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Original article

Surgical bed stereotactic radiotherapy of brain metastases: Clinical outcome and predictors of local and distant brain failure

Radiothérapie stéréotaxique sur les berges opératoires des métastases cérébrales : résultats thérapeutiques et facteurs prédictifs de rechutes cérébrales locales et à distance

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ABSTRACT

Purpose. – To retrospectively analyze the outcomes of stereotactic radiotherapy (SRT) targeted at surgical bed of brain metastases (BM) and identify patterns of local/distant brain relapses (LR/DBR).
Patients/methods. – Seventy patients were treated with SRT between 2008–2017. Marginal dose prescription on the 70% isodose line depended on the maximal diameter of the target volume and range between 15–18 Gy for single fraction radiosurgery and 23.1–26 Gy in 3–5 fractions for fractionated SRT.
Results. – At 12 months, the overall survival (OS) was 69% [CI $_{95\%}$ = 59%–81%]. At 6 and 12 months, the cumulative incidence functions (CIF) of local relapse were 4% [1%–13%] and 15% [8%–26%], respectively. According to univariate analysis, factors associated with LR were an initial volume larger than 7cc (hazard ratio: 4.6 [1.0–20.8], $P = 0.046$) and a positive resection margin [hazard ratio: 3.6 [1.1–12.0], $P = 0.037$. DBR occurred in 54.3% of patients with a median time of 8 months. None of the variables tested (histology, location or number of lesions) were found correlated with the DBR. Leptomeningeal disease occurred in 12.9% of cases. Salvage whole brain radiotherapy (WBRT) was required in 45.7% of patients and delayed by a median time of 9.6 months. Symptomatic radionecrosis (RN) occurred in 7.1%.
Conclusions. – Adjuvant SRT was an effective and well-tolerated treatment to control the postoperative risk of recurrence of BM without compromising OS. Positive resection margins and large volumes were predictors factor of local relapse.

Mots clés :
Métastases cérébrales
Contrôle local
Postopératoire
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RÉSUMÉ

Objectif de l'étude. – Analyse rétrospective des résultats de la radiothérapie stéréotaxique des berges opératoires des métastases cérébrales et des facteurs prédictifs de rechutes cérébrales locales/à distance.
Patients et méthodes. – Soixante-dix cavités opératoires ont été traitées par irradiation stéréotaxique adjuvante entre 2008 et 2017. La dose marginale prescrite à l'isodose d'enveloppe 70 % était comprise entre 15–18 Gy pour les radiochirurgies et entre 23,1–26 Gy (3–5 fractions) pour les radiothérapies stéréotaxiques hypofractionnées.

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Résultats. – La probabilité de survie globale était de 69 % [IC $_{95\ \%}$ (intervalle de confiance à 95 %) = 59 %–81 %] à 12 mois. L'incidence cumulative des rechutes locales était de 4 % [1 %–13 %] et 15 % [8 %–26 %], respectivement à 6 et 12 mois. En analyse unifactorielle, le volume de la tumeur initiale dépassant 7 cc (*hazard ratio*: 4,6 [1,0–20,8], $p = 0{,}046$) et la marge de résection atteinte (*hazard ratio*: 3,6 [1,1–12,0], $p = 0{,}037$) étaient des facteurs significatifs de rechute locale. À distance, 54,3 % de rechutes cérébrales ont étaient notées avec un délai médian d'apparition de 8 mois sans facteur prédictif significatis identifis. Des rechutes leptoméningées ont été notées dans 12,9 % des cas. La radiothérapie panencéphalique de rattrapage était nécessaire dans 45,7 % après un délai médian de 9,6 mois. Le taux de radionécrose symptomatique était de 7,1 %.

Conclusions. – La radiothérapie stéréotaxique adjuvante est une alternative thérapeutique efficace sur le contrôle local des cavités opératoires des métastases cérébrales sans majoration de la toxicité et sans compromettre la survie globale. Les marges de résection atteintes et les volumineuses lésions sont prédictives de rechute locale nécessitant une meilleure optimisation de la dose et du fractionnement.

