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Clinical Investigation

Hypofractionated Versus Standard Radiation Therapy With or Without Temozolomide for Older Glioblastoma Patients

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Summary

In this retrospective study of 135 patients ≥65 years of age receiving radiation therapy for glioblastoma, we demonstrate that significant selection bias exists in the administration of hypofractionated radiation therapy (HRT). Patients receiving HRT were older and had worse performance status, even after excluding patients

Purpose: Older patients with newly diagnosed glioblastoma have poor outcomes, and optimal treatment is controversial. Hypofractionated radiation therapy (HRT) is frequently used but has not been compared to patients receiving standard fractionated radiation therapy (SRT) and temozolomide (TMZ).

Methods and Materials: We conducted a retrospective analysis of patients ≥65 years of age who received radiation for the treatment of newly diagnosed glioblastoma from 1994 to 2013. The distribution of clinical covariates across various radiation regimens was analyzed for possible selection bias. Survival was calculated using the Kaplan-Meier method. Comparison of hypofractionated radiation (typically, 40 Gy/15 fractions) versus standard fractionation (typically, 60 Gy/30 fractions) in the setting of temozolomide was conducted using Cox regression and propensity score analysis.

Results: Patients received SRT + TMZ (n = 57), SRT (n = 35), HRT + TMZ (n = 34), or HRT (n = 9). Patients receiving HRT were significantly older (median: 79 vs

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who were enrolled in clinical trials. Controlling for this, there were no significant overall survival differences between patients receiving HRT with temozolomide and those receiving standard courses of radiation therapy with temozolomide.

69 years of age; $P<.001$) and had worse baseline performance status ($P<.001$) than those receiving SRT. On multivariate analysis, older age (adjusted hazard ratio [AHR]: 1.06; 95% confidence interval [CI]: 1.01-1.10, $P=.01$), lower Karnofsky performance status (AHR: 1.02; 95% CI: 1.01-1.03; $P=.01$), multifocal disease (AHR: 2.11; 95% CI: 1.23-3.61, $P=.007$), and radiation alone (vs SRT + TMZ; SRT: AHR: 1.72; 95% CI: 1.06-2.79; $P=.03$; HRT: AHR: 3.92; 95% CI: 1.44-10.60, $P=.007$) were associated with decreased overall survival. After propensity score adjustment, patients receiving HRT with TMZ had similar overall survival compared with those receiving SRT with TMZ (AHR: 1.10, 95% CI: 0.50-2.4, $P=.82$).

Conclusions: With no randomized data demonstrating equivalence between HRT and SRT in the setting of TMZ for glioblastoma, significant selection bias exists in the implementation of HRT. Controlling for this bias, we observed similar overall survival for HRT and SRT with concurrent TMZ among elderly patients, suggesting the need for a randomized trial to compare these regimens directly.

Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor (1) and is associated with a poor prognosis, with older age being an especially poor prognostic factor (2). Half of all patients with GBM are 65 years of age or older at diagnosis, and the incidence of GBM in this age group is rapidly increasing over time (3, 4). Comorbidities, more aggressive tumor biology, and treatment de-intensification may all be causes of poor outcomes in elderly populations.

The optimal treatment regimen for older patients with newly diagnosed GBM is not clear. Randomized trials have shown the benefit of radiation therapy over observation in a molecularly unselected population (5) and over chemotherapy in O^6-methylguanine DNA methyltransferase (MGMT) promoter-unmethylated patients (6, 7). Hypofractionated radiation therapy (HRT) has also been shown to result in similar (8) or perhaps improved (7) outcomes for older patients receiving radiation alone. It is unclear whether hypofractionated regimens have similar outcomes to standard fractionation in the setting of concurrent temozolomide, however. Although the results of the NCIC CTG CE.6, European Organization for Research and Treatment of Cancer (EORTC) 26062-22061, and Trans Tasman Radiation Oncology Group (TROG) 08.02 studies will help answer whether concurrent temozolomide (TMZ) therapy in the setting of HRT adds value, the role of hypofractionated regimens in comparison with standard fractionation chemoradiation remains unclear.

We conducted a retrospective review of patients >65 years of age who received radiation for newly diagnosed GBM at the Dana-Farber/Brigham and Women's Cancer Center in order to illustrate how published data on hypofractionation has been applied in 1 clinical setting and to determine whether there is a suggestion of therapeutic superiority of 1 regimen or another in the setting of concurrent chemotherapy.

