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Outcome of patients with malignant glioma and synchronous or metachronous non-central nervous system primary neoplasms

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Abstract

Patients with malignant glioma who are also diagnosed with one or more primary neoplasms of other organs present a unique challenge in both determining prognosis and clinical management. The overlapping impact of the malignancies and their treatment result in confounding variables that may adversely affect optimal management of such patients. Additionally, the glioma-related characteristics and survival outcome of these patients is not well-defined. In this retrospective chart and data review from our longitudinal database, we identified patients with malignant glioma including anaplastic glioma and glioblastoma, diagnosed between January 2005 and June 2011, who were also diagnosed with other non-CNS primary neoplasms. Patients with known genetic syndromes were excluded. The data was analyzed to determine the clinical characteristics and glioma-related survival. A total of 204 patients with malignant glioma (165 glioblastoma and 39 anaplastic glioma) were identified. There was no significant difference in the overall survival or progression-free survival between patients with malignant glioma plus non-CNS primary neoplasm when compared with patients with malignant glioma only. In patients with glioblastoma and non-CNS malignancy, the duration between diagnosis of glioblastoma and non-CNS neoplasms did not significantly alter glioma-related survival. Patients with malignant glioma who were diagnosed with other non-CNS malignancy have survival outcome comparable to those with malignant glioma only. The duration between diagnosis of glioblastoma and diagnosis of non-CNS neoplasms did not affect survival. Further prospective studies specifically addressing survival and molecular characteristics of patients with malignant glioma plus non-CNS cancers are recommended.

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Compliance with ethical standards

Conflict of interest The authors declare that they do not have conflict of interest.

Keywords

Malignant glioma; Second primary malignancy; Prognosis; Characteristics

Introduction

Individuals with cancer are at increased risk of subsequently developing other primary malignancies [1]. In addition, recent advances in diagnosis and treatment of malignancies have resulted in improved survival of cancer patients, with increased chances of such patients being diagnosed with more than one primary malignancy. Patients with multiple primary malignant neoplasms were described as early as the end of the 19th century. Patients with malignant glioma who were also diagnosed with other non-CNS malignant neoplasms have been reported in small case series [2, 3], or individual case reports [4–6]. In addition, most clinical trials tend to exclude patients with malignant glioma who were recently diagnosed or treated for non-CNS primary malignancy, as these patients could potentially have complicated clinical courses and because the natural history and/or treatment could confound the measured outcome in glioma trials. Due to these factors, the patterns of occurrence of other primary malignancies in patients with malignant glioma (glioblastoma or anaplastic glioma) as well as the survival outcome of these patients are largely unknown. In this study we retrospectively investigated the survival outcome of patients with malignant glioma and other non-CNS primary cancers.

Methods

Patients

This retrospective chart review study was approved by the institutional review board (IRB) of the University of Texas MD Anderson Cancer Center through a waiver of consent. Data on 1547 patients who were diagnosed with WHO grade III anaplastic glioma (AG) (including anaplastic astrocytoma, anaplastic oligodendroglioma or anaplastic oligoastrocytoma) or WHO grade IV astrocytoma (GB) (including glioblastoma and gliosarcoma) between January 2005 and June 2011 were collected from our longitudinal database. Patients included in this study were adults with malignant gliomas who also had a diagnosis of one or more non-CNS primary neoplasms and had histologic confirmation of their cancer diagnosis. Patients with known genetic syndromes predisposing to multiple malignancies (e.g. Turcot's syndrome, Li-Fraumeni syndrome, etc.) were excluded due to their distinct clinical course. Collected data included sex, age at diagnosis of malignant glioma, date of diagnosis of malignant glioma, date of diagnosis of non-CNS neoplasms, date of first recurrence of malignant glioma, Karnofsky performance score (KPS), date of death or last follow-up, in addition to number of lesions including solitary or multiple lesions (which include multicentric glioma where there is no macroscopic connection between the lesions and multifocal glioma where there is evidence of macroscopic connectivity or cerebrospinal fluid dissemination). The time between diagnosis of malignant glioma and diagnosis of non-CNS primary neoplasm was determined for every patient. For comparison of survival outcomes, patients with malignant gliomas and without non-CNS

primary neoplasms were randomly chosen from the database and were used as control groups.