1. Background

Surgical resection of a unique brain metastasis (BM) has been shown to have a survival benefit [1]. However, there is approximately a 50% risk of local recurrence (LR) in the surgical bed, even after confirmed gross tumor resection [2]. Postoperative whole brain radiotherapy (WBRT) improves local (LC) and distant brain control rates and reduces the death rate from neurological causes; however, there is no overall survival (OS) improvement [3]. It is also associated with inferior quality of life and neurocognitive functions (NCF) decline, especially in patients with expected long-term survival. Such undesirable side effects may be avoided by irradiating the resection cavity with stereotactic radiation therapy (SRT) [4]. A growing body of evidence supports SRT as an established adjuvant treatment by providing 1-year LC rates of 65–90% [5–9]. To assess the effect of stereotactic radiosurgery (SRS) on surgical cavity control, a single institution, prospective phase III trial randomly assigned 132 patients with complete resection to SRS of the surgical cavity or observation. LC rates at 1 year were significantly improved after SRS compared to resection alone [72% vs 43%, respectively; $P = 0.015$] [10]. Because SRT has the advantage of sparing patients from the acute and late toxicities of WBRT, many physicians consider SRT alone to the resection cavity, at the condition of close – typically three-monthly-magnetic resonance imaging (MRI) monitoring. Recently, an American multicentric randomized trial compared SRS to WBRT, showing that SRS provided a lower intra cranial control, without a difference in OS but significantly spared NCF at 3 months [4]. Since only SRS was used, marginal dose was decreased for larger target volumes, which is paradoxical since higher volumes yield the higher risks of recurrence and thus need at least biologically equivalent doses to smaller volumes [10]. Therefore, the debate on adjuvant treatment is still open with active surveillance, WBRT or SRT as potential treatment options [2]. In our hospitals network, we offer postoperative SRS or hypofractionated SRT (HFSRT) to patients with BM since 2010.

The aims of this study were:

- to retrospectively evaluate the outcomes of SRT after BM resection: overall survival, progression free survival (PFS), cumulative incidence of both local and distant brain recurrence (DBR) and identify their clinical predictors;
- to identify the patterns of failures and salvage treatments;
- finally, to evaluate late toxicities, especially symptomatic radionecrosis (RN).

2. Materials and methods

2.1. Patients selection

We systematically screened the cranial SRT database of the CHU-UCL-Namur to retrospectively identify the patients with newly diagnosed BM who had undergone prior craniotomy and treated with adjuvant SRT to the surgical cavity, treated from April 2008 to July 2017. Surgical resection was performed to relieve neurological symptoms [e.g. motor deficits or intracranial hypertension], for large lesions [≥ 4 cm of greater diameter] or in case of need of pathology examination. Patients prognosis was assessed according to the recursive partitioning analysis (RPA), graded prognostic assessment (GPA) score and the disease specific graded prognostic assessment (DSGPA).

2.2. Radiation therapy

Between January 2008 and June 2010, treatments were delivered on a Varian Clinac 2300 CD (Varian, Palo Alto, CA, USA) with a Brainlab M3 (Brainlab, Feldkirchen, Germany) micro multi leaf collimator (mMLC) add-on. Head-positioning accuracy was ensured by the six degrees of freedom (6DoF) head plate with micrometrical screws (Brainlab AG, Feldkirchen, Germany) and verified with portal images. From June 2010, a dedicated Novalis TX (Varian, Palo Alto, CA, USA and Brainlab AG, Feldkirchen, Germany) was used with embarked high definition MLC (HD MLC) and 6DoF robotic couch ExacTrac X-Ray positioning system with submillimetric repositioning capacity at all couch positions.

A post-gadolinium enhanced 3D T1-weighted MRI planning with 1.0 to 1.6-mm slices was obtained with a median time of 8 days [range = 1–34] before simulation. Head fixation was performed with patients in a supine position with double shell stereotactic thermoplastic masks from Brainlab AG (Feldkirchen, Germany), except for SRS treatments between January 2008 and June 2010 when invasive head ring from the same vendor was screwed on the patient's head. Stereotactic planning computed tomography (CT), planning MRI and postoperative MRI, if available, were imported to iPlan RT image software (versions 3.5 to 4.2, Brainlab AG, Feldkirchen, Germany) for image registration and delineations. If applicable, the gross tumor volume (GTV) was defined as any residual tumor; the clinical target volume (CTV) consisted of the GTV and the resection cavity plus a safety margin accounting for potential microscopic spread of 1 to (preferentially) 2 mm at the treating physician discretion. The surgical track and edema areas were excluded from the CTV. The planning target volume (PTV) margin was 0 mm, except when masks were used during the "M3 era" [January 2008–June 2010], when a 1 mm margin

was added. Surrounding organs at risk (OAR) were delineated as well. Marginal dose prescription and schedule of SRT depended exclusively on the maximal diameter of the PTV: ≤ 2.0 cm = 18 Gy SRS; 2.1–3.0 cm = 15–16 Gy SRS; > 3.0 cm = 23.1 Gy in 3 fractions of 7.7 Gy or 5 fractions of 5.2 Gy HFSRT. The treatment delivery techniques used were either dynamic conformal arctherapy (DCA) or volumetric modulated arc therapy (VMAT) with a mix of 4 to 6 coplanar and non-coplanar arcs of 6 MV photons. Dose calculations were computed with iPlan RT dose (versions 3.5 and 4.0, Brainlab AG, Feldkirchen, Germany) or Varian Eclipse (versions 11 and 13, Varian, Palo Alto, CA, USA) treatment planning systems, for DCA and VMAT treatments, respectively. Marginal dose to the PTV was prescribed at the 70% isodose line and conformity index (CI, calculated according to the Paddick formula = (Target Volume in Planned Isodose Volume)^2/Target Volume × Tumor Volume Covered in Planned Isodose Volume) had to narrow a value of 1 with a maximum of 2. All treatments were delivered with a short anti-inflammatory prophylaxis with corticoids.