Methods and Materials

This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board. We identified patients 65 years of age or older with a histological diagnosis of glioblastoma who were treated with radiation from 1994 to 2013 at the Dana-Farber/Brigham and Women's Cancer Center. Patients receiving less than 40 Gy were excluded. The standard follow-up schedule was to obtain brain magnetic resonance imaging (MRI) scans 1 month after completing radiation therapy and approximately every 2 months thereafter.

HRT was delivered in 15 daily fractions of 2.67 Gy over 3 weeks for a total of 40.05 Gy as stated in the study by Roa et al (8). "Standard" fractionation was either 59.4 Gy in 33 fractions of 1.8 Gy per fraction or 60 Gy in 30 fractions of 2 Gy per fraction. Concurrent TMZ dosage was 75 mg/m^2 given daily, 7 days per week, during radiation, whereas adjuvant TMZ was initiated at 150 mg/m^2 on days 1 to 5 of 28-day cycles 1 month after radiation and escalated to 200 mg/m^2, if toxicity was acceptable, for 5 to 11 additional cycles thereafter.

Statistical analysis

Baseline patient characteristics between treatment groups were compared using Fisher exact test for categorical variables and the Kruskal-Wallis test for continuous variables. Overall survival (OS) and progression-free survival were calculated by the Kaplan-Meier method. Progression was defined retrospectively by clinical note assessments that included integration of imaging and clinical status. This strategy was chosen because therapeutic choices were determined based on the clinician's real-time assessment of imaging and clinical factors. Associations of clinical variables with overall and progression-free survival were evaluated using the Cox proportional hazards modeling. Analyses were performed using R Studio (version 0.98.1028) software running R (version 3.1.0) with the

survival plug-in. Propensity scores derived from a logistic regression model for receipt of HRT + TMZ versus SRT + TMZ were generated using the following covariates: age, extent of resection, Karnofsky performance status (KPS), MGMT promoter methylation status, sex, year of treatment, and EGFR amplification status. Propensity scores were then used as continuous covariates in a Cox proportional hazards model to assess the impact of HRT on OS. Propensity scores were generated using SAS version 9.3 software (SAS Institute, Cary, NC).

Results

Patient characteristics

Median follow-up for the entire cohort was 10 months, and 13 months for survivors (range: 2.5-45 months). Of the 135 patients identified, 9 received HRT, 34 received HRT + TMZ, 35 received SRT, and 57 received SRT + TMZ. Distribution of baseline clinical variables across the various treatment cohorts is shown in Table 1. Patients receiving HRT with or without TMZ had median age 1 decade older than those receiving SRT with or without TMZ (79 vs 69 years old, $P<.001$) and had significantly lower baseline KPS. Patients receiving SRT were mostly treated before 2007, but otherwise there were few differences in year of diagnosis among the other 3 groups. Most patients had unknown MGMT promoter methylation status, making further analyses using this variable limited.

Clinical factors associated with OS

Of the 135 patients in the overall cohort, there were 120 deaths. Overall median survival was 10.2 months (Table 2). Older age (hazard ratio [HR]: 1.04, 95% confidence interval [CI]: 1.01-1.07), lower KPS (HR: 1.02, 95% CI: 1.01-1.03), and multifocal disease (HR: 1.69, 95% CI: 1.04-2.77) were associated with shorter OS on univariate analysis (Table 3). Of the treatment cohorts, HRT alone was associated with shorter OS than SRT + TMZ (HR: 5.33, 95% CI: 2.55-11.1), but neither SRT alone nor HRT + TMZ was statistically significantly different than SRT + TMZ, although both trended toward shorter survival times (HR: 1.47 and 1.44, respectively). In a multivariate model including treatment variables and variables significant on univariate analysis, older age (HR: 1.06, 95% CI: 1.01-1.10), lower KPS (HR: 1.02, 95% CI: 1.01-1.03), and multifocal disease (HR: 2.11, 95% CI: 1.2-3.6) remained significantly associated with shorter OS, as did HRT without TMZ (HR: 3.9, 95% CI: 1.4-10.6) and SRT without TMZ (HR: 1.72, 95% CI: 1.06-2.8) compared with SRT + TMZ.

