Neuro-Oncology 13(11):1244–1251, 2011.
doi:10.1093/neuonc/nor117
Advance Access publication August 10, 2011

Serum YKL-40 is a marker of prognosis and disease status in high-grade gliomas†

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The objective of this study was to evaluate whether longitudinal levels of serum YKL-40 correlate with disease status or survival in adults with gliomas. Patients with histologically confirmed gliomas were eligible for this longitudinal study. Serum samples were collected prospectively and concurrently with MRI scans at multiple time points during the course of the disease. YKL-40 levels determined by ELISA were correlated with radiographic disease status and survival. We performed a multivariate survival analysis including well-known prognostic factors such as age, performance status, and extent of surgical resection. Three hundred and forty-three patients with gliomas (41 low-grade, 105 anaplastic, and 197 glioblastoma) were accrued. Two-year survival from registration was 29% for glioblastomas, 62% for anaplastic gliomas, and 83% for low-grade gliomas. A total of 1740 serum samples were collected, and 95.6% of samples had matching MRI scans. Serum YKL-40 level was significantly lower in patients with no radiographic disease compared with patients with radiographic disease in both the anaplastic glioma ($P = .0008$) and the glioblastoma ($P = .0006$) cohorts. Serum levels of YKL-40 in patients with low-grade gliomas were not associated with radiographic disease status. Increases in YKL-40 were independently associated with worse survival in anaplastic gliomas (hazard ratio [HR] = 1.4, $P = .01$) and glioblastomas (HR = 1.4, $P < .0001$). Longitudinal increases in serum YKL-40 are associated with increased risk of death in patients with glioblastomas and anaplastic gliomas. YKL-40 is also a putative indicator of disease status in these patients.

Keywords: glioblastoma, glioma, serum marker YKL-40.

Gliomas, the most common primary brain tumors in adults, are graded according to the World Health Organization (WHO) classification from I to IV based on proliferative potential and malignant features.[1] Grade I gliomas are rare in adults. Grade II (low-grade) and grade III (anaplastic) gliomas can be subdivided into astrocytoma, oligodendroglioma, and oligoastrocytoma, depending on the presumed cell of origin and morphology.[1] Glioblastoma multiforme (GBM; grade IV gliomas), the most common and aggressive primary brain tumor in adults, has a median survival of only 14.6 months.[2] However, survival of glioma patients with the

Received April 26, 2011; accepted June 24, 2011.

†This study was presented in part at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, IL, May 30–June 3, 2008; and at the 13th Annual Society for Neuro-Oncology Scientific Meeting, Las Vegas, NV, November 20–23, 2008.

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same tumor histology and grade can vary significantly, and some low-grade gliomas transform to a more malignant phenotype. Currently available molecular prognostic markers require evaluation of tumor tissue, such as 1p and 19q chromosome co-deletion in oligodendroglial tumors,[3,4] *MGMT* (O6-methylguanine-DNA methyltransferase) promoter methylation for GBMs,[5] and isocitrate dehydrogenase mutations in several glioma subtypes.[6] Less invasive prognostic and predictive markers are needed because multiple brain tumor sampling is not feasible over the course of the illness.[7,8]

Serum markers that correlate with tumor status and prognosis could significantly improve the care of patients with glioma. A microarray analysis of 10 000 genes showed that YKL-40, a chitinase homolog also called human cartilage glycoprotein 39 or chitinase 3-like 1, is the most highly expressed gene in gliomas compared with normal brain.[9] The exact function of YKL-40 in gliomas or other cancers is unknown but YKL-40 may be involved in cell proliferation, differentiation, protection against apoptosis, angiogenesis, and extracellular tissue remodeling.[10–12] Interestingly, YKL-40 is secreted by both tumor cells and tumor-associated macrophages into the bloodstream and can be determined by an ELISA procedure. YKL-40 levels are stable in collected blood for up to 7 days, and there is no significant circadian variation of serum levels.[9,13] Finally, peripheral blood YKL-40 levels are increased and have prognostic utility in other cancers.[14–22]

A previous preliminary report suggested that serum YKL-40 levels correlate with disease status and have an inverse association with survival in patients with GBM and anaplastic glioma.[23] However, due to a small sample size, no multivariate analysis was performed in this preliminary study. Herein we report a large sample population followed for a longer period to ascertain whether serum YKL-40 is an independent prognostic marker after adjusting for known prognostic factors. This study represents an expanded longitudinal study of the serum level of YKL-40 measured prospectively in consecutive adult patients with grades II–IV gliomas seen in our institution.

