% (20, 45)	45% (30, 59)	45% (30, 59)	45% (30, 59)
	Stereotactic RT		35% (20, 50)	52% (35, 67)	59% (41, 74)	59% (41, 74)

Figure 1. Kaplan-Meier survival curves for cumulative incidence function considering death as a competing event for local control (**A**), distal control (**B**), and extracranial control (**C**) according to radiotherapy (RT) technique

to the year of surgery, no difference was observed (Supplementary File — Figure S1).

Univariable and multivariable analyses

Univariate analyses are summarized in the Supplementary File — Table S4. On multivariable analysis including the type of postoperative radiotherapy, stereotactic RT after metastasectomy was a statistically significant positive prognostic factor for OS compared with postoperative WBRT [hazard ratio (HR): 0.47, p = 0.004]. Other independent positive prognostic factors for OS were KPS, controlled primary disease, lower number of BM (HR: 2.47; p = 0.003 for > 2 BM), and absence of steroid administration during RT. The multivariable model for OS also included the primary tumor type and incorporated the types of systemic treatment prior to RT. The results of the multivariable analyses for localC and distalC are summarized in Table 2. The type of postoperative radiotherapy was not significant for localC but was for distalC. The multivariable models included age, KPS. For localC, the primary tumor type was added; for distalC, the number of BM.

Table 2. Multivariable analyses

	OS			localC			distalC		
Characteristic	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Type of RT			0.004			0.539			0.029
WBRT	–	–		–	–		–	–	
Stereotactic RT	0.47	0.28, 0.79		0.78	0.35, 1.74		1.92	1.07, 3.44	
Age [years]				0.95	0.91, 0.99	0.007	0.95	0.92, 0.97	< 0.001
KPS			0.002			0.088			0.058
≤ 70	–	–		–	–		–	–	
80	0.39	0.23, 0.65		7.61	1.21, 47.9		2.77	0.89, 8.65	
90–100	0.46	0.26, 0.82		3.97	0.78, 20.3		3.75	1.15, 12.3	
Number of BM			0.003						0.068
1–2	–	–					–	–	
> 2	2.47	1.41, 4.32					1.97	0.95, 4.08	
Primary tumor			0.061			<0.001			
Breast	–	–		–	–				
GI	3.45	1.54, 7.74		2.18	0.76, 6.19				
Melanoma	1.16	0.51, 2.66		0.87	0.35, 2.17				
Lung	1.08	0.57, 2.05		0.38	0.13, 1.15				
Other	0.73	0.35, 1.51		0.63	0.20, 2.04				
RCC	1.38	0.59, 3.21		0.00	0.00, 0.00				
Control primum			<0.001						
Yes	–	–							
No	2.47	1.51, 4.04							
Systemic treatment before RT			0.060						
No	–	–							
Yes	1.69	0.98, 2.91							
Steroids during RT			0.011						
No	–	–							
Yes	1.95	1.13, 3.34							

OS — overall survival; localC — local control; distalC — distal brain control; HR — hazard ratio; CI — confidence interval; RT — radiotherapy; WBRT — whole brain radiotherapy; KPS — Karnofsky performance status; BM — brain metastases; GI — gastrointestinal; RCC — renal clear cell carcinoma

Discussion

This single-center retrospective study analyzed a consecutive cohort of 118 patients with BM treated by surgery and adjuvant radiotherapy over 15 years. Radiotherapy targeted to the tumor bed was an independent positive prognostic factor for overall survival (HR = 0.47, p = 0.004) with no difference in localC between adjuvant WBRT *vs.* targeted RT but with better distalC after WBRT. In general, a given RT procedure is always a compromise between local control (local control separately at the post-resection site and separately in distant brain regions) and toxicity (edema, cognitive function) [12]. The current standard of care generally involves local radiotherapy to the metastasis or tumor bed following resection, reserving whole-brain radiotherapy (WBRT) for rapidly progressing disease or patients with a high number of metastases at baseline [13–16]. Of note, the seminal Patchell et al., in which the role of postoperative (single brain metastasis) WBRT to a dose of 50.4 Gy was compared to postoperative observation, is a key example of the tradeoff between toxicity and tumor control [17]. Today, WBRT of 50.4 Gy for a single brain metastasis would be considered unethical, despite the promise of excellent local and distant brain disease control.

