福岡大医紀（*Med. Bull. Fukuoka Univ.*）：30(3)，159–168，2003

Tumor Location Affecting Survival in Patients with Supratentorial Astrocytic Tumors

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Abstract : Object : To assess the value of tumor location as a prognostic factor in patients suffering from supratentorial astrocytic tumors.

Methods : We retrospectively evaluated 117 patients in terms of the prognostic factors influencing survival after a surgical resection and external beam radiotherapy, with or without adjuvant chemotherapy. Survival was evaluated using a univariate analysis, and a multivariate analysis by the proportional hazards method proposed by Cox and was estimated by Kaplan–Meier survival analysis using both the generalized Wilcoxon and log–rank tests.

Results : Although the prognosis was strongly influenced by histological grade, the frontal lobe and non–eloquent areas as primary sites were shown by a multivariate analysis to be significant positive prognostic factors, when the survival was evaluated the factors excluding the histological grade. In grade 2 tumors, the operative resectability and non–eloquent area involvement positively influenced the survival time, but a primary location in the cerebral lobes did not. In grade 3 and 4 tumors, the survival time was increased for frontal lobe tumors, however, the difference was statistically insignificant, and radiotherapy was the only statistically significant prognostic factor influencing survival.

Conclusion : Cytoreductive surgery, which can be carried out in non–eloquent areas and might be influenced by the primary site of the tumor, is important to obtain an increased survival for patients with grade 2 tumors. With grade 3 and 4 tumors, the prognosis was not found to be influenced by the primary site of the tumor. Therefore, the authors recommend either a partial or subtotal removal of the tumor and postoperative irradiation above 55 Gy under in order to obtain a relatively good quality of life if the astrocytic tumor is located in a critical area.

Key words : astrocytoma, anaplastic astrocytoma, glioblastoma, tumor location, prognostic factor

Introduction

In the treatment of astrocytic tumors, it is important to maintain good quality of life with a minimal decline in the performance status while also trying to improve the survival rate. Multiple prognostic factors have been reported for astrocytic tumors, including age, race, gender, duration of symptoms, primary site of tumor, histologic type, extent of surgery and irradiation.[1)–34)] Some investigators have reported that the extent of surgery influences survival time,[1)3)6)11)12)14)21)22)25)]

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[27)-29)32)33)] and there have been a few reports indicating that the primary site of the tumor is a prognostic factor in survival.[6)10)13)20)23)-25)33)] However, few details in this regard have so far been provided.

The authors retrospectively evaluated the potential prognostic factors for astrocytic tumors, with special consideration of the primary tumor site, which might have a bearing on tumor resectability as well as the postoperative quality of life.

Patients and Methods

Between 1979 and 1996, 117 patients in our institution underwent either initial surgery or a biopsy confirming a diagnosis of astrocytic tumor. The tumors were classified by histological type based on the World Health Organization (WHO) morphology codes[35)]: glioblastoma multiforme (grade 4), anaplastic astrocytoma (grade 3) and astrocytoma (grade 2). The aim of surgical treatment in all patients was the removal of as much of the tumor tissue as possible. The extent of a surgical resection was determined by reviewing the information in the surgical records. Surgeries were classified as either a biopsy, partial, subtotal or total resections. A biopsy was performed on tumors located in critical areas. Information regarding postoperative radiation therapy was available for all patients, and conventional external beam radiotherapy and chemotherapy were performed for anaplastic astrocytoma and glioblastoma multiforme. A histologic analysis confirmed the tumor diagnosis in all 117 patients, which included 23 patients with astrocytoma, 34 with anaplastic astrocytoma and 60 with glioblastoma multiforme. Pilocytic astrocytomas (grade 1) were excluded in this analysis. A statistical analysis was performed to ascertain the prognostic importance of the following variables: age, histological grade, primary site, extent of surgery, radiotherapy, and chemotherapy. The primary sites were subdivided into the right and left cerebral hemispheres and then were analyzed according to the following areas: frontal lobe, temporal and occipital lobes, parietal lobe and corpus callosum, thalamus, eloquent and non-eloquent areas. These areas have been previously reported to influence tumor resectability.

