Radiotherapy and Oncology 118 (2016) 16–23

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Glioblastoma

Adverse prognosis and distinct progression patterns after concurrent chemoradiotherapy for glioblastoma with synchronous subventricular zone and corpus callosum invasion

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ARTICLE INFO

Article history:
Received 4 August 2015
Received in revised form 10 November 2015
Accepted 21 November 2015
Available online 8 December 2015

Keywords:
Glioblastoma
Subventricular zone
Corpus callosum
Anatomical prognostic factor
Progression patterns and sites

ABSTRACT

Background and purpose: The subventricular zone (SVZ) and the corpus callosum (CC) invasion status are separately associated with adverse prognosis for glioblastoma. We investigated the prognosis and progression patterns of glioblastoma with and without synchronous SVZ and CC (sSVZCC) invasion.
Material and methods: Glioblastoma patients completing concurrent chemoradiotherapy with temozolomide were retrospectively categorized by the preoperative sSVZCC invasion status. The associations between sSVZCC invasion and the survival and progression patterns were analyzed.
Results: In total, 108 patients, including 36 with sSVZCC invasion, were followed for a median period of 60.2 (range 34.2–86.3) months. The median overall survival (OS) of patients with and without sSVZCC were 18.6 and 26.4 months, respectively ($p = 0.005$). Using multivariate analyses with the factors of age, performance, surgery extent, and tumor size, sSVZCC invasion remained significant for a poor OS (hazard ratio, 1.96; 95% confidence interval, 1.19–3.21). The rates of progression at tumor bed, preoperative edematous areas, bilateral hemispheres, and ventricles for tumors with and without sSVZCC invasion were 75% and 63.9% ($p = 0.282$), 41.7% and 9.7% ($p < 0.001$), 47.2% and 13.9% ($p < 0.001$), and 38.9% and 13.9% ($p = 0.006$), respectively.
Conclusions: The sSVZCC invasion status determined the distinct prognosis and progression areas of glioblastoma, which suggests individualized radiotherapy and drug administration strategies.
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Glioblastoma is the most prevalent primary brain tumor in adults; its prognosis is multifactorial and the common prognostic factors include age, performance status, and tumor resection extent [1–3]. In addition, the methylation status of O6-methylguanin-DNA methyltransferase (MGMT) promotor substantially identifies patients most likely to benefit from the standard treatment of concurrent chemoradiotherapy (CCRT) with temozolomide [4]. The median overall survival (OS) and 2-year survival rates for patients receiving definitive or adjuvant CCRT are 13.4–16.0 months and 26.5–31%, respectively [5–7]. Most progression patterns after CCRT with temozolomide are central and in-field (72–93%), and the rates of distant and out-field recurrence range from 2% to 28% [8–10].

Some published studies have explored the association between the single anatomical factor and clinical outcome of glioblastoma, including subventricular zone (SVZ) invasion and corpus callosum (CC) involvement [11–13]. The SVZ hosts potential neural progenitor cells, and the CC provides the interhemispheric connections. For adult mammalian brain, neurogenesis occurs in 2 germinal regions: the SVZ on the walls of the lateral ventricles and the subgranular layer of the dentate gyrus in the hippocampus [14–16]. In humans, the lateral ventricles comprise the anterior, occipital, and temporal horns with different astrocytes and ependymal, proliferating cells, and migratory patterns [14]. Patients with glioblastoma involving the SVZ present with a significant decline in progression-free survival (PFS) and OS [12,13,17], and the progression is highly

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http://dx.doi.org/10.1016/j.radonc.2015.11.017
0167-8140/

associated with distant cerebral and multifocal progression [12,18].

Cerebral commissures, including the CC and the anterior commissure, provide interhemispheric connections. The ventral surface of the CC forms the roof of the lateral ventricles [19]. The anterior (the genu) and posterior (the splenium) sections of the CC connect the bilateral frontal and occipital lobes through the radiating fibers, respectively. The anterior commissure is a bundle of axons that cross the midline in the lamina terminalis, traverses the corpora striata, and provides communication between the temporal lobes [19]. Glioblastoma with preoperative contrast-enhanced tumors or edema involving the CC has a poor prognostic factor for OS [3,11]. Butterfly glioblastoma, a tumor involving the bilateral hemispheres through the CC, is associated with adverse prognosis [20,21].

For glioblastoma patients, the anatomical interactions between the SVZ and CC and its associated clinical impacts remain undetermined. In this study, we hypothesize that glioblastoma patients with combined SVZ and CC invasion have adverse prognosis and distinct progression patterns associated with the interhemispheric and lateral ventricular involvement. Neuroimaging, including magnetic resonance imaging (MRI) and computed tomography (CT), provides a clinically noninvasive tool for macroscopic investigation. Through the neuroimaging study, we analyze the prognosis after complete CCRT with temozolomide for glioblastoma with and without synchronous SVZ and CC (sSVZCC) invasion and compare the survival analysis by using published anatomical prognostic factors of SVZ invasion and CC involvement [11–13]. Moreover, we compare the progression patterns and sites of glioblastoma with and without sSVZCC invasion to investigate the interactions between glioblastoma and the structures of the SVZ and CC.

