Supratentorial Astrocytomas and Oligodendrogliomas Treated in the MRI Era

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Background: There is at present no consensus on the policy for the treatment of patients with low-grade gliomas (LGGs).

Methods: This report is a retrospective multi-institutional study of 100 patients (ages 16–65 years) with astrocytoma (grade II), oligodendroglioma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma of the supratentorial areas which were treated with surgery and postoperative radiotherapy at five university hospitals in northern Japan between 1990 and 1997 when MRI was routinely used to determine the target volume. Most patients were irradiated with 50–60 Gy. The target volume usually covered the areas with T2 prolongation of MRI with a margin of 2 cm.

Results: The disease-specific 5-year survival rate was 87.4% for patients with oligodendroglioma and 75.3% for patients with astrocytoma. Survival for patients with astrocytoma in the MRI era appears to be improved compared with historical controls in the literature. Patients with astrocytoma aged 40 years and under had a significantly better disease-specific survival rate than those over 40 years (P < 0.05) and patients with oligodendroglioma and oligoastrocytoma showed a similar tendency. Patients with astrocytoma who had over 50% of their tumor removed had a significantly better survival rate than those who had less than 50% removed (P < 0.05). Chemotherapy appeared to improve the disease-specific survival rate of patients with oligodendroglioma but not that of patients with astrocytoma.

Conclusion: Oligodendroglioma has a more protracted course of disease progression than astrocytoma. This particular feature and the sensitivity of LGGs to chemotherapy as well as their relevant prognostic factors, such as age, histopathology and amount of tumor removal, should be taken into account before any decision on treatment methods for LGGs is made.

Key words: astrocytoma – oligodendroglioma – radiotherapy – prognostic factors

INTRODUCTION

There is at present no consensus on the policy for the treatment for patients with low-grade gliomas (LGGs). Surgery is usually attempted and either biopsy or subtotal or total excision is undertaken. In some situations, where eloquent areas of the brain are involved with the tumor, stereotactic biopsy is a possibility. After surgery or histopathological verification, in general, different policies are pursued. Some institutions treat the patients immediately with planned postoperative radiotherapy (1–3). Others follow a wait-and-see policy and they initiate treatment, usually by surgery followed by radiotherapy, on progression of the disease (4).

In order to obtain the optimal treatment for LGGs, a prospective randomized trial is required. However, the incidence of LGG is low and its course of progression is long, hence it is not easy to perform such trials. Indeed, only a very small number...
of trials have been reported (5). No single report contains the necessary information to devise a definitive treatment for tumors that are not frequently encountered. Therefore, the accumulated experience of various institutions may be useful in treating this tumor more effectively.

Radiological diagnosis has recently been developed remarkably. The use of computed tomography (CT) has improved the survival of patients with low-grade astrocytoma (6), indicating that the results obtained before the CT era are less meaningful as data for making a decision as to the optimal treatment of LGG. When introduced into the radiological diagnosis of CNS tumors, MRI was found to delineate tumor volumes better than CT, particularly in the case of low-grade neoplasms. Therefore, we collected data on as many patients as possible who had been treated in the MRI era, and we analyzed the treatment results. The participating institutions in this study, chosen here for elucidating the prognostic factors of LGGs, are important sites for radiotherapy in northern Japan. Cases of LGG were accumulated and analyzed and the results of treatment were compared with those for cases of anaplastic oligodendroglioma and mixed oligodendroglioma (grade III). By sharing our observations about the treatment results for these tumors, we hope to be able to help improve patient management and treatment decisions for LGG.

SUBJECTS AND METHODS

We analyzed 100 patients with astrocytoma or oligodendroglioma treated with radiotherapy at Sapporo Medical University Hospital, Hokkaido University Hospital, Tohoku University Hospital, Akita University Hospital and Niigata University Hospital between 1990 and 1997. During this period, CT and MRI were performed as routine examinations.