Statistical Methods

Potential prognostic factors with adequate data to permit univariate and multivariate analyses of patient survival included: age (<20 yrs vs. 20-64 yrs vs. >65 yrs), type of surgery (biopsy vs. partial vs. subtotal vs. total resection), radiotherapy (none vs. <54 Gy vs. >55 Gy), chemotherapy (vs. none).

The endpoint of this study was the postoperative survival time. The prognostic significance of each individual factor was evaluated using computer-generated survival curves estimated by the method of Kaplan and Meier[36)]. Group survival differences were assessed by univariate analysis using the proportional hazards model and according to both the generalized Wilcoxon (Breslow)[37)] and log-rank (Mantel-Cox) tests.[38)] The primary tumor sites were evaluated using a multivariate survival analysis, based on Cox proportional hazard model.

According to the histological grade, survival differences for each of the primary sites, the operative resectability, and radiotherapy were estimated by the method of Kaplan and Meier, with group survival differences assessed using both the generalized Wilcoxon and log-rank tests. Univariate and multivariate analyses were performed using a computer algorithm based on the statistical analysis system (SAS).

Results

A univariate analysis showed the histological grade ($p=0.0001$), primary site ($p=0.0001$), type of surgery ($p=0.0018$), non-eloquent area involvement ($p=0.0025$), and radiotherapy ($p=0.0319$) to positively influence the 1-year and 3-year survival rates (Table 1). The fidings regarding the hemisphere and chemotherapy never reached levels of statistical significance. For a clearer understanding of the influence of each cerebral lobe and the area involvement, the survival

Table 1. Univariate analysis for prognostic factors.

	Alive	Death	Survival rates %		mean survival (days)	P-value
			1 year	3 years		
Age						0.0001
4–19	1	6	57.1	14.3	384	
20–39	16	22	89.3	63.8	2,148	
40–64	7	51	70.0	36.4	936	
65≦	1	13	14.3	7.1	177	
Histological grade						0.0001
grade 2	13	10	100.0	81.4	2,968	
grade 3	9	25	85.1	57.1	1,297	
grade 4	2	58	46.7	14.7	479	
Surgery						0.0018
biopsy	1	10	63.6	27.3	656	
partial	7	42	70.6	42.5	1,158	
subtotal	7	30	54.3	36.9	998	
total	10	10	100.0	59.2	1,493	
Radiation Therapy						0.0319
none	2	10	16.7	16.7	67	
＜55 Gy	6	20	61.6	40.9	1,112	
55≦	17	62	78.3	44.5	1,366	
Chemotherapy*						0.0864
none	13	34	66.0	48.7	1,606	
yes	9	53	71.0	35.0	964	
Tumor location						
left cerebrum	12	42	70.1	43.3	1,404	0.9703
right cerebrum	11	44	70.9	37.6	1,059	
corpus callosum	2	6	62.5	50.0	730	
F**	17	41	82.7	56.0	1,751	0.0001
T＋O	6	25	26.9	26.9	922	
P＋C	2	19	28.6	28.6	630	
Tha	0	7	14.3	14.3	478	
eloquent area	4	40	59.1	27.1	809	0.0025
non-eloquent area	21	52	76.6	49.4	1,458	

*Eight cases were excluded here due to unavailability of their clinical records concerning postoperative chemotherapy.
**F, frontal ; T, temporal ; O, occipital ; P, parietal ; C, corpus callosum ; Tha, thalamus

curves were evaluated. The frontal lobe and non-eloquent area as primary sites had a significantly positive impact on survival, as shown in Figure 1.