Comparison of fractionation regimens in the setting of TMZ

Although multivariate analysis showed a HR of 0.83 (95% CI: 0.45-1.56, $P=.57$) for HRT + TMZ versus SRT + TMZ in the entire cohort for OS, we sought a more direct comparison, given the importance of the result to clinical decision making. For this analysis, we reduced the overall cohort to the 2 treatment groups in an attempt to reduce potential confounding from prognostic factors associated with the poor survival of the group receiving HRT alone. Furthermore, we used propensity scores to allow for inclusion of multiple prognostic factors while not over-parameterizing the final model. Prior to adjustment, considering only patients that had received TMZ, HRT + TMZ produced a trend toward poorer OS compared with SRT + TMZ (HR: 1.45, 95% CI: 0.91-2.30, $P=.12$). After we adjusted for confounding variables using propensity scores in a multivariate Cox regression model, receipt of HRT + TMZ was associated with no significant differences in survival compared with SRT + TMZ (HR: 1.10, 95% CI: 0.50-2.42, $P=.82$).

Discussion

Age has long been considered one of the most important prognostic factors for patients with malignant glioma (2). Given the shorter OS times relative to that of younger patients, there have been efforts to de-intensify treatment in order to improve quality of life. Although the administration of radiation therapy has been shown to confer a survival benefit (5), the optimal radiation dose schedule is not well characterized, particularly in the setting of concurrent and adjuvant TMZ. In the absence of TMZ, the study by Roa et al (8) showed that 40 Gy in 15 daily fractions was similar to 60 Gy in 30 fractions for patients ≥60 years of age with KPS of ≥50. One caveat to these data is that it was a small, underpowered study that only ruled out a 13.7% absolute survival difference at 6 months. Nonetheless, the survival curves were almost entirely overlapping with a HR of 1.0 (95% CI: 0.65-1.53). The Nordic trial randomized patients ≥60 years of age with World Health Organization performance status (PS) of 0 to 2 to either TMZ alone, 34 Gy in 10 fractions over 2 weeks, or 60 Gy in 30 fractions over 6 weeks (7). In the overall cohort, there were no differences between the 2-week and 6-week course of radiation, but there was improved survival for the 2-week course in patients older than 70 years of age (7). It is unknown whether these data still apply in the setting of concurrent TMZ. One argument against this idea is that a 3-week course of daily TMZ is half the amount of TMZ given in standard course regimens. If daily TMZ has an independent effect from purely radiosensitization (perhaps overwhelming the MGMT enzyme in unmethylated patients), then patients may be getting less chemotherapy than is optimal. Furthermore, if there is a benefit from radiosensitization, it may require longer concurrent treatment.

Multiple noncomparative studies have reported on clinical outcomes following HRT + TMZ in the elderly, with median survival ranging between 6.9 and 12.4 months (9-15), but there are no randomized data to guide decision making. A single-arm phase 2 study demonstrated that the approach was safe

