Clinical Oncology xxx (2018) 1–8

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

A Retrospective Review of Re-irradiating Patients' Recurrent High-grade Gliomas

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Received 25 November 2016; received in revised form 19 April 2018; accepted 24 April 2018

Abstract

Aims: After radical treatment, most high-grade gliomas (HGG) recur locally. Upon recurrence, no standard treatment exists. Options include re-resection, salvage systemic therapy and re-irradiation. This retrospective study evaluated patients who underwent re-irradiation for recurrent HGGs and assessed prognostic factors and their influence on management.

Materials and methods: Eighty-two patients who underwent re-irradiation for HGG from 2009 to 2014 were retrospectively identified. Re-irradiation consisted of either standard three-dimensional conformal, intensity-modulated radiotherapy or highly conformal stereotactic radiotherapy using mostly volumetric modulated arc therapy. Patient survival from re-irradiation was the primary end point. Survival was estimated via the Kaplan–Meier method with differences assessed using the Log-rank test; hazard ratios were estimated using Cox regression analysis.

Results: The median overall survival from re-irradiation was 9.5 months. Re-irradiation, to a median dose of 35 Gy in 10 fractions, was well tolerated: 4% developed grade 3 toxicity, no patients experienced grade ≥4 or radionecrosis. In the multivariate analysis, factors significantly associated with increased survival included: longer duration from initial radiotherapy, better performance status at re-irradiation of 0–1 versus ≥2, unifocal versus multifocal recurrence and higher total re-irradiation dose (≥35 Gy versus <35 Gy). Re-resection, salvage systemic therapy and age were unrelated to survival.

Conclusion: Patients with recurrent HGG tolerated re-irradiation well with minimal toxicity. Those patients in good prognostic groups, including good performance status can achieve durable control, suggesting managing patients with regular magnetic resonance imaging surveillance post-radical treatment, identifying early radiological progression and instituting salvage therapy when performance status is best.

Key words: Anaplastic glioma; glioblastoma; radiotherapy; re-irradiation; recurrent

Introduction

High-grade gliomas (HGGs), including glioblastoma multiforme and anaplastic astrocytoms, are aggressive brain tumours. They are commonly treated with maximal surgical resection followed by radiotherapy and, in our practice, concurrent and adjuvant temozolomide [1]. Despite radical treatment, most patients recur locally and prove difficult to treat [2,3]. At recurrence, no standard treatment exists; options include further resection, salvage systemic therapy or re-irradiation [4]. Frequently, two or more salvage modalities are offered and a multidisciplinary approach is optimal, as currently there are no guidelines to facilitate decisions in the recurrent setting and clinicians often make decisions based on minimal evidence.

Recurrent HGGs are frequently diagnosed with magnetic resonance image (MRI) scans. However, prior irradiation can often mimic tumour growth and this 'pseudoprogression' must be considered. To guide treatment response, guidelines have been published by the Response Assessment in Neuro-Oncology (RANO) working group [5].

Ideally, patients with recurrent HGGs should be discussed at a neuro-oncology multidisciplinary meeting (MDM), where re-resection is often considered first, despite

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https://doi.org/10.1016/j.clon.2018.05.004
0936-6555/

conflicting evidence to support its efficacy in the recurrent setting in asymptomatic patients [6]. Whether the patient has re-resection or not, further treatment of re-irradiation and or salvage systemic therapy is necessary to obtain sustained local control.

Initial studies of re-irradiation reported use of single-fraction stereotactic radiosurgery in order to limit dose to surrounding normal structures, delivered to small recurrences with median planning target volumes (PTV) of up to 11 cm^3 and a rate of symptomatic radiation brain necrosis of up to 21% [7,8]. With larger recurrences, stereotactic radiosurgery delivered in a single fraction would probably cause unacceptable late toxicity due to volume effect [9]. To minimise late toxicity, larger HGG recurrences have been treated with hypofractionated stereotactic radiotherapy given in up to 10 fractions, with a <1% rate of radiation brain necrosis and a median survival of 11 months [10,11].

In light of the above, we undertook this study with the aim of elucidating clinically relevant prognostic and treatment factors and evaluating survival benefit and toxicity with their relevance to patient management.