The univariate and multivariate adjusted hazard ratios for survival are presented in Table 2 for each cerebral lobe and in Table 3 for the area of involvement. In both cases, the histological grade had the greatest influence on prognosis ; therefore, suvival was evaluated with other factors excluding the histological grade based on the multivariate adjusted hazard ratios. The cerebral lobe sites showed a significantly positive influence

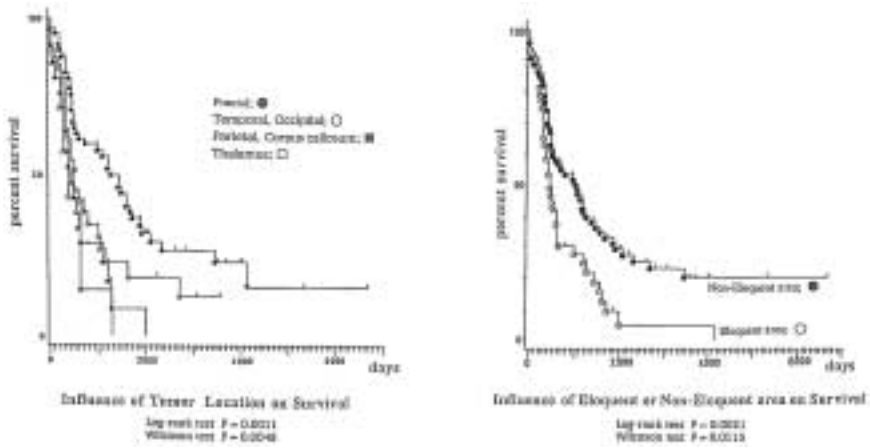

Fig. 1. The influence of tumor location (left) and the area of involvement (eloquent / non-eloquent area) (right) on the survival are in all 117 patients with supratentorial astrocytic tumors.

Table 2. Univariate and multivariate adjusted hazard ratios for survival based on the cerebral lobes.

Variable and model	Hazard ratio	95%CI	P-value
Univariate	1.527	1.235–1.888	0.0001
Adjusted for age	1.472	1.180–1.837	0.0006
Adjusted for grade	1.123	0.896–1.406	0.3141
Adjusted for surgery	1.427	1.126–1.808	0.0001
Adjusted for radiation therapy	1.511	1.212–1.883	0.0001
Adjusted for chemotherapy	1.492	1.196–1.862	0.0001
Adjusted for age, surgery, radiation, and chemotherapy	1.389	1.265–1.814	0.0016
Adjusted for age, grade, surgery, radiation, and chemotherapy	1.231	0.634–1.363	0.2358

Table 3. Univariate and multivariate adjusted hazard ratios for survival based on the area of involvement, eloquent/non-eloquent areas.

Variable and model	Hazard ratio	95%CI	P-value
Univariate	0.521	0.342–0.795	0.0021
Adjusted for age	0.541	0.355–0.825	0.0038
Adjusted for grade	0.755	0.491–1.159	0.1975
Adjusted for surgery	0.644	0.400–1.036	0.0684
Adjusted for radiation therapy	0.486	0.316–0.747	0.0015
Adjusted for chemotherapy	0.497	0.321–0.771	0.0011
Adjusted for age, surgery, radiation, and chemotherapy	0.634	0.326–0.746	0.0430
Adjusted for age, grade, surgery, radiation, and chemotherapy	0.836	0.447–1.564	0.2110

on survival when adjusted for age ($p=0.0006$), surgery ($p=0.0001$), radiotherapy ($p=0.0001$) and chemotherapy ($p=0.0001$). The non-eloquent area involvement showed a significantly positive influence on survival when adjusted for age ($p=0.0038$), radiotherapy ($p=0.0015$) and chemotherapy ($p=0.0011$).

The survival curves were created for significant variables based on the histological

Table 4. Summary of the prognostic significance of each individual factor based on the histological grades, as evaluated using computer-generated survival curves determined by the Kaplan-Meier method (see Figs. 2, 3, 4, 5).

