Supratentorial Low-Grade Astrocytoma

Correlation of Computed Tomography Findings with Effect of Radiation Therapy and Prognostic Variables

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Background. **In supratentorial low-grade astrocytoma, radiation therapy effects and prognostic factors, especially with respect to computed tomography (CT) findings, are not yet well established. A retrospective analysis of 119 patients with this disease (histologically confirmed ordinary astrocytoma) therefore was conducted.**

Methods. **Between 1965 and 1989, 101 patients received postoperative radiation therapy, whereas 18 patients received surgery alone. Radiation was directed to the tumor plus a 1- to 3-cm margin in almost all cases; the dose range was 41 to 66 Gy (mean, 57 Gy). CT scan was performed before treatment on 74 patients. Postoperative survival rates were compared by both univariate and multivariate analyses.**

Results. **The 5- and 10-year survival rates for the irradiated group were 60% and 41%, respectively, which were significantly better than those for the surgery-alone group (37% and 11%, $P = 0.048$). Among various potential prognostic factors for the irradiated patients, only a lower age was associated with a better prognosis. Sex, tumor site (deep-seated or not), extent of surgery, radiation dose and field, and adjuvant chemotherapy did not influence the prognosis significantly. Among various CT findings, a clear tumor margin, a maximum tumor area less than 25 cm^2, presence of a cyst, and lack of mass effect were associated with a better prognosis on univariate analysis (P = 0.02–0.12), but contrast enhancement was not related to prognosis. On multivariate analysis, however, mass effect was the only significant factor.**

Conclusions. **Radiation therapy appears definitely to be effective in improving the prognosis for low-grade astrocytoma. Younger age, and the absence of mass effect determined by CT, were associated significantly with a better prognosis. *Cancer* 1993; 72:190–5.**

Key words: brain neoplasm, low-grade astrocytoma, radiation therapy, prognostic factor, computed tomography.

Supratentorial low-grade astrocytoma is a relatively rare disease, and not many reports have been published on its treatment. Accordingly, controversy still exists with respect to the role of radiation therapy treatment of this disease, as well as general prognostic factors. Radiation therapy generally is thought to be quite effective, but some studies have found no benefit with radiation.[1,2] Unfortunately, there has been no randomized trial examining the value of radiation therapy, and such a trial would be ethically impossible to perform. Accordingly, the first aim of this study was to evaluate the efficacy of radiation therapy by a retrospective analysis.

A number of prognostic factors for this tumor have been reported, but they differ from study to study. Generally, age is considered to be an important factor,[2–7] but no consensus has been obtained as to other factors, including sex, site, extent of surgery, radiation dose and field, and the use of chemotherapy. Most previous series reported have included special types of astrocytoma with a more favorable prognosis (cerebellar astrocytoma, pilocytic astrocytoma, xanthoastrocytoma, and the like) together with the common type, which has a relatively poor prognosis,[8,9] resulting in uncertainty in identifying the true prognostic factors. Therefore, the

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second purpose of this study was to analyze various potential prognostic factors for ordinary astrocytoma, excluding those special subtypes with a favorable prognosis.

Although this disease is known to exhibit a variety of features on computed tomography (CT), virtually no detailed reports exist on the correlation between CT findings and prognosis. Since the introduction of CT in 1976 at our hospital, a large number of patients have been treated, so we also evaluated the relationship of CT findings to prognosis.

Patients and Methods

All the pathologic specimens of intracranial astrocytic tumor treated after 1965 at our hospital were reviewed and reclassified into glioblastoma, anaplastic astrocytoma, and low-grade astrocytoma. The results of treatment were reported previously for the former two tumors.[10] Excluding cerebellar astrocytoma, optic glioma, brain stem glioma, pilocytic astrocytoma, giant cell astrocytoma, and xanthoastrocytoma, the remaining supratentorial astrocytomas were reviewed in this study. Seven patients whose tumors had an oligodendroglioma component (astrocytoma was dominant) also were included. Two patients lost to follow-up within 3 months, and three patients who died within 1 month after surgery were excluded, leaving 119 patients treated between 1965 and 1989. Among them, 101 received postoperative radiation therapy, whereas 18 did not owing to decisions of the attending neurosurgeons or the reluctance of the patients and their families. All 18 patients were in a condition such that they could have been irradiated if necessary. The clinical characteristics of the patients are shown in Table 1. All patients studied survived for at least 3 months after surgery. The minimum follow-up period for the patients living at the time of writing was 2.5 years.