All patients with a definite histopathological diagnosis of astrocytomas (grade II), oligodendroglioma or mixed oligoastrocytomas of the supratentorial areas were included for analysis. The mean age was 37 years (range, 16–65 years). The histopathological type and grade were based on the principles of the World Health Organization (WHO) classification (7). Anaplastic oligodendrogliomas and mixed oligoastrocytoma (grade III) were also included in this study. Since pilocytic astrocytomas are more amenable to total resection than non-pilocytic astrocytomas and have a better prognosis than the latter, we excluded pilocytic astrocytomas from this analysis.

The patients’ general condition was evaluated with the Karnofsky index.

Preoperative CT scans and MRI were performed in all patients. The amount of tumor removed by surgery was classified into biopsy, minimal excision (<50% of the estimated volume of the tumor removed), bulk removal (50–89%) or almost total (≥90%) removal of the tumor. The amount of tumor removal was estimated with postoperative CT and MRI.

Radiation was administered using a linear accelerator. Among the astrocytoma cases, four were irradiated with <50 Gy (30, 35, 44, 46 Gy), 12 with 50 Gy, 16 with 54 or 56 Gy and 24 with 60 Gy. Among the oligodendroglioma and mixed oligoastrocytoma cases, one was irradiated with 40 Gy, nine with 50 Gy, 13 with 60 Gy and three with >60 Gy (64, 66, 81 Gy). Among the anaplastic oligodendroglioma cases, one patient was irradiated with 30 Gy, six with 54 or 56 Gy, 10 with 60 Gy and one with 66 Gy. The irradiation technique was individualized by using the radiation treatment planning system. Parallel opposing oblique wedge fields, multiple crossfiring fields or conformation therapy were used. The target volume was decided with MRI in almost all cases. The target volume usually covered the areas with T2 prolongation of MRI with a margin of 2 cm. In the case of patients treated with ≥60 Gy, the treatment volume was usually reduced after 40 Gy.

Chemotherapy was performed simultaneously with radiotherapy. The chemotherapy consisted of nimustine alone or a combination of nimustine and vincristine or nimustine,
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vincristine and dacarbazine administered intravenously or intra-arterially.

Follow-up with routine and neurological examinations as well as CT and MRI were advised to detect progression of the disease. End-points of the study were disease-specific survival and progression-free survival (PFS). Survival was calculated from the date of operation to the date of death. The PFS was calculated from the date of operation to the date of progression with definite regrowth or recurrence of the disease. The progression-free status of a patient was defined when neither clinical nor radiological (MRI) evidence of tumor activity was noted during follow-up. Patients who died of causes other than cancer were excluded from the progression-free survival analysis at the date of death.

Survival and progression-free survival were estimated by the Kaplan–Meier method (8). Differences were analyzed by the generalized Wilcoxon test with significance taken at \( P < 0.05 \). Univariate and multivariate analyses were included in the assessment of prognostic factors. The Kaplan–Meier method

**RESULTS**

The median length of follow-up for survivors was 49 months, with a range of 4–182 months. The characteristics of the patients and the tumors are listed in Table 1.
Fig. 1 shows overall survival and Fig. 2 shows disease-specific survival according to histopathology. Among astrocytoma cases, 12 of 58 patients died of their tumors and 11 of these 12 patients died within 4 years after surgery. In contrast to astrocytoma, death due to oligodendroglioma and mixed oligodendroglioma occurred later at 4, 49, 80, 106 and 116 months after surgery. The disease-specific 5-year survival rate was 87.4% for patients with oligodendroglioma and 75.3% for patients with astrocytoma. However, at 10 years, these rates showed a reverse relationship at 49.1% and 75.3%, respectively. Anaplastic oligodendroglioma and anaplastic oligoastrocytoma appeared to have a worse prognosis than astrocytoma and oligodendroglioma. However, the difference was not statistically significant, most likely because of the inadequate sample size. Fig. 3 shows the proportion of PFS according to histopathology. The PFS curves exhibited a similar tendency to the disease-specific survival curves.

Fig. 4 demonstrates the relationship between age and disease-specific survival for astrocytoma and oligodendroglioma and oligoastrocytoma cases. Astrocytoma cases aged 40 years and under had a significantly better disease-specific survival rate than those over 40 years ($P < 0.05$) and the same tendency was observed with oligodendroglioma, although the difference was not significant, probably because of the inadequate sample size.

