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Impact of timing of radiotherapy in patients with newly diagnosed glioblastoma

David M. Randolph II[a,*], Emory R. McTyre[a], Anna K. Paulsson[b], Jordan A. Holmes[c], William H. Hinson[a], Glenn J. Lesser[d], Roy Strowd[e], Hui-Wen Lo[f], Adrian W. Laxton[e,g], Stephen B. Tatter[e], Waldemar Debinski[f], Michael D. Chan[a]

[a] Department of Radiation Oncology, Wake Forest School of Medicine, Winston-Salem, NC, United States
[b] Department of Radiation Oncology, UCSF School of Medicine, San Francisco, CA, United States
[c] Department of Radiation Oncology, UNC School of Medicine, Chapel Hill, NC, United States
[d] Department of Internal Medicine, Section on Hematology & Oncology, Wake Forest School of Medicine, Winston-Salem, NC, United States
[e] Department of Neurology, Wake Forest School of Medicine, Winston-Salem, NC, United States
[f] Department of Cancer Biology, Wake Forest School of Medicine, Winston-Salem, NC, United States
[g] Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, NC, United States

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ABSTRACT

Objective: To further evaluate if a delay in the start of radiation therapy (RT) affects patient outcomes for glioblastoma (GBM).
Patients and methods: From May 1999 to May 2010, a total of 161 patients underwent surgery followed by RT for GBM. We assessed overall survival (OS) and progression free survival (PFS), stratified by extent of surgical resection. Included in the analysis were genomic predictors of progression.
Results: Median time from surgery to start of RT was 20 days for biopsy alone, 28 days for subtotal resection (STR) and 28 days for gross total resection (GTR). For all patients, a delay >28 days did not result in a difference in PFS when compared to no delay (6.7 vs. 6.9 months, p = 0.07). PFS was improved in biopsy or STR patients with a >28 day delay to start of RT (4.2 vs. 6.7 months, p = 0.006). OS was also improved in patients receiving biopsy or STR with a >28 day delay to start of RT (12.3 vs. 7.8 months, p = 0.005). Multivariable analysis (MVA) demonstrated an improvement in OS and PFS with time to RT >28 days for biopsy or STR patients (HR 0.52 p = 0.008 and HR 0.48 p = 0.02, respectively).
Conclusion: In this retrospective review of GBM patients treated at a single institution, OS and PFS were not different between time to RT >28 days compared to <28 days. There was a modest improvement in both PFS and OS in patients who received biopsy or STR with time to RT >28 days.

1. Introduction

Glioblastoma (GBM) is an aggressive and rapidly progressive brain tumor. Several prior series have demonstrated a survival advantage associated with greater extent of surgical resection [1,2]. Due to the benefit of the reduction of tumor burden and the concern for rapid recurrence of these aggressive tumors, a bias amongst practitioners has existed for minimizing the time delay between surgery and the commencement of radiotherapy (RT). It has been assumed that starting RT prior to tumor repopulation may lead to an advantage for patients with greater extent of resection.

The actual evidence for minimizing the delay to RT is conflicting. Some series have been published suggesting that delaying RT can worsen survival [3,4], while others actually suggest that a short delay may be beneficial [5]. The latter may be helpful in cases where patients need time for recovery of performance status prior to starting aggressive therapy. Furthermore, many of these studies were performed prior to the era of concurrent temozolomide, which calls into question their applicability to modern treatment paradigms. As the evidence is unclear, the ideal time for starting RT after biopsy or surgery for GBM remains undefined.

The goal of the current study was to evaluate the significance of the timing of RT for patients with newly diagnosed GBM. In a single-institution retrospective series, we assessed the effect of

* Corresponding author at: Medical Center Blvd, Winston-Salem, NC 27157, United States.
E-mail address: dmrandolph@gmail.com (D.M. Randolph II).

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time delay to RT on overall survival (OS) and progression free survival (PFS). We also explored the role of genomic subgroups and O^6-methylguanine DNA methyltransferase (MGMT) methylation status on outcomes.

2. Methods

2.1. Patient population

This study was approved by the Wake Forest School of Medicine Institutional Review Board. Our departmental database was queried for patients with a diagnosis of GBM who were treated with RT at our institution. Patients were excluded if radiation therapy was not performed at our facility. Between August 2000 and May 2010, 161 patients with GBM were treated with RT using modern treatment planning techniques.

