Radiotherapy and Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Glioblastoma recurrence patterns near neural stem cell regions

Linda Chen [a], Kaisorn L. Chaichana [b], Lawrence Kleinberg [a], Xiaobu Ye [c], Alfredo Quinones-Hinojosa [b,c,*], Kristin Redmond [a,*]

[a] Department of Radiation Oncology and Molecular Radiation Sciences; [b] Department of Neurosurgery and Oncology; and [c] Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, The Johns Hopkins University, Baltimore, United States

ARTICLE INFO

Article history:
Received 28 December 2014
Received in revised form 14 July 2015
Accepted 25 July 2015
Available online xxxx

Keywords:
Glioblastoma
Subventricular zone
Recurrence

ABSTRACT

Purpose: Glioblastoma (GBM) cancer stem cells and their neural stem cell counterparts are hypothesized to contribute to tumor progression. We examined whether GBM contrast enhancement contact with neurogenic regions (NR) affect recurrence patterns, as contrast enhancement reflects regions of blood–brain barrier breakdown.

Methods: 102 patients with primary GBM, treated at Johns Hopkins Hospital between 2006 and 2009, were included. All patients underwent surgical resection followed by adjuvant IMRT (60 Gy/30 fractions) and concomitant temozolomide. Initial and recurrent tumor distance from the subventricular zone (SVZ) or subgranular zone (SGZ) was measured. Tumors were categorized as NR contacting or non-contacting. The chi-square test was used to analyze the association between tumor contact and recurrence pattern.

Results: 49 of 102 (48.0%, 95% CI: 0.386–0.576) tumors contacted NRs at initial presentation, and, of these tumors, 49/49 (100%) contacted NRs at recurrence. Of 53 tumors that were initially non-contacting, 37/53 (69.8%, 95% CI: 0.565–0.804) recurred contacting NRs. In total, 86/102 (84.3%, 95% CI: 0.760–0.901) recurrent GBM contacted NRs compared with 49/102 (48%, 95% CI: 0.386–0.576) at initial presentation. Of the recurrent tumors that did not contact NRs, 16/53 (30.1%, 95% CI: 0.195–0.435) recurred medially toward NRs with a significant decrease in distance between tumor contrast enhancement and NRs. 16/49 (32.6%, 95% CI: 0.212–0.466) initially NR-contacting GBMs recurred out-of field while 7/53 (13.2%, 95% CI: 0.0655–0.248) initially non-contacting recurred out of the radiation treatment field ($p = 0.0315$, Odds ratio: 3.19, 95% CI: 1.18–8.62).

Conclusions: GBM contrast-enhancing recurrence is significantly associated with proximity to NRs. NR-contacting initial tumors were more likely to recur out of radiation treatment fields.

 Radiotherapy and Oncology xxx (2015) xxx–xxx

The prognosis of patients with glioblastoma (GBM) is poor, and most tumors recur despite maximal surgical resection and adjuvant concurrent chemo and radiation therapy [1]. GBMs have the potential to recur with widespread infiltration, and historically whole brain radiation treatment was used to ensure coverage of distant progression [2]. However, the majority of GBMs recur in close proximity to the initial tumor bed and modern radiation treatment fields have shifted to treatment of the gross tumor volume and a 1–2 cm margin that is thought to contain residual microscopic disease at high risk for local progression [3,4]. Despite inclusion of this additional volume at risk for recurrence, the majority of glioblastomas progress locally within radiation treatment fields [5], and attempts at dose escalation or hypofractionation have not improved outcomes or changed the patterns of recurrence [6,7].

