ORIGINAL ARTICLE

Prognostic Factors and Treatment Patterns in the Management of Giant Cell Glioblastoma

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■ BACKGROUND: **There is a lack of literature guiding treatment of giant cell glioblastoma (gcGBM), a rare subtype of glioblastoma (GBM). We used a national hospital-based registry to explore treatment patterns and outcomes associated with gcGBM.**

■ METHODS: **Adult patients (age ≥18 years) diagnosed with gcGBM or GBM between 2004 and 2014 were identified from the National Cancer Database. χ^2 analysis and Wilcoxon rank sum testing were used to compare characteristics between the gcGBM and GBM cohorts. Kaplan-Meier statistics, univariable and multivariable Cox regression, and propensity score matching were used to evaluate association between patient, tumor and treatment factors, and survival outcomes. Correlation analysis was used to evaluate historical trends in the treatment of gcGBM. Landmark analysis allowed for accounting of immortal time.**

■ RESULTS: **In total, 683 patients with gcGBM were identified. Patients with gcGBM had improved survival compared with patients with GBM (15.5 months from landmark vs. 11.7; $P < 0.001$). Increased age ($P < 0.001$) was associated with worse survival whereas being of female sex ($P = 0.023$) and having a median income >$63,000 ($P = 0.004$) predisposed patients to improved outcomes. Patients receiving trimodal therapy (biopsy and/or surgery, radiotherapy, and chemotherapy) experienced better outcomes compared with those receiving either biopsy and/or surgery only or biopsy and/or surgery and radiotherapy without systemic therapy (median survival, 17.55 months vs. 6.68 months; $P < 0.001$).**

■ CONCLUSIONS: **gcGBM has favorable prognosis compared with GBM and should be aggressively managed with trimodal therapy. Prospective studies of gcGBM are warranted to better characterize gcGBM treatment outcomes.**

INTRODUCTION

Giant cell glioblastoma (gcGBM) is an exceptionally rare variant of glioblastoma multiforme (GBM) that affects approximately 1% of adults and 3% of children with GBM.[1-5] Common demographic characteristics include a relatively young age at diagnosis, with mean age of 51 years, and common localization to the frontal or temporal lobes.[1] Histopathology of gcGBM is characterized by multinucleated giant cells containing large amounts of eosinophilic cytoplasm.[2] Although gcGBM cells express proliferation markers, such as Ki-67 and proliferation of cell nuclear antigen, no specific immunochemistry profile for gcGBM has been identified, although separate studies have identified positive expression of vimentin, S-100, glial fibrillary acidic protein, and α_1-antichymotrypsin.[6-9]

There is a lack of literature informing prognosis or treatment of gcGBM. Existing studies suggest that younger age of presentation, size of tumor, extent of resection, and adjuvant radiotherapy (RT) affect outcomes.[2,10,11] A previous study in addition reported that gcGBM histology, adjuvant RT, and adjuvant chemotherapy were each independently prognostic for improved survival in a combined cohort consisting of glioblastoma, gcGBM, and gliosarcoma.[11] However, gcGBM constituted only 0.8% of the combined cohort, which was largely dominated by GBM, not

Key words
- Adjuvant
- Chemotherapy
- Giant cell glioblastoma
- Glioblastoma
- Neuro-oncology

Abbreviations and Acronyms
CI: Confidence interval
GBM: Glioblastoma multiforme
gcGBM: Giant cell glioblastoma
GTR: Gross total resection
HR: Hazard ratio
NOS: Not otherwise specified
RT: Radiotherapy

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otherwise specified (NOS). There are few data on risk-stratifying features of and optimal management strategies for gcGBM.

We present the largest cohort of patients with gcGBM analyzed to date and aim to identify prognostic factors, patterns of care, and treatment outcomes for this rare disease entity.

METHODS

We identified patients diagnosed with gcGBM and GBM, NOS (defined as glioblastoma excluding gcGBM and gliosarcoma) between 2004 and 2014 in the National Cancer Database, a repository of de-identified cases from Commission on Cancer–accredited facilities jointly assembled by the American College of Surgeons and the American Cancer Society. Data integrity is maintained through a series of quality assurance mechanisms and participating institutions are required to report follow-up encounters for ≥90% of known living patients annually.[12] Our cohort selection criteria are outlined in **Table 1**. Survival analyses included all patients who received biopsy or surgical resection and had histologically confirmed disease before therapy, whereas comparative analyses of cohort demographics and treatment patterns included all patients with histologic disease confirmation either at diagnosis or during autopsy.

