Cancer/Radiothérapie xxx (2017) xxx–xxx

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Original article

Reirradiation of gliomas under stereotactic conditions: Prognostic factors for survival without relapse or side effects, a retrospective study at Tours regional university hospital (France)

Réirradiation des gliomes de haut grade en conditions stéréotaxiques : facteurs pronostiques de la survie sans rechute et effets secondaires, une étude rétrospective au CHRU de Tours

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ARTICLE INFO

Article history:
Received 19 January 2017
Received in revised form 6 May 2017
Accepted 16 May 2017

Keywords:
Glioblastoma
High-grade glioma
Radiotherapy
Reirradiation
CyberKnife®
Stereotactic radiotherapy

ABSTRACT

Purpose. – To search for factors correlated with relapse-free survival following stereotactic reirradiation in patients with recurrent glioma following radiochemotherapy and evaluate tolerance to this treatment.
Patients and methods. – Initial radiotherapy was given according to the protocol of Stupp and al. Reirradiation was performed using the CyberKnife® system. Patients could have had surgical resection initially and at the time of recurrence. We analysed 13 patients treated between July 2010 and September 2014. The median age was 55 years. The doses delivered ranged from 20 to 36 Gy, in one to ten fractions.
Results. – Median survival after stereotactic radiotherapy was 14 months. Survival without relapse was 3.7 months. Factors significantly influencing duration of relapse-free survival were: age ($P = 0.04$), total dose ($P = 0.02$), dose per fraction ($P = 0.04$) and number of fractions ($P = 0.01$). We found no correlation between gross tumour volume, clinical target volume, grade of tumour or prescription isodose and relapse-free survival following radiochemotherapy. Three patients developed radionecrosis.
Conclusion. – Reirradiation under stereotactic conditions is well tolerated. A dose of more than 30 Gy delivered in 5 or more fractions seems to prolong relapse-free survival.

Mots clés :
Glioblastome
Gliomes de haut grade
Radiothérapie
Réirradiation
Radiothérapie stéréotaxique
CyberKnife®

RÉSUMÉ

Objectif de l'étude. – Chez des patients atteints d'un gliome récidivant après chimioradiothérapie, rechercher les facteurs corrélés avec la survie sans rechute après réirradiation en conditions stéréotaxiques et évaluer la tolérance de ce traitement.
Patients et méthodes. – La radiothérapie initiale suivait le protocole de Stupp et al. La réirradiation a été réalisée par CyberKnife®. Les patients pouvaient avoir eu une exérèse chirurgicale initialement et lors de la récidive.
Résultats. – Nous avons analysé les dossiers de 13 patients pris en charge entre juillet 2010 et septembre 2014. L'âge médian était de 55 ans. Les doses délivrées allaient de 20 à 36 Gy en une à dix séances. La durée médiane de survie après radiothérapie en conditions stéréotaxiques était de 14 mois, celle de survie sans rechutede 3,7 mois. Les facteurs influençant significativement la durée de survie sans rechute étaient : l'âge ($p = 0,04$), la dose totale ($p = 0,02$), la dose par fraction ($p = 0,04$), le nombre de fractions ($p = 0,01$). Nous n'avons pas trouvé de corrélation entre le volume tumoral macroscopique, le volume cible prévisionnel, le grade tumoral, l'isodose de prescription, la couverture du volume cible prévisionnel et la survie sans rechute. Trois patients ont été atteints de radionécrose.

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https://doi.org/10.1016/j.canrad.2017.05.006

Please cite this article in press as: Lévy S, et al. Reirradiation of gliomas under stereotactic conditions: Prognostic factors for survival without relapse or side effects, a retrospective study at Tours regional university hospital (France). Cancer Radiother (2017), https://doi.org/10.1016/j.canrad.2017.05.006

Conclusion. – Une réirradiation en conditions stéréotaxiques est bien tolérée. Une dose supérieure à 30 Gy au minimum en cinq fractions semble allonger la survie sans rechute.

1. Introduction

Gliomas are the most common primary brain tumours in adults. They have an unfavourable prognosis. The median survival for glioblastoma is 14.6 months. It has not improved since the results from the protocol of Stupp et al. were published [1]. These are invasive tumours with low radiosensitivity.