	grade 2 (Log-rank/Wilcoxon) mean survival (days)	grade 3 (Log-rank/Wilcoxon) mean survival (days)	grade 4 (Log-rank/Wilcoxon) mean survival (days)
Tumor location			
	(0.2187/0.2583)	(0.1410/0.2302)	(0.5765/0.6993)
F	3,117.8	1,411.0	571.7
T+O	1,004.8	1,265.8	397.7
P+C	604	711.7	566.1
Tha	—	766.5	363.6
	(0.0174/0.0093)	(0.1543/0.2721)	(0.9046/0.7913)
eloquent area	2,239.6	1,010.4	476.7
non-eloquent area	2,888.4	1,434	507.2
Surgery	(0.0029/0.0106)	(0.2925/0.3316)	(0.1801/0.0687)
biopsy	—	986.6	379.8
partial	2,150.5	1,063.5	413.1
subtotal	2,355	1,798.9	468
total	—	1,587.4	1,007.8
Radiation therapy	(0.5138/0.6059)	(0.0001/0.0001)	(0.0001/0.0001)
none	—	38.0	45.9
<55 Gy	1,374.2	1,677.8	461.6
55 Gy<	2,861.7	1,232.5	621.1

F, frontal ; T, temporal ; O, occipital ; P, parietal ; C, corpus callosum ; Tha, thalamus

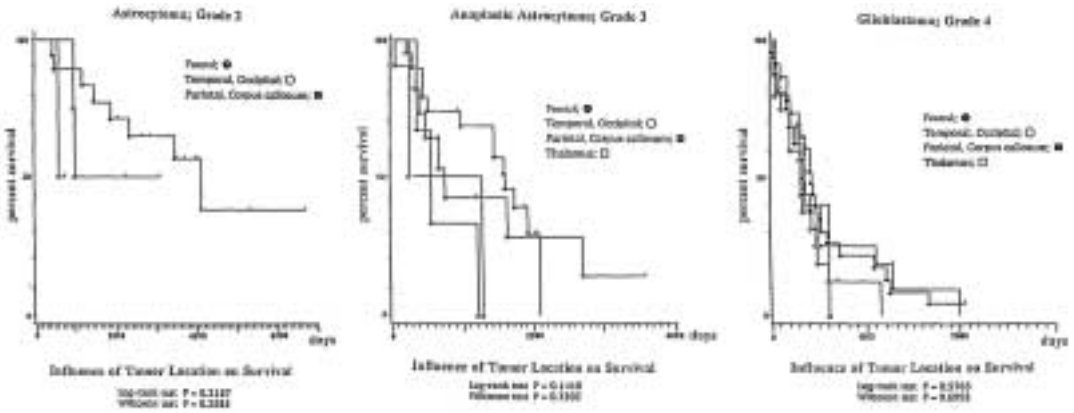

Fig. 2. The influence of tumor location on survival based on the histological grade are shown for patients with supratentorial astrocytic tumors.

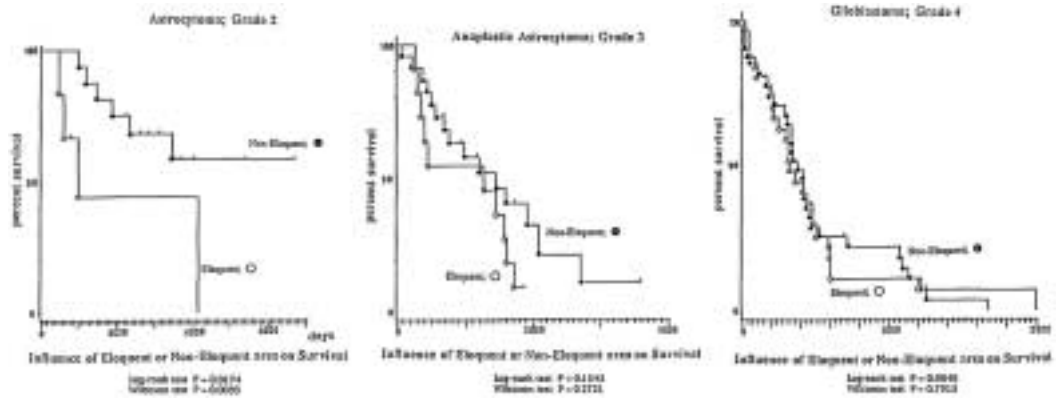

Fig. 3. The influence of the area of involvement (eloquent/non-eloquent) on survival based on the histological grade are shown for patients with supratentorial astrocytic tumors.