2.3. Follow-up

After treatment, the patients were followed-up with clinical examinations and MRI every 3-monthly during the first 18 months and 6-monthly for the next 30 months. LR was defined as the presence of any new progressive nodular enhancement involving the resection cavity on T1 gadolinium-enhanced MRI. In some cases, MR perfusion imaging was used, and an increased cerebral blood volume was considered suspect of LR. The differential diagnosis of RN was defined as the appearance of contrast enhancement on MRI in the previously irradiated tumor bed, occurring between 6 and 12 months after irradiation with a T1-T2 mismatch on MRI [11]. Addition functional imaging could be used on physician request, such as perfusion MRI or ^{18}Fluoro-deoxy-glucose positron emission tomography. Stability or decrease of contrast enhancement on the close follow-up MRI under corticoids were suggestive of RN. The diagnosis of RN was finally established on a set of clinical and radiological arguments and validated by a multidisciplinary team board. Histological confirmation was obtained in some cases when patients presenting with disabling and persistent neurological symptoms were operated. DBR was defined as the presence of any new enhancing brain metastases or leptomeningeal disease outside the postoperative cavity which was diagnosed based on MRI, clinical symptoms, and/or cerebrospinal fluid cytology. All cases were examined for the use of salvage therapies and cause of death.

2.4. Statistical analyses

Descriptive statistics included the median and ranges for continuous variables or counts and percentages for categorical variables. For the overall survival, the follow-up begins with the diagnostic and ends with the follow-up closure. For other censored variables involving relapses, the follow-up begins with the end of SRT and ends with the last MRI imaging. OS and PFS were computed with Kaplan-Meier method while the cumulative incidence function (CIF) of LR, DBR, meningeal relapse, neurologic death and salvage radiotherapy were computed using competing risk analysis with death (or non-neurologic death when appropriate) as a competing event.

The potential predictors of OS were RPA, GPA, DSGPA classes, controlled primary tumor, extracranial metastasis status. The potential predictors of LR were piecemeal resection, interval time between surgery and SRT, pre- and postoperative tumor volumes, marginal total dose, technique (SRS or HFSRT), Conformity index and for DBR multiple versus solitary BM as well as location (supra vs sub-tentorial).

Table 1
Patient characteristics..

Characteristics	*n*	%
Gender		
M	40	57.1
F	30	42.9
Age [years]		
< 65	45	64.3
≥ 65	25	35.7
Primary disease		
NSCLC	43	61.4
Breast cancer	10	14.3
GI	4	5.7
Renal cell carcinoma	3	4.3
Melanoma	3	4.3
Other	7	10
KPS		
< 70	6	8.6
> = 70	64	91.4
DSGPA score		
0–2	13	18.6
2.5–3	41	58.6
> = 3.5	9	12.8
NS	7	10
Extracranial metastases		
No	49	70
Stable	16	22
Progressive	5	8
Number of BM		
1	50	71.4
2–3	20	28.6
Location		
Infra-tentorial	27	38.6
Supra-tentorial	43	61.4
Superficial	26	37
Deep	44	62.8
Diameter of lesion		
< 3 cm	28	40
> = 3 cm	42	60
Surgery		
En bloc	42	60
Piecemeal	21	30
Unknown	7	10
Resection margin		
Negative	59	84.3
Positive	11	15.7

n: number of patients; NSCLC: non-small cell lung cancer; GI: gastro intestinal; KPS: Karnofsky performance status; DSGPA: diagnosis-specific graded prognostic assessment.

Univariate analyses rely on Cox models in order to compute the hazard ratio or the cause-specific hazard ratio when competing events are present. Statistical significance was set for P-values ≤ 0.05. Statistical analyses were performed with R, version 3.3.2 (R Foundation for Statistical Computing, Vienna, 2016).

3. Results

3.1. Population

Eighty-five patients were retrospectively identified in our database. Ten were excluded because of previous irradiation to the brain, three because of upfront combination treatment with WBRT and two cases treated with salvage SRT after early recurrence, leaving 70 patients available for analysis. A summary of the cohort as well as the characteristics of the treated lesions can be found in Table 1. The median age was 60 years [40–84]. The sex ratio was 1.33. Twenty-five patients (35.7%) presented with cardio-vascular risk factors (i.e. hypertension, diabetes and/or ischemic cardiopathy). The most common primary tumor was non-small cell lung cancer (NSCLC) [61.4%]. The median time between BM diagnosis and surgery was 19 days [0–272]. At the time of surgery, 21% had active systemic disease, and 30% had extracranial metastases.