Radiation was given using a cobalt 60 machine until 1980, and using 10-MV x-rays from a linear accelerator thereafter. It was delivered via parallel opposing, rectangular, or three- or four-field methods with 1.5 to 2 Gy as the daily fraction. The radiation policy remained almost unchanged throughout the study period. The radiation field covered the tumor plus a 1- to 3-cm margin in most cases; a whole-brain field was used in only two patients. In general, larger fields were used in the post-CT era than in the pre-CT era (Table 1). The total radiation dose ranged between 41 and 66 Gy, with a mean of 57.0 Gy. Ninety-four patients received 50 Gy or more, but only five patients received more than 61 Gy (because of large or aggressive tumors).

Both plain and contrast-enhanced CT was performed before surgery, usually using a 1-cm slice thickness, in 67 irradiated and 7 nonirradiated patients since 1976. The tumor size was defined as the maximum tumor (or low-density) area on sequential CT slices, and a mass effect was judged to be positive when midline shift or distortion of the ventricular system was observed. The clarity of the tumor (or low-density area) margin, and the presence or absence of contrast-enhancement and cyst formation were evaluated.

Twenty-two patients received adjuvant chemotherapy. The most common agent used was ACNU (1-[4-amino-2-methyl-5-pirimidinyl]-methyl-3-[2-chloroethyl]-3-nitrosourea hydrochloride) given intraarterially (50 mg/m^2) or intravenously (100 mg/m^2) before or after radiation therapy. A regimen of intraarterial bromodeoxyuridine and methotrexate[10] was given to five patients. The other agents used were vincristine, procarbazine, 5-fluorouracil, and cyclophosphamide.

The effect of therapy was evaluated by the survival time after operation because all known deaths were due directly to or related to tumor regrowth. Survival curves were calculated by the Kaplan–Meier method and differences in survival were assessed by the generalized Wilcoxon test. Various potential prognostic factors also were evaluated by multivariate analysis using the Cox proportional hazard model. All these statistical analyses were carried out using a computer program (HALBAU, Gendaisuugakusha, Kyoto, Japan).

Results

Univariate Analysis

The 5- and 10-year survival rates were 60% and 41%, respectively, for the 101 irradiated patients, whereas they were 37% and 11% for the 18 nonirradiated patients (Fig. 1). The difference in survival was significant ($P = 0.048$).

The survival rates for the irradiated group in relation to various potential prognostic factors are shown in Table 2. Among all these factors, age was the only one found to be significant, with a lower age being associated with a better prognosis (Fig. 2). Survival rates tended to be higher for the 67 patients treated in the post-CT era than for the 34 patients treated in the pre-CT era ($P = 0.061$). Radiation dose and field size did not influence the prognosis, probably because patients with larger tumors tended to receive higher radiation doses delivered to larger fields. Sex, extent of surgery, chemotherapy, and tumor site (deep-seated or not) also had no influence on prognosis.

The survival in relation to various CT features is shown in Table 3 and Figures 3 through 5. A mass effect

Table 1. Patient Characteristics

	Surgery alone	Radiation therapy		
		Total	*Pre-CT*	*Post-CT*
No. of patients	18*	101	34	67
Male:female	11:7	65:36	21:13	44:23
Mean age (yr) (range)	37 (21–61)	34 (3–62)	33 (3–61)	35 (6–62)
Site				
Deep-seated†	1	11	5	6
Others	17	90	29	61
Surgery				
Extensive‡	7	15	4	11
Nonextensive	11	86	30	56
Mean field size§ (cm^2) (range)	—	84.6 (16–238)	72.8 (30–165)	90.1 (16–238)
Mean dose (Gy) (range)	—	57.0 (41–66)	57.7 (47.5–66)	56.7 (41–66)
Chemotherapy				
(+)	0	22	6	16
(−)	18	79	28	51

CT: computed tomography.

* Eleven patients in the pre-CT era and seven patients in the post-CT era.

† Tumors in the basal ganglia, thalamus, hypothalamus, corpus callosum, third and lateral ventricles, and pineal region.