Materials and Methods

Ethical approval to undertake this retrospective study was granted by Auckland City Hospital (ACH) Research Committee. The study population comprised consecutive patients ($n = 82$) who underwent re-irradiation for HGG from 2009 to 2014 at ACH public hospital or Auckland Radiation Oncology (ARO), a private oncology centre. Following radical treatment, patients were followed up every 3 months clinically and with MRI. The decision to offer re-irradiation was based mainly on clinical status. Before undergoing re-irradiation, all patients were discussed at a neuro-oncology MDM and recurrences were noted on MRI utilising RANO guidelines when they became available, taking into account clinical status. All patients had MRI including multiparametric cerebral blood volume mapping and spectroscopy, so in only a few patients was it difficult to differentiate progression from pseudo-progression; these patients were re-imaged usually a month later before undertaking salvage therapy. In a number of cases, 18F-fluoro-ethyl-tyrosine (FET) positron emission tomography (PET) scans were used to ascertain whether the tumour progressed or pseudo-progressed, where tumour progression was considered likely where the mean tumour standardised uptake value to background ratio was >1.6 and definite at ratio of >2 [12]. The final assessments were based on a combination of MRI and PET scan results, as well as genomic factors, especially 06-methylguaninie-DNA methyl transferase (MGMT) status, as those patients with a MGMT promoter methylation were offered adjuvant temozolomide post re-irradiation. Patient records were examined to assess potential prognostic factors, toxicity from re-irradiation being new symptoms thought to be attributable to re-irradiation occurring during or following re-irradiation, and the development of radiation brain necrosis as seen on MRI after re-irradiation. The

Table 1
Demographic and clinical characteristics of glioma patients during initial radiotherapy and at re-irradiation ($n = 82$)

Variable	Initial radiotherapy	Re-irradiation
Age (years), *n* (median)	82 (52.9)	82 (55.5)
Gender, *n* (%)		
Female		33 (40.2)
Male		49 (59.8)
Type of radiotherapy, *n* (%)*		
Stereotactic	46 (56.1)	46 (56.1)
Conformal	36 (43.9)	36 (43.9)
Surgery type, *n* (%)		
Resection	70 (85.4)	35 (42.7)
Biopsy	10 (12.2)	1 (1.2)
None	2 (2.4)	46 (56.1)
Carmustine wafer, *n* (%)		
No	–	79 (96.3)
Yes	–	3 (3.7)
Histology, *n* (%)		
GBM	53 (64.6)	23 (28.1)
Anaplastic glioma	16 (19.5)	11 (13.4)
Low-grade glioma	11 (13.4)	2 (2.4)
Unknown	2 (2.4)	46 (56.1)
MGMT promoter, *n* (%)		
Methylated	7 (8.5)	6 (7.3)
Unmethylated	17 (20.7)	2 (2.4)
Unknown	58 (70.7)	74 (90.2)
IDH1, *n* (%)		
Wild-type	25 (30.5)	5 (6.1)
Mutated	1 (1.2)	5 (6.1)
Unknown	56 (68.3)	72 (87.8)
EGFR amplification, *n* (%)		
Negative	17 (20.7)	5 (6.1)
Positive	6 (7.3)	3 (3.7)
Unknown	59 (72.0)	74 (90.2)
Performance status before radiotherapy, *n* (%)		
0	24 (29.3)	14 (17.1)
1	48 (58.5)	37 (45.1)
2	4 (4.9)	21 (25.6)
3	0 (0.0)	7 (8.5)
Unknown	6 (7.3)	3 (3.7)
Percentage Ki-67, *n* (median)	50 (20.0)	19 (15.0)
Total radiation dose (Gy), *n* (median)	82 (60.0)	82 (35.0)
Number of fractions, *n* (median)	82 (30.0)	82 (10.0)
PTV (cm^3), *n* (median)	55 (176.0)	65 (73.0)
Concurrent chemotherapy, *n* (%)		
No	23 (28.1)	67 (81.7)
Yes	59 (72.0)	15 (18.3)
Adjuvant/salvage chemotherapy, *n* (%)		
No	17 (20.7)	28 (34.2)
Yes	65 (79.3)	54 (65.9)

Percentages may not add up to 100 due to rounding.
EGFR, epidermal growth factor receptor; GBM, glioblastoma multiforme; IDH1, isocitrate dehydrogenase 1; MGMT, O6-methylguanine-DNA methyltransferase; PTV, planning target volume.
* See methods for definition of conformal and stereotactic radiotherapy.

Please cite this article in press as: Klobukowski L, et al., A Retrospective Review of Re-irradiating Patients' Recurrent High-grade Gliomas, Clinical Oncology (2018), https://doi.org/10.1016/j.clon.2018.05.004