Treatment

Treatment characteristics recorded included extent of resection (biopsy only, subtotal or gross total resection) as determined by reviewing reports of post-operative imaging (MRI or CT), or operative reports (if imaging was not available). In addition, data related to radiation and/or chemotherapy was collected.

Statistical analysis

We estimated glioma-related survival in patients with GB or AG plus non-CNS primary neoplasms in comparison with control groups of patients with malignant glioma only (single primary). For the purpose of analyzing survival in relation to duration between diagnosis of non-CNS neoplasms and diagnosis of glioblastoma, we excluded those with date of diagnosis of non-CNS neoplasms either unknown or was more than 3 months after diagnosis of glioblastoma, as the survival of this group of patients will be biased by selection of this group of patients who survived long enough to develop a non-CNS neoplasm.

Overall survival (OS) and progression-free survival (PFS) times were estimated using the Kaplan–Meier method and the comparisons between or among patients' characteristics groups were assessed for significance using the log-rank test. Stratified log-rank test was used to evaluate effect of the time interval between a non-CNS tumor and the glioblastoma diagnosis on patient outcome. We used Martingale residual assessment to determine the point in the duration between diagnosis of non-CNS neoplasms and glioblastoma that, most likely, separates the patients into two distinct groups regarding survival. The patients were divided into two groups the analysis results that showed that the point of 4 years before diagnosis of glioblastoma is the most likely to separate the patients into two distinct groups regarding survival. All computations were carried out in SAS 9.3 (SAS Institute Inc., Cary, NC, USA) and SPlus 8.2 (TIBCO Software Inc) or R 2.15.1.

Results

Patient characteristics

A total of 1547 patients with malignant glioma were identified, of whom 204 patients were also diagnosed with non-CNS primary neoplasms (13.1 %); the primary CNS neoplasm in these patients included grade IV glioma in 165 patients and grade III glioma (33 anaplastic astrocytoma, 5 anaplastic oligodendroglioma and 1 anaplastic oligoastrocytoma) in 39 patients.

Non-CNS tumors

In patients with glioblastoma, the non-CNS primary cancers included skin (all types: n = 48, 29.1 %; melanoma: n = 14, 8.5 %), genitourinary (n = 36, 21.8 %), breast (n = 20, 12.1 %), gastrointestinal (n = 11, 6.7 %), thyroid (n = 9, 5.5 %) and hematological (n = 9, 5.5 %). Thirteen patients (7.8 %) were diagnosed with miscellaneous cancers. Nineteen patients (11.5 %) were diagnosed with more than one non-CNS primary neoplasm. In patients with

anaplastic glioma, the non-CNS primary cancers included skin (all types: $n = 13$, 33.3 %; melanoma: $n = 6$, 15.4 %), genitourinary ($n = 8$, 20.5 %), breast ($n = 6$, 15.4 %) and gastrointestinal ($n = 3$, 7.7 %). Seven patients (17.9 %) were diagnosed with miscellaneous cancers. Two patients (5.2 %) were diagnosed with more than one non-CNS primary neoplasm. The stage of non-CNS neoplasm was known in only 47 (28.5 %) patients with glioblastoma and 17 (43.6 %) patients with anaplastic glioma (Supplemental Table 1).

The duration between diagnosis of non-CNS neoplasm and diagnosis of glioblastoma ranged between 32.8 years prior to and 8.6 years after diagnosis of glioblastoma (median 2.1 years prior to diagnosis of glioblastoma). The duration between diagnosis of non-CNS neoplasm and anaplastic glioma ranged between 37.9 years prior to and 5.2 years after diagnosis of anaplastic glioma (median 2.5 years prior to diagnosis of anaplastic glioma).

