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Original article

Patterns of relapse in patients with high grade glioma receiving combined treatments including stereotactic re-irradiation for a first relapse

Types de rechute chez les patients atteints de gliomes de haut grade et recevant une radiothérapie en conditions stéréotaxiques associées ou non à une chimiothérapie/thérapie ciblée

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ABSTRACT

Purpose. – Bevacizumab and stereotactic treatment are efficient combined or alone in relapse glioma. However, patterns of relapse after this kind of salvage treatment have never been studied. The purpose of this unicentric retrospective analysis was to assess and understand the patterns of relapse of high grade glioma treated with stereotactic radiation, with or without bevacizumab.

Patients and methods. – Twenty patients with high grade glioma relapse received a stereotactic radiation; among them two patients received temozolomide and eight patients received bevacizumab; among the latter, four received also irinotecan. We matched the stereotactic radiation treatment planning scan with the images of the first treatment and of the second relapse in order to determine the patterns of failure and associate dosimetric profile.

Results. – For the total population, median follow-up from the first diagnosis and relapse were 46.1 and 17.6 months, respectively. Among the 13 patients who relapsed, ten did not receive chemotherapy and three received it ($P < 0.05$), two received temozolomide and one bevacizumab. Patients who received bevacizumab had no "out-of-field" recurrences. Among the 32 irradiated relapses, 15 were "in-field" recurrences; among them two were treated with bevacizumab and 13 were not ($P < 0.05$). For the 32 lesions, a favourable prognostic factor of control was the association of a high-dose of irradiation and the use of bevacizumab.

Conclusion. – For patients with relapsed high grade glioma, local control was higher with combined bevacizumab and high-dose stereotactic radiation.

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RÉSUMÉ

Objectif de l'étude. – Le bévacizumab et l'irradiation en conditions stéréotaxiques sont deux traitements efficaces, seuls ou associés, pour les gliomes en rechute. Cependant, les sites de rechute après ce type de traitement n'ont jamais été étudiés. L'objectif de cette étude unicentrique rétrospective était d'identifier les sites de rechute des gliomes de haut grade après un traitement de rattrapage par irradiation en conditions stéréotaxiques avec ou sans bévacizumab.

Patients et méthodes. – Vingt patients atteints d'un gliome de haut grade en récidive ont reçu une irradiation en conditions stéréotaxiques ; parmi ces patients, dix ont reçu une chimiothérapie concomitante : deux par témozolomide et huit par bévacizumab, dont pour quatre associé à l'irinotécan. Nous avons recalé l'IRM réalisée avant le traitement initial, celle avant la réirradiation et celle au moment de la rechute. La distribution de dose du traitement initial et de l'irradiation en conditions stéréotaxiques ont été reportées sur les coupes remnographiques, la première sur celles réalisées avant la réirradiation et celles au moment de la rechute et la seconde sur celles réalisées avant le traitement initial et celles au moment de la rechute. Nous avons pu ainsi déterminer les sites de récidive en fonction des différentes dosimétries et y associer les profils de doses reçues.

Résultats. – Le suivi médian après la rechute réirradiée était de 17,6 mois. Treize tumeurs ont rechuté. Dix patients n'avaient pas eu de chimiothérapie, deux avaient reçu du témozolomide et un du bévacizumab ($p < 0{,}05$). Aucun patient ayant reçu de la chimiothérapie n'a été atteint de rechute en dehors du site réirradié. Parmi les 32 lésions irradiées, il y a eu 15 rechutes locales. Deux de ces lésions avaient été traitées par bévacizumab et 13 non. Pour ce qui concerne les 32 lésions, le facteur pronostique favorable de contrôle local était une association d'une haute dose de radiothérapie et de bévacizumab.

Conclusion. – Les patients atteints d'une rechute de gliome de haut grade traitée par irradiation en conditions stéréotaxiques de haute dose et le bévacizumab ont bénéficié d'un meilleur taux de contrôle local.

1. Introduction

Glioblastoma multiform is an aggressive brain tumour. Despite multimodal therapy, failure seems inevitable. Two-year overall survival rate remains at approximately 25% [1]. Recurrence management includes re-excision, re-irradiation, and systemic therapy [2–6]. In selected patients, hypofractionated stereotactic radiation as re-irradiation constitutes a reasonable, acceptable, safe and effective option [7,8]. However, in several series, efficacy seems limited. Several hypothesis of this lack of efficiency have been proposed [7,9–11]. To improve irradiation local control and likely overall survival, bevacizumab has been combined to stereotactic radiation as a putative radiation response modulator [12,13]. Recent series demonstrated safety, and efficacy of the combined treatment [13–15].

In this series, we compared the patterns of relapse after re-irradiation in patients who received either stereotactic radiation alone or combined with bevacizumab.

2. Patients and methods

The study received institutional review board approval. There were 15 male and 5 female patients. Median age at relapse time was 55.7 years (mean: 56.6 years; range: 33.9–82.9 years). The definitive pathology after the first surgery was glioblastoma in 12 cases, grade III oligodendroglioma in seven cases, and gliosarcoma in one case.

2.1. Initial multimodal treatment

2.1.1. Surgery

All patients underwent resection. Surgery was considered as gross total resection in 12 cases, incomplete in seven cases and biopsy alone in one case (Table 1).

2.1.2. Radiotherapy

Irradiation was delivered with a 3D technique. The tumour volume was delineated on matched CT and MRI scans. The gross tumour volume (GTV) was the operative cavity and area of contrast-enhancement on T1-weighted MRI. The clinical target volume (CTV) was defined as the sum of a volume including the GTV plus a margin of 1–2 cm and the oedema visualized on T2 weighted and fluid-attenuated inversion recovery (FLAIR) MRI. The CTV was then corrected to anatomic borders. The planning target volume (PTV) was defined as the CTV plus a 3–5 mm margin (Table 1).

The prescribed dose to the PTV was 60 or 61 Gy, per fraction of 1.8 to 2 Gy, five fractions a week. Median percent of PTV covered by the 95% of the prescribed dose was 97.9% (mean: 95.8%; 80–100) (Table 2).

2.1.3. Chemotherapy

Nineteen patients received concomitant temozolomide (TMZ) at the daily dose of 75 mg/m^2. One patient received carmustine and one patient received cilengitide with temozolomide. Adjuvant temozolomide was prescribed to 19 patients at the daily dose of 150–200 mg/m^2, 5 consecutive days per month for at least 6 months. One patient received carmustine and one patient received cilengitide with temozolomide (Table 1).

2.2. Imaging follow-up

Patients underwent follow-up with history, physical exam and MRI every 3 months after radiation completion until either progression or death. The response was evaluated based on Response Assessment in Neuro-Oncology Working Group (RANO) criteria [16,17]. To describe the pattern of relapse after 3D-radiotherapy, we fused the MRI at the first relapse with the MRI at the time of irradiation. To describe the pattern of second relapse after stereotactic radiation treatment, we fused the MRI at the time of second relapse with the MRI at time of stereotactic radiation treatment and with the MRI at time of 3D-radiotherapy. To be consistent all along the text, "initial glioma" is used to name the tumour treated