2.2. Radiotherapy

Patients were treated using a standard cone down field technique [6]. Treatment volume delineation was generally performed using the immediate post-operative magnetic resonance imaging (MRI) study. The clinical target volume (CTV) margins in this series varied from 0.5 to 2.0 cm, based on physician discretion and margin definitions for those enrolled on clinical trials. Planning target volume (PTV) margins were 5 mm. Intensity modulated radiation therapy (IMRT) was generally used in cases where treatment volumes were in close proximity to the optic apparatus or brainstem. RT dose was 46 Gy prescribed to the pre-boost CTV, which included peritumoral edema demonstrated by the T2 or FLAIR signal abnormality. The boost volume received 60 Gy and included residual enhancing tumor and resection cavity with a CTV margin. Temozolomide was started concurrently with the start of RT in patient receiving temozolomide.

2.3. Patient follow-up and response assessment

Patients were followed clinically and with serial MRIs. Imaging was generally performed within 24 h of surgery, at 1 month after completion of RT, and then every 2 months for the first six months after completion of RT. Subsequent imaging was performed every 3 months, unless patients developed new or progressive neurologic symptoms warranting an earlier scan. Electronic medical records and imaging review were used to retrospectively determine date of initial progression using the response assessment in neuro-oncology (RANO) criteria recently defined by Wen et al [7].

2.4. Genomic analysis

Gene expression and methylation data were available from 41 subjects. Techniques for data processing and evaluation were previously described by Holmes et al [8].

2.5. Statistics

Median follow-up and time-to-event outcomes were defined as the time from biopsy or surgery to the time of most recent follow-up or to the event of interest. The Kaplan–Meier method was used to estimate PFS and OS. The log-rank test was used to compare differences in PFS and OS as stratified by time to RT (>28 days vs. ≤28 days) and other variables of interest. Univariate Cox proportional hazards models were constructed for both PFS and OS for all putative predictor variables. Statistically significant predictor variables ($p < 0.05$) on univariate analysis were then included in multivariate Cox proportional hazards models which were constructed for both PFS and OS. Statistical analysis was performed using R version 3.2.1 software (R Foundation for Statistical Computing, Vienna, Austria).

Table 1
Patient characteristics.

Total Number of patients		161
Age (median [range])		60.80 [14.60, 84.10]
Gender (%)	Female	59 (36.6)
	Male	102 (63.4)
Ethnicity (%)	White	146 (90.7)
	African-American	11 (6.8)
	Asian	4 (2.5)
Surgery (%)	Biopsy	36 (22.4)
	STR	45 (28.0)
	GTR	80 (49.7)
KPS	≤ 70	51 (31.7)
	>70	110 (68.3)
Time to RT (%)	≤ 28d	92 (57.1)
	>28d	69 (42.9)
Field reduction (%)	No	9 (5.6)
	Yes	152 (94.4)
Radiation Technique (%)	3D	123 (76.4)
	IMRT	38 (23.6)
Clinical trial participant (%)	No	110 (68.8)
	Yes	50 (31.2)
Concurrent chemotherapy (%)	No	46 (28.6)
	Yes	115 (71.4)
Completed concurrent chemotherapy (%)	No	23 (20.2)
	Yes	91 (79.8)
Chemotherapy agent (%)	Temodar	107 (93.0)
	Other	8 (7.0)
	Yes	8 (5.0)
TCGA group (%)	Classical	6 (14.6)
	Mesenchymal	21 (51.2)
	Neural	7 (17.1)
	Proneural	7 (17.1)
Phillips group (%)	Mesenchymal	21 (51.2)
	Proliferative	12 (29.3)
	Proneural	8 (19.5)
MGMT-methylation (%)	No	19 (46.3)
	Yes	22 (53.7)
G-CIMP (%)	No	36 (87.8)
	Yes	5 (12.2)

3. Results

3.1. Patient characteristics

Patient characteristics for this population study are summarized in Table 1. The median time from surgery to RT for patients receiving a GTR was 28 days, a STR was 28 days, and a biopsy alone was 20 days. The median time from surgery to RT for all patients was 27 days.

3.2. Progression free survival

Median PFS for all patients was 6.8 months. Our analysis demonstrated an improvement in PFS when a GTR was performed compared to biopsy or STR (7.8 months vs. 5.3 and 5.5, respectively, $p = 0.005$). For all patients, a delay >28 days resulted in no difference in PFS when compared to no delay (6.7 vs 6.9 months, $p = 0.07$) (Fig. 1). However, when evaluating the subgroup of patients receiving only a biopsy or STR, a benefit in PFS was seen in the patients