Treatment of non-CNS neoplasm included surgery alone or with radiation and/or chemotherapy, in addition to chemotherapy and/or radiation without surgery (Supplemental Table 2). Patients who received treatment for non-CNS neoplasm concurrently with treatment or during surveillance of malignant glioma included 28 (17 %) patients with glioblastoma and 16 (41 %) patients with anaplastic glioma. In patients with glioblastoma, treatment of non-CNS neoplasm included surgery only ($n = 4$), radiation only ($n = 2$), chemotherapy only ($n = 8$), radiation and chemotherapy ($n = 1$), surgery and chemotherapy ($n = 9$), and surgery with radiation and chemotherapy ($n = 4$). In patients with anaplastic glioma, treatment of non-CNS neoplasm included

Clinical outcome

The median OS of patients with glioblastoma plus non-CNS cancers ($n = 165$, 18.7 months) was not significantly different from the control group ($n = 234$, 21.9 months) ($p = 0.10$) (Fig. 1). The percentage of censored patients in the group of patients with glioblastoma plus non-CNS cancers was 18.2 % ($n = 30$). The median OS varied according to the type of the tumor, with 25.4 months for skin cancers, 18.4 months for breast cancer, 17.8 months for thyroid cancer, 15.4 months for gastrointestinal cancer, 14.7 months for genitourinary cancers, 14.2 months for hematological cancers, 18.7 months for patients with more than one non-CNS cancers and 22 months for miscellaneous cancers. However, no statistically significant difference was detected between different groups ($p = 0.59$).

For patients with anaplastic glioma plus non-CNS neoplasms ($n = 39$), the median OS of patients was again not significantly different (Fig. 1S) from the median OS of the control group ($n = 46$) (42.4 months vs. 46.5 months, $p = 0.10$). The percentage of censored patients in the group of patients with anaplastic glioma plus non-CNS cancers was 35.9 % ($n = 14$). As with glioblastoma, the median OS of these patients also varied by cancer type and was 69.8 months in gastrointestinal cancers, 57 months in genitourinary cancers, 42.1 months in breast cancers, 23.9 months in skin cancers, 27.3 months in miscellaneous cancers and 60.1 months in patients with more than one non-CNS neoplasm. There was no statistically significant difference among these groups ($p = 0.16$).

In patients with glioblastoma plus non-CNS neoplasms, we investigated whether glioblastoma-related survival outcome is affected by the duration between diagnosis of non-

CNS neoplasm and diagnosis of glioblastoma. We excluded 13 patients from the survival analysis because the date of diagnosis of non-CNS neoplasms was unknown. We also excluded 15 patients who were diagnosed more than 3 months after diagnosis of glioblastoma as their survival will be biased by selection of those patients with glioblastoma who survived long enough (median survival of those 15 patient was 29.5 months) to develop a non-CNS neoplasm. A total of 137 patients with glioblastoma plus non-CNS neoplasms were included in the analysis in addition to a control group of 234 patients with glioblastoma only (Table 1). The median follow up time was 25.2 months (the range was 2.3–96 months). Patients with glioblastoma plus non-CNS neoplasms were divided into those who were diagnosed with non-CNS neoplasms within the period of 4 years before to 3 months after diagnosis with glioblastoma (GB plus non-CNS ≤ 4 years) and those who were diagnosed with non-CNS neoplasms more than 4 years before diagnosis of glioblastoma (GB plus non-CNS >4 years). There was no significant difference in OS between the two groups (median survival 17.4 months for GB plus non-CNS ≤ 4 years vs. 18.5 months for GB plus non-CNS >4 years, $P = 0.16$) (Fig. 2), neither when compared to the control group ($P = 0.2$). In addition, there was no significant difference in PFS between the two groups (median survival 6.6 months for GB plus non-CNS ≤ 4 years vs. 8.9 months for GB plus non-CNS >4 years, $P = 0.72$) (Fig. 2S), neither when compared to the control group ($P = 0.49$). We investigated the possibility that the differences in prognostic factors could have influenced survival results. We compared the overall survival of patients with GB plus non-CNS neoplasm with a prognostic factors-matched control group of patients with GB only ($n = 110$) (supplemental Table 5). There was no statistically significant difference in overall survival between the two groups (median survival was 20.8 months for the control group versus 19.8 months for the GB plus non-CNS neoplasm group, $P = 0.2$).