Materials and Methods

Patient Eligibility

Patients with histologically confirmed gliomas were enrolled in the study from August 2002 to September 2008. Follow-up extended through December 2009. Patients were able to enroll any time during their disease course, and patients with suspected brain tumor identified by imaging who had not yet undergone resection were also eligible for the study. Those patients enrolled before their initial surgical procedure continued on study only if they had histologic confirmation of a glioma. Other eligibility criteria included age $\geq$18 years, KPS $\geq$40, and absence of any active systemic malignancy, infection, rheumatoid arthritis, or severe osteoarthritis, because these conditions are associated with elevated serum YKL-40 levels. Postsurgical samples were obtained more than 2 weeks from resection or biopsy because serum YKL-40 increases immediately following surgery. One hundred and forty-three patients reported in a preliminary study[23] were included in the current analysis. Patients were considered to have a newly diagnosed glioma at study entry if their first serum YKL-40 measurement fell within 3 months of the diagnosis date, including 58 newly diagnosed GBM patients who enrolled in a Memorial Sloan-Kettering Cancer Center (MSKCC) randomized phase II trial of chemoradiation with temozolomide and 2 different regimens of adjuvant temozolomide.[24] Pathology from all patients enrolled in the study was reviewed at our institution using the WHO classification scheme.[1]

Study Design

This prospective longitudinal study collected serum samples and obtained imaging studies at baseline and every 2 to 3 months when patients were evaluated at their follow-up visits. Blood samples were collected and YKL-40 levels were determined by ELISA in a blinded fashion as described.[15] Radiographic disease status was assessed by MRI, and tumor size was determined by measuring contrast-enhancing lesions and fluid attenuated inversion recovery (FLAIR) hyperintensity for nonenhancing gliomas, using Response Evaluation Criteria in Solid Tumors (RECIST)[25] and Macdonald criteria.[26] Response was assessed according to Macdonald criteria, accounting for radiographic response, corticosteroid use, and clinical status;[26] to ensure uniformity, all MRI scans were reviewed by at least 2 of 3 authors (A.F.H., S.K., and F.M.I.), who were blinded to the YKL-40 levels and patients' outcomes. Patients with complete response were considered as having no evidence of radiographic disease, while patients with partial response, stable disease, and progressive disease were classified as having evidence of radiographic disease. MRI scans and YKL-40 levels were matched if they were performed within a period of 1 month.

Statistical Analysis

The values of the YKL-40 measurements were log transformed before all statistical testing because their distribution was skewed. We tested the associations between YKL-40 and glioma type and YKL-40 and disease status (dichotomized by no evidence of radiographic disease vs evidence of radiographic disease) by incorporating all measurements in a logit model with generalized estimating equations that corrected for within-patient correlations.[27] We also calculated the area under the curve (AUC) of the receiver operating characteristic or concordance index of YKL-40 and disease status. Survival was defined as time from study registration to date of death or last follow-up and was estimated by Kaplan–Meier methodology.

The effect of YKL-40 (on the log-scale due to skewed distribution) on survival was analyzed as a time-dependent covariate in a Cox proportional hazards model.[28] Multivariate Cox proportional hazards models were used to examine the independent effect of YKL-40 on survival. Age at registration, extent of resection at diagnosis, and baseline KPS (dichotomized at 70) were used in the multivariate models. In addition, longitudinal measurements of tumor burden (defined as either the sum of tumor length by RECIST, or area measurements by Macdonald criteria), from each MRI date, were used as time-dependent covariates in the multivariate models to examine whether YKL-40 was an independent predictor of survival even after adjusting for tumor burden. Associations between tumor size and serum YKL-40 levels across all patients were assessed by Pearson's correlation coefficient. We also performed a subset analysis on newly diagnosed GBM patients. For these patients, we examined serum YKL-40 as a time-dependent covariate and also examined the association of the baseline YKL-40 value on survival.

Protocol Approval and Patient Consent

This study was approved by the MSKCC Institutional Review Board, and all patients signed written informed consent.