In accordance with our clinical practice, the management of patients after brain metastasis surgery was reassessed in 2017 when two large randomized phase III trials addressing this issue were published in extenso. The multicenter randomized trial NCCTG N107C/CEC-3 compared postoperative stereotactic radiosurgery with postoperative WBRT in a total of 194 patients. The majority of patients had solitary brain metastasis, with a maximum number of 4 [13]. Our patient cohort had a similar proportion of metastasis, with 66% having solitary lesions and only 11% presenting with more than 3 metastases.

In Brown et al. study [13], patients with radioresistant and more radiosensitive tumors were equally enrolled in arms comparing WBRT with targeted RT, with a common primary endpoint of overall survival and survival without cognitive deterioration. With comparable overall survival, targeted stereotactic radiotherapy led to better outcomes in terms of better cognitive preservation (33% difference in 6-month cognitive function deterioration after WBRT *vs.* targeted RT 85 *vs.* 52%). In contrast, patients in the WBRT arm had better local and distant disease control. Long-term survivors, assessed 1 year after surgery, were significantly more likely to have cognitive deterioration after WBRT (24/27 patients; 89%) than after radiosurgery (10/27 patients; 37%) [13]. Our cohorts are compared with these data in Supplementary Table 5; notably, our cohorts had fewer lung primary patients. On the other hand, almost half of the patients randomized to WBRT in the prospective study were prescribed biologically higher doses of 15 × 2.5 Gy. Our patients had similar outcomes with targeted RT to post-surgery cavity. Conversely, our patients treated with WBRT had lower 1-year distalC. This comparison must be interpreted with caution owing to differences in patient and treatment characteristics. Nevertheless, our data from real-world practice reinforces published practice-changing trials.

The second seminal study randomized 132 patients after surgery for 1–3 brain metastases to postoperative stereotactic RT *vs.* postoperative observation. The primary endpoint was time to local recurrence, defined as the occurrence of a new confluent lesion following postoperative cavitation. Postoperative radiotherapy did not lead to improved OS or a risk reduction of death from neurological causes. However, 12-month freedom from local recurrence (FFLR) was improved: 43% (95% CI 31-59) in the observation arm and 72% (60-87) in the targeted radiotherapy arm [HR: 0.46 (95% CI: 0.24–0.88); p = 0.015] [18]. The study confirmed that even with advanced surgical techniques, local control is better achieved through the use of postoperative radiotherapy to the post-resection cavity [18]. Numerous other prospective randomized studies confirmed the superiority or noninferiority of local RT compared to WBRT, mostly with respect to cognitive functioning and quality of life preservation [19–27]. These outcomes are currently important endpoints in almost all trials focused on brain RT, particularly with regard to hippocampal avoidance [28].

Several statistical metrics are used in the evaluation of postsurgery tumor bed irradiation outcomes. Clinically, local control is the most recognized, but the importance of competing risk analysis, incorporating death or loss from follow-up, is a significant consideration. Cumula-

tive incidence of tumor progression may be more appropriate for treatment outcomes reporting. Alternatively, FFLR may be used. Real world retrospective data allows for rapid assessment of the current state of affairs, and so local control may be suitable [29, 30]. Nevertheless, prospective randomized trials remain the best means by which bias may be properly considered. Inherent limitations of all retrospective studies thus remain here, such as the limited availability of valid toxicity information apart from incidence of radionecrosis, and results should be cautiously applied. When using appropriate statistical tools, such as multivariable analysis, it is possible to adjust the outcomes from confounding factors. On the other hand, it must be acknowledged, that with significant differences in baseline characteristics in WBRT and targeted RT group the direct comparison of OS between these two cohorts is not meaningful even with multivariable analysis. Still, this real world data analysis presents the valuable data showing also the patterns of patients indicated to metastasectomy as seen in the fact that there was no selection for WBRT or FSRT in patients enrolled in last years of our study (all patients operated in 2019 underwent postoperative targeted therapy).

In all patients in whom targeted radiotherapy is indicated after metastasectomy, adequate follow-up is necessary, with the recommendation of follow-up brain MRI at least 3 months after RT in the first year. Patients (and referring extramural oncologists) should be repeatedly informed about the potential for additional, distant lesions to occur following targeted RT, and that these lesions can generally be treated with further RT. This recommendation is also highlighted by our observation of significantly lower distalC in patients without postoperative WBRT (HR: 1.92; $p = 0.029$ for stereotactic RT). Patients, especially those with a presumption of significantly longer survival, such as those in better clinical condition following neurosurgery, should also be informed of the non-zero risk of targeted RT in terms of cognitive decline and quality of life. This is how targeted RT is often presented in relation to the risks of WBRT. Cognitive function and quality of life are complex phenomena influenced by many factors both in and outside the patient. The type of radiotherapy is only one variable, and deterioration of a given patient's overall condition and cognition can occur even if WBRT is omitted.