Table 2
Stereotactic parameters and treatment characteristics.

Stereotactic Parameters	SRS	HFSRT
Number [%]	26 [37.14%]	44 [62.86%]
Fractionation	16 Gy [15–21 Gy]	23,1 [3 × 7,7 Gy] 24 [4 × 6 Gy] 26 [5 × 5,2 Gy]
Conformity index	1.5 [1.38–2.2]	1.46 [1.3–2.3]
Median SB volume (cc)	3.6 [0.86–26]	12 [2–31]
Median PTV volume (cc)	7.9 [2–47]	20 [4–64]
D_{max} (Gy)	22.87 [16.3–37.3]	24 [15.2–44.6]
D_{min} (Gy)	13.76 [11.7–20]	14.4 [8.7–29.5]
V_{12Gy} (cc)	14,5 [1,2–27]	–
V_{21Gy} (cc)	–	13 [0–57]

SRS: stereotactic radiosurgery; HFSRT: hypo fractionated Stereotactic Radiotherapy; SB: surgical bed; PTV: planning target volume; D max: maximal dose; D min: minimal dose; V × : volume receiving × dose.

The median Karnofsky Performance Status (KPS) scale was 80% [range = 60–100]. The patient median GPA and DSGPA classifications were 2.5 [0.5–4] and 2.5 [1–4], respectively. Single brain metastasis was noted in 71.4% of cases. The median preoperative lesion volume was 7.2 cc [0.5–29.5]. Most patients (83%) underwent gross tumor resection, defined by the neurosurgeon at the time of surgery and, when available, immediate postoperative MRI (performed in 18% of cases due to limited access within the postoperative 48–72 hours). En bloc resection was documented in 60% of the cases. The SRT was delivered at a median time of 28 days after surgery [range = 3–99].

3.2. Treatment characteristics

Radiotherapy treatment characteristics are listed in Table 2. Seventy resection cavities treated with a median single marginal dose of 16 Gy ($n = 26$) or HFSRT 23.1–26 Gy in 3–5 fractions ($n = 44$). The most common schedule was 3 × 7.7 Gy. Patients were more likely to have a larger median resection cavity volume (12 cc vs 3.6 cc) and PTV volume (20 cc vs 7.9 cc) in HFSRT versus SRS groups, respectively. Mean conformity index were similar in both groups (1.5 vs 1.46).

3.3. Survival

The median follow-up of surviving patients was 64 months [1–120]. At 6 and 12 months, the overall survival rates [$CI_{95\%}$] were 90% [83%–97%] and 69% [59%–81%], respectively. The progression-free survival rates were 69% [59%–81%] and 40% [30%–53%] at the same time points (Fig. 1).

3.4. Failure patterns

At 6 and 12 months, the CIF [$CI_{95\%}$] of LR were 4% [1%–13%] and 15% [8%–26%], respectively. At longer follow-up times, the CIF of LR seemed to stabilize around 20% (Fig. 2). In the 14 patients who developed LR, median time to progression was 8.3 months after SRT. The CIF of DBR were 22% [14%–34%] and 34% [24%–48%] at 6 and 12 months, respectively. At the same time points, the CIF of meningeal relapses were 3% [0%–12%] and 9% [4%–19%], respectively (Fig. 2). Leptomeningeal disease occurred in 9 of 70 patients (12.9%) at a median time of 10.7 months. Two nodular meningeal relapses happened in the vicinity of the target volume: one along the surgical track and one in the meningeal wall (1.4% each).

Of 38 patients who experienced DBR, 5 underwent salvage SRS, 27 salvage WBRT, 2 underwent surgery, one received systemic chemotherapy and 3 were not treated at all. Seven patients who presented an isolated LR received repeated SRT. Seven patients who developed concurrently LR and DBR received WBRT as salvage therapy. The CIF of salvage WBRT at 6 and 12 months were 10% [5%–21%] and 27% [18%–40%], respectively (Fig. 2). Finally, salvage WBRT was required in less than 50% [45.7%] of patients and delayed by a median time of 9.6 months [2–91] from BM diagnostic. At 6 and 12 months, the CIF of neurologic death were 4% [1%–13%] and 10% [5%–21%], respectively (Fig. 2).

3.5. Subgroup analysis

Overall survival was better for patients with DSGPA > 3.5 (Table 3). However, we did not find evidence of association between survival and RPA, control of the primary or the extracranial disease.