One hypothesis is that GBM progression is driven by a subpopulation of cancer stem cells identified in GBMs, which are capable of propagating tumors and have chemotherapeutic and radio-resistant properties *in vitro* [8,9]. The origin of this cell population is unclear, but it is hypothesized that GBM cancer stem cells may represent dedifferentiated cancer cells or that they may stem from dysregulated normal neural stem cells. Normal neural stem cells reside in two areas: the subventricular zone (SVZ), a group of cells that line the lateral wall of the lateral ventricles, and the subgranular zone (SGZ) a group of cells within the subgranular layer of the hippocampus [10]. GBMs that spatially involve the SVZ have been demonstrated to have a higher

* Corresponding authors at: The Johns Hopkins University School of Medicine, Department of Neurosurgery, 301 Mason Lord Dr., Suite 2010, Baltimore, MD 2224, United States (A. Quinones-Hinojosa). The Johns Hopkins University School of Medicine, Department of Radiation Oncology and Molecular Radiation Sciences, 401 N. Broadway, Baltimore, MD 21231, United States (K. Redmond).

E-mail addresses: aquinon2@jhmi.edu (A. Quinones-Hinojosa), kjanson3@jhmi.edu (K. Redmond).

http://dx.doi.org/10.1016/j.radonc.2015.07.032
0167-8140/

propensity to recur at distant locations [11,12]. Moreover, those with subventricular involvement have been demonstrated to have more rapid progression and decreased overall survival [8,12–14].

However, the contribution of these neurogenic regions as potential sources of cancer stem cells as well as their role in GBM recurrence is controversial [15]. Stem cells within the SVZ and SGZ are thought to play functional roles in memory, neurocognition, and neuro-regeneration [9,16,17]. Radiation-induced injury to neural stem cells within the hippocampus is one mechanism that may mediate cranial irradiation neurotoxicity [18–21]. As a result, hippocampal sparing radiation treatment plans have been evaluated in pediatric populations as well as in the setting of whole brain radiation for metastases and has been prospectively correlated with memory preservation [22]. Thus, the evidence supporting neural stem cells as mediators of neurocognition and their potential for glioma initiation creates a complex challenge when examining neural stem cell region irradiation in glioblastoma.

While neurogenic regions are not typically targeted with radiation therapy, several groups have retrospectively correlated higher radiation doses to the SVZ and SGZ with improved patient survival outcome in GBM patients [23–26]. Given this potential relationship between regions containing neural stem cells and GBM recurrence, we aimed to explore this further. Specifically, we evaluated whether GBMs have a propensity to have contrast enhancing recurrence near neurogenic regions and whether spatial relationships between GBMs and neural stem cells affected recurrence with respect to radiation treatment fields.

Materials and methods

Patient selection and recorded variables

Medical charts were reviewed under institutional review board approval. Selection criteria for patients included in this analysis were patients with primary histo-pathologically diagnosed GBM, treated at Johns Hopkins University between 2006 and 2009. Only adult (age > 18 years) patients who underwent non-biopsy surgical resection [either subtotal (STR) or gross-total resection (GTR)] followed by standard of care adjuvant therapy involving IMRT (60 Gy/30 fractions) and concomitant temozolomide were included. All patients had a minimum follow-up of 7 months after completion of radiation therapy treatment.

Based on these criteria 102 patients were included in this analysis. Clinical data collected included patient demographics, treatment course, and disease course. Operative notes were reviewed for surgical resection approaches that penetrated the lateral ventricles. Cases of post-operative meningitis, encephalitis, cerebral infarcts, as well as CD4 count nadirs were also recorded. Residual disease was measured volumetrically by contouring the volume of contrast enhancing residual tumor after resection on T1 weighted MRI post-contrast, excluding the surgical resection cavity [27,28].

Tumor categorization and recurrence characterization

We reviewed the diagnostic imaging at a minimum of 3 time points: (1) pre-operative, (2) post-operative radiotherapy treatment planning, and (3) date of initial tumor recurrence (Fig. 1). Time of tumor recurrence was defined as the date that tumor progression was documented by both the neuro-radiologist and the treating neuro-oncologist. In instances where follow-up imaging was equivocal for recurrence vs. pseudoprogression, the date that the treating neuro-oncologist documented a change in management was defined as the date of recurrence.