Demographic and disease-specific variables including age at diagnosis, sex, race, insurance status, income, Charlson Comorbidity Index, primary site of disease, tumor focality, and *MGMT* promotor methylation were obtained from the database and included in our analysis. Treatment variables included extent of surgical resection and receipt of RT and/or chemotherapy after biopsy or surgery. Extent of resection, tumor focality, and *MGMT* status were available from 2010 onward. Wilcoxon rank sum and χ^2 testing were used to compare continuous and categorical variables, respectively. Pearson correlation analysis was used to determine significance of historical trends in gcGBM treatment.

To address immortal time bias, landmark analysis was performed with inclusion of only patients alive for ≥2 months after surgery or biopsy in the survival analyses.[2,13] All survival analyses started time accrual at the landmark point. Kaplan-Meier analysis and univariable Cox regression were used to determine the association between demographic, disease-specific, and treatment-related factors and survival. Multivariable Cox regression of covariates with a univariable P value <0.2 was used to determine variables with independent prognostic value.

To further address confounding by indication, propensity score matching was performed between patients receiving trimodal therapy (biopsy and/or surgery followed by RT and adjuvant or concomitant chemotherapy) and those who did not.[14] Matched cohorts were generated using a logistic regression model with receipt of trimodal therapy as the dependent variable. Clinical features prognostic for outcome by univariable Cox regression were included as independent variables and a greedy matching algorithm was applied to generate propensity score–matched cohorts. Standardized mean differences were used to evaluate balance between groups before and after matching. Shared frailty univariable modeling was used to evaluate the survival impact of receiving trimodal therapy in the case-matched cohorts. Statistical analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria) and graphic representations of findings were generated using GraphPad Prism 7 (GraphPad Software, San Diego, California, USA).

RESULTS

Cohort Description

A total of 683 patients with gcGBM and 78,860 patients with GBM, NOS diagnosed between 2004 and 2014 were identified (**Table 2**). Compared with patients with GBM, NOS, patients diagnosed with gcGBM tended to be of a younger age (median age, 57 vs. 62 years; $P < 0.001$). Furthermore, gcGBM tumors were more frequently found in the frontal lobe (31.3% vs. 27.0%) and less frequently found in the occipital lobe (2.5% vs. 4.3%). Gross total resection (GTR) was more frequently achieved in patients with gcGBM (17.6% vs. 11.9%; $P < 0.001$) and a larger fraction of patients with gcGBM received RT

Table 1. Patient Cohort Selection

Characteristic	Giant Cell Glioblastoma n	Giant Cell Glioblastoma %	Glioblastoma n	Glioblastoma %
Patients with giant cell glioblastoma multiforme (9441/3) or glioblastoma multiforme, not otherwise specified (9440/3) diagnosed between 2004 and 2014	899	100	108,141	100
Exclude patients whose diagnosis date precedes reference date	880	97.9	105,903	97.9
Exclude patients with invalid vital status data	790	87.9	95,697	88.5
Exclude patients with previous cancer diagnoses	686	76.3	83,347	77.1
Exclude patients without positive histologic/cytologic confirmation of disease	683	76.0	78,860	72.9

Table 2. Patient, Tumor, and Treatment Characteristics.