According to univariate analysis, a large initial tumor diameter more than 2.5 cm, tumor volume more than 7 cc and a positive resection margin were associated with a higher rate of local relapses (Table 4). The CIF [$CI_{95\%}$] of LR was 19% [11%–33%] at 1 year for patient with tumor diameter >= 2.5 cm against 0% for smaller tumors. A tumor volume >= 7 cc yielded a CIF of LR of 23% [12%–42%] against 7% [2%–25%] for smaller tumor volume ($P = 0.045$). A positive margin yielded a CIF of LR of 40% [19%–85%] compared to 11% [5%–23%] at 1 year for R0 resections [$P = 0.037$] (Fig. 3).

Concerning the DBR, we did not observe significant associations between the potential predictors [histology, location supra or subtentorial, DSGPA and GPA] and the occurrence of relapse (Table 5).

3.6. Toxicity

RN occurred in 13 patients, with a CIF [$CI_{95\%}$] of 0% and 3% [1%–12%] at 6 and 12 months, respectively. SRT was well tolerated with severe acute side effects (intracranial hyper pressure symptoms) in only 2 cases. There were two cases of leukoencephaloathy. Thirteen patients (18.6%) developed radiological RN at a median time of 18 months [3.6–105.0] of which 5 were symptomatic and 5 were histologically proven (7.1%). Surgery was performed in 5 cases of non-response to steroids and confirmed the RN at pathological examination. In univariate analysis, we identified the deep location of BM as the main predictive factor of RN ($P = 0.04$).

4. Discussion

In this retrospective study on postoperative SRT to BM surgical cavity, we could show it is an effective strategy, leading to satisfactory long-term LC without compromising OS. At 12 months, the cumulative incidence functions of LR was 15%, which compares favorably with prior published studies [12,13]. Comparatively to the recent prospective study published in 2017, we have better a LC [10]. This may be due to methodological differences related to the inclusion of a 2 mm CTV margin in most cases versus 1 mm in the Mahajan study [10]. The inclusion of this margin around the resection cavity may improve LC rates [14]. In a retrospective single institution series, it was shown that LC increased from 75% for the more conformal plans to 100% for the least conformal plans, leading to the recommendation of a corresponding 2 mm CTV margin [13]. Secondly, the choice of hypofractionation for larger volumes could have played a role since it allowed to prescribe a higher biologically effective dose to the larger volumes, HFSRT allowing a safe dose escalation without compromising toxicity [15,16]. In case of voluminous lesions > 15–30 cc, lower doses are generally used with SRS to control the risk of RN [4,10]. This may be insufficient to control such tumor bed since the risk of relapse is higher for bigger lesions [10]. In a systematic literature review, the relation between SRT dose and LC at 1 year after SRS was highly dose-dependent, being > 80% after 21 Gy or more, but < 50% after 15 Gy or less. They concluded that SRT dose should be at least 40 Gy with a $BED_{\alpha/\beta = 12Gy}$ [17]. In our study, we used HFSRT to treat target volumes with diameters beyond 3 cm of great axis instead of reducing the SRS

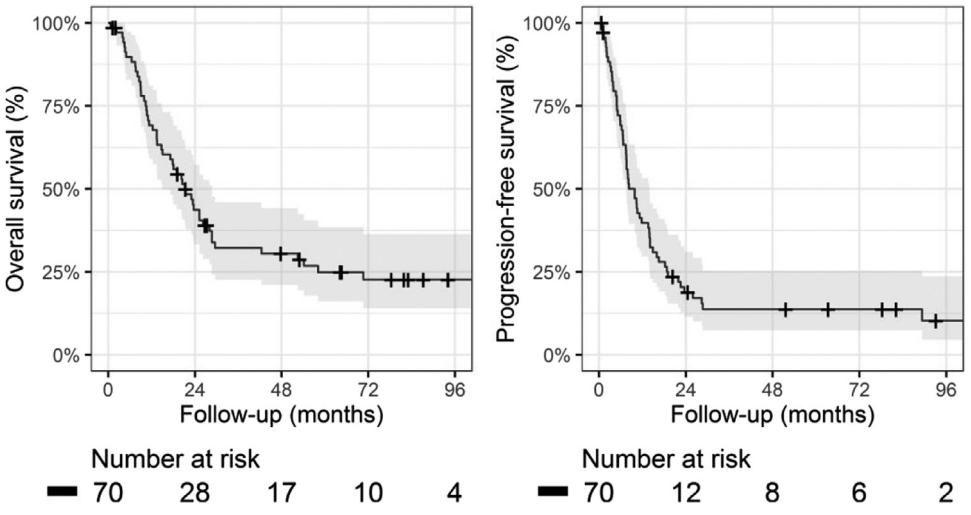

Fig. 1. Overall (left) and progression-free (right) survival estimated with the Kaplan-Meier method.

