Clinical and Translational Radiation Oncology 27 (2021) 70–74

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

The individual risk of symptomatic radionecrosis after brain metastasis radiosurgery is predicted by a continuous function of the V12Gy ☆

Jean-François Daisne [a,b,*], Clémentine De Ketelaere [a,1], Jacques Jamart [c]

[a] Radiation Oncology Department, Université Catholique de Louvain, CHU-UCL-Namur (site Ste-Elisabeth), 5000 Namur, Belgium
[b] Radiation Oncology Department, Katholieke Universiteit Leuven - University of Leuven, University Hospitals Leuven, 3000 Leuven, Belgium
[c] Unité de Support Scientifique, Université Catholique de Louvain, CHU-UCL-Namur (site Godinne), 5530 Yvoir, Belgium

ARTICLE INFO

Article history:
Received 5 January 2021
Revised 5 January 2021
Accepted 8 January 2021
Available online 14 January 2021

Keywords:
Brain
Metastases
Stereotactic radiosurgery
Necrosis

ABSTRACT

Introduction: Brain metastases are frequently treated with stereotactic radiosurgery (SRS). Radionecrosis (RN) is the late side effect in up to 24% of patients, being symptomatic in 8–10%. Fixed values of the radiosurgical volume receiving 12 Gy or more (V12Gy) are used to roughly predict the global risk. The aim of this retrospective study is to fine-tune the model of individual risk prediction for symptomatic radionecrosis and identify modulating factors.

Materials and methods: Data of patients treated with SRS for ≤3 BM of solid tumours at CHU-UCL-Namur were retrospectively reviewed. Doses ranging from 15 to 24 Gy were prescribed to the 70% isodose in function of the lesion diameter. Treatment was administered with a stereotactic linear accelerator. Follow-up magnetic resonance imaging was performed 3-monthly for 18 months and 6-monthly thereafter. RN was prospectively diagnosed and confirmed by the tumour board. V12Gy, previous or salvage whole-brain radiotherapy (WBRT), smoking history, diabetes, postoperative SRS, diagnosis-specific graded prognostic assessment score, cerebral lobe location and relative location (superficial versus deep) were retrieved. Univariate and multivariate analyses were performed to assess their predictive values and derive a model.

Results: 128 patients with 220 lesions were analysed. The risk of RN was predicted by a continuous function of the V12Gy ($p = 0.005$). No other factor had a significant impact, particularly WBRT that did not increase the risk.

Conclusion: The risk of symptomatic RN is predicted on an individual basis by a model in function of the V12Gy and must be confirmed in a prospective study.

1. Introduction

Brain metastases (BM) from solid tumours is a growing problem in oncology due to improved survival rates, the global increase in cancer incidence in an aging population and the generalization of magnetic resonance imaging (MRI) for screening and diagnosis. The true prevalence is largely unknown, varying between 5 and 40% of the cancer patients, because of differences in time periods, primary tumours and detection methods [1,2]. Until the end of the twentieth century, the prognosis was dismal, and the therapeutic options were limited to surgical resection, whole brain radiotherapy (WBRT) or best supportive care. The landscape dramatically changed over the last 20 years with the recognition of the improved prognosis of oligometastatic patients, an increased access to stereotactic radiosurgery (SRS) and the development of targeted therapies and immunotherapies [3]. As a consequence, patients with a metastatic cancer live longer, with an increased risk of developing BM and living many months after their treatment – with particular subgroups showing median overall survival (OS) times up to 3–4 years [4,5].

Most patients are treated nowadays with a combination of systemic therapies and radiotherapy, preferably with SRS instead of WBRT to avoid the risk of subacute and late cognitive dysfunctions

☆ Presented as an oral communication during the International Stereotactic Radiosurgery Society (ISRS) bi-annual congress in Montreux (CH), May 28th–June 1st, 2017.