In patients with high-grade glioma and non-CNS neoplasm, we investigated whether glioma-related survival was affected by concurrent treatment of non-CNS neoplasm (either during active treatment or during the follow up of high-grade glioma). In patient with glioblastoma and non-CNS neoplasm, 28 patients were treated concurrently for non-CNS neoplasm and 137 patients did not receive concurrent treatment for non-CNS neoplasm. Although overall survival in the first group was higher than the second group, the difference was not statistically significant (median survival 31.2 versus 18.5 months, $P = 0.2$). In patients with anaplastic glioma and non-CNS neoplasm, 9 patients were treated concurrently for non-CNS neoplasm and 30 patients did not receive concurrent treatment for non-CNS neoplasm, with median overall survival of 43.9 and 38.6 months; respectively. There was no statistically significant difference between the overall survival in both groups ($P = 0.4$).

Univariable analysis demonstrated that age and KPS were the strongest predictors of OS and PFS (Table 2 and supplemental Table 3). Multivariable analysis demonstrated that age and KPS were significantly associated with OS (Table 3), while only KPS was associated with PFS (Supplemental Table 4). Neither co-existence of glioblastoma and non-CNS neoplasms nor duration between non-CNS neoplasm and glioblastoma diagnosis affected survival.

Discussion

The phenomenon of multiple malignant cancers was first observed by Billroth in the late nineteenth century [7]. Individual cases and small case series of patients with primary brain tumors and non-CNS neoplasms have been described, most frequently as a part of known genetic syndromes of multiple malignancies. The survival of patients with malignant glioma who were also diagnosed with non-CNS neoplasms, excluding those with known syndromes of multiple malignancies (i.e. sporadic), is largely unknown due to the lack of large case series, retrospective or prospective studies addressing this question. In addition, a subgroup of these patients, who were recently diagnosed or received treatment for non-CNS malignancy is excluded from most clinical trials. To the best of our knowledge, this is the largest study of patients with malignant glioma plus non-CNS malignancy. We did not include patients with low-grade gliomas because these tumors are less common, the median age of patients at diagnosis is less and median survival is relatively longer than malignant gliomas.

The prevalence of non-CNS primary neoplasms among patients with malignant glioma was higher than expected, when compared to the prevalence of cancer in general population (approximately 3.9 %) or when compared to the 8%-prevalence of patients with more than one primary malignancy among cancer survivors population in the US between 1975 and 2001 [8]. A previous study of 329,705 autopsy cases in the Japan autopsy registry from 1975 to 1984 showed 123 double cancers and 12 cases of triple cancers cases that included primary brain tumor, with most frequent other sites for primary cancers being thyroid (23 %), stomach (15 %), lungs (12 %) and colon (10 %) [9]. Another retrospective study showed 3 cases of 14 patients with second malignant neoplasms in 509 long-term survivors of osteosarcoma [10]. The causes of increased prevalence of other primary malignancies in cancer patients are unknown, but one possible explanation is that improved survival of cancer patients increases their risk of developing a second primary malignancy. Previous studies suggested that diagnosis with cancer at a younger age may predispose patients to a higher risk of other malignancy [1]. Another possible mechanism is the presence of an unknown genetic predisposition to multiple cancers. Examining the molecular profile of these tumors may help identifying this potential mechanism.

As expected, age and performance status were the strongest predictors of survival outcomes in this population of patients. Other factors, including co-existence of glioblastoma and non-CNS neoplasm and duration between glioblastoma and non-CNS neoplasm diagnosis, did not affect survival outcomes. Since multifocal glioblastoma may have a different outcome, this factor was included in analyzing survival, and it did not affect survival outcomes. However, there were a significantly higher percentage of those with three or more enhancing glioma lesions in patients with non-CNS neoplasms in comparison to patients without non-CNS neoplasm. The significance of this finding is unknown and more studies are required.