Results

Patient Characteristics

Three hundred and forty-three patients with gliomas (59% men) were included in this study (Table 1). After pathology review at MSKCC, 41 patients were classified as having low-grade gliomas, 105 as having anaplastic gliomas, and 197 as having GBM. Among the 41 low-grade gliomas, there were 14 astrocytomas, 19 oligodendrogliomas, and 8 oligoastrocytomas. Anaplastic glioma subtypes included 65 anaplastic astrocytomas, 25 anaplastic oligodendrogliomas, and 15 anaplastic oligoastrocytomas. The majority of patients had good performance status (89% with KPS $\geq$ 70) and had undergone either gross total (37%) or partial resection (38%). Seventy-two percent of GBM and 40% of anaplastic glioma patients were enrolled in this study within the first 3 months of diagnosis. Follow-up extended through December 2009, by which 81% of GBM, 48% of anaplastic glioma, and 24% of low-grade glioma patients had died. Median follow-up for survivors was 29 months for GBM patients, 44 months for anaplastic glioma patients, and 52 months for low-grade glioma patients (Table 1). Two-year survival from date of registration estimates were 29%, 62%, and 83% for GBM, anaplastic glioma, and low-grade glioma patients, respectively.

Table 1. Patient characteristics, follow-up, survival, and number of YKL-40 assessments

Characteristics	Low-Grade Glioma (n = 41)	Anaplastic Glioma (n = 105)	Glioblastoma (n = 197)
Median age, y (range)	43 (23–63)	46 (23–81)	56 (23–83)
Gender			
Men	25 (61%)	56 (53%)	121 (61%)
Women	16 (39%)	49 (47%)	76 (39%)
Baseline KPS			
Median (IQR)	90 (90–100)	90 (70–100)	80 (70–90)
<70	0	6 (6%)	9 (5%)
≥70	40 (100%)	95 (94%)	170 (95%)
Missing	1	4	18
Extent of tumor resection			
Gross total resection	10 (24%)	39 (37%)	78 (40%)
Partial resection	20 (49%)	40 (38%)	69 (35%)
Biopsy	8 (20%)	21 (20%)	36 (18%)
Unknown	3 (7%)	5 (5%)	14 (7%)
Median months from diagnosis to registration (range)	12.3 (0–131)	3.5 (0–137)	0.6 (0–21)
Number of patients followed from initial diagnosis	12 (29%)	42 (40%)	141 (72%)
Median follow-up for survivors, mo (range)	52 (4–77)	44 (0.1–79)	29 (0–77)
Number of patients who died during study follow-up	10 (24%)	50 (48%)	160 (81%)
2-y survival (95% CI)	0.83 (0.66–0.92)	0.62 (0.51–0.71)	0.29 (0.22–0.35)
Median number of YKL-40 measurements (IQR)	5 (2–10)	5 (2–8)	3 (1–5)
Number of patients with both YKL-40 and radiographic assessments available	39 (95%)	104 (99%)	189 (96%)

Abbreviations: IQR, interquartile range.

Serum YKL-40 Level and Tumor Grade

A total of 1740 serial serum samples were collected: 269 in low-grade glioma, 635 in anaplastic glioma, and 836 in GBM. A total of 1664 serum samples had a matched MRI scan: 779 GBM, 621 anaplastic glioma, and 264 low-grade glioma. Seventy-six (4.4%) serum samples had no matching MRI. Eighty-one percent of YKL-40 samples were obtained within 1 week of the MRI, with 58% obtained the same day. Nineteen percent were performed between 1 week and 1 month of the MRI. There were a total of 1183 YKL-40 samples with matching MRIs that showed evidence of disease. Among patients with radiographic disease, YKL-40 levels were significantly different by glioma grade ($P = .02$, Fig. 1A). This result was driven by the significantly higher YKL-40 levels in GBM and anaplastic glioma patients compared with low-grade glioma patients ($P = .003$ for both). However, the YKL-40 levels in GBMs were similar to those in anaplastic gliomas ($P = .83$), and serum YKL-40 values in patients with anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma with radiographic disease were similar to each other ($P = .73$, Fig. 1B).

Serum YKL-40 Level and Radiographic Evidence of Disease

Serum YKL-40 levels were significantly lower in patients who had no radiographic disease compared with those with radiographic disease in both anaplastic glioma ($P = .0008$) and GBM ($P = .0006$) subgroups (Figs 2A and B). Serum levels of YKL-40 in patients with low-grade glioma were not associated with radiographic disease status ($P = .72$) (Fig. 2C). The concordance index of YKL-40 to differentiate between patients with no radiographic disease and those with radiographic disease was AUC = .65 (95% CI: .60–.69, $P = .0008$) for anaplastic gliomas, AUC = 0.65 (95% CI: 0.61–0.70, $P = .0006$) for GBM, and AUC = 0.56 (95% CI: 0.50–0.61, $P = .72$) for low-grade gliomas. The anaplastic oligodendroglioma and oligoastrocytoma cohorts were not analyzed separately because of their small sample size.