* Corresponding author at: Radiation Oncology Department, KU Leuven – University of Leuven, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.
E-mail address: jean-francois.daisne@uzleuven.be (J.-F. Daisne).
[1] Current professional address: Radiation Oncology Department, CHR Verviers East Belgium (site La Tourelle), 4800 Verviers, Belgium.

https://doi.org/10.1016/j.ctro.2021.01.003

[6,7]. The shortcomings of SRS are an increased risk of distant brain failure (DBF) in patients older than 50 years [8] and late radionecrosis (RN) in up to 24% patients [9]. The risk largely depends on the radiosurgical volume receiving intermediate to high doses from 8 Gy (V8Gy) to 16 Gy (V16Gy) [10]. The most published dosimetric parameter is the V12Gy, varying between 4.8 and 10 cc for a risk prediction of 10–35% [9–13]. However, using one absolute cut-off value is arbitrary and unclear since the risk is not binary but rather a continuous sigmoid function of the V12Gy as was demonstrated in two series of arteriovenous malformations (AVM) [14,15] and both BM and benign tumours [11]. Last, other clinical factors may interplay like the target location [13,14], genetic susceptibility or theoretical etiological vascular factors [16].

In a population of patients treated with SRS for BM in one Belgian centre, our aim was to retrospectively review the patients presenting a symptomatic RN to identify the risk factors and develop a model for a clear, individual prediction of the risk in function of the V12Gy.

2. Materials and methods

2.1. Study inclusion criteria

We retrospectively reviewed the SRS database of CHU-UCL-Namur, site Ste-Elisabeth, from April 2008 through October 2016. Treatments were performed for patients with solid tumours BM; recursive partitioning analysis class I-II; postoperative or exclusive SRS for $\leq$3 BM per treatment; a follow-up of at least 6 months. Salvage treatment with SRS after WBRT, or salvage treatment with WBRT after SRS were authorized. Patients receiving extra courses of SRS for salvage treatment of DBF were included too.

Patients were excluded if they were treated with stereotactic hypofractionated radiotherapy (SFRT), had $\geq$4 lesions or had a histology of hematological primary tumour or lung small cell carcinoma (because standardly treated with upfront WBRT), received a second course of SRS for a local relapse, or had a follow-up <6 months.

2.2. Treatment planning and delivery

A planning MRI was acquired with at least an axial 3D (1 mm slice thickness) set with gadolinium contrast injection. Head fixation was performed with a stereotactic frame from April 2008 through June 2010 and with a stereotactic thermoplastic mask from July 2010 through October 2016 (Brainlab, Munich, Germany). A dosimetric 1.25 mm or 0.625 mm volumetric computed tomography scan (CT-scan) was then acquired without iodine contrast injection with a localization box containing spatial fiducials (Brainlab, Munich, Germany). Both the CT-scan and the MRI images were exported to the SRS-dedicated iPlan RT software platform (Brainlab, Munich, Germany) for localization, fusion and segmentation of both gross tumour volume (GTV) and organs at risk (OAR). The GTV was further expanded by 1 mm (exclusive irradiation) or 2 mm (postoperative irradiation) to cover the microscopic extension in the clinical target volume (CTV). No margin was added to obtain the planning target volume (PTV). The dose was prescribed to the PTV at the 70% isodose line in function of the greatest diameter according to the RTOG 90-05 study [17]. Two different planning techniques were available in the department and the choice was made by the planner. Dynamic conformal arcs with iPlan RT dose version 3 or 4 (Brainlab, Munich, Germany) or volumetric modulated arc therapy with Eclipse version 11 or 13 (Varian, Palo Alto, CA, USA) treatment planning systems (TPS) were used to generate the plan (4 or 5 6-MV bundles).

From April 2008 through June 2010, the treatments were delivered on a Clinac 2300 EX (Varian, Palo Alto, CA, USA) with a micro multileaf collimator M3 add-on (Brainlab, Munich, Germany). After, they were delivered on a robotic platform Novalis TX from the same vendors, allowing frameless SRS with the same precision.