	Giant Cell Glioblastoma		Glioblastoma		
Characteristic	n	%	n	%	P Value
Total	683	100	78,860	100	
Year of diagnosis					
2004–2009	337	49.3	39,254	49.8	0.851
2010–2014	346	50.7	39,606	50.2	
Age (years), median (25%–75% range)	57 (46–67)	NA	62 (54–71)	NA	<0.001*
Sex					0.494
Male	387	56.7	45,707	58.0	
Female	296	43.3	33,153	42.0	
Race					0.683
White	612	89.6	71,429	90.6	
Black	41	6.0	4340	5.5	
Other/unknown	30	4.4	3091	3.9	
Charlson Comorbidity Index					0.007*
0	531	77.7	57,218	72.6	
1	98	14.4	13,110	16.6	
2+	54	7.9	8532	10.8	
Insurance status					<0.001*
No insurance	30	4.4	3137	4.0	
Privately insured	361	52.8	36,883	46.8	
Medicaid	58	8.5	4802	6.1	
Medicare	215	31.5	30,704	38.9	
Unknown/other	19	2.8	3334	4.2	
Income ($)					0.060
<38,000	79	11.6	11,874	15.1	
38,000–47,999	159	23.3	17,916	22.7	
48,000–62,999	188	27.5	21,016	26.6	
>63,000	246	36.0	26,184	33.2	
Unknown	11	1.6	1870	2.4	
MGMT status					0.070
Nonmethylated	42	6.1	3580	4.5	
Methylated	26	3.8	2445	3.1	
Unknown	615	90.1	72,835	92.4	
Karnofsky Performance Status					0.653
>70	25	3.7	2458	3.1	
≤70	17	2.5	1818	2.3	
Unknown	641	93.8	74,584	94.6	
Primary site					0.007*
Cerebrum, not otherwise specified	17	2.5	3056	3.9	
Frontal lobe	214	31.3	21,323	27.0	
Temporal lobe	175	25.6	19,127	24.3	
Parietal lobe	112	16.4	12,606	16.0	
Occipital lobe	17	2.5	3404	4.3	
Other	148	21.7	19,344	24.5	
Surgery					<0.001*
Gross total resection	120	17.6	9401	11.9	
Subtotal resection	86	12.6	9494	12.0	
Local excision	62	9.1	6745	8.6	
No surgery	81	11.8	16,782	21.3	
Other/unknown	334	48.9	36,438	46.2	
Chemotherapy					<0.001*
No	185	27.1	26,156	33.2	
Yes	498	72.9	52,704	66.8	
Radiation therapy					<0.001*
No	143	20.9	21,554	27.3	
Yes	540	79.1	57,306	72.7	

*P value < 0.05

(79.1% vs. 72.7%; $P < 0.001$) and chemotherapy (72.9% and 66.8%; $P < 0.001$) than did patients with GBM, NOS. Among patients who underwent either biopsy and/or surgical tumor resection, those with gcGBM had longer median survival compared with those with GBM, NOS (median survival, 15.5 months from landmark vs. 11.7 months; $P < 0.001$). Among patients with GBM, NOS, and patients with gcGBM who received surgery and both postoperative radiation and chemotherapy and matched on age, sex, race, income, insurance status, Charlson Comorbidity Index, and tumor focality, patients with gcGBM continued to have improved survival outcomes (median survival, 17.55 months from landmark vs. 15.76 months; $P = 0.020$) (Figure 1A).

Factors Prognostic for Survival in gcGBM

Younger age, residence in areas with high median household, and female gender were independently associated with better survival (Table 3). Among the 239 patients with gcGBM with documented tumor focality, patients with multifocal gcGBM showed significantly worse survival than did those with unifocal tumors in univariable analyses ($P = 0.015$; hazard

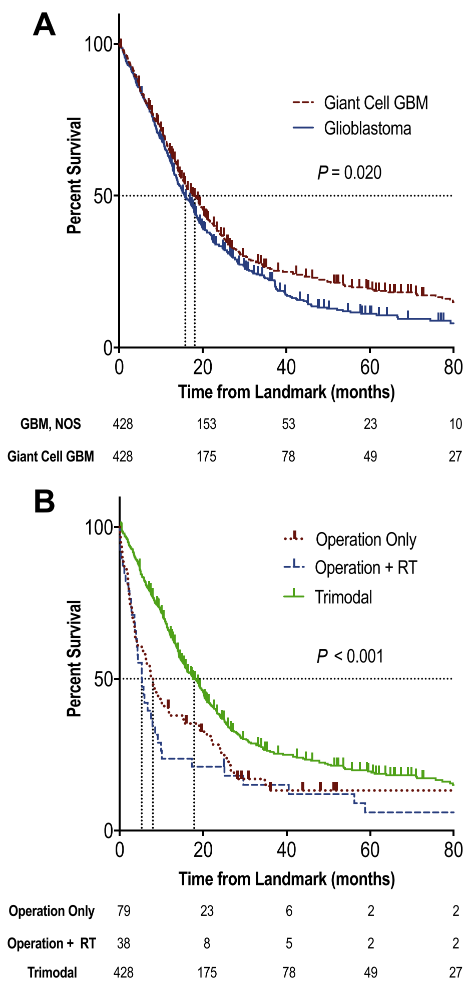

Figure 1. Kaplan-Meier analysis of giant cell glioblastoma (GBM). (**A**) Patients with giant cell glioblastoma have improved survival compared with those with glioblastoma multiforme, not otherwise specified (GBM, NOS). (**B**) Patients receiving trimodal therapy experience improved outcomes compared with those receiving only surgery or surgery and adjuvant radiotherapy (RT) without chemotherapy.