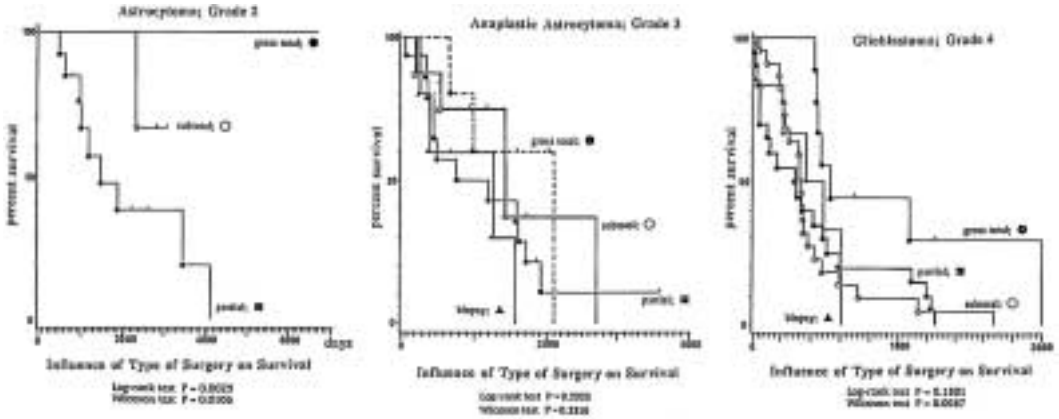

Fig. 4. The effect of the type of surgery on survival based on the histological grade are shown for patients with supratentorial astrocytic tumors.

grade (Table 4). For the cerebral lobes, the difference in survival was not statistically significant between the grades; however, the mean survival time was the longest for patients with tumors in the frontal lobe (Fig. 2). For grade 2 tumors, a statistically significant positive relationship was seen between the survival time and either the non-eloquent area involvement ($p<0.05$; Fig. 3) or a surgical resection ($p<0.01$; Fig. 4). With grade 3 and 4 tumors, no statistically significant positive relationship existed between the survival time and either the area of involvement (Fig. 3) or the surgical resection (Fig. 4). For grade 3 tumors, the mean survival time was 1010.4 days when the primary site was an eloquent area and 1434 days when it was a non-eloquent area, in contrast for grade 4 tumors, the survival time was 476.7 days when the primary site was an eloquent area and 507.2 days when it was a non-eloquent area. In terms of a surgical resection, grade 3 tumors showed a mean survival time of 1,587.4 days after a total resection and 1,063.5 days after a partial resection, and grade 4 tumors showed a mean survival time of 1,007.8 days after a total resection and 413.1 days after a partial resection. Concerning radiotherapy, the mean survival time was 1,232.5 days for

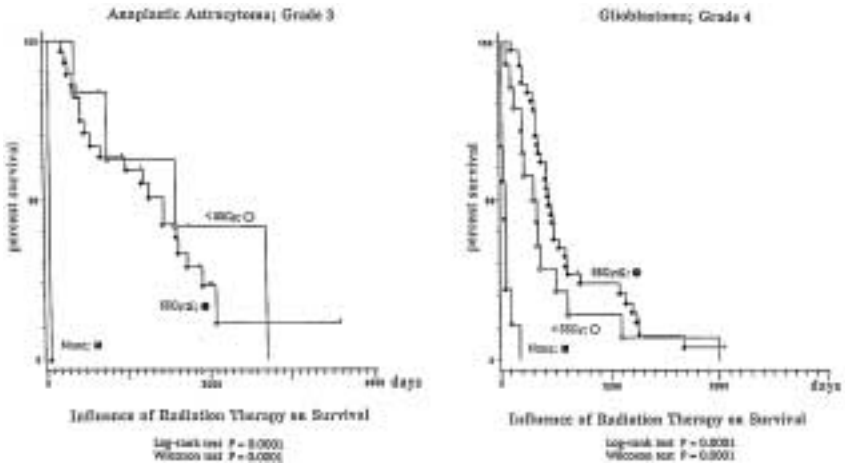

Fig. 5. The effect of radiation therapy on survival are shown for grade 3 and grade 4 patients.

patients with grade 3 tumors and 621.1 days for patients with grade 4 tumors irradiated at over 55 Gy, thus indicating a significant difference in the survival time between grade 3 and 4 tumors (Table 4, Fig. 5).