Despite the emerging systemic therapy for brain metastases and the promising results of preoperative stereotactic radiosurgery, a significant proportion of patients with brain metastases can be expected to be referred for upfront surgery. These are generally patients with large metastases and more pronounced perifocal edema where it is not possible to delay surgery, for example, due to the risk of herniation. Finally, inclusion criteria often limit the lesion size to 3–4 cm in studies with preoperative stereotactic radiosurgery. In patients with larger lesions and thus larger postoperative cavity, fractionated postoperative regimens may be considered. Our study demonstrates the efficacy of fractionated radiotherapy to the tumor bed when compared with single-dose stereotactic RT presented in prospective clinical trials. The most common fractionation in our cohort (40% of patients) was targeted radiotherapy to a dose of 5×5 Gy. Slightly more aggressive regimens such as 5×6 Gy or 3×9 Gy are currently advocated. It should also be emphasized that all our patients were irradiated on a linear accelerator, compared to other studies using a Leksel gamma knife (LGK). Although frame-less fixation is currently also used in LGK and, thus, fractionated radiotherapy is feasible there as well. We anticipate that linear accelerators will remain the most used technology in postoperative RT of large brain metastases. These machines continue to evolve and improve over the years. Some technical improvements are essential to reduce, for example, the risk of local recurrence due to inaccurate radiation (image-guided RT) or the risk of miscalculations during treatment planning (small field dosimetry).

In addition to the aforementioned limitations in the various statistical metrics assessing the local control, our study has several other limitations, arising mainly from its nature as a retrospective study. Although multivariate analysis can minimize the risk of bias, comparisons between WBRT and targeted radiotherapy cohorts will be affected by differences in their baseline characteristics. Finally, the inherent limitation of all retrospective studies evaluating patients enrolled during longer period (2007–2019 in our study), is the influence of evolving systemic treatment used over time, which can bias the OS comparisons.

Once the indications for preoperative stereotactic radiotherapy are established, an update of indications and procedures for patients requiring upfront surgery followed by radiotherapy to the bedside after resection can be expected. Our study can serve as reference data for control groups from real-world data that facilitate the design of the upcoming clinical trials dealing with postoperative radiotherapy in newly identified cohorts of patients.

Conclusions

In virtually all patients with brain metastases, despite the increasing indications for modern systemic treatment, local treatment is necessary sometimes later in the course of their disease, consisting in patients with larger brain metastases most often of a combination of surgery and radiotherapy targeted at the resection bed. Numerous prospective studies have defined this current standard of local treatment for brain metastases. Patients with brain metastases constitute a specific cohort of patients in whom there is a very thin line between indications for anti-cancer or straight symptomatic therapy. For this reason, the cohorts of patients treated in clinical trials may differ significantly from those in real clinical practice. In our retrospective study of a consecutive cohort of patients treated with a combination of surgery and postoperative radiotherapy from 2007–2019, we observed, on multivariable analysis taking into account the baseline characteristics differences, better overall survival in patients treated with postoperative targeted radiotherapy compared with postoperative WBRT. On the other hand, WBRT was the independent factor for better distal brain control. The majority of patients with targeted radiotherapy had a fractionated dose schedule with outcomes comparable to single-dose radiation in the major trials of postoperative targeted radiotherapy. Our data confirm the current standard of postoperative targeted radiotherapy for BM.

Author contributions

Conceptualization: T.K., P.F. and V.V.; methodology: P.F., V.V., I.R., M.S., R.J., P.P., L.H., J.G., R.B., J.K., A.SP., Z.M., V.J., M.S., E.N., H.V., R.L., M.H., R.H., P.S and T.K.; formal analysis: K.P., I.K., M.S.; investigation I.S., T.K., P.F., J.S., O.S.; Resources: T.K., M.S., R.H.; data curation: I.S.; writing—original draft preparation, T.K., I.S., P.F.; writing — review and editing: all coauthors. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University Hospital Brno No. EKFNB-17-06-28-01.

Informed Consent Statement

All patients signed an informed consent for anonymized/pseudonymized analysis of their clinical data for research purposes.

Data Availability Statement

data are available from corresponding author per request.

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