Cancer/Radiothérapie 21 (2017) 4–9

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Original article

# Stereotactic radiotherapy following surgery for brain metastasis: Predictive factors for local control and radionecrosis

## *Radiothérapie stéréotaxique postopératoire de métastase cérébrale : facteurs prédictifs de contrôle local et de radionécrose*

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ARTICLE INFO

*Article history:*
Received 23 May 2016
Received in revised form 27 June 2016
Accepted 30 June 2016

*Keywords:*
Stereotactic
Brain
Metastasis
Surgery

ABSTRACT

*Purpose.* – To evaluate local control and adverse effects after postoperative hypofractionated stereotactic radiosurgery in patients with brain metastasis.
*Methods.* – We reviewed patients who had hypofractionated stereotactic radiosurgery (7.7 Gy × 3 prescribed to the 70% isodose line, with 2 mm planning target volume margin) following resection from March 2008 to January 2014. The primary endpoint was local failure defined as recurrence within the surgical cavity. Secondary endpoints were distant failure rates and the occurrence of radionecrosis.
*Results.* – Out of 95 patients, 39.2% had metastatic lesions from a non-small cell lung cancer primary tumour. The median Graded Prognostic Assessment score was 3 (48% of patients). One-year local control rates were 84%. Factors associated with improved local control were no cavity enhancement on pre-radiation MRI ($P < 0.00001$), planning target volume less than 12 $cm^3$ ($P = 0.005$), Graded Prognostic Assessment score 2 or above ($P = 0.009$). One-year distant cerebral control rates were 56%. Thirty-three percent of patients received whole brain radiation therapy. Histologically proven radionecrosis of brain tissue occurred in 7.2% of cases. The size of the preoperative lesion and the volume of healthy brain tissue receiving 21 Gy ($V_{21}$) were both predictive of the incidence of radionecrosis ($P = 0.010$ and 0.036, respectively).
*Conclusion.* – Adjuvant hypofractionated stereotactic radiosurgery to the postoperative cavity in patients with brain metastases results in excellent local control in selected patients, helps delay the use of whole brain radiation, and is associated with a relatively low risk of radionecrosis.
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*Mots clés :*
Stéréotaxique
Cerveau
Métastase
Chirurgie

RÉSUMÉ

*Objectif de l'étude.* – Évaluation du contrôle local et de la toxicité d'une radiothérapie hypofractionnée en conditions stéréotaxiques adjuvante à l'exérèse chirurgicale d'une métastase cérébrale.
*Matériel et méthode.* – Analyse rétrospective des dossiers de patients ayant reçu une irradiation hypofractionnée en conditions stéréotaxiques de 23,1 Gy délivrée en trois fractions sur l'isodose 70 %, avec une marge de 2 mm entre le volume cible anatomoclinique et le volume cible prévisionnel, après exérèse neurochirurgicale, de mars 2008 à janvier 2014. Le critère principal était la rechute locale, définie par la récidive dans la cavité traitée. Les critères secondaires étaient la rechute cérébrale et la survenue d'une radionécrose.
*Résultats.* – Sur les 95 patients étudiés, 39,2 % étaient atteints d'un cancer primitif broncho-pulmonaire non à petites cellules. Le score GPA (Graded Prognostic Assessment) médian était de 3 (48 %). Le taux

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http://dx.doi.org/10.1016/j.canrad.2016.06.010
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de contrôle local à 1 an était de 84 %. Les facteurs associés à un meilleur taux de contrôle local étaient l'absence de prise de contraste sur l'IRM postopératoire ($p < 0{,}00001$), un volume cible prévisionnel de moins de 12 $cm^3$ ($p = 0{,}005$) et un score GPA d'au moins 2 ($p = 0{,}009$). Le taux de contrôle cérébral à 1 an était de 56 %. Une irradiation panencéphalique de rattrapage a été délivrée dans 33 % des cas. Le taux de radionécrose histologique était de 7 %. La taille de la lésion préopératoire et le volume de tissu cérébral sain recevant 21 Gy ($V_{21}$) étaient prédictifs de la survenue de radionécrose (respectivement $p = 0{,}010$ et 0,036).

*Conclusion.* – Une exérèse neurochirurgicale suivie d'une radiothérapie hypofractionnée en conditions stéréotaxiques de la cavité permet un taux de contrôle local satisfaisant chez des patients sélectionnés, diffère le recours à l'irradiation panencéphalique et est associée à un risque de radionécrose relativement faible.