Unexpectedly, the survival of patients with glioblastoma plus non-CNS primary malignancy was not statistically different from those patients without other malignancy indicating that diagnosis with other non-CNS cancer may not adversely affect the survival outcome in

glioblastoma. One possible explanation is that the survival of patients with glioblastoma is too poor to be adversely affected by other cancers.

The duration between the diagnosis of non-CNS neoplasm and glioblastoma did not affect survival outcome within our patients with glioblastoma plus non-CNS malignancy. This is relevant in the light of the common practice of excluding patients from clinical trials based on recent diagnosis or treatment of non-CNS cancers. It is possible that these patients may benefit from revising the criteria of exclusion in the clinical trials or initiating clinical trials that are designed to allow their participation within specific contexts such as an expansion cohort.

Patients with glioblastoma plus non-CNS cancers appear to have a higher incidence of multifocal or multicentric glioblastoma than those with glioblastoma only. It is not certain whether this is by chance or whether the biology of glioblastoma is different in patients with non-CNS cancers. Previous studies showed evidence of signaling-interaction and modulation of microenvironment between different malignancies [11]. Further investigations to characterize the molecular profile of glioblastoma in patients with non-CNS cancers will be needed to better characterize this finding.

There are several limitations in this study. The study is retrospective and other unknown confounding factors may have affected the results. The low number of patients with anaplastic glioma did not allow us to fully analyze their survival data. The relatively small overall number of patients—because of the infrequent diagnosis of more than one primary neoplasm in one patient—and multiple areas of comparisons are two additional problems that decrease the power of the study. There was a trend for differences, although not statistically significant, in glioma-related survival among different groups of non-CNS neoplasms, and further study on a larger number of patients might allow a better characterization of the survival pattern of these patients. Lastly, there was no data available to assess whether these patients had germ line mutations that may have influenced development of multiple primaries.

In summary, this retrospective study shows that patient with malignant glioma plus other non-CNS neoplasms comprise a significant subpopulation with unexpected survival outcomes. Further translational and clinical trials are necessary to understand prognostic factors and therapeutic strategies for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Frodin JE, Ericsson J, Barlow L. Multiple primary malignant tumors in a national cancer registry. *Acta Oncol.* 1997; 36(5):465–469. [PubMed: 9292741]
2. Nagane M, Shibui S, Nishikawa R, et al. Triple primary malignant neoplasms including a malignant brain tumor: report of two cases and review of the literature. *Surg Neurol.* 1996; 45(3):219–229. [PubMed: 8638217]

3. Piccirilli M, Salvati M, Bistazzoni S, et al. Glioblastoma multiforme and breast cancer: report on 11 cases and clinicopathological remarks. *Tumori*. 2005; 91(3):256–260. [PubMed: 16206651]
4. Pöyhönen L, Heikkinen J, Vehkalahti I. Two different primary tumours of the brain in a patient with breast cancer. *Eur J Nucl Med*. 1979; 4(6):483–484. [PubMed: 230047]
5. Lamaida E, Caputi F, Rapanà A, Bracale C, Graziussi G. Waldenström's macroglobulinemia associated with glioblastoma. A case report. *Rev Neurol*. 1996; 152(10):637–639. [PubMed: 9033958]
6. Freedman RA, Wirth LJ, Chirieac LR, et al. Glioblastoma in a patient with early-stage tonsil cancer. *J Clin Oncol*. 2007; 25(19):2848–2850. [PubMed: 17602090]
7. Moertel CG. Incidence and significance of multiple primary malignant neoplasms. *Ann N Y Acad Sci*. 1964; 114:886–895.
8. Mariotto AB, Rowland JH, Ries LA, et al. Multiple cancer prevalence: a growing challenge in long-term survivorship. *Cancer Epidemiol Biomark Prev*. 2007; 16(3):566–571.
9. Hayashi K, Ohtsuki Y, Sonobe H, et al. An autopsy case of triple primary cancers consisting of glioblastoma multiforme of the pons, colon cancer and rectal carcinoid—a statistical analysis of cases of brain tumor combined with other primary cancers in Japan autopsy annuals. *Gan No Rinsho*. 1987; 33(14):1846–1853. [PubMed: 2826842]
10. Aung L, Gorlick RG, Shi W, et al. Second malignant neoplasms in long-term survivors of osteosarcoma: Memorial Sloan-Kettering Cancer Center experience. *Cancer*. 2002; 95(8):1728–1734. [PubMed: 12365021]
11. Elkabets M, Gifford AM, Scheel C, et al. Human tumors instigate granulysin-expressing hematopoietic cells that promote malignancy by activating stromal fibroblasts in mice. *J Clin Invest*. 2011; 121:784–799. [PubMed: 21266779]