Recurrences are usually local, within a 2 cm radius of the initial lesion [2]. In 80 to 86% of cases, progression occurs within the irradiated volume and takes place within 2 years of the initial diagnosis [3]. Treatment is based on further resection, reirradiation, systemic treatment, or a combination of these different treatments. Management is not standardised. It must be personalised and decided collectively.

A macroscopically complete resection at recurrence can prolong median survival, regardless of the quality of the original resection [4]. It can be combined with the placement of carmustine implants, but the value of doing so is a subject of debate [5,6].

Stereotactic reirradiation may be a good therapeutic option [7–9]. It delivers a large dose per fraction, making it possible to counter the radioresistance of high-grade gliomas. The sharp dose gradient at the periphery of the target volume minimises the dose received by the adjacent healthy tissues. The main limitation of reirradiation is the risk of radionecrosis [10]. The optimum fractionation scheme has not been determined.

Our primary objective was to study the prognostic factors for relapse-free survival following CyberKnife® reirradiation in patients with recurrent high-grade glioma. Our secondary objective was to evaluate tolerance to this treatment.

2. Materials and methods

2.1. Inclusion criteria

All adult patients treated using CyberKnife® at Tours (France) university hospital for reirradiation of a glioma prior to 5 September 2014 were included. In order to have an observation period of at least ten months, we did not include patients treated after that date.

Patients could have had surgical resection initially and at the time of recurrence.

2.2. Stereotactic radiotherapy: CyberKnife® treatment procedure

The CyberKnife® comprises a linear accelerator mounted on a robotic arm with six degrees of freedom. It delivers 6 MV photons.

Patients were immobilised using a noninvasive device: a "3-point" thermoplastic mask made at the time of the planning CT scan (Siemens, Somatom sensation open, slice thickness of 1.5 mm; without injection of contrast medium).

A planning MRI scan of the brain (General Electric, Signa HDxt, 1.5 T, birdcage antenna) was performed on the same day as the CT scan. The sequences were performed systematically: T1, T1 with gadolinium injection and T2, slice thickness of 1 mm. This MRI made it possible to perform image registration. Fusion of the MRI and CT images, contouring and dose planning were performed using dedicated inverse planning software: Multiplan version 3.5 (Accuray®).

The target volumes were contoured on the MRI images following fusion and registration with the CT images. The gross tumour volume was determined by pathological contrast enhancement on sequence T1 with injection. The clinical target volume was equal to the gross tumour volume. The margin needed to obtain the planning target volume varied from 1 to 3 mm. The organs at risk were the brainstem, optic tract, lenses and cochleas. Skull-based tracking was used, i.e. repositioning by reference to the bony structures of the skull.

The constraints we used are shown in Table 1 [11]. They were adjusted for each patient and dose received at organs at risk level during radiochemotherapy, according to the protocol of Stupp et al. [1].

Quality control was performed on the CyberKnife® system daily. It included checking the consistency of dose rate and a test for isocentric targeting accuracy (AQA). More comprehensive checks were done once a month, in compliance with the recommendations of the French medicine agency (ANSM).

Patients received corticosteroid therapy, i.e. prednisolone 1 mg/kg during the week of treatment and then at decreasing doses over a one-month period.

2.3. Clinical and radiological surveillance and definition of judgement criteria

Patients were examined by the radiation therapist in alternation with the oncologist or surgeon. A surveillance MRI was performed every two to three months after treatment. It was performed with diffusion, perfusion and spectroscopic sequences in order to differentiate between progression and radionecrosis. Results and correct course of action were discussed at a multidisciplinary consultative meeting.

A recurrence was defined as progression seen by imaging or clinical progression leading to a change in line of treatment. Progression on MRI corresponded to an increase in volume or contrast enhancement in T1 following injection.

2.4. Parameters collected

Parameters were collected retrospectively with the help of DPP and WINNIX intrahospital software and the paper files maintained for each patient. For patients follow-up outside the hospital, we retrieved mail regarding consultations, hospital admissions and imaging reports.

Missing dates of death were requested from municipal records offices.

2.5. Statistical analyses

Non-parametric tests were used to analyse factors potentially influencing time to relapse: Mann–Whitney *U* test for small sample size for qualitative factors; and Spearman's rank correlation for quantitative factors.

All tests were two-tailed, and differences compared with respective null hypotheses were considered significant only for *P* values < 0.05.

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