Table 1 Baseline patient and treatment characteristics

Characteristic	HRT (n=9)		HRT + TMZ (n=34)		SRT (n=35)		SRT + TMZ (n=57)			Overall (N=135)	
	No. of patients	% of total	No. of patients	% of total	No. of patients	% of total	No. of patients	% of total	*P*	No. of patients	% of total
Age (y)									<.001		
Median	79		78		70		68			71	
65-74	2	22.2	11	32.4	28	80.0	54	94.7		95	70.4
75-84	4	44.4	17	50.0	7	20.0	2	3.5		30	22.2
85+	3	33.3	6	17.6	0	0.0	1	1.8		10	7.4
Sex									.41		
Male	4	44.4	22	64.7	19	54.3	27	47.4		72	53.3
Female	5	55.6	12	35.3	16	45.7	30	52.6		63	46.7
KPS									<.001		
Median	50		70		80		80			80	
<50	3	33.3	2	5.9	0	0.0	0	0.0		5	3.7
50-60	4	44.4	14	41.2	5	14.3	8	14.0		31	23.0
70-80	0	0.0	16	47.1	18	51.4	33	57.9		67	49.6
90-100	1	11.1	2	5.9	10	28.6	16	28.1		29	21.5
Unknown	1	11.1	0	0.0	2	5.7	0	0.0		3	2.2
RPA class									<.001		
IV	0	0.0	7	20.6	11	31.4	29	50.9		47	34.8
V	2	22.2	20	58.8	13	37.1	27	47.4		62	45.9
VI	6	66.7	7	20.6	5	14.3	1	1.8		19	14.1
Unknown	1	11.1	0	0.0	6	17.1	0	0.0		7	5.2
Diagnosis year									<.001		
1994-2000	0	0.0	0	0.0	18	51.4	0	0.0		18	13.3
2001-2007	2	22.2	14	41.2	16	45.7	9	15.8		41	30.4
2008-2013	7	77.8	20	58.8	1	2.9	48	84.2		76	56.3
Multifocal									.27		
No	5	55.6	27	79.4	31	88.6	40	70.2		103	76.3
Yes	4	44.4	7	20.6	4	11.4	17	29.8		32	23.7
Tumor size (cm)*									.33		
Median	5.1		4.4		4.0		4.3			4.3	
≤3 cm	0	0.0	5	14.7	9	25.7	8	14.0		22	16.3
>3 cm	9	100	26	76.5	16	45.7	40	70.2		91	67.4
Unknown	0	0.0	3	8.8	10	28.6	9	15.8		22	16.3
EGFR status									.08		
Not amplified	4	44.4	20	58.8	1	2.9	34	59.6		59	43.7
Amplified	4	44.4	8	23.5	4	11.4	13	22.8		29	21.5
Unknown	1	11.1	6	17.6	30	85.7	10	17.5		47	34.8
MGMT status									.55		
Unmethylated	4	44.4	6	17.6	1	2.9	19	33.3		30	22.2
Partially methylated	1	11.1	1	2.9	0	0.0	7	12.3		9	6.7
Methylated	2	22.2	10	29.4	0	0.0	13	22.8		25	18.5
Unknown	2	22.2	17	50.0	34	97.1	18	31.6		71	52.6
Extent of resection									.80		
Biopsy/STR	6	66.7	26	76.5	24	68.6	43	75.4		99	73.3
GTR	3	33.3	8	23.5	11	31.4	14	24.6		36	26.7
RT dose (cGy)									-		
Median	4005		4005		5940		6000				-
Range	4000-4405		4005-4005		5938-6000		5940-6000				-
No. of adjuvant TMZ cycles									-		
Median	-		2		-		3				-
Range	-		1-13		-		1-13				-

Abbreviations: EGFR = epidermal growth factor receptor; GTR = gross total resection; HRT = hypofractionated radiation therapy; KPS = Karnofsky performance status; MGMT = O^6-methylguanine DNA methyltransferase; RPA = recursive partitioning analysis (2); RT = radiation therapy; SRT = standard course radiation therapy; STR = subtotal resection; TMZ = temozolomide.

* Maximal dimension of contrast-enhancing tumor on magnetic resonance imaging.

Table 2 Survival according to treatment group

Survival	HRT (n=9)	HRT + TMZ (n=34)	SRT (n=35)	SRT + TMZ (n=57)
Progression-free survival (mo)				
Median	2.2	4.5	6.0	6.1
Range	1.2-4.8	1.0-73.0	0.4-30.8	1.5-30.4
Overall survival (mo)				
Median	4.1	9.6	9.5	11.1
Range	1.8-12.8	2.7-75.8	2.5-41.7	3.4-45.3

Abbreviations: HRT = hypofractionated radiation therapy; SRT = standard course radiation therapy; TMZ = temozolomide.

and tolerable (15), although the lack of a control arm limits any further conclusions. In a retrospective observational study of patients between 65 and 75 years of age, Gzell et al (16) showed that patients receiving 60 Gy with TMZ had longer OS than those receiving 40 Gy with TMZ, although the numbers were quite small (less than 10 patients in both groups), and controls for potential confounding prognostic factors due to selection bias were not incorporated. Our institutional data showed that 40 Gy in 15 fractions was generally administered to older patients and/or those with lower performance status. Patients receiving HRT alone had the lowest median baseline KPS (score of 50) of the treatment cohorts and did particularly poorly, with a median survival of only approximately 4 months. Although the study by Roa et al (8) allowed patients with baseline KPS as low as 50 in the trial, low performance status was not an inclusion criterion, and the median KPS in that trial was 70 (range: 60-80). Furthermore, although the Nordic trial showed an interaction between treatment arm and age, there was no such relationship between treatment arm and performance score (7). The imbalances demonstrated in our data are evidence for significant bias in selecting patients for hypofractionated regimens, likely due to lack of direct data showing similar outcomes for these regimens in the setting of TMZ or enrollment in clinical trials that use standard fractionation. It is worth noting that when patients enrolled in clinical trials were excluded, the imbalances of age and performance status remained statistically significant (data not shown). These selection biases show that more definitive data for hypofractionated regimens in the setting of concurrent and adjuvant TMZ may have a significant impact on practice patterns among centers with similar selection practices as our institution. These biases make retrospective head-to-head comparison of treatment regimens more difficult, however.