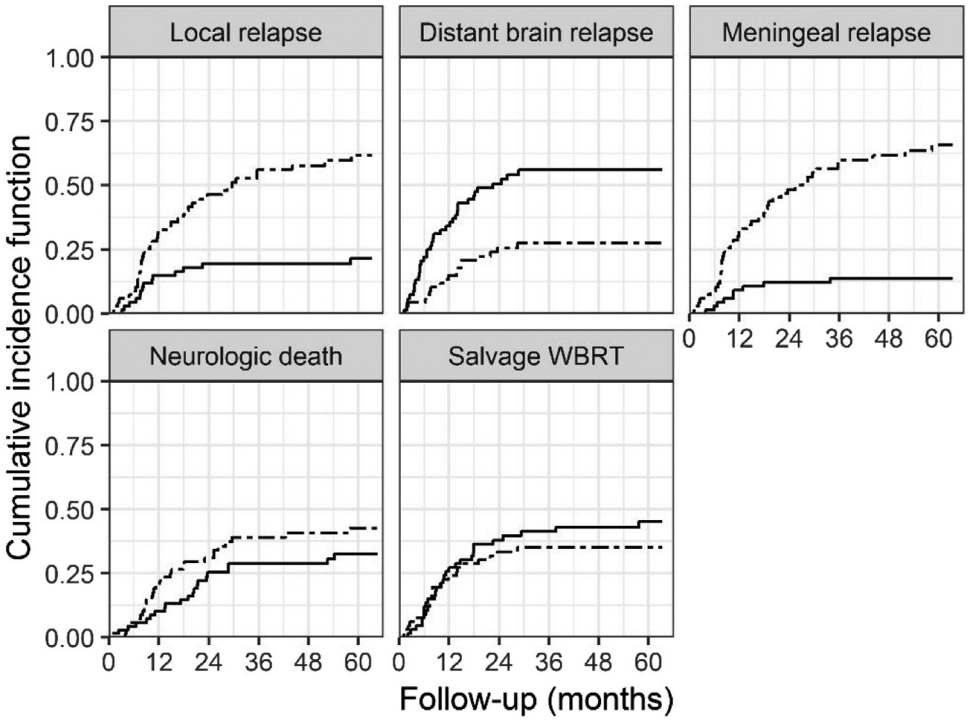

Fig. 2. Cumulative incidence function of local relapse, distant brain relapse, meningeal relapse, neurologic death and salvage WBRT (black line). The cumulative incidence function of the competing event is represented in gray. The competing event is death except for the event "neurologic death" where the competing event is "non-neurologic death".

Table 3
Univariate analysis of factors associated with overall survival..

Variables	Subgroup	*n*	Evt	PY	IR	HR	*P*
DSGPA	1–3	54	43	123	34.9	–	
	3.5–4	9	4	44	9.2	0.31 [0.11–0.86]	0.024
RPA	1	30	18	98	18.3	–	
	1–2	40	33	88	37.5	1.76 [0.99–3.14]	0.055
Primary control	0	22	18	49	36.7	-	
	1	48	33	137	24.1	0.69 [0.39–1.24]	0.22
EC control	0	48	33	132	25.0	–	
	1	22	18	54	33.3	1.24 [0.7–2.22]	0.46

Evt: events [number of local relapses], PY: person-years; IR: Incidence rate [per 100 person-years]; HR: Hazard ratio [95% confidence interval]; *P*: P-value [Cox models]; DSGPA: diagnosis-specific graded prognostic assessment; EC: extracranial.

Table 4
Univariate analysis of factors associated with local recurrence.

Variable	Subgroup	*n*	Evt	PY	IR	HR	*P*
Histology	Pulmonary	42	8	96.7	8.3	–	
	Other	28	6	48.5	12.4	1.14 [0.39 - 3.31]	0.81
n	1	50	13	108.6	12	–	
	2–3	20	1	36.6	2.7	0.22 [0.03–1.67]	0.14
Initial volume (cc)	[0.8–7[	31	2	52.8	3.8	–	
	[7–29.5]	37	12	88.5	13.6	4.64 [1.03–20.81]	0.045
GA (cm)	[1–2.5[	14	0	29.5	0	–	
	[2.5–5]	56	14	115.7	12.1	Undeterminated	0.041*
DSGPA	[1–3.5[	54	8	105.4	7.6	–	
	[3.5–4]	9	4	22.1	18.1	2.44 [0.73–8.15]	0.15
GPA	[0.5–3[	42	8	77.4	10.3	–	
	[3,4]	28	6	67.8	8.8	0.93 [0.32–2.67]	0.89
Resection	En bloc	45	8	96.1	8.3	–	
	Piecemeal	24	6	47.9	12.5	1.37 [0.47–3.97]	0.56
Resection margin	Negative	58	10	134.9	7.4	–	
	Positive	11	4	9.1	44	3.6 [1.08–11.97]	0.037
Delay (days)	[13–30[	41	7	89.4	7.8	–	
	[30–NA]	29	7	55.8	12.5	1.51 [0.53–4.3]	0.44
PTV	[1.6–10[	18	4	34.5	11.6	–	
	[10–64.5]	46	9	98.1	9.2	0.9 [0.28–2.94]	0.87
Conformity index	[1.21–1.4[	17	3	38.4	7.8	–	
	[1.4–2.22]	53	11	106.7	10.3	1.41 [0.39–5.07]	0.60