Initial and recurrent tumors were categorized as contacting or non-contacting neurogenic regions by measuring the distance of tumor associated contrast enhancement on T1-weight MRI post gadolinium to the SGZ and the SVZ (Fig. 1). The SGZ was identified within the hippocampus, as the hypointense signal medial to the temporal horn on T1-weighted MRI axial sequences [22]. The SVZ was defined as a 5 mm region along the lateral wall of the lateral ventricle [23,29,30]. Contacting tumors were defined as tumors having a distance of 0 cm between the contrast enhancing tumor edge and either of these neurogenic regions.

Recurrent tumor on T1-weighted MR post-contrast was characterized as in-field or out-of field with respect to the planning target volume-1 (PTV1). PTV1 was defined as the gross tumor volume on T1 weighted MRI post gadolinium plus T2 FLAIR sequence MRI tumor volume including the surgical resection cavity with an additional 1–1.5 cm margin. GTV2 was defined as gross tumor volume, including the surgical resection cavity, as seen on T1 weighted MRI post gadolinium alone. PTV2 was defined as this GTV2 volume with an additional 1–1.5 cm margin. Recurrent tumors with >80% of enhancement volumes within the 95% isodose line were defined as in-field recurrence (Fig. 1). Multicentric recurrent tumors with any volume of recurrence outside of the 95% isodose line with respect to PTV1 were defined as out-of-field recurrence. Multicentric tumors were defined as those with multiple lesions without a clear path of tumor spread. All other recurrent tumors with >20% of enhancement volumes outside of the 95% isodose line were defined as out-of-field.

Contouring and dosimetry collection

Contouring and dosimetry data collected for this cohort of patients were previously described [23]. Briefly, ipsilateral, contralateral, and bilateral SVZs were contoured on treatment plans using a co-registered MRI and the radiation treatment planning computed tomography. The SVZ was defined as a 5-mm margin along the lateral wall of the LVs. Dose–volume histograms were calculated, and mean doses were extracted for ipsilateral, contralateral, and bilateral SVZ regions of interest, as well as GTV1, GTV2, PTV1, and PTV2. Contrast enhancement on post-operative T1-weighted axial MRIs was also contoured, with surgical resection cavity excluded, to obtain a volumetric measurement of residual tumor.

Statistical analysis

The collected data were reviewed and statistical analyses were performed using SPSS (version 20; SPSS; Chicago, IL). Proportions and confidence intervals of NR contacting and non-contacting recurrences at initial diagnosis relative to the number of tumors that contacted these regions at the time of recurrence were calculated. Survival analysis was completed using univariate and multivariate Cox Regression with age, performance status, and extent of resection used as covariates. Patient age was stratified as younger than 70 years versus 70 years or older. Karnofsky performance status (KPS) at diagnosis was stratified as less than 90 vs. 90 or greater. Surgical resection was categorized as subtotal resection, in which there was residual contrast enhancement on MRI or gross total resection, in which there was no residual contrast enhancement on MRI after resection. Patients lost to follow-up or those who were alive and had not progressed at the time of analysis were censored from the analysis. Patients lost to follow-up or those who were alive at the time of analysis were censored from the OS analysis. Logistic regression was used to identify if initial NR contact, age, extent of resection and KPS were predictors of NR contact at recurrence. The Student *t*-test was used to assess whether there were significant differences in age, residual tumor volume, and CD4 counts, between contacting and non-contacting groups. Paired *t*-tests were used to compare the minimum distances from initial and recurrent tumor to NR for NR-contacting and non-contacting groups. Chi-squared tests were used to analyze

Please cite this article in press as: Chen L et al. Glioblastoma recurrence patterns near neural stem cell regions. Radiother Oncol (2015), http://dx.doi.org/10.1016/j.radonc.2015.07.032