2.3. Follow-up

Follow-up MRI were prescribed three-monthly for 18 months, and then six-monthly until 48 months. RN was defined as any enlarging lesion on T1 images with gadolinium enhancement, located at the place of a metastasis previously treated with SRS with a minimum delay of six months, with secondary characteristics not compatible with a local progression (i.e., «bubble soap» aspect and/or T1–T2 mismatch; spontaneous regression on further MRI; asymptomatic or paucisymptomatic patient; symptomatic patient responding dramatically to corticosteroids). Complimentary metabolic imaging like perfusion MRI or ^{18}fluoro-deoxyglucose positron emission tomography (FDG-PET) could be performed on an individual basis. Surgical resection was proposed for life-threatening symptoms, insufficient response to corticosteroids or dubious diagnosis with local relapse. The final diagnosis of RN was decided by the multi-disciplinary tumour board. Any RN was defined as symptomatic (in case of neurological impairment temporally and anatomically related to the radionecrotic spot) or asymptomatic.

2.4. Data collection

Dosimetric and clinical variables were retrospectively retrieved for each patient and each treated lesion. The V12Gy was calculated in cc with the TPS, without subtraction of the PTV but the bone in superficial lesions. In case two lesions would have laid close to each other with merging V12Gy, only one V12Gy would have been counted. History of previous WBRT, salvage WBRT, smoking, diabetes, postoperative SRS, diagnosis-specific graded prognostic assessment (DS-GPA) score, cerebral lobe location and relative location (superficial versus deep = brainstem, cerebral peduncles, thalamus, hypothalamus or basal ganglia) were recorded from the hospital electronic medical records in compliance with general data protection regulation (GDPR). In accordance with the Belgian Law, no Ethics Committee approval was required for a retrospective trial.

2.5. Statistics

OS was estimated from the time of the first SRS using the Kaplan-Meier method. The crude rates of RN were calculated for the whole population of patients and for the total number of lesions. The time from SRS to symptomatic RN or to WBRT was measured for each lesion individually since patients could have received more than one course of SRS over the time. Univariate analysis was performed with the Mann-Whitney test for continuous variables or the Pearson's Chi squared test for the nominal variables to assess their predictive value. Multivariate analysis used logistic regression with a backward selection of variables (history of previous WBRT, salvage WBRT, postoperative SRS, DS-GPA and cerebral lobe) allowing to derive a general formula helping to prospectively predict the risk on an individual basis. All P-values for statistical significance were $\leq$0.05, except for multivariate logistic regression where $P \leq 0.10$ was accepted. The goodness of fit was estimated by measuring the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. All calculations were performed using the MedCalc software version 19.1 (MedCalc Software bv, Ostend, Belgium).

3. Results

A total of 267 patients received SRS between April 2008 and October 2016 at CHU-UCL-Namur for 1–3 brain metastases per treatment. After exclusion of patients not fulfilling inclusion criteria, it left 128 patients with 220 lesions (among which 29 postoperative cavities). Median DS-GPA was 2.5 in 119 assessable patients. Seventy-eight patients had a history of former or current smoking while 10 had diabetes; 5 diabetic patients were smokers. The total number of lesions treated per patient ranged from 1 to 7 (median = 1) in 1 to 4 (median = 1) different treatment sessions. Metastases were predominantly located in the frontal, parietal, occipital lobes and the cerebellum (Table 1). Prescribed dose ranged from 15 to 24 Gy (median = 21 Gy). Median V12Gy was 6.5 cc (range = 0.7–51.6). The median OS was 24 months and median follow-up after SRS was 1.5 years (range = 0.5–8.8) for the different lesions.

Fifty-six patients (110 lesions) received previous or salvage WBRT. Forty-eight lesions (22 patients) were treated with SRS at a median time of 16.1 month (range = 105.4–1.6) after a WBRT; salvage WBRT was administered for local relapse or DBF after SRS on 62 lesions (34 patients) with a median time of 10.5 months (range = 2.6–90.5). Two patients received SRS before and after WBRT. Death occurred at a median time of 7 months after salvage WBRT.