There was very weak or no correlation between either unidimensional (length) or bidimensional (area) tumor size and serum YKL-40 levels in patients with low-grade glioma, anaplastic glioma, or GBM. Correlation coefficient values ranged from −0.09 to 0.21. Only 4 patients with low-grade glioma progressed to an anaplastic tumor (2 patients) or to GBM (2 patients), so correlation of markers with transformation could not be analyzed.

YKL-40 and Survival

At least a doubling of the serum YKL-40 level was seen in 93 (47%) GBM cases, 58 (54%) anaplastic glioma cases, and 19 (48%) low-grade glioma cases during the study. Increases in serum YKL-40 were associated with increased risk of death (hazard ratio [HR] =1.5 per each doubling in YKL-40 level) in the cohorts for anaplastic glioma (95% CI: 1.2–2.0, $P = .0009$), anaplastic astrocytoma (95% CI: 1.1–2.1, $P = .008$), and GBM (95% CI: 1.3–1.7, $P < .0001$) (Table 2). The same effect was seen in the subgroups of newly diagnosed anaplastic gliomas and GBMs. Survival analysis for the low-grade glioma cohort was not performed due to the small number of deaths in that group ($n = 10$).

We also performed a multivariate analysis including well-known clinical factors such as age, performance status, and extent of surgical resection and showed that increases in YKL-40 were independently associated with worse survival among patients with anaplastic gliomas ($P = .01$) and GBMs ($P < .0001$), as well as among the subset of patients with newly diagnosed

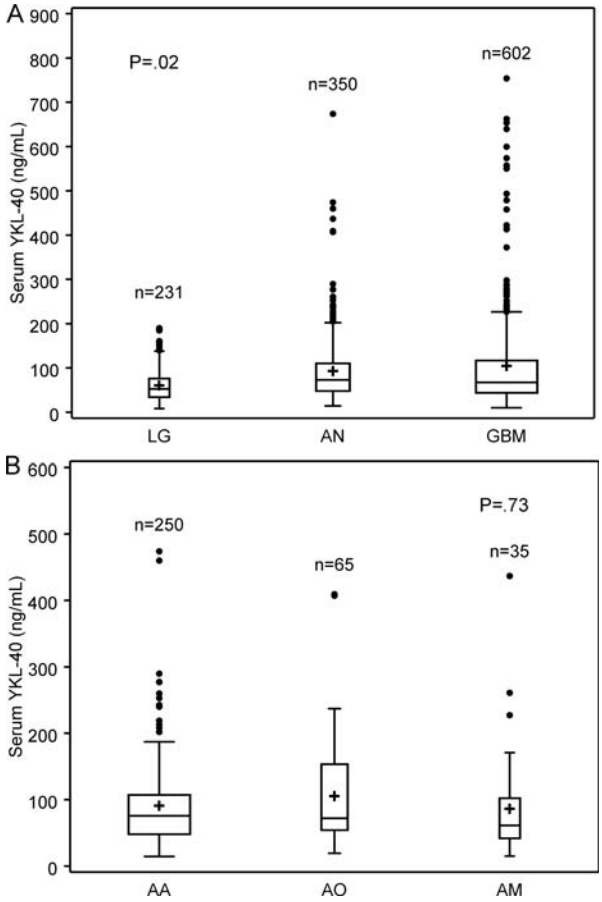

Fig. 1. (A) Box plot illustrating serum YKL-40 values in patients with low-grade glioma (LG), anaplastic glioma (AN), and glioblastoma (GBM) with evidence of radiographic disease. In the GBM group, there were 6 YKL-40 measurements >800 ng/mL that are not displayed. (B) Box plot illustrating serum YKL-40 values in patients with anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and anaplastic mixed glioma (oligoastrocytoma) (AM) with evidence of radiographic disease. In the AA group, there was one YKL-40 measurement >600 ng/mL that is not displayed. +, mean; horizontal line, median. Lower line of the box represents 25th percentile and upper box represents 75th percentile. n, number of YKL-40 measurements.