Fig. 1. Kaplan–Meier estimates of overall survival (OS) by glioblastoma with non-CNS neoplasms (*broken line*) and glioblastoma only (*black line*)

Fig. 2.

Kaplan–Meier estimates of overall survival (OS) by glioblastoma with non-CNS neoplasms diagnosed within the period of 4 years before to 3 months after diagnosis with glioblastoma (*broken line*) and those who were diagnosed with non-CNS neoplasms more than 4 years before diagnosis of glioblastoma (*black line*)

Table 1

Patient characteristics

Characteristic	GB only	GB plus non-CNS neoplasm	p value
Age (years)			
Median (range)	51.6 (18–78.6)	58.86 (20.6–84.8)	< 0.001 *
Resection			
Biopsy	9.4 %	13.9 %	0.001 *
Gross total	70.1 %	51.1 %	
Subtotal	20.5 %	35 %	
KPS			
100	22.2 %	18.2 %	0.1
70–90	67.1 %	77.3 %	
30–60	10.7 %	4.5 %	
Number of lesions			
1	85.9 %	79 %	0.02 *
2	12 %	13 %	
3	2.1 %	8 %	

KPS Karnofsky performance score

* Statistically significant difference

Table 2

Univariable Cox model for overall survival

Covariate	Estimate	SE	Hazard ratio	95 % CI	p value
Age	0.016	0.005	1.016	1.007 1.026	0.001 [*]
Multi-tumor					
GB versus GB Plus non-CNS cancer	-0.089	0.121	0.915	0.722 1.159	0.4
Duration between diagnoses					
GB plus non-CNS > 4 year versus GB only	0.214	0.140	1.239	0.941 1.631	0.1
GB plus non-CNS 4 year versus GB only	-0.114	0.182	0.892	0.625 1.274	0.5
Resection					
Gross total versus biopsy	-0.302	0.195	0.739	0.505 1.083	0.12
Subtotal versus biopsy	-0.109	0.214	0.897	0.590 1.363	0.1
KPS					
30–60 versus 100	1.247	0.236	3.481	2.193 5.525	<0.001 [*]
70–90 versus 100	0.410	0.149	1.507	1.125 2.017	0.006 [*]
Number of lesions					
1 versus 3	-0.471	0.289	0.624	0.354 1.100	0.10
2 versus 3	-0.067	0.327	0.936	0.493 1.775	0.8

95 % CI: 95 % confidence interval

KPS Karnofsky performance score

^{*} Statistically significant difference

Table 3

Multi-covariable COX model for overall survival

Covariate	Estimate	SE	Hazard ratio	95 % CI	p value
Age	0.014	0.005	1.014	1.004–1.023	0.005 [*]
Duration between diagnoses					
GB plus non-CNS > 4 year versus GB only	0.264	0.147	1.302	0.976–1.737	0.07
GB plus non-CNS 4 year versus GB only	−0.172	0.191	0.842	0.579–1.224	0.3
KPS					
30–60 versus 100	1.276	0.243	3.582	2.225–5.768	< 0.001 [*]
70–90 versus 100	0.395	0.151	1.484	1.104–1.994	0.008 [*]

95 % CI: 95 % confidence interval

KPS Karnofsky performance score

^{*} Statistically significant difference