GPA: graded prognostic assessment; DSGPA: disease specific graded prognostic assessment; *n*: number of brain metastases, GA greatest axis; PTV: planning target volume, HR: cause-specific hazard ratio; *P*: *P*-value [Cox models].
* *P*-value obtained with log-rank test.

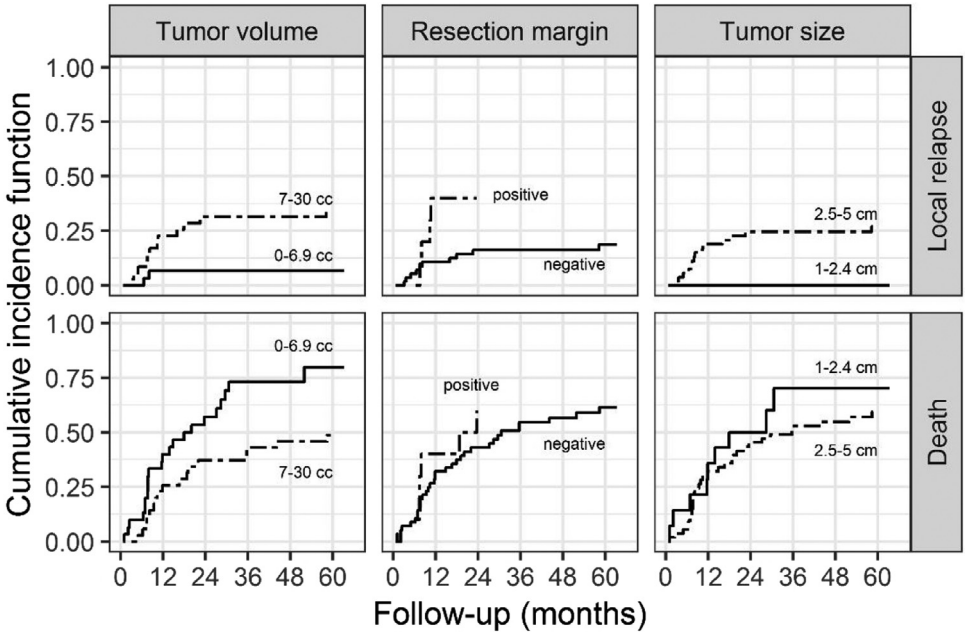

Fig. 3. Cumulative function of local relapse in different subgroups [in solid and discontinued lines]. The cumulative incidence function of the competing event [death] in the different subgroups is represented in the curves below.

Table 5
Univariate analysis of factors associated with distant brain recurrence.

Variable	Subgroup	*n*	Evt	PY	IR	HR	*P*
Number	1	50	25	92.1	27.1	–	
	2–3	20	13	22.8	57	1.92 [0.97–3.78]	0.78
Location	Sub-tentorial	27	17	34.9	48.7	–	
	Supra-tentorial	43	21	80	26.2	0.72 [0.38–1.38]	0.059
DSGPA	[1–3.5[	54	31	72.9	42.5	–	
	[3.5–4]	9	5	26.6	18.8	0.57 [0.22–1.49]	0.64

DSGPA: disease specific graded prognostic assessment; *P*: *P*-value [Cox model]; Evt: events [number of local relapses]; PY: person-years; IR: incidence rate [per 100 person-years]; HR: hazard ratio [95% confidence interval].

dose and the most prescribed schedule was 23.1 Gy in 3 fractions [$BED_{\alpha/\beta=12Gy}$ = 34.5 Gy]. In the recent years, we increased the dose to 3 fractions of 9 Gy that seems to be a popular schedule nowadays. Hypofractionation is popular in the radiation oncology community because, according to the linear-quadratic model, it allows to deliver isocytotoxic doses to the tumor while decreasing the risk of side effects [18]. Anyway, HFSRT was never prospectively compared to SRS in a randomized study and this strategy deserves it to get a definitive validation.

BM greater than 7 cc in volume and 2.5 cm in size were significant predictors of LR in the univariate analysis in this study, consistent with the recent randomized study [10]. In a metanalysis, Gans et al. found that positive margin was predicting LR knowing that quality of margin is linked to the volume since it leads to piecemeal resection [14].