Fig. 5 demonstrates the relationship between disease-specific survival and the degree of tumor surgically removed in astrocytoma cases. Patients who had $>50\%$ removal had a significantly better survival rate than those who had $<50\%$ tumor removal ($P < 0.05$). We could not examine whether the same relationship existed among oligodendroglioma cases because there were only four patients who underwent $<50\%$ tumor removal.

Fig. 6 demonstrates the relationship between disease-specific survival and the radiation dose in patients with astrocytoma who underwent $<50\%$ tumor removal. Patients who were irradiated with $\geq 60\ Gy$ appeared to have a better survival than those irradiated with $<60\ Gy$, although the difference was not statistically significant, probably because of the inadequate sample size. However, there were no such differences in cases who underwent $\geq 50\%$ tumor removal.

Fig. 7 demonstrates the relationship between chemotherapy and disease-specific survival for astrocytoma and oligodendroglioma and oligoastrocytoma. There were no significant differences in disease-specific survival between patients with chemotherapy and those without. However, patients with...
oligodendroglioma who were treated with chemotherapy appeared to have better disease-specific survival than those without chemotherapy, although the difference was not significant, probably because of the inadequate sample size.

Age, tumor site, Karnofsky index, amount of tumor surgically removed, histopathology, radiation dose and chemotherapy were analyzed for prognostic significance for disease-specific survival by multivariate analysis. The amount of tumor removal by surgery was the only significant prognostic factor ($P = 0.0092$). Patients who had $>50\%$ of the tumor removed had an odds ratio of 0.22 (95% confidence interval: 0.07–0.688). In other words, patients who had $<50\%$ tumor removal had a 4.55 (1/0.22) times higher risk of dying from LGG than patients who underwent removal of $>50\%$. Age reached the borderline of significance ($P = 0.0756$). The other factors did not reach statistical significance.

Long-term sequelae, to the extent they were assessable from follow-up CT scans, were rare. Four cases had late complications. Two patients who were treated with 50 and 64 Gy underwent brain necrosis. Brain atrophy occurred in two patients who received 50 Gy of irradiation. However, none of these complications were fatal.

**DISCUSSION**

LGGs are not encountered very frequently. They are diagnosed in ~20% of patients with gliomas and represent ~10% of all primary intracranial tumors. However, presentation usually occurs in younger generations compared with anaplastic astrocytoma or glioblastoma occurrence, which usually takes place in the third or fourth decade of life (10). Therefore, the treatment for LGG is important both socially and medically.

However, the relative rarity of these lesions, the absence of mature randomized trials and the long progression period of these lesions make it difficult to elucidate the optimal treatment. A European Organization for Research on Treatment of Cancer trial which randomized patients between immediate postoperative or deferred radiation therapy is ongoing. However, no results of this trial are available yet. In this situation, the accumulated experiences of various institutions may be useful in elucidating prognostic factors and optimal treatments.

The 5- and 10-year survival rates for patients with astrocytoma in our series were 75.3% with surgery and postoperative radiotherapy. The Mayo Clinic reported a 40% 5-year survival rate in patients treated between 1976 and 1983 (11). Our results appeared to be better than those in other reports of treatment with surgery and postoperative radiation therapy in the CT era. Contrast enhancement in CT is not usually noted in astrocytoma or oligodendroglioma. Therefore, for the target volume it was decided to include the hypodense area on CT when MRI was not available. The resolution of the parenchyma is much better with MRI and tumor volumes are better delineated than with CT, particularly with low-grade neoplasms. The area of increased T2 signal of astrocytoma or oligodendroglioma on MRI generally includes the hypodense area on CT, but the MRI typically identifies a larger edema volume than the corresponding CT scan. Kelly et al. performed stereotactic serial biopsies and analyzed histologically 195 biopsy specimens obtained from various locations within the volumes defined by CT and MRI (12). Twenty-two specimens of astrocytoma were obtained from CT isodense areas which had prolonged T2 on MRI and 19 of these 22 specimens contained tumor cells. All of 36 specimens of oligodendroglioma obtained from hypodense areas defined by CT and within areas of prolonged T2 on MRI contained tumor cells. This indicated that the decision regarding the target volume with CT had the possibility of not including all tumor cells. We routinely used MRI to decide the target volume and the target volume covered the areas with T2 prolongation with a margin of 2 cm. The use of MRI to assist in the decision of the target volume may have contributed to our improved results. Other reasons for our better results may be improved surgical techniques and the use of sophisticated irradiation techniques such as conformal radiation therapy to concentrate radiation doses on the target volume.