Materials and methods

Eligibility

Patients with pathologically confirmed glioblastoma from a single institute between August 2004 and January 2014 were evaluated retrospectively under the approval of the Institutional Review Board. Patients receiving brain tumor resection or biopsy followed by complete CCRT with temozolomide were enrolled to investigate the survival and progression pattern after CCRT. Patients were excluded if they were younger than 18 years, had concomitant malignancies in addition to glioblastoma, received RT through 2-dimensional (2D) techniques and RT dosage < 54 Gy, or did not receive neuroimaging follow-up after CCRT.

Treatment modalities

The extent of tumor excision was classified as gross total and subtotal resection according to the findings of postoperative neuroimaging or neurosurgeons' records. Biopsy was adopted for unresectable lesions.

Radiotherapy (RT) techniques, including 3-dimensional conformal RT (3DCRT), intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), and tomotherapy, were employed using 6-MV linear accelerators. Gross tumor volume (GTV)1 was defined as gadolinium-enhanced lesions on T1-weighted images and hyperintense lesions on fluid-attenuated inversion recovery (FLAIR) or T2-weighted images. GTV2 was defined as gadolinium-enhanced lesions on T1-weighted images. Clinical target volume (CTV)1 and CTV2 were defined, respectively, as the GTV1 and GTV2 plus a 1.5–2-cm margin for potential microscopic disease with a margin reduced to 0.5 cm around natural boundaries or the optic nerve/chiasm. Planning target volume (PTV)1 and PTV2 were CTV1 and CTV2 plus 0.3–0.5-cm margin, respectively. An RT dosage—administered at a daily dose of 2 Gy, once per day and 5 days per week—of 46 Gy was prescribed for PTV1 and an additional 14 Gy for PTV2. The RT dosage was adjusted according to normal tissue tolerance or other clinical considerations. The SVZ that was free from invasion was not irradiated in this study.

Concurrent chemotherapy with temozolomide was administered at a daily dose of 75 mg/m^2, 7 days per week, from the first to the last day of RT. After a 4-week break, patients received up to 6 cycles of adjuvant temozolomide for 5 days over a 28-day period. The dose was 150 mg/m^2 for the first adjuvant cycle and was increased to 200 mg/m^2 at the beginning of the second cycle [7]. The regimen was adjusted according to patients' individual conditions.

Anatomical features of preoperative imaging

Neuroimaging, including MRI and CT, was interpreted by neuroradiologists. Preoperative imaging findings, including tumor locations, number, and anatomical extension to ventricles and cerebral commissures, were evaluated. SVZ invasion and cerebral commissures involvement were defined according to published studies, respectively [11,12]. SVZ invasion was defined by contrast-enhanced lesions involving the lateral wall of the lateral ventricle, comprising frontal, occipital, and temporal horns [12], and cerebral commissures involvement was defined by any of the following lesions involving the CC or anterior commissure: contrast-enhanced lesions on T1-weighted images, edematous lesions presenting with bright signals on T2-weighted or FLAIR images, and hypodense lesions on CT images [11]. The sSVZCC invasion was defined by the presence of contrast-enhanced lesions synchronously involving lateral walls of the lateral ventricles and cerebral commissures (the CC or anterior commissure) (Fig. 1A).

Tumor progression patterns and sites after CCRT

Neuroimaging after CCRT was performed primarily through MRI, and through CT in some cases, at intervals of 3–6 months. The tumor progression was assessed only by the imaging definition of response assessment in neuro-oncology (RANO) criteria, including either of the following: $\geqslant$ 25% enlargement of contrast-enhanced lesions compared with the smallest tumor measured either at the baseline (if no decrease) or best response, or the appearance of any new contrast-enhanced lesions [22,23]. We adopted the imaging definition rather than combining the clinical definition of RANO criteria, such as corticosteroid use or neurologic deterioration, in order to identify specific tumor progression patterns for developing further treatment strategy.

The patterns of tumor progression were categorized as local (tumors involving the original tumor bed) (Fig. 1, B1), regional (tumors involving the preoperative edematous areas and located beyond the original tumor bed) (Fig. 1, B2), and distant (tumors located beyond the original tumor bed and preoperative edematous areas) (Fig. 1, B3). Tumor progression sites involving the CC, bilateral hemispheres, and ventricles were specifically identified by the involvement of the anatomical structures. Ventricular progression was defined as any continuous or discrete tumors contacting the ventricles outside the tumor bed. CC progression was defined as any continuous or discrete tumors involving the CC. Tumors, either continuous or discrete, at bilateral hemispheres were defined as bilateral hemispheric progression. Multifocal progression was defined as the progression tumor number greater than 1.