Symptomatic RN was diagnosed in 21 patients (16.4% of all patients) on 21 different lesions (9.5% of all lesions), pathologically confirmed in eight patients. Median time from SRS to RN was 9 months (range = 3–45). Thirteen patients were smokers and two had diabetes. Four patients were treated with salvage SRS after a WBRT and two received salvage WBRT after SRS. The risk of RN was lower in the population with a history of WBRT (4.5%) compared to no WBRT (14.5%). The median V12Gy was anyway significantly lower in the WBRT group (5.5 cc) than in the non-WBRT group (7.8 cc) (P = 0.038).

Univariate analysis identified the V12Gy and the prescribed dose as risk factors for symptomatic RN (P = 0.001 and 0.036, respectively) and WBRT as a protective factor (P = 0.039). Median V12Gy of lesions with symptomatic RN was 10.6 cc (range = 2.4–51.6) compared to 5.8 cc (range = 0.7–50.0) for lesions without. The multivariate analysis identified the V12Gy as a risk factor (P = 0.005) and a salvage WBRT as a protective factor (P = 0.068). Salvage WBRT was anyway excluded from the prediction model because it would be unknown at the time of SRS. The AUC of the ROC curve was 0.735 (IC95% = 0.671–0.792). The logistic regression allowed to derive the formula $\exp(\beta)/[1 + \exp(\beta)]$ with $\beta = -2.88\ 9 + 0.062$ (V12Gy) to predict the individual risk of symptomatic RN at the time of SRS in function of V12Gy (Fig. 1).

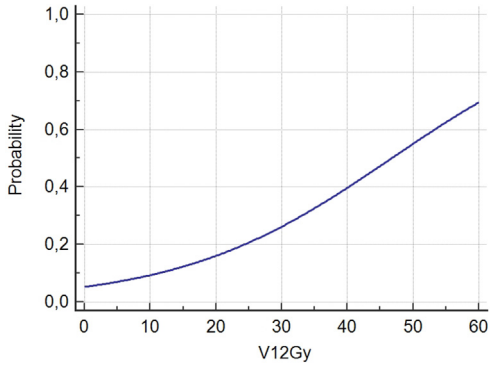

Fig. 1. Logistic regression of the predicted risk of symptomatic radionecrosis according to V12Gy.

4. Discussion

In this monocentric retrospective study in a homogeneous population of patients with BM treated with SRS, the crude rate of symptomatic RN was 9.5% of all lesions and 16.4% of all patients. With a median OS of 24 months, the population is well selected for the SRS treatments, and the risk is not underestimated. Our study confirms that the risk of symptomatic RN after BM SRS is a direct function of the V12Gy that highly looks like the model published nearly three decades ago for AVM. None of the other risk factors (location, cardio-vascular factors, DS-GPA, post-operative SRS or previous WBRT) were significant.

Table 1
Cerebral locations of the metastases in absolute number and in percent.

Location	N (%)
Frontal	76 (35)
Parietal	44 (20)
Cerebellum	40 (18)
Occipital	34 (16)
Temporal	20 (9)
Basal ganglia	3 (1)
Brainstem	3 (1)

Some limitations are pinpointed, such as biases inherent to retrospective studies (lack of reporting or interpretation of risk factors or symptoms, of less strictly applied follow-up protocol and a lack of quality of life data). Moreover, a monocentric study reflects the local policy for selection of patients and treatment. Last, the predictive model is not yet validated in an independent population.

The reported risk of RN in the retrospective literature varies widely from 1% [6] to 24% [9], that may be due to different factors. First, patients populations and prognosis evolved with the time. Historically, patients with BM treated with SRS had a median OS around 11 months in the early reports [9,10,18], contrasting with the 24 months of this series (that is in line with the most recent reports [13,19]). With a median time to RN ranging between 9 and 11 months [9,10], death competes less with RN nowadays, the risk of RN is thus relatively higher. Second, target delineation and prescription protocols differ with a potential impact on the crude RN risk. While some prescribe to the GTV only [18], others use a GTV-to-PTV margin of 1–2 mm [9]. In a prospective randomized study testing a 1 mm against a 3 mm margin, there was no difference in the 1-year local control (LC) (>90%), at the cost of a non-statistically significant increase in RN (3% versus 15%). Third, most RN diagnoses rely on imaging, with poor sensitivity and specificity rates ranging between 44–97% and 19–75%, respectively [20,21]. Fourth, there may be a reporting bias in retrospective studies, since the rates in prospective studies are lower (0–6%) [7,17,22]. Last, a distinction must be made between symptomatic and asymptomatic RN. The crude rate of symptomatic RN lies between 8.4 and 16% patients, with our series lying at the upper range [9,10,13,19]. It must be stressed that most patients usually evolve favourably after a corticosteroids treatment, less than 5% requiring a surgical resection for long-lasting impairment [19].