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## 1. Introduction

Historically, single intracranial metastases were treated with surgical resection followed by whole brain radiation therapy. This standard adjuvant therapy decreases the rate of local and distant recurrence in the brain [1,2]. However, no survival benefit has been demonstrated for whole brain radiation therapy in addition to surgery, and it is associated with a decline in quality of life and neurocognitive function [3]. Adjuvant radiotherapy targeting the resection cavity has therefore been developed as an alternative. Several retrospective studies and one prospective study have reported good rates of local control at one year (87%) after stereotactic radiosurgery [4–9]. A few studies have investigated hypofractionated stereotactic radiotherapy for this indication, though the doses and margins studied were variable [10–14]. Our study reports a retrospective analysis of patients who underwent surgical resection of intracranial metastases followed by trifractionated stereotactic radiosurgery. The primary objective of the study was to analyse local control. Secondary endpoints were survival rate, distant failure rate, and the adverse effects of treatment.

## 2. Materials and methods

### 2.1. Patients and tumours

We reviewed our institutional database of patients who had stereotactic irradiation after resection for brain metastasis from March 2008 to January 2014. Patients who had received prior whole brain radiation therapy were excluded. The patients' Graded Prognostic Assessment score (GPA), diagnosis-specific GPA (DS-GPA) and score index for radiosurgery in brain metastases (SIR) were retrieved.

### 2.2. Radiotherapy

Patient immobilization was performed using the Brainlab® frameless head mask fixation system (Brainlab AG, Feldkirchen, Germany). Target volumes were identified using computed tomography (CT) images (slice thickness of 1 mm) fused with 1-mm gadolinium enhanced axial magnetic resonance imaging (MRI) obtained at four postoperative weeks. The gross target volume was the resection cavity, including any area of MRI/CT contrast enhancement. The clinical target volume considered as the same of gross target volume. The skin incision and the bone flap were excluded. The planning target volume was defined by an automatic extension of clinical target volume with a 2 mm isotropic margin. Trajectory planning was performed using the Brainscan® Treatment Planning System (TPS) until 2009, and iPlanRT Dose® thereafter. Treatment volumes were achieved with 3–5 dynamic non-coplanar arcs (max 120°). At least 98% of the planning target volume was covered with the prescription dose. Dose was prescribed to the 70% isodose line. All cavities were treated using frameless Novalis® hypofractionated stereotactic radiosurgery given in three daily fractions of 770 cGy (1100 cGy to isocentre). Treatment with corticosteroids was started on the first day of treatment (prednisolone 1 mg/kg), maintained for one week, and then tapered progressively.

### 2.3. Follow-up

Patients were examined before radiation and at least every three months thereafter. MRI was performed every three months, and more frequently as appropriate, guided by neurological symptoms. Local failure was defined as new or increased contrast enhancement within the surgical cavity and increased cerebral blood volume on perfusion, with or without associated symptoms. Distant failure was defined as new intracranial metastasis outside the treated volume including leptomeningeal disease and relapse on the surgical track. Radiological radionecrosis was defined on MRI, by appearances on T1 contrast-enhanced MRI (no cerebral blood volume increase, stable or relapsing on later follow-up in the absence of additional treatment and with no evidence of local failure), whether or not associated with clinical neurological symptoms. Patients presenting with disabling and persistent neurological symptoms associated with radionecrosis in whom repeat excision was indicated had a diagnosis of radionecrosis made on the finding of gross or histological necrosis in the absence of histological evidence of metastatic tumour recurrence.

### 2.4. Statistical analysis

Continuous variables were summarized by their median and range and qualitative variables by frequency of their modalities. Survival curves were calculated by the Kaplan–Meier method. Times to local relapse, distant relapse, and death were calculated from the last day of radiotherapy to the date of the related event if any (or to the last follow-up date). Each patient's status was determined on the 31 December 2014. Comparison between groups was performed according to the nature of the variables, using the Mann–Whitney or Kruskal–Wallis tests for continuous variables, the Pearson $\chi^2$ test or exact Fisher test for qualitative variables, and a log rank test or univariate Cox model for censored variables. All tests were performed in a bilateral way, with statistical significance defined as $P < 0.05$.

## 3. Results

### 3.1. Patient characteristics

One hundred and one patients (103 cavities) were treated. Six patients had previously received cerebral irradiation (one

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