Discussion

Multiple prognostic factors have been reported in the literature for patients with astrocytic tumors, excluding pilocytic astrocytoma.[1)–13)15)17)–20)23)–27)29)–34)] Among these factors, age, initial performance status, histological grade, extent of surgery and radiotherapy have all been reported to be important prognostic indicators influencing survival. The primary site and its influence on tumor resectability have been evaluated prognostically.[6)8)10)13)14)20)–25)33)] The EORTC Brain Tumor Group,[7)] Jeremic et al.,[13)] Kowalczuk et al.,[15)] Roth and Elvidge[23)] and Scanlon and Taylor[24)] reported the frontal lobe to be the primary site associated with an increased survival for patients with malignant glioma. In contrast, Baker et al.[3)] and Wurschmidt et al.[34)] indicated no prognostic difference between the cerebral lobes. Simpson et al.[25)] concluded an age under 40 years, a high Karnofsky performance status, primary location in the frontal lobe and radical removal to be the best indicators for a good prognosis in glioblastoma patients.

We evaluated survival in patients with astrocytic tumors based on the tumor location and histological grade. Although it was not statistically positive for each tumor grade, the mean survival time was longer in patients with tumors in the frontal lobe than in patients with tumors in other lobes. Jelsma et al.[12)] evaluated the survival with respect to central and non-central sites, and Vecht et al.[27)] evaluated survival with respect to each cerebral lobe. They both suggested thet survival time to be longer for patients with tumors at sites not influencing resectability than for patients with tumors in critical areas. Devaux et al.[6)] reported the median survival time to be longer for patients with cortical tumors than for patients with midline tumors (cortical site, 135.4 weeks vs midline, 27.7 weeks; grades 3 and 4). No differences in survival time were reported between patients with tumors in different cerebral lobes[33)] or between patients with tumors in a cerebral lobe or midline side.[17)] However, patients with tumors in the thalamus, basal ganglia and corpus callosum have shown a poorer survival than patients with tumors in the cerebral lobes. Stelzer et al. reported the corpus callosum to be the poorest primary site with respect to prognosis.[26)]

There have been quite a few reports on the median survival time for patients with astrocytic tumors at various primary sites,[6)12)13)20)23)-25)33)] but it is still unclear as to whether or not the primary site influences survival time. We evaluated the survival time for the patients with astrocytic tumors at each location, namely, the left and right cerebral hemispheres, each cerebral lobe, and eloquent and non-eloquent areas. Based on the tumor grade, statistically no significant difference was observed in the median survival time between the cerebral lobes. However, the frontal lobe and non-eloquent area as primary sites had a statistically positive impact on survival for patients with grade 2 tumors, and resectability, influenced by the primary site, also positively influenced the survival time for grade 2 patients.

For the patients with grade 3 and 4 tumors, the survival time increased depending upon resectability, as seen in the survival curves, but the difference was not statistically significant. However radiotherapy at a dose of over 55 Gy was found to be associated with a longer survival than were the other variables for grade 4 patients.

Conclusion

We conclude that for grade 2 tumors, an increased survival is influenced by resectability, which depends upon the primary site. In contrast, for grade 4 tumors, an increased survival is influenced by the total removal and radiotherapy over 55 Gy. However, the mean survival times are so short that we recommend either a partial or subtotal removal of the tumor following radiotherapy over 55 Gy to maintain a relatively good quality of life.

Acknowledgments

We thank Noriya Taki, PhD, (Statistical Analysis of Medicine, Fukuoka, Japan) for useful advice on the statistical analyses.

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(Received on May 10, 2003,
Accepted on June 10, 2003)