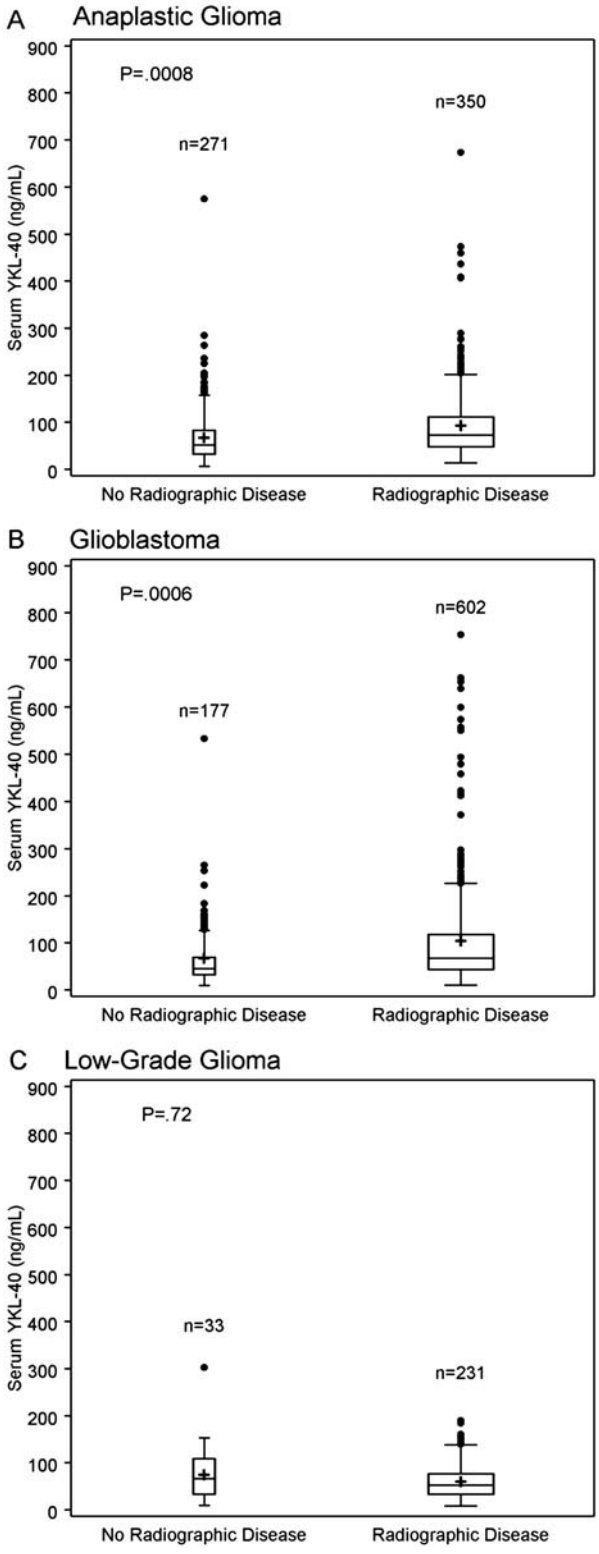

Fig. 2. Box plot comparing serum YKL-40 values and radiographic disease in patients with anaplastic glioma (A), glioblastoma, (B) and low-grade glioma (C). Serum YKL-40 was significantly higher in patients with radiographic disease in both anaplastic glioma ($P = .0008$) and glioblastoma subgroups ($P = .0006$) but did not correlate with disease status in patients with low-grade glioma ($P = .72$). There was one YKL-40 measurement >800 ng/mL in the GBM-no-radiographic-disease group and there were 6 YKL-40 measurements >800 ng/mL in the GBM-radiographic-disease group that were not displayed in (B). +, mean; horizontal line, median. Lower line of the box represents 25th percentile and upper box represents 75th percentile. n, number of YKL-40 measurements.

Table 2. Univariate analysis of the effect of longitudinal increases in serum YKL-40 on survival

Cohort	N	N Events (death)	Each Doubling in YKL-40 Value	
			HR (95% CI)	*P*
Anaplastic gliomas*	107	52	1.5 (1.2–2.0)	.0009
Newly diagnosed anaplastic gliomas	42	23	2.0 (1.2–3.1)	.004
Anaplastic astrocytomas	65	36	1.5 (1.1–2.1)	.008
Glioblastomas	197	161	1.5 (1.3–1.7)	<.0001
Newly diagnosed glioblastomas	141	118	1.5 (1.3–1.8)	<.0001

Abbreviations: N, number; HR, hazard ratio; CI, confidence interval.
*Includes 2 patients who progressed from low-grade to anaplastic glioma.