Table 3 Univariate and multivariable analyses of factors associated with overall survival

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	AHR	95% CI	*P*
Age (y)	1.04	1.01-1.07	.008	1.06	1.01-1.10	.01
Sex						
Female	1	-	-			
Male	0.85	0.59-1.22	.379			
KPS	0.98	0.97-0.99	.003	0.98	0.97-0.995	.01
RPA class						
IV	1	-	-			
V	1.30	0.89-2.04	.163			
VI	3.60	2.00-6.42	<.001			
Later diagnosis year	0.97	0.94-1.01	.204			
Multifocal						
No	1	-	-	1	-	-
Yes	1.69	1.04-2.77	.036	2.11	1.23-3.61	.007
Tumor size (cm)	1.02	0.89-1.16	.810			
EGFR amplified						
No	1	-	-			
Yes	1.01	0.62-1.63	.990			
MGMT status						
Methylated	1	-	-			
Unmethylated	2.14	1.24-3.72	.007			
Extent of resection						
GTR	1	-	-	1	-	-
Biopsy/STR	1.32	0.88-1.99	.177	1.44	0.90-2.29	.13
Treatment group						
SRT + TMZ	1	-	-	1	-	-
HRT + TMZ	1.44	0.91-2.28	.122	0.83	0.45-1.55	.57
SRT	1.47	0.94-2.30	.095	1.72	1.06-2.79	.03
HRT	5.33	2.55-11.10	<.001	3.92	1.44-10.60	.007

Abbreviations: AHR = adjusted hazard ratio; EGFR = epidermal growth factor receptor; GTR = gross total resection; HR = hazard ratio; HRT = hypofractionated radiation therapy; KPS = Karnofsky performance status; MGMT = O^6-methylguanine DNA methyltransferase; RPA = recursive partitioning analysis (2); SRT = standard-course radiation therapy; STR = subtotal resection; TMZ = temozolomide.

Although only randomization can control for unknown prognostic variables, propensity scores have been useful to help control for known prognostic variables when comparing treatment regimens. The propensity score is the conditional probability of receiving a specific treatment, given the individual's covariates, and is used to mitigate bias in observational studies (17). Following adjustment using the propensity score model, we did not find a statistically significant difference in OS between HRT + TMZ and SRT + TMZ. This could be related to power (the difference between treatment groups was not significant on univariate analysis either) or be model-specific, but the HR for treatment group was substantially mitigated once controls for prognostic variables were included.

There was clearly bias in selection of patients for hypofractionated regimens, and once this bias was controlled for, there was no longer a trend toward worse OS for HRT + TMZ. Our results are hypothesis-generating, and although the results of the NCIC CTG CE.6, EORTC 26062-22061, and TROG 08.02 studies may provide the answer to whether the addition of TMZ to HRT is better than HRT alone and thereby reduce selection bias and treatment variation, the question of SRT + TMZ versus HRT + TMZ will still remain. It remains possible that SRT + TMZ could result in better outcomes due to TMZ treatment intensification (doubling of daily exposure) and/or longer time for adequate radiosensitization. Alternatively, HRT + TMZ may have several benefits to the patient, particularly from the quality-of-life standpoint, and if HRT + TMZ truly affords the same survival as a longer course of radiation therapy, the shorter course would be preferable. Furthermore, if longer concurrent treatment does not influence the degree of radiosensitization and daily TMZ functions purely as a radiosensitizer, halving the amount of total TMZ may result in improved toxicity profiles. Any future clinical trials attempting to answer this question would therefore certainly benefit from the use of several patient-centric endpoints, in addition to OS, to quantify such benefits.

Conclusions

HRT for newly diagnosed GBM in the elderly is often administered to the oldest patients and those with lower performance status. Controlling for this selection bias, we observed no OS differences between SRT and HRT when given with concurrent TMZ. Previous and ongoing trials of HRT among older patients with GBM have not compared outcomes to the standard regimen of SRT + TMZ. Although a randomized trial of SRT + TMZ versus HRT + TMZ may be the most clinically useful in defining optimal management for elderly patients, the amount of patients required for an appropriately powered non-inferiority trial may limit interest, necessitating reliance on developing other sources of data and analytical methods such as population-based studies or multi-institutional registries (18).

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