‡ Removal of more than 80% of the tumor.

§ Initial field size; in seven patients, the field was reduced after 35–45 Gy.

was seen in 48% (32/67) of the patients and its presence was associated with a poor prognosis ($P = 0.018$). The tumor (or low-density area) margin was clear in 27% (18/67) of patients, and they tended to have a better prognosis ($P = 0.070$). A maximum tumor area less than 25 cm^2 also was associated with a better prognosis ($P = 0.025$). Tumors with a cystic component were not common (10/67, 15%), but also tended to have a better prognosis ($P = 0.12$). Patchy or weak, diffuse contrast enhancement was seen in 37% (25/67) of the tumors, but it did not influence the prognosis significantly.

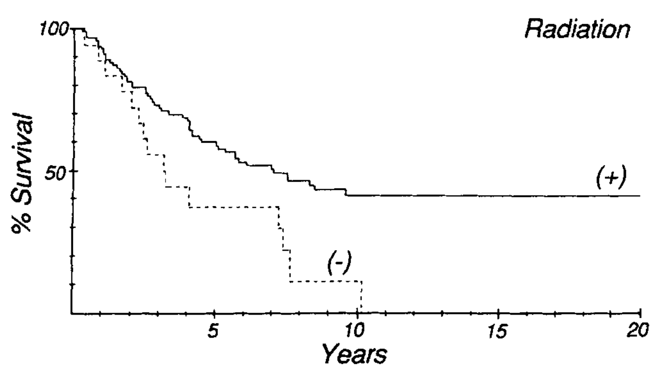

Figure 1. Survival curves for the 101 irradiated patients and the 18 nonirradiated patients ($P = 0.048$).

Multivariate Analysis

First, to confirm the effect of radiation therapy, the application of radiation therapy was analyzed in association with variables 1 to 5 and 8 in Table 2 for all 119 patients. Radiation therapy was found to be associated significantly with a better prognosis ($P = 0.012$). Sex (female > male, $P = 0.046$), era (post-CT > pre-CT, $P = 0.014$), and age (young > old, $P = 0.009$) also were significant. Women tended to fare better in the nonirradiated group (univariate $P = 0.11$). When tumor site, extent of surgery, and chemotherapy were excluded, radiation ($P = 0.012$), era ($P = 0.020$), and age ($P = 0.011$) again were significant, but sex ($P = 0.069$) became insignificant. Thus, the beneficial effect of radiation therapy was confirmed by multivariate analyses.

Second, an analysis of the eight variables listed in Table 2 was performed for the 101 irradiated patients. As shown in Table 2, age was the only significant factor. Third, the 67 patients irradiated in the post-CT era were analyzed in relation to the six factors in Table 3, and mass effect was found to be the only significant factor.

An analysis also was performed for the 74 patients treated in the post-CT era, including seven patients who received surgery alone. Factors in Table 3 and the application of radiation were analyzed, but in this anal-

Table 2. Survival Rates for the 101 Irradiated Patients According to Various Prognostic Variables

Variable	No. of patients	Survival rate (%)		P value	
		5-year	*10-year*	*Univariate*	*Multivariate*
1. Era					
Pre-CT	34	47	38	0.061	0.083
Post-CT	67	66	43		
2. Sex					
Male	65	60	35	0.490	0.268
Female	36	59	55		
3. Age					
< 30 yr	31	73	60	0.025	0.033
≥ 30 yr	70	54	33		
4. Site					
Deep-seated	11	55	45	0.446	0.806
Others	90	60	41		
5. Surgery					
Extensive	15	64	56	0.300	0.242
Nonextensive	86	59	39		
6. Field					
< 80 cm^2	52	65	50	0.504	0.490
≥ 80 cm^2	49	54	32		
7. Dose					
≤ 55 Gy	30	60	47	0.768	0.945
> 55 Gy	71	60	39		
8. Chemotherapy					
(+)	22	49	49	0.751	0.638
(−)	79	62	39		

CT: computed tomography.

ysis the effect of radiation did not reach statistical significance ($P = 0.15$), probably owing to the small number of patients treated by surgery alone.