ratio [HR], 1.769; 95% confidence interval [CI], 1.118–2.800). However, this effect was not significant after controlling for other factors in multivariable analysis. Several tumor characteristics, including tumor size, primary site, MGMT methylation status, and extent of resection were not significantly associated with survival.

Treatment Patterns and Outcomes of gcGBM

From 2010 to 2014 when extent of resection data were available, the proportion of GTR increased (15.9% to 53.8%; $P = 0.025$), whereas the proportion of patients receiving biopsies without surgery decreased (30.2% to 12.3%; $P = 0.035$) (**Figure 2**). Of patients who underwent biopsy or surgery, most received RT ($n = 476$, 69.7%). Of the patients treated with RT, 37.2% ($n = 177$) received intensity-modulated radiation therapy. Of the patients receiving RT after biopsy or surgery, 430 (90.3%) also received concomitant or adjuvant chemotherapy. Between 2004 and 2014, patients with gcGBM were less likely to receive RT without chemotherapy after biopsy and/or surgery (18.8% to 1.9%; $P < 0.001$) (**Figure 2**).

Addition of radiation therapy was associated with improved survival compared with biopsy and/or surgery alone (median survival, 16.25 months from landmark vs. 7.98 months; $P < 0.001$; HR, 0.631; 95% CI, 0.486–0.820). However, patients receiving radiation alone without concomitant or adjuvant chemotherapy did not have improved survival. Patients who received both radiation and chemotherapy after biopsy and/or surgery (i.e., trimodal therapy) showed significantly improved survival compared with those who did not (median survival, 17.55 months from landmark vs. 6.68 months; $P < 0.001$; HR, 0.566; 95% CI, 0.434–0.738) (**Figure 1B**, **Table 3**). For our propensity score analysis, we matched 118 patients who received trimodal therapy with 118 patients who did not (**Supplementary Table 1**) and again found that trimodal therapy was associated with improved survival (median survival, 13.43 months from landmark vs. 6.68 months; $P = 0.005$; HR, 0.668; 95% CI, 0.503–0.886).

DISCUSSION

Until this study, there has been a lack of comprehensive multi-institutional data on gcGBM because of the rarity of this histology. In this large retrospective analysis of a national hospital-based registry, we found that patients with gcGBM treated with trimodal therapy experienced longer survival compared with patients receiving less aggressive disease management. In addition, we confirmed improved survival associated with gcGBM compared with other GBM histologies.

Previous studies have shown that patients with gcGBM experience improved survival compared with those with GBM.[2,3] A large cohort of patients with gcGBM ($n = 171$) compared with patients with non-giant cell GBM ($n = 16,259$) from the SEER (Surveillance Epidemiology and End Results) database also showed the more favorable prognosis of gcGBM compared with GBM (HR, 0.76; 95% CI, 0.59–0.97).[2] We similarly found that patients with gcGBM also experienced improved survival compared with those with GBM. Because patients with gcGBM tend to be younger and thus more fit to receive adjuvant therapy, it was not clear whether tumor biology or treatment selection drove the improved survival outcomes. In our study, we conducted a propensity score–matched analysis among only those patients with gcGBM and GBM, NOS who received radiation and chemotherapy after biopsy and/or surgery and found that the survival advantage associated with gcGBM still persisted, suggesting that tumor biology is prognostically important.

Among patients with gcGBM, we found that various demographic characteristics, including age, sex, and income, were associated with survival. This finding parallels findings from previous studies of GBM, gliosarcoma, and other tumor histologies.[15,16] We found that tumor multifocality was also associated with poor survival in univariable analysis but, likely because of a lack of statistical power resulting from incomplete data, did not meet the threshold for significance in our multivariable Cox

Table 3. Univariate and Multivariate Models of Factors Associated with Overall Survival Among Patients with Giant Cell Glioblastoma.