GBMs ($P = .0007$) (Table 3). Increases in YKL-40 levels were still independently associated with worse survival in these groups of patients after including longitudinal measurements of tumor burden in the multivariate model (data not shown). A single measurement of the YKL-40 level at baseline was also a prognostic factor for worse outcome in newly diagnosed GBM (HR = 1.2; 95% CI: 1.0–1.4, $P = .03$) (Fig. 3) when comparing patients with levels below the median of 98 ng/mL with those with levels equal to or above the median. However, a single baseline measurement of YKL-40 was not a prognostic factor when adjusted for known clinical prognostic factors. In addition, we analyzed a subset of newly diagnosed GBM patients ($n = 58$) treated uniformly in a phase II trial at MSKCC, and doubling of the serum YKL-40 level was associated with shorter overall survival time (HR = 1.5; 95% CI: 1.1–2.0, $P = .01$). However, in 50 GBM patients included in this phase II trial, we found no correlation between doubling of the serum YKL-40 level and progression-free survival (HR = 0.93; 95% CI: 0.7–1.2, $P = .51$).

Discussion

Our data show that a longitudinal increase in YKL-40 serum level is an independent prognostic factor for overall survival in patients with anaplastic glioma or GBM, after adjusting for other known variables associated with outcome, such as extent of resection, age, and performance status. Our prior preliminary study was not powered for multivariate analysis due to the

Table 3. Multivariate analyses including standard prognostic factors and the effect of any longitudinal increase in serum YKL-40

Variable	Anaplastic Glioma ($n = 98$, 49 deaths)*		Glioblastoma ($n = 165$, 140 deaths)*		Newly Diagnosed Glioblastoma ($n = 118$, 103 deaths)*	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Each doubling of YKL-40 value	1.4 (1.1–1.9)	.01	1.4 (1.2–1.6)	<.0001	1.4 (1.1–1.6)	.0007
Age (per 10-y increase)	1.2 (0.9–1.6)	.11	1.1 (0.9–1.4)	.09	1.2 (1.1–1.5)	.04
Extent of resection						
GTR	1	.05	1	.02	1	.005
Partial resection	1.0 (0.5–2.0)		0.9 (0.7–1.4)		0.9 (0.6–1.5)	
Biopsy	2.2 (1.1–4.6)		1.7 (1.1–2.7)		2.1 (1.2–3.6)	
KPS						
<70	1	.02	1	.72	1	.43
≥70	0.3 (0.1–0.8)		0.9 (0.4–1.9)		0.7 (0.3–1.7)	

Abbreviations: HR, hazard ratio; CI, confidence interval; GTR, gross total resection.
*Only patients with complete information for all prognostic factors were included in the multivariate analysis.

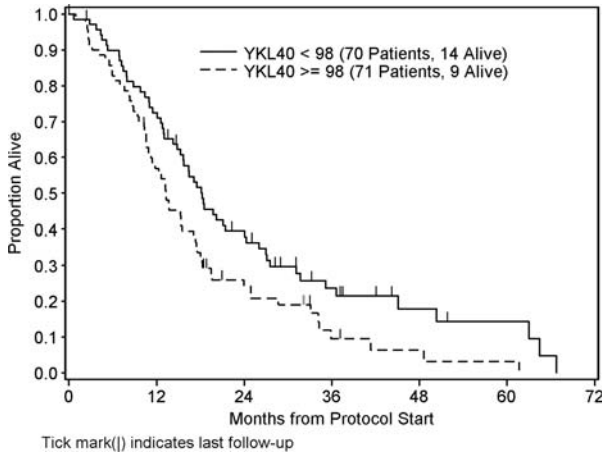

Fig. 3. Overall survival curves of newly diagnosed glioblastoma patients divided according to median (98 ng/mL) baseline YKL-40 levels ($P = .03$).