Adverse Effect

As a major adverse effect of radiation, brain necrosis occurred in one male patient. He received 59.4 Gy in 33 fractions over 50 days together with intraarterial ACNU (100 mg) at the age of 23 years, and had brain necrosis 1 year and 8 months later. This patient currently is alive and well after removal of the necrotic tissue.

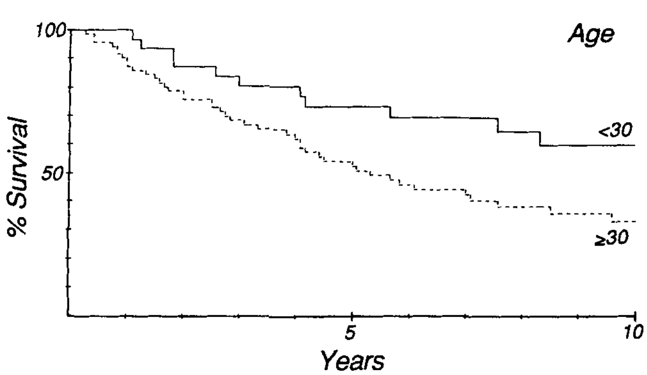

Figure 2. Survival curves for patients younger than 30 years of age (N = 31) and those aged 30 years or older (N = 70; P = 0.025).

Discussion

The prognosis of the 101 irradiated patients was significantly better than that of the 18 nonirradiated patients on both univariate and multivariate analyses. The backgrounds of these two groups differed to some extent in that most of the latter group were not irradiated because it was not thought to be absolutely indicated. Also, the proportion of patients receiving extensive surgery was higher in the nonirradiated group (Table 1). Thus, the nonirradiated group was thought to have a better prognosis at the time of surgery. Nevertheless, our results indicate that radiation therapy had a beneficial effect. Low-grade astrocytoma appears to be more radiosensitive than high-grade tumors, although the response on CT or MRI is slow. Although there has been no randomized trial of the efficacy of radiation, our data, as well as those of others[8,11–13] strongly suggest that radiation therapy improves survival.

Among the various potential prognostic factors examined, age was the only significant one when all irradiated patients were analyzed. This finding agrees with

Table 3. Survival Rates for the 67 Patients Irradiated in the Post-CT Era According to Age and Various CT Findings of Their Tumors

Variable	No. of patients	Survival rate (%)		P	
		5-year	*10-year*	*Univariate*	*Multivariate*
Age					
< 30 yr	18	75	56	0.157	0.267
≥ 30 yr	49	66	43		
Mass effect					
(+)	32	53	20	0.018	0.024
(−)	35	79	62		
Margin					
Clear	18	83	65	0.070	0.280
Unclear	49	60	35		
Maximal area					
< 25 cm^2	30	79	56	0.025	0.367
≥ 25 cm^2	37	57	31		
Cyst					
(+)	10	88	55	0.121	0.835
(−)	57	63	40		
Contrast enhancement					
(+)	25	61	48	0.484	0.283
(−)	42	70	40		

CT: computed tomography.

many other reports,[2-7] but Shaw et al.[8] recently have pointed out that age has less influence when pilocytic astrocytomas (which predominantly affect the young and show a good prognosis) are excluded and only ordinary astrocytomas are analyzed. Therefore, we excluded pilocytic astrocytomas, but still found that age was a significant prognostic factor. It is our impression that the response to therapy generally is better in younger rather than older patients. There are controversial reports on the influence of sex[7,8,14] or the extent of surgery,[2-4,6,8] but our study failed to find any significant influence of these factors in the irradiated group.

We also evaluated various potential prognostic factors among the CT findings. Cysts were found to be a favorable prognostic factor in two previous reports,[2,4] but had no influence in another study.[14] Our series showed a trend in the former direction. Cyst formation may be associated with slower tumor growth. Larger tumors might be expected to exhibit a poorer prognosis, but previous studies[4,8,13] have failed to confirm this. As far as we know, our study is the first one to indicate a clear relationship between tumor size and prognosis. In addition, tumor margin and mass effect have never been evaluated previously for their correlation with prognosis, but we found that these two CT features also were important prognostic factors. It seems reasonable that tumors with a clear margin or no mass effect, as well as small tumors, are less aggressive and hence have