	Univariate			Multivariate		
Characteristic	**Hazard Ratio**	**95% Confidence Interval**	***P* Value**	**Hazard Ratio**	**95% Confidence Interval**	***P* Value**
Age at diagnosis (years)	1.027	1.020–1.034	<0.001*	1.027	1.020–1.039	<0.001*
Year of diagnosis	0.979	0.948–1.011	0.198			
Sex						
Male	1.000			1.000		
Female	0.806	0.664–0.979	0.029	0.795	0.653–0.969	0.023*
Race						
White	1.000					
Black	0.905	0.583–1.405	0.657			
Other	1.115	0.718–1.730	0.629			
Charlson Comorbidity Index						
0	1.000					
1	1.006	0.755–1.341	0.965			
2+	1.236	0.846–1.806	0.274			
Insurance status						
No insurance	1.000			1.000		
Privately insured	0.704	0.446–1.113	0.133	0.675	0.423–1.076	0.098
Medicaid	0.717	0.415–1.239	0.233	0.704	0.403–1.231	0.218
Medicare	1.232	0.768–1.975	0.386	0.643	0.385–1.074	0.091
Unknown/other	0.843	0.371–1.916	0.684	0.752	0.327–1.731	0.503
Income ($)						
<38,000	1.000			1.000		
38,000–47,999	0.736	0.524–1.032	0.076	0.777	0.553–1.092	0.146
48,000–62,999	0.804	0.577–1.120	0.197	0.810	0.577–1.137	0.222
>63,000	0.607	0.440–0.837	0.002*	0.615	0.444–0.854	0.004*
Unknown	1.167	0.529–2.576	0.702	1.518	0.677–3.402	0.311
MGMT methylation						
No	1.000					
Yes	1.317	0.694–2.499	0.399			
Unknown	1.179	0.787–1.768	0.425			
Tumor focality						
Unifocal	1.000			1.000		
Multifocal	1.769	1.118–2.800	0.015*	1.518	0.939–2.455	0.088
Unknown	1.209	0.984–1.485	0.071	0.944	0.674–1.323	0.739
Surgery						
Gross total resection	1.000			1.000		
Less than gross total resection	1.139	0.878–1.553	0.412	1.000	0.733–1.385	0.964
Other/unknown	1.322	1.012–1.727	0.041*	1.268	0.926–1.956	0.120

*P value < 0.05.

Continues

Table 3. Continued

Characteristic	Univariate			Multivariate		
	Hazard Ratio	95% Confidence Interval	*P* Value	Hazard Ratio	95% Confidence Interval	*P* Value
Trimodal therapy						
Yes	1.000			1.000		
No	1.773	1.419—2.217	<0.001*	1.481	1.174—1.867	<0.001*

**P* value < 0.05.

regression. However, previous studies have associated tumor multifocality with poor survival in other GBM subtypes, and additional studies are warranted to explore this association.[15] Other tumor characteristics, such as *MGMT* methylation status, were not prognostic in gcGBM.[15]

gcGBM has been managed overall similarly to GBM. Most of both cohorts received a surgical procedure and postoperative RT or chemotherapy. Among patients with gcGBM, the rate of GTR has increased over time whereas the rate of biopsies alone has declined over time. This trend is unsurprising because studies over the past 2 decades have extensively shown the importance of increased extent of resection.[17,18] Although extent of resection was not associated with increased survival in our cohort, these data were available only for patients diagnosed after 2010 and additional studies are needed to validate this result. Furthermore, from 2004 to 2014, we noticed a decrease in the fraction of patients receiving RT alone, without systemic treatment, after surgery; this similarly is a result of the introduction of the Stupp protocol for GBM, which shows survival benefit associated with the addition of adjuvant or concomitant temozolomide to RT.[19]

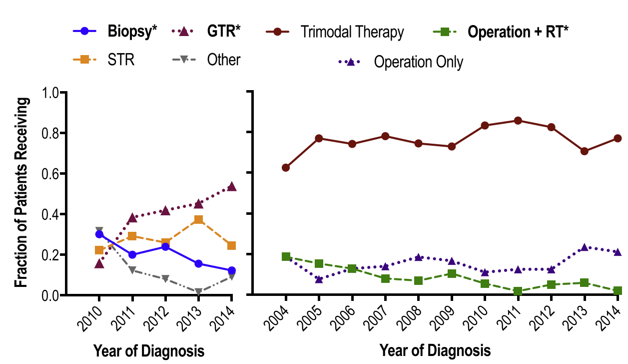

Figure 2. Trends in management approaches for giant cell glioblastoma over time. Patients with giant cell glioblastoma undergoing surgery are more likely to achieve gross total resection (GTR) and less likely to receive postoperative radiotherapy (RT) without chemotherapy. *indicates a significant trend ($P < 0.05$); extent of resection data only available in patients diagnosed 2010+. STR, subtotal resection.