small sample size, but this expanded prospective study confirms that the serum YKL-40 level can be a useful prognostic marker. The current data also suggest that serum YKL-40 level can help predict prognosis independently of the longitudinal changes in tumor burden measured on MRI scans. Although some prior studies used a cutpoint derived from the upper 95% reference level of age-matched healthy controls, the optimal cut level for serum YKL-40 has not been defined.[16] Consequently, most of our analyses are based on longitudinal changes of serum YKL-40 levels. This serial evaluation proved to be a consistent prognostic marker even when serum collection started any time during the course of disease. In a subset of newly diagnosed patients, we also showed that higher baseline serum YKL-40 levels were associated with shorter survival, suggesting that elevated serum YKL-40 levels may identify a biologically distinct subtype of anaplastic glioma or GBM that carries a worse prognosis. In fact, high expression of YKL-40 by immunohistochemistry on tumor tissue of newly diagnosed gliomas seemed to predict a subset of patients with tumor radioresistance[29] and worse prognosis.[30]

Although the exact function of YKL-40 in gliomas is unknown, its overexpression in vitro can promote tumor invasion and survival following radiation of immortalized human astrocytes.[31] Proteomic analysis of GBM surgical samples showed that YKL-40 overexpression and decreased activation of mitogen-activated protein kinase and phosphatidylinositol-3 kinase were associated with loss of the neurofibromatosis-1 gene.[32] In addition, large mRNA expression studies have shown that YKL-40 is often overexpressed in gliomas and is associated with worse outcome.[33–35] One of these studies defined a subgroup of gliomas with a "mesenchymal" signature characterized by YKL-40 overexpression and shorter survival.[35] Moreover, this study also showed that gliomas often shifted to the more aggressive mesenchymal subtype at tumor progression, based on evaluation of matched specimens of newly diagnosed and recurrent gliomas from the same individuals.[35] These observations, along with our data, suggest that serum YKL-40 is a potentially useful biomarker that may reflect underlying changes within the glioma tissue. YKL-40 should be studied further as a potential prognostic marker to stratify patients at diagnosis and recurrence. Studies correlating YKL-40 serum levels and mRNA expression in tumor tissue at diagnosis and recurrence are especially needed to clarify this issue. If serum YKL-40 proves to be a reliable noninvasive marker of specific molecular subtypes of glioma such as the so-called mesenchymal glioblastoma, it could significantly facilitate drug development using customized targeted therapies for this patient population.

Elevation of serum YKL-40 is also associated with glioma grade. This result is supported by a study of YKL-40 mRNA and immunohistochemical expression in glioma tissue.[36] In addition, our data suggest that serum YKL-40 levels correlate with disease status on neuroimaging in patients with anaplastic glioma and GBM, but not in those with low-grade tumors.

However, we found very weak correlation between tumor size on MRI scan, as measured by contrast-enhancing areas for tumors or FLAIR hyperintensity areas for nonenhancing gliomas, and YKL-40 level. It is possible that these correlations between tumor size and serum YKL-40 levels would be stronger if analyses were restricted to the biological subtype of glioma that highly expresses YKL-40. Our prior study was unable to correlate serum YKL-40 levels and YKL-40 tumor expression by immunohistochemistry.[23] However, it is possible that serum YKL-40 level would correlate better with tumor mRNA expression, but we could not perform that analysis, as fresh frozen tumor tissue was not available for all patients in this study.

Our study shows that YKL-40 can be useful in assessing disease status and prognosis in patients with high-grade glioma regardless of the time point in their disease course. Our patients did not receive an identical treatment regimen, although those patients with GBM and anaplastic astrocytoma were treated routinely with standard radiotherapy and temozolomide as their initial regimen during the period of this study. In addition, the prognostic value of YKL-40 was still evident in 58 newly diagnosed GBM patients who were treated in a uniform manner in a phase II trial of radiation and temozolomide.[24]

In conclusion, we showed that longitudinal increases in serum YKL-40 levels are associated with worse survival and that the level may correlate with radiographic disease status in patients with anaplastic glioma and GBM. Serum YKL-40 is currently being incorporated into therapeutic clinical trials for gliomas. While our work identified that YKL-40 is a serum biomarker for prognosis in patients with high-grade gliomas, these studies will help validate the value of YKL-40 in determining response to treatment and early detection of progression or relapse. Finally, more preclinical studies are needed to understand the role of YKL-40 in glioma and cancer biology.

Conflict of interest statement. None declared.

Funding

Adília Hormigo received a grant from the Society for Memorial Sloan-Kettering Cancer Center.

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