Unfortunately, we could not identify supplementary clinical risk factors. Since the physiopathology of RN largely depends on vascular damage, vascular co-factors may play an aggravating role, but it was never demonstrated, presumably because of the multiple confounding factors [16]. In AVM, the cerebral lobe was an important modulator of RN risk [14]. Results are more conflicting in BM with the temporal and occipital lobes [11] or the deep structures of the brain [13] identified as higher risk regions. We do not confirm these results, probably due to the low number of deep metastases in our series. Since the shape and the values of our logistic regression matches the ones of the AVM [15], we can reasonably hypothesize that the differential models used in func-

tion of the cerebral lobes for AVM could also be used for BM, a hypothesis that needs a prospective confirmation on a larger number of patients. Contrary to other retrospective studies [11,23], previous WBRT was not a risk factor. We fall in line with prospective randomized studies comparing SRS versus SRS + WBRT where patients in the second arm did not develop significantly more RN [7,22,24]. We even found salvage WBRT could have a protective effect but excluded it from the prediction model because the future requirement of a salvage WBRT would not be known at the time of prescribing SRS and estimating the risk of RN. The data are nonetheless reassuring because they show that salvage WBRT can be applied without increased risk after SRS treatments.

The control of RN is key throughout the BM SRS literature. An isotoxic dose prescription model was retrospectively developed on 30 SRS unique BM treatments and prospectively validated on 65 patients with 138 lesions [12]. It allows to prescribe the dose in function of the PTV volume. The prescription is thus based mostly on toxicity and not on LC. But LC is also important to consider when treating BM: doses 20 Gy or $\leq$15 Gy give 1-year LC of 80% and 50%, respectively [25]. Taking the patients' perspectives, we think that models for RN risk prediction are useful to prescribe the dose, but also to discuss the risk and benefit with the patient. We prefer to individualize the prescription in function of the pursued aims by modulating the V12Gy rather than using fixed values that may seem arbitrary to a given extent.

Hypofractionation is increasingly used to improve the therapeutic ratio by diminishing the risk of RN and/or improving the local control of larger metastases (>2 cm diameter). A meta-analysis identified 24 studies and concluded that multi-fraction SRS improved the LC by 20% in metastases of 2–3 cm diameter and reduced the risk of RN by a factor 2–3 [26]. An individualized isotoxic dose prescription model was developed to select either single- or multi-fraction SRS based on PTV size [27].

Most patients were treated before the era of immunotherapy. Since the majority of patients with BM have a primary lung, renal or melanoma tumour, there is a greater chance that patients receive a checkpoint inhibitor nowadays. If delivered concurrently, it improves both survival and disease control results; the risk of RN is scarcely reported and does not seem to be higher, but this needs further studies that may eventually modify the prediction model [28].

The diagnostic accuracy also needs to be improved. FDG-PET with a two-phase examination has sensitivity, specificity and accuracy rates around 90% [29]. In the near future, the broader availability of radiomics analysis on MRI images could also be of help without requiring additional examinations, with reported sensitivity and specificity of 66 and 87% [21].

In conclusion, this retrospective study confirms the individual predictive power of V12Gy for symptomatic RN after BM SRS. Metachronous WBRT is safe and may be prescribed independently of SRS need or history. While the impact of immunotherapies needs clarification and diagnostic accuracy must be improved, hypofractionation helps to improve the therapeutic ratio of BM $\geq$ 2–3 cm.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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