We found that the use of both radiation and chemotherapy after biopsy and/or surgery was associated with improved survival. The benefit of trimodal therapy has been previously explored in a single-institution study of 20 patients with gcGBM, showing an improvement in progression-free survival after adjuvant RT and temozolomide compared with those receiving alternative treatments.[20] However, there is a dearth of large multi-institutional studies examining the effect of combining adjuvant RT and chemotherapy in gcGBM.[20] A previous SEER study[2] identified RT as being prognostic for improved survival; however, data on chemotherapy were not available in that study. Our study of a larger cohort of patients (683 vs. 171 patients), in which we were able to look specifically at chemotherapy as well as address the concern of immortal time bias, suggests that inclusion of RT alone was not sufficient to improve survival in patients with gcGBM and only patients receiving both RT and chemotherapy experienced a survival benefit.

Despite our findings, important limitations must be addressed, including the retrospective nature of the study. Although we tried to adjust for measured confounding factors in our survival analyses using multivariable regression as well as propensity score matching, we were not able to address unmeasured confounders that were not available in the database. For example, Karnofsky Performance Status is an important confounder that has great influence over treatment selection as well as outcomes in the treatment of GBM but was available for only a few patients ($n = 42$ [6.2%], Table 2) and thus was not included in our analyses. Landmark analysis helped address this confounding by excluding those patients who were too sick or whose Karnofsky Performance Status was too poor to receive adjuvant therapy (those who died within 2 months of biopsy and/or surgery). Errors in data entry or inconsistencies in variable coding present additional challenges.[21] Other important clinical variables, such as disease control, chemotherapy details, and clinically significant genetic signatures, such as *IDH1* mutation status, were also not available as part of the National Cancer Database dataset. Furthermore, although pathologic classification of GBM into gcGBM and gliosarcoma was available, more recently defined subclasses of GBM, such as epithelioid glioblastoma, were not distinguishable from GBM, NOS. The lack of a centralized review of disease pathology is an additional limitation of our study. Study strengths include our large cohort of patients, allowing for greater statistical power when conducting subset analyses and matched comparisons.

CONCLUSIONS

In this study, we identified younger age, higher income, and being female as positive prognostic factors among patients with gcGBM. Aggressive disease management with trimodal therapy was associated with improved survival compared with either biopsy and/or surgery and only RT or biopsy and/or surgery alone. Additional prospective institutional investigation into the natural history and optimal management of gcGBM is warranted.

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Author contributions: M.C.J., A.W., G.L., and E.L.P. conceived the project. M.C.J. and A.W. acquired requisite data, conducted statistical analyses, interpreted data, generated figures and tables, drafted the manuscript, and received final manuscript submission. M.X., T.D.A., S.G.S., G.L., and E.L.P. critically revised the draft manuscript.

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Supplementary Table 1. Demographic and Clinical Factors: Propensity Score Matching Summary

	Before Propensity Score Matching			After Propensity Score Matching		
Characteristic	**No Trimodal Therapy**	**Trimodal Therapy**	**Standardized Mean Difference**	**No Trimodal Therapy**	**Trimodal Therapy**	**Standardized Mean Difference**
Total	118	428		118	118	
Mean age (years)	60.86	52.30	***0.565****	60.86	59.54	0.090
Sex			0.065			0.034
Male	65	248		65	63	
Female	53	180		53	55	
Income ($)			***0.301****			0.070
<38,000	16	42		16	17	
38,000—47,999	24	108		24	22	
48,000—62,999	39	107		39	42	
>63,000	38	164		38	36	
Unknown	0	7		0	0	
Surgery			0.066			0.079
Gross total resection	24	86		24	27	
Less than gross total resection	26	107		26	23	
Other/unknown	67	235		67	67	
Tumor focality			0.091			0.054
Unifocal	42	170		42	45	
Multifocal	7	20		7	7	
Unknown	68	238		68	65	