After SRT, the rates of radiologic RN reported in the literature are highly variable, ranging from 1.5% to 24% [9,19,20]. In our study, 18.6% developed radiological RN at a median time of 18 months [3.6–105.0] of which 5 were symptomatic (7.1%). The ratio symptomatic/radiologic RN were 0.38 in our series and conform to the rate of 33% found in the literature [21]. We identified the deep location of BM as a potential predictive factor of RN ($P = 0.04$). The main risk factors for symptomatic RN after SRT of BM are the treated volume, the prescribed dose, the fractionation schedule and the use of systemic therapies [21].

One key point that remains unsolved until now is the target volume delineation strategy. The uncertainty induced by image alterations and modifications dynamics in the postoperative setting could alter the LC of tumor bed as well as increase the risk of RN [19,22]. Recently, an experts-based contouring delineation consensus was proposed [22]. It was suggested to cover the CTV along the meningeal margin, to include the entire surgical tract regardless of the preoperative location (even for deep lesions) and to extend up to 5 mm along the dura overlying the bone flap in case of dural contact and into the adjacent sinus if there is venous sinus contact. This may lead to include large volumes and consequently increase the risk of RN. Our delineation strategy systematically avoided these suggested extensions. This did not significantly preclude the LC rate with only 2 marginal relapses in the dura and in the surgical track (2.8% in total). An alternative could be preoperative SRT because not suffering of all the uncertainties inherently linked to postoperative SRT. It was tested first in 47 patients with 6 and 12-months LC rates of 97.8 and 85.6%, respectively [23]. In a multi-institutional retrospective comparison of preoperative SRS (with a GTV to PTV margin of 0 mm) to postoperative SRS (CTV to PTV margin of 2 mm) in 180 patients, no statistical difference was observed for LR, DBR, and OS rates but demonstrated a significantly lower rate of symptomatic RN (4.9% vs. 16.4%, respectively, $P = 0.01$) [24].

DBR occurred in 54% of patients with a median time of 8 months, which was almost similar to the 49% rate observed in a meta-analysis [14]. In the randomized study NCCTG, this rate was 40.7% in the SRS group with a median time of 6.4 months [4]. This substantial rate of DBR highlights the importance of maintaining a close clinical and imaging follow-up for patients not treated with WBRT. In the univariate analysis, DBR was more likely to happen in the case of multiple BM [10]. In our series, we did not observe a significant relation between DBR and number of BM.

The salvage WBRT was required in less than 50% of the patients and delayed by a median time of nearly 10 months. In case of DBR, there is no consensus on the most effective salvage treatment modality. Recognizing that there is a need to prevent the occurrence of new BM, there has been a flurry of reports of possible synergy between SRS and various immunomodulatory and targeted systemic agents with better blood brain barrier mostly for patients with targetable mutations [25]. The response rates with use of erlotinib, gefitinib, and osimertinib in EGFR mutation–positive lung cancer BM have been reported in prospective trials to range from 50% to 80%, resulting in progression-free survival of 6 to 12 months and overall survival of 15 to 22 months [26]. Two recent trials reported in abstract form (CheckMate 204 and ABC) demonstrated intracranial objective response rates of 56% and 44%, respectively, for patients with melanoma BM treated with ipilimumab and nivolumab [27,28]. Anyway, the recent leaps observed with systemic therapies should not lead to the withholding of cranial radiotherapy. A multi-institution retrospective study of 202 patients with EGFR-mutant NSCLC metastatic to the brain showed that the treatment with EGFR-TKIs alone and SRT deferral altered the survival probability in comparison to upfront radiotherapy followed by EGFR-TKIs [29]. SRS in conjunction with immunotherapy has been associated with improved response, OS and reduced incidence of DBF in retrospective studies [30].

The present study inevitably suffers from the shortcomings of the retrospective collection of data. The most important ones are the selection bias of patients with a better prognosis treated aggressively, the largely incomplete data about molecular biology characteristics of the tumors and the poor use of targeted therapies and/or immunotherapies in most patients at the time of treatment. Anyway, our findings are hypothesis-generating and stimulate further validation in. planned prospective clinical trials.

5. Conclusion

With this study, we bring observations that suggest that postoperative SRT is an effective treatment, leading to satisfactory long term LC and well-tolerated strategy to control the surgical bed of BM after surgery, partly related to the use of HFSRT in case of large target volume. Salvage WBRT was required in less than 50% of the patients and delayed by a median time of nearly 10 months. However, future prospective studies are needed to refine the radiosurgery technique, fractionation, dose, timing to surgery, preoperative SRS strategies, combination with targeted therapies or immunotherapies that altogether may significantly change the way patients with operated BM will be treated in the future.

Disclosure of interest

The authors declare that they have no competing interest.

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