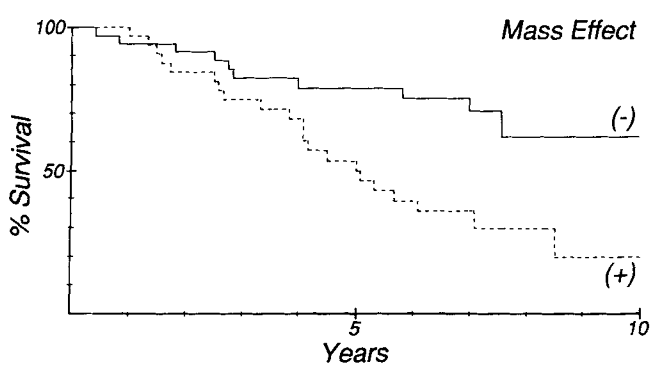

Figure 3. Survival curves for tumors with a mass effect on CT (N = 32) and those without such an effect (N = 35; $P = 0.018$).

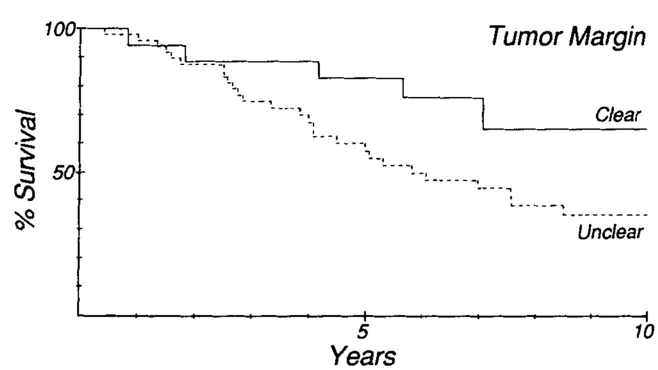

Figure 4. Survival curves for tumors with a clear margin (N = 18) and those with an unclear margin (N = 49; $P = 0.070$).

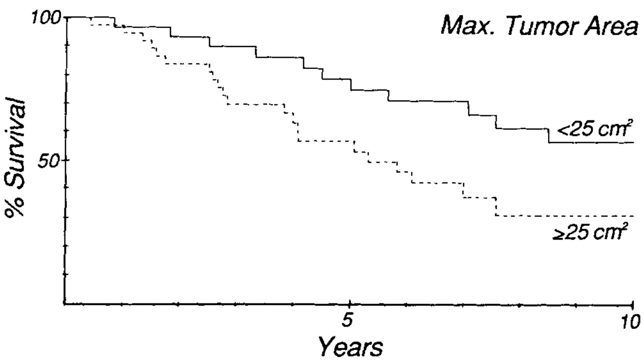

Figure 5. Survival curves for tumors with a maximum area less than 25 cm^2 (N = 30) and larger tumors (N = 37; $P = 0.025$).

a better prognosis. Among these CT features, we found that mass effect was the most important, because relatively large tumors without a mass effect had a better response to therapy. Contrast enhancement of tumors did not influence prognosis in one previous study,[15] whereas it was associated with a poorer prognosis in another.[2] Contrast enhancement is seen more often in high-grade gliomas, so it may be postulated that enhancement of low-grade astrocytoma is suggestive of dedifferentiation to a higher grade and hence associated with a poorer prognosis.[2] Our data, however, did not support this hypothesis.

Our radiation therapy technique was relatively uniform throughout the study period, and most patients received 55 to 60 Gy with a localized field covering the tumor plus a 2-cm margin. Very few reports suggest any benefit of whole-brain irradiation for low-grade astrocytoma, and focal irradiation would seem to be more appropriate. Some studies[5,8,12] have indicated an increase in survival with increasing radiation doses, whereas others[3,16] have not found any dose–survival relationship. Our data were not useful for evaluating this relationship, because patients with worse background factors such as a large tumor size tended to receive higher radiation doses. The average radiation dose in our series, however, was somewhat higher than that reported in most previous studies, and this may have contributed to the slightly better survival rate in our series. Randomized trials being performed elsewhere are comparing high-dose (60–65 Gy) and low-dose (45–50 Gy) radiation,[9] and the results are awaited with interest. At present, we believe that doses between 55 and 60 Gy with a 1.8-Gy daily fraction are appropriate.

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