The 5-year survival rate for oligodendroglioma appeared to be better than that for astrocytoma. However, at 10 years, the relationship between them was reversed. This is related to the fact that death due to oligodendroglioma and mixed oligodendroglioma occurred later. The Royal Marsden Hospital reported that the 5-year survival rate was 64% for patients with oligodendroglioma and 36% for patients with low-grade astrocytoma. However, at 10 years, the difference was less marked (35 and 26%, respectively) (11).

Anaplastic oligodendroglioma and anaplastic oligoastrocytoma appeared to have worse prognoses than astrocytoma or oligodendroglioma in this study. There have been reports indicating that anaplastic oligodendroglioma has a more aggressive course than low-grade oligodendrogliomas, although the outlook is still considerably better compared with glioblastoma multiforme. Maximal surgical resection followed by adjuvant radiotherapy (60 Gy in 30–33 fractions to the preoperative volume with a 2–3 cm margin) is recommended for the treatment of anaplastic oligodendroglioma (10).

With regard to patients treated by surgery alone, 5-year survival rates reported by various institutions ranged from 32 to 66% (3,6,13,14). In our study, both the 5- and 10-year survival rates of astrocytoma were 75.3%. However, it is impossible to draw a conclusion regarding the optimal timing of radiation with retrospective studies. The ongoing prospective randomized study hopefully will clarify the role of radiotherapy.

Patients with oligodendroglioma who were treated with chemotherapy appeared to have a better disease-specific survival rate than those without chemotherapy. Other reports have shown a particular sensitivity of oligodendroglioma to chemotherapy (15,16). High response rates have been seen for recurrent lesions in trials using PCV (procarbazine, CCNU, vincristine). Phase I–II data also suggest that adjuvant PCV chemotherapy improves survival in these patients (17). However, in astrocytoma cases, there were no significant differences in disease-specific survival between patients with chemotherapy and those without in our study. There have
been few papers reporting the results of chemotherapy for astrocytoma (18) and chemotherapy has no established role in the primary treatment of astrocytoma.

Astrocytoma cases aged 40 years and under had a significantly better disease-specific survival rate than those over 40 years. The same tendency was seen in oligodendroglioma cases. Age reached borderline significance in the multivariate analysis. Other reports also indicated that age is one of the most important determinants of prognosis (3,19,20).

By univariate analysis, patients with astrocytoma who had >50% tumor removal had a significantly better survival rate than those who had <50% tumor removal. The amount of tumor surgically removed was the only significant prognostic factor for disease-specific survival in multivariate analysis. The extent of surgical resection is a significant prognostic factor for anaplastic astrocytoma (21) and glioblastoma multiforme (22). However, the extent of surgery is of variable prognostic significance in astrocytoma cases. Shaw et al. found that survival is directly related to the completeness of resection in pilocytic astrocytoma, but prognosis appears to be independent of the degree of resection for the more unfavorable, diffuse astrocytomas (3).

In conclusion, our results for treatment in the MRI era appeared to be better than those in other reports relating to the CT era. The use of MRI in assisting with the decision about the target volume and the use of sophisticated irradiation techniques may have contributed to our improved results, in addition to improved surgical management. Death due to oligodendroglioma frequently occurred over 5 years after irradiation and the 10-year survival rate was similar to that for astrocytoma, indicating that oligodendroglioma has a more protracted course of progression than astrocytoma. This particular feature and the sensitivity to chemotherapy of LGGs, as well as prognostic factors such as age, histopathology and amount of tumor removal, should be taken into consideration before any